Title	An Open Label Phase 1b/2 Study of Orally Administered PLX3397 in Combination with Radiation Therapy and Temozolomide in Patients With Newly Diagnosed Glioblastoma
Protocol Number	PLX108-08
IND Number	105,521
Sponsor	Plexxikon Inc. 91 Bolivar Drive Berkeley, CA 94710, USA
Medical Monitor	[redacted] Plexxikon Inc. 91 Bolivar Dr. Berkeley, CA 94710, USA Phone: [redacted] Fax: [redacted]
Date/Version	14 December 2017/Amendment 5

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1.0 SPONSOR SIGNATURE

I have read and approved this protocol.

[redacted]

Medical Monitor/Regional Director Signature

15 DEC 2017

Date of Signature
(DD Mmm YYYY)

[redacted]

Medical Monitor/Regional Director Name
(print)

2.0 INVESTIGATOR SIGNATURE

I have read and approved this protocol. My signature, in conjunction with the signature of the Sponsor, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonisation Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), and the ethical principles that have their origins in the Declaration of Helsinki.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care under applicable regulations.

Investigator Signature

Date of Signature
(DD Mmm YYYY)

Investigator Name and Title (print)

3.0 TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

4.0 CONTACTS

4.1 Emergency Contacts – Medical Monitor:

Name: [redacted]
Address: 91 Bolivar Dr
Berkeley, CA94710
Phone: [redacted]
Fax: [redacted]
Email: [redacted]

4.2 Additional Contacts

Name: [redacted]
Phone: [redacted]
Fax: [redacted]
Email: [redacted]

4.3 SAE Reporting Contact

Report all SAEs, whether related or not to study drug, by completing the SAE eCRF (preferred method). If the electronic data capture (EDC) system is not accessible, fax or email a completed paper SAE form within 24-hours of receiving knowledge of the event to:

SynteractHCR Safety SAE Facsimile
Fax: 760-268-6500
Phone: [redacted]
Email: safetyfax@synteracthcr.com

5.0 LIST OF ABBREVIATIONS

Abbreviation or Term[a]	Definition/Explanation
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
$AUC_{0-\infty}$	Area under the concentration-time curve from time zero extrapolated to infinite time
AUC_{0-6}	Area under the concentration-time curve from time zero to 6 hrs post dosing
AV	Atrioventricular
β-HCG	Beta-human chorionic gonadotropin
BID	Twice daily
BLQ	Below limit of quantification
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca++	Calcium
CBC	Complete blood count
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
Cl-	Chloride
CLcr	Creatinine clearance
C_{max}	Maximum observed concentration
C_{min}	Trough observed concentration
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CSF-1	Colony stimulating factor-1 [also known as macrophage stimulating factor (M-CSF)]
CSF-1R	Colony stimulating factor receptor (also known as Fms)
CTA	Clinical Trial Agreement
CT	Computed tomography
CTCs	Circulating Tumor Cells
CTCAE	Common Toxicity Criteria for Adverse Events
CV	Coefficient of variation
CYP	Cytochrome P450
D/C	Discontinue
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram

Abbreviation or Term[a]	Definition/Explanation
ED_{50}	Effective dose
Eg	Exempli gratia (for example)
ESR	Erythrocyte sedimentation rate
F	Bioavailability
FACS	Fluorescence Activated Cell Sorting
FDA	Food and Drug Administration
GC	Gas chromatography
FDG-PET	Fluorodeoxyglucose (FDG)-positron emission tomography (PET)
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase
GLP	Good laboratory practice
GVHD	Graft vs. host disease
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCO3-	Bicarbonate
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HNSTD	Highest non-severely toxic dose
HPF	High-power field
HPLC	High-performance liquid chromatography
HR	Heart rate
hr	Hour or hours
IC_{50}	Half maximal inhibitory concentration
i.e.	Id est (that is)
IEC	Independent ethics committee
IL-1β	Interleukin-1β
IL-6	Interleukin-6
IL-34	Interleukin-34
INR	International normalized ratio
IRB	Institutional review board
IU	International unit
IV	Intravenous, intravenously
LD_{50}	Median lethal dose
LDH	Lactate dehydrogenase
LC	Liquid chromatography
LLQ	Lower limit of quantitation
Ln	Natural logarithm
MedRA	Medical Dictionary for Drug Regulatory Activities
MIC	Minimum inhibitory concentration
MMP-3	Matrix metallopeptidase-3
MRI	Magnetic resonance imaging

Abbreviation or Term[a]	Definition/Explanation
MRSD	Maximum recommended starting dose
MRT	Mean residence time
MS	Mass spectrometry
MTD	Maximum tolerated dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect-level
PD	Pharmacodynamic(s)
PFS	Progression Free Survival
PK	Pharmacokinetic(s)
PO	Per os (administered by mouth)
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
QC	Quality control
RBC	Red blood cell
RT	Radiation therapy
QD	Once daily
QTc	QT interval corrected
QTcF	QT interval corrected using Fredericia equation
SAE	Serious adverse event
SD	Standard deviation or stable disease
STD	Severely toxic dose
STD_{10}	Severly toxic dose in 10% of animals
$T_{1/2}$	Terminal elimination half-life
T3	Triiodothyronine
T4	Thyroxine
T_{max}	Time of maximum observed concentration
TAMs	Tumor-associated macrophages
TEAE	Treatment-emergent adverse event
TID	Three times daily
TMZ	Temozolomide
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
ULQ	Upper limit of quantitation
UV	Ultraviolet
Vz	Volume of distribution during the terminal phase
Vz/F	Apparent volume of distribution during the terminal phase
Vss	Volume of distribution at steady state
WBC	White blood cell
WOCBP	Women of childbearing potential
WONCBP	Women of nonchildbearing potential

[a] All of these abbreviations may or may not be used in protocol.

6.0 STUDY SYNOPSIS

<table>
<tr><td>Title</td><td>An Open Label Phase 1b/2 Study of Orally Administered PLX3397 in Combination with Radiation Therapy and Temozolomide in Patients With Newly Diagnosed Glioblastoma</td></tr>
<tr><td>Study Objective(s)</td><td>The study objectives are to assess the potential for PLX3397 to improve the efficacy of standard of care radiation therapy (RT) + temozolomide (TMZ) in patients with newly diagnosed glioblastoma (GBM). For Phase 1b dose escalation, the primary objective is identification of the recommended Phase 2 dose (RP2D). For Phase 2, the primary objective is the comparison of median Progression Free Survival (PFS) to a historical control. Secondary objectives include the evaluation of overall survival (OS), pharmacokinetics (PK), correlative imaging studies, safety, and exploratory endpoints of pharmacodynamic (PD) effects of PLX3397.</td></tr>
<tr><td>Study Design</td><td>This will be an open label, uncontrolled Phase 1b/2 trial in patients with newly diagnosed GBM who have recovered from complete or partial surgical resection. All patients will be treated with PLX3397 in addition to standard-of-care combination radiation therapy (RT) plus temozolomide (TMZ) followed by adjuvant TMZ. During Phase 1b dose escalation, two PLX3397 administration schedules, 7 days/week vs. 5 days/week (M-F) will be explored. During Phase 2, patients will be treated with the RP2D.

There are 4 sequential periods: 1-week PLX3397 monotherapy; 6-week PLX3397/RT/TMZ combination therapy; 4-week recovery; and, PLX3397/TMZ adjuvant therapy. PLX3397 will be administered twice daily either 7 days/week or 5 days/week (Monday through Friday) starting 1 week prior to the initiation of RT and will continue twice daily either 7 days/week or 5 days/week (Monday through Friday) during the 6-week course of RT.

Phase 1b PLX3397 dose and schedule cohorts are:
<table>
<tr><th rowspan="2">Cohort</th><th colspan="2">Combination PLX3397/RT/TMZ</th><th colspan="2">Adjuvant PLX3397/TMZ</th></tr>
<tr><th>PLX3397 Dose</th><th>PLX3397 Schedule</th><th>PLX3397 Dose</th><th>PLX3397 Schedule</th></tr>
<tr><td>-2</td><td>600 mg/day</td><td>5 days/week (M-F)[b]</td><td>800 mg/day[b]</td><td>7 days/week</td></tr>
<tr><td>-1</td><td>600 mg/day</td><td>7 days/week[a]</td><td>600 mg/day[a]
800 mg/day[b]</td><td>7 days/week</td></tr>
<tr><td>1</td><td>800 mg/day</td><td>7 days/week[a]
5 days/week (M-F)[b]</td><td>1000 mg/day[b]</td><td>7 days/week</td></tr>
<tr><td>2</td><td>1000 mg/day</td><td>5 days/week (M-F)[b]</td><td>1200 mg/day[b]</td><td>7 days/week</td></tr>
</table>
[a] Amendment 1.
[b] Amendment 2.

For combination PLX3397/RT/TMZ PLX3397 treatment, dose escalation to the next highest cohort may occur after all patients have completed the 11-week DLT-observation period (i.e., 1-week PLX3397 monotherapy; 6-week PLX3397/RT/TMZ combination therapy; 4-week recovery). For adjuvant PLX3397/TMZ PLX3397 treatment, dose escalation to the next highest cohort may occur after all patients have completed an 8-week DLT-observation period (i.e., 2 cycles of adjuvant treatment). For patients participating in Phase 1b, intra and inter patient dose escalation to a higher dose level/schedule will be permitted after that dose level/schedule has been established to be safe.

The RT schedule will be once 5 days/week (Monday through Friday) for 6 weeks (total radiation dose of 60 Gy using either conformal or IMRT planning). Oral temozolomide will be administered once daily (7 days per week) for the duration of RT. Four weeks after the completion of the course of RT, patients will be started on once-daily adjuvant temozolomide (Day 1-5 of a 28 day cycle) for up to 12 cycles as long as there is no disease progression or unacceptable toxicity and PLX3397 twice daily (28 days of a 28 day cycle) for as long as there is no disease progression or unacceptable toxicity. After discontinuation of study drug, patients will continue to be followed for OS every 6 months.</td></tr>
</table>

Number of Patients/Sites	For Phase 1b, 5 cohorts (2 cohorts from Amendment 1 and 3 from Amendment 2) are planned to be enrolled at approximately 7 to 10 sites. Each cohort will consist of approximately 7 patients. Therefore, approximately 35 patients will be enrolled in Phase 1b. Additional patients may be required for replacement patients. Phase 2 will enroll approximately 44 patients.
Study Procedures	After providing informed consent, patients will undergo screening for eligibility to participate in the study. Screening will start within 3 weeks prior to PLX3397 dosing. Following recovery from surgical resection, patients who meet inclusion/exclusion criteria will start study drug on the morning of any Monday through Friday (Cycle 1 Day 1; C1D1). This visit should occur between 3 weeks and 5 weeks after surgery. Patients will continue to dose study drug twice daily either 7 days/week or 5 days/week (Monday through Friday) and return to the clinic for evaluation on C1D8, the day they initiate radiation therapy plus temozolomide. For the Phase 1b portion of the study, a blood sample will be obtained pre-dose on C1D1for the baseline PK. On C1D8 and on C1D15, blood samples will be obtained pre-dose and 1, 2, 4, and 6 hours post-dose to estimate PLX3397 PK. Patients will return to the clinic on Cycle 2 Day 1 (C2D1) for evaluation. If PLX3397 has been well tolerated and there has been no clinical evidence of disease progression, continued dosing will be permitted. Patients will be monitored for response and disease progression with MRI brain scans every 2 cycles, with the brain scan obtained approximately 3-4 weeks after the completion of RT serving as the baseline scan for determination of progression. For Phase 1b PLX3397 dose and schedule cohorts and escalation, see Study Design (above.) For the Phase 2 portion of the study, patients will be treated with PLX3397 at the RP2D level. For both phases, patients will be monitored throughout the study for adverse reactions to the study drug and/or study procedures. Hematology assessments (i.e., CBC, differential count, and platelet count) will be performed weekly starting with C1D1 and continuing through the first week of the Recovery Period (RPD8). Serum chemistry assessments will be performed at Screening, C1D1, C1D15, C2D1, and C2D22 (completion of RT). For the adjuvant treatment period, assessments will be made on the day of treatment initiation (C3D1), C3D22, and D22 of each subsequent cycle, and at study completion or upon early withdrawal. A serum pregnancy test will be completed at Screening for applicable patients. Blood pressure, respiratory rate, pulse rate and temperature will be measured at each study visit. A standard 12-lead electrocardiogram (ECG) will be performed for each patient at Screening, C1D1, C2D1, and study completion. A complete physical examination will be performed for each patient at Screening. A neurological exam and a symptom-directed physical exam will be completed on each subsequent visit while continuing study therapy, and at study completion or upon early withdrawal. Patients will also complete the MD Anderson Symptom Inventory-Brain Tumor Module at the time points noted in the Trial Flow Chart, and Karnofsky performance status will be recorded as noted. A surgical paraffin tumor block (or at least 20 unstained slides) will be identified during Screening for subsequent shipment to the central pathologist. Blood samples for circulating CSF-1, biomarkers of kinase inhibition and myeloid cell recruitment will be obtained pre-dose on C1D1, C1D8, C2D1, and C3D1. CD14/16 mononuclear cell counts will be obtained pre-dose on C1D1 and C1D8. **Commencing on 01 October 2017, patient visits, clinical laboratory testing, and MRI brain scans will be performed approximately every 12 weeks (please refer to the TRIAL FLOW CHART – Phase 2 for details).**

