PHASE 1, MULTICENTER, OPEN-LABEL, DOSE-ESCALATION, COMBINATION STUDY OF MARIZOMIB AND BEVACIZUMAB IN BEVACIZUMAB-NAÏVE SUBJECTS WITH WHO GRADE IV MALIGNANT GLIOMA FOLLOWED BY PHASE 2 STUDIES OF SINGLE AGENT MARIZOMIB AND COMBINATION MARIZOMIB AND BEVACIZUMAB, AND PHASE 1 DOSE-ESCALATION STUDY OF ENTERALLY-ADMINISTERED MARIZOMIB WITH BEVACIZUMAB

INVESTIGATIONAL PRODUCT (IP):	**Marizomib (CC-92763, NPI-0052)**
PROTOCOL NUMBER:	**MRZ-108**
Original Protocol:	**10 October 2014 (Not Implemented)**
Amendment 1:	**09 January 2015**
Amendment 2:	**10 January 2016**
Amendment 3:	**27 March 2017**
Amendment 4:	**19 April 2018**
Amendment 5	**18 March 2020**
EudraCT NUMBER:	**Not applicable**
IND NUMBER:	**123765**
SPONSOR NAME / ADDRESS:	**Celgene International II Sàrl Rue des Moulins 4 Couvet 02108, Neuchatel Switzerland**

MEDICAL MONITOR / EMERGENCY CONTACT INFORMATION

Name:	[redacted]	
Title:		
Address:		
Phone:		
E-mail:		

Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

Back-up 24-hour Global Emergency Contact Call Center: [redacted]

CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

{See appended electronic signature page}

Signature of Celgene Therapeutic Area Head **dd mmm yyyy**

[redacted]

Printed Name of Celgene Therapeutic Area Head and Title

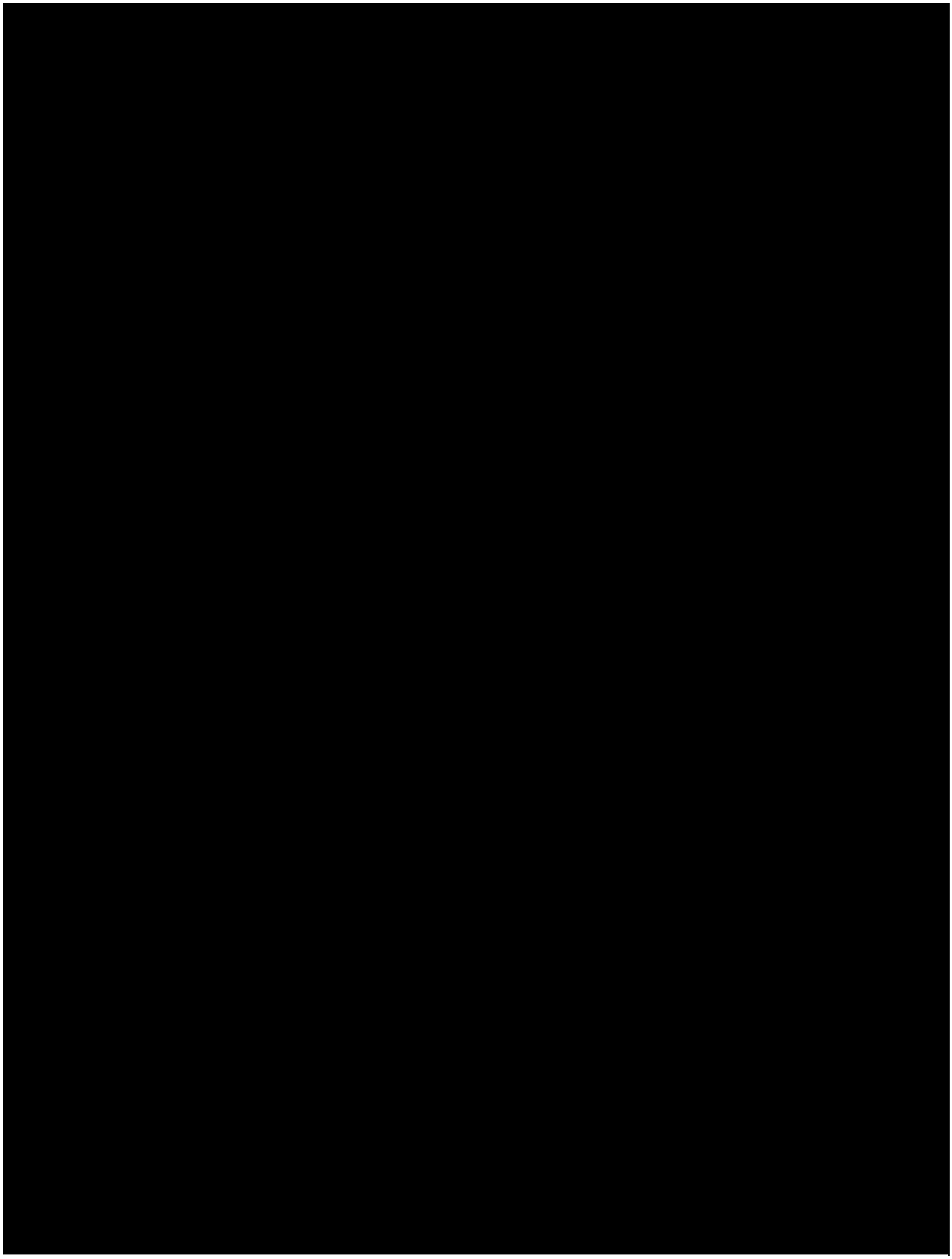
By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Site Principal Investigator	**Date**
Printed Name of Site Principal Investigator **Institution Name:**_____ By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from the Sponsor representatives, the Declaration of Helsinki, ICH Good Clinical Practice Guidelines, and local regulations governing the conduct of clinical studies.	

PROTOCOL SYNOPSIS

Proposed Title	**Phase 1, Multicenter, Open-label, Dose-escalation, Combination Study of Marizomib and Bevacizumab in Bevacizumab-Naïve Subjects with WHO Grade IV Malignant Glioma Followed by Phase 2 Studies of Single Agent Marizomib and Combination Marizomib and Bevacizumab, and Phase 1 Dose-Escalation Study of Enterally-administered Marizomib With Bevacizumab**
Study No.	MRZ-108
Sponsor	Celgene International II Sàrl
Phase	1/2
Indication	WHO Grade IV Malignant Glioma (G4 MG) in bevacizumab-naïve subjects
No. of Sites	5-10 study centers in the United States, Canada, and possibly other regions
[redacted]	



Objectives	**Part 1 Phase 1** **Primary Objective** • To determine the maximum tolerated dose (MTD) or Maximum Administered Dose (MAD) and recommended Phase 2 dose (RP2D) of the combination of marizomib (MRZ) + bevacizumab (BEV), with MRZ as a once weekly dose for 3 weeks of a 28-day cycle and with a fixed dose and schedule of BEV (10 mg/kg administered on Days 1 and 15) in subjects with progressive or recurrent G4 MG, who have not previously been treated with either an anti-angiogenic agent including but not limited to, BEV or a proteasome inhibitor including, but not limited to, MRZ. **Secondary Objectives** • To evaluate the safety of the combination of MRZ + BEV in the subject population. • To evaluate activity of the combination of MRZ + BEV in the subject population including: o Radiographic Overall Response Rate (ORR) (RANO 2010 criteria) o Progression-free Survival (PFS) o Overall Survival (OS) • To evaluate the pharmacokinetics (PK) of MRZ and BEV when administered in combination in the subject population. • To assess the blood proteasome inhibition pharmacodynamic (PD) activity of the combination of MRZ + BEV in the subject population.
	[redacted]
	Part 2 Phase 2 **Primary Objective** • To assess the activity of a once weekly dose for 3 weeks of a 28-day cycle of MRZ in subjects with progressive or recurrent G4 MG, who have not previously been treated with either an anti-angiogenic agent or a proteasome inhibitor. **Secondary Objectives** • To evaluate the safety of single agent MRZ in the subject population.

[redacted]

Part 3 Phase 2

Primary Objective

- To assess the activity of the of the combination of marizomib (MRZ) + bevacizumab (BEV), with MRZ as a once weekly dose for 3 weeks of a 28-day cycle (with intra-patient dose escalation) and every other week dosing of BEV with a fixed dose and schedule of (10 mg/kg administered on Days 1 and 15) in subjects with progressive or recurrent G4 MG, who have not previously been treated with either an anti-angiogenic agent or a proteasome inhibitor.

Secondary Objectives

- To evaluate the safety of combination of MRZ (with intra-patient dose escalation) and BEV at a fixed dose in the subject population.

[redacted]

Part 4 Phase 1

Primary Objective – to be assessed during Cycle 1

- To determine the maximum tolerated dose (MTD) of marizomib (MRZ) administered enterally by NG tube once weekly for 3 weeks of a 28-day cycle during the first treatment cycle. BEV will be administered IV at a fixed dose (10 mg/kg administered on Day 15 and Days 1 and 15 of subsequent cycles). Subjects are those with progressive or recurrent G4 MG and who have not previously been treated with either an anti-angiogenic agent or a proteasome inhibitor.

	Secondary Objectives – to be assessed during Cycle 1 • To evaluate the safety (in particular gastrointestinal (GI) tolerability) of enterally administered MRZ by NG tube in the subject population. • To assess the frequency of CNS adverse events (including ataxia, dizziness, dysarthria, fall, gait disturbances, and hallucinations) after enterally administered MRZ in the subject population. • To evaluate the pharmacokinetics (PK) of MRZ administered enterally by NG tube in the subject population on Cycle 1 Day 1 and Cycle 1 Day 8. • To assess the blood proteasome inhibition pharmacodynamic (PD) activity of MRZ administered enterally by NG tube on Cycle 1 Day 1 and Cycle 1 Day 8, and to compare this with the PD activity of MRZ administered IV in combination with IV BEV on Cycle 2 Day 1 and Cycle 2 Day 8 in the subject population.
	[redacted]
	Part 5 Phase 1 **Primary Objective** • To determine the repeat-dose pharmacokinetics of MRZ administered IV in subjects with progressive or recurrent G4 MG, who have not previously been treated with either an anti-angiogenic agent or a proteasome inhibitor. **Secondary Objectives** • To monitor the safety of the combination of MRZ and BEV at a fixed dose in the subject population. • To describe the activity of the combination of MRZ + BEV, with MRZ as a once weekly dose for 3 weeks of a 28-day cycle and every other week dosing of BEV with a fixed dose and schedule in the study population. • To evaluate MRZ cardiac safety comparing PK to ECG.
Study Design	Part 1 of this protocol is a Phase 1, open-label, 3+3, dose-escalation study in subjects with WHO Grade IV Malignant Glioma (G4 MG) who are in first or second relapse and who have not previously received any BEV or other anti-angiogenic agent, including sorafenib, sunitinib, axitinib, pazopanib, everolimus, or cilengitide or MRZ or any other proteasome inhibitor, including BTZ, CFZ, or IXZ. Three to 6 evaluable subjects per cohort will be enrolled: approximately 24 subjects, to determine the MTD or MAD (Part 1 Dose-escalation) and an addition of at least 12 more subjects to confirm the MTD/MAD and determine the RP2D (Part 2 Expansion Cohort) and assess preliminary activity to a total of up to 36 subjects. Subjects may not be enrolled in more than 1 cohort and there will be no intra-subject dose escalation. The Phase 1 portion will be followed by Part 2 a Phase 2 study of single agent MRZ administered as a 10-minute infusion at a dose of 0.8 mg/m^2 (the RP2D from Phase

	1) every week for 3 weeks in 28-day cycles. This part will be conducted as a 2-stage sequential design of up to 30 response-evaluable subjects. The Part 2 Phase 2 will be followed by Part 3, a Phase 2 study of combination MRZ using intra-patient dose escalation, and BEV at a fixed dose. MRZ will be administered as a 10-minute infusion every week for 3 weeks in 28-day cycles at a starting dose of 0.8 mg/m^2 (the RP2D from Part 1 Phase 1). After the first cycle without a dose-limiting adverse event (DLAE), the dose of MRZ will be increased to 1.0 mg/m^2 and after 1 more cycle without a DLAE the dose of MRZ will be increased to 1.2 mg/m^2. BEV will be administered every 2 weeks (Days 1 and 15 of each 28-day cycle) at a fixed dose of 10 mg/kg. DLAEs are MRZ-related AEs which are: 1) related to disturbances in the cerebellum (ie, ataxia, dizziness, dysarthria, fall, gait disturbances) plus hallucinations of any grade or 2) Grade $\geq$ 2 other AEs. This portion of the study will be conducted in approximately 40 eligible subjects of which, based on the AEs seen in Part 1 of the study, about 24 subjects are expected to be eligible for intra-patient dose escalation. Part 4 (Phase 1) of this protocol is an open-label, dose-escalation study (during Cycle 1) in subjects with WHO Grade IV Malignant Glioma (G4 MG) who are in first or second relapse and who have not previously received any BEV or other anti-angiogenic agent, or MRZ or any other proteasome inhibitor. Subjects will be treated with MRZ enterally administered via NG tube for one 28-day treatment cycle, with three doses administered on Days 1, 8 and 15. Subjects must receive at least 3 doses of MRZ, with two of them administered enterally during Cycle 1, to be evaluable for dose-limiting toxicity (DLT). One to 6 evaluable subjects per cohort will be enrolled in the first 3 dose-escalation cohorts, and 3 to 6 evaluable subjects per cohort will be enrolled in the next 6 dose cohorts, to determine the MTD (Part 4 dose-escalation). Approximately 6 additional subjects will be enrolled to confirm the MTD (Part 4 dose-expansion) and assess preliminary activity to a total of up to approximately 24 subjects. Subjects may not be enrolled in more than 1 cohort and there will be no intra-subject dose escalation. Part 5 Phase 1 of this protocol is an open-label MRZ PK study in approximately 12 subjects with WHO Grade IV Malignant Glioma (G4 MG) who are in first or second relapse and who have not previously received any BEV or other anti-angiogenic agent, or MRZ or any other proteasome inhibitor. Subjects will be treated with MRZ IV (0.8 mg/m^2) on Days 1, 8, and 15 of each 28-day treatment cycle. BEV will be administered IV (10 mg/kg) on Day 15 of Cycle 1, after completion of MRZ PK sample collection, and subsequently on Days 1 and 15 (10 mg/kg) of each subsequent 28-day cycle.
Study Treatments	MRZ is an investigational product that will be provided by the Sponsor. BEV is available commercially and will be provided by the Investigator via prescription to subjects who are enrolled into the Part 1 Phase 1, Part 3 Phase 2, Part 4 Phase 1, and Part 5 Phase 1 portions of this study.

	Study Treatment **Part 1 Phase 1** All subjects will receive intravenous (IV) MRZ infusion followed by IV BEV infusion as follows: IV MRZ will be administered as a 10-minute (or longer) IV infusion on Days 1, 8, and 15 of every 28-day cycle. IV hydration will be given both before and after the infusion. IV BEV will be administered as an IV infusion (90 minutes 1st dose, 60 minutes 2nd dose and 30 minutes afterward assuming tolerability) at a dose of 10 mg/kg on Days 1 and 15 of every 28-day cycle. BEV will be administered approximately 10 minutes after the end of the MRZ infusion when co-administered on the same day. **Part 2 Phase 2** All subjects will receive IV MRZ infusion. MRZ will be administered as a 10-minute, IV infusion on Days 1, 8, and 15 of every 28-day cycle. IV hydration will be given before the infusion. **Part 3 Phase 2** All subjects will receive IV MRZ infusion and IV BEV infusion. MRZ will be administered as a 10-minute, IV infusion on Days 1, 8, and 15 of every 28-day cycle using intra-patient dose escalation. Starting dose will be 0.8 mg/m^2 (RP2D dose). If the starting dose is tolerated and no DLAE is observed, the dose will be increased to 1.0 mg/m^2 after 1 cycle. If the increased dose is tolerated again and no DLAE is observed, the dose of MRZ will be increased to 1.2 mg/m^2 after 1 more cycle. Dose reductions will be applied as necessary and according to the toxicities noted. If the starting dose of 0.8 mg/m^2 is not tolerated (after appropriate medical treatment of adverse events, if applicable), the dose will be decreased to 0.7 mg/m^2. A further reduction to 0.55 mg/m^2 is allowed, if necessary. BEV will be administered as an IV infusion (90 minutes 1st dose, 60 minutes 2nd dose and 30 minutes afterward assuming tolerability) at a fixed dose of 10 mg/kg on Days 1 and 15 of every 28-day cycle. BEV will be administered approximately 10 minutes after the end of the MRZ infusion when co-administered on the same day. Dose reductions of BEV will not be made, but dose delay or discontinuation will be made depending upon the observed adverse events. **Part 4 Phase 1** In Cycle 1, all subjects will receive MRZ enterally by NG tube (reconstituted IV formulation) as a bolus on Days 1, 8, and 15 of the first 28-day cycle. BEV will be administered as an IV infusion on Day 15, approximately 10 minutes after the completion of the MRZ enteral dose administration. In Cycle 2 and all subsequent cycles, MRZ will be administered IV at the recommended dose and schedule determined in Phase 1 Part 1: MRZ 0.8 mg/m^2 IV weekly for three weeks (Days 1, 8 and 15) of a 28-day cycle and BEV 10 mg/kg IV

	on Days 1 and 15. IV MRZ will be infused over 10-minutes, and BEV will be administered as an IV infusion (90 minutes 1st dose, 60 minutes 2nd dose and 30 minutes afterward assuming tolerability) at a dose of 10 mg/kg on Days 1 and 15 of every 28-day cycle. BEV will be administered approximately 10 minutes after the end of the MRZ IV infusion when co-administered on the same day. **Part 5 Phase 1** In Cycle 1, all subjects will receive MRZ infused over 10-minutes IV at the dose and schedule recommended from Phase 1 Part 1: MRZ 0.8 mg/m^2 IV weekly for 3 weeks (Days 1, 8, and 15) of a 28-day cycle. BEV will be administered as an IV infusion over 90 minutes on Day 15, after the completion of the 60-minute MRZ PK blood sample collection. In Cycle 2 and all subsequent cycles, MRZ will be administered IV at the same dose and schedule (0.8 mg/m^2 IV weekly for 3 weeks (Days 1, 8, and 15) of a 28-day cycle), with IV MRZ infused over 10 minutes. BEV will be administered as an IV infusion (90 minutes 1st dose, 60 minutes 2nd dose, and 30 minutes afterward assuming tolerability) at a dose of 10 mg/kg on Days 1 and 15 of every 28-day cycle. In all subsequent cycles, BEV will be administered approximately 10 minutes after the end of the MRZ IV infusion.
Dose-Limiting Toxicity	**Part 1 Phase 1 (only)** For the Phase 1 portion of the study, dose-limiting toxicity (DLT) is defined as the occurrence of any of the following adverse events (AEs) related to study treatment observed during Cycle 1, using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI-CTCAE v 4.03) to determine severity: • Grade 3 thrombocytopenia or Grade 2 thrombocytopenia with bleeding. • Grade 4 neutropenia or anemia lasting for more than 4 days. • Febrile neutropenia. • Any ≥ Grade 2 neurological event lasting more than 4 days. • Grade 3 or 4 non-hematological toxicity (excluding alopecia) lasting for more than 4 days despite adequate supportive therapy or preventing the next scheduled dose from being administered within 4 days of scheduled day; for ≥ Grade 3 fatigue to be considered a DLT, it must be present for more than 7 days. Subjects without DLT in Cycle 1 who do not receive 3 MRZ doses or 2 BEV doses within 5 weeks from first dose will not be evaluable for DLT and will be replaced.
Dose Limiting Adverse Events	**Part 3 Phase 2 only** For the Part 3 Phase 2 portion of the study initiated with Amendment 3, DLAEs are defined as MRZ-related AEs observed which are: • related to disturbances in the cerebellum (ie, ataxia, dizziness, dysarthria, fall, gait disturbances) plus hallucinations of any grade • any other AEs of Grade ≥ 2.

<table>
<tr><td>Dose-Limiting Toxicity</td><td>
Part 4 Phase 1
Dose-limiting toxicity (DLT) is defined as the occurrence of any of the following adverse events (AEs) related to study treatment observed during Cycle 1, using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI-CTCAE v 4.03) to determine severity:
• Grade ≥3 non-hematological toxicity (excluding alopecia), including GI toxicities such as nausea, vomiting, constipation, and/or diarrhea, lasting for more than 4 days despite adequate supportive therapy or preventing the next scheduled dose from being administered within 7 days of scheduled day
o For ≥ Grade 3 fatigue to be considered a DLT, it must be present for more than 7 days.
• Grade 3 thrombocytopenia or Grade 2 thrombocytopenia with bleeding.
• Grade 4 neutropenia or anemia lasting for more than 4 days.
• Febrile neutropenia.
• Any ≥ Grade 2 neurological event lasting more than 4 days.
Subjects who do not have a DLT in the first cycle of a dose cohort will be replaced if they do not receive at least two doses of enterally-administered MRZ, with the second dose administered no more than 7 days after the scheduled dose.
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<tr><td>Part 1 Phase 1 Dose Escalation</td><td>
Subjects who have completed Screening procedures and meet all eligibility criteria may be enrolled into the study.
A 3+3 design will be used to define the MTD/MAD for MRZ + BEV combination treatment in 28-day cycles, with MRZ administered on Days 1, 8, and 15 and BEV on Days 1 and 15.
MRZ dosing will begin at 0.55 mg/m^2 once weekly (Cohort 1). Additional dose cohorts are planned as shown below (Table S-1):
Table S-1. Dose Cohorts for MRZ + BEV Combination
<table>
<tr><th>Cohort</th><th>IV MRZ
Days 1, 8, and 15</th><th>IV BEV
Days 1 and 15</th></tr>
<tr><td>-2</td><td>0.3 mg/m^2</td><td>10 mg/kg</td></tr>
<tr><td>-1</td><td>0.4 mg/m^2</td><td>10 mg/kg</td></tr>
<tr><td>1</td><td>0.55 mg/m^2</td><td>10 mg/kg</td></tr>
<tr><td>2</td><td>0.7 mg/m^2</td><td>10 mg/kg</td></tr>
<tr><td>3</td><td>0.8 mg/m^2</td><td>10 mg/kg</td></tr>
<tr><td>4</td><td>Additional cohorts with extended infusion duration if required</td><td>10 mg/kg</td></tr>
</table>
Initially 3 subjects will be enrolled into a cohort, commencing with Cohort 1 and the doses shown in Table S-1 above. Dose escalation will proceed as follows:
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	• If none of the first 3 evaluable subjects in a dose cohort experience a DLT during Cycle 1, then enrollment into the next dose cohort can be initiated. • If ≥ 2 of the first 3 evaluable subjects in a dose cohort experience a DLT during Cycle 1, then the MTD has been exceeded and dose escalation will not proceed. • If 1 of the first 3 evaluable subjects in a dose cohort experiences a DLT during Cycle 1, then an additional 3 subjects will be enrolled into the same cohort. • If 1/6 evaluable subjects in the expanded 6-subject cohort experiences a DLT during Cycle 1, then the next higher dose cohort can be tested and enrollment of the next 3 subjects at the next higher dose level can be initiated. • If ≥ 2/6 evaluable subjects in the expanded 6-subject cohort experience a DLT during Cycle 1, then the MTD has been exceeded and no further dose escalation will occur. The MTD is defined as the dose level below the cohort where DLT is observed in at least 2 subjects in the same cohort during Cycle 1. Intermediate dosing levels may be explored if indicated. If the Sponsor and Investigators agree, then additional cohorts starting below the MTD for the 10-minute infusion may be enrolled to explore extended infusion lengths. The dose of 0.8 mg/m^2 will not be exceeded and will be the MAD. The RP2D is the MTD/MAD unless further safety information suggests a lower dose for future trials. Teleconferences between Triphase and the clinical study sites will occur at least every other week to discuss safety. Additional teleconferences may be scheduled at the end of each cohort to decide on the dose and/or MRZ infusion length of the next cohort. Once the MTD or Maximum Administered Dose (MAD) has been identified, a cohort of at least 12 additional, evaluable subjects will be treated at the MTD/MAD to further confirm the safety and to assess preliminary activity for the combination treatment. This cohort may be used to determine the RP2D.
Part 2 Phase 2 Dose Escalation	Dose escalation of MRZ was not allowed in this portion of the study.
Part 3 Phase 2 Intra-patient Dose Escalation	MRZ dosing will start at 0.8 mg/m^2 given on Days 1, 8, and 15 in 28-day cycles as a 10-minute IV infusion. If the subject tolerates the MRZ dose during the first cycle without a DLAE, the dose of MRZ will be increased to 1.0 mg/m^2. After 1 more cycle without a DLAE, the dose of MRZ will be increased to 1.2 mg/m^2. All dose increases require approval by the Sponsor's Medical Monitor. DLAEs are MRZ-related AEs 1) related to disturbances in the cerebellum (ie, ataxia, dizziness, dysarthria, fall, gait disturbances) plus hallucinations of any grade or 2) Grade ≥ 2 other AEs. If the MRZ starting dose of 0.8 mg/m^2 is not tolerated after appropriate medical treatment of AEs in the first cycle, then the dose will be decreased to 0.7 mg/m^2 with no further dose increases allowed. BEV will be administered as an IV infusion (90 minutes 1st dose, 60 minutes 2nd dose and 30 minutes afterward assuming tolerability) at a dose of 10 mg/kg on Days 1 and 15 of every 28-day cycle. BEV will be administered approximately 10 minutes after the end of the MRZ infusion when co-administered on the same day. The dose of

<table>
<tr><td></td><td>BEV will not increase. No dose adjustments will be made to BEV dosing, although doses may be delayed or discontinued.</td></tr>
<tr><td>Part 4 Phase 1 Dose Escalation and MTD Dose Expansion Cohort</td><td>
Subjects who have completed Screening procedures and meet all eligibility criteria may be enrolled into the study.

A modified 3+3 design will be used to define the MTD for MRZ IV formulation reconstituted and administered enterally via NG tube in the first 28-day cycle, with MRZ administered on Days 1, 8, and 15 and BEV on Day 15, with initially one subject enrolled into each of the first 3 dose cohorts to expedite dose-escalation into the anticipated therapeutically effective dose range.

MRZ dosing will begin at 0.075 mg/m^2 once weekly (Cohort 1). Additional dose cohorts are planned as shown below (Table S-2):
Table S-2. Dose Cohorts for MRZ + BEV Combination, Part 4 Phase 1
<table>
<tr><th>Cohort</th><th>Number of Subjects</th><th>Enteral MRZ (mg/m^2) Cycle 1 Days 1, 8, and 15</th><th>IV MRZ (mg/m^2) Cycle 2+ Days 1, 8 and 15*</th><th>IV BEV (mg/kg) Cycle 1 Day 15 Cycle 2+ Days 1 and 15</th></tr>
<tr><td>-1</td><td>3-6</td><td>0.025</td><td>0.8</td><td>10</td></tr>
<tr><td>1</td><td>1-6</td><td>0.075</td><td>0.8</td><td>10</td></tr>
<tr><td>2</td><td>1-6</td><td>0.225</td><td>0.8</td><td>10</td></tr>
<tr><td>3</td><td>1-6</td><td>0.675</td><td>0.8</td><td>10</td></tr>
<tr><td>4</td><td>3-6</td><td>1.0</td><td>0.8</td><td>10</td></tr>
<tr><td>5</td><td>3-6</td><td>1.35</td><td>0.8</td><td>10</td></tr>
<tr><td>6</td><td>3-6</td><td>1.7</td><td>0.8</td><td>10</td></tr>
<tr><td>7</td><td>3-6</td><td>2.0</td><td>0.8</td><td>10</td></tr>
<tr><td>8</td><td>3-6</td><td>2.3</td><td>0.8</td><td>10</td></tr>
<tr><td>9</td><td>3-6</td><td>2.6</td><td>0.8</td><td>10</td></tr>
</table>
* For Cycle 2 and all subsequent cycles, MRZ will be administered IV at 0.8 mg/m^2 given on Days 1, 8, and 15 in 28-day cycles as a 10-minute IV infusion.

Initially 1 subject will be enrolled into the first three dose cohorts and 3 subjects will be enrolled into the next 6 dose cohorts. Enteral MRZ dose escalation will proceed as follows:
• If the first DLT-evaluable subject in dose cohort 1 does not experience a DLT or intermediate toxicity during Cycle 1, then enrollment into the next dose cohort can be initiated.
• If the first DLT-evaluable subject in a 1-subject dose cohort experiences a DLT during Cycle 1, then up to 5 additional subjects will be enrolled into the same cohort.
• The 1-subject cohorts will be expanded to 3 subjects with the second instance of first-cycle intermediate toxicity. Intermediate toxicity is defined as any Grade 2
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</table>

	or higher adverse event that is deemed clinically significant by the Investigator and which cannot be clearly identified as being related to the underlying condition, comorbid condition, or concomitant medication. Once a 1-subject cohort has been expanded, all subsequent cohorts will have at least 3 subjects (unless the first 2 subjects have DLT prior to the enrollment of a third subject). • If there are 2 subjects with DLT in Cohort 1, then 3 subjects can be enrolled in Cohort -1. The decision to explore Cohort -1 will be made by the participating Investigators and Sponsor's Medical Monitor(s). If Cohort -1 proceeds without any subject with a DLT, participating Investigators and Sponsor's Medical Monitor(s) may decide to revisit Cohort 1 and, if tolerated, continue with the escalation as shown in Table S-2, or with intermediate dose levels. • If 1 of the first 3 evaluable subjects in a 3-subject dose cohort experiences a DLT during Cycle 1, then an additional 3 subjects will be enrolled into the same cohort. • If no more than 1 of the 6 DLT-evaluable subjects in an expanded dose cohort experiences a DLT during Cycle 1, then the next higher dose cohort can be initiated with 3 subjects enrolled at the next higher dose level. • If $\geq$ 2/6 evaluable subjects in an expanded dose cohort experiences a DLT during Cycle 1, then the MTD has been exceeded and no further dose escalation will occur. The MTD is defined as the dose level below the cohort where DLT is observed in at least 2 subjects in the same cohort during Cycle 1. Intermediate dosing levels may be explored if indicated. The dose of 2.6 mg/m^2 is expected to be above the MTD for enterally-administered MRZ. If this is not the case, additional cohorts can be explored with dose escalations between cohorts kept at approximately 20%. Once the MTD has been determined, a cohort of approximately 6 additional, response-evaluable subjects will be enrolled in the Part 4 Phase 1 Expansion Cohort, to further explore the safety profile of enterally-administered MRZ combined with IV BEV. Teleconferences between Sponsor and the clinical study sites will occur at least every other week to discuss safety. Additional teleconferences may be scheduled at the end of each cohort to decide on the dose of the next cohort.
No. Subjects	**Part 1 Phase 1:** 36 subjects were enrolled in the study at multiple centers. **Part 2 Phase 2:** Up to 30 response-evaluable subjects will be enrolled in the study at multiple centers. **Part 3 Phase 2:** Up to 40 eligible subjects will be enrolled in the study at multiple centers. **Part 4 Phase 1:** Up to 24 eligible subjects will be enrolled in the study at multiple centers. **Part 5 Phase 1:** Approximately 12 eligible subjects will be enrolled in the study at a single center.

Study Population	The study population includes subjects with G4 MG (including glioblastoma and gliosarcoma) who are in first or second relapse and who have not previously received any BEV or other anti-angiogenic agent, including sorafenib, sunitinib, axitinib, pazopanib, everolimus, or cilengitide or MRZ or any other proteasome inhibitor, including BTZ, CFZ, or IXZ. The eligibility criteria are the same for both Phase 1 and Phase 2 portions of the study except where noted. **Inclusion Criteria (applicable for all Parts including Part 5):** Subjects must meet the following criteria to be eligible for study participation: 1. Understand and voluntarily sign and date an informed consent document prior to any study related assessments/procedures are conducted. 2. Males and females of age ≥ 18 years at the time of signing of the informed consent document. 3. All subjects must have histologic evidence of G4 MG (including glioblastoma and gliosarcoma) and radiographic evidence of recurrence or disease progression (defined as either a greater than 25% increase in the largest bidimensional product of enhancement, a new enhancing lesion, or significant increase in T2 FLAIR). Subjects must have at least 1 measurable lesion by RANO criteria (≥ 10 mm in 2 perpendicular diameters). 4. Subjects must have previously completed standard radiation therapy and been exposed to temozolomide. Subjects must be in first or second relapse. 5. No prior treatment with MRZ or any other proteasome inhibitors, including BTZ, CFZ, or IXZ or BEV or any other anti-angiogenic agents, including sorafenib, sunitinib, axitinib, pazopanib, everolimus, or cilengitide. 6. No investigational agent within 4 weeks prior to first dose of study drug. 7. At least 4 weeks from surgical resection and at least 12 weeks from end of radiotherapy prior to enrollment in this study, unless relapse is confirmed by tumor biopsy or new lesion outside of radiation field, or if there are two MRIs confirming progressive disease that are approximately 8 weeks apart. 8. Subjects with a history of seizures must be on a stable dose of anti-epileptic drugs (AEDs) and without seizures for 14 days prior to enrollment in patients enrolled prior to Amendment 2. Subjects enrolled after Amendment 2 is approved with a history of seizures must be on a stable dose of anti-epileptic drugs (AEDs)for 7 days prior to enrollment. 9. All AEs resulting from prior chemotherapy, surgery, or radiotherapy, must have resolved to NCI-CTCAE (v. 4.03) Grade ≤1 (except for laboratory parameters outlined below). 10. Laboratory results within 7 days prior to MRZ administration (transfusions and/or growth factor support may not be used to meet this criteria): • Platelet count ≥ 100 × 109/L. • Hemoglobin ≥ 9 g/dL. • Absolute neutrophil count (ANC) ≥ 1.5 × 109/L.