Key Patient Selection Criteria	Inclusion 1. Male or female patients ≥18 years old. 2. Histologically confirmed definitive GBM or gliosarcoma by partial or complete surgical resection (i.e. not by biopsy only) within 5 weeks prior to PLX3397 administration (C1D1). Tumor must have a supratentorial component. For all patients, availability of a surgical paraffin tumor block sufficient to generate at least 20 unstained slides; or, if a paraffin tumor block is unavailable, at least 20 unstained slides. 3. The patient must have recovered from the effects of surgery, post-operative infection, and other complications before study registration. 4. A diagnostic contrast-enhanced MRI or CT scan of the brain must be performed preoperatively and postoperatively prior to the initiation of radiotherapy, within 28 days (preferably 14 days) prior to C1D1. 5. Patients unable to undergo MR imaging because of non-compatible devices can be enrolled, provided pre- and post-operative contrast-enhanced CT scans are obtained and are of sufficient quality. 6. Patients must receive RT at the participating institution. 7. Women of child-bearing potential must have a negative pregnancy test within 14 days of initiation of dosing and must agree to use an acceptable method of birth control while on study drug and for 3 months after the last dose. Women of non-childbearing potential may be included if they are either surgically sterile or have been postmenopausal for ≥1 year. Men of child-bearing potential must also agree to use an acceptable method of birth control while on study drug, and for 3 months after the last dose. 8. Karnofsky performance status of ≥70. 9. Adequate hematologic, hepatic, and renal function (absolute neutrophil count ≥1.5x 10^9/L, Hgb >10 g/dL, platelet count ≥100 x 10^9/L, AST/ALT ≤2.5x ULN, creatinine ≤1.5x ULN). 10. Willing and able to provide written informed consent prior to any study related procedures and to comply with all study requirements. Exclusion 1. Evidence of recurrent GBM or metastases detected outside of the cranial vault. 2. Investigational drug use within 28 days of the first dose of PLX3397 or concurrently. 3. Prior use of Gliadel wafers or any other intratumoral or intracavitary treatment. 4. Prior radiation or chemotherapy for glioblastoma or glioma. 5. Prior chemotherapy or radiosensitizers for cancer of the head and neck (except for T1 glottic cancer) that would result in an overlap of radiation fields. 6. Prior allergic reaction to temozolomide. 7. History of Grade 2 (CTCAE v4) or greater acute intracranial hemorrhage. 8. Active cancer (either concurrent or within the last 3 years) that requires non-surgical therapy (e.g. chemotherapy or radiation therapy), with the exception of surgically treated basal or squamous cell carcinoma of the skin, melanoma in-situ, or carcinoma in-situ of the cervix. 9. Chronic active hepatitis B or C. 10. Refractory nausea and vomiting, malabsorption, biliary shunt, or significant bowel resection that would preclude adequate absorption of study drug. 11. Patients with serious illnesses, uncontrolled infection, medical conditions, or other medical history including abnormal laboratory results, which in the investigator's opinion would be likely to interfere with a patient's participation in the study, or with the interpretation of the results.

	12. Women of child-bearing potential who are pregnant or breast feeding. 13. At Screening QTcF ≥450 msec for males and ≥470 msec for females.
Dosage and Regimen	Study drug will be administered orally using a capsule formulation (200 mg per capsule). The total daily dose of PLX3397 will be divided and administered BID. For an uneven number of capsules, the larger dose will be administered in the morning. For Phase 1b PLX3397 dose and schedule cohorts and escalation, see Study Design (above). The Phase 2 portion of the study will use the RP2D selected from the Phase 1b portion of the study. As a part of standard of care, patients will receive the following: • 60 Gy of radiation therapy Monday-Friday for a total of 30 radiation treatments over approximately 6 weeks. • Temozolomide 75 mg/m^2 PO once daily for approximately 6 weeks beginning the first day of RT until RT end, followed by adjuvant treatment at a dose of 150 mg/m^2 once daily on Days 1-5 of the first 28 day cycle after completion of radiation therapy (start of Cycle 3). The dose can be escalated to 200 mg/m^2 if the non-hematologic toxicity is Grade ≤2 (except for alopecia, nausea, and vomiting), absolute neutrophil count (ANC) is ≥1.5 x 10^9/L, and the platelet count is ≥100 x 10^9/L. • During the 4-week break after the completion of RT, neither temozolamide nor study drug will be administered.
Safety and Tolerability Assessments	Physical examinations, vital signs, 12-lead ECGs, adverse events, hematology, and serum chemistry will be used to assess safety and tolerability. As this is an open label study, ongoing safety will be continuously and rigorously monitored by the Sponsor. Additionally, biweekly teleconferences are planned to review in detail the safety across all study sites. Prior to dose escalation in the Phase 1b portion, safety data will be collated and reviewed by the Sponsor and study sites by teleconference.

Dose Limiting Toxicities (Phase 1b)	Using CTCAEv4 grading criteria:
	<u>Hematologic DLTs</u>
	• Grade ≥3 febrile neutropenia
	• Grade 4 neutropenia lasting for >7 days (growth factors allowed)
	• Grade 3 thrombocytopenia (platelets ≤50.0/μL) lasting for >7 days
	Grade 3-4 lymphopenia is NOT considered a DLT.
	<u>Non-hematologic DLTs</u>
	• Any Grade ≥3 non-hematologic toxicity, probably related to study drug, EXCEPT for the following:
	  • Grade ≥3 neurologic deficits considered to be due to the effects of tumor, resection, or expected post-surgical morbidities
	  • Seizures of any grade, as this is commonly observed in this patient population
	  • Grade ≥3 thromboembolic event, as this is commonly observed in this patient population
	  • Grade 3 nausea, vomiting, or diarrhea that resolves to Grade ≤2 within 3 days of onset
	  • Grade 3 headache, insomnia, or amnesia that resolves to Grade ≤2 within 14 days of onset
	  • Grade 3 fatigue that resolves to ≤Grade 2 within 21 days of onset
	  • Grade 3 AST or ALT that resolves to ≤Grade 2 within 21 days of onset
	  • Grade ≥3 CPK, GGT, ALP, hypomagnesemia, or hypophosphatemia that is felt by the investigator to be clinically insignificant

	• Alopecia of any Grade
Stopping Rules	For Phase 1 dose escalation, a dose level will be considered unacceptable if 2 or more patients of the 6 eligible patients experience a DLT (see below). Should all 7 patients in the Cohort be analyzable for adverse events, only the first 6 will be considered in the determination of DLTs. A patient who misses more than 7 days of PLX3397 administration during the 7-week dosing period of Cycle 1 (4 weeks) and Cycle 2 (3 weeks) for reasons other than having had a DLT will be replaced. If 2 or more patients in a Cohort experience a DLT, no patients in the Cohort will be replaced. If >2 of the first 6 patients in Dose Level -2 (400 mg/day of PLX3397) experience a protocol-defined DLT, the combination will be considered too toxic and the study will be discontinued. After approximately 50% of the planned Phase 2 patients have completed their concurrent radiation therapy, an overall interim safety summary will be reviewed by the Medical Monitor and principal investigators to ensure that the potential clinical benefit outweighs the observed clinical risk to date. If the safety observations do not warrant continued enrolment, the study will be discontinued.
PK Parameters	For the Phase 1b portion of the study, a partial AUC (AUC_{0-6}) will be calculated using samples collected from C1D8 (pre-temozolomide) and C1D15 (concurrent temozolomide). Values for C_{max} and T_{max} will be determined from the concentration-time profile.
PD Parameters	CD14/16 mononuclear cell counts, CSF-1, and biomarkers of kinase inhibition and myeloid cell recruitment. Surgical tissue will be evaluated for MGMT methylation, CSF-1, CSF1R, tumor-associated macrophages, and other prognostic biomarkers in order to correlate with treatment response and inform enrichment strategies for subsequent studies in this patient population. If the MGMT methylation status of the study population differs from that observed in the RTOG 0525 study, the benchmark mPFS of 5.5 months will be adjusted appropriately.
Endpoints	Primary: Median PFS by RANO criteria Secondary: Safety, OS, PK, correlative imaging Exploratory: PD biomarkers
Statistical Considerations	For the primary endpoint of median PFS, based on a one-sided log rank test with a significance level of 0.1 and power of 80%, 22 events (death or progression) in approximately 31 patients would be required to detect a 50% relative hazard reduction in progression-free survival due to the addition of PLX3397 compared to the recent historical control median PFS of 5.5 months (RTOG 0525). Assuming a ~ 30% rate of non-evaluability, approximately 37 patients are planned to be enrolled in the Phase 2 portion of the study, which when combined with the 7 patients treated at that dose level in the Phase 1 portion of the study will yield approximately 44 patients.

TRIAL FLOW CHART – Phase 1b Dose Escalation Phase

	Screening	4 Week Cycle				3 Week Cycle				4 Week Recovery Period				4 Week Cycle		4 Week Cycle	
STUDY DAY►	**Day –21 to -1**	**C1D1 (-2d)**	**C1D8 ±2d**	**C1D15 ±2d**	**C1D22 ±2d**	**C2D1 ±2d**	**C2D8 ±2d**	**C2D15 ±2d**	**C2D22[1] ±2d**	**RPD 1 ±2d**	**RPD 8 ±2d**	**RPD 15 ±2d**	**RPD 22 ±2d**	**C3D1[2] ±7d**	**C3D22 ±2d**	**Day 22 of Cycle 4+[3] ± 7d**	**End of Rx**
EVENT▼																	
Informed Consent	X																
Medical History	X																
Height	X																
Weight	X	X				X			X					X	X	X	X
Vital Signs	X	X	X	X		X			X					X	X	X	X
Physical Exam[4]	X	X	X	X		X			X					X	X	X	X
ECG[13]	X					X											X
Chem	X	X		X		X			X					X	X	X	X
Hematology[5]	X	X	X	X	X	X	X	X	X		X			X	X	X	X
Plasma for PK[6]		X	X	X													
Plasma PD Biomarkers[7]		X	X			X								X			
Whole Blood for CD14/16		X	X														
Serum Pregnancy Test[8]	X																X
Surgical Specimen for PD	X																
Karnofsky Performance Status	X	X				X			X					X	X	X	X
MDA Symptom Inventory		X							X					X	X	X	X
MRI Brain Scan[9]	X													X		X	
Study Drug Dosing[10]		X----------X												X----------X			
Study Drug Compliance		X	X	X		X			X						X	X	X
Radiation Therapy			X----------X														
Temozolomide[11]			X----------X											X[9]			
Concomitant Medications	X	X	X	X		X			X					X	X	X	X
Adverse Events[12]		X	X	X		X			X					X	X	X	X

EXPLANATION OF SUPERSCRIPTS:

1. The cycle length for Cycle 2 is 3 weeks, to complete the 6 weeks total of radiation therapy.
2. C3D1 is the first dose of the adjuvant retreatment with temozolomide and study drug, beginning approximately 4 weeks after the completion of RT.
3. If well tolerated and no tumor progression; clinic visits, laboratories every 4 weeks with radiographic assessment performed every 8 weeks (every 2 cycles).
4. Complete physical exam (including neurological exam) at Screening, and neurological exam plus symptom-directed physical exam subsequently.
5. Hematology: CBC, differential count, platelet count.
6. On C1D1, obtained pre-dose. On C1D8 and C1D15, obtained pre-dose, 1, 2, 4, and 6 hours post-dose.
7. Blood samples for circulating CSF-1 and biomarkers of kinase inhibition and myeloid cell recruitment will be obtained pre-dose on C1D1, C1D8, C2D1, and C3D1. CD14/16 mononuclear cell counts will be obtained pre-dose on C1D1 and C1D8. Samples will be collected and processed by LabCorp according to the study-specific laboratory manual. LabCorp will perform the MGMT analyses.
8. For women of child-bearing potential. At screening, obtained within 14 days of the first dose of study drug.
9. A diagnostic contrast-enhanced MRI or CT scan of the brain must be performed preoperatively and postoperatively prior to the initiation of radiotherapy, i.e. within 28 days (14 days preferred) prior to study drug administration (C1D1). Patients unable to undergo MR imaging because of non-compatible devices can be enrolled, provided pre- and post-operative contrast-enhanced CT scans are obtained and are of sufficient quality.
10. Two PLX3397 BID administration schedules, 7 days/week vs. 5 days/week (M-F) will be explored for Cycle 1 and 2. PLX3397 will be administered BID 7 days/week for Cycle 3 and subsequebt cycles until diasease progression disease or unacceptable toxicity.
11. Temozolomide is taken orally once daily for 5 days followed by 23 days without treatment for each cycle beginning with C3D1 for up to 12 cycles.
12. Monitored throughout the study via safety assessments, observation, and participant reporting.
13. Standard 12-lead ECG with QTcF calculation. Fridericia's formula is required. $QTcF = (QT)/\sqrt[3]{(RR)}$

TRIAL FLOW CHART – Phase 2

STUDY DAY►	Screening	4 Week Cycle			3 Week Cycle		4 Week Recovery Period	4 Week Cycle		4 Week Cycle	End of Rx
	Day –21 to -1	C1D1 (-2d)	C1D8 ±2d	C1D15 ±2d	C2D1 ±2d	C2D22[1] ±2d		C3D1[2] ±7d	C3D22 ±2d	Day 22 of Cycle 4+ [3] ±7d	
EVENT▼											
Informed Consent	X										
Medical History	X										
Height	X										
Weight	X	X			X	X		X	X	X	X
Vital Signs[12]	X	X	X		X	X		X	X	X	X
Physical Exam[4, 12]	X	X	X		X	X		X	X	X	X
ECG[11]	X				X						X
Hem, Chem[12]	X	X	X	X	X	X		X	X	X	X
Plasma PD Biomarkers[5]		X	X		X			X			
Whole Blood for CD14/16		X	X								
Serum Pregnancy Test[6]	X										X
Surgical Specimen for PD	X										
Karnofsky Performance Status[12]	X	X			X	X		X	X	X	X
MDA Symptom Inventory		X				X		X	X	X	X
MRI Brain Scan[7,12]	X							X		X	
Study Drug Dosing[8,12]		X----------X						X----------X			
Study Drug Compliance[12]		X	X	X	X	X			X	X	X
Radiation Therapy			X----------X								
Temozolomide[9]			X----------X					X[7]			
Concomitant Medications[12]	X	X	X	X	X	X		X	X	X	X
Adverse Events[10,12]		X	X	X	X	X		X	X	X	X

EXPLANATION OF SUPERSCRIPTS:

1. The cycle length for Cycle 2 is 3 weeks, to complete the 6 weeks total of radiation therapy.
2. C3D1 is the first dose of the adjuvant retreatment with temozolomide and study drug, beginning 4 weeks after the completion of RT.
3. If well tolerated and no tumor progression; clinic visits, laboratories every 4 weeks with radiographic assessment performed every 8 weeks (every 2 cycles)
4. Complete physical exam (including neurological exam) at Screening and neurological exam plus symptom-directed physical exam subsequently.
5. Blood samples for circulating CSF-1 and biomarkers of kinase inhibition and myeloid cell recruitment will be obtained pre-dose on C1D1, C1D8, C2D1, and C3D1. CD14/16 mononuclear cell counts will be obtained pre-dose on C1D1 and C1D8. Samples will be collected and processed by LabCorp according to the study-specific laboratory manual. LabCorp will perform the MGMT analyses.
6. For women of child-=bearing potential. At screening, obtained within 14 days of the first dose of study drug.
7. A diagnostic contrast-enhanced MRI or CT scan of the brain must be performed preoperatively and postoperatively prior to the initiation of radiotherapy, i.e., within 28 days (14 days preferred) prior to study drug administration (C1D1). Patients unable to undergo MR imaging because of non-compatible devices can be enrolled, provided pre- and post-operative contrast-enhanced CT scans are obtained and are of sufficient quality
8. Two PLX3397 BID administration schedules, 7 days/week vs. 5 days/week (M-F) will be explored for Cycle 1 and 2. PLX3397 will be administered BID 7 days/week for Cycle 3 and subsequebt cycles until diasease progression disease or unacceptable toxicity.
9. Temozolomide is taken orally once daily for 5 days followed by 23 days without treatment for each cycle beginning with C3D1 for up to 12 cycles.
10. Monitored throughout the study via safety assessments, observation, and participant reporting.
11. Standard 12-lead ECG with QTcF calculation. Fridericia's formula is required. $QTcF = (QT)/\sqrt[3]{(RR)}$
12. Commencing on 01 October 2017, patient visits, clinical laboratory testing, and MRI brain scans will be performed approximately every 12 weeks.

7.0 INTRODUCTION

7.1 Background

Kinases play a ubiquitous role in the signaling pathways for proliferation, metastasis, and survival of most tumor types. PLX3397 is a potent and selective inhibitor of Fms (the receptor for colony stimulating factor 1, CSF1, also known as macrophage-colony stimulating factor, M-CSF), Kit (the receptor for stem cell factor, SCF) and oncogenic Flt3 (the receptor for Flt3 ligand). Fms and Kit are regulators of key components of the tumor microenvironment, namely microglia, macrophages, osteoclasts, and mast cells.

PLX3397 is a novel, orally active, small molecule inhibitor that targets Fms, Kit and oncogenic Flt3, but remains highly selective versus other kinases. The potent inhibition of these three kinases can be exploited to attack tumors via different mechanisms: 1) directly inhibiting oncogenic drivers such as oncogenic Kit and Flt3 mutant proteins, 2) inhibiting paracrine loops between stromal cells and tumors, 3) blocking migration and angiogenesis, and 4) disrupting osteolytic metastases. The inhibition of these activities by PLX3397 has been characterized in cellular and in vivo assays. The pharmacologic efficacy demonstrated to date and the therapeutic promise support further development of PLX3397 as an anti-cancer therapeutic.

Glioblastoma (GBM) is the most frequent brain tumor, accounting for approximately 12% to 15% of all brain tumors. The peak incidence occurs between the ages of 45 and 70 years. For patients with glioblastoma (World Health Organization grade IV), there is no cure, and standard local treatment of surgery plus radiotherapy ± chemotherapy is associated with only a modest improvement in outcome parameters. According to the National Cancer Institute, patients with brain tumors that are either infrequently curable or unresectable should be considered candidates for clinical trials that evaluate new drugs and biological response modifiers following radiation therapy.

The rationale for testing the Fms/Kit inhibitor PLX3397 in GBM is provided by the following scientific evidence:

1. Infiltrating microglia are associated with a markedly reduced survival (Komohara 2008)
2. A mesenchymal signature also predicts reduced survival in GBM (Phillips 2006). This signature includes well-described microglial markers such as CD68, PTPRC, TNF, and NF1 mutations (Verhaak 2010)
3. A microglial-weakening polymorphism (V249I) is associated with increased survival (Rodero 2008)
4. Many glioma cell lines established from patient samples express high concentrations of ligands for Fms (CSF-1 and IL-34) or Kit (SCF). This secretion in turn attracts and activates surrounding microglia, which facilitate tumor invasion via elaboration of proteases such as MT1-MMP and MMP2.
5. Depletion of microglia in orthotopic GBM models reduces tumor burden and spread.
6. Macrophages and microglial cells are recruited by tumor cells as a resistance mechanism in response to radiotherapy (Ahn 2010).

In pharmacology studies, PLX3397 (1 μM) has been shown to markedly reduce the invasion of GL261 glioblastoma cells when co-cultured with microglia in a matrigel invasion assay. Furthermore, PLX3397 administered by chow for 10 days resulted in a significant reduction (p=0.029) in tumor growth in the 9L Fisher rat glioma model. Also,PLX3397 avidly crosses into the CNS of rats (similar to the positive brain penetration control compound, antipyrine) and is not a substrate for active transport, suggesting that PLX3397 will reach GBM tumors and surrounding stromal tissue within the CNS even with an intact blood brain barrier. Finally, PLX3397 has shown a synergistic effect when combined with radiation therapy in pharmacology models of prostate cancer and GBM.

7.2 Pharmacodynamics

In brief, biochemical data support Fms, Kit and oncogenic Flt3 as key targets of PLX3397. Consequently, proliferation of cell lines that alternatively depend on CSF-1 or SCF ligands, or are driven by Flt3 that is oncogenically activated by internal tandem duplications (Flt3-ITD), is inhibited by PLX3397 at IC_{50} values below 1 μM. Furthermore, CSF-1-induced autophosphorylation of Fms and SCF-induced autophosphorylation of Kit are potently inhibited by PLX3397. By contrast, both autophosphorylation and proliferation of cells induced by addition of Flt3 ligand are only weakly inhibited by PLX3397, suggesting preferential inhibition of the oncogenically-activated Flt3 kinase. Finally, the RANK-L and CSF-1-dependent differentiation of osteoclast precursors is also potently inhibited by PLX3397. These in vitro effects translated to effects in a variety of in vivo models designed to test the effects of PLX3397 on Fms-dependent proliferation, Fms-dependent osteoclast differentiation, and Flt3-ITD dependent tumor growth.

7.2.1 In Vitro Pharmacodynamics

PLX3397 shows significant selectivity versus a panel of over 200 kinases. Fms, Kit, and mutant Flt3-ITD appear to be the most sensitive target kinases, with IC_{50} values of 17, 12, and 9 nM, respectively (see Table 1).

Table 1: IC_{50} Values of PLX3397 Aganst Selected Kinases

Kinase	Fms	Kit	Flt3-ITD	Kdr	Lck	Flt1	TrkC
PLX3397	17 nM	12 nM	9 nM	213 nM	860 nM	880 nM	890 nM

Kdr kinase activity is only modestly affected, and other kinases tested are even less sensitive to PLX3397. While physiologic effects due to the inhibition of Fms and Kit are expected, the selectivity of PLX3397 suggests that minimal off-target effects should be observed. When screened against a broad panel of additional kinases, IC_{50} values were >1 μM for all, with the majority >10 μM.

PLX3397 also demonstrated negligible activity in a standard Novascreen panel. This is a screen for off-target activity against a broad array of 71 targets in 8 families (Neurotransmitter-related,

Steroids, Ion Channels, Nitric Oxide, Prostaglandins, Growth Factors, Brain/Gut Peptides, and Enzymes). At a serum-free concentration of 10 μM of PLX3397, all results were within 40% of Baseline, indicating no relevant off-target activity.

M-NFS-60 cells and BAC1.2F5 cells are mouse cell lines that require CSF-1 to proliferate, and Mo7E cells are human cells that require SCF to proliferate. The ligand dependent proliferation of these cells is inhibited by PLX3397 with IC_{50} values of 0.33, 0.23 and 0.31 μM, respectively. In THP-1 cells, Fms autophosphorylation induced by CSF-1 can be inhibited by 7 nM concentrations of PLX3397. By contrast, in RS4;11 cells, Flt3 autophosphorylation can be induced by Flt3 ligand and this autophosphorylation requires high levels of PLX3397 (1500 nM) for inhibition, suggesting that PLX3397 binds only weakly to unactivated Flt3. On the other hand, proliferation of MV4-11 cells (that express Flt3-ITD) is potently inhibited by PLX3397 with an IC_{50} value of 26 nM. Finally, human osteoclast precursor cells can be induced to differentiate into mature osteoclasts by the combination of RANK-L and CSF-1. PLX3397 inhibits this osteoclast differentiation with an IC_{50} value of 33 nM.

7.2.2 In Vivo Pharmacodynamics

Models of Fms-dependent proliferation and Fms-dependent osteoclast activity can be inhibited by 5-10 mg/kg doses of PLX3397 in vivo. This was demonstrated in a Fms-dependent splenomegaly model, a metastatic breast cancer model, and a murine collagen-induced arthritis model.

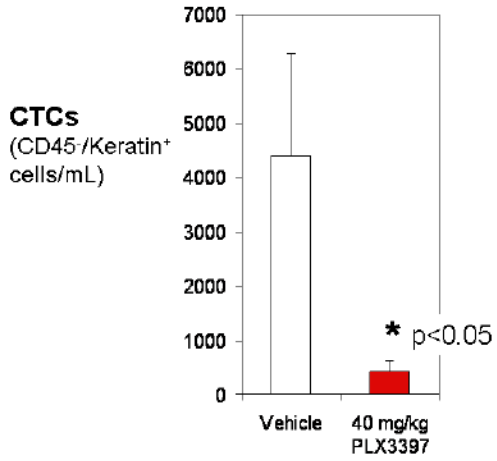
BaF3 cells are mouse pre-B cells that depend on interleukin-3 (IL-3) for survival. By engineering BaF3 cells to express BCR-activated Fms kinase activity, the dependence on IL-3 can be replaced. Consequently, these BCR-Fms expressing BaF3 cells are dependent on Fms kinase activity for survival. In vitro, proliferation of these cells can be potently inhibited by PLX3397, with an IC_{50} value of 7 nM. A corresponding BaF3 cell line expressing BCR-Kit is also quite sensitive to PLX3397, with an IC_{50} value of 130 nM.

Injection of the BCR-Fms-expressing BaF3 cells into the tail vein of nude mice results in homing of these cells to the spleen and subsequent cellular proliferation that results in dramatic splenomegaly over the course of 14-18 days. Oral dosing of PLX3397 for the final 8 days of this model results in dose-dependent inhibition of the splenomegaly. The ED_{50} of this effect is between 2 and 5 mg/kg. Therefore, we believe that a 5 mg/kg oral dose of PLX3397 in mice corresponds to an efficacious dose. Pharmacokinetic analysis reveals that this 5 mg/kg dose achieves an AUC_{0-24} of 99.8 μM•h, and a C_{max} of 13.4 μM. We will use these values to define an efficacious exposure, and this will be used as the denominator in calculations of therapeutic multiples.