- Serum bilirubin ≤ 1.5 × upper limit of normal (ULN) or ≤ 3 × ULN if Gilbert's disease is documented.
- Aspartate transaminase (AST) ≤ 2.5 ULN.
- Alanine transaminase (ALT) ≤ 2.5 ULN.
- Serum creatinine ≤ 1.5 × ULN.
- Urine protein: creatinine ratio ≤ 1.0 at screening.

11. Karnofsky Performance Status (KPS) score ≥ 70%.
12. For women of child-bearing potential and for men with partners of child-bearing potential, subject must agree to take contraceptive measures for duration of treatments and for 3 months after the last dose of MRZ or 6 months after the last dose of BEV, whichever is longer. A female subject of childbearing potential (FCBP) is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).
13. Willing and able to adhere to the study visit schedule and other protocol requirements.

Exclusion Criteria (applicable for all Parts including Part 5):

Subjects with any of the following will be excluded from participation in the study:

1. Co-medication that may interfere with study results, eg, immuno-suppressive agents other than corticosteroids. Steroid therapy for control of cerebral edema is allowed at the discretion of the Investigator. Subjects should be on a stable dose of steroids for at least 1 week prior to first dose of MRZ. Co-medications must not be taken for 2 hours prior to and up to 2 hours after enteral administration of MRZ (Part 4 Phase 1).
2. Evidence of CNS hemorrhage on baseline MRI or CT scan (except for post-surgical, asymptomatic Grade 1 hemorrhage that has been stable for at least 3 months for subjects enrolled prior to Amendment 2 and for at least 4 weeks in subjects enrolled after Amendment 2 is approved).
3. History of thrombotic or hemorrhagic stroke or myocardial infarction within 6 months.
4. Chemotherapy administered within 4 weeks (except 6 weeks for nitrosoureas, 12 weeks for an implanted nitrosoureas wafer, and 1 week from metronomic chemotherapy, such as daily temozolomide and etoposide) prior to Day 1 of study treatment, unless the subject has recovered from all expected toxicities from the chemotherapy.
5. (Part 4 Phase 1) Recent nasal or esophageal surgery, of history of GI-related medical conditions, or any other condition which, in the opinion of the Investigator, would interfere or cause undue risk with insertion of NG tube or enteral administration of marizomib through the NG tube.

	6. Pregnancy or breast feeding. 7. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection requiring IV antibiotics & psychiatric illness/social situations that would limit compliance with study requirements, or disorders associated with significant immunocompromised state. 8. Known previous/current malignancy requiring treatment within ≤ 3 years except for cervical carcinoma *in situ*, squamous or basal cell skin carcinoma, and superficial bladder carcinoma. 9. Any comorbid condition that confounds the ability to interpret data from the study as judged by the Investigator or Medical Monitor. BEV-Specific Concerns (All Parts) (Note: These exclusion criteria also apply to the Part 2 Phase 2 portion of the study even though BEV is not administered so that the subject populations among Part 1, Part 2, Part 3, Part 4, and Part 5 are similar): 1. Any prior history of hypertensive crisis or hypertensive encephalopathy. 2. Systolic blood pressure (BP) > 150 mmHg or diastolic BP > 100 mmHg. 3. Unstable angina. 4. New York Heart Association Grade ≥ II congestive heart failure. 5. History of myocardial infarction within 6 months. 6. Subjects with mean QTcF interval > 500 ms. 7. Clinically significant peripheral vascular disease 8. Evidence of bleeding diathesis, coagulopathy as documented by an elevated (≥ 1.5 x ULN) prothrombin time (PT), partial thromboplastin time (PTT), or bleeding time. The use of full-dose oral or parenteral anticoagulants is permitted as long as the PT or aPTT is within therapeutic limits (according to the medical standard of the enrolling institution) and the subject has been on a stable dose of anticoagulants for at least 2 weeks prior to the first study treatment. 9. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to Day 1 or anticipation of need for major surgical procedure during course of the study. 10. Minor surgical procedures, fine needle aspirations or core biopsies within 7 days prior to Day 1. 11. History of abdominal fistula, GI perforation, or intra-abdominal abscess within 6 months prior to Day 1. 12. Serious, non-healing wound, ulcer, or bone fracture requiring surgical intervention.
Length of Study Participation	Subjects may continue on study treatment until disease progression, unacceptable toxicity, withdrawal of consent, or termination of the study. For subjects who discontinue study drug for reasons other than disease progression, whenever possible, tumor assessment will continue as per protocol until disease progression. After disease progression, subjects will be followed for survival and the start of first new anti-GBM therapy and its outcome.

Investigational Product/ Background Therapy/ Route/ Regimen	**Part 1 Phase 1** MRZ will be administered IV over 10 minutes. Other infusion lengths may be explored. Volume of administration will vary based on assigned dose (Table S-1) and subject body surface area (BSA). To mitigate the possibility of renal dysfunction, subjects will receive normal saline administered at 350 mL/hour for 1 hour before and for 2 hours after the MRZ infusion. The MRZ infusion will be started after approximately 350 mL of saline have been given over 1 hour. After the MRZ infusion has been completed, approximately 700 mL of saline will be given over 2 hours, for a total volume of saline infusion equal to approximately 1 L. Post infusion hydration may be reduced at the discretion of the Investigator. The lyophilized drug product contains 2 mg API and 60 mg sucrose bulk excipient. Cartons contain one vial of lyophile together with a Diluent vial containing 55% propylene glycol, 5% ethanol, and 40% citrate buffer pH 5 (20 mL fill; 10 mL intended for use). BEV will be administered as an IV infusion (90 minutes 1st dose, 60 minutes 2nd dose and 30 minutes afterward assuming tolerability) as described in the current package insert. BEV will be administered approximately 10 minutes after the end of the MRZ infusion when co-administered on the same day. **Part 2 Phase 2** MRZ will be administered IV over 10 minutes at a dose of 0.8 mg/m^2. To mitigate the possibility of renal dysfunction, subjects will receive normal saline administered at 250 mL for 30 minutes before the MRZ infusion. The lyophilized drug product is the same as used in the Phase 1 portion. **Part 3 Phase 2** MRZ will be administered IV over 10 minutes at a starting dose of 0.8 mg/m^2. Based on the subject's tolerability, the dose of MRZ may be increased after the first cycle without a dose-limiting adverse event (DLAE) and again after 1 more cycle without a DLAE. The lyophilized drug product is the same as used in the other portions of the study. In Amendment 3, pre and post MRZ dose hydration is not required, except where assessed as clinically necessary by Investigator. BEV will be administered as an IV infusion (90 minutes 1st dose, 60 minutes 2nd dose and 30 minutes afterward assuming tolerability) as described in the current package insert. BEV will be administered approximately 10 minutes after the end of the MRZ infusion when co-administered on the same day. **Part 4 Phase 1** MRZ IV formulation will be reconstituted and administered enterally via NG tube in a dose-escalation design on Days 1, 8, and 15 of the first 28-day treatment cycle. BEV will be administered IV on Day 15 during Cycle 1. For the subsequent 28-day treatment cycles, MRZ will be administered as an IV at the recommended dose and schedule determined in Phase 1 Part 1: MRZ 0.8 mg/m^2 IV weekly for three weeks (Days 1, 8 and 15, 10 min infusion) of a 28-day cycle, with BEV 10 mg/kg IV on Days 1 and 15.

	BEV will be administered as an IV infusion (90 minutes 1st dose, 60 minutes 2nd dose and 30 minutes afterward assuming tolerability) as described in the current package insert. BEV will be administered approximately 10 minutes after the end of the MRZ administration when co-administered on the same day. Volume of MRZ administration will vary based on assigned dose (Table S-2) and subject body surface area (BSA). The volume of MRZ administration is calculated by: Volume = Dose (mg) * BSA (m^2) / 0.2 (conc. of MRZ in solution in mg/mL). The lyophilized drug product contains 2 mg API and 60 mg sucrose bulk excipient. Cartons contain one vial of lyophile together with a Diluent vial containing 55% propylene glycol, 5% ethanol, and 40% citrate buffer pH 5 (20 mL fill; 10 mL intended for use). **Part 5 Phase 1** MRZ will be administered IV over 10 minutes at a dose of 0.8 mg/m^2. In Amendment 5, pre and post MRZ dose hydration is not required, except where assessed as clinically necessary by Investigator. BEV will be administered as an IV infusion over 90 minutes on Cycle 1 Day 15 immediately following the completion of the 60-minute MRZ PK blood sample collection. Beginning with Cycle 2, BEV will be administered as an IV infusion (60 minutes on Cycle 2 Day 1 if tolerated at 90 min on Cycle 1 Day 15, and 30 minutes on Cycle 2 Day 15 and afterwards assuming tolerability at 60 min on Cycle 2 Day 1) as described in the current package insert. BEV will be administered approximately 10 minutes after the end of the MRZ infusion when co-administered on the same day in Cycle 2 and all subsequent cycles.
Procedures	For Part 1 Phase 1, Part 2 Phase 2, and Part 3 Phase 2, study visits and procedures will be performed as outlined in Table 1. For Part 4 Phase 1, study visits and procedures will be as outlined in Table 2. For Part 5 Phase 1, study visits and procedures will be as outlined in Table 3. The study will consist of Screening, Baseline, Treatment, and Follow-up periods. **Screening** The screening period may not exceed a 28-day window (with an extra 3-day window for unavoidable delays) prior to start of study treatment (Cycle 1 Day 1). Assessments will include medical history, cancer history including previous treatments, and tumor assessments. Tumor assessment must have a baseline MRI scan with contrast within 14 (+3) days prior to first treatment with investigational product. **Baseline** Physical examination including Karnofsky Performance Status (KPS), neurological evaluation, vital signs measurement, electrocardiogram (ECG), and laboratory tests are to be conducted within 7 (+2) days prior to Cycle 1 Day 1. [redacted]

	Treatment Subjects may continue on study treatment until disease progression, unacceptable toxicity, withdrawal of consent, or termination of the study. Assessment will include MRI scans at the end of every even numbered cycle (± 7 days) using RANO 2010 criteria for assessment. Responses (complete response [CR] and partial response [PR]) should be confirmed by repeat scans performed 4 weeks (± 2 days) later. Subjects in Parts 2, 3, 4, and 5 may continue treatment with MRZ for 1 or 2 cycles after an MRI indicates progression of disease, if according to the Investigator's judgement, the MRI is interpreted as showing possible pseudo-progression, and there is no significant clinical deterioration of the subject. Functional status using the KPS [redacted] will be assessed regularly [redacted]. Subjects who discontinue study drug for reasons other than disease progression whenever possible will continue tumor assessment as per protocol schedule until progression. **End-of-Treatment Visit** Subjects will be followed for safety for 28 (+ 7) days after discontinuation of study therapy (Part 1 Phase 1, Part 3 Phase 2, Part 4 Phase 1, and Part 5 Phase 1: both MRZ and BEV; Part 2 Phase 2: MRZ). **Post Study Follow-up** All subjects will be followed in the long-term survival follow-up period for as long as they are alive. Long-term follow-up will occur every 3 months (± 7 days) after the End-of-Treatment visit. Telephone contact will be sufficient to document survival status. During the follow-up period, the following information will be collected: survival, and first subsequent anti-malignant glioma regimens (regimen, start and end date, and treatment outcome).
Overview of Assessments	**Activity (Efficacy) Assessments** Tumor response, including progressive disease, will be assessed with MRI every 2 cycles (at the end of each even-numbered cycle of therapy) according to the RANO 2010 criteria, including: • Radiographic Response Rate • Progression-free Survival (PFS) • Overall Survival (OS) **Pharmacokinetic (PK) Assessments: MRZ (Part 1 Phase 1, Part 4 Phase 1, and Part 5 Phase 1)** In Part 1 Phase 1, blood samples will be taken for peak and trough measurements, pre-dose and immediately prior to (end of infusion) EOI, on Cycle 1 Day 1. In Part 1 Phase 1, on Cycle 1 Day 15 full PK sampling will be done: pre-dose, immediately prior to EOI and then 2, 5, 15, 30, 45, 60, 90 and 120 minutes post infusion.

	In Part 4 Phase 1, full PK sampling will be done on Cycle 1 Day 1 and on Cycle 1 Day 8: pre-dose, immediately prior to EOI and then 2, 5, 15, 20, 30, 45, 60, 90 and 120 minutes post administration. In Part 5 Phase 1, full PK sampling will be done on Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 1 Day 15, with blood samples collected pre-dose, immediately prior to the end of infusion (EOI), and then 2, 5, 15, 20, 30, 45, and 60 minutes post-EOI. **Pharmacokinetic Assessments: BEV (Part 1 Phase 1 only)** Pre-dose and immediately prior to EOI serum samples will be taken on Cycle 1 Days 1 and 15 to assess BEV peak and trough levels in plasma. **Blood Pharmacodynamic (PD) Assessments (Part 1 Phase 1 and Part 4 Phase 1)** In Part 1 (Phase 1), proteasome activity levels in packed whole blood (PWB) lysates and peripheral blood mononuclear cell (PBMC) lysates, comparing pre- and post-MRZ administration levels, will be determined on Days 1, 8, and 15 of Cycle 1; Days 1 and 15 of each cycle thereafter; and at the End-of Treatment Visit. In Part 4 (Phase 1), proteasome activity levels in packed whole blood (PWB) lysates and peripheral blood mononuclear cell (PBMC) lysates, comparing pre- and post-MRZ administration levels, will be determined on Days 1 and 8 of Cycle 1 and Cycle 2. [redacted]
Statistical Analyses	**Overview** **<u>Part 1 Phase 1</u>** A 3 + 3 design will be utilized to determine the MTD/MAD for MRZ + BEV combination treatment in 28-day cycles. (Subjects who do not have a DLT will be replaced if they discontinue treatment with MRZ or BEV in Cycle 1 for any other reasons.) After MTD/MAD has been determined in the dose-escalation part of the study, at least 12 additional subjects will be treated at the MTD/MAD to confirm the safety and assess the preliminary activity for the combination of MRZ + BEV. For all analyses by dose cohorts, the MTD/MAD confirmation cohort subjects will be combined with the corresponding dose cohort in the MTD/MAD determination phase as one single dose cohort. **<u>Part 2 Phase 2</u>** A 2-stage sequential design will be utilized in Phase 2. Fifteen response-evaluable subjects will be in the first stage. If at least 1 response is observed, then the study will be expanded, and an additional 15 response-evaluable subjects will be treated. If at least 5 responses are observed in the 30 response-evaluable subjects, then MRZ will be considered active as a single agent.

	Part 3 Phase 2 Forty eligible subjects will be treated. Assuming there are 30 deaths observed (ie, 25% of the subjects are censored), the resulting 95 % confidence interval (CI) is 7.2 – 14.8 months, with a width equal to 7.6 months for an estimated median survival of 10 months. **Part 4 Phase 1** A modified 3 + 3 design will be utilized to determine the MTD for MRZ administered enterally via NG tube in the first 28-day treatment cycle. (Subjects who do not have a DLT in Cycle 1 will be replaced if they discontinue treatment with enterally administered MRZ in Cycle 1 before receiving at least 2 doses for any other reasons.) After MTD has been determined in the dose-escalation part of the study, approximately 6 additional response-evaluable subjects will be treated at the MTD to confirm the safety of MRZ administered enterally via NG tube. For all analyses by dose cohorts, the MTD confirmation cohort subjects will be combined with the corresponding dose cohort in the MTD determination (dose-escalation) phase as one single dose cohort. **Part 5 Phase 1** Tumor response, including progressive disease (PD), progression-free survival (PFS), and overall survival (OS) will be assessed. Tumor response will be assessed by the Investigators using RANO 2010 criteria. The overall confirmed response rate will be presented. Endpoints of response based on tumor assessments will be calculated for subjects who received at least 3 doses of MRZ and had at least 1 post-dose tumor evaluation. Disease Progression (PD), PFS, and OS will be tabulated for Part 5. **Safety (All Parts)** All subjects will be evaluated for safety analysis if they receive at least one dose of MRZ (or BEV in Parts 1, 3, 4 and 5). The safety data will be presented in individual listings and summary tables, including frequency tables for adverse events and frequency and shift tables for laboratory variables. The safety population will be all subjects who received at least one dose of either study drug in any part of the study. **Pharmacokinetics (PK) (Part 1 Phase 1, Part 4 Phase 1, and Part 5 Phase 1)** Non-compartmental analyses will be performed. The following PK parameters will be calculated using standard non-compartmental analysis: maximum observed blood drug concentration (C_{max}), time of maximum blood concentration (T_{max}), elimination half-life ($T_{1/2}$), area under the blood concentration-time curve ($AUC_{0\text{-}inf}$), clearance (CL), and volume of distribution. Blood concentrations and computed PK parameters for MRZ will be listed and summarized by cohort (mean, geometric mean, standard deviation, coefficient of variation, minimum, maximum and number of observations). Subject population for PK will be all subjects who received at least one dose of either study drug and had at least one post-MRZ administration sample analyzed. Compartmental PK modeling may be conducted, as appropriate.

	Pharmacodynamics (Part 1 Phase 1 and Part 4 Phase 1) Change in proteasome activity levels in PWB lysates and PBMC lysates, comparing pre- and post-MRZ administration.

Table 1: Schedule of Assessments and Procedures, Part 1 Phase 1 and Parts 2 and 3 Phase 2: All Cycles

	Screen [1]	Baseline [1]	Cycle 1			Cycle 2+			End of Treatment [22]	Post Study Follow-up [23]
Study Day	**-28 to -1**	**-7 to -1**	**1**	**8**	**15**	**1**	**8**	**15**		
Window	**Up to Day -31**	**Up to Day -9**		**±1**	**±1**	**±1**	**±1**	**±1**	**+7**	**±7**
Informed consent	X									
Medical history/Demographics	X									
Concomitant medications [1]	X	X	X	X	X	X	X	X	X	X
Physical examination, height [2]		X								
Targeted physical, weight, BSA [2]		X	X			X			X	
Karnofsky Performance Status (KPS) [3]		X	X			X			X	
[redacted]										
Toxicity evaluation [6]			X	X	X	X	X	X		
Vital signs (HR, temp, BP) [7]		X	X	X	X	X	X	X	X	
ECG [8]		X							X	
Complete Blood Count, Differential, Platelets [9]		X		X	X	X		X	X	
Serum Chemistry [10]		X		X	X	X		X	X	
PT/PTT [11]		X				X			X	
Urinalysis [12]		X				X			X	
Marizomib infusion [13]			X	X	X	X	X	X		
Bevacizumab infusion [14]			X		X	X		X		
Blood PK sampling (MRZ) [15]			X		X					
Blood PK sampling (BEV) [16]			X		X					
Pregnancy test [17]		X							X	
Blood Proteasome assay [18]			X	X	X	X		X	X	
Tumor measurement [19]	X (-14 to -1) (3-day window)					At the end of each even numbered cycle			X	
[redacted]										

1. Within 7 (+2) days of starting treatment except Informed Consent, demographics, medical history, concomitant medications, complete physical examination, radiographic/tumor assessments, and consent to acquire and test archival tumor tissue samples, which can be obtained within 28 days (+3) prior to the start of treatment.
2. Height measured at baseline only. Physical Examination is a complete physical as per institutional guidelines (genitourinary examination not required unless there are related signs or symptoms) at baseline, but thereafter as directed by signs and symptoms (targeted physical examination).
3. Functional assessment using the Karnofsky Performance Status (KPS) is to be completed at baseline, at the beginning of each cycle, and at the end of treatment. See Appendix A.

[redacted]

6. Toxicity evaluation is an assessment of reported and observed adverse events, in all parts of the study compared to pre-dose evaluation.
7. Vital Signs: (blood pressure, heart rate, and temperature) during the Part 1 Phase 1 and Part 3 Phase 2 portions of the study in Cycle 1, Days 1 and 15: immediately before the MRZ infusion and immediately before the BEV infusion and approximately 10 (±2) minutes, 30 (±5) minutes and 1 hour (±5 minutes) following the BEV infusion. Cycle 2+, Days 1 and 15: prior to the MRZ infusion and prior to the BEV infusion and 30 (±5) minutes following each BEV infusion. In all cycles, Day 8, immediately before the MRZ infusion and 30 (±5) minutes following each MRZ infusion. During the Part 2 Phase 2 portion of the study, in Cycle 1, Days 1, and 15: immediately before the MRZ infusion and approximately 10 (±2) minutes, 30 (±5) minutes and 1 hour (±5 minutes) following the MRZ infusion. Cycle 2+, Days 1, 8, and 15: prior to the MRZ infusion and 30 (±5) minutes following each MRZ infusion. In all cycles, Day 8, immediately before the MRZ infusion and 30 (±5) minutes following each MRZ infusion. For all portions of the study vital signs are also collected as part of the physical examination.
8. ECG: Eligibility ECGs must be performed within 7 (+2) days prior to Day 1. In Part 1 and Part 2 Phase 2 ECGs will be collected on Cycle 1 only (Days 1 and 15), within 60 minutes prior to the MRZ infusion and within 5 (±1) minutes following the MRZ infusion. An End-of-Treatment ECG is to be collected. Additional ECGs should be obtained if clinically indicated. In Part 3 Phase 2, only Screening and End-of-Treatment ECGs will be conducted unless others are clinically indicated. (Cycle 1 Day 1 Cycle 1 Day 15 ECGs will not be collected.)
9. Hemoglobin (Hgb), hematocrit (Hct), red blood cell (RBC) count, white blood cell (WBC) count with differential, and platelets. Hematology tests can be performed within 72 hours of scheduled dosing on Days 1 and 15 except prior to Cycle 1, which can be done within 7 (+2) days prior to dosing. Should a subject experience a Grade 4 hematologic toxicity, the appropriate test will be monitored in accordance with institutional guidelines (at minimum: weekly) until Grade ≤ 2. The following tests should meet minimum stipulations prior to entry into Cycle 2+: Hgb ≥ 8 g/dL; platelets ≥ 75 x 10^9 /L.
10. Sodium, potassium, chloride, bicarbonate, calcium, magnesium, glucose, BUN, serum creatinine, uric acid, ALT, AST, alkaline phosphatase, total protein, albumin, and total bilirubin. Chemistry will be performed within 72 hours of scheduled dosing, on Days 1 and 15 except prior to Cycle 1, which can be done within 7 (+2) days prior to dosing. Minimum re-treatment criterion prior to the beginning of each new cycle: creatinine ≤ 1.5 x ULN.
11. Coagulation tests will be performed within 72 hours of scheduled dosing on Day 1, except prior to Cycle 1, which can be done within 7 (+2) days prior to dosing. Prothrombin time (PT) or International Normalized Ratio (INR) and partial thromboplastin time (PTT) may be performed more often if clinically indicated.
12. Urinalysis: protein, blood, glucose, pH; microscopic (RBC, WBC, casts) if abnormal urinalysis. Urinalysis performed within 72 hours of scheduled dosing on Day 1, except prior to Cycle 1, which can be done within 7 (+2) days prior to dosing.
13. Subjects are to be encouraged to maintain good oral hydration during the study (eg, 2 liters per day, as considered appropriate by the Investigator**). Part 1** MRZ infusion: injected over 10 minutes (or longer depending upon cohort). The volume of infusate will vary per subject depending on dose and BSA. In Part 1 Phase 1 subjects will receive normal saline starting prior to and following the infusion administered at ~350 mL/hour, with the infusion to occur after ~350 mL have been given with a total volume of infusion to equal one liter. In **Part 2** Phase 2 subjects will receive 250 mL normal saline over 30 minutes prior to the MRZ infusion. At the discretion of the Investigator,

additional normal saline can be given after the MRZ infusion is complete**. Part 3** Phase 2: No pre or postdose hydration is required unless re-instituted after safety review by the Medical Monitor, representatives of the Sponsor, and the Investigators. In each subject the dose will be increased if tolerated to 1.0 mg/m^2 after Cycle 1 and to 1.2 mg/m^2 after Cycle 2. Dose escalation after dose reduction is not recommended but will be allowed only with the approval of the Sponsor's Medical Monitor.

14. BEV administered as an IV infusion. First dose should be infused over 90 minutes and if tolerated, the second infusion may be given over 60 minutes, and if tolerated, subsequent infusions may be given over 30 minutes. Infusions may be interrupted or lengthened to treat or prevent infusion-related reactions. BEV is administered approximately 10 minutes after the end of the MRZ infusion. BEV is not given during Part 2 Phase 2.
15. Blood PK Sampling (MRZ) (during Part 1 Phase 1 dose escalation only): On Cycle 1 Day 1, MRZ samples will be obtained before treatment and just prior to end of infusion. On Cycle 1 Day 15, MRZ samples will be obtained before treatment, just prior to end of infusion, and 2, 5, 15, 30, 45, 60, 90, and 120 minutes after the infusion. Every effort should be made to collect samples at the prescribed times, but deviations up to 10% of the time point are allowed. Additional samples may be collected if the subject experiences a potentially drug-related SAE. Use Sponsor-provided PK kits. Process, store and ship samples per instructions in Study Reference Manual.
16. Blood PK Sampling (BEV) (during Part 1 Phase 1 dose escalation only): For BEV Cycle 1 Day 1 and 15, BEV plasma samples will be obtained before treatment and just prior to end of infusion. Use Sponsor-provided PK kits. Every effort should be made to collect samples at the prescribed times, but deviations up to 10% of the time point are allowed. Use Sponsor-provided PK kits. Process, store and ship samples per instructions in Study Reference Manual.
17. Pregnancy test (serum or urine) to be performed at Baseline, End-of-Treatment visit, and more frequently if clinically indicated.
18. Blood proteasome assay (during Part 1 Phase 1 dose escalation only): Cycle 1 Day 1 (before treatment and 1 hour post MRZ infusion), Day 8 (before treatment and 1 hour post MRZ infusion), and Day 15 (before treatment and 1 hour post MRZ infusion). Starting Cycle 2 and thereafter, Day 1 (before treatment and 1 hour post MRZ infusion) and on Day 15 (before treatment and 1 hour post MRZ infusion). A sample will be drawn at the End of Treatment visit. On Cycle 2 Day 1 (pre MRZ infusion or on Cycle 1 Day 29 if the subject does not go on to Cycle 2 or Cycle 2 is delayed. A sample will be drawn at the time that a complete response or partial response or disease progression is determined.
19. Tumor assessment: Baseline tumor assessments are to be made within 14 days (+3-day window) prior to Cycle 1 Day 1. Response should be assessed (RANO 2010) during the rest period of Cycle 2 and during the rest period of every 2 cycles thereafter (± 7 days). If a subject is determined to have an overall disease response of CR or PR, then disease assessments should be repeated approximately 4 (± 2 days) weeks later to confirm the response. If tumor assessments have not been performed in the 4 weeks prior to the End-of Treatment Visit, then tumor assessments are to be done at the End-of Treatment Visit. If a subject has a standard of care tumor assessment done prior to giving Informed Consent, but within the 14 day (+3-day window), that is available to the Investigator, then that tumor assessment can serve as a baseline and another screening MRI is not required.

[redacted]

22. Subjects with drug-related AEs of Grade ≥2 observed at the End-of-Treatment assessment should be followed-up at least monthly until the AE has resolved to Grade 1, the event is believed to be chronic or subject receives other anticancer therapy.
23. Post Study Follow-up visits may be made in person or other means of communication. Purpose of the follow up, which should occur every 3 months (±7 days), is to determine survival and the start of first new anti-GBM systemic treatment and its outcome.

Table 2: Schedule of Assessments and Procedures, Part 4 Phase 1: All Cycles

	Screen 1	Baseline 1	Cycle 1			Cycle 2+			End of Treatment[19]	Post Study Follow-up[20]
Study Day	**-28 to -1**	**-7 to -1**	**1**	**8**	**15**	**1**	**8**	**15**		
Window	**Up to Day -31**	**Up to Day -9**		**±1**	**±1**	**±1**	**±1**	**±1**	**+7**	**±7**
Informed consent	X									
Medical history/Demographics	X									
Concomitant medications [1]	X	X	X	X	X	X	X	X	X	X
Physical examination, height [2]		X								
Targeted physical, weight, BSA [2]		X	X			X			X	
Karnofsky Performance Status (KPS) [3]		X	X			X			X	
Toxicity evaluation [4]			X	X	X	X	X	X		
Vital signs (HR, temp, BP) [5]		X	X	X	X	X	X	X	X	
ECG [6]		X							X	
Complete Blood Count, Differential, Platelets [7]		X		X	X	X		X	X	
Serum Chemistry [8]		X		X	X	X		X	X	
PT/PTT [9]		X				X			X	
Urinalysis [10]		X				X			X	
Marizomib administration [11]			X	X	X	X	X	X		
Bevacizumab infusion [12]					X	X		X		
Blood PK sampling (MRZ) [13]			X	X						
Pregnancy test [14]		X							X	
Blood Proteasome assay [15]			Pre & 1h Post MRZ	Pre & 1h Post MRZ		Pre & 1h Post MRZ Cycle 2	Pre & 1h Post MRZ Cycle 2			
Tumor measurement [16]	X (-14 to -1) (3-day window)					At the end of each even numbered cycle			X	
[redacted]										

1. Within 7 (+2) days of starting treatment except Informed Consent, demographics, medical history, concomitant medications, complete physical examination, radiographic/tumor assessments, and consent to acquire and test archival tumor tissue samples, which can be obtained within 28 days (+3) prior to the start of treatment.
2. Height measured at baseline only. Physical Examination is a complete physical as per institutional guidelines (genitourinary examination not required unless there are related signs or symptoms) at baseline, but thereafter as directed by signs and symptoms (targeted physical examination).
3. Functional assessment using the Karnofsky Performance Status (KPS) is to be completed at baseline, at the beginning of each cycle, and at the end of treatment. See Appendix A.
4. Toxicity evaluation is an assessment of reported and observed adverse events, in all parts of the study compared to pre-dose evaluation.
5. Vital Signs: (blood pressure, heart rate, and temperature) in Cycle 1, Day 1: immediately before the MRZ enteral administration and approximately 10 (±2) minutes, 30 (±5) minutes and 1 hour (±5 minutes) following the MRZ infusion. Cycle 1, Day 15: immediately before the MRZ enteral administration and immediately before the BEV infusion and approximately 10 (±2) minutes, 30 (±5) minutes and 1 hour (±5 minutes) following the BEV infusion. Cycle 2+, Days 1 and 15: prior to the MRZ infusion and prior to the BEV infusion and 30 (±5) minutes following each BEV infusion. In all cycles, Day 8, immediately before the MRZ administration and 30 (±5) minutes following each MRZ administration. For all portions of the study vital signs are also collected as part of the physical examination.
6. ECG: Eligibility ECGs must be performed within 7 (+2) days prior to Day 1. ECGs will be collected on Cycle 1 only (Days 1 and 15), within 60 minutes prior to the MRZ enteral administration and within 5 (±1) minutes following the MRZ enteral administration. An End-of-Treatment ECG is to be collected. Additional ECGs should be obtained if clinically indicated.
7. Hemoglobin (Hgb), hematocrit (Hct), red blood cell (RBC) count, white blood cell (WBC) count with differential, and platelets. Hematology tests can be performed within 72 hours of scheduled dosing on Days 1 and 15 except prior to Cycle 1, which can be done within 7 (+2) days prior to dosing. Should a subject experience a Grade 4 hematologic toxicity, the appropriate test will be monitored in accordance with institutional guidelines (at minimum: weekly) until Grade ≤ 2. The following tests should meet minimum stipulations prior to entry into Cycle 2+: Hgb ≥ 8 g/dL; platelets ≥ 75 x 10^9 /L.
8. Sodium, potassium, chloride, bicarbonate, calcium, magnesium, glucose, BUN, serum creatinine, uric acid, ALT, AST, alkaline phosphatase, total protein, albumin, and total bilirubin. Chemistry will be performed within 72 hours of scheduled dosing, on Days 1 and 15 except prior to Cycle 1, which can be done within 7 (+2) days prior to dosing. Minimum re-treatment criterion prior to the beginning of each new cycle: creatinine ≤ 1.5 x ULN.
9. Coagulation tests will be performed within 72 hours of scheduled dosing on Day 1, except prior to Cycle 1, which can be done within 7 (+2) days prior to dosing. Prothrombin time (PT) or International Normalized Ratio (INR) and partial thromboplastin time (PTT) may be performed more often if clinically indicated.
10. Urinalysis: protein, blood, glucose, pH; microscopic (RBC, WBC, casts) if abnormal urinalysis. Urinalysis performed within 72 hours of scheduled dosing on Day 1, except prior to Cycle 1, which can be done within 7 (+2) days prior to dosing.
11. Enteral administration of MRZ in Cycle 1 requires insertion of NG tube on Days 1, 8, and 15. Subjects should not eat or drink for 2 hours prior to and 2 hours after enteral administration of MRZ via NG tube. Subjects are to be encouraged to maintain good oral hydration during the study (eg, 2 liters per day, as considered appropriate by the Investigator**).** Part 4 Phase 1: No pre or postdose hydration is required unless re-instituted after safety review by the Medical Monitor, representatives of the Sponsor, and the Investigators (See Footnote 13 in Table 1).
12. BEV administered as an IV infusion. First dose should be infused over 90 minutes and if tolerated, the second infusion may be given over 60 minutes, and if tolerated, subsequent infusions may be given over 30 minutes. Infusions may be interrupted or lengthened to treat or prevent infusion-related reactions. BEV is administered approximately 10 minutes after the end of the MRZ infusion. BEV is not given during Part 2 Phase 2.
13. Blood PK Sampling (MRZ) (Part 4 Phase 1): On Cycle 1 Day 1 and on Cycle 1 Day 8, MRZ samples will be obtained before treatment, just prior to end of infusion, and 2, 5, 15, 20, 30, 45, 60, 90, and 120 minutes after the infusion. Every effort should be made to collect samples at the prescribed times, but deviations up to 10% of the time point are allowed. Additional samples may be collected if the subject experiences a potentially drug-related SAE. Use Sponsor-provided PK kits. Process, store and ship samples per instructions in Study Reference Manual.
14. Pregnancy test (serum or urine) to be performed at Baseline, End-of-Treatment visit, and more frequently if clinically indicated.