In a separate model, mice expressing the polyoma middle T antigen (PyMT) behind a mammary promoter develop breast cancer that metastasizes after several months. During the metastatic process, circulating tumor cells that express PyMT can be measured among circulating blood cells. Since Fms activity is a critical component of extravasation into the blood stream, reduction

in the number of these circulating tumor cells can be a measure of anti-Fms activity. Within 24 hours of a single oral dose of 40 mg/kg PLX3397, a 10-fold decrease in these circulating tumor cells can be determined (see Figure 1).

Figure 1: PLX3397-induced Reduction of Circulating Tumor Cells in PyMT Mouse Model of Breast Cancer



In order to determine effects of PLX3397 on osteoclastic activity in vivo, a murine collagen-induced arthritis model was implemented. In this model, double immunization of the mice with collagen leads to progressive clinical symptoms resembling rheumatoid arthritis. Histology can be used to measure osteoclasts that contribute bone-destructive pathology in this model. Osteoclasts are measured using an osteoclast-specific marker, namely tartrate-resistant acid phosphatase 5B (TRAP 5B). Treatment of these mice with 50 mg/kg PLX3397 over the course of 24 days results in significant stabilization of disease, and this is accompanied by dramatic reductions in macrophages infiltrating the joints. Importantly, joint-infiltrating osteoclasts are also reduced by 10-fold, illustrating the potent anti-osteoclastic effects of PLX3397.

Since PLX3397 permeates the blood-brain barrier and Fms-dependent microglia are likely mediators of pain transmission, PLX3397 was tested in a formalin-pain model. This formalin model measures both acute nociceptive and acute inflammatory pain responses. PLX3397 showed reduction in both phases of the formalin pain response, suggesting that effects on both acute and inflammatory pain may be expected in further studies.

Please refer to the Investigator's Brochure for updated information and detailed description of the nonclinical pharmacology data.

7.3 Nonclinical Metabolism and Pharmacokinetics

Please refer to the Investigator's Brochure for updated information and detailed description of the nonclinical metabolism and PK.

PLX3397 has low aqueous solubility and modest permeability. It is not a substrate or inhibitor of Pgp. Several studies in four species (mouse, rat, dog and monkey) evaluated formulations to optimize absorption and systemic exposure following oral administration. PLX3397 was absorbed within two to three hours following oral administration. In several studies, plasma exposure (based on AUC values) was greater in females (up to 34% in rats). Elimination half lives ranged from 2 to 5 hours in these four species. A study conducted in cynomolgus monkeys showed that food does not inhibit or delay absorption of PLX3397 following oral (gavage) administration.

The extent to which PLX3397 binds to the plasma proteins was evaluated in vitro using a Rapid Equilibrium Dialysis inverted method. PLX3397 is strongly protein bound in plasma for all four species tested (mouse, rat, dog, and human). With regards to potential species differences, the binding in mouse, dog and human plasma at 75 µM was approximately equal (99.8%, 99.7%, and 99.8% respectively) while rat protein binding was marginally lower (98.3%).

Two experiments evaluated the partitioning of PLX3397 between blood and brain, based on measurements of test article in brain tissue, cerebrospinal fluid and plasma. In one study, appreciable amounts of PLX3397 were recovered in whole blood (vs. plasma), suggesting that PLX3397 associates with cellular elements of blood. In experiments that quantified PLX3397 concentration in brain tissue and cerebrospinal fluid 4 and 6 hours following oral administration in rats, the brain:plasma ratio averaged 0.41 and 0.36, respectively–values close to that of antipyrene, a positive control (0.50 and 0.54). The ratios of CSF:plasma at these timepoints for PLX3397, however, were lower (0.026 and 0.014) than those for antipyrene (1.06 and 0.92).

A series of in vitro studies examined the metabolic stability of PLX3397 using either liver S9 fraction or intact hepatocytes from several species, including rats and dogs, the two species used in toxicology studies, as well as humans. Studies with intact hepatocytes revealed that PLX3397 was very slowly metabolized in all three species, especially human liver cells. Although the exact molecular species were not identified, in the presence of human hepatocytes, several molecular species corresponding to glucuronide conjugates were detected, with minimal evidence of breakdown. These data, along with the high protein binding, suggests that the clearance of PLX3397 from human plasma may be slow. Another study was conducted to evaluate the CYP450 phenotypes of PLX3397 metabolism in vitro. Of the five major CYP isoforms, 3A4 (BFC) may be involved in Phase I metabolism of PLX3397, with possibly CYP1A2 playing a minor role.

PLX3397 does not appear to inhibit CYP drug-metabolizing enzymes to an important extent. Studies using human liver microsomes yielded enzyme inhibitory constant (Ki) values exceeding 30 µM for CYP1A2 and 3A4 (testosterone substrate), >12 µM for 3A4 (midazolam substrate), 2D6 and 2C9. A Ki value <10 µM was obtained for only one CYP isozyme: 2C19 (Ki = 8.4 µM). It is worth noting that the latter experiment was conducted in the absence of human serum albumin (HSA). When PLX3397 was evaluated for its ability to inhibit the major human CYP isozymes in the presence of 10 µM HSA, IC_{50} values greater than 30 µM were uniformly obtained.

In another series of experiments, PLX3397 was demonstrated not to induce the expression of genes that encode CYP enzymes and several other proteins involved in metabolism and transport.

In aggregate, an extensive series of non-clinical studies evaluating PLX3397 reveal a metabolically stable drug that displays extensive protein binding. Clinically relevant drug-drug interactions are not anticipated based upon experimental evidence of negligible CYP inhibition or induction in vitro.

7.4 Summary of Nonclinical Toxicology, Genotoxicity, and Safety Pharmacology

A total of 12 toxicology studies were completed in rats and dogs with five and three studies in each of these two species, respectively, performed under GLP conditions. The initial two GLP toxicology studies involved daily (BID in dogs and QD in rats) oral (gavage) administration of PLX3397 for four weeks, with 14-day (dog) or 16-day (rat) recoveries. Neither a no-effect-level (NOEL) nor a no-adverse-effect-level (NOAEL) of PLX3397 could be determined in either species in these studies. The significant adverse, test article-related observations seen in these two high-dose GLP studies appear to be related to the mechanism of PLX3397-mediated inhibition of Fms and Kit kinase. All adverse findings were partially or fully reversible. Two additional GLP toxicology studies at lower dose levels involved daily (QD in rats and dogs) oral (gavage) administration of PLX3397 for four weeks, with 8-week recoveries at doses of 1, 6, and 30 mg/kg/day in dogs and 0.5, 2 and 10 mg/kg/day in rats. NOAELs of PLX3397 were determined to be 6 mg/kg/day in dogs and 10 mg/kg/day in rats in these additional studies. Two 13-week GLP toxicology studies involved daily (QD in rats and dogs) oral (gavage) administration of PLX3397 for 13 weeks, with 8-week recoveries at doses of 1, 6, and 30 mg/kg/day in dogs and 0.5, 4 and 20 mg/kg/day in rats. NOAELs of PLX3397 were determined to be 6 mg/kg/day in dogs and 4 mg/kg/day in rats in these additional studies.

Three genotoxicity studies were performed, including the Ames assay, chromosomal aberrations in human peripheral blood lymphocytes, and mouse bone marrow micronucleus assay, under GLP-compliant conditions. An additional spot test mutagenicity assay in *Salmonella* and *E. coli* was not performed under GLP-compliant conditions. On the basis of these studies, PLX3397 was concluded not to exert any mutagenic, clastogenic effects.

In GLP-compliant respiratory and central nervous system safety studies, the NOEL for PLX3397 was 200 mg/kg in rats. Additionally, three GLP-compliant safety pharmacology studies addressed the potential adverse cardiovascular or cardiac electrophysiological effects of PLX3397. When evaluated in a serum free hERG study, PLX3397 was shown to bind to the channel (IC_{50} 0.7 μM). However, in a follow-up cardiac Purkinje fiber study, no test article-related effects on repolarization, AP amplitude or speed of cardiac depolarization were observed. Furthermore, in a dog in vivo GLP cardiovascular safety study, all electrocardiographic parameters were qualitatively and quantitatively within normal limits, demonstrating that PLX3397 does not prolong cardiac repolarization up to the highest dose tested (1000 mg/kg).

7.4.1 Repeat-dose Toxicity in Rats

7.4.1.1 4-week Rat Studies

In the initial GLP 28-day study with a 14-day recovery period, Sprague-Dawley rats were dosed at 20, 60, and 200 mg/kg/day. Non-adverse lower body weights and food consumption were noted for the 200 mg/kg/day group females. Body and food consumption effects resolved during the recovery period.

Changes in hematology parameters consisted of dose-related lower WBC, RBC, PT, aPTT, and lower reticulocyte counts in all test article-treated groups. At study day 43 recovery evaluation, the WBC counts had rebounded, the RBC mass partially recovered, reticulocyte counts were higher than the control group, and fibrinogen, PT, and APTT had resolved in the 200 mg/kg/day groups. Microscopic alterations included dose-related minimal to moderate subphyseal hyperostosis in the femur, minimal to moderate physeal hypertrophy in the femur, and dose-related reduction in the density of hematopoietic cells of all lineages within the bone marrow (sternum and femur). Dose-related hepatocellular centrilobular hypertrophy was noted for the 200 mg/kg/day groups, and correlated with higher liver enzyme levels and higher liver weights, and a higher incidence and/or severity of chronic progressive nephropathy was noted for the 200 mg/kg/day groups. This finding is a normal spontaneous change in Sprague-Dawley rats and was also noted in the vehicle control groups. Microscopic findings in the skin and lymphoid tissues included a dose-related higher incidence of minimal to mild myxomatous change in the skin/subcutis and lymphoid depletion of the thymic cortex. Microscopic findings in endocrine and reproductive tissues included dose-related higher incidence and severity of hemorrhagic corpora luteal cysts in the ovaries and higher incidence and/or severity of thyroid follicular cell hypertrophy in the 200 mg/kg/day groups. Minimal to moderate depletion of spermatogenic epithelium was noted in the 60 and 200 mg/kg/day group males, and the 200 mg/kg/day group males were often completely devoid of spermatogonia and pachytene spermatocytes. At study Day 43, there was an increase in the spermatogonial population. Alterations in testes and ovaries are likely related to the mechanism of PLX3397-mediated inhibition of Fms and Kit kinase.

The majority of alterations in morphologic pathology parameters, except for luteal cysts and chronic progressive nephropathy, partially or completely resolved following the recovery period. A NOAEL was not determined. This study also did not establish a lethal dose in 50% of rats LD_{50} or severely toxic dose in 10% of rats (STD_{10}).

A follow-up study evaluated the potential toxicity at doses of 0.5, 2 and 10 mg/kg/day to Sprague-Dawley rats for 28 consecutive days, with a recovery period of 8 weeks to assess the reversibility, persistence, or delayed occurrence of potential test article-related effects. There were no test article-related effects on clinical or macroscopic observations. Body weights, food consumption, and urinalysis parameters were unaffected by test article administration.

Non-adverse hematology alterations were noted, including higher RDW, lower absolute neutrophil counts, higher fibrinogen, and lower RBC count. Small and non-adverse serum

chemistry alterations included higher serum albumin, total protein, and ALT levels. The mean values for all affected parameters were within the historical control range rand recovered by Week 12. Decreases in splenic extramedullary hematopoiesis were observed for the 10 mg/kg/day group males and females at the primary necropsy. These effects on the spleen were reversible and not noted at the Week 12 recovery necropsy, and were therefore considered non-adverse. All systemic effects of PLX3397 in this study were reversible and not considered by the study director to be adverse. Therefore, the NOAEL for oral (gavage) administration of PLX3397 was 10 mg/kg/day (AUC_{last} of 24515 ng•h/mL and C_{max} of 3390 ng/mL for males and females combined).

7.4.1.2 13-week Rat Study

A 13-week study evaluated the potential toxicity and toxicokinetic profile of PLX3397 HCl, when administered orally (gavage) at doses of 0.5, 4 and 20 mg/kg/day to Sprague-Dawley rats for 13 consecutive weeks, with a recovery period of 8 weeks. Systemic exposure to PLX3397 generally increased proportionally as dosage increased over the 0.5 to 20 mg/kg/day range. Exposure to PLX3397 was consistently slightly higher for females than for males (up to 1.8-fold for AUC_{last}). There were no test article-related clinical observations or effects on body weights, food consumption, ophthalmic examinations, urinalysis, or macroscopic examinations.

At 20 mg/kg/day, PLX3397 was associated with clinical pathology changes suggestive of anemia (erythron changes) generalized stress (lymphopenia and eosinopenia), dehydration (higher albumin, globulin, and total protein), higher AST and ALT, higher fibrinogen, calcium, and cholesterol in males, and lower potassium in females. Additionally, lower absolute and relative spleen and thymus weights were noted for both sexes. Microscopically, males were observed with minimal to mild accumulation of pigment resembling hemosiderin in the proximal tubules of the kidney which was consistent with the observed anemia, minimal or moderate hepatocellular vacuolation, and mild thymic atrophy. Animals from both sexes were noted with mild to moderate generalized bone marrow depletion and minimal to moderate hemosiderin in the spleen. Following an 8 week recovery period, persistent effects consisted of mild hepatocellular vacuolation in 1 of 6 males and mild hemosiderin deposition in the spleen of 5 of 6 females. Taken together, the observed anemia and bone marrow depletion are suggestive of an adverse effect on the hematopoietic system, which was reversible following an 8-week recovery period. Hepatocellular vacuolation observed in males was associated with higher AST, ALT, and cholesterol values at the primary necropsy, persisted to the end of the recovery period, and was considered adverse. There were no histologic abnormalities noted in the epididymides or testes. The NOAEL was considered to be 4 mg/kg/day. This dosage level corresponded to AUC_{last} and C_{max} values of 11440 ng•hr/mL and 1271 ng/mL, respectively.

7.4.2 Repeat-dose Toxicity in Dogs

7.4.2.1 4-week Dog Studies

In the initial GLP toxicity study, groups of Beagle dogs were administered PLX3397 for 28 days at doses of 100, 300, and 1000 mg/kg/day which was then reduced to 50, 100, and

300 mg/kg/day after the first week due to lethargy, weight loss, and lack of food consumption in several high dose animals. Mean exposure generally increased as dosage increased. There were no test-article-related ophthalmic or macroscopic findings or effects on urinalysis, ECG or organ weight parameters.

Three dogs in the high dose group were euthanized in extremis on study days 8, 15, and 17 due to prostration, tremors, impaired coordination, and tachypnea. Emesis and modest body weight declines were noted in all groups with an increased incidence in the mid and high dose groups. These changes correlated with decreased food consumption and were reversible during the recovery period.

Changes in hematology parameters consisted of time- and dose-related declines in RBC mass and reticulocyte counts. The anemia increased in severity at study Week 4, despite a rebound in absolute numbers of reticulocytes. These effects were considered adverse though reversible, based on partial recovery noted at study Week 6. Higher fibrinogen levels were also noted in all dose groups. .

PLX3397 caused significant, partially reversible testicular atrophy at all three doses. PLX3397-related alterations were less prominent in the ovary, possibly because most ovaries were immature. Alterations in testes and ovaries are likely related to the mechanism of PLX3397-mediated inhibition of Fms and Kit kinase. Bone marrow exhibited a dose-related minimal to mild hypocellularity with recovery. In the spleens, minimal to mild increased extramedullary hematopoiesis was noted in all dose groups. In the femur, minimal to moderate subphyseal hyperostosis was evident, considered a reversible consequence of pharmacologic effect on osteoclasts. Lymphoid depletion was evident in the thymus, lymph nodes, Peyer's patches, and spleen more frequently, compared to vehicle controls. These effects were considered to be secondary to PLX3397-related nonspecific stress factors.

Due to the adverse clinical observations of emesis-related findings, body weight losses with associated low food consumption, and microscopic findings of the testes, bone marrow, kidneys, spleen, and lymphoid depletion in the thymus, a NOAEL was not determined. This study also did not establish a lethal dose in 50% of dogs LD_{50}.

A follow-up study was completed at doses of 1, 6 and 30 mg/kg/day for 28 consecutive days, followed by a recovery period of 8 weeks. Mean systemic exposure increased as dosage increased over the 1 to 30 mg/kg/day range. Body weights, food consumption, clinical pathology parameters, and organ weights were unaffected by test article administration. There were no test article-related macroscopic findings. In the 30 mg/kg/day group, there was an increased incidence of emesis 4 hours post-dosing. Test article-related, completely reversible, adverse spermatogonial/spermatocytic depletion and minimal depletion of round spermatids were noted in the 30 mg/kg/day group males. Based on the findings of emesis and reversible spermatogonial depletion, the NOEL and NOAEL was 6 mg/kg/day, corresponding to gender-combined AUC_{last} of 3960 ng•h/mL and C_{max} of 780 ng/mL.

7.4.2.2 13-week Study

In this GLP study, doses of 1, 6 and 30 mg/kg/day were administered for 13 consecutive weeks with an 8-week recovery period. Systemic exposure to PLX3397 generally increased proportionally as dosage increased. There were no test article-related macroscopic findings. Body weights, food consumption, ophthalmic, and electrocardiography parameters were unaffected by test article administration. There was a high incidence of emesis for the 30 mg/kg/day group which was not considered adverse due to the absence of effects on body weight or food consumption.

Adverse test article-related microscopic findings consisted of moderate to severe depletion of the spermatogonia, spermatocytes, round spermatids, and/or elongate spermatids in the testes, moderate hypospermatogenesis, and moderate or severe hypospermia in the epididymides of all 30 mg/kg/day group males at the study week 13 primary necropsy. Qualitatively, spermatogenesis was normal in all other males, based upon evaluations of PASH-stained tissue sections. These alterations were reversible within an 8-week recovery interval. The NOAEL was 6 mg/kg/day for males, corresponding to an AUC_{last} of 3039 ng•h/mL and C_{max} of 575 ng/mL, and 30 mg/kg/day for females, corresponding to an AUC_{last} of 17940 ng•h/mL and C_{max} of 1948 ng/mL.

7.5 Previous Human Experience

The ongoing Phase 1 dose escalation study PLX108-01 in patients with solid tumors is designed to evaluate the safety and PK of PLX3397. As of June 2012, a total of 62 patients have been treated with PLX3397, including 41 patients in the dose escalation cohorts and 21 patients in the Extension cohorts. The recommended Phase 2 dose has been established at 1000 mg/day. Plasma concentrations of PLX3397 demonstrate a T_{max} of approximately 2 hours, a mean elimination half-life of approximately 20 hours, and a mean accumulation ratio compared to Day 1 values of approximately 2-fold. In general, there is increasing exposure with increasing dose. Other single agent studies ongoing or completed include refractory Hodgkin lymphoma, Flt3-ITD+ AML, castrate-resistant prostate cancer, and recurrent GBM. Combination studies with paclitaxel and Eribulin are also ongoing.

In the recurrent GBM study, as of 13-Dec-2012, a total of 34 patients have been enrolled. Of these, 23 patients have discontinued study drug due to progressive disease (n = 21) or SAEs (n = 2). A total of 11 patients are ongoing, with 6 patients to be recruited. In general, the tolerability of study drug in this patient population has been similar to other patients with solid tumors, with few patients requiring drug holidays or dose reductions. Importantly, the concentration of PLX3397 measured in the tumor tissue of the 12 patients treated with 7 days of neoadjuvant therapy was similar to plasma concentrations, confirming the robust penetration of PLX3997 across the blood brain barrier in humans with GBM.

As of June 2012, a total of 107 patients have been treated to date. There have been no safety signals in vital signs, physical examinations, or ECGs (including careful evaluation of potential

QT prolongation). At dose levels of ≥600 mg/day, transient increases in AST and/or ALT have been observed in approximately half the patients. Among the 92 patients with solid tumors treated to date, the most common AEs of all grades have been fatigue, decreased appetite, nausea, vomiting, anemia, hair color change (depigmentation), and diarrhea. With the exception of vomiting and diarrhea, most of these AEs have been considered possibly or probably treatment-related. In the AML study (PLX108-05; n = 15), the most common AEs to date have been fatigue, febrile neutropenia, decreased appetite, nausea, diarrhea, and vomiting. In all studies, drug-related Grade 3 adverse events have been very uncommon. For more details concerning safety, please consult the Investigator's Brochure.

A number of response biomarkers are being assayed to profile the inhibitory activity of PLX3397 on Fms and Kit activity as a function of dose and exposure. These biomarkers include circulating tumor cell (CTC) and CD14+/CD16+ proinflammatory macrophage cell numbers; serum IL-6, IL-1beta and MMP3 concentrations; and markers of osteoclast activity. Most of the soluble markers are not elevated at Baseline in the oncology patients treated to date, so no decrease with treatment can be anticipated. However, in 5 patients to date, CTC counts were elevated at Baseline. In 3 of those 5 patients, CTC values decreased after treatment with PLX3397.

Reductions in the CD14+/CD16+ cell populations have also been observed in all patients treated to date. Serum CSF-1 levels have increased in all patients after initiation of PLX3397 dosing, as would be anticipated from Fms inhibition, resulting in reduced clearance of the ligand. Importantly, higher plasma PLX3397 concentrations are associated with higher elevations of CSF-1, supporting a concentration-dependent pathway inhibition. Urinary NTX concentrations showed a concentration-dependent decrease from Baseline, consistent with osteoclast inhibition. Clinically relevant increases in adiponectin were also observed, with 2-3 fold increases from Baseline generally observed in patients treated at dose levels of 900 mg/day and higher.

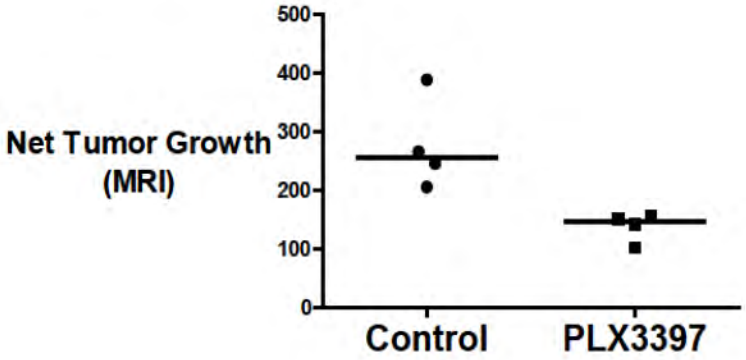
Approximately half of patients treated at doses of ≥600 mg/day have had a modest elevation of AST and ALT. During the first 4 weeks, the transaminases tend to increase to approximately 1.5x ULN without symptoms or increases in ALP or bilirubin. Then the transminases tend to decrease again and return to Baseline or remain slightly elevated within the normal range. We believe this pattern of mild increase, observed in the high dose toxicology studies as well, is due to target inhibition of CSF1R in the Kupffer cells that are responsible for clearing transminases that leak from hepatocytes and other tissues in the body. Over time, there appears to be an adaptive response for the most part. Nonetheless, some patients can show G3 elevations that require a drug holiday and possible dose reduction.

One important PD biomarker is hair depigmentation that has been observed in virtually all patients who have dark hair at Baseline and received doses of 600 mg/day or higher. This is believed due to Kit inhibition, due to its role in melanogenesis. There is no loss of hair, and the depigmentation appears to be completely reversible with drug discontinuation. Because PLX3397 is equipotent on CSF1R and Kit, this change can be considered a reliable biomarker of target inhibition.

7.6 Preclinical Evidence for Synergy of PLX3397 with Radiation

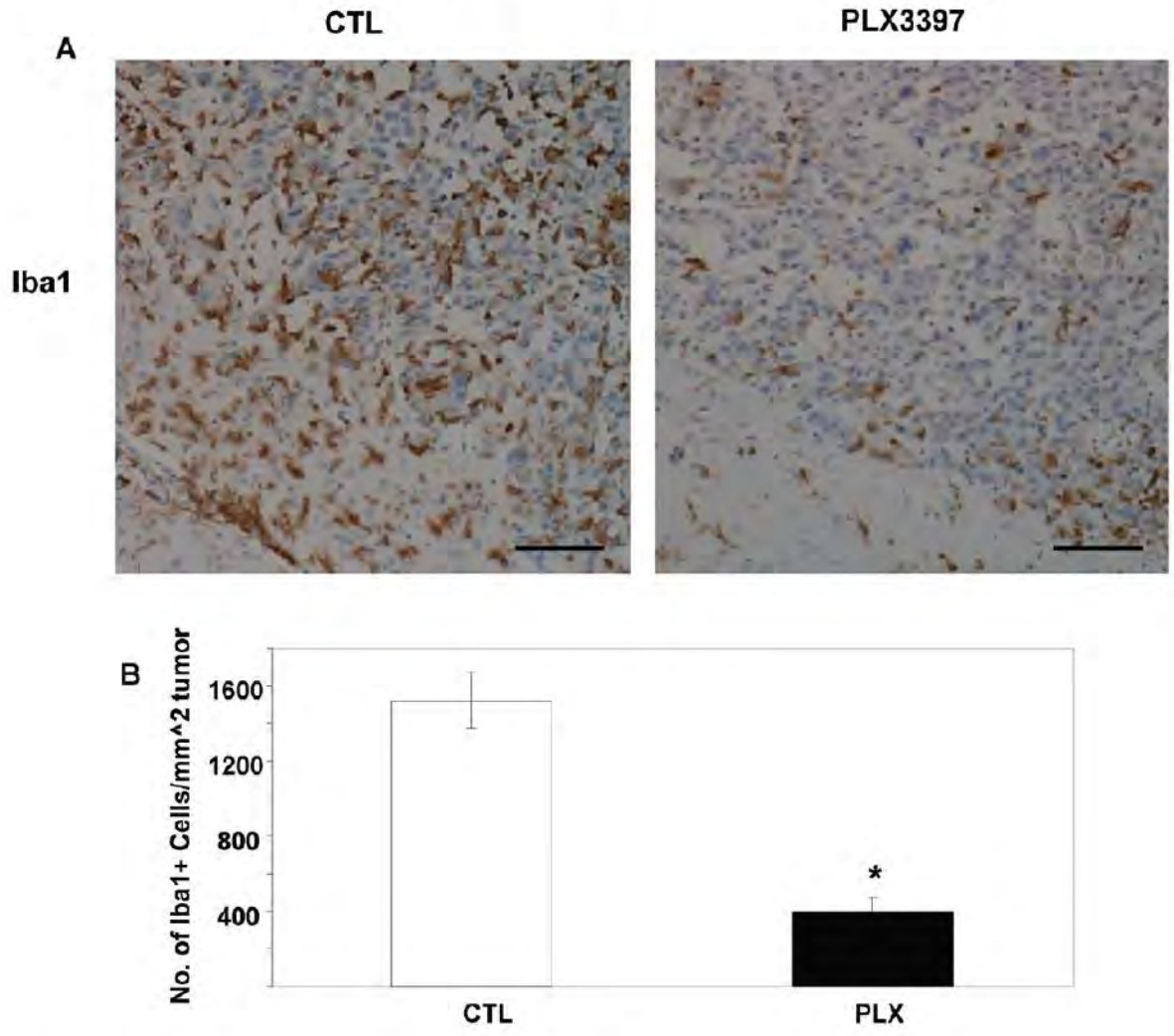
Just as macrophages support tumor growth, invasion and metastasis in non-CNS cancers, microglial cells have been shown to support the growth and invasion of gliobastomas (Markovic 2009). This supportive role relies on a paracrine system in which the glioblastoma cells attract microglial cells (presumably by secreting CSF-1) and the microglial cells secrete growth factors such as EGF which stimulate glioblastoma migration. To explore its therapeutic potential in glioblastoma, PLX3397 was tested in an orthotopic tumor model in which 9L Fisher glioblastoma cells are implanted intracranially to syngeneic rats. As shown in Figure 2, PLX3397 inhibits the growth of the 9L tumors when dosed for 10 days using a chow formulation (nominal dose of 80 mg/kg). Tumor growth was determined using volumetric MRI.