15. Blood proteasome assay (Part 4 Phase 1): Before treatment and 1 hour after the end of MRZ enteral administration on Cycle 1 Day 1, Cycle 1 Day 8, Cycle 2 Day 1, and Cycle 2 Day 8.
16. Tumor assessment: Baseline tumor assessments are to be made within 14 days (+3-day window) prior to Cycle 1 Day 1. Response should be assessed (RANO 2010) during the rest period of Cycle 2 and during the rest period of every 2 cycles thereafter (± 7 days). If a subject is determined to have an overall disease response of CR or PR, then disease assessments should be repeated approximately 4 (± 2 days) weeks later to confirm the response. If tumor assessments have not been performed in the 4 weeks prior to the End-of Treatment Visit, then tumor assessments are to be done at the End-of Treatment Visit. If a subject has a standard of care tumor assessment done prior to giving Informed Consent, but within the 14-day (+3-day window), that is available to the Investigator, then that tumor assessment can serve as a baseline and another screening MRI is not required.

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19. Subjects with drug-related AEs of Grade ≥2 observed at the End-of-Treatment assessment should be followed-up at least monthly until the AE has resolved to Grade 1, the event is believed to be chronic or subject receives other anticancer therapy.
20. Post Study Follow-up visits may be made in person or other means of communication. Purpose of the follow up, which should occur every 3 months (±7 days), is to determine survival and the start of first new anti-GBM systemic treatment and its outcome.

Table 3: Schedule of Assessments and Procedures, Part 5 Phase 1: All Cycles

	Screen 1	Baseline 1	Cycle 1			Cycle 2+			End of Treatment[15]	Post Study Follow-up[16]
Study Day	**-28 to -1**	**-7 to -1**	**1**	**8**	**15**	**1**	**8**	**15**		
Window	**Up to Day -31**	**Up to Day -9**		**±1**	**±1**	**±1**	**±1**	**±1**	**+7**	**±7**
Informed consent [1]	X									
Medical history/Demographics [1]	X									
Concomitant medications [1]	X	X	X	X	X	X	X	X	X	X
Physical examination, height [2]		X								
Targeted physical, weight, BSA [2]		X	X			X			X	
Karnofsky Performance Status (KPS) [3]		X	X			X			X	
Toxicity evaluation [4]			X	X	X	X	X	X		
Vital signs (HR, temp, BP) [5]		X	X	X	X	X	X	X	X	
ECG [6]		X	X	X	X				X	
Complete Blood Count, Differential, Platelets [7]		X				X			X	
Serum Chemistry [8]		X				X			X	
PT or INR and PTT [9]		X				X			X	
Urinalysis [10]		X								
Marizomib administration			X	X	X	X	X	X		
Bevacizumab infusion [11]					X	X		X		
Blood PK sampling (MRZ) [12]			X	X	X					
Pregnancy test [13]		X							X	
Tumor measurement [14]	X (-14 to -1) (3-day window)					At the end of each even numbered cycle			X	

1. Within 7 (+2) days of starting treatment except Informed Consent, demographics, medical history, concomitant medications, complete physical examination, and radiographic/tumor assessments.
2. Height measured at baseline only. Physical Examination is a complete physical as per institutional guidelines (genitourinary examination not required unless there are related signs or symptoms) at baseline, but thereafter as directed by signs and symptoms (targeted physical examination). Body Surface Area (BSA).
3. Functional assessment using the Karnofsky Performance Status (KPS) is to be completed at baseline, at the beginning of each cycle, and at the end of treatment. See Appendix A.

4. Toxicity evaluation is an assessment of reported and observed adverse events, in all parts of the study compared to pre-dose evaluation.
5. Vital Signs: (blood pressure, heart rate, and temperature) in Cycle 1, on Days 1 and 8, immediately before the MRZ enteral administration and approximately 1 hour (±5 minutes) following the MRZ infusion, and on Day 15 immediately before the MRZ infusion and immediately before the BEV infusion and approximately 1 hour (±5 minutes) following the BEV infusion. In Cycle 2+, on Days 1 and 15, immediately prior to the MRZ infusion and immediately before the BEV infusion and approximately 30 (±5) minutes following each BEV infusion. In all cycles, on Day 8, immediately before the MRZ administration and 30 (±5) minutes following each MRZ administration. For all portions of the study, vital signs are also collected as part of the physical examination.
6. ECG: Eligibility ECGs must be performed within 7 (+2) days prior to Day 1. ECGs will be collected on Days 1, 8, and 15 of Cycle 1 only, within 60 minutes prior to the MRZ IV infusion and within 5 (±1) minutes following the MRZ IV infusion. An End-of-Treatment ECG is to be collected. Additional ECGs should be obtained if clinically indicated. On Cycle 1 Day 1, continuous 12-Lead ECG recording will be collected using a Holter recorder through the 60-minute PK blood collection, and by bedside 12-Lead ECG monitor at all other visits (see footnote 12). Cycle 1 Day 1 Holter recorder will be sent to central ECG vendor and replicate ECGs will be extracted at 3 time points prior to infusion (-45, -30, and -15 minutes) and at the end of infusion, and 2, 5, 15, 20, 30, 45, and 60 minutes after the infusion. Subjects should be supinely or semi-recumbently resting for at least 10 minutes prior to the time points of the ECG extractions.
7. Hemoglobin (Hgb), hematocrit (Hct), red blood cell (RBC) count, white blood cell (WBC) count with differential, and platelets. Hematology tests can be performed within 72 hours of scheduled dosing on Day 1 except prior to Cycle 1, which can be done within 7 (+2) days prior to dosing. Should a subject experience a Grade 4 hematologic toxicity, the appropriate test will be monitored in accordance with institutional guidelines (at minimum: weekly) until Grade ≤ 2. The following tests should meet minimum stipulations prior to entry into Cycle 2+: Hgb ≥ 8 g/dL; platelets $\geq 75 \times 10^9$ /L.
8. Sodium, potassium, chloride, bicarbonate, calcium, magnesium, glucose, BUN, uric acid, creatinine, ALT, AST, alkaline phosphatase, total protein, albumin, and total bilirubin. Chemistry will be performed within 72 hours of scheduled dosing, on Day 1 except prior to Cycle 1, which can be done within 7 (+2) days prior to dosing. Minimum re-treatment criterion prior to the beginning of each new cycle: creatinine $\leq 1.5 \times$ ULN.
9. Coagulation tests will be performed within 72 hours of scheduled dosing on Day 1, except prior to Cycle 1, which can be done within 7 (+2) days prior to dosing. Prothrombin time (PT) or International Normalized Ratio (INR) and partial thromboplastin time (PTT) may be performed more often if clinically indicated.
10. Urinalysis: protein, blood, glucose, pH; microscopic (RBC, WBC, casts) if abnormal urinalysis. Urinalysis performed within 7 (+2) days prior to dosing on Cycle 1 Day 1. Additional urinalysis should be obtained if clinically indicated.
11. BEV administered as an IV infusion. Cycle 1 Day 15 dose should be infused over 90 minutes and if tolerated, the second infusion (Cycle 2 Day 1) may be given over 60 minutes, and if tolerated, subsequent infusions may be given over 30 minutes. Infusions may be interrupted or lengthened to treat or prevent infusion-related reactions. The first dose of BEV is administered on Cycle 1 Day 15 immediately following the 60-minute PK blood collection, and approximately 10 minutes after the end of the MRZ infusion at all subsequent visits.
12. On Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 1 Day 15, MRZ PK samples will be obtained before treatment, just prior to end of infusion, and 2, 5, 15, 20, 30, 45, and 60 minutes after the infusion. Every effort should be made to collect samples at the prescribed times, but excursions up to 10% of the time point are allowed. Additional samples may be collected if the subject experiences a potentially drug-related SAE. Use Sponsor-provided PK kits. Process, store, and ship samples per instructions in Study Reference Manual.
13. Pregnancy test (serum or urine) to be performed at Baseline, End-of-Treatment visit, and more frequently if clinically indicated.
14. Tumor assessment: Baseline tumor assessments are to be made within 14 days (+3-day window) prior to Cycle 1 Day 1. Response should be assessed (RANO 2010) during the rest period of Cycle 2 and during the rest period of every 2 cycles thereafter (± 7 days). If a subject is determined to have an overall disease response of CR or PR, then disease assessments should be repeated approximately 4 (± 2 days) weeks later to confirm the response. If tumor assessments have not been performed in the 4 weeks prior to the End-of-Treatment Visit, then tumor assessments are to be done at the End-of-Treatment Visit. If a subject has a standard of care tumor assessment done prior to giving Informed Consent, but within the 14-day (+3-day) window, that is available to the Investigator, then that tumor assessment can serve as a baseline and another screening MRI is not required.
15. Subjects with drug-related AEs of Grade ≥ 2 observed at the End-of-Treatment Visit assessment should be followed-up at least monthly until the AE has resolved to Grade 1, the event is believed to be chronic or subject receives other anticancer therapy.

16. Post Study Follow-up visits may be made in person or other means of communication. Purpose of the follow up, which should occur every 3 months (±7 days), is to determine survival and the start of first new anti-GBM systemic treatment and its outcome.

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1. INTRODUCTION

1.1. Glioblastoma: Current Clinical Outcome

There is an unmet clinical need for the therapy of progressive or recurrent malignant gliomas (MG) with a median survival of < 12 months despite available chemotherapy. Recurrence following current "standard of care" surgery, radiation therapy and adjuvant chemotherapy is nearly universal. The traditional therapies rely on DNA damage and disruption of mitotic machinery, with limited effect in prolonging subject survival (Stupp 2005). The reported data show a 6 month progression-free-survival of 15% and median progression-free survival of only 9 weeks among 225 subjects with recurrent glioblastoma (GBM) (Wong 1999). Upon progression, subjects typically develop progressive physical and mental debilitation culminating in death 40 to 50 weeks from diagnosis. Novel therapies are being developed in an attempt to target specific molecular mechanisms involved in abnormal signaling and resistance to apoptosis.

1.2. Anti-angiogenic Therapy

Malignant gliomas have long been known to be one of the most densely vascularized tumors (Brem 1972). Malignant gliomas express high levels of vascular endothelial growth factor (VEGF), a key regulator of angiogenesis. Levels of VEGF expression correlate with both tumor grade and microvessel density (Plate 1992; Schmidt 1999; Samoto 1995). These findings suggest that therapeutic strategies targeting VEGF may provide an effective approach to suppress MG growth. Several preclinical studies in MG have shown promising antitumor activity of targeting VEGF and its cognate receptors (Kunkel 2001; Rubenstein 2000). In addition, inhibition of VEGF receptor signaling was shown to reverse the resistance of GBM to radiation therapy in a preclinical study (Geng 2001).

Avastin® (bevacizumab, BEV) (Genentech Inc., South San Francisco, CA), an anti-VEGF, humanized, monoclonal antibody, has been examined extensively in preclinical models (Avastin® Prescribing Information 2014 and 2015). These studies found that single-agent therapy with BEV resulted in tumor growth inhibition of 20 different human tumor cell lines (13 tumor types) implanted into nude mice irrespective of the route of administration or tumor location (Gerber 2005). A murine equivalent of BEV, A4.6.1 was shown to decrease tumor vascularity, enhance tumor apoptosis and prolong survival of rats intracranially implanted with glioblastoma cells (Rubenstein 2000). Various studies have examined the feasibility of combining anti-VEGF therapy with cytotoxic or biological agents. Combining BEV with doxorubicin, topotecan, paclitaxel, docetaxel, or radiotherapy resulted in additive or synergistic tumor growth inhibition. Changes in vascular functions were frequently reported, including decreased vessel diameter, density, and permeability in response to treatment. A reduction in interstitial fluid pressure was also observed. In some studies, these improvements resulted in an increase in intratumoral uptake of chemotherapy, implying that the most effective use of anti-VEGF therapy is in combination with chemotherapy (Chauhan 2005).

1.3. Bevacizumab Clinical Experience

BEV has been studied in at least 5000 subjects in a number of Phase 1, 2, and 3 clinical trials. BEV is indicated in the United States for a variety of cancer indications including GBM, as a

single agent for adult subjects with progressive disease following prior therapy (Avastin® Prescribing Information 2014 and 2015).

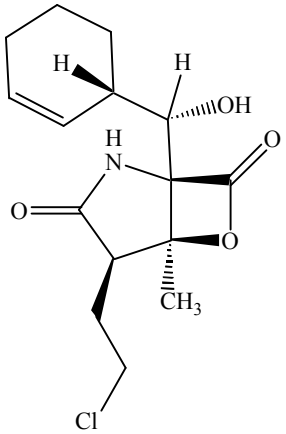
The efficacy and safety of BEV was evaluated in an open-label, multicenter, randomized, non-comparative study of subjects with previously treated GBM (Friedman 2009). Subjects received BEV (10 mg/kg IV) alone or BEV plus irinotecan every 2 weeks until disease progression or until unacceptable toxicity. All subjects received prior radiotherapy (completed at least 8 weeks prior to receiving BEV) and temozolomide. Subjects with active brain hemorrhage were excluded. Of the 85 subjects randomized to the BEV arm, the median age was 54 years, 32% were female, 81% were in first relapse, Karnofsky performance status (KPS) was 90−100 for 45% and 70−80 for 55%. The efficacy of BEV was demonstrated using response assessment based on both WHO radiographic criteria and by stable or decreasing corticosteroid use, which occurred in 25.9% (95% CI 17.0%, 36.1%) of the subjects. Median duration of response was 4.2 months (95% CI 3.0, 5.7). Radiologic assessment was based on MRI imaging (using T1 and T2/flair). MRI does not necessarily distinguish between tumor, edema, and radiation necrosis.

Another study was a single-arm, single institution trial with 56 subjects with GBM. All subjects had documented disease progression after receiving temozolomide and radiation therapy (Avastin® Prescribing Information 12/2016). Subjects received BEV 10 mg/kg IV every 2 weeks until disease progression or unacceptable toxicity. The median age was 54, 54% were male, 98% Caucasian, and 68% had a KPS of 90−100. The efficacy of BEV was supported by an objective response rate of 19.6% (95% CI 10.9%, 31.3%) using response assessment based on both WHO radiographic criteria and by stable or decreasing corticosteroid use. Median duration of response was 3.9 months (95% CI 2.4, 17.4).

1.4. Marizomib

Marizomib (MRZ, also known as NPI-0052, Salinosporamide A, or CC-92763) is a highly potent 20S proteasome inhibitor originally derived from a marine actinomycete (Figure 1). Pharmacology data support the clinical development of this investigational agent in the treatment of a variety of solid tumors (including MG) and hematologic malignancies (including multiple myeloma).

Figure 1: Chemical Structure of Marizomib (NPI-0052/CC-92763)



Pharmacology and toxicology studies were performed to support initial dosing in subjects with advanced malignancies. The pharmacology program consisted of single- and multiple-dose testing in the mouse, rat, and monkey; cytochrome P450 inhibition studies; and a variety of *in vitro* mechanism-of-action and *in vivo* tumor-efficacy studies. Toxicology studies included dose-range finding, Good Laboratory Practice (GLP) repeat-dose safety studies, and pivotal long-term toxicity studies in rats and primates with toxicokinetics and assessment of pharmacodynamics by proteasome inhibition. Cardiovascular safety parameters, such as blood pressure, heart rate, electrocardiogram (ECG), troponin I, and creatine kinase (CK) isoforms, have been measured as part of the GLP toxicology studies. No-observed-adverse-effect levels (NOAELs) and severely toxic doses have been identified in the rat and primate to establish a safe starting human dose in the initial Phase 1 trials of single agent MRZ.

1.4.1. Pharmacology

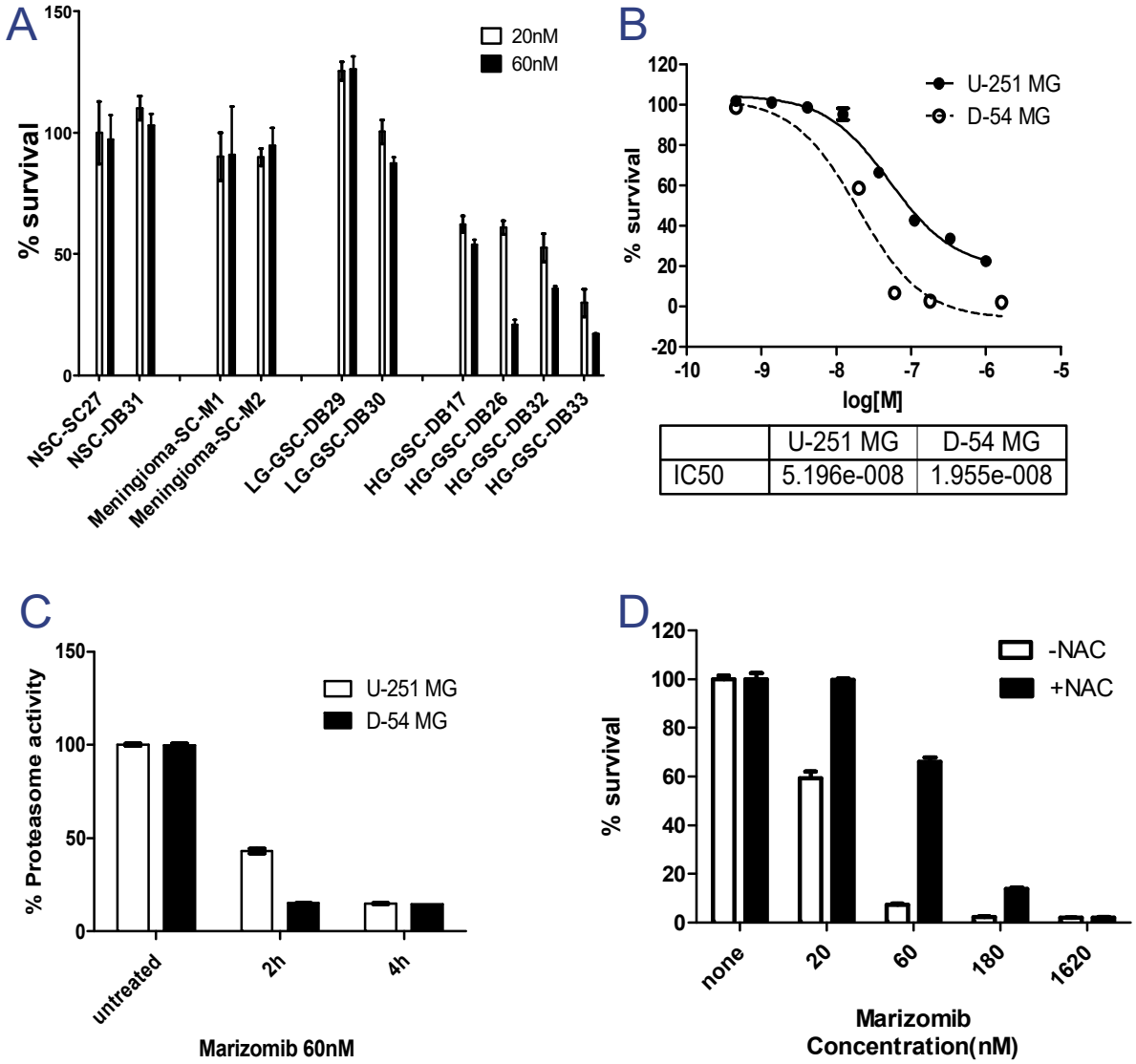
MRZ inhibits proteasome activities with a significantly different profile and at different concentrations compared to bortezomib (BTZ). Initial *in vitro* studies demonstrated that MRZ is a potent inhibitor of the CT-L (IC50 3.5 nM) and T-L (IC50 29 nM) activities of human erythrocyte-derived derived 20S proteasomes but is less potent at inhibiting the C-L activity (IC50 430 nM). Bortezomib exhibited a similar inhibition of CT-L activity compared to MRZ (IC50 8 nM) but different profiles on the T-L (IC50 590 nM) and C-L (IC50 53 nM) activities. MRZ is also a more potent inhibitor of NF-κB activation and cytokine synthesis compared to bortezomib (Chauhan 2005).

Proteasome inhibition holds potential for therapeutic activity in incurable brain tumors such as GBM. Due to high mutation rates, malignant cells generate excessive amounts of misfolded proteins in comparison to normal cells, a situation that is exacerbated, particularly in brain tumors, by reactive oxygen species (ROS). Upon reduction or elimination of proteasome activity, these waste products accumulate, leading to cellular stress and apoptosis. Thus, to prevent cell death, cancer cells rely on the residual proteasome activity, rendering them potentially more vulnerable to proteasome inhibition in comparison to normal cells. Thus, apoptosis may be selectively induced in cancer cells by inhibiting their proteasome activity. Bortezomib has been evaluated as a potential anti-GBM drug. Although showing good activity against GBM cells *in vitro* (Bota 2013), bortezomib does not cross the blood brain barrier (Yu 2006) and thus has proven ineffective in animal models and in the clinic (Labussiere 2008; Phuphanich 2006).

Bota and coworkers (Bota 2013) investigated the *in vitro* activity of MRZ in primary cell cultures derived from human brain tumors (high-grade and low-grade glioma and meningioma), normal neural stem/progenitor cells (NSC) and the established MG lines, U251-MG and D54-MG. Malignant glioma stem cells (GSCs) and the two cells lines were highly sensitive to MRZ (IC_{50} 20-50 nM) (Figure 2-AB), in contrast to the low-grade glioma, meningioma, and NSC-derived cells (no effect at 60 nM) (Figure 2-A). Treatment with MRZ at 60 nM for 4 hours inhibited proteasome activity by 89-90% in U251-MG and D54-MG cells (Figure 2-C). MRZ cytotoxicity was dependent upon increased free radical production and apoptosis in glioma cells since these effects were partially suppressed by the ROS quenching agent N-acetyl cysteine (Figure 2-D).

MRZ has relatively little effect on neural stem/progenitor cells (Figure 2-A), suggesting minimal neurotoxicity while severely affecting both MG stem cells and glioma cell lines (Di 2014).

Figure 2: ***In Vitro*** **Activity of Marizomib in Primary Cell Cultures Derived from Human Brain Tumors (High-grade and Low-grade Gliomas and Meningiomas), Normal Neural Stem/progenitor Cells (NSC) and the Established Malignant Glioma Lines, U251-MG and D54-MG**



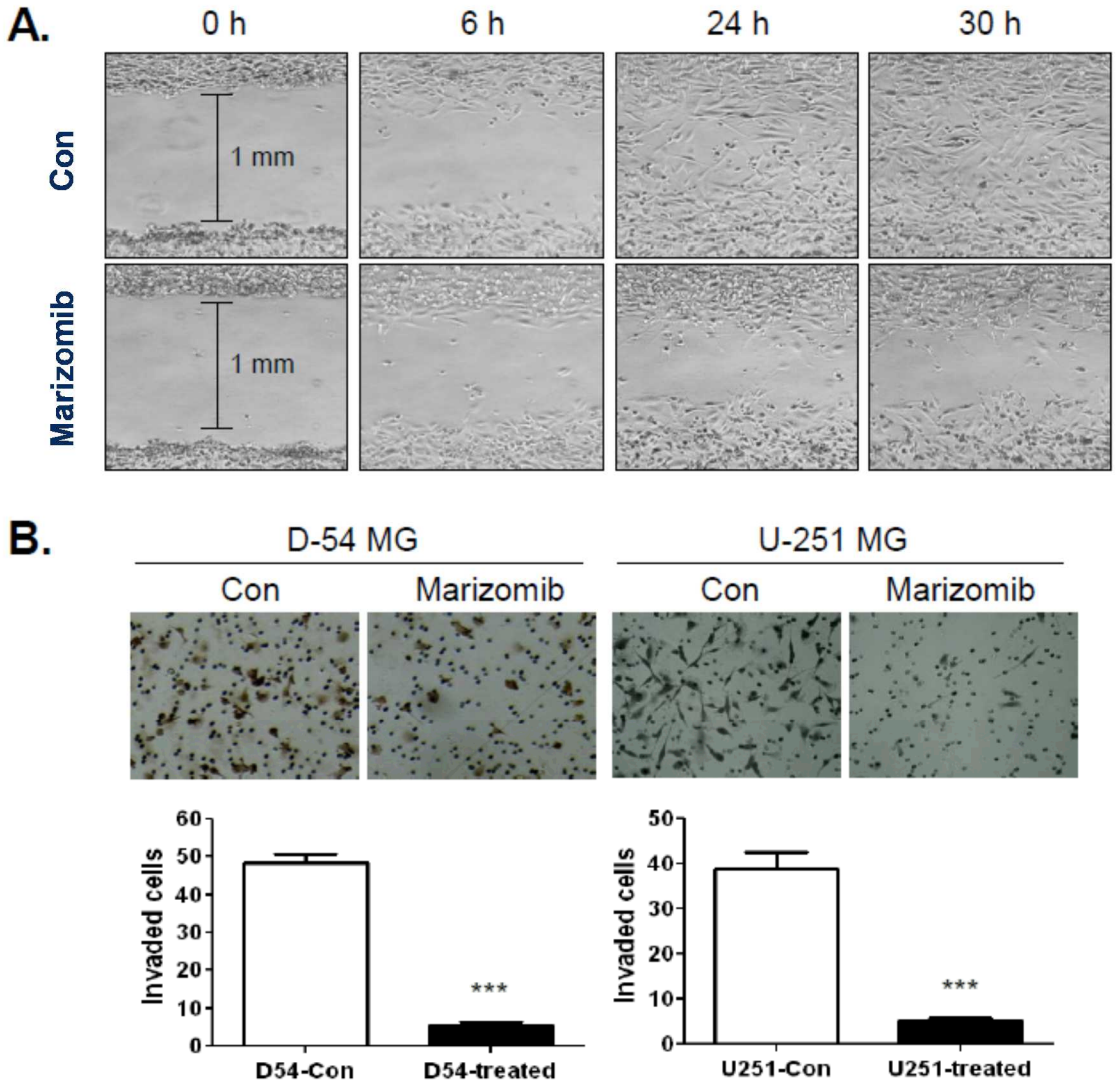
	U-251 MG	D-54 MG
IC50	5.196e-008	1.955e-008

High-grade and low-grade glioma and meningioma cells, normal neural stem/progenitor cells (NSC) and primary glioma stem cells (GSC) (**A**) or glioma cell lines (**B**) were treated with MRZ at the indicated concentrations for 72h and viability assessed by XTT assay. (**C**) CT-L proteasome activity was inhibited by up to 80% by brief treatment with 60 nM MRZ. (**D**) D54-MG glioma cell killing by MRZ was dependent in part on ROS generation, as it could be partially reversed by the ROS quenching agent N-acetyl cysteine (NAC).

Glioblastomas rarely metastasize, causing death through local growth in the CNS alone, so a particularly important factor in progression of GBM is the colonization of the surrounding brain tissue by invasive tumor cells. As shown in Figure 3, MRZ potently and robustly inhibited

migration and invasion of human GBM cell lines in two assays. In the 'wound healing' assay with U251-MG cells, 60 nM MRZ partially prevented wound closure for > 24 hours (Panel A) and in the more physiological Matrigel invasion assay, treatment with the proteasome inhibitor decreased matrix invasion by either of two GBM lines by approximately 90%, a highly significant effect (Panel B).

Figure 3: Marizomib Inhibits Migration and Invasion of Glioblastoma Cells



Wound closure assay was performed using U-251 MG cells with or without 60 nM MRZ treatment. The time required for 'wound closure' was monitored and photographed at indicated time points. (B) Invasion capability of the cells treated or untreated with 60 nM MRZ for 24 hours was analyzed using Matrigel Invasion chambers. The average of invaded cells for each counting grid is shown in lower panel. ***$p < 0.001$.

1.4.2. Pharmacokinetics

In animal models, MRZ distributes rapidly (within 2 to 5 minutes) from whole blood into tumors and other tissues; however, penetration into central and peripheral nervous system organs was

low at the dose studied (0.6 mg/m^2). The terminal half-life in whole blood is short, in the range of 7 to 15 minutes for both humans and monkeys, although some individuals may exhibit a half-life of up to 30 minutes.

The short half-life is consistent with the very rapid clearance from the vascular compartment, in the range of several liters/min in man. Clearance is independent of dose level and duration of administration. A rapid clearance is also observed in monkeys. The volume of distribution (Vd) is large, approaching or exceeding total body mass.

In an animal model using [^{3}H]-MRZ, MRZ is excreted via both the urinary and fecal routes. Blood levels of radioactivity decrease rapidly and attain a baseline plateau within 10 minutes; parent compound is detected in blood for at least 1 hour. Tissues with high levels of radioactivity include lung, small intestine wall, kidney, adrenal gland and liver. Tissues with lower levels of radioactivity include brain (approximately 10% of peak blood levels), spinal cord, testis and skin, whereas no radioactivity was detected in adipose tissue or bone. Radioactivity remains in the body for at least 10 days, consistent with the irreversible binding of MRZ to proteasomes and other tissue components.

Protein binding could not be determined due to the short half-life or MRZ. The disappearance of MRZ *in vitro* in human liver microsomes does not appear to be P450-mediated. Based on *in vitro* cytochrome P450 isoform inhibition studies, the potential for clinically important *in vivo* drug interactions with substrates for CYP1A2, 2C9, 2C19, 2D6, and 3A4 is considered to be low.

1.4.3. Toxicology

1.4.3.1. IV MRZ

The toxicity profile of MRZ following IV injection to rats and monkeys was similar between the 2 species as the same general array of treatment-related effects occurred in both species. These included lack of adverse in-life signs, changes in RBCs (decrease) and leukocytes (increase) and serum chemistry parameters (notably increases in indices of hepatic and renal functions), organ weight effects, and histopathological alterations. The data from the rat study suggested target organs of kidney, liver, spleen and adrenal gland whereas in the monkey study the target organs were kidney, nerve fibers in deep cerebellar white matter and spinocerebellar tracts pathways and pancreas. The effects occurred mainly in the high dose groups (0.60 increased to 0.75 mg/m^2/dose in the rat and 0.45 increased to 0.60 mg/m^2/dose in the monkey). In addition, inhibition of proteasome activity was noted, with CT-L activity being the most sensitive indicator of exposure to MRZ and exhibiting inhibition at all doses.

The observations from the pivotal toxicity studies suggest that 6 to 9 month prolonged exposure to MRZ is not associated with an increased incidence or severity of toxicity, or the induction of any new toxicity as compared to the findings from the previous 1-month studies. In fact fewer target organs were noted in the long-term studies.

Based on the findings observed in the pivotal GLP studies, the following dose levels were determined: a NOAEL in rats of 0.30 mg/m^2 and in monkeys of 0.225 mg/m^2; a highest non-severely toxic dose (HNSTD) or maximally tolerated dose (MTD) was determined to be 0.75 mg/m^2 in rats and 0.6 mg/m^2 in monkeys.

The genotoxic potential of MRZ has been investigated *in vitro* in the bacterial reverse mutation assay and in the micronucleus test in human lymphocytes. In the bacterial reverse mutation assay, no signs of toxicity and no evidence of mutagenic activity were observed following exposure to MRZ with or without added S9 mix. In the micronucleus test, concentrations of up to 70 nM in the absence of S9 mix and 150 nM in the presence of S9 mix did not induce significant induction of micronuclei; at higher concentrations MRZ showed evidence of causing an increase in the induction of micronuclei in cultured human lymphocytes. It should be noted that the concentrations inducing micronuclei in this study are considerably higher (by a factor of $\geq$ 20-fold) than the IC_{50} values observed for inhibition of human proteasome inhibition (3.5 nM). Thus, one possible interpretation of the data is that the induction of micronuclei may be related to cellular cytotoxicity as it is not observed at non-cytotoxic, yet pharmacologically active, concentrations of MRZ.

In summary, the toxicological effects profile for IV administered MRZ has been well established in rats and monkeys. No unique species or gender effects were observed. In addition, any potential safety concerns for the clinical studies (as identified in the toxicology studies) have been addressed in the current clinical protocols via an extensive monitoring schedule.

1.4.3.2. Oral MRZ

The toxicological effects profile of orally administered MRZ have also been established in the nonhuman primate. In a GLP study in cynomolgus monkeys (ITR 30948), the toxicity, toxokinetic (TK), and PD profiles of MRZ were determined following oral capsule administration to the cynomolgus monkey on Days 1, 8 and 15, as well as the reversibility of any changes following a 14-day recovery period. The test and Control/Excipient items were administered to groups of 7 monkeys per gender per dose (4 monkeys/gender/dose terminated one day after the last dose, 3 monkeys/gender/dose terminated after the 14-day recovery period). Dosages administered were 0, 0.0083, 0.025, and 0.0375 mg/kg/dose (corresponding to 0, 0.1, 0.3 and 0.45 mg/m^2, respectively).

Parameters evaluated in this study included daily mortality and clinical signs and observations along with weekly body weight measurements. Serial blood samples were obtained on Days 1 and 15 of treatment for quantification of marizomib and the bioanalytical data obtained were used for toxicokinetic parameter evaluation. Blood samples were also collected for pharmacodynamics on Days 1 and 15 for evaluation of chymotrypsin-like, caspase-like and trypsin-like proteolytic activities. Blood and urine samples were also obtained for clinical pathology evaluation (hematology, clinical chemistry and coagulation parameters) prior to start of treatment, on Day 2 and prior to necropsy for all main animals as well as at the end of recovery. Fecal occult blood collections and analysis were performed on Days 2, 3, 7, 9, 10, 14 and 16 as well as prior to termination on Day 30 for recovery animals. At termination, a gross external and internal evaluation was conducted, selected organs were weighed and histopathology evaluation was performed.

Treatment of cynomolgus monkeys with oral capsule administration of MRZ on Days 1, 8, and 15 was well tolerated at a dose level of 0.0083 mg/kg/dose. Treatment of cynomolgus monkeys with MRZ at dose levels of 0.025 and 0.0375 mg/kg/dose caused significant clinical signs of emesis and diarrhea a few hours after dosing and were related to the microscopic changes noted in the stomach and small intestines (see below), such as edema, hemorrhage, necrosis, erosion

and inflammation in the mucosa and submucosa. The inflammation in the stomach and small intestines correlated with an increase in circulating white blood cells populations, most notably neutrophils and monocytes and changes in the spleen (sinus neutrophilia and/or histiocytosis), mesenteric lymph node (sinus neutrophilia), and/or bone marrow (myeloid hypercellularity). All findings were completely reversed following a 14-day recovery period.

In this study, no gender differences in marizomib pharmacokinetics were observed following once a week oral capsule administration of marizomib in cynomolgus monkeys. Although there was a dose related increase in C_{max} and AUC_{last} on both treatment days, the C_{max} and AUC_{last} estimates obtained on Day 15 were lower than those obtained on Day 1 in the low (0.0083 mg/kg) and mid dose (0.025 mg/kg) group, but were comparable on both treatment days in the high dose group (0.0375 mg/kg). Since the exposure on both treatment days was similar in the high dose group (the likely therapeutic dose), the observed trend of change in accumulation index with dose is not likely to have any impact on the pharmacodynamics/efficacy in a clinical setting using higher therapeutically relevant doses.

Macroscopic and microscopic findings in the stomach and small intestines were considered to be related to the administration of MRZ at dose levels of ≥ 0.0083 mg/kg/occasion including inflammation, edema/hemorrhage, epithelial degeneration/necrosis, and/or erosion noted in the mucosa and/or submucosa of the cardia, fundus, and pylorus portions of the stomach and inflammation, edema/hemorrhage, and/or villous atrophy noted in the mucosa of the duodenum and jejunum. The incidence and severity of microscopic changes were proportional to dose of MRZ and reversed completely following a 14-day recovery period. The microscopic changes in the stomach and small intestines were considered adverse based on the incidence and severity of change at dose levels of 0.025 and 0.0375 mg/kg/occasion of MRZ.

The No Observed Adverse Effect Level (NOAEL) of MRZ administered orally was considered to be the 0.0083 mg/kg/dose, based on the adverse findings of the clinical signs, microscopic changes (stomach, small intestines and spleen) and hematology changes that resulted from the administration of marizomib at the two higher dose levels tested on this study. Changes that were noted in the low dose animals were considered to be of low magnitude and reversible. The Highest Non-Severely Toxic Dose (HNSTD) was considered to be the high dose, 0.0375 mg/kg/occasion (0.45 mg/m^2), based on the absence of mortality and reversibility of the adverse findings following the 14-day recovery period.

1.4.4. Clinical Experience

As of 05 Feb 2020, under IND 123765, a total of 465 subjects have received one or more doses of MRZ in Phase 1 and Phase 1/2 studies evaluating MRZ as a single agent or in combination with other anticancer drugs, including 185 subjects in clinical studies for newly diagnosed and recurrent glioblastoma.

In the first 4 Phase 1 dose ranging studies in subjects with Multiple Myeloma (MM), lymphoma and solid tumors where MRZ was infused at doses ranging from 0.0125 to 0.9 mg/m^2 over 1 to 120 minutes (n=242), the most common AEs related to study drug were fatigue, nausea, diarrhea, headache, vomiting, dizziness, infusion site pain, and anorexia with the most common serious adverse events (SAEs) related to study drug including coordination abnormal, confusional state, nausea, and pneumonia (Protocols NPI-0052-100, NPI-0052-101, NPI-0052-102, and

NPI-0052-103). In the NPI-0052-107 study in subjects with relapsed and refractory multiple myeloma, where MRZ was given in combination with pomalidomide (POM) and low-dose dexamethasone (Lo-DEX), the duration of the MRZ infusion was 2 hours on days 1, 4, 8 and 11 of a 28-day cycle to minimize the risk of central nervous system (CNS) toxicity (n=38). The most common AEs related to MRZ in this study were fatigue, neutropenia, thrombocytopenia, anemia, and nausea. CNS AEs were relatively uncommon and when they occurred did not present a substantial safety concern. In addition, the incidence of hematologic AEs related to any of the study drugs in this study was comparable to large-scale studies evaluating the combination of POM/ dexamethasone (DEX) in subjects with MM. Therefore, MRZ does not appear to increase the incidence or severity of hematologic AEs reported for the POM/DEX combination.

Preliminary Results from Ongoing Studies in G4 MG

To date, 187 subjects have been enrolled in 3 completed and 2 ongoing studies in subjects with glioblastoma under IND 123765. Additional information can be found in the Investigator's Brochure.

Study MRZ-108 Amendment 1 (NCT02330562, Recurrent Glioblastoma)

In Part 1 (Phase 1) of this MRZ-108 study, subjects received MRZ IV 0.55 to 0.8 mg/m^2 on days 1, 8, and 15 and BEV IV 10 mg/kg on days 1 and 15 of each 28-day cycle. The RP2D for dose-expansion was MRZ 0.8 mg/m^2. As of 04 January 2018, 36 of the target 36 subjects enrolled had discontinued for AEs (3), subject decision (5), and disease progression (28). Subjects received an average of 5 cycles of MRZ and BEV, the MRZ dose was reduced in 36% of subjects predominantly for AEs (10 of 14 reductions), and 17% of subjects had MRZ discontinued for an AE.

The most common AEs related to MRZ are fatigue (67%), nausea (64%), vomiting (50%), headache (47%), and hallucinations (36%). The most common AEs related to BEV are fatigue (64%), hypertension (42%), headache (31%), and dysphonia (31%). The only MRZ-related Grade $\geq$ 3 AEs that occurred in 2 or more subjects are headache (3), confusional state (3), fatigue (2), and hallucination (2). There was one dose-limiting toxicity (DLT) during Cycle 1 for a subject in Cohort 1 (MRZ 0.5 mg/m^2): Grade 3 fatigue, dysarthria, and weakness. There were 4 Grade 4 treatment-emergent adverse events (TEAEs): optic nerve disorder (BEV-related), hypertension (BEV-related), appendicitis perforated (not related) and depressed level of consciousness (not related). There were 3 Grade 5 TEAEs: intracranial hemorrhage (BEV-related) and disease progression x 2 (not related). Four subjects had MRZ-related SAEs: one subject with hallucinations and confusional state, one subject with confusion, fatigue, and muscle weakness, one subject with confusional state, and one subject with cough and dyspnea (subject hospitalized primarily for a [redacted] – not related). Twenty-five of 36 subjects died from progressive disease, while one subject died from an intracranial hemorrhage related to BEV in Cycle 1, and two subjects died from unknown causes, one 113 days after the last MRZ dose and the other 281 days after the last MRZ dose.

Overall, the combination of MRZ + BEV has demonstrated encouraging efficacy in this completed study. The best overall Response Assessment in Neuro-Oncology Criteria (RANO) response for the 36 subjects as determined by the investigators included: 1 complete response (CR), 15 partial responses (PRs), and 11 stable diseases (SDs) with an overall response rate

(ORR) of 44%. The median PFS and overall survival (OS) were 3.9 and 9.4 months, respectively, and the 6-month PFS and 9-month OS rates were 34% and 60%, respectively.

Study MRZ-108 Amendment 2 (NCT02330562, Recurrent Glioblastoma)

In Part 2 (Phase 2) of this MRZ-108 study, subjects received MRZ monotherapy at a dose of 0.8 mg/m^2; MRZ was administered as a 10-minute infusion on Days 1, 8, and 15 of every 28-day cycle. As of 04 January 2018, 30 of the 30 target subjects enrolled on study had discontinued for disease progression (27), subject decision (2), or other (1). Subjects received a median of 2 cycles of MRZ (range 1 to 11 cycles), the MRZ dose was reduced in 17% of subjects predominantly for AEs (5 of 30 subjects), and 7% of subjects had MRZ discontinued for an AE.

The most common AEs related to MRZ were fatigue (67%), headache (43%), hallucination (37%), nausea (30%), vomiting (27%). The only MRZ-related Grade ≥ 3 AEs that occurred in 2 or more subjects were fatigue (2) and hallucination (2). There was 1 Grade 4 AE of hallucination related to MRZ and no Grade 5 AEs. Three subjects had MRZ-related SAEs: one subject with hallucination Grade 4 and delusion Grade 3, one subject with hypertension Grade 3, mental disorder Grade 2 and lethargy Grade 3, and one subject with ataxia Grade 2. All three subjects recovered with supportive therapy. One subject died 70 days after his last dose of MRZ due to increased intracranial pressure leading to herniation related to disease progression. Four subjects died from unknown causes 360, 157, 97, and 252 days following the last MRZ dose.

This portion of the trial was a 2-stage sequential design with 15 response-evaluable subjects in each stage for a total of 30 subjects. In the first stage of the study, one subject had a partial response, so the second stage was opened. As of 04 January 2018, all subjects completed the study. Out of 30 subjects enrolled in Phase 2, Part 2 of Study MRZ-108, 1 subject (3%) had a PR; 7 subjects (23%) had stable disease, 21 subjects (70%) had progressive disease, and 1 subject (3%) was not response evaluable.

Study MRZ-108 Amendment 3 (NCT02330562, Recurrent Glioblastoma)

MRZ-108 Amendment 3 was designed to determine the maximally tolerated dose for MRZ by intra-subject dose escalation. Forty-one subjects with progressive or recurrent WHO Grade IV GBM, were enrolled in MRZ-108 Phase 2, Amendment 3 and received the combination of MRZ and BEV, with MRZ administered as a 10-minute IV infusion every week for three weeks in 28-day cycles (on Days 1, 8 and 15) at a starting dose of 0.8 mg/m^2. As of 04 January 2018, 33 subjects completed the study. After the first cycle without a dose-limiting adverse event (DLAE) the dose of MRZ was increased to 1.0 mg/m^2, and after one more cycle without a DLAE the dose of MRZ was to be increased to 1.2 mg/m^2. BEV was administered every 2 weeks on Days 1 and 15 of each 28-day cycle, at a fixed dose of 10 mg/kg.

DLAEs are MRZ-related AEs which are: 1) related to disturbances in the cerebellum (ie, ataxia, dizziness, dysarthria, fall, gait disturbances) plus hallucinations of any grade or 2) Grade ≥ 2 other AEs.

Out of the first 36 subjects, 10 were escalated in Cycle 2 to a dose of MRZ 1.0 mg/m^2; no subjects were escalated to a dose of MRZ 1.2 mg/m^2. The MRZ dose was reduced in 37% of subjects at 0.8 mg/m^2 and 80% of subjects at 1.0 mg/m^2, predominantly due to AEs. The most common TEAEs related to MRZ were fatigue (63%), confusional state (44%), vomiting (41%), nausea (41%) and hallucination (41%). The frequency of these AEs was generally higher for

subjects who were escalated to the 1.0 mg/m^2 dose level as compared to those who were not escalated to the higher dose. Ninety percent of subjects who were dose escalated to the 1.0 mg/m^2 dose of MRZ had at least 1 Grade ≥ 3 TEAE, compared to 63% of subjects who received the 0.8 mg/m^2 dose of MRZ. Most CNS-related AEs of special interest were Grades 1 and 2 in severity. None of the 33 subjects who had completed the study were discontinued due to an adverse event. In this ongoing study, the RP2D for MRZ was determined to be 0.8 mg/m^2 in recurrent GBM (in agreement with Part 1 of the study).

Study MRZ-108 Amendment 4 (NCT02330562, Recurrent Glioblastoma)

Part 4 of the study was added to assess the feasibility of enterally-administered MRZ. The MRZ IV formulation was reconstituted and administered enterally via NG tube for the first 28-day treatment cycle. In Cycle 2 and all subsequent cycles, MRZ was administered IV at the recommended dose and schedule determined in Part 1. Fourteen subjects have been enrolled in Part 4 of this ongoing study.

Study MRZ-112 (NCT02903069; Newly Diagnosed Glioblastoma (ndGBM)

The study is examining the effect of the addition of MRZ to standard of care treatment utilizing two study arms: Concomitant Treatment in which MRZ is combined with temozolomide (TMZ) + radiation therapy (RT) and Adjuvant Treatment in which MRZ is combined with TMZ. The study is being conducted as follows:

- Stage 1 (Dose-Escalation): 3 to 6 evaluable subjects per MRZ dose cohort were enrolled in each study arm (MRZ 0.55 to 1.2 mg/m^2). A total of 33 subjects were enrolled.
- Stage 2 (Dose-Expansion): Concomitant Treatment was followed by Adjuvant Treatment to confirm the MTD for each treatment regimen as determined in the Dose-Escalation (Stage 1), and to assess preliminary activity of the RP2D.
- Stage 2, Amendment 2: The protocol was amended (Amendment 2) to add another treatment arm to include MRZ 0.8 mg/m^2 + TMZ + Optune®.

As of 10 Jul 2019, 66 subjects have been enrolled in Study MRZ-112 (35 in the concomitant treatment arm, 18 in the adjuvant treatment arm, and 13 in the Optune arm). Twenty-five of the 35 subjects enrolled in the concomitant treatment arm also continued to receive adjuvant treatment. Overall, 47 (71.2%) subjects experienced at least 1 Grade ≥ 3 TEAE. Fatigue, vomiting, ataxia, and hypertension were the most frequently reported Grade ≥ 3 TEAEs. Grade 3 or higher TEAEs occurred most frequently in the SOCs of nervous system disorders, general disorders and administration site conditions, psychiatric disorders, and gastrointestinal disorders.

Six (6) DLTs occurred during dose-escalation, with 5 of the 6 DLTs occurring in the 1.0 mg/m^2 cohort:

- In adjuvant Cohort 2 (0.7 mg/m^2), one subject experienced Grade 3 fatigue for > 7 days;
- In concomitant Cohort 4 (1.0 mg/m^2), DLTs included Grade 3 ataxia/diarrhea (1 subject), Grade 3 ataxia/confusion (1 subject), and Grade 3 myocardial infarction (1 subject) for which the relationship to MRZ could not be excluded;

- In adjuvant Cohort 4 (1.0 mg/m^2), DLTs included Grade 3 delirium/ataxia (1 subject) and Grade 3 ataxia/fatigue (1 subject).

A total of 7 subjects (21%) had a TEAE that led to discontinuation of MRZ treatment of which five of these subjects received MRZ at 1.0 mg/m^2. Eleven of the 12 subjects (92%) dosed at 1.0 mg/m^2 experienced at least one Grade ≥ 3 TEAE. In contrast, 5 of the 21 subjects in the lower dose cohorts experienced at least one Grade ≥ 3 TEAE, including 2 subjects (33%) at 0.55 mg/m^2, 2 subjects (22%) at 0.7 mg/m^2, and 1 subject (17%) at the 0.8 mg/m^2 dose. Based on the totality of these data, the RP2D for MRZ was determined to be 0.8 mg/m^2 added to the standard of care radiation and TMZ in newly diagnosed GBM.

1.4.5. Pharmacodynamics

Pharmacodynamic (PD) data demonstrate that MRZ is a potent inhibitor of all 3 proteasome activities and that the inhibition pattern is dose-, cycle-, and schedule-dependent. The PD profile of MRZ-induced proteasome inhibition has been assessed in clinical studies at 10 dose levels (0.0125 to 0.9 mg/m^2). Importantly, preliminary clinical PD activity detected in early trials of MRZ closely mirrored the encouraging data from preclinical studies in rodents and primates. In the first-in-human trial Study NPI-0052-100, where sample sizes were small and PD activity was collected only during Cycle 1, CT-L activity was inhibited modestly (up to 20%) even in the first cohort (0.025 mg/m^2), more robustly at intermediate doses (eg, 50-80% at 0.25 mg/m^2) and was completely inhibited at high doses of 0.7 mg/m^2 and above. For T-L activity, inhibition was observed at lower doses (up to 20% at 0.25 mg/m^2) but a robust effect (over 50%) was noted at doses of 0.7 mg/m^2 and above, even by C1D15. The C-L activity was the least affected, with little to no inhibition seen within the first cycle at doses up to 0.55 mg/m^2, although several subjects receiving at least 0.7 mg/m^2 achieved a 30-40% inhibition of C-L activity.

In trials NPI-0052-101 and -102, partial or complete inhibition of all three proteasome subunits was achieved with both once- and twice-weekly MRZ dosing, with the rank order of sensitivity (CT-L > T-L > C-L; Levin, 2016) consistent with the biochemical potency of MRZ (Teicher, 2015). For CT-L activity, both initial (C1D1) and peak proteasome inhibition was dose-dependent, with complete (100%) inhibition of CT-L activity in PWB, and maximal (60-80%) inhibition of CT-L activity in PBMC, within the first dosing cycle. Increasing MRZ dose exposure resulted in increasing inhibition of CT-L activity in PWB, with estimated 50% inhibitory dose levels of 0.3 and 0.8 mg/m^2 in the once- and twice-weekly infusion arms, respectively (95% Confidence Intervals: AM, 0.02 – 4.3; MM, 0.14 – 4.5), indicating equivalent proteasomal inhibitory activity of MRZ in PWB between tumor types or infusion regimens. Importantly, proteasome inhibition in the nucleated cells (PBMCs) was comparable at all dose levels to that observed in PWB samples after both a single dose or repeated doses. These data suggest that the irreversible binding mode of MRZ can overcome the resynthesis of proteasome subunits in nucleated cells, as expected for an irreversible proteasome inhibitor.

In contrast to the rapid and robust inhibition of CT-L activity, C-L and T-L activities were unchanged or increased in the first cycle of MRZ dosing, suggesting compensatory hyperactivation in response to effective blockade of CT-L activity (Levin, 2016). Importantly, this response was overcome by further treatment with MRZ, with inhibition of T-L and C-L activity noted across dose levels with repeated dosing. These data suggest that initial potent inhibition of CT-L activity leads to a compensatory hyperactivation of the C-L and T-L subunits.

As CT-L activity becomes fully inhibited by the irreversible activity of MRZ, progressive inhibition of the hyperactivated C-L and T-L subunits occurs, ultimately resulting in robust pan-proteasome inhibition within 2 cycles in the majority of subjects.

Similar patterns of pan-proteasome inhibition by MRZ have been observed in more recent, multiple agent studies, as in the single agent studies detailed above. In Study NPI-0052-107, in which MRZ is administered twice weekly in combination with pomalidomide and DEX, mean CT-L inhibition of 80% is observed in Cycle 1 at the 0.4 mg/m^2 dose, and ~100% inhibition of CT-L is observed by the last infusion of Cycle 1 (Day 11) at the 0.5 mg/m^2 dose (RP2D). As in the single agent studies, minimal inhibition with some activation of T-L and C-L activity were observed during Cycle 1, however with repeated administration of MRZ, inhibition of these hyperactivated subunits becomes apparent in Cycles 2 and 3. Similarly, preliminary data demonstrate pan-proteasome inhibition of MRZ in subject samples of PWB and PBMC in subjects with Grade IV malignant glioma (MRZ-108). In this ongoing study, MRZ is infused once weekly, in combination with bevacizumab. Preliminary data from the RP2D MRZ dose cohort (0.8 mg/m^2) demonstrate pan-proteasome inhibition of MRZ in subject samples of PWB and PBMC, with mean CT-L inhibition of ~70% was observed after the first MRZ dose of Cycle 1, and persisted at the time of the second MRZ dose of Cycle 1. Subsequent MRZ doses resulted in 100% inhibition of CT-L post-infusion, and 60-80% inhibition prior to the next infusion. A slight increase in T-L and C-L activity in PWB samples was observed after the first MRZ infusion, after which inhibition of T-L (up to 70% post-infusion) and of C-L (up to 50% post-infusion) through Cycle 6. Persistent inhibition of T-L and C-L was observed at the time of the next MRZ dose, demonstrating the irreversible nature of pan-proteasome inhibition induced by MRZ in these non-nucleated cells. Pre- and post-infusion inhibition of T-L and C-L was less robust in the PBMC samples as compared with PWB specimens, with maximum levels of 40-60% inhibition observed for both T-L and C-L activity.

1.4.6. Pharmacokinetics

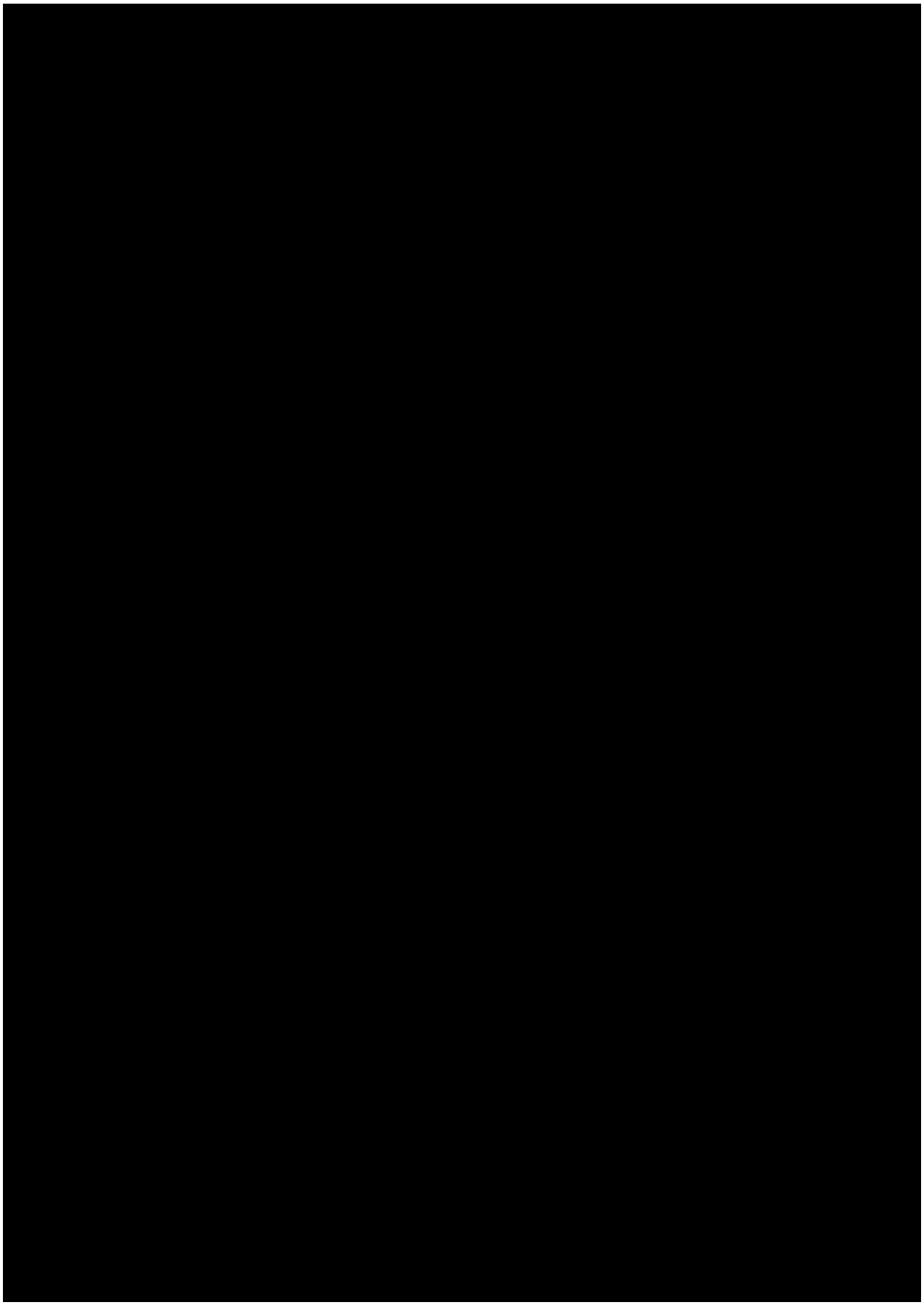
The whole blood human pharmacokinetics (PK) of MRZ administered as a single agent have been assessed in clinical Studies NPI-0052-100, NPI-0052-101, and NPI-0052-102. Blood levels have been measured following intravenous (IV) doses of MRZ from 0.025 to 0.9 mg/m2. Depending on the study, doses were administered either as a bolus over 1 minute or as a bolus and as an infusion with a nominal infusion time of 10 to 120 minutes. Preliminary PK analyses indicate the PK profile in humans is similar to the profile observed in animal studies, ie, the drug has a short half-life in whole blood with initial t1/2 estimates in the range of 3.6 ± 0.6 to 8.7 ± 6.8 min following a 1-10 min IV infusion. Similar t1/2 values were observed (range 6-15 minutes) following a 120-minute infusion.

More recently, the PK of MRZ in whole blood were assessed in Study NPI-0052-107, in which MRZ is administered twice weekly as an infusion for 120 min on Days 1, 4, 8, and 11 of a 28-day cycle, in combination with pomalidomide (administered orally, 3 or 4 mg/day, days 1-21) and DEX (administered orally, 5 or 10 mg, Days 1, 2, 4, 5, 8, 9, 11, 12, 15, 16, 22, and 23). Blood levels have been measured following IV MRZ doses of 0.3, 0.4, and 0.5 mg/m^2 (lyophile formulation) on Study Day 8. Noncompartmental pharmacokinetic analysis of these data revealed similar parameter estimates to those obtained from prior clinical studies. MRZ demonstrated a very short half-life (6-11 min), with a very rapid clearance and large volume of distribution of MRZ, implying extensive metabolism and the involvement of extra hepatic

clearance or non-CYP mediated biotransformation mechanisms, and a wide tissue distribution or binding of MRZ to blood components. MRZ did not appear to affect the PK of either co-administered pomalidomide or DEX.

PK of MRZ in whole blood were also assessed in Study MRZ-108, in which MRZ is administered once weekly as an infusion for 10 min on Days 1, 8, and 15 of a 28-day cycle, in combination with bevacizumab (BEV, administered IV at a dose of 10 mg/kg). Blood MRZ levels were measured following IV MRZ doses of 0.55, 07, and 0.8 mg/m^2 (lyophile formulation) on Study Days 1 (pre-dose and end-of-infusion only) and 15 (full PK sampling). Serum BEV concentrations were measured on Days 1 and 15, pre-dose and at the end-of-infusion. Noncompartmental analysis of the MRZ PK data revealed similar $T_{1/2}$, Vd, and CL parameter estimates to those obtained from in the NPI-0052-107 study, and again these parameter estimates appeared to be dose-independent. Earlier T_{max} values and higher C_{max} values were observed in MRZ-108 than in NPI-0052-107, which were anticipated based on the shorter MRZ infusion time. MRZ did not appear to affect the PK of co-administered BEV.

The PK of MRZ in whole blood was also assessed in Study MRZ-112 in which MRZ was administered as a 10 min IV infusion on Days 1, 8, 15, 29 and 36 of the 6-week concomitant treatment cycle, in combination with temozolomide (TMZ), administered orally at a dose of 75 mg/m2/day and radiotherapy delivered 5 days/week for 6 weeks. Blood MRZ levels were measured following IV MRZ doses of 0.55, 0.7, 0.8, and 1.0 mg/m^2 on study Days 1 and 8. Blood samples were taken at pre-dose, immediately prior to the end of infusion, and then at 5 and 60 minutes post-infusion on Day 1; and pre-dose and immediately prior to end of infusion, and then 2, 5, 15, 30, 45, and 60 minutes post-infusion on Day 8. PK parameters (Cmax, Tmax, t1/2, AUC0-t, AUC0-inf, CL, Vd) were estimated from the Day 8 data by non-compartmental analysis (NCA). Serum TMZ concentrations were measured on Days 1 and 15, pre-dose, 1-hour post-dose, and 24 hours post-dose (prior to the next TMZ dose). Plasma TMZ concentrations were measured to assess TMZ peak and trough levels. Analysis of the MRZ PK data revealed similar t1/2 (6.6 to 15.4 min), Vd (64 to 122 L), and CL (341 to 4164 L/hr) parameter estimates to those obtained in previous clinical studies with MRZ administered as a single agent, and again these parameter estimates appeared to be dose-independent. MRZ did not appear to affect the PK of co-administered TMZ.