Figure 2: PLX3397 Inhibits Intracranial Tumor Growth in the 9L Fisher Glioblastoma Rat Model



In an additional glioblastoma model it was demonstrated that co-cultured microglial cells enable invasion of GL261 glioblastoma cells in a manner that depends on both Fms and the epidermal growth factor (EGF) receptor (Coniglio 2012). Thus, both PLX3397 and erlotinib block invasion in this co-culture assay. Pharmacology studies demonstrate that the microglia depend on CSF-1 (secreted by the GL261 cells) and the GL261 cells are stimulated by microglial-derived EGF. In xenograft studies, PLX3397 reduced the number of tumor-associated microglia and glioblastoma invasion (Figure 3).

Figure 3: PLX3397 Inhibits Microglia/Macrophage Recruitment to GL261 Tumors in Vivo

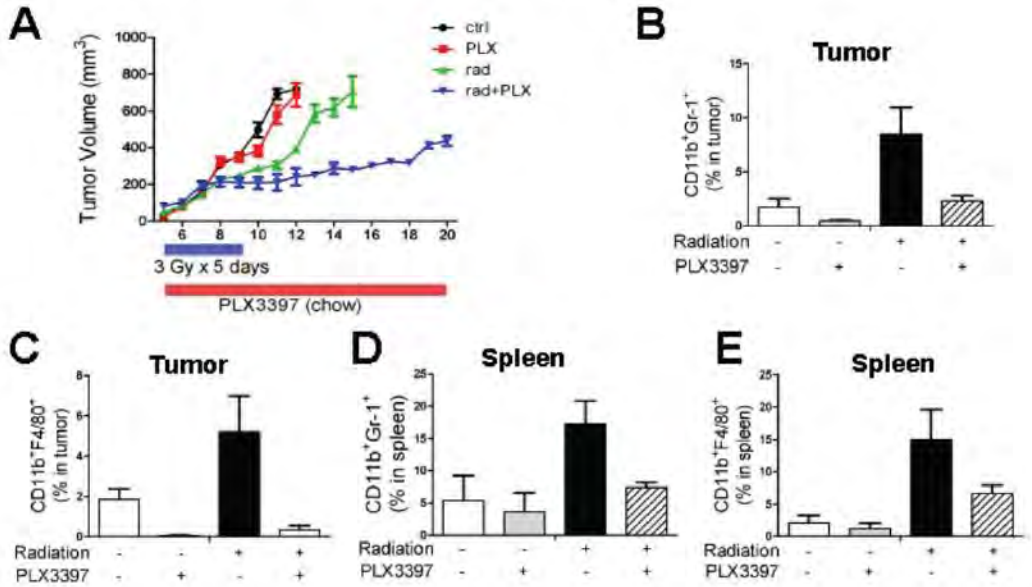


Note: Scale bar = 100 µm; *p <0.001 compared with control)

Growing evidence in the literature suggests that macrophages and microglial cells are recruited by tumor cells as a resistance mechanism in response to radiotherapy (Ahn 2010). Accordingly, in subcutaneously implanted RM-1 syngeneic prostate cancer tumor cells, there is enhanced recruitment of both tumor associated macrophages (TAMs) and myeloid derived suppressor cells (MDSCs) after 5 days of irradiation. In this model, irradiation has a modest effect on tumor growth, and PLX3397 treatment has essentially no single agent effect. However, the combination provides highly synergistic tumor control as shown in Figure 4 (panel A). The relative resistance to irradiation appears to correlate with higher levels of TAMs (panels B, D) and MDSCs (panels C, E) in both tumor and spleen. PLX3397 substantially reduces levels of TAMs and MDSCs, and blockade of these cells likely leads to radiosensitization. These results along with ongoing

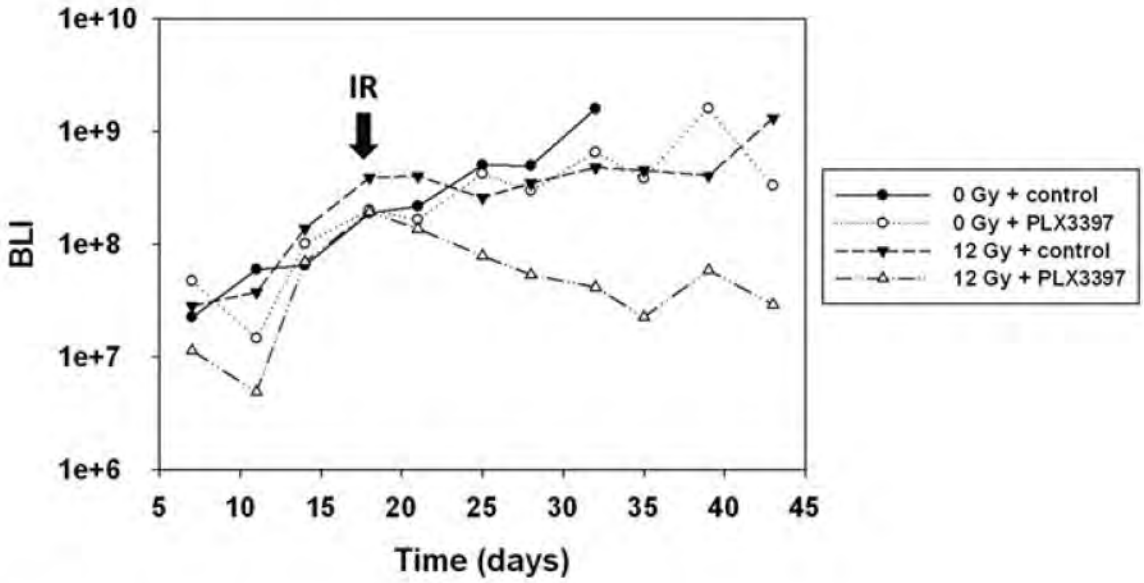
studies combining irradiation with PLX3397 in glioblastoma animal models strongly support the clinical evaluation of PLX3397 as a radiosensitizing anti-tumor agent.

Figure 4: PLX3397 Inhibits RM-1 Tumor Regrowth After Irradiation in Vivo



In a preliminary study, the radiosensitizing activity of PLX3397 has been explored directly in a mouse model of glioblastoma. In this model, U251 glioblastoma cells are implanted orthotopically within the cranium or nude mice. This study included 4 groups: (1) Control, (2) PLX3397 alone daily for 6 weeks, (3) Whole brain Irradiation with 12 Gy, and (4) Whole brain Irradiation with 12 Gy with PLX3397 given daily for 6 weeks starting the day of irradiation. As shown in Figure 5, the combination of PLX3397 with irradiation is clearly synergistic.

Figure 5: PLX3397 Synergizes with Irradiation in the U251 Glioblastoma Model



8.0 RATIONALE

As described above, there is a strong rationale for the use of a selective Fms inhibitor to decrease the role of activated microglia in GBM and to increase the efficacy of radiation and concurrent temozolomide. This study will provide an assessment of the safety and efficacy of PLX3397 added to standard radiation and temozolomide in patients with newly diagnosed GBM, compared to historical control data.

8.1 Route and Regimen

PLX3397 will be administered orally twice daily in capsule form at the dose described in Section 13.13.

8.2 Treatment Period

There are 4 sequential periods: 1-week PLX3397 monotherapy; 6-week PLX3397/RT/TMZ combination therapy; 4-week recovery; and, PLX3397/TMZ adjuvant therapy. PLX3397study drug will be administered twice daily either 7 days/week or 5 days/week (Monday through Friday) starting 1 week prior to the initiation of RT and will continue twice daily either 7 days/week or 5 days/week (Monday through Friday) during the 6-week course of RT. Four weeks after the completion of the course of RT, patients will be started on once-daily adjuvant temozolomide (Day 1-5 of a 28 day cycle) for up to 12 cycles as long as there is no disease progression or unacceptable toxicity and PLX3397 twice daily (28 days of a 28 day cycle) for as long as there is no disease progression or unacceptable toxicity.

9.0 OBJECTIVES

The study objectives are to assess the potential for PLX3397 to improve the efficacy of standard of care radiation therapy (RT) + temozolomide in patients with newly diagnosed glioblastoma (GBM). For Phase 1b dose escalation, the primary objective is identification of the recommended Phase 2 dose (RP2D). For Phase 2, the primary objective is the comparison of median Progression Free Survival (PFS) to historical control. Secondary objectives include the evaluation of overall survival (OS), pharmacokinetics (PK), correlative imaging studies, safety, and the exploratory endpoint of pharmacodynamic (PD) effects of PLX3397.

10.0 DESIGN

10.1 Description

This will be an open label, uncontrolled Phase 1b/2 trial in patients with newly diagnosed GBM who have recovered from from complete or partial surgical resection. All patients will be treated with PLX3397 in addition to standard-of-care combination radiation therapy (RT) plus temozolomide (TMZ) followed by adjuvant TMZ. During Phase 1b dose escalation, two PLX3397 administration schedules, 7 days/week vs. 5 days/week (M-F) will be explored. During Phase 2, patients will be treated with the RP2D.

There are 4 sequential periods: 1-week PLX3397 monotherapy; 6-week PLX3397/RT/TMZ combination therapy; 4-week recovery; and, PLX3397/TMZ adjuvant therapy. PLX3397 will be administered twice daily either 7 days/week or 5 days/week (Monday through Friday) starting 1 week prior to the initiation of RT and will continue twice daily either 7 days/week or 5 days/week (Monday through Friday) during the 6-week course of RT.

Phase 1b PLX3397 dose and schedule cohorts are shown in Table 2.

A detailed Trial Flow Chart is available in Section 6.0, and procedures by study day are provided in Section 13.0.

10.2 Number of Patients

For the Phase 1b portion of the study, 5 cohorts (2 cohorts from Amendment 1 and 3 from Amendment 2) are planned to be enrolled. Each cohort will consist of approximately 7 patients. Therefore, approximately 35 patients will be enrolled in Phase 1b. Additional patients may be required for replacement patients, or if lower dose cohorts (600 mg or 400 mg) are required. Phase 2 will enroll approximately 44 patients.

10.3 Number of Study Centers

The study will be performed at approximately 7-10 sites.

10.4 Duration of Patient Participation

Each patient will be offered continued dosing with PLX3397 and standard temozolomide up to 12 cycles of adjuvant treatment after radiation if this is well tolerated and there is no disease progression.

10.5 Duration of Study

The duration of the Phase 1b portion of the study will depend on the number of cohorts required and the need for replacement patients. For the Phase 2 portion of the study, a recruitment rate of 1 patient per site per month is anticipated. The total duration of enrollment is expected to be approximately 18 months. The duration of follow-up will depend on the prolongation of the median PFS; the study is powered to detect a median PFS of approximately 8 months.