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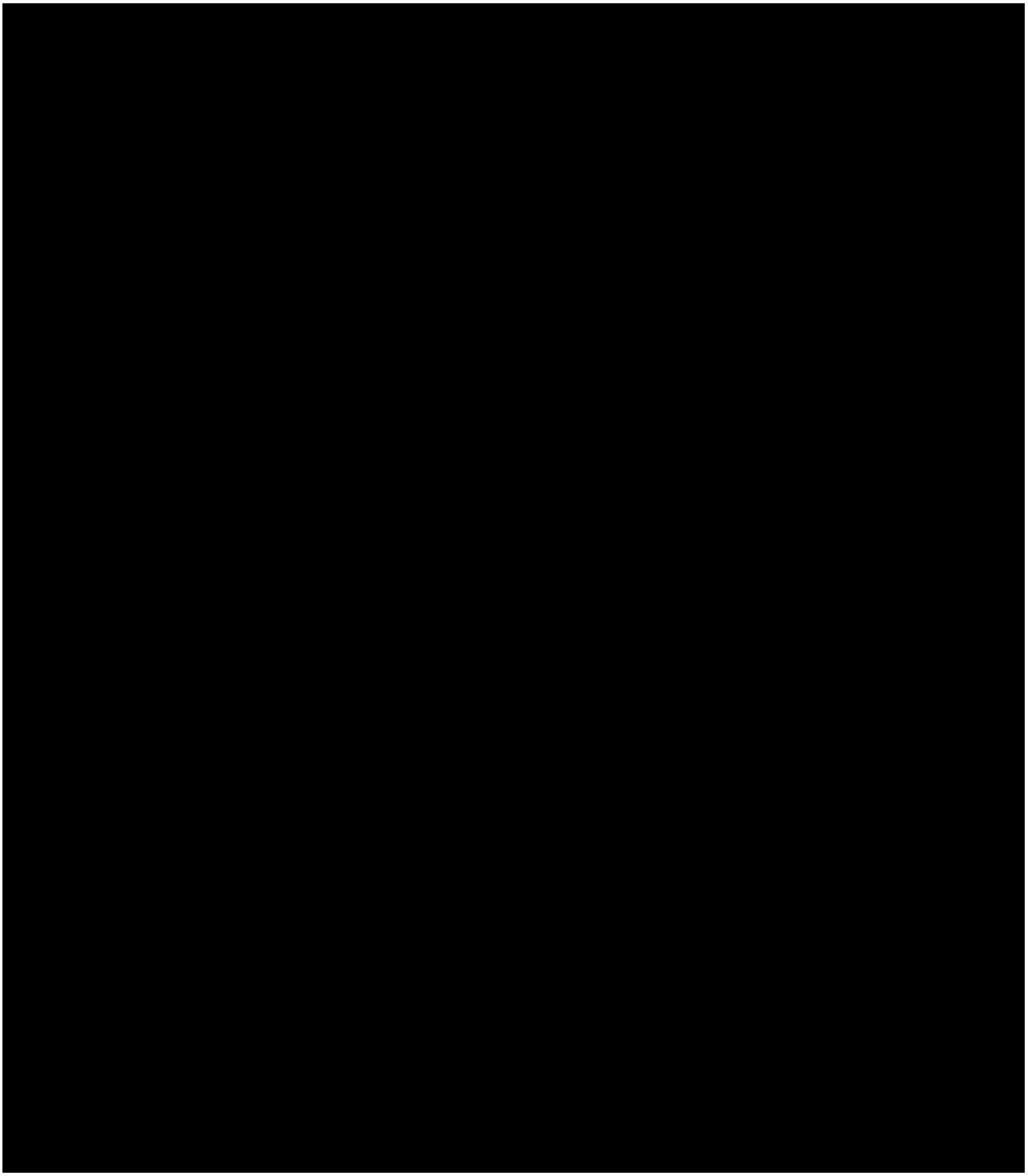

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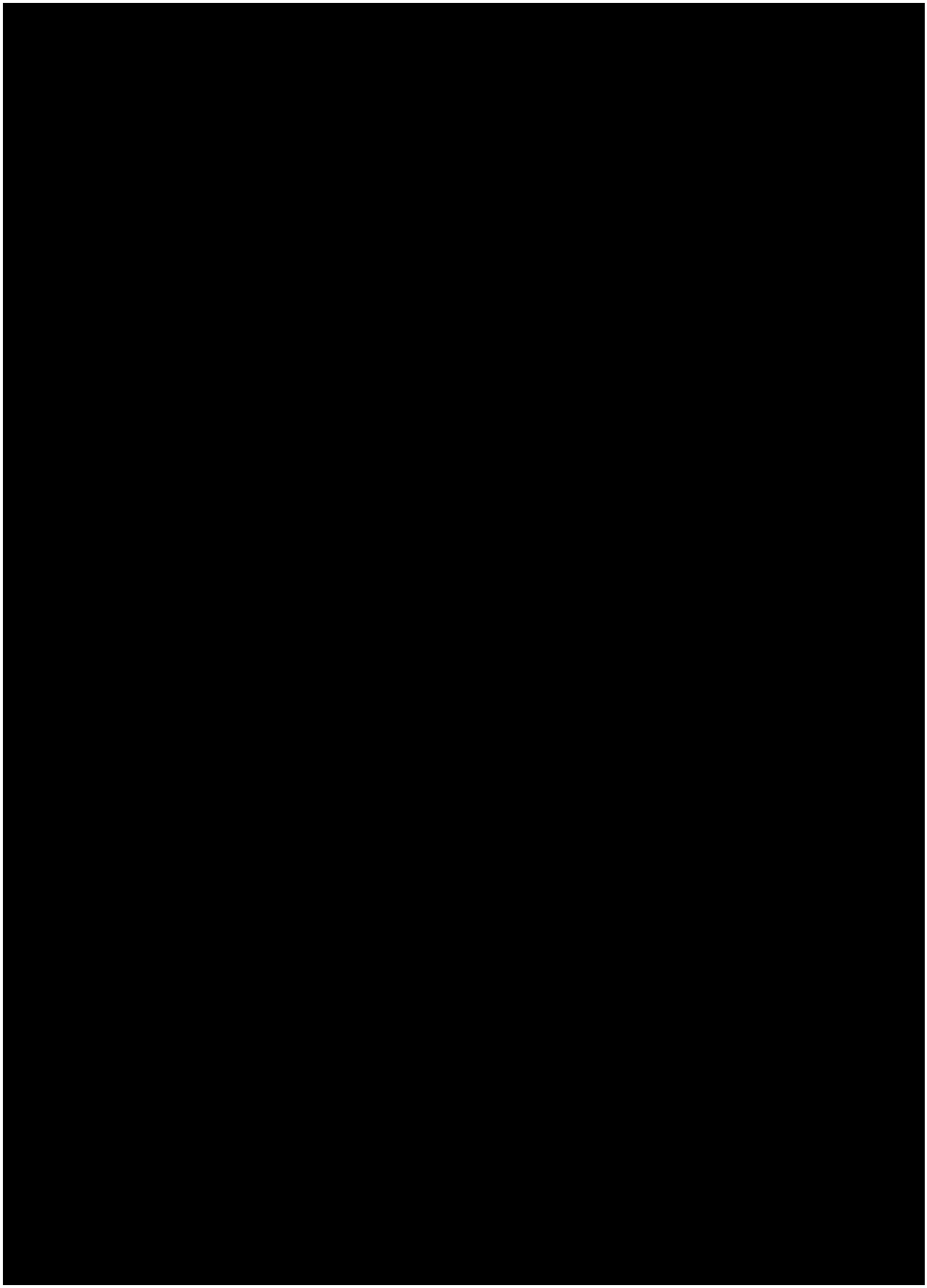

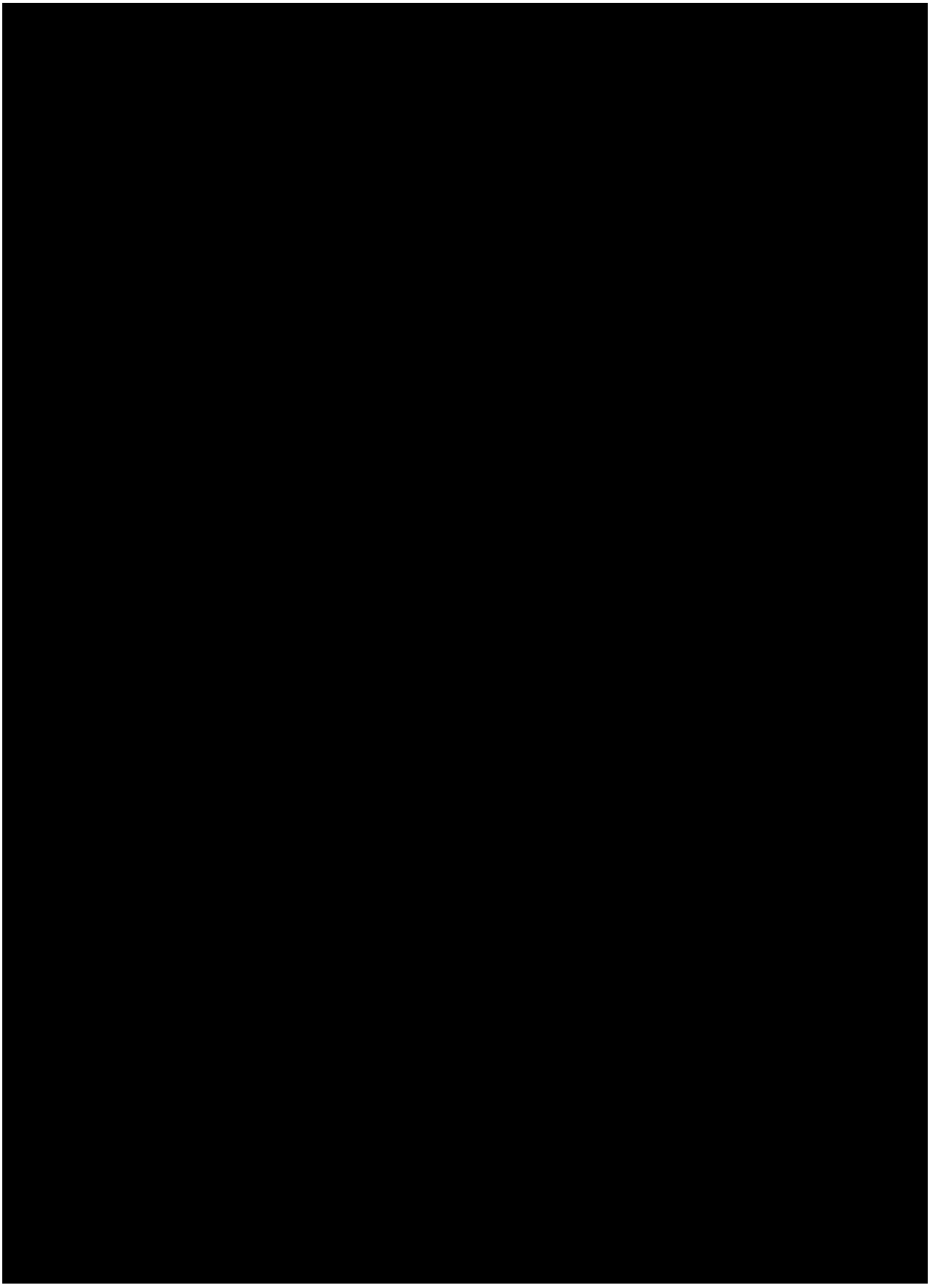

2. STUDY OBJECTIVES

2.1. Primary Objective

Part 1 Phase 1

The primary objective of the study is:

- To determine the maximum tolerated dose (MTD) or maximum administered dose (MAD) and recommended Phase 2 dose (RP2D) of the combination of marizomib (MRZ) + bevacizumab (BEV) with MRZ as a once weekly dose for 3 weeks of a 28-day cycle and a fixed dose and schedule of BEV (10 mg/kg administered on Days 1 and 15) in subjects with WHO Grade 4 malignant glioma (G4 MG), who have not previously been treated with either an anti-angiogenic agent including, but not limited to, BEV or a proteasome inhibitor including, but not limited to, MRZ.

Part 2 Phase 2

- To assess the activity of a once weekly dose for 3 weeks of a 28-day cycle of MRZ in subjects with progressive or recurrent G4 MG, who have not previously been treated with either an anti-angiogenic agent or a proteasome inhibitor.

Part 3 Phase 2

- To assess the activity of the combination of once weekly MRZ dosing for 3 weeks (allowing for intra-patient dose escalation) and every other week dosing of BEV at 10 mg/kg in a 28-day cycle in subjects with progressive or recurrent G4 MG, who have not previously been treated with either an anti-angiogenic agent or a proteasome inhibitor.

Part 4 Phase 1

- To determine the maximum tolerated dose (MTD) of marizomib (MRZ) administered enterally by NG tube once weekly for 3 weeks of a 28-day cycle during the first treatment cycle. BEV will be administered IV at a fixed dose (10 mg/kg administered on Day 15 and Days 1 and 15 of subsequent cycles). Subjects are those with progressive or recurrent G4 MG, who have not previously been treated with either an anti-angiogenic agent or a proteasome inhibitor.

Part 5 Phase 1

- To determine the repeat-dose pharmacokinetics of MRZ administered IV in subjects with progressive or recurrent G4 MG, who have not previously been treated with either an anti-angiogenic agent or a proteasome inhibitor.

2.2. Secondary Objectives

Part 1 Phase 1

The secondary objectives of the study are:

- To evaluate the safety of the combination of MRZ + BEV in the subject population.
- To evaluate activity of the combination of MRZ + BEV in the subject population:

  - Radiographic Response Rate
  - Progression-free Survival (PFS)
  - Overall Survival (OS)
- To evaluate the pharmacokinetics (PK) of MRZ and BEV when administered in combination in the subject population.
- To assess the whole blood proteasome pharmacodynamic (PD) activity of the combination of MRZ + BEV in the subject population.

Part 2 Phase 2

- To evaluate the safety of single agent MRZ in the subject population.

Part 3 Phase 2

- To evaluate the safety of combination of MRZ and BEV with intra-patient dose escalation and BEV at a fixed dose in the subject population.

Part 4 Phase 1

- To evaluate the safety (in particular GI tolerability) of MRZ administered enterally by NG tube in the subject population.
- To assess the frequency of CNS adverse events (including ataxia, dizziness, dysarthria, fall, gait disturbances, and hallucinations) after enterally administered MRZ in the subject population.
- To evaluate the pharmacokinetics (PK) of MRZ administered enterally by NG tube in the subject population on Cycle 1 Day 1 and Cycle 1 Day 8.
- To assess the blood proteasome inhibition pharmacodynamic (PD) activity of MRZ administered enterally by NG tube on Cycle 1 Day 1 and Cycle 1 Day 8, and to compare this with the PD activity of MRZ administered IV in combination with IV BEV on Cycle 2 Day 1 and Cycle 2 Day 8 in the subject population.

Part 5 Phase 1

- To monitor the safety of the combination of MRZ and BEV at a fixed dose in the subject population.
- To describe the activity of the of the combination of MRZ + BEV, with MRZ as a once weekly dose for 3 weeks of a 28-day cycle and every other week dosing of BEV with a fixed dose and schedule in the study population.
- To evaluate MRZ cardiac safety comparing PK to ECG.

3. STUDY ENDPOINTS

3.1. Primary Endpoint(s)

Part 1 Phase 1

- Maximum tolerated dose (MTD) or Maximum Administered Dose (MAD)
- Recommended Phase 2 Dose (RP2D)

Part 2 Phase 2

- Best response

Part 3 Phase 2

- Overall survival (OS)

Part 4 Phase 1

- Maximum tolerated dose (MTD)

Part 5 Phase 1

- Pharmacokinetics for MRZ
  - Maximum observed blood drug concentration (C_{max})
  - Time of maximum blood concentration (t_{max})
  - Elimination half-life ($t_{1/2}$)
  - Area under the blood concentration-time curve (AUC_{0-t}, AUC_{0-inf})
  - Clearance (CL)
  - Volume of distribution (Vd)

3.2. Secondary Endpoint(s)

Part 1 Phase 1 and Part 2 Phase 2

Safety

- Type, incidence and severity of adverse events (AEs)
- Type, incidence and severity of serious adverse events (SAEs)
- Type, incidence and severity of dose-limiting toxicities (DLTs)

Activity

- Radiographic overall response rate (ORR)
- Progression-free survival (PFS)
- Overall survival (OS)

Part 3 Phase 2 and Part 4 Phase 1

Safety

- Type, incidence and severity of adverse events (AEs)
- Type, incidence and severity of serious adverse events (SAEs)
- Type, incidence and severity of dose-limiting adverse events (DLAEs)(Part 3 Phase 2)
- Type, incidence and severity of dose-limiting toxicities (DLTs)(Part 4 Phase 1)

Activity

- Radiographic overall response rate (ORR)
- Progression-free survival (PFS)

Part 5 Phase 1

Safety

- Type, incidence and severity of adverse events (AEs)
- Type, incidence and severity of serious adverse events (SAEs)
- MRZ cardiac safety comparing PK to ECG

Activity

- Radiographic overall response rate (ORR)
- Progression-free survival (PFS)

4. OVERALL STUDY DESIGN

4.1. Study Design

Part 1 is a Phase 1, multicenter, open-label, 3+3, dose-escalation study in subjects with G4 MG who are in first or second relapse and who have not previously received any BEV or other anti-angiogenic agent, including: sorafenib, sunitinib, axitinib, pazopanib, everolimus, or cilengitide or MRZ or any other proteasome inhibitor, including bortezomib (BTZ), carfilzomib (CFZ), or ixazomib (IXZ). Three to 6 evaluable subjects per cohort will be enrolled: up to 24 subjects to determine the MTD/MAD (Part 1 dose-escalation) and an addition of 12 or more subjects to confirm the MTD/MAD (Part 2 MTD/MAD expansion) and assess preliminary activity, to a total of up to 36 subjects. Subjects may not be enrolled in more than 1 cohort.

The Part 1 Phase 1 portion will be followed by a Part 2 Phase 2 study of single agent MRZ administered as a 10-minute infusion at a dose of 0.8 mg/m^2 (the MAD) every week for 3 weeks in 28-day cycles. This portion of the study will be conducted as a 2-stage sequential design of up to 30 response-evaluable subjects.

Part 2 Phase 2 will be followed by Part 3 Phase 2 study of combination MRZ and BEV. MRZ will be administered as a 10-minute infusion every week for 3 weeks in 28-day cycles at a starting dose of 0.8 mg/m^2 (the RP2D from Phase 1). After 1 cycle without a DLAE, the dose of MRZ will be increased to 1.0 mg/m^2. If the increased dose is tolerated with no DLAEs, the dose will be further increased to 1.2 mg/m^2 in the next cycle. BEV will be administered every 2 weeks (Days 1 and 15 of each 28-day cycle) at a fixed dose of 10 mg/kg.

DLAEs are MRZ-related AEs which are: 1) related to disturbances in the cerebellum (ie, ataxia, dizziness, dysarthria, fall, gait disturbances) plus hallucinations of any grade or 2) Grade ≥ 2 other AEs.

This portion of the study will be conducted in approximately 40 eligible subjects of which, based on the AEs seen in Part 1 of the study, about 24 subjects are expected to be eligible for intra-patient dose escalation.

Part 4 Phase 1 will also study the combination of MRZ and BEV. MRZ IV formulation will be reconstituted and administered enterally via NG tube for the first 28-day treatment cycle, with three doses administered on Days 1, 8 and 15. BEV will be administered as an IV infusion on Day 15, approximately 10 minutes after the completion of the MRZ enteral dose administration. In Cycle 2 and all subsequent cycles, MRZ will be administered IV at the recommended dose and schedule determined in Phase 1 Part 1: MRZ 0.8 mg/m^2 IV weekly for three weeks (Days 1, 8 and 15) of a 28-day cycle and BEV 10 mg/kg IV on Days 1 and 15.

Subjects must receive at least 2 doses of MRZ via NG tube during Cycle 1 to be evaluable. One to six evaluable subjects per cohort will be enrolled in the first 3 dose-escalation cohorts, and three to six evaluable subjects per cohort will be enrolled in the next 6 dose cohorts, to determine the MTD (Part 4 dose-escalation). Approximately 6 additional subjects will be enrolled to confirm the MTD (Part 4 dose-expansion) and assess preliminary activity to a total of up to approximately 24 subjects. Subjects may not be enrolled in more than 1 cohort and there will be no intra-subject dose escalation. This portion of the study will be conducted in approximately 24 eligible subjects.

In Part 5 Phase 1 of the study, all subjects will receive MRZ infused over 10-minutes IV at the dose and schedule recommended from Phase 1 Part 1: MRZ 0.8 mg/m^2 IV weekly for 3 weeks (Days 1, 8, and 15) of a 28-day cycle. Full PK sampling will be done on Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 1 Day 15, with blood samples collected at pre-dose, immediately prior to end of infusion (EOI), and then 2, 5, 15, 20, 30, 45, and 60 minutes post-EOI, for determination of blood MRZ concentrations. BEV will be administered as an IV infusion over 90 minutes on Cycle 1 Day 15, immediately following the MRZ PK blood sample collection.

In Cycle 2 and all subsequent cycles, MRZ will be administered IV at the same dose and schedule (0.8 mg/m^2 IV weekly for 3 weeks (Days 1, 8, and 15) of a 28-day cycle), with IV MRZ infused over 10 minutes. BEV will be administered as an IV infusion (90 minutes 1st dose, 60 minutes 2nd dose, and 30 minutes afterward assuming tolerability) at a dose of 10 mg/kg on Days 1 and 15 of every 28-day cycle. BEV will be administered approximately 10 minutes after the end of the MRZ IV infusion. Approximately 12 eligible subjects will be enrolled in the study at a single center.

[redacted]

4.3. Study Duration

Subjects may continue on study treatment until disease progression, unacceptable toxicity, withdrawal of consent, or termination of the study. Once discontinued from the study treatment, subjects will enter a long-term follow-up period (Post Study Follow-Up) for documentation of survival and the start of first new anti-GBM therapy and its outcome. Post Study Follow-up will occur every 3 months (± 7 days) after the 28-day post-treatment discontinuation visit (End-of-Treatment visit).

4.4. End of Study

The End of Study is defined as the date of receipt of the last data point from the last remaining subject that is required for primary, secondary [redacted] analysis.

5. PROCEDURES

Study visits and procedures will be performed as outlined in Table 1 for subjects in Parts 1, 2, and 3, Table 2 for subjects in Part 4 Phase 1, and Table 3 for subjects in Part 5 Phase 1.

The study will consist of Screening, Baseline, Treatment, and Follow-up periods. Except where otherwise stated, the procedures apply to all Phase 1 and Phase 2 parts of the study. Neurological coordination assessment and quality of life assessment will not be done in Part 4 Phase 1.

5.1. Screening

Screening procedures may not be done prior to the signing and dating of the Informed Consent Form (ICF). However, the results of tumor assessments done as part of standard of care that are within the 14-day (+3 days) screening period do not have to be repeated if they were done at the participating site. However, if results are not available, then tumor assessments are to be conducted within 14 days prior to Cycle 1 Day 1. The screening period for assessments that include medical history (including demographics and cancer history), prior medications and procedures may not exceed a 28 day (+3 days for scheduling conflicts) window prior to start of study treatment (Cycle 1 Day 1).

5.2. Baseline

Physical examination including height, weight, and vital signs, Karnofsky Performance Status (KPS) scale (see Appendix A), ECGs, laboratory tests including hematology, coagulation, chemistry, urinalysis; and, as appropriate, pregnancy tests. [redacted]

5.3. Treatment

Safety tests and procedures will be performed according to the Schedule of Assessments and Procedures (Table 1 for Part 1 Phase 1, Part 2 Phase 2, and Part 3 Phase 2; Table 2 for Part 4 Phase 1; Table 3 for Part 5 Phase 1). PK samples correlated with ECG will be obtained prior to the start of treatment and then after dosing at selected time points for Part 1 Phase 1, Part 4 Phase 1, and Part 5 Phase 1. Part 5 Cycle 1 Day 1 ECGs will be collected by Holter monitor continuously through completion of the 60-minute PK blood collection. Tumor assessments will include MRI scans at the end of every even numbered cycle (± 7 days) using RANO 2010 criteria for assessment. Subjects may continue treatment with MRZ for 1 or 2 cycles after an MRI indicates progression of disease, if according to the Investigator's judgement, the MRI is interpreted as showing possible pseudo-progression, and there is no significant clinical deterioration of the subject or if it is in the best interest of the subject.

Functional status using the KPS will be conducted in both Phases. [redacted]

Subjects may continue on study treatment until disease progression, unacceptable toxicity, withdrawal of consent, or termination of the study.

5.4. End-of-Treatment Visit

An End-of-Treatment Visit should occur when a subject discontinues study treatment. Tests are primarily to ensure there are no late occurring AEs and that AEs have resolved or have stabilized. Additional follow-up visits may be conducted to follow ongoing AEs that are resolving. If a subject cannot or will not make this visit, attempts to gather information on the status of AEs should be made by telephone or other means.

5.5. Post Study Follow-up

All subjects will be followed for survival during the follow-up period for as long as they are alive. Post Study follow-up will occur every 3 months (± 7 days) after the End-of-Treatment Visit. During long-term follow-up, the following information will be collected: survival, first subsequent anti-GBM systemic regimens, and treatment outcomes.

5.6. Activity Assessments

Tumor response, including progressive disease, will be assessed with MRI at the end of every 2 cycles of therapy according to the RANO criteria (Wen 2010), including:

- Radiographic Overall Response Rate
- Progression-free Survival (PFS)
- Overall Survival (OS)

Confirmation of response at 4 weeks (± 2 days) after the response is to be performed.

If the Investigator believes that an MRI indicating tumor progression by RANO criteria may reflect pseudo-progression, and there is no significant clinical deterioration of the subject, the subject may be continued for 1 or 2 additional cycles (at the discretion of the Investigator based on the subject's clinical condition) before another MRI assessment is conducted. If a subject is taken off study for progressive disease by imaging and subsequent biopsy or surgical resection shows no evidence of disease, the subject will be counted as a responder. In this case, the subject may return to the study for additional treatment with MRZ, using a post-procedure MRI as the new baseline.

5.7. Pharmacokinetic (PK) Assessments: MRZ (Part 1 Phase 1, Part 4 Phase 1, and Part 5 Phase 1)

Blood should be drawn from the contralateral arm to the infusion site and using an indwelling catheter to avoid multiple needle sticks is recommended. Sample collection time should be recorded on the tube label and Case Report Form (CRF) as day: hour: minute. Nominal time of blood collection are given as "time points"; it is critical that an accurately collected ***actual time*** of the sample is written on the CRF and on the blood tubes (date entered as dd:mm:yyyy; time entered using a 24-hour clock, hh:mm).

- In Part 1 Phase 1, MRZ samples will be obtained before treatment and just prior to end of infusion on Cycle 1 Day 1. In Part 1 Phase 1, on Cycle 1 Day 15, MRZ blood samples will be obtained before treatment, just prior to end of infusion, and 2, 5, 15, 30, 45, 60, 90, and 120 minutes after the infusion.

- In Part 4 Phase 1, MRZ blood samples will be obtained before treatment and just prior to the end of infusion, and 2, 5, 15, 20, 30, 45, 60, 90 and 120 minutes after the infusion on Cycle 1 Day 1 and on Cycle 1 Day 8.
- In Part 5 Phase 1, MRZ blood samples will be obtained before treatment (pre-dose) and just prior to the end of infusion (EOI), and then 2, 5, 15, 20, 30, 45, and 60 minutes post-EOI, on Days 1, 8, and 15 of Cycle 1. Every effort should be made to collect samples at the prescribed times, but excursions up to 10% of the time point are allowed. Additional samples may be collected if the subject experiences a potentially drug-related SAE. After blood collection, neutralizing solution must be added. Use Sponsor-provided PK kits. Process, store and ship samples per instructions in Study Reference Manual.

PK parameters that will be determined include:

- Maximum observed blood drug concentration (C_{max})
- Time of maximum blood concentration (t_{max})
- Elimination half-life ($t_{1/2}$)
- Area under the blood concentration-time curve (AUC_{0-t}, AUC_{0-inf})
- Clearance (CL)
- Volume of distribution (Vd)

5.8. PK Assessments: BEV (Part 1 Phase 1 only)

For BEV pre-dose and immediately prior to EOI, plasma samples will be taken on Days 1 and 15 to assess BEV peak and trough levels. Process, store and ship samples per instructions in Study Reference Manual. PK assessment of BEV is not done in Phase 2.

5.9. Pharmacodynamic (PD) Assessments (Part 1 Phase 1 and Part 4 Phase 1)

Change in proteasome activities (whole blood lysates and PBMC lysates), comparing pre-drug and post drug levels

The laboratory correlates include assessment of the percentage inhibition of proteasome function (evaluated by measurement of CT-L, T-L and C-L activity in blood isolates such as whole blood and PBMC lysates.

In Part 4 (Phase 1), proteasome activity levels in packed whole blood (PWB) lysates and peripheral blood mononuclear cell (PBMC) lysates, comparing pre- and post-MRZ administration levels, will be determined on Days 1 and 8 of Cycle 1 and Cycle 2.

Process, store and ship samples per instructions in Study Reference Manual.

[redacted]

[redacted]

5.12. Karnofsky Performance Status

The Karnofsky Performance Status (KPS) allows subjects to be classified as to their functional impairment (Schag 1984). This can be used to measure changes in a subject's ability to function. The Karnofsky Performance Status scores range from 0 to 100. A higher score signifies the subject is better able to carry out daily activities. The KPS questionnaire is provided in Appendix A.

[redacted]

6. STUDY POPULATION

The study population includes subjects with G4 MG (including glioblastoma and gliosarcoma) who are in first or second relapse and who have not previously received any BEV or other anti-angiogenic agent, including sorafenib, sunitinib, axitinib, pazopanib, everolimus, or cilengitide or MRZ or any other proteasome inhibitor, including BTZ, CFZ, or IXZ. The eligibility criteria are the same for both Phase 1 and Phase 2 portions of the study except where noted.

6.1. Number of Subjects and Sites

Thirty-six subjects were enrolled in the study at multiple sites in Part 1 Phase 1 and 30 response-evaluable subjects will be enrolled in Part 2 Phase 2. Forty-one (41) response-evaluable subjects in Part 3 Phase 2 were enrolled in Amendment 3. Fourteen (14) response-evaluable subjects were enrolled in Amendment 4. Approximately twelve (12) response-evaluable subjects will be enrolled at a single site in Amendment 5.

6.2. Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study. These criteria apply to the Part 5 Phase 1 portion under Amendment 5 (see earlier versions of the protocol for criteria for Parts 1, 2, 3, and 4).

1. Understand and voluntarily sign and date an informed consent document prior to any study related assessments/procedures are conducted.
2. Males and Females ≥ 18 years of age at the time of signing the informed consent document.
3. All subjects must have histologic evidence of G4 MG (including glioblastoma and gliosarcoma) and radiographic evidence of recurrence or disease progression (defined as either a greater than 25% increase in the largest bi-dimensional product of enhancement, a new enhancing lesion, or significant increase in T2 FLAIR). Subjects must have at least 1 measurable lesion by RANO criteria (≥ 10 mm in 2 perpendicular diameters).
4. Subjects must have previously completed standard radiation therapy and been exposed to temozolomide. Subjects must be in first or second relapse.
5. No prior treatment with MRZ or any other proteasome inhibitors, including BTZ, CFZ, and IXZ or BEV or any other anti-angiogenic agents, including sorafenib, sunitinib, axitinib, pazopanib, everolimus or cilengitide.
6. No investigational agent within 4 weeks prior to first dose of study drug.
7. At least 4 weeks from surgical resection and at least 12 weeks from end of radiotherapy prior to enrollment in this study, unless relapse is confirmed by tumor biopsy, or new lesion outside of radiation field, or if there are two MRIs confirming progressive disease that are approximately 8 weeks apart.
8. Subjects with a history of seizures must be on a stable dose of anti-epileptic drugs (AEDs) and without seizures for 14 days prior to enrollment in subjects enrolled prior to Amendment 2. Subjects enrolled after Amendment 2 is approved with a history of

seizures must be on a stable dose of anti-epileptic drugs (AEDs) for 7 days prior to enrollment.

9. All AEs resulting from prior chemotherapy, surgery, or radiotherapy, must have resolved to US National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (NCI-CTCAE v. 4.03) Grade ≤1 (except for laboratory parameters outlined below).
10. Laboratory results within 7 days prior to MRZ administration (transfusions and/or growth factor support may not be used to meet this criteria):
    - Platelet count ≥ 100×10^9/L.
    - Hemoglobin ≥ 9 g/dL.
    - Absolute neutrophil count (ANC) ≥ 1.5×10^9/L.
    - Serum bilirubin ≤ 1.5 × upper limit of normal (ULN) or ≤ 3 x ULN if Gilbert's disease is documented.
    - Aspartate transaminase (AST) ≤ 2.5 ULN.
    - Alanine transaminase (ALT) ≤ 2.5 ULN.
    - Serum creatinine ≤ 1.5 × ULN.
    - Urine protein: creatinine ratio ≤ 1.0
11. Karnofsky Performance Status (KPS) score ≥ 70%.
12. For women of child-bearing potential and for men with partners of child-bearing potential, subject must agree to take contraceptive measures for duration of treatment and for 3 months after the last dose of MRZ or 6 months after the last dose of BEV, whichever is longer. A female subject of childbearing potential (FCBP) is a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).
13. Willing and able to adhere to the study visit schedule and other protocol requirements.

6.3. Exclusion Criteria

The presence of any of the following will exclude a subject from enrollment in Part 4 Phase 1 under Amendment 4 (see earlier versions of the protocol for criteria for Parts 1, 2, and 3).

1. Co-medication that may interfere with study results, eg, immuno-suppressive agents other than corticosteroids. Steroid therapy for control of cerebral edema is allowed at the discretion of the Investigator. Subjects should be on a stable dose of steroids for at least 1 week prior to first dose of MRZ. Co-medications must not be taken for 2 hours prior to and up to 2 hours after enteral administration of MRZ (Part 4 Phase 1).
2. Evidence of CNS hemorrhage on baseline MRI or CT scan (except for post-surgical, asymptomatic Grade 1 hemorrhage that has been stable for at least 3 months for subjects

enrolled prior to Amendment 2 and for at least 4 weeks in subjects enrolled after Amendment 2 is approved).

3. History of thrombotic or hemorrhagic stroke or myocardial infarction within 6 months.
4. Chemotherapy administered within 4 weeks (except 6 weeks for nitrosoureas, 12 weeks for nitrosourea wafer, and 1 week from metronomic chemotherapy, such as daily temozolomide and etoposide) prior to Day 1 of study treatment, unless the subject has recovered from all expected toxicities from the chemotherapy.
5. (Part 4 Phase 1) Recent nasal or esophageal surgery, history of GI-related medical conditions, or any other condition which, in the opinion of the investigator, would interfere or cause undue risk with insertion of NG tube or enteral administration of marizomib through the NG tube.
6. Pregnancy or breast feeding.
7. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection requiring IV antibiotics & psychiatric illness/social situations that would limit compliance with study requirements, or disorders associated with significant immunocompromised state.
8. Known previous/current malignancy requiring treatment within ≤ 3 years except for cervical carcinoma *in situ*, basal cell carcinoma, and superficial bladder carcinoma.
9. Any comorbid condition that confounds the ability to interpret data from the study as judged by the Investigator or Medical Monitor.

BEV-Specific Concerns (All Parts) (Note: These exclusion criteria apply to the Part 2 Phase 2 portion of the study even though BEV is not administered so that the subject populations among Part 1, Part 2, Part 3, Part 4, and Part 5 are similar):

10. Any prior history of hypertensive crisis or hypertensive encephalopathy.
11. Systolic blood pressure (BP) > 150 mmHg or diastolic BP > 100 mmHg.
12. Unstable angina.
13. New York Heart Association Grade ≥ II congestive heart failure.
14. History of myocardial infarction within 6 months.
15. Subjects with mean QTcF interval > 500 ms.
16. Clinically significant peripheral vascular disease.
17. Evidence of bleeding diathesis or coagulopathy as documented by an elevated (≥ 1.5 x ULN) prothrombin time (PT), partial thromboplastin time (PTT), or bleeding time. The use of full-dose oral or parenteral anticoagulants is permitted as long as the PT or aPTT is within therapeutic limits (according to the medical standard of the enrolling institution) and the subject has been on a stable dose of anticoagulants for at least 2 weeks prior to the first study treatment.
18. Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to Day 1 or anticipation of need for major surgical procedure during course of the study.

19. Minor surgical procedures, fine needle aspirations or core biopsies within 7 days prior to Day 1.
20. History of abdominal fistula, GI perforation, or intra-abdominal abscess within 6 months prior to Day 1.
21. Serious, non-healing wound, ulcer, or bone fracture requiring surgical intervention.

7. DESCRIPTION OF STUDY TREATMENTS

7.1. Description of Investigational Product(s)

MRZ is an investigational product that will be provided by the Sponsor. BEV is available commercially and will be provided by the Investigator via prescription to subjects who are enrolled into this study.

7.2. Treatment Administration and Schedule

7.2.1. Administration of MRZ in Part 1 Phase 1

MRZ will be administered IV over 10 minutes or longer depending upon cohort (refer to Directions for Use regarding directions for administration time). Volume of administration will vary based on assigned dose and subject body surface area (BSA). To mitigate the possibility of renal dysfunction, subjects will receive normal saline administered at 350 mL/hour for 1 hour before and for 2 hours after the MRZ infusion. The MRZ infusion will be started after approximately 350 mL of saline have been given over 1 hour. After the MRZ infusion has been completed, approximately 700 mL of saline will be given over 2 hours, for a total volume of saline infusion equal to approximately 1 L.

Subjects should maintain good oral hydration during the study (eg, 2 L/day). The volume and duration of hydration may be reduced at the discretion of the Investigator, especially for subjects with low body weight or with conditions sensitive to fluid overload.

Subjects must not drive a vehicle or operate heavy machinery while on this study.

The lyophilized drug product contains 2 mg API and 60 mg sucrose bulk excipient. Cartons contain one vial of lyophile together with a Diluent vial containing 55% propylene glycol, 5% ethanol, and 40% citrate buffer pH 5 (20 mL fill; 10 mL intended for use). The lyophile drug product reconstituted with 10 mL diluent results in a dosing solution comprised of 55% propylene glycol, 40% citrate buffer and 5% ethanol, with 6 mg/mL sucrose as a pharmaceutical excipient. The drug is delivered at 0.2 mg/mL at a final dosing solution of pH ~6. A dose of 0.7 mg/m^2 will result in approximately 7 mL of infusate.

7.2.2. Administration of BEV in Part 1 Phase 1, Part 3 Phase 2, Part 4 Phase 1, and Part 5 Phase 1

BEV will be administered as an IV infusion (90 minutes 1st dose, and if tolerated 60 minutes 2nd dose and 30 minutes on subsequent doses if tolerated) as described in the current package insert. During Part 5 Phase 1, the first dose of BEV will be administered on Cycle 1 Day 15 immediately following the 60-minute PK blood collection. During all other treatment cycles, BEV will be administered approximately 10 minutes after the end of the MRZ administration when co-administered on the same day.

7.2.3. Administration of MRZ in Part 2 Phase 2

MRZ (0.8 mg/m^2) will be administered IV over 10 minutes (refer to Directions for Use). To mitigate the possibility of renal dysfunction, subjects will receive normal saline administered at

250 mL over ~30 minutes before the MRZ infusion. The lyophilized drug product is the same as used in Phase 1.

Subjects should maintain good oral hydration during the study (eg, 2 L/day). The volume and duration of hydration may be reduced at the discretion of the Investigator, especially for subjects with low body weight or with conditions sensitive to fluid overload.

Subjects must not drive a vehicle or operate heavy machinery while on this study.

7.2.4. Administration of MRZ in Part 3 Phase 2

MRZ will be administered IV over 10 minutes (refer to Directions for Use). The lyophilized drug product is the same as used in previous parts.

Starting dose in each subject will be 0.8 mg/m^2. Intra-patient dose escalation will be used. After the first cycle without a DLAE, the dose will be increased by 0.2 mg/m^2 to 1.0 mg/m^2 (an increase of 25%). After one more cycle without a DLAE the dose of MRZ will be increased to 1.2 mg/m^2 (an increase of 20%) for that cycle and subsequent cycles.

Subjects should be encouraged to maintain good oral hydration during the study (eg, 2 L/day). Renal dysfunction has not been observed during the conduct of the study, including in Part 2 Phase 2 where volume and duration of pre and post dose hydration was reduced. It is therefore not considered a safety concern and will not be required in Part 3 Phase 2. Should renal function become a safety issue, pre-dose hydration will be reinstated if thought necessary by the Sponsor's medical monitor and study team and the Investigators.

Subjects must not drive a vehicle or operate heavy machinery while on this study.

7.2.5. Administration of MRZ in Part 4 Phase 1

Subjects should not eat or drink for 2 hours prior to and 2 hours after enteral administration of MRZ via NG tube.

In Cycle 1, MRZ IV formulation will be reconstituted and administered enterally via NG tube over up to 10 minutes (refer to Directions for Use). Volume of administration will vary based on assigned dose and subject body surface area (BSA). The volume of MRZ administration is calculated by: Volume = Dose (mg) * BSA (m^2) / 0.2 (conc. of MRZ in solution in mg/mL). The lyophilized drug product is the same as used in previous parts of the protocol.

In Cycle 2 and all subsequent cycles, MRZ (0.8 mg/m^2) will be administered IV over 10 minutes (refer to Directions for Use).

Subjects should be encouraged to maintain good oral hydration during the study (eg, 2 L/day). Renal dysfunction has not been observed during the conduct of the clinical studies in GBM, including in Part 2 Phase 2 where volume and duration of pre and post dose hydration was reduced, and in Part 3 Phase 2 where pre and post dose hydration was not required. It is therefore not considered a safety concern and will not be required in Part 4 Phase 1.

Subjects must not drive a vehicle or operate heavy machinery while on this study.

7.2.6. Administration of MRZ in Part 5 Phase 1

MRZ will be administered IV at the dose of 0.8 mg/m^2 over 10 minutes. Volume of administration will vary based on subject BSA. The volume of MRZ administration is calculated by: Volume = Dose (mg) * BSA (m^2) / 0.2 (conc. of MRZ in solution in mg/mL). The lyophilized drug product is the same as used in previous parts of the protocol.

Subjects must not drive a vehicle or operate heavy machinery while on this study.

7.2.6.1. Dose Schedules

Part 1 Phase 1

All subjects will receive MRZ + BEV as follows:

IV Marizomib (MRZ)

- MRZ will be administered as a 10-minute IV infusion on Days 1, 8, and 15 of every 28-day cycle. Infusion durations may be lengthened to ameliorate toxicity for individual subjects or for cohorts with agreement between the Investigators and the Sponsor. For dosing details, see Table 5.
- Minimum re-treatment criterion prior to the beginning of each new cycle: creatinine ≤ 1.5 x ULN, Hgb ≥ 8 g/dL, platelets ≥ 75 x 10^9/L.

IV BEV

BEV will be administered as an IV infusion (90 minutes 1st dose, 60 minutes 2nd dose and 30 minutes afterward) at a dose of 10 mg/kg on Days 1 and 15. BEV will be administered approximately 10 minutes after the end of the MRZ infusion when co-administered on the same day.

In the case of dosing delay, BEV should always be given on the day that MRZ is administered. If BEV is discontinued for AEs, the subject may continue on MRZ alone. If MRZ is discontinued, then the subject will be discontinued from the trial. If MRZ is delayed, BEV should also be delayed. Both drugs will be discontinued once disease progression is documented.

MRZ dosing will begin at 0.55 mg/m^2 once weekly (Cohort 1). Additional dose cohorts are planned as shown in Table 5.

Table 5: Dose Cohorts for MRZ + BEV Combination

Cohort	IV MRZ Day 1, 8, and 15 of Each 28-Day Cycle	IV BEV Day 1 and 15 of Each 28-Day Cycle
-2	0.3 mg/m^2	10 mg/kg
-1	0.4 mg/m^2	10 mg/kg
1	0.55 mg/m^2	10 mg/kg
2	0.7 mg/m^2	10 mg/kg

Table 5: Dose Cohorts for MRZ + BEV Combination (Continued)

Cohort	IV MRZ Day 1, 8, and 15 of Each 28-Day Cycle	IV BEV Day 1 and 15 of Each 28-Day Cycle
3	0.8 mg/m^2	10 mg/kg
4	Additional cohorts with extended infusion duration if required	10 mg/kg

Part 1 Phase 1 Expansion Cohort and Part 2 Phase 2

IV Marizomib (MRZ)

MRZ (0.8 mg/m^2) will be administered as a 10-minute IV infusion on Days 1, 8, and 15 of every 28-day cycle. Infusion durations may be lengthened to ameliorate toxicity for individual subjects with agreement between the Investigator and the Sponsor.

Detailed instructions for MRZ dose modifications and actions are provided in Table 6.

Table 6: Marizomib Dose Modification Guidelines for Part 1 Phase 1 Expansion and Part 2 Phase 2

Toxicity	MRZ Dose Modification & Action
Grade 2 Central Nervous System Disorders	Consider holding MRZ until toxicity resolves. When toxicity resolves, consider reinitiating with reduced dose of MRZ (to be determined in discussion with the Medical Monitor, but at least a decrease of 0.1 mg/m2).
Grade 3 Nervous System Disorder AEs	Hold MRZ until toxicity resolves. When toxicity resolves, reinitiate with reduced dose of MRZ (to be determined in discussion with the Medical Monitor, but at least a decrease of 0.1 mg/m2 at start of next cycle).
Other Grade 3 MRZ-related AEs	Hold MRZ until toxicity resolves. When toxicity resolves, reinitiate with reduced dose of MRZ (to be determined in discussion with the Medical Monitor, but at least a decrease of 0.1 mg/m2 at start of next cycle).
Grade 4 Hematologic MRZ-related AEs	Hold MRZ until toxicity resolves. When toxicity resolves, reinitiate with reduced dose of MRZ (to be determined in discussion with the Medical Monitor, but at least a decrease of 0.1 mg/m2 at start of next cycle).
Nonhematological Grade 4 MRZ-related AEs	Permanently discontinue all study treatment.

This table was added with Amendment 2 and applies to subjects entered under Amendment 2 whether in the Phase 1 Dose Expansion or Phase 2 portions of the study.

In addition to the guidelines in Table 6 if a subject has a drug-related event that requires a 14-day delay in therapy, then MRZ dose reduction is appropriate. If recovery from toxicities is prolonged beyond 14 days, then the dose of MRZ will be decreased by 0.1 mg/m^2 when dosing resumes. After MRZ dose interruption, reassessment of safety laboratory tests is required prior

to resuming MRZ treatment. Prior to initiation of subsequent cycles, results for the following tests must meet study entry criteria: liver functions tests (LFTs), serum creatinine, and complete blood count.

The minimum permitted dose level for MRZ is 0.5 mg/m^2. If toxicity recurs at the minimum permitted dose of MRZ, all study treatment should be discontinued. Dose re-escalation is not permitted for MRZ.

Part 3 Phase 2

IV Marizomib

- MRZ will be administered as a 10-minute IV infusion on Days 1, 8, and 15 of every 28-day cycle.
- Starting dose for each subject will be 0.8 mg/m^2.
- Doses will be rounded to the nearest tenth of a mg.
- After the first cycle without a dose-limiting adverse event (DLAE), the dose of MRZ will be increased to 1.0 mg/m^2 and after 1 more cycle without a DLAE the dose of MRZ will be increased to 1.2 mg/m^2.
- DLAEs are MRZ-related AEs 1) related to disturbances in the cerebellum (ie, ataxia, dizziness, dysarthria, fall, gait disturbances) plus hallucinations of any grade or 2) Grade ≥ 2 other AEs.
- Doses will be delayed and/or reduced or discontinued for DLAEs related to MRZ as described in Table 7.

Table 7: Marizomib Dose Modification Guidelines in Part 3 Phase 2, Part 4 Phase 1, and Part 5 Phase 1

Marizomib-Related Adverse Event	Severity	Recommended MRZ Dose Modification
Central Nervous System		
Common CNS AEs include: Hallucinations, ataxia, dizziness, gait disturbance, balance disorder, fall, dysarthria, confusion	Grade 1	Maintain current MRZ dose schedule without dose modification.
	Grade 2	Consider other supportive treatment; generally no dose-reductions are recommended. Dose-reduction is recommended if intolerable by patient due to interference with daily routine and/or if duration of event lasts longer than 3 days.
	Grade 3	At the next scheduled MRZ dose administration, dose-reduce one dose level. If AE has not resolved to ≤ Grade 1 (or baseline), skip the MRZ dose and resume with the next scheduled dose at reduced level. In addition, consider other supportive treatment.

Table 7: Marizomib Dose Modification Guidelines in Part 3 Phase 2, Part 4 Phase 1, and Part 5 Phase 1 (Continued)

Marizomib-Related Adverse Event	Severity	Recommended MRZ Dose Modification
	Grade 4	Stop MRZ until resolution to ≤ Grade 1 (or baseline). Discuss with Medical Monitor. If re-challenge is an option, reduce MRZ dose level (see MRZ dose reduction table) in agreement with Medical Monitor.
Gastrointestinal		
Nausea, Vomiting	Grade 1 or 2	Implement prophylactic anti-emetic regimen according to local guidelines. Maintain current MRZ dose schedule without dose modification. If (re)occurrence despite appropriate prophylaxis, dose-reduce one dose level (see MRZ dose reduction table) at the next scheduled MRZ dose administration.
	Grade 3 or 4	Implement prophylactic anti-emetic regimen according to local guidelines. If (re)occurrence despite appropriate prophylaxis, dose-reduce one dose level (see MRZ dose reduction table) at the next scheduled MRZ dose administration. In addition, consider other supportive treatment per local guidelines.
Other Adverse Events		
	Grade 2	Maintain current MRZ dose schedule without dose modification. Consider dose-reduction if intolerable by patient due to interference with daily routine and/or not resolved to ≤ Grade 1 (or baseline) at the next scheduled MRZ dose administration.
	Grade 3	At the next scheduled MRZ dose administration, dose-reduce one dose level (see MRZ dose reduction table). If AE has not resolved to ≤ Grade 1 (or baseline), skip the MRZ dose and resume with the next scheduled dose at reduced level.
	Grade 4	Stop MRZ until resolution to ≤ Grade 1 (or baseline). Discuss with Medical Monitor. If re-challenge is an option, reduce MRZ dose level (see MRZ dose reduction table) in agreement with Medical Monitor.

- In addition to the guidelines in Table 7, if a subject has an MRZ-related event that requires a 14-day delay in therapy (calculated from the scheduled date of the next dose), then MRZ dose reduction is appropriate. If recovery from MRZ-related AEs is prolonged beyond 14 days, then the dose of MRZ will be decreased by 0.1 mg/m^2 when dosing resumes unless an alternative plan is approved by the Sponsor's Medical Monitor.
- Dose re-escalation is not permitted for MRZ unless approved by the Sponsor's Medical Monitor.
- All dose increases (Part 3 Phase 2 only) require approval of the Sponsor's Medical Monitor.

IV BEV

BEV will be administered as an IV infusion (90 minutes 1st dose, 60 minutes 2nd dose, and 30 minutes afterward) at a dose of 10 mg/kg on Days 1 and 15. BEV will be administered approximately 10 minutes after the end of the MRZ infusion when co-administered on the same day.

In the case of dosing delay, BEV should always be given on the day that MRZ is administered. If MRZ is delayed, BEV should also be delayed. If BEV is discontinued for AEs, the subject may continue on MRZ alone. If MRZ is discontinued, the subject will be discontinued from the study. Both drugs will be discontinued once disease progression is documented.

There are no recommended dose reductions. According to the Warnings and Precautions and Dose Modification sections of the Avastin® United States Prescribing Information, the following actions are recommended:

- Perforation or Fistula: Discontinue BEV if perforation or fistula occurs.
- Wound Healing: Discontinue BEV for wound dehiscence and wound healing complications requiring medical intervention
- Hemorrhage: Discontinue BEV in subjects with serious hemorrhage
- Arterial Thromboembolic Events (ATE) (eg, myocardial infarction, cerebral infarction): Discontinue BEV for severe ATE.
- Venous Thromboembolic Events (VTE): Discontinue BEV for life-threatening (Grade 4) VTE, including pulmonary embolism
- Hypertension: Monitor blood pressure and treat hypertension. Temporarily suspend BEV if not medically controlled. Discontinue BEV for hypertensive crisis or hypertensive encephalopathy.
- Posterior Reversible Encephalopathy Syndrome (PRES): Discontinue BEV.
- Proteinuria: Monitor proteinuria by dipstick urine analysis for the development or worsening of proteinuria with serial urinalyses during BEV therapy. Subjects with a 2+ or greater urine dipstick reading should undergo further assessment with a 24-hour urine collection. Suspend BEV administration for ≥ 2 grams of proteinuria/24 hours and resume when proteinuria is < 2 gm/24 hours. Discontinue BEV in subjects with nephrotic syndrome.
- Infusion Reactions: Stop BEV for severe infusion reactions and administer appropriate medical therapy.

Part 4 Phase 1

Enterally Administered Marizomib

- MRZ will be administered enterally as a bolus over ≤10 min via NG tube on Days 1, 8, and 15 of the first 28-day cycle.
- MRZ dosing will begin at 0.075 mg/m^2 once weekly (Cohort 1). Additional dose cohorts are planned as shown in Table 8.
- Doses will be rounded to the nearest tenth of a mg.

Table 8: Dose Cohorts for Enteral (Cycle 1) and IV (Cycles 2→) MRZ + IV BEV Combination

Cohort	Number of Subjects	Enteral MRZ (mg/m^2) Cycle 1 Days 1, 8, and 15	IV MRZ (mg/m^2) Cycle 2+ Days 1, 8 and 15*	IV BEV (mg/kg) Cycle 1 Day 15 Cycle 2+ Days 1 and 15
-1*	3-6	0.025	0.8	10
1	1-6	0.075	0.8	10
2	1-6	0.225	0.8	10
3	1-6	0.675	0.8	10
4	3-6	1.0	0.8	10
5	3-6	1.35	0.8	10
6	3-6	1.7	0.8	10
7	3-6	2.0	0.8	10
8	3-6	2.3	0.8	10
9	3-6	2.6	0.8	10

* Refer to Section 7.2.8, Part 4 Phase 1.

- Doses will be delayed and/or reduced or discontinued for DLTs related to MRZ as described in Table 7.
- Subjects must receive at least 3 doses of MRZ during Cycle 1, with 2 MRZ doses administered enterally during Cycle 1 to be evaluable for DLT.

IV Marizomib

- For Cycle 2 and all subsequent cycles, MRZ will be administered as a 10-minute IV infusion on Days 1, 8, and 15 of every 28-day cycle.
- Starting dose for each subject will be 0.8 mg/m^2. No dose increases are permitted.
- Doses will be rounded to the nearest tenth of a mg.
- Doses will be delayed and/or reduced or discontinued for adverse events related to MRZ as described in Table 7.

- In addition to the guidelines in Table 7, if a subject has a MRZ-related event that requires a 14-day delay in therapy (calculated from the scheduled date of the next dose), then MRZ dose reduction is appropriate. If recovery from MRZ-related AEs is prolonged beyond 14 days, then the dose of MRZ will be decreased by 0.1 mg/m^2 when dosing resumes unless an alternative plan is approved by the Sponsor's Medical Monitor.

Dose re-escalation is not permitted for MRZ unless approved by the Sponsor's Medical Monitor.

IV BEV

BEV will be administered as an IV infusion (90 minutes 1st dose, 60 minutes 2nd dose, and 30 minutes afterward) at a dose of 10 mg/kg on Day 15 of Cycle 1, and on Days 1 and 15 of Cycle 2 and all subsequent cycles. BEV will be administered approximately 10 minutes after the end of the MRZ infusion when co-administered on the same day.

In the case of dosing delay, BEV should always be given on the day that MRZ is administered. If MRZ is delayed, BEV should also be delayed. If BEV is discontinued for AEs, the subject may continue on MRZ alone. If MRZ is discontinued, the subject will be discontinued from the study. Both drugs will be discontinued once disease progression is documented.

There are no recommended dose reductions. According to the Warnings and Precautions and Dose Modification sections of the Avastin® United States Prescribing Information, the following actions are recommended:

- Perforation or Fistula: Discontinue BEV if perforation or fistula occurs.
- Wound Healing: Discontinue BEV for wound dehiscence and wound healing complications requiring medical intervention
- Hemorrhage: Discontinue BEV in subjects with serious hemorrhage
- Arterial Thromboembolic Events (ATE) (eg, myocardial infarction, cerebral infarction): Discontinue BEV for severe ATE.
- Venous Thromboembolic Events (VTE): Discontinue BEV for life-threatening (Grade 4) VTE, including pulmonary embolism
- Hypertension: Monitor blood pressure and treat hypertension. Temporarily suspend BEV if not medically controlled. Discontinue BEV for hypertensive crisis or hypertensive encephalopathy.
- Posterior Reversible Encephalopathy Syndrome (PRES): Discontinue BEV.
- Proteinuria: Monitor proteinuria by dipstick urine analysis for the development or worsening of proteinuria with serial urinalyses during BEV therapy. Subjects with a 2+ or greater urine dipstick reading should undergo further assessment with a 24-hour urine collection. Suspend BEV administration for ≥ 2 grams of proteinuria/24 hours and resume when proteinuria is < 2 gm/24 hours. Discontinue BEV in subjects with nephrotic syndrome.
- Infusion Reactions: Stop BEV for severe infusion reactions and administer appropriate medical therapy.

Part 5 Phase 1

- All subjects will receive MRZ + BEV as follows:

IV Marizomib (MRZ)

- MRZ will be administered as a 10-minute IV infusion on Days 1, 8, and 15 of every 28-day cycle. Infusion durations may be lengthened to ameliorate toxicity for individual subjects with agreement between the Investigator and the Sponsor.
- Starting dose for each subject will be 0.8 mg/m^2.
- Doses will be rounded to the nearest tenth of a mg.
- Doses will be delayed and/or reduced or discontinued for AEs related to MRZ as described in Table 7.
- Intra-patient dose escalation is not permitted in Part 5 Phase 1.
- In Part 5 Phase 1, an additional subject(s) will be enrolled for any subject(s) who has a reduction in their MRZ dose in Cycle 1.

IV BEV

BEV will be administered as an IV infusion (90 minutes 1st dose, 60 minutes 2nd dose and 30 minutes afterward) at a dose of 10 mg/kg on Day 15 of Cycle 1, and on Days 1 and 15 of Cycle 2 and all subsequent cycles. BEV will be administered approximately 10 minutes after the collection of the last MRZ PK blood sample on Day 15 of Cycle 1, and approximately 10 minutes after the end of the MRZ infusion when co-administered on the same day in Cycle 2 and all subsequent cycles.

In the case of dosing delay, BEV should always be given on the day that MRZ is administered. If MRZ is delayed, BEV should also be delayed. If BEV is discontinued for AEs, the subject may continue on MRZ alone. If MRZ is discontinued, the subject will be discontinued from the study. Both drugs will be discontinued once disease progression is documented.

There are no recommended dose reductions. According to the Warnings and Precautions and Dose Modification sections of the Avastin® United States Prescribing Information, the following actions are recommended:

- Perforation or Fistula: Discontinue BEV if perforation or fistula occurs.
- Wound Healing: Discontinue BEV for wound dehiscence and wound healing complications requiring medical intervention
- Hemorrhage: Discontinue BEV in subjects with serious hemorrhage
- Arterial Thromboembolic Events (ATE) (eg, myocardial infarction, cerebral infarction): Discontinue BEV for severe ATE.
- Venous Thromboembolic Events (VTE): Discontinue BEV for life-threatening (Grade 4) VTE, including pulmonary embolism
- Hypertension: Monitor blood pressure and treat hypertension. Temporarily suspend BEV if not medically controlled. Discontinue BEV for hypertensive crisis or hypertensive encephalopathy.

- Posterior Reversible Encephalopathy Syndrome (PRES): Discontinue BEV.
- Proteinuria: Monitor proteinuria by dipstick urine analysis for the development or worsening of proteinuria with serial urinalyses during BEV therapy. Subjects with a 2+ or greater urine dipstick reading should undergo further assessment with a 24-hour urine collection. Suspend BEV administration for ≥ 2 grams of proteinuria/24 hours and resume when proteinuria is < 2 gm/24 hours. Discontinue BEV in subjects with nephrotic syndrome.
- Infusion Reactions: Stop BEV for severe infusion reactions and administer appropriate medical therapy.

7.2.7. Dose-Limiting Toxicity

Part 1 Phase 1

Dose-limiting toxicity (DLT) is defined as the occurrence of any of the following AEs related to one of the drugs or the combination observed during Cycle 1, using NCI-CTCAE (v 4.03):

- ≥ Grade 3 thrombocytopenia or Grade 2 thrombocytopenia with bleeding.
- Grade 4 neutropenia or anemia lasting for more than 4 days.
- Febrile neutropenia.
- Any ≥ Grade 2 neurological event lasting more than 4 days.
- Grade 3 or 4 non-hematologic toxicity (excluding alopecia), lasting for more than 4 days despite adequate supportive therapy or preventing the next scheduled dose from being administered within 4 days of scheduled day; for ≥ Grade 3 fatigue to be considered a DLT, it must be present for more than 7 days.

Subjects without DLT in Cycle 1 who do not receive 3 MRZ doses or 2 BEV doses within 5 weeks from first dose will not be evaluable for DLT and will be replaced.

Part 2 Phase 2

If at any time after 3 subjects are enrolled, the incidence of AEs that fit the definition of DLT from Phase 1 occurs in >33% of the subjects, then enrollment will be paused. Available data will be reviewed and a decision regarding continuing to enroll subjects at the 0.8 mg/m^2 over 10 minutes dose in Phase 2 is agreed between the Sponsor and Investigators. Adjustment downward on dose or lengthening infusion duration will be considered and the Phase 2 portion restarted at the selected dose and infusion time.

Part 3 Phase 2

The term DLT is not applicable to this portion of the study. DLAEs, defined as MRZ-related AEs which are: 1) related to disturbances in the cerebellum (ie, ataxia, dizziness, dysarthria, fall, gait disturbances) plus hallucinations of any grade or 2) Grade ≥ 2 other AEs will be used to determine if MRZ doses should be delayed, reduced, or discontinued.

Part 4 Phase 1

Dose-limiting toxicity (DLT) is defined as the occurrence of any of the following AEs related to one of the drugs or the combination observed during Cycle 1, using NCI-CTCAE (v 4.03) to determine severity:

- Grade ≥ 3 non-hematological toxicity (excluding alopecia), including GI toxicities such as nausea, vomiting, constipation, and/or diarrhea, lasting for more than 4 days despite adequate supportive therapy or preventing the next scheduled dose from being administered within 7 days of scheduled day
  - For ≥ Grade 3 fatigue to be considered a DLT, it must be present for more than 7 days.
- Grade 3 thrombocytopenia or Grade 2 thrombocytopenia with bleeding.
- Grade 4 neutropenia or anemia lasting for more than 4 days.
- Febrile neutropenia.
- Any ≥ Grade 2 neurological event lasting more than 4 days.

Subjects who do not have a DLT in the first cycle of a dose cohort will be replaced if they do not receive at least two doses of enterally-administered MRZ, with the second dose administered no more than 7 days after the scheduled dose. Subjects who demonstrate intolerability to enteral MRZ administration for any reason may continue to receive subsequent MRZ treatments intravenously.

Part 5 Phase 1

Amendment 5 does not include an assessment of dose-limiting toxicity, as MRZ will be administered by IV infusion at the MTD as confirmed in Part 3 Phase 2 (0.8 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle).

7.2.8. Dose Escalation Process and MTD/MAD Determination

Part 1 Phase 1

Initially 3 subjects will be enrolled into a cohort, commencing with Cohort 1 and the doses shown in Table 5. Dose escalation will proceed as follows:

- If none of the first 3 evaluable subjects in a dose cohort experience a DLT during Cycle 1, then enrollment into the next dose cohort can be initiated.
- If ≥ 2 of the first 3 evaluable subjects in a dose cohort experience a DLT during Cycle 1, then the MTD has been exceeded and dose escalation will not proceed.
- If 1 of the first 3 evaluable subjects in a dose cohort experiences a DLT during Cycle 1, then an additional 3 subjects will be enrolled into the same cohort.
- If 1/6 evaluable subjects in the expanded 6-subject cohort experiences a DLT during Cycle 1, then the next higher dose cohort can be tested and enrollment of the next 3 subjects at the next higher dose level can be initiated.
- If ≥ 2/6 evaluable subjects in the expanded 6-subject cohort experience a DLT during Cycle 1, then the MTD has been exceeded and no further dose escalation will occur.

The MTD is defined as the dose level below the cohort where DLT is observed in at least 2 subjects in the same cohort during Cycle 1. Intermediate dosing levels may be explored if indicated. The dose of 0.8 mg/m^2 will not be exceeded and will be the MAD.

During the dose escalation phase of the protocol, if 2 DLTs are noted in the first 2 subjects of a cohort prior to the third subject being enrolled, the third subject will not be enrolled in that cohort. If there is 1 DLT in the first 3 subjects and the cohort is expanded and another DLT is noted prior to enrolling all 6 subjects in the cohort, further enrollment in that cohort will be halted. If during the dose expansion phase there are ≥ 3 DLTs in the first 6 or fewer subjects then the MTD will be reassessed by the Investigators and Sponsor.

Teleconferences between Triphase and the clinical study sites will occur at least every other week to discuss safety. Once the MTD/MAD has been identified, a cohort of at least 12 additional, evaluable subjects for a total of 36 subjects will be treated at the MTD/MAD to further confirm the safety and to assess preliminary activity for the combination treatment. This cohort may be used to determine the RP2D.

Part 4 Phase 1

A modified 3+3 design will be used to define the MTD for MRZ IV formulation reconstituted and administered enterally via NG tube in the first 28-day cycle, with MRZ administered on Days 1, 8, and 15 and BEV on Day 15. Initially one subject will be enrolled into each of the first 3 dose cohorts to expedite dose-escalation into the anticipated therapeutically effective dose range, followed by enrollment of 3 subjects each into the next 6 dose cohorts.

Enteral MRZ dose escalation will proceed as follows:

- If the first DLT-evaluable subject in dose cohort 1 does not experience a DLT or intermediate toxicity during Cycle 1, then enrollment into the next dose cohort can be initiated. Intermediate toxicity is defined as any Grade 2 or higher adverse event that is deemed clinically significant by the Investigator and which cannot be clearly identified as being related to the underlying condition, comorbid condition, or concomitant medication.
- If the first DLT-evaluable subject in a 1-subject dose cohort experiences a DLT during Cycle 1, then up to 5 additional subjects will be enrolled into the same cohort.
- The 1-subject cohorts will be expanded to 3 subjects with the second instance of first-cycle intermediate toxicity. Intermediate toxicity is defined as any Grade 2 or higher adverse event that is deemed clinically significant by the Investigator and which cannot be clearly identified as being related to the underlying condition, comorbid condition, or concomitant medication. Once a 1-subject cohort has been expanded, all subsequent cohorts will have at least 3 subjects (unless the first 2 subjects have DLT prior to the enrollment of a third subject).
- If there are 2 subjects with DLT in Cohort 1, then 3 subjects can be enrolled in Cohort -1. The decision to explore Cohort -1 will be made by the participating Investigators and Sponsor's Medical Monitor(s). If Cohort -1 proceeds without any subject with a DLT, participating Investigators and Sponsor's Medical Monitor(s) may decide to revisit Cohort 1 and, if tolerated, continue with the escalation as shown in Table S-2, or with intermediate dose levels.

- If 1 of the first 3 evaluable subjects in a 3-subject dose cohort experiences a DLT during Cycle 1, then an additional 3 subjects will be enrolled into the same cohort.
- If no more than 1 of the 6 DLT-evaluable subjects in an expanded dose cohort experiences a DLT during Cycle 1, then the next higher dose cohort can be initiated with 3 subjects enrolled at the next higher dose level.
- If ≥ 2/6 evaluable subjects in an expanded dose cohort experiences a DLT during Cycle 1, then the MTD has been exceeded and no further dose escalation will occur.

The MTD is defined as the dose level below the cohort where DLT is observed in at least 2 subjects in the same cohort during Cycle 1. Intermediate dosing levels may be explored if indicated.

The dose of 2.6 mg/m^2 is expected to be above the MTD for enterally-administered MRZ. If this is not the case, additional cohorts can be explored with dose escalations between cohorts kept at approximately 20%.

Once the MTD has been identified, a cohort of approximately 6 additional, evaluable subjects will be treated at the MTD to further confirm the safety of the combination treatment.

Teleconferences between Sponsor and the clinical study sites will occur at least every other week to discuss safety. Additional teleconferences may be scheduled at the end of each cohort to decide on the dose of the next cohort.

7.3. Method of Treatment Assignment

Part 1 Phase 1

Treatments consist of IV doses of MRZ and BEV. Subjects will enter the study sequentially and be assigned to a cohort (dose level) based on the evaluation of subjects who were previously treated according to the dose escalation scheme. Once the RP2D is determined, subjects will be treated at the RP2D in the expansion cohort unless the Investigators and Sponsor agree to a lower dose for safety reasons.