11.0 SELECTION OF STUDY POPULATION

All patients must participate in the consent process. During the consent process, the person obtaining consent must inform the patient of all elements of informed consent. No protocol-specific procedures, including screening procedures, are to be performed until the patient has signed and dated an institutional review board (IRB)/independent ethics committee (IEC)-approved informed consent form. The study begins with the signing and dating of the informed consent form. Patients must also meet the inclusion and exclusion criteria to be enrolled in the study.

11.1 Inclusion Criteria

1. Male or female patients ≥18 years old.
2. Histologically confirmed definitive GBM or gliosarcoma by partial or complete surgical resection (i.e. not by biopsy only) within 5 weeks prior to PLX3397 administration (C1D1). Tumor must have a supratentorial component. For all patients, availability of an archival paraffin tumor block sufficient to generate at least 20 unstained slides; or, if a paraffin tumor block is unavailable, at least 20 unstained slides.
3. The patient must have recovered from the effects of surgery, post-operative infection, and other complications before study registration.

    a. A diagnostic contrast-enhanced MRI or CT scan of the brain must be performed preoperatively and postoperatively prior to the initiation of radiotherapy, i.e., within 28 days (14 days preferred) prior to study drug administration (C1D1).

    b. Patients unable to undergo MR imaging because of non-compatible devices can be enrolled, provided pre- and post-operative contrast-enhanced CT scans are obtained and are of sufficient quality.

2. Patients must receive RT at the participating institution.

3. Women of child-bearing potential must have a negative pregnancy test within 14 days of initiation of dosing and must agree to use an acceptable method of birth control while on study drug and for 3 months after the last dose. Women of non-childbearing potential may be included if they are either surgically sterile or have been postmenopausal for ≥1 year. Men of child-bearing potential must also agree to use an acceptable method of birth control while on study drug, and for 3 months after the last dose.

4. Karnofsky performance status of ≥70.

5. Adequate hematologic, hepatic, and renal function (absolute neutrophil count ≥1.5x 10^9/L, Hgb >10 g/dL, platelet count ≥100 x 10^9/L, AST/ALT ≤2.5x ULN, creatinine ≤1.5x ULN).

6. Willing and able to provide written informed consent prior to any study related procedures and to comply with all study requirements.

11.2 Exclusion Criteria

1. Evidence of recurrent GBM or metastases detected outside of the cranial vault.

2. Investigational drug use within 28 days of the first dose of PLX3397 or concurrently.

3. Prior use of Gliadel wafers or any other intratumoral or intracavitary treatment.

4. Prior radiation or chemotherapy for glioblastoma or glioma.

5. Prior chemotherapy or radiosensitizers for cancer of the head and neck (except for T1 glottic cancer) that would result in an overlap of radiation fields.

6. Prior allergic reaction to temozolomide.

7. History of Grade 2 (CTCAE v4) or greater acute intracranial hemorrhage.

8. Active cancer (either concurrent or within the last 3 years) that requires non-surgical therapy (e.g. chemotherapy or radiation therapy), with the exception of surgically treated basal or squamous cell carcinoma of the skin, melanoma in-situ, or carcinoma in-situ of the cervix.

9. Chronic active hepatitis B or C.

10. Refractory nausea and vomiting, malabsorption, biliary shunt, or significant bowel resection that would preclude adequate absorption of study drug.

11. Patients with serious illnesses, uncontrolled infection, medical conditions, or other medical history including abnormal laboratory results, which in the investigator's opinion would be likely to interfere with a patient's participation in the study, or with the interpretation of the results.

12. Women of child-bearing potential who are pregnant or breast feeding.

13. At Screening QTcF ≥450 msec for males and ≥470 msec for females.

11.3 Screen Failures

Patients who sign an informed consent form, are not assigned to a treatment, and do not receive study drug are defined as screen failures. For all screen failures, the investigator is to maintain a screening log that documents the screening number, patient initials, and reason(s) for screen failure. This information will be tracked in the EDC system and retained in the investigator's study files.

12.0 CONCOMITANT TREATMENT

Concomitant treatment is permitted if the medication is not expected to interfere with the evaluation of safety or efficacy of the study drug. During the study, if the use of any concomitant treatment becomes necessary (e.g., for treatment of an adverse event), the treatment must be recorded on the eCRF, including the reason for treatment, generic name of the drug, dosage, route, and date of administration.

Patients enrolling in studies with PLX3397 who are also receiving concomitant warfarin should have their anti-coagulation status carefully monitored, especially shortly after initiation of PLX3397, for the potential need to make adjustments in warfarin dosing. In particular, INR should be obtained just prior to initiation of PLX3397, within 1-2 weeks after initiation, and periodically thereafter. Dose adjustments of warfarin should be made as medically indicated.

Although PLX3397 does not appear to inhibit CYP drug-metabolizing enzymes to an important extent, caution is warranted when administering PLX3397 to subjects taking drugs that are highly dependent on CYP3A4 for metabolism and have a narrow therapeutic index. It is not known whether systemic exposure to these medications will demonstrate an increase while patients are receiving PLX3397.

Of the five major CYP isoforms, 3A4 (BFC) may be involved in Phase I metabolism of PLX3397, with possibly CYP1A2 playing a minor role. Until information regarding exposure-toxicity and exposure-response relationships are available with PLX3397, concomitant CYP3A4 inhibitors and inducers should be administered with caution, in the event they alter the systemic exposure to PLX3397 (see Attachment 2 for a list of strong CYP3A4 inhibitors and inducers). In general, strong inhibitors or inducers of CYP3A4 should be avoided unless absolutely necessary. These include anticonvulsants (phenytoin, carbamazepine, phenobarbital), mycin antimicrobials, and antiretrovirals. Strong CYP 3A4 inducers or inhibitors should be discontinued at least 14 days prior to the initiation of dosing with PLX3397.

13.0 PROCEDURES

13.1 Screening Evaluation

Within 21 days before study drug administration on C1D1 to radiation therapy, all patients will have a Screening evaluation that includes the following:

[Note: Safety assessments obtained as Standard of Care may be used for screening purposes.]

1. Sign and date an IRB/IEC-approved informed consent form before any study-specific screening procedures are performed.
2. Medical history.
3. Height, weight, vital signs (sitting blood pressure, pulse rate, respiratory rate, and temperature), and physical examination.
4. Standard 12-lead ECG.
5. Clinical laboratory evaluation [hematology, chemistry, serum pregnancy test (women of child-bearing potential); see Attachment 1]. Safety assessments obtained as Standard of Care may be used for screening purposes.
6. Availability of archival paraffin tumor block sufficient to generate at least 20 unstained slides (or at least 20 unstained slides).
7. Karnofsky performance status assessment.
8. MRI brain scan within 28 days (14 days preferred) of C1D1.
9. Recording of concomitant medications.

If screening tests and procedures are performed within 2 days prior to C1D1 PLX3397 administration and their results are available for the investigator to review within the 2-day period prior to C1D1 PLX3397 administration, the screening tests and procedures that would be repeated at C1D1 do not need to be repeated before C1D1 PLX3397 administration.

Patients who do not meet all inclusion and exclusion criteria will be noted as screen failures in the EDC system.

13.2 Cycle 1 Day 1 (- 2 Days), [4 week cycle]

The C1D1 visit must occur any Monday through Friday ≥3 weeks and ≤5 weeks since surgery. At this visit, all patients will return to the clinic and undergo the following procedures:

1. Weight, vital signs, neurological exam plus symptom-directed physical examination.

2. Clinical laboratory evaluation (hematology and serum chemistry).
3. For Phase 1b dose escalation patients only: Pre-dose blood sample collection for PK.
4. Pre-dose blood sample collection for PD response biomarkers and CD14/16 mononuclear cell counts.
5. Karnofsky performance status assessment.
6. MDA Symptom Inventory.
7. Recording of concomitant medications.
8. Initiation of dosing with study drug either 7 days/week or 5 days/week (Monday through Friday).
9. AE Monitoring, beginning after first dose of study drug.

13.3 Cycle 1 Day 8 (± 2 Days), [4 week cycle]

On C1D8, all patients will return to the clinic and undergo the following procedures:

1. Vital signs, neurological exam plus symptom-directed physical examination.
2. Clinical laboratory evaluation (hematology and serum chemistry).
3. For Phase 1b dose escalation patients only: Pre-dose and 1, 2, 4, and 6 hours post-dose blood sample collection for PK.
4. Pre-dose blood sample collection for PD response biomarkers and CD14/16 mononuclear cell counts.
5. Study drug compliance.
6. Recording of concomitant medications.
7. AE monitoring.
8. Initiation of radiation therapy and temozolomide.

13.4 Cycle 1 Day 15 (± 2 Days), [4 week cycle]

On C1D15, all patients will return to the clinic and undergo the following procedures:

1. For Phase 1b dose escalation patients only: Vital signs, neurological exam plus symptom-directed physical examination.

2. Clinical laboratory evaluation (hematology and serum chemistry).
3. For Phase 1b dose escalation patients only: Pre-dose and 1, 2, 4, and 6 hours post-dose blood sample collection for PK.
4. Study drug compliance.
5. Recording of concomitant medications.
6. AE monitoring.
7. Instruct patient to obtain C1D22 (± 2 days) hematology evaluation (CBC, differential count, platelet count) either at study site or local laboratory.

13.5 Cycle 2 Day 1 (± 2 Days), [3 week cycle]

On C2D1, all patients will return to the clinic and undergo the following procedures:

1. Weight, vital signs, neurological exam plus symptom-directed physical examination.
2. Standard 12-lead ECG.
3. Clinical laboratory evaluation (hematology and serum chemistry).
4. Pre-dose blood sample collection for PD response biomarkers.
5. Karnofsky performance status assessment.
6. Study drug compliance.
7. Recording of concomitant medications.
8. AE monitoring.
9. Instruct patient to obtain C2D8 (± 2 days) and C2D15 (± 2 days) hematology evaluation (CBC, differential count, platelet count) either at study site or local laboratory.

13.6 Cycle 2 Day 22 (± 2 Days), [3 week cycle]

On C2D22, all patients will return to the clinic and undergo the following procedures:

1. Weight, vital signs, neurological exam plus symptom-directed physical examination.
2. Clinical laboratory evaluation (hematology and serum chemistry).
3. Karnofsky performance status assessment.
4. MDA Symptom Inventory.
5. Study drug compliance.

6. Recording of concomitant medications.

7. AE monitoring.

8. Instruct patient to obtain RPD8 (± 2 days) hematology evaluation (CBC, differential count, platelet count) either at study site or local laboratory.

13.7 Day 1 of Cycle 3 (± 7 Days), [4 week cycle]

Following a 4 week recovery period, all patients will return to the clinic on C3D1 and undergo the following procedures:

1. Weight, vital signs, neurological exam plus symptom-directed physical examination.

2. Clinical laboratory evaluation (hematology and serum chemistry).

3. Pre-dose blood sample collection for PD response biomarkers.

4. Karnofsky performance status assessment.

5. MDA Symptom Inventory.

6. MRI brain scan to be obtained at the end of each even-numbered cycle.

7. Re-initiation of study drug dosing 7 days/week.

8. Initation of temezolomide adjuvant therapy. Temozolomide is taken orally once daily for 5 days followed by 23 days without treatment for each cycle beginning with C3D1.

9. Recording of concomitant medications.

10. AE monitoring.

13.8 Day 22 of Cycle 3 (± 2 Days), [4 week cycle]

On C3D22, all patients will return to the clinic and undergo the following procedures:

1. Weight, vital signs, neurological exam plus symptom-directed physical examination.

2. Clinical laboratory evaluation (hematology and serum chemistry).

3. Karnofsky performance status assessment.

4. MDA Symptom Inventory.

5. Study drug compliance.

6. Recording of concomitant medications.

7. AE monitoring.

13.9 Day 22 of Cycle 4+ (± 7 Days), [4 week cycle]

On Day 22 of Cycle 4 and all subsequent cycles, all patients will return to the clinic and undergo the following procedures:

1. Weight, vital signs, neurological exam plus symptom-directed physical examination.

2. Clinical laboratory evaluation (hematology and serum chemistry).

3. Karnofsky performance status assessment.

4. MDA Symptom Inventory.

5. MRI brain scan to be obtained at the end of each even-numbered cycle.

6. Study drug compliance.

7. Recording of concomitant medications.

8. AE monitoring.

13.10 Assessments After 01 October 2017 to Be Performed Approximately Every 12 Weeks

Commencing on 01 October 2017, patient visits, clinical laboratory testing, and MRI brain scans will be performed approximately every 12 weeks (please refer to the TRIAL FLOW CHART – Phase 2 for details).

13.11 End of Treatment

All patients who permanently discontinue PLX3397 are expected to return to the clinic within 30 days and undergo the following procedures:

1. Weight, vital signs, neurological exam plus symptom-directed physical examination.

2. Standard 12-lead ECG.

3. Clinical laboratory evaluation [hematology, serum chemistry, serum pregnancy test (women of child-bearing potential)].