Part 2 Phase 2

Treatments consist of IV doses of MRZ. Subjects will enter the study sequentially.

Part 3 Phase 2

Treatment consists of IV doses of MRZ and BEV. Subjects will enter the study sequentially.

Part 4 Phase 1

Treatments consist of once-weekly enterally administered doses of MRZ IV formulation reconstituted and administered via NG tube (Days 1, 8, and 15), with a single IV dose of BEV on Day 15. Subjects will enter the study sequentially and be assigned to a cohort (dose level) based on the evaluation of subjects who were previously treated according to the dose escalation scheme. Once the MTD is determined, subjects will be treated at the MTD in the expansion cohort unless the Investigators and Sponsor agree to a lower dose for safety reasons.

Part 5 Phase 1

Treatments consist of IV doses of MRZ administered by IV infusion at the MTD as confirmed in Part 3 Phase 2 (0.8 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle), and BEV.

7.4. Packaging and Labeling

The label(s) for Investigational Product (IP) MRZ will include Sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

7.5. Investigational Product Accountability and Disposal

Triphase (or designee) will review with the Investigator and relevant site personnel the process for Investigational Product return, disposal, and/or destruction including responsibilities for the site vs. Triphase (or designee).

7.6. Investigational Product Compliance

Both investigational products are given intravenously by trained site personnel and records of administration are maintained at the site. Subjects will be monitored for adherence to visit days for drug administration. Dosing delays for AEs or administrative reasons (eg, clinical closure for holidays) will not be considered protocol deviations.

8. CONCOMITANT MEDICATIONS AND PROCEDURES

8.1. Permitted Concomitant Medications and Procedures

Concomitant medications to treat comorbid conditions and adverse events are permitted. Enzyme-inducing anti-epileptic drugs (EIAEDs) are allowed. Steroids are allowed and dosing is at the discretion of the Investigator. Consideration should be given to treating hallucinations with anti-psychotic drugs such as olanzapine or quetiapine and fatigue with stimulating agents such as methylphenidate.

In studies to date, MRZ has caused clinically significant nausea and vomiting requiring the use of antiemetics as therapy and also as prophylaxis. Therefore, both the therapeutic and prophylactic use of antiemetics is allowed in this study at the discretion of the Investigator.

8.2. Prohibited Concomitant Medications and Procedures

Medications to treat the underlying malignancy are not permitted and their use constitutes progressive disease and subjects must discontinue study treatment. Investigational agents of any kind are not permitted.

8.3. Required Concomitant Medications and Procedures

There are no required concomitant medications or procedures.

9. STATISTICAL ANALYSES

9.1. Overview

Part 1 Phase 1

A 3 + 3 design will be utilized to determine the MTD/MAD for combination treatment of MRZ + BEV in each 28-day cycle. Subjects who do not have a DLT in the first cycle of a dose cohort will be replaced if they discontinue treatment with MRZ or BEV in Cycle 1 for any other reason. Subjects who miss a dose of MRZ or BEV or cannot receive all doses within 5 weeks from first dose during Cycle 1 and do not have a DLT will not be evaluable for DLT and will be replaced. After MTD/MAD has been determined in the dose-escalation part of the study, at least 12 additional subjects will be treated at the MTD/MAD in an expansion cohort to confirm the safety and assess the preliminary activity for the combination of MRZ + BEV administered up to a total of 36 subjects.

For all analyses by dose cohorts, the MTD/MAD confirmation cohort subjects will be combined with the corresponding dose cohort in the MTD/MAD determination phase as one single dose cohort.

Part 2 Phase 2

Subjects enrolled in the Part 2 Phase 2 portion of the protocol will receive 0.8 mg/m^2 MRZ IV on Days 1, 8, and 15 of 28-day cycles. A minimum of 15 response-evaluable subjects will be enrolled in Stage 1, and up to 15 additional response-evaluable subjects will be enrolled in Stage 2, for a maximum of 30 response-evaluable subjects. After the first 15 response-evaluable subjects in the first stage have received 2 or more cycles of therapy, available study data will be reviewed by the Phase 2 Review Committee consisting of the Investigators at each study center, the Medical Monitor, and the Sponsor's Chief Medical and Scientific Officers and Study Coordinator. The Phase 2 Review Committee will recommend whether to enroll the second stage based on an assessment of both safety and efficacy. If there are no safety concerns and clinical benefit is demonstrated with evidence of disease response, defined as at least one response (partial response (PR) or better) as determined by RANO criteria, in 15 response-evaluable subjects, then 15 additional response-evaluable subjects will be enrolled in Phase 2. Otherwise, there will be no further enrollment into the study.

Efforts will be made to ensure the correct number of subjects is accrued, and enrollment will be carefully monitored and communicated with the sites. There may be instances where, as a result of simultaneous screening activities, subjects may qualify for the study at the same time, resulting in slight over-enrollment.

Part 3 Phase 2

A sample size of 40 eligible subjects is based on wanting a reasonably precise estimate of median OS.

Efforts will be made to ensure the correct number of subjects is accrued, and enrollment will be carefully monitored and communicated with the sites. There may be instances where, as a result of simultaneous screening activities, subjects may qualify for the study at the same time, resulting in slight over-enrollment.

Part 4 Phase 1

A modified 3 + 3 design will be utilized to determine the MTD for MRZ IV formulation reconstituted and administered enterally via NG tube on Days 1, 8, and 15 of a 28-day cycle, with BEV administered IV on Day 15. Subjects who do not have a DLT in the first cycle of a dose cohort will be replaced if they do not receive at least two doses of enterally-administered MRZ, with the second dose administered no more than 7 days after the scheduled dose. After MTD has been determined in the dose-escalation part of the study, approximately 6 additional subjects will be treated at the MTD in an expansion cohort to confirm the safety and assess the PK and pharmacodynamic activity for enterally administered MRZ, for up to a total of approximately 24 subjects.

For all analyses by dose cohorts, the MTD confirmation cohort subjects will be combined with the corresponding dose cohort in the MTD determination phase as one single dose cohort.

Part 5 Phase 1

A subject who has at least 1 full PK profile in Cycle 1 with quantifiable PK parameters will be included in the PK analysis. PK parameters from noncompartmental analysis will be summarized by study day across subjects, and by subject across study days using simple summary statistics presented in tables and graphs.

In Amendment 5, any subject that discontinues treatment in Cycle 1 without completing all PK assessments will be replaced. Further, an additional subject(s) will be enrolled for any subject(s) who has a reduction in their MRZ dose in Cycle 1.

9.2. Study Population Definitions

All subjects who receive at least one dose of study medication (MRZ or BEV) will be considered enrolled in the study and will be in the Safety Population. All subjects who receive at least one dose of study medication and have at least 1 post dose PK sample will be in the PK Population. All subjects who receive at least 1 cycle of therapy and have at least 1 post treatment tumor assessment will be in the Activity (Efficacy) Population (Response-evaluable Population).

9.3. Sample Size

Part 1 Phase 1

Up to 36 subjects will be enrolled in the MTD/MAD determination and confirmation (expansion cohort) parts of the study.

Part 2 Phase 2

Fifteen response-evaluable subjects will be enrolled in the first stage of a 2-stage design (Green 1992). If there is at least 1 PR or better and there are no safety concerns in the first 15 response-evaluable subjects, then the second stage of 15 response-evaluable subjects will be opened. If ≥ 5 subjects respond by the end of the second accrual stage (n = 30), the conclusion can be drawn that MRZ is promising, unless other considerations indicate otherwise.

Assuming the effect size of interest is at least 20%, a sample size of 30 subjects for Phase 2 will have 80% power to reject the null hypothesis of H0: response rate is ≤ 5% in favor of the

alternative hypothesis (H1) that the effective size is > 5% with a 0.050 two-sided significance level.

Part 3 Phase 2

A sample size of 40 subjects is based on wanting a reasonably precise estimate of OS. Assuming 10 subjects will be alive at the time of statistical analysis, there will be 30 deaths observed (ie, 25% of the subjects are censored). The resulting 95% confidence interval (CI) is 7.2 – 14.8 months, with a width equal to 7.6 months, around an estimated median survival of 10 months.

Part 4 Phase 1

Approximately 24 subjects will be enrolled in the MTD determination and confirmation (expansion cohort) parts of the study.

Part 5 Phase 1

The sample size of 12 was determined to provide sufficient PK exposure data to quantify the between and within subject variability. A subject who has at least 1 full PK profile with quantifiable PK parameters will be included in the PK analysis. Any subject that discontinues treatment in Cycle 1 without completing all PK assessments will be replaced. Further, an additional subject(s) will be enrolled for any subject(s) who has a reduction in their MRZ dose in Cycle 1.

9.4. Background and Demographic Characteristics

Subjects' age, height, weight, and baseline characteristics will be summarized using descriptive statistics, while gender, race and other categorical variables will be provided using frequency tabulations. Medical history data including cancer history will be listed. Results of Phase 1 and Phase 2 portions of the study will not be combined.

9.5. Subject Disposition

Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent for both treatment and follow-up phases. A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations. Results of the two Phase 1 and the two Phase 2 portions of the study will not be combined.

9.6. Activity (Efficacy) Analysis

Tumor response including PD, progression-free survival (PFS), and overall survival (OS) will be assessed by the Investigators using RANO 2010 criteria. The overall confirmed response rate will be examined. The overall response rate, PFS, and OS will also be tabulated by dose cohorts. Results of Phase 1 and the two Phase 2 portions of the study will not be combined.

9.7. Safety Analysis

All subjects in all parts of the study will be evaluated for safety analysis if they receive at least one dose of MRZ (or BEV for subjects in Parts 1, 3, 4 and 5). The safety data will be presented in individual listings and summary tables, including frequency tables for adverse events and

listings of abnormalities for laboratory variables. Results of Phase 1 and Phase 2 portions of the study will not be combined.

9.8. Pharmacokinetic Analysis (Part 1 Phase 1, Part 4 Phase 1, and Part 5 Phase 1)

Non-compartmental analyses will be performed. The following PK parameters will be calculated: maximum observed blood drug concentration (C_{max}), time of maximum blood concentration (T_{max}), elimination half-life ($T_{1/2}$), area under the blood concentration-time curve ($AUC_{0\text{-}inf}$), clearance (CL), and volume of distribution (Vd).

Blood concentrations and computed PK parameters for MRZ will be listed and summarized by cohort (mean, geometric mean, standard deviation, coefficient of variation, minimum, maximum and number of observations). Compartmental PK modeling may be conducted, as appropriate.

9.9. Pharmacodynamic Analysis (Part 1 Phase 1 and Part 4 Phase 1)

In Part 1 (Phase 1), PD analysis will include change in proteasome activities (whole blood lysates and PBMC lysates) by comparing levels of proteasome activity pre-drug and post-drug on Days 1, 8, and 15 (ie, for each dose) of Cycle 1 and Days 1 and 15 (ie, for the first and last doses) of each cycle thereafter.

In Part 4 (Phase 1), PD analysis will include change in proteasome activities (whole blood lysates and PBMC lysates) by comparing levels of proteasome activity pre-drug and post-drug on Days 1 and 8 of Cycles 1 and 2.

9.10. Interim Analysis

Part 1 Phase 1

This is a Phase 1 study and no interim analysis is planned.

Part 2 Phase 2

Response to MRZ will be assessed in the 15 response-evaluable subjects in Stage 1 of the 2-stage design. Once at least 1 response (PR or better) has been determined, the second stage will be implemented. If no confirmed, objective responses have been observed after all subjects have received at least 2 cycles of therapy, Phase 2 will end without implementing the second stage. If the second stage is implemented, an additional 15 response-evaluable subjects will be enrolled.

Part 3 Phase 2

No interim analysis is planned.

Part 4 Phase 1

This is a Phase 1 study and no interim analysis is planned.

Part 5 Phase 1

This is a Phase 1 study and no interim analysis is planned.

10. ADVERSE EVENTS

10.1. Monitoring, Recording and Reporting of Adverse Events

An adverse event (AE) is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 10.3), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the CRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Overdose (accidental or intentional), abuse, withdrawal, sensitivity or toxicity to study treatment should be reported as an AE. If an overdose is associated with an AE, the overdose and AE should be reported as separate terms. Any sequelae of an accidental or intentional overdose of an investigational product should be reported as an AE on the AE CRF. If the sequelae of an overdose are an SAE, then the sequelae must be reported on an SAE report form and on the AE CRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and CRF but should not be reported as an SAE itself. Medication errors, defined as an overdose with > 105% of drug administered, or underdose, defined as < 95% of dose administered, are to be reported as AEs. Prescribed dose reductions for AEs are not considered medication errors. On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency. On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate. Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.

All SAEs will be recorded by the Investigator from the time the subject signs informed consent until 28 days after the last dose of study treatment and those SAEs made known to the Investigator at any time thereafter that are suspected of being related to study treatment. AEs are recorded from the start of the first infusion of study treatment. AEs occurring before the first infusion of IP are considered medical history and should be recorded on the medical history CRF. AEs and serious adverse events (SAEs) will be recorded on the AE page of the CRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

10.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to:

10.2.1. Seriousness

A serious adverse event (SAE) is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (ie, in the opinion of the Investigator, the subject is at immediate risk of death from the AE);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Events **not considered** to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (ie, planned prior to starting of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of or an elective procedure for a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page of the CRF and the SAE Report Form must be completed.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to study treatment, action taken regarding study treatment, and outcome.

10.2.2. Severity / Intensity

For both AEs and SAEs, the Investigator must assess the severity/intensity of the event.

The severity / intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of the Common Terminology Criteria for Adverse Events (NCI-CTCAE, Version 4.03).

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as "serious" which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

10.2.3. Causality

The Investigator must determine the relationship between the administration of study treatment and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	Means a causal relationship of the adverse event to study treatment administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	Means there is a **reasonable possibility** that the administration of study treatment caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the study treatment and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available. For regulatory purposes, it is the Sponsor that is responsible for making the final causality assessment.

10.2.4. Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event. For AEs that become SAEs, the start date of the SAE will be when the seriousness criteria are met. The original AE will have a stop date the same as the start date of the SAE. The SAE will have a stop date of when the seriousness criteria are no longer met. If the AE continues after the seriousness criteria are no longer met, then a new AE will be recorded with a start date the same as the SAE stop date and a stop date when the AE is completely resolved. In all cases, the

AE must have the same verbatim term throughout. Within the duration of the SAE or AE, the maximum grade should be used to categorize severity.

10.2.5. Action Taken

The Investigator will report the action taken with each study drug as a result of an AE or SAE, as applicable (eg, discontinuation, interruption, or reduction of study treatment, as appropriate) and report if concomitant and/or additional treatments were given for the event.

10.2.6. Outcome

The Investigator will report the outcome of the event for both AEs and SAEs.

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered, recovered with sequelae, returned to baseline, stabilized, or died (due to the SAE or due to another cause).

10.3. Abnormal Laboratory Values

An abnormal laboratory value is to be considered an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IP dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

10.4. Pregnancy

All pregnancies or suspected pregnancies occurring in either a female subject or partner of a male subject are immediately reportable events.

10.4.1. Females of Childbearing Potential:

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on study treatment or within 28 days of the subject's last dose of MRZ or 6 months of the subject's last dose of BEV are considered immediately reportable events. Study treatment is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, spontaneous abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

10.4.2. Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking study treatment should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately.

10.5. Reporting of Serious Adverse Events

Any AE that meets any serious criterion requires reporting as an SAE within 24 hours of the Investigator's knowledge of the event. This instruction pertains to initial SAE reports as well as any follow-up reports.

This requirement applies to all SAEs (regardless of relationship to IP) that occur during the study (from the time the subject signs informed consent until 28 days after the last dose of IP) or any SAE made known to the Investigator at any time thereafter that are suspected of being related to IP. Serious adverse events occurring prior to treatment (after signing the ICF) are to be recorded within the CRF, but do not require reporting to Celgene Drug Safety.

Where required by local legislation, the Investigator is responsible for informing the Institutional Review Board/Ethics Committee (IRB/EC) of the SAE and providing them with all relevant initial and follow-up information about the event. The Investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

The SAE is reported directly to Celgene Drug Safety by facsimile, or other appropriate method using the SAE Report Form or approved equivalent form. The SAE report should provide a detailed description of the SAE and include a concise summary of hospital records and other relevant documents. If a subject died and an autopsy has been performed, results of the autopsy report and/or death certificate are to be reported to Celgene Drug Safety as soon as these become available. Any follow-up data, including responses to safety queries, should be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Celgene Drug Safety. Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via

facsimile or electronic mail. Urgent queries (eg, missing causality assessment) may be handled by phone.

10.5.1. Safety Queries

Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than five (5) business days. Urgent queries (eg, missing causality assessment) may be handled by phone.

10.6. Expedited Reporting of Adverse Events

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to MRZ based on the Investigator Brochure and BEV based on the local prescribing information.

In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

Celgene Drug Safety or its authorized representative shall notify the Investigator of the following information:

- Any AE suspected of being related to the use of IP in this study or in other studies that is both serious and unexpected (ie, SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Where required by local legislation, the Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all pertinent safety information on file including correspondence with Triphase/Celgene Drug Safety and the IRB/EC. (See Section 14.3 for record retention information).

Drug Safety Contact Information:

For Celgene Drug Safety contact information, please refer to the Serious Adverse Event Report Form Completion Guidelines or to the Pregnancy Report Form Completion Guidelines.

11. DISCONTINUATIONS

The following events are considered sufficient reasons for discontinuing a subject from the investigational product and/or from the study:

- Protocol Violation
- Non-Compliance
- Adverse Event
- Subject Developed a DLT
- Subject Decision
- Withdrew Consent
- Investigator Decision
- Disease Progression
- Pregnancy
- Death
- Other

The reason for discontinuation should be recorded in the CRF and in the source documents.

The decision to discontinue a subject remains the responsibility of the treating physician, which will not be delayed or refused by the Sponsor. However, prior to discontinuing a subject, the Investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

12. EMERGENCY PROCEDURES

12.1. Emergency Contact

In emergency situations, the Investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

12.2. Emergency Identification of Investigational Products

This is an open-label study; therefore, this section is not applicable.

13. REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Sponsor, its authorized representative, and Investigator abide by Good Clinical Practice (GCP), as described in International Conference on Harmonization (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

13.2. Investigator Responsibilities

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. Celgene staff or an authorized representative will evaluate and approve all Investigators who in turn will select their staff.

The Investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions. The Investigator should maintain a list of Sub-Investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The Investigator is responsible for keeping a record of all subjects who sign an informed consent document and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of CRFs and queries.

The information contained in the protocol and amendments (with the exception of the information provided by Celgene on public registry websites) is considered Celgene confidential information. Only information that is previously disclosed by Celgene on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Trial Agreement. Celgene protocol, amendment and IB information is not to be made publicly available (for example on the Investigator's or their institution's website) without express written approval from Celgene. Information proposed for posting on the Investigator's or their institution's website must be submitted to Celgene for review and approval, providing at least 5 business days for review.

At the time results of this study are made available to the public, Celgene will provide Investigators with a summary of the results that is written for the lay person. The Investigator is responsible for sharing these results with the subject and/or their caregiver as agreed by the subject.

13.3. Protocol Amendments

Any amendment to this protocol must be approved by the Sponsor and submitted to appropriate Regulatory Authority by the Sponsor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the Investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

13.4. Subject Information and Informed Consent

The Investigator must obtain informed consent of a subject and/or a subject's legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original informed consent document signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the Investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the informed consent document must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the informed consent document. The revised informed consent document signed and dated by the study subject and by the person consenting the study subject must be maintained in the Investigator's study files and a copy given to the study subject.

13.5. Confidentiality

Celgene and its authorized representatives affirm the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Celgene requires the Investigator to permit Celgene and its authorized representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's signed informed consent document, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

13.6. Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, informed consent document, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

Study treatment can only be supplied to an Investigator by Celgene and/or Triphase or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by Celgene and/or Triphase or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should also be revised.

The Investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating Investigator and the IRB/EC. This statement also applies to any communication between the Investigator (or Coordinating Investigator, if applicable) and regulatory authorities.

Any advertisements used to recruit subjects for the study must be reviewed by Celgene and/or Triphase and the IRB/EC prior to use.

13.7. Ongoing Information for Institutional Review Board / Ethics Committee

If required by legislation or the IRB/EC, the Investigator must submit to the IRB/EC:

- Information on serious or unexpected adverse events as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

13.8. Termination of the Study

The Sponsor reserves the right to terminate this study at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities, etc.).

In addition, the Investigator or the Sponsor has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;

- Failure to adhere to the study protocol.

14. DATA HANDLING AND RECORDKEEPING

14.1. Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of CRFs or CD-ROM.

14.2. Data Management

Data will be collected via CRF and entered into the clinical database per Triphase SOPs, or if delegated to a vendor, according to the vendor's SOPs. This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

14.3. Record Retention

Essential documents must be retained by the Investigator for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. The investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed informed consent documents for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the Investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the Investigator, the Sponsor, and their authorized representative(s);
- List of Sub-Investigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);

- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The Investigator must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The Investigator must obtain approval in writing from Celgene prior to destruction of any records. If the Investigator is unable to meet this obligation, the Investigator must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator/Institution should take measures to prevent accidental or premature destruction of these documents.

15. QUALITY CONTROL AND QUALITY ASSURANCE

All aspects of the study will be carefully monitored by Triphase or its authorized representative for compliance with applicable government regulations with respect to current GCP and standard operating procedures.

15.1. Study Monitoring and Source Data Verification

Triphase ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an Investigator meeting. Prior to enrolling subjects into the study, a Triphase representative will review the protocol, CRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the Investigator. Monitoring will include on-site visits with the Investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. During monitoring visits, the facilities, investigational product storage area, CRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Triphase representative in accordance with the Study Monitoring Plan.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the CRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the Investigator and/or his/her staff. Any necessary corrections will be made directly to the CRFs or via queries by the Investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

15.2. Audits and Inspections

The Investigator is required to permit direct access to the facilities where the study took place, source documents, CRFs, and applicable supporting records of study subject participation for audits and inspections by IRB/IECs, regulatory authorities (eg, FDA, EMA, Health Canada) and company authorized representatives. The Investigator should make every effort to be available for the audits and/or inspections. If the Investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene and/or Triphase immediately.

A Product Quality Complaint (PQC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, purity, or performance of any drug product manufactured by or on behalf of Celgene Corporation after it is released for distribution. PQCs may reduce the usability of the product for its intended function or affect performance of the product and therefore pose a significant risk to the subject. Examples of PQCs include (but are not limited to): mixed product, mislabeling, lack of effect, seal/packaging breach, product missing/short/overage, contamination, suspected falsified, tampered, diverted or stolen material, and general product/packaging damage. If you become aware of a suspected PQC, you are obligated to report the issue immediately. You can do so by emailing customercomplaints@celgene.com or by contacting the Celgene Customer Care Center (1-888-423-5436).

16. PUBLICATIONS

The results of this study may be published in a medical publication, journal, or may be used for teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations. Selection of first authorship will be based on several considerations, including, but not limited to study participation, contribution to the protocol development, analysis and input into the manuscript, related abstracts, and presentations in a study. Individual Investigators or a subset of Investigators may not publish their experience until a report of the total experience by all Investigators has been published.

As described in Section 13.2, all protocol- and amendment-related information, with the exception of the information provided by Celgene on public registry websites, is considered Celgene confidential information and is not to be used in any publications. Celgene protocol-related information proposed for use in a publication must be submitted to Celgene for review and approval, and should not be utilized in a publication without express written approval from Celgene, or as described in the Clinical Trial Agreement.

Celgene will ensure Celgene-sponsored studies are considered for publication in the scientific literature in a peer-reviewed journal, irrespective of the results. At a minimum, this applies to results from all Phase 3 clinical studies, and any other study results of significant medical importance. This also includes results relating to investigational medicines whose development programs have been discontinued.

Study results may also be presented at one or more medical congresses, and may be used for scientific exchange and teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations.

Eligibility for external authorship, as well as selection of first authorship, will be based on several considerations, including, but not limited to, contribution to protocol development, study recruitment, data quality, participation in data analysis, participation in study steering committee (when applicable) and contribution to abstract, presentation and/or publication development

17. REFERENCES

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18. APPENDICES

APPENDIX A. KARNOFSKY PERFORMANCE STATUS SCALE

Activity Level	Score
Normal, no complaints	100
Able to carry on normal activity; minor signs or symptoms of disease	90
Normal activity with effort	80
Unable to carry on normal activity or perform active work; cares for self	70
Requires occasional assistance but is able to care for most own needs	60
Requires considerable assistance and frequent medical care	50
Disabled; requires special medical care and assistance	40
Severely disabled; hospitalization indicated although death not imminent	30
Very sick; hospitalized and requires active supportive care.	20
Moribund; fatal processes progressing rapidly	10
Dead	0

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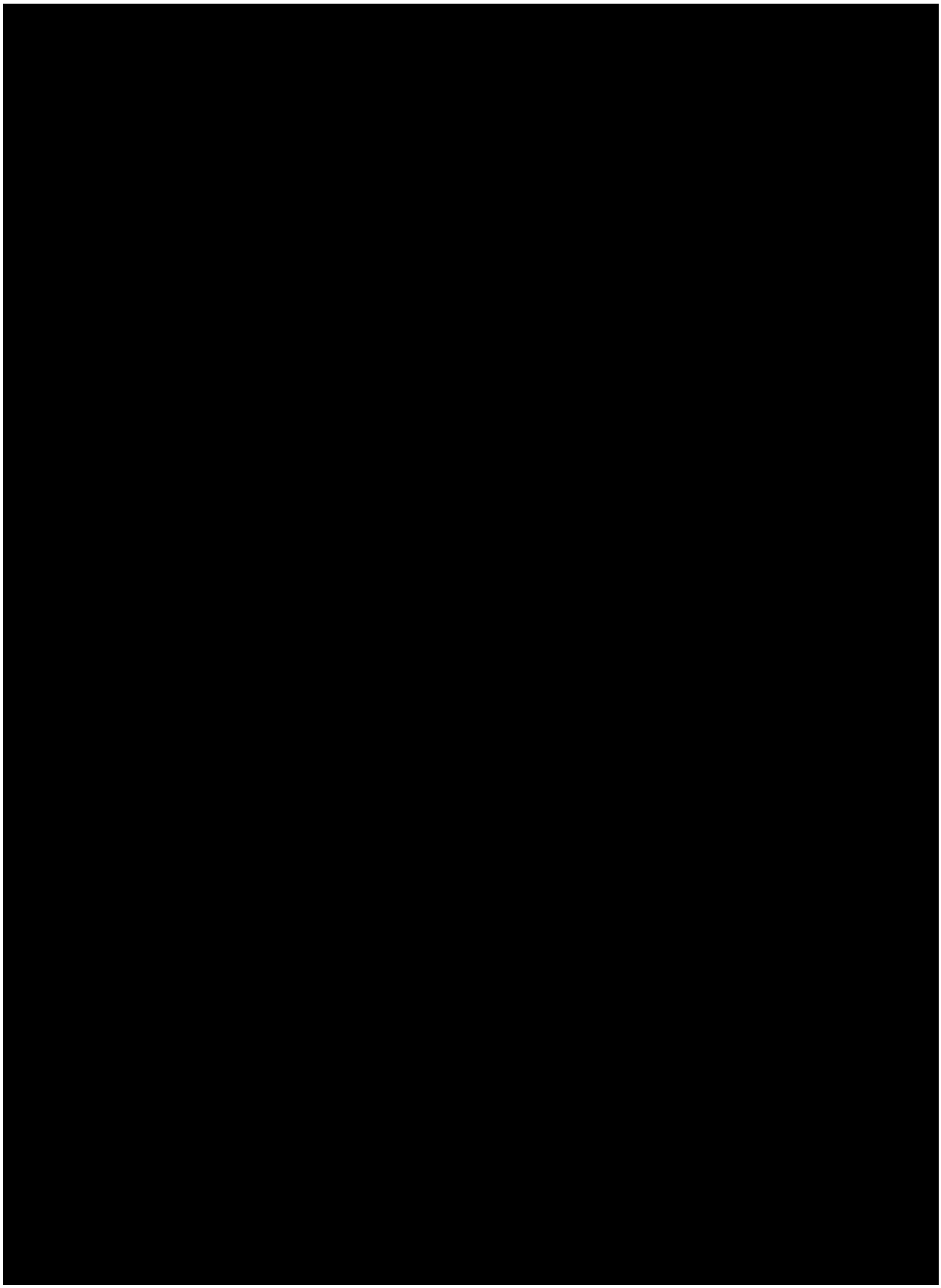
Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: reliability, validity, and guidelines. J Clin Oncol Mar;2(3):187-93, 1984.



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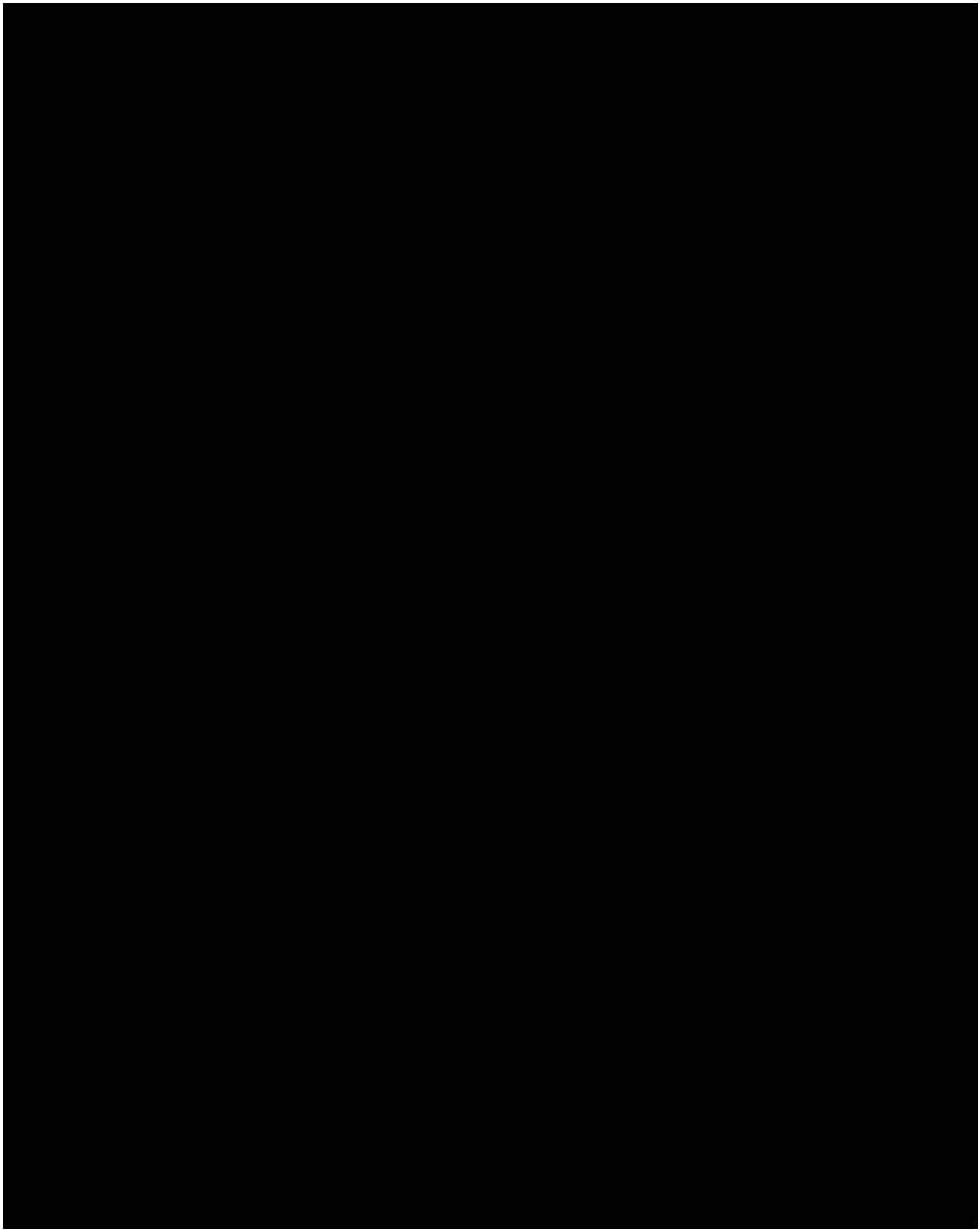

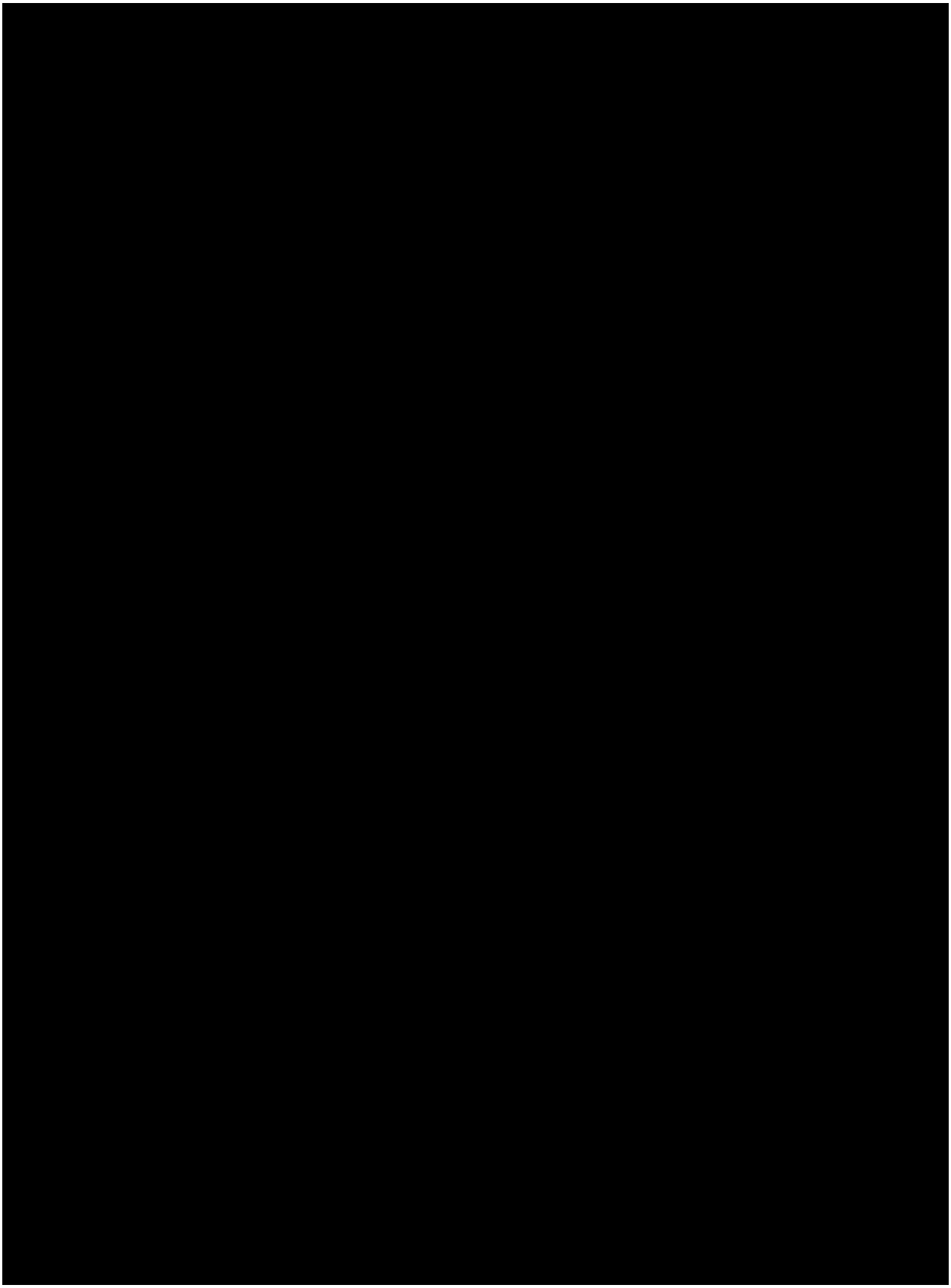

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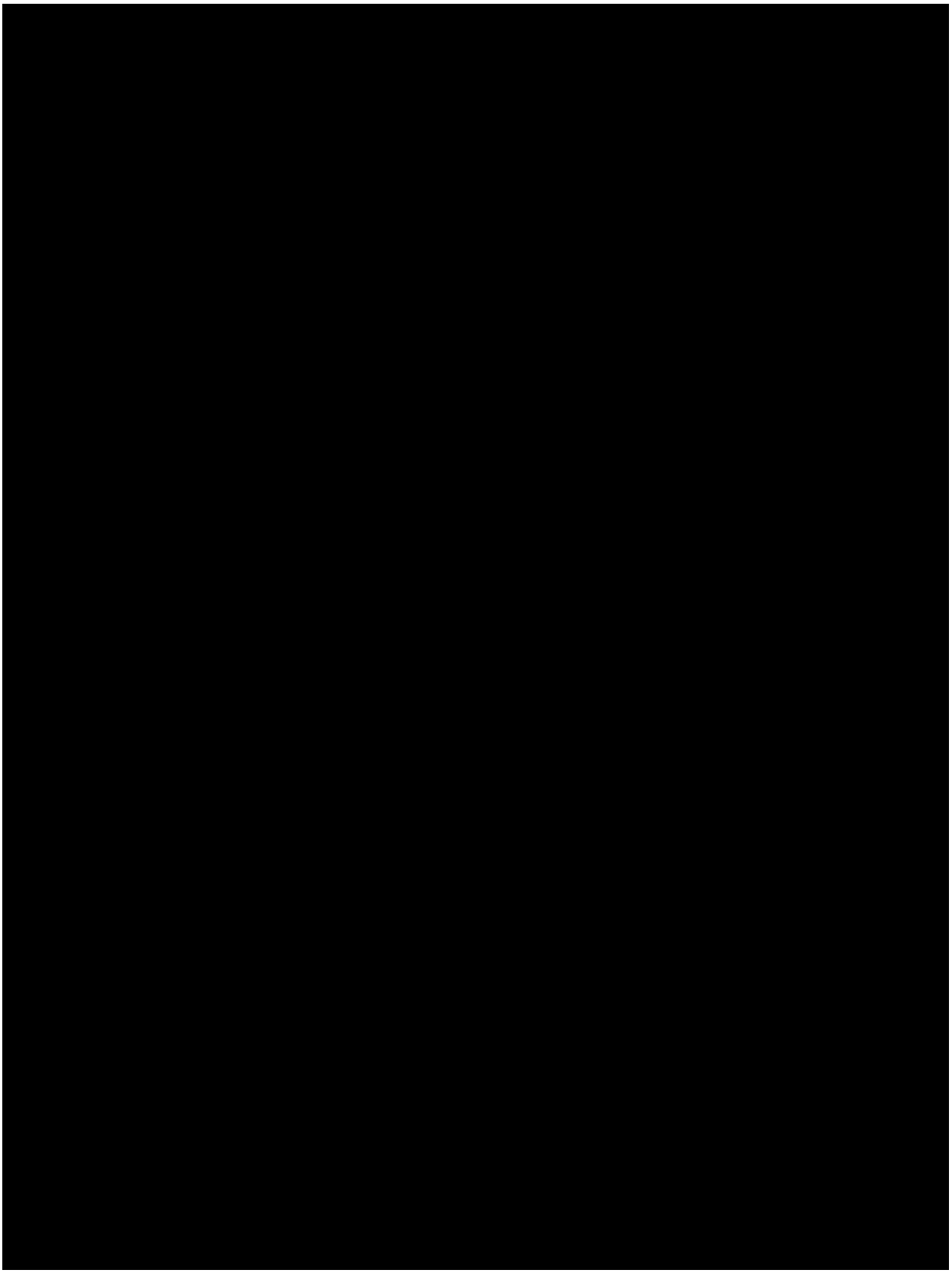

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Celgene Signing Page

This is a representation of an electronic record that was signed electronically in Livelink. This page is the manifestation of the electronic signature(s) used in compliance with the organizations electronic signature policies and procedures.

UserName: [redacted]
Title: [redacted]
Date: Friday, 20 March 2020, 09:40 AM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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Celgene Signing Page

This is a representation of an electronic record that was signed electronically in Livelink. This page is the manifestation of the electronic signature(s) used in compliance with the organizations electronic signature policies and procedures.

UserName: [redacted]
Title: [redacted]
Date: Wednesday, 01 April 2020, 12:47 PM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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1. JUSTIFICATION FOR AMENDMENT

The purpose of this amendment is to include Part 5 (Phase 1) further characterizing pharmacokinetics (PK) in correlation with time-matched electrocardiogram (ECG) to further evaluate the cardiovascular safety of intravenous (IV) Marizomib administered at 0.8 mg/m^2.

In the Part 5 (Phase 1) portion of the study, full PK sampling will be done on Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 1 Day 15, with blood samples collected pre-dose, immediately prior to the end of infusion (EOI), and then 2, 5, 15, 20, 30, 45, and 60 minutes post-EOI. ECGs will be continuously collected via Holter monitor throughout the Cycle 1 Day 1 visit for correlation with PK.

Changes directly associated with the addition of Part 5 (Phase 1) are as follows:

[redacted]

Objectives

Primary and Secondary Objectives were added for Part 5 (Phase 1).

Revised sections include the protocol Synopsis and Sections 2.1 and 2.2

Study Endpoints

Primary Endpoint and Secondary Endpoints including pharmacokinetics and ECG were added for Part 5 (Phase 1). Revised sections include the protocol Synopsis and Sections 3.1 and 3.2.

Study Design

Study Design was updated to include Part 5 (Phase 1).

Revised sections include the protocol Synopsis and Sections 4.1 [redacted].

Table of Events

A new Table of Events was created for Part 5 labeled Table 3: Schedule of Assessments and Procedures, Part 5 Phase 1: All Cycles; all subsequent table numbering was updated as appropriate.

Procedures

Study procedures were clarified and added for Part 5 (Phase 1).

Revised sections include protocol Synopsis, Table 3, protocol Sections 5, 5.3, 5.7, [redacted].

Number of Subjects and Sites (Study Population)

Number of subjects were updated in accordance with Part 5 (Phase 1).

Revised sections include the protocol Synopsis and Sections 6.1 and 9.3.

Inclusion Criteria

Clarification of the patient population specific to Part 5 (Phase 1) were made in Sections 6.1 and 6.2.

Exclusion Criteria

Clarification of the patient population specific to Part 5 (Phase 1) were made in Section 6.3.

Treatment Administration and Schedule

Study Treatment Administration and Schedule were updated to include Part 5 (Phase 1).

Revised sections include protocol Synopsis and Sections 7.2.2 and 7.2.6.

Dose Schedules

Part 5 (Phase 1) dose schedule was included in Section 7.2.6.1.

Revised sections include the protocol Synopsis and Section 7.2.6.1 and Table 7.

The volume of MRZ administration formula was corrected to Volume = Dose (mg) * BSA (m^2) / 0.2 (conc. of MRZ in solution in mg/mL) throughout the protocol.

Dose Limiting Toxicity

Clarified that Part 5 (Phase 1) will not be evaluated for DLT.

Revised Section 7.2.7.

Method of Treatment Assignment

Method of Treatment Assignment was updated to include Part 5 (Phase 1) will be IV only.

Revised sections include Section 7.3.

Statistical Analysis

Statistical Analysis was updated for Part 5 (Phase 1).

Revised sections include the protocol Synopsis and Sections 9.1, 9.3, 9.8, and 9.10.

Overview of Assessments

Assessments were described for Part 5 (Phase 1) in the protocol Synopsis.

This amendment also includes other clarifications and minor corrections unrelated to the addition of Part 5 (Phase 1):

- Medical Monitor / Emergency Contact Information was updated to reflect the address of the Medical Monitor.
- Clinical Experience Section 1.4.4 was updated to reflect the most recent information from previous and ongoing studies with MRZ; Table 3 in Amendment 4 was removed.
- Reporting of Serious Adverse Events Section 10.5 was updated with the most recent Celgene standard language.
- Section 9.3 Sample Size. Part 2 Phase 2, second paragraph edited to include the following for clarity.

Assuming the effect size of interest is at least 20%, a sample size of 30 subjects for Phase 2 will have 80% power to reject the null hypothesis of H0: response rate is ≤ 5% in favor of the alternative hypothesis (H1) that the effective size is > 5% with a 0.050 two-sided significance level.

- Previous recommendations for hydration in earlier Parts of the study are no longer required; hydration recommendations were not included with Part 5 Phase 1.
- Clarified throughout protocol, where appropriate, Part 5 Phase 1 will not collect [redacted] GBM tumor tissue, and blood for pharmacodynamics (PD) and proteasome activity.
- Typos and punctuation were corrected throughout the document as appropriate.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

Addition of Part 4 (Phase 1) Dose-Escalation Study of Enterally-Administered Marizomib With Bevacizumab

A Part 4 (Phase 1) portion of the study (added with Amendment 4) is to determine the safety profile of dose-escalated enterally-administered marizomib (MRZ) with bevacizumab. In order to administer MRZ in a manner consistent with that used in the nonclinical safety assessment, MRZ will be reconstituted in the intravenous (IV) formulation and administered via naso gastric (NG) tube. The safety and tolerability information collected in this study, combined with pharmacodynamic assessments, will inform further development of a pharmaceutically appropriate oral dosage form (eg, capsule or tablet).

Changes directly associated with the addition of Part 4 (Phase 1) are as follows:

Study Title

The study title has been updated accordingly throughout the document.

Introduction

A description of previous studies with oral MRZ was added as Section 1.4.3.2.

[redacted]

Objectives

Primary and Secondary Objectives were added for Part 4 (Phase 1) [redacted].

Revised sections include the protocol synopsis and Sections 2.1, 2.2, [redacted]

Study Endpoints

Primary Endpoint and Secondary Endpoints including pharmacokinetics and pharmacodynamics, were added for Part 4 (Phase 1) [redacted]. Revised sections include Sections 3.1, 3.2, [redacted].

Study Design

Study Design was updated to include Part 4 (Phase 1).

Revised sections include the protocol synopsis and Sections 4.1 [redacted].

Procedures

Study procedures were clarified and added for Part 4 (Phase 1).

Revised sections include Sections 5, 5.3, 5.7, and 5.9.

Number of Subjects and Sites (Study Population)

Number of Subjects were updated in accordance with Part 4 (Phase 1).

Revised sections include the protocol synopsis and Sections 6.1 and 9.3.

Inclusion Criteria

Clarification of the patient population specific to Part 4 (Phase 1) were made in Section 6.2.

Exclusion Criteria

Clarification of the patient population specific to Part 4 (Phase 1), along with the addition of two Exclusion Criteria, were made in Section 6.3.

Revised sections include the protocol synopsis (Study Population) and Section 6.3.

Treatment Administration and Schedule

Study Treatment Administration and Schedule were updated to include Part 4 (Phase 1).

Revised sections include protocol synopsis, Sections 7.2.2 and 7.2.5, and the addition of Table 8.

Investigational Product/Background Therapy/Route/Regimen

A description of the Part 4 (Phase 1) investigational products was added.

Revised sections include the protocol synopsis and Section 7.2.5.

Dose Limiting Toxicity

Dose Limiting Toxicity was expanded to include Part 4 (Phase 1).

Revised sections include the protocol synopsis and Section 7.2.7.

Dose Escalation and Expansion

The Dose Escalation, Expansion, and DLT description for Part 4 (Phase 1) was added.

Revised sections include the protocol synopsis, Section 7.2.8, and the addition of Table S-2 and Table 8.

Method of Treatment Assignment

Method of Treatment Assignment was updated to include Part 4 (Phase 1).

Revised sections include Section 7.3.

Statistical Analysis

Statistical Analysis was updated for Part 4 (Phase 1).

Revised sections include the protocol synopsis and Sections 9.1, 9.3, 9.8, 9.9 and 9.10.

Schedule of Assessments

A separate Schedule of Assessments was added for Part 4 (Phase 1).

Revised section includes Table 2.

Overview of Assessments

Assessments were described for Part 4 (Phase 1) in the protocol synopsis.

This amendment also includes several other clarifications and minor corrections unrelated to the addition of Part 4 (Phase 1):

- Marizomib compound identification NPI-0052 has been changed to NPI-0052/CC-92763 to include Celgene nomenclature.
- On November 17, 2016, Triphase Research and Development I Corporation and marizomib were acquired by Celgene Corporation. Effective March 30, 2018, Celgene International II, Sàrl (CIS II), a wholly-owned subsidiary of Celgene Corporation, became the sponsor for all clinical trials for which Triphase was previously named sponsor. Sponsor Name/Address and Header has been updated from Triphase Research and Development I Corporation to Celgene International II Sàrl to reflect the change in Sponsor. Throughout Protocol Amendment 4 and associated documents, Celgene has been listed as the sponsor where appropriate, and continued responsibilities specific to Triphase are noted as such.
- Medical Monitor/Emergency Contact Information has been updated.
- Triphase Officer Signature Page has been replaced with Celgene Therapeutic Area Head Signature Page and updated.
- The collection of Vital Signs was clarified in Schedule of Assessments and Procedures table. Revised footnote in Table 1.
- Clinical Experience Section 1.4.4 was updated to reflect the most recent information from ongoing studies MRZ-108 and MRZ-112.
- Pharmacokinetics Section 1.4.6 was updated to include additional information from the ongoing study MRZ-112.
- Based on the data generated in MRZ-108 and MRZ-112, revised MRZ dose modification guidelines have been developed that consider the adverse event, duration and potential impact on patient's daily routine. Table 5 has been replaced with the revised guidance for Marizomib Dose Modifications as per memo dated 21 December 2017 sent to all Investigators for MRZ-108 and MRZ-112.
- The reporting of Serious Adverse Events has been assumed by Celgene Corporation as of 30MAR2018 and is described in Sections 10.1, 10.4.1, 10.5, 10.5.1, and 10.6.
- References were updated to include recent prescribing information for bevacizumab and three additional toxicology studies.
- This Summary of Changes document focuses on changes to scientific content or study design. Unless incidentally shown or otherwise specified, administrative changes (ie, formatting, spelling, punctuation corrections, hyphenations, or the spelling out of numbers or symbols or abbreviations for clarity) will not be individually identified with a rationale.

AMENDMENT SUMMARY

Protocol MRZ-108 Amendment 3

1. AMENDMENT RATIONALE AND DESCRIPTION

Summary

In Amendment 3, all subjects will receive IV MRZ infusion followed by IV BEV infusion. MRZ will be administered as a 10-minute, IV infusion on Days 1, 8, and 15 of every 28-day cycle using intra-patient dose escalation. Starting dose will be 0.8 mg/m^2 (RP2D dose). If the starting dose is tolerated and no Dose Limiting Adverse Event (DLAE) is observed, the dose will be increased to 1.0 mg/m^2 after1 cycle. If the increased dose is tolerated again and no DLAE is observed, the dose of MRZ will be increased to 1.2 mg/m^2 after 1 more cycle. Dose reductions will be applied as necessary and according to the toxicities noted. DLAEs are defined as MRZ related AEs observed which are: 1) related to disturbances in the cerebellum (i.e. ataxia, dizziness, dysarthria, fall, gait disturbances) plus hallucinations of any grade. 2) Any other AEs of Grade ≥ 2.

If the starting dose of 0.8mg/m^2 is not tolerated (after appropriate medical treatment of adverse events, if applicable), the dose will be decreased to 0.7 mg/m^2. A further reduction to 0.55 mg/m^2 is allowed, if necessary.

Rationale

Central nervous system (CNS) AEs were noted during the early development of MRZ in subjects with solid tumors, lymphoma, and multiple myeloma. Based on this early data the assumption was made that the drug was blood-brain barrier penetrant, and this assumption led to exploring MRZ in G4 MG.

In Part 1 of this study, conducted under Amendment 1 (note: original protocol was not implemented), the combination of MRZ and a fixed dose of BEV was studied in a Phase 1 study; the maximum dose level for MRZ to be studied was set at 0.8 mg/m^2 because of the CNS AEs observed in the early studies. The RP2D of MRZ was determined to be 0.8 mg/m^2 with BEV, however a MTD for MRZ + BEV (as defined in the protocol) was not determined.

In Part 2 of this study (Amendment 2) MRZ was studied as a single agent in the same subject population in order to explore whether MRZ has activity as a single agent in relapsed or recurrent G4 MG. A Phase 2, 2-stage design was used to assess the activity of MRZ as a single agent. The preliminary results of the Phase 2 portion (Part 2) of the study, determined that single agent MRZ at a starting dose of 0.8 mg/m^2 is active with 1 partial response documented in 15 subjects the first stage of the 2-stage design. The second stage is ongoing/recruiting at present, for a total of 30 subjects.

Analysis of safety and efficacy data from the MRZ + BEV combination (Part 1 of this protocol) suggests that subjects experiencing certain AEs associated with the central nervous system (CNS) have a better outcome in terms of ORR, PFS, and OS than subjects not experiencing any of these CNS AEs. The assumption and justification for adding Part 3 to this protocol is that these CNS AEs are indicative of higher MRZ concentrations in the brain leading to both toxicity

and efficacy. It seems reasonable that CNS AEs may be a marker for higher drug concentrations in the brain.

On 4 January 2017, an analysis of data from all 36 subjects enrolled in Part 1 with a median follow up of 9.2 months for surviving subjects was performed. Interestingly, when a group of 6 AEs related to disturbances in the cerebellum (plus hallucinations), were combined (i.e. ataxia, dizziness, dysarthria, fall, gait disturbances and hallucinations) and related to efficacy parameters, an apparent difference was observed between the 23 subjects with any of these AEs of any grade during treatment as compared to the 13 subjects without occurrence of any of these AEs at any time; the median PFS was 5.5 months as compared to 2.8 months, and the median OS was 10.4 months as compared to 6.3 months respectively.

When further analyzing this group of 6 AEs, it was the case that 19/23 (83%) of subjects experienced one of more of these AEs during Cycle 1 or Cycle 2, and 15/23 subjects (65%) experienced one or more of these AEs during the first cycle of MRZ + BEV treatment. These AEs were generally reversible with treatment delay and/or dose reduction.

This analysis of a fairly mature dataset from all subjects included in Part 1 of this study generated the hypothesis that subjects with certain CNS events do better than those without, which suggests that those with the highest MRZ levels in the brain, as suggested by these AEs, do better than those without these events, which suggests lower brain levels of MRZ. This portion of the study (Part 3) presented in Amendment 3 is designed to deliver to each subject a high dose of MRZ as long as they can tolerate it and to get point estimates for efficacy parameters including ORR, PFS, and OS. For the same reason that the Part 2 Phase 2 was added to this study rather than as a separate protocol (namely, to keep the population homogenous), the results from subjects in this Part 3 can be compared to those in Part 1.

Revisions are shown in detail in the sections that follow. Significant changes introduced with Amendment 3 are as follows:

1. The title page, headers and footers were revised to reflect the addition of this Amendment.
2. **Table 1 Schedule of Assessments and Procedures,** updated to reflect increased Screening and Baseline window, removal of Cycle 1 ECGs, allowance for PT/PTT and Urinalysis to be collected up to 7 days prior to Cycle 1 Day1, clarification of when vital signs should be taken on Day 8 of each cycle, and removal of hydration.
3. **Section 1.4.4 Clinical Experience** updated with more recent safety information.
4. **Section 1.4.5 Pharmacodynamics** updated to include more recent PD findings.
5. **Section 1.4.6 Pharmacokinetics** updated to include more recent PK findings.

[redacted]

7. **Section 2.1 Primary Objective** was added to describe the primary objective in Part 3 Phase 2
8. **Section 2.2 Secondary Objective** was added to describe the secondary objective in Part 3 Phase 2
9. **Section 3.2 Secondary Endpoint(s)** was added to describe the secondary endpoints of Part 3 Phase 2

10. **Section 4.1 Study Design** describes the intra-patient dose escalation of MRZ and Dose Limiting Adverse Events (DLAEs)

[redacted]

12. **Section 5.1 Screening,** updated to allow for a +3 day window due to scheduling conflicts
13. **Section 5.2 Baseline** update to allow +2 day window for scheduling conflicts
14. **Section 5.3 Treatment** updated to allow for continued treatment if the investigator believes the patient has pseudoprogression.
15. **Section 5.4 End of Treatment Visit** updated EOT timeframe.
16. **Section 5.6 Activity Assessments** updated to reflect changes made in Amendment 3.
17. **Section 6.1 Number of Subjects and Sites** updated to reflect an additional 40 subjects for Part 3 Phase 2.
18. **Section 6.2 Inclusion Criteria**
    a. **#3** revised wording that all enrolling patients must have measurable lesions per RANO criteria,
    b. **#8** revised to clarify time from end of radiotherapy and time between MRIs confirming progression
    c. **#13** added that contraceptive measures are to be continued for 6 months after the last dose of BEV or 3 months after the last dose of MRZ, whichever is longer
19. **Section 6.3 Exclusion Criteria** revised to reflect clinically insignificant deviations from these criteria are acceptable if approved by the Sponsor's Medical Monitor.
20. **Section 7.2.4 Administration of MRZ in Part 3 Phase 2** added to describe intra-patient dose escalation in Amendment 3.
21. **Section 7.2.5 Dose Schedules** revised to reflect MRZ and BEV dosing schedules in Part 3 Phase 2, **Table 5** added to define dose modification guidelines in Part 3.
22. **Section 7.3 Method of Treatment Assignment,** updated to include Amendment 3
23. **Section 8.1 Permitted Concomitant Medications and Procedures,** updated to include the treatment of hallucinations.
24. **Section 9.1 Statistical Analysis Overview, Part 3 Phase 2** was added to reflect the samples size of 40 subjects for OS
25. **Section 9.3 Sample Size** was added to describe the significance of 40 subjects.
26. **Section 9.7 Safety Analysis** updated to add Amendment 3.
27. **Section 9.10 Interim Analysis Phase 2** updated to reflect that Part 3 Phase 2 will be implemented.
28. **Section 17 References** updated Avastin Prescribing Information date, added Levin 2016 and Teicher 2015.

AMENDMENT SUMMARY

Protocol MRZ-108 Amendment 2

1. AMENDMENT RATIONALE AND DESCRIPTION

Amendment 2 was to amend the study to a Phase 1/2 study and add up to 30 response-evaluable patients. During the Phase 1 dose-escalation portion of the study, responses to treatment were demonstrated. These responses justify the expansion cohort within the Phase 1 portion of the study to obtain a preliminary estimate of the response rate to the combination of MRZ and BEV. However, it will take a larger randomized study to determine if the combination of MRZ and BEV has greater activity than BEV alone. Prior to undertaking such a trial, it would be important to determine if MRZ as a single agent has activity in relapsed or recurrent Grade 4 malignant glioma (G4 MG). A small Phase 2 study, at the dose and schedule of MRZ determined in Phase 1, is warranted to assess the activity of MRZ as a single agent. The results of the Phase 2 will help determine if it is worthwhile developing MRZ as a single agent or in combination with BEV in relapsed or recurrent G4 MG.

Because the dose level of 0.8 mg/m^2 was tolerated in the Phase 1, dose escalation portion of the study where MRZ was combined with BEV, it is expected that the single agent will also be tolerated at this dose. Because this and other MRZ trials do not suggest renal damage as a direct result of MRZ, the IV hydration will be shortened to 250 mL infused over 30 minutes prior to MRZ dosing in the Phase 2 portion. Renal function will continue to be monitored and, if necessary, hydration can be increased in specific patients at the discretion of the investigator.

Revisions are shown in detail in the sections that follow. Significant changes introduced with Amendment 2 are as follows:

1. The title was changed accordingly to include the Phase 2 portion of the trial: Phase 1, Multicenter, Open-Label, Dose-Escalation, Combination Study of Marizomib and Bevacizumab in Bevacizumab-Naïve Subjects with WHO Grade IV Malignant Glioma **followed by a Phase 2 Trial of Single Agent Marizomib**.
2. Avastin® (bevacizumab, BEV) prescribing information updated to reflect most recent December 2015 update.
3. **Section 1.4.4 Clinical Experience** updated to reflect preliminary response data in the Dose Escalation portion of this study.

[redacted]

5. **Section 2 Study Objectives** and **Section 3 Endpoints** updated to include the Phase 2 portion of the study.
6. **Section 4 Overall Study Design** updated to include the Phase 2 portion of the study. The study is a modified 2-stage design (Green 1992). Standard evaluations for safety and activity are employed. Fifteen response-evaluable patients will be entered in the first stage. If no objective responses are observed, the trial will be terminated. If 1 or more responses are observed, then the second stage will be implemented with an additional

15 response-evaluable patients treated. If at least 5 responses are observed, MRZ will be considered active as a single agent.

8. **Section 6.2 Inclusion Criteria** was updated for the Phase 2 portion of the study. Subjects with a history of seizures must be on a stable dose of anti-epileptic drugs (AEDs) and without seizures for 14 days prior to enrollment in patients enrolled prior to Amendment 2. Subjects enrolled after Amendment 2 is approved with a history of seizures must be on a stable dose of anti-epileptic drugs (AEDs) for 7 days prior to enrollment.
9. **Section 6.3 Exclusion Criteria** was updated for the Phase 2 portion of the study. Evidence of CNS hemorrhage on baseline MRI or CT scan (except for post-surgical, asymptomatic Grade 1 hemorrhage that has been stable for at least 3 months for subjects enrolled prior to Amendment 2 and for at least 4 weeks in subjects enrolled after Amendment 2 is approved). BEV-Specific Exclusion Criteria only applies to patients dosed with BEV as in the Phase 1 portion of the study.
10. **Section 7.2.4 Dose Schedule** updated to include Phase 2 portion of the study. MRZ (0.8 mg/m^2) will be administered as a 10-minute IV infusion on Days 1, 8, and 15 of every 28-day cycle. Infusion durations may be lengthened to ameliorate toxicity for individual subjects with agreement between the Investigator and the Sponsor.
11. **Section 9.1 Statistical Analysis Overview** updated to include the Phase 2 portion of the study. Patients enrolled in the Phase 2 portion of the protocol will receive 0.8 mg/m^2 MRZ IV on Days 1, 8, and 15 of 28-day cycles. A minimum of 15 response-evaluable patients will be enrolled in Stage 1, and up to 15 additional response-evaluable patients will be enrolled in Stage 2, for a maximum of 30 response-evaluable patients. After the first 15 response-evaluable patients in the first stage have received 2 or more cycles of therapy, available study data will be reviewed by the Phase 2 Review Committee consisting of the Principal Investigators at each study center, the Medical Monitor, and the Sponsor's Chief Medical and Scientific Officers and Study Coordinator. The Phase 2 Review Committee will recommend whether to enroll the second stage based on an assessment of both safety and efficacy. If there are no safety concerns and clinical benefit is demonstrated with evidence of disease response, defined as at least one

response (partial response (PR) or better) as determined by RANO criteria, in 15 response-evaluable patients, then 15 additional response-evaluable patients will be enrolled in Phase 2. Otherwise, there will be no further enrollment into the study.

12. **Section 9.3 Sample Size** updated to include the Phase 2 portion of the study. Fifteen response-evaluable patients will be enrolled in the first stage of a 2-stage design (Green 1992). If there is at least 1 PR or better and there are no safety concerns in the first 15 response-evaluable patients, then the second stage of 15 response-evaluable patients will be opened. If ≥ 5 patients respond by the end of the second accrual stage (n = 30), the conclusion can be drawn that MRZ is promising, unless other considerations indicate otherwise.
13. **Section 9.7 Safety Analysis** updated to include the Phase 2 portion of the study. All subjects will be evaluated for safety analysis if they receive at least one dose of MRZ. The safety data will be presented in individual listings and summary tables, including frequency tables for adverse events and listings of abnormalities for laboratory variables. Results of Phase 1 and Phase 2 portions of the study will not be combined.
14. **Section 9.10 Interim Analysis** updated to include the Phase 2 portion of the study. Response to MRZ will be assessed in the 15 response-evaluable patients in Stage 1 of the 2-stage design. Once at least 1 response (PR or better) has been determined, the second stage will be implemented. If no confirmed, objective responses have been observed after all patients have received at least 2 cycles of therapy, Phase 2 will end without implementing the second stage. If the second stage is implemented, an additional 15 response-evaluable patients will be enrolled.
15. **Section 17 References** updated to reflect changes in the document accordingly.

AMENDMENT SUMMARY

Protocol MRZ-108 Amendment 1

1. AMENDMENT RATIONALE AND DESCRIPTION

[redacted] Revisions are shown in detail in the sections that follow. Significant changes introduced with Amendment 1 are as follows:

1. The frequency and rationale of the Karnofsky Performance Status was clarified in Table 1, and Section 3.

[redacted]

4. Dexamethasone (DEX) dosing requirement removed from protocol: The use of steroids to ameliorate toxicities of MRZ including nausea and vomiting and some of the central nervous system effects was suggested by an investigator on the multiple myeloma studies. However, no formal analysis of the ability of steroids to counteract these effects was under taken. This requirement has been removed from Table 1. Adverse events requiring treatment will be treated with standard of care procedures and/or medications. Steroids may be used if such standard of care treatments are unsuccessful. Section 8.1 was amended to include the use of antiemetic steroids, such as dexamethasone.
5. Inclusion criteria:
   - The study population was clarified to include subjects with glioblastoma and gliosarcoma.
   - Subjects with a history of seizures must be on a stable dose of anti-epileptic drugs (AEDs) and without seizures for 14 days prior to enrollment.
   - Transfusions and/or growth factor support may not be used in order to meet laboratory inclusion criteria.
   - Alanine transaminase (ALT) ≤ 2.5 ULN was added to the laboratory inclusion criteria.

   Section 6.2 was amended accordingly.

6. Subjects must not drive a vehicle or operate heavy machinery while on this study. Section 7.2.1 was amended accordingly.
7. Dose-limiting toxicity (DLT) was amended to include:
   - ≥ Grade 3 thrombocytopenia or Grade 2 thrombocytopenia with bleeding.
   - Febrile neutropenia.
   - Any ≥ Grade 2 neurological event lasting more than 4 days.

   Section 7.2.3 was amended accordingly.