4. Karnofsky performance status assessment.

5. MDA Symptom Inventory.

6. Study drug compliance.
7. Recording of concomitant medications.
8. AE monitoring.

13.12 Continued Dosing

Patients may continue once-daily adjuvant temozolomide (Day 1-5 of a 28-day cycle) for up to 12 cycles as long as there is no disease progression or unacceptable toxicity and PLX3397 twice daily (28 days of a 28-day cycle) for as long as there is no disease progression or unacceptable toxicity. After discontinuation of study drug, patients will continue to be followed for OS every 6 months. Study visits will occur at approximately 4-week intervals. Brain MRI scans should be obtained approximately every 8 weeks. The same method used at Screening should be used for all serial measurements.

13.13 Dose Levels for the Phase 1b Portion

13.13.1 Dose Escalation

A total of approximately 7 patients will be enrolled in each dose level (see Table 2). The starting dose level of PLX3397 will be 800 mg/day administered 7 days/week (Cohort 1).

Table 2: PLX3397 Dosing Cohorts

Cohort	Combination PLX3397/RT/TMZ		Adjuvant PLX3397/TMZ	
	PLX3397 Dose	PLX3397 Schedule	PLX3397 Dose	PLX3397 Schedule
-2	600 mg/day	5 days/week (M-F)[b]	800 mg/day[b]	7 days/week
-1	600 mg/day	7 days/week[a]	600 mg/day[a] 800 mg/day[b]	7 days/week
1	800 mg/day	7 days/week[a] 5 days/week (M-F)[b]	1000 mg/day[b]	7 days/week
2	1000 mg/day	5 days/week (M-F)[b]	1200 mg/day[b]	7 days/week

[a] Amendment 1.

[b] Amendment 2.

Study drug will be administered orally using a capsule formulation (200 mg per capsule). The total daily dose of PLX3397 will be divided and administered BID. For an uneven number of capsules, the larger dose will be administered in the morning.

For combination PLX3397/RT/TMZ PLX3397 treatment, dose escalation to the next highest cohort may occur after all patients have completed the 11-week DLT-observation period (i.e., 1-week PLX3397 monotherapy; 6-week PLX3397/RT/TMZ combination therapy; 4-week recovery). For adjuvant PLX3397/TMZ PLX3397 treatment, dose escalation to the next highest cohort may occur after all patients have completed an 8-week DLT-observation period (i.e.,

2 cycles of adjuvant treatment). For patients participating in Phase 1b, intra and inter patient dose escalation to a higher dose level/schedule will be permitted after that dose level/schedule has been established to be safe.

Prior to dose escalation, safety data will be collated and reviewed by the Sponsor and study sites by teleconference. A dose level will be considered unacceptable if 2 or more patients of the 6 eligible patients experience a DLT (see below). Should all 7 patients in the Cohort be analyzable for adverse events, only the first 6 will be considered in the determination of DLTs. A patient who misses more than 7 days of PLX3397 administration during the 7-week dosing period of Cycle 1 (4 weeks) and Cycle 2 (3 weeks) for reasons other than having had a DLT will be replaced. If 2 or more patients in a Cohort experience a DLT, no patients in the Cohort will be replaced.

If 2 or more of the first 6 patients in Cohort -2 (600 mg/day of PLX3397; 5 days/week [M-F]) experience a protocol-defined DLT, the combination will be considered too toxic and the study will be discontinued.

13.13.2 Dose-Limiting Toxicities

Dose-limiting toxicities will be assessed using CTCAEv4 grading criteria. During the Phase 1b portion of the study, the DLT window will consist of 11 weeks (1 week PLX3397 run-in, 6 weeks of PLX3397 in combination with RT/temozolomide, and 4 weeks of post-RT recovery). The following will be considered DLTs:

Hematologic DLTs

- Grade ≥3 febrile neutropenia
- Grade 4 neutropenia lasting for >7 days (growth factor support allowed)
- Grade 3 thrombocytopenia (platelets ≤50.0/μL) lasting for >7 days

Grade 3-4 lymphopenia is NOT considered a DLT.

Non-hematologic DLTs

- Any Grade ≥3 non-hematologic toxicity, **probably related to study drug,** EXCEPT for the following related AE's:
  - Grade ≥3 neurologic deficits considered to be due to the effects of tumor, resection, or expected post-surgical morbidities
  - Seizures of any grade, as this is commonly observed in this patient population
  - Grade ≥3 thromboembolic event, as this is commonly observed in this patient population
  - Grade 3 nausea, vomiting, or diarrhea that resolves to Grade ≤2 within 3 days of onset
  - Grade 3 headache, insomnia, or amnesia that resolves to Grade ≤2 within 14 days of onset
  - Grade 3 fatigue that resolves to ≤Grade 2 within 21 days of onset

- Grade 3 AST or ALT that resolves to ≤Grade 2 within 21 days of onset
- Grade ≥3 CPK, GGT, ALP, hypomagnesemia, or hypophosphatemia that is felt by the investigator to be clinically insignificant
- Alopecia of any Grade.

13.13.3 Liver Enzyme Abnormalities

PLX3397 can cause abnormalities in liver function that in some cases have been considered severe. Taking PLX3397 together with other medications that can cause liver function abnormalities may further increase the risk of severe liver injury. Liver laboratory abnormalities should be managed with dose reduction, treatment interruption, or treatment discontinuation.

Discontinuation of treatment should be considered if any of the following occurs:

- ALT or AST >8 x ULN
- ALT or AST >5 x ULN for more than 2 weeks
- ALT or AST >3 x ULN and Total bilirubin (Tbili) >2 x ULN or INR >1.5
- ALT or AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Plexxikon should be informed as soon as possible when any of the above occurs.

In the event that study medication is discontinued for any of the reasons above, and if enzyme elevations persist for more than 2 weeks and no clear alternative cause of the abnormalities are found, consideration should be given towards obtaining a liver biopsy, if there are no contraindications (e.g., bleeding diathesis).

Generally, rechallenge of patients with significant AST/ALT elevations (>5 x ULN, Grade 3) should not be attempted. Rechallenge can be considered if the patient has shown important benefit from the drug and other options are not available but must be discussed with the medical monitor prior to re-starting. The patient should be made aware of the potential risk, and consent to the rechallenge, and the institutional review board consulted.

If there is Grade 2 or higher ALT or AST elevation (i.e. >3x upper limit of normal) at any time during treatment, the patient should be followed closely, which includes the following:

- Repeating liver enzyme and serum bilirubin tests two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the patient is asymptomatic.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.

- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).
- Considering gastroenterology or hepatology consultations.

13.14 Dose Modification

13.14.1 Phase 1

PLX3397 or temozolomide dose reductions and interruptions will be permitted during the 11-week DLT window (Cycle 1 through Cycle 2, i.e., 1 week PLX3397 run-in, 6 weeks of PLX3397 + RT + temozolomide, and 4 weeks of post-RT recovery) only if a patient experiences a DLT (see Section 13.13.2 Dose-Limiting Toxicities). PLX3397 interruptions during the 11-week DLT window are also permitted for Grade 3 vomiting that persists despite optimal supportive care.

If a patient experiences a DLT during the 11-week DLT window, treatment continuation at a lower dose may be permitted at the discretion of the Investigator and in consultation with the Medical Monitor. PLX3397 dose reductions should occur in increments of 200 mg/day, depending on the toxicity grade, as noted in Table 3, PLX3397 Dose Modifications. For dose reductions see Section 13.13.1 Dose Escalation.

If dose interruption continues after the patient's scheduled C3D1 PLX3397 dose administration, the patient should discontinue study treatment and have the procedures outlined in Section 13.11 End of Treatment.

During the adjuvant treatment period, PLX3397 or temozolomide dose reductions and interruptions will be permitted in consultation with the Medical Monitor. PLX3397 dose reductions should occur in increments of 200 mg/day, depending on the toxicity grade, as noted in Table 3 PLX3397 Dose Modifications. For dose reductions see Section 13.13.1 Dose Escalation.

If a patient experiences a DLT, temozolomide dose reduction should be made according to the prescribing information noted in Attachment 4 and also summarized in Section 16.

13.14.2 Phase 2

Phase 2 will not include a separate dose escalation design, as there has been no delayed toxicity observed for PLX3397 in extensive nonclinical and clinical evaluations to date, and temozolomide is given at a lower intensity schedule compared to the daily schedule during concomitant radiation therapy. During Phase 2, reduction/interruption of dosing for adverse events may take place at any time during the study according to the guidelines in Table 3.1, Table 3.2, and Table 3.3.

Dose reduction/interruption guidelines for hematologic and nonhematologic treatment-related TEAEs are based on severity. Dose interruptions can be implemented at the discretion of the treating Investigator to manage intolerable or clinically significant toxicity. If a dose interruption is required, study assessments should be performed as scheduled, irrespective of the study drug delay, with the exception of PK assessments, which should be deferred until treatment is resumed. Interruptions due to toxicity lasting >14 days require treatment discontinuation unless the medical monitor approves continuation.

Dose reductions of temozolomide should be made according to the prescribing information noted in Attachment 4 and also summarized in Section 16.

Below are guidelines for dosage modification for PLX3397-related toxicities as well as guidelines for their management. Dose reductions should occur in increments of 200 mg/day, depending on the toxicity grade, as noted in Table 3, Table 4, and Table 5. As the capsules are provided in 200 mg strengths, dose reduction should occur by a reduction of one capsule from either the morning or evening dose.

Up to 5 days of treatment interruption are permitted for any reason. Interruptions of 6 to 7 treatment days will be considered an acceptable protocol deviation. For interruptions of 8 days or greater, continuation of patients in the study should be discussed with the medical monitor.

Temozolomide dose reduction should be made according to the prescribing information noted in Attachment 4 and also summarized in Section 16.

These parameters are only a guide and are not intended to supersede the clinical judgment of the treating physician. All adjustments should be made in consultation with the Medical Monitor.

Table 3: PLX3397 Dose Modification Guidelines for Treatment-Related Toxicities, Excluding Liver Function

All Drug-Related Toxicities	Frequency	When to Hold or Stop	When to Restart and Restart Dose (See Table 2 for dose levels.)
Grade 3 or 4 neutropenia	1st Appearance	Interrupt until ANC recovers to $\geq 1 \times 10^9$/L; growth factor support permitted	If recovered to ANC $\geq 1 \times 10^9$/L in $\leq$7 days, resume at same dose.
			If not recovered to ANC $\geq 1 \times 10^9$/L after 7 days, reduce dose by 1 dose level.
	2nd Appearance	Interrupt until ANC recovers to $\geq 1 \times 10^9$/L; growth factor support permitted	If recovered to ANC $\geq 1 \times 10^9$/L in $\leq$7 days, reduce dose by 1 dose level.
			If not recovered to ANC $\geq 1 \times 10^9$/L after 7 days, reduce dose by 2 dose levels.
	3rd Appearance	Interrupt until ANC recovers to $\geq 1 \times 10^9$/L; growth factor support permitted	If recovered to ANC $\geq 1 \times 10^9$/L in $\leq$7 days, reduce dose by 1 dose level.
			If not recovered to ANC $\geq 1 \times 10^9$/L after 7 days, discontinue permanently.
	4th Appearance	Discontinue permanently; growth factor support permitted	N/A
Grade 3 or 4 febrile neutropenia	1st Appearance	Interrupt until ANC and fever recover; provide growth factor support	If recovered to ANC $\geq 1 \times 10^9$/L and T $\leq$38°C in $\leq$7days, reduce dose by 1 dose level.
			If not recovered to ANC $\geq 1 \times 10^9$/L after 7 days, discontinue permanently.
	2nd Appearance	Interrupt until ANC and fever recover; provide growth factor support	If recovered to ANC $\geq 1 \times 10^9$/L and T $\leq$38°C, reduce dose by an additional 1 dose level.
			If not recovered to ANC $\geq 1 \times 10^9$/L after 7 days, discontinue permanently.
	3rd Appearance	Discontinue permanently; provide growth factor support	N/A
Grade 4 thrombo-cytopenia	1st Appearance	Interrupt until PLT $\geq 75 \times 10^9$/L	If recovered to PLT $\geq 75 \times 10^9$/L $\leq$7 days, resume at same dose.
			If not recovered to PLT $\geq 75 \times 10^9$/L after 7 days, reduce dose by 1 dose level.
	2nd Appearance	Interrupt until PLT $\geq 75 \times 10^9$/L	If recovered to PLT $\geq 75 \times 10^9$/L in $\leq$7 days, reduce dose by 1 dose level.
			If not recovered to PLT $\geq 75 \times 10^9$/L after 7 days, reduce dose by 2 dose levels.
	3rd Appearance	Interrupt until PLT $\geq 75 \times 10^9$/L	If recovered to PLT $\geq 75 \times 10^9$/L in $\leq$7 days, reduce dose by 1 dose level.
			If not recovered to PLT $\geq 75 \times 10^9$/L after 7 days, discontinue permanently.
	4th Appearance	Discontinue permanently	N/A

All Drug-Related Toxicities	Frequency	When to Hold or Stop	When to Restart and Restart Dose (See Table 2 for dose levels.)
Non-Hematologic Grade 3 (excluding trans-aminase increases)	1st Appearance[a]	Interrupt until resolved (Grade 0 -1); start symptomatic treatment if possible	If recovered ≤5 days, resume at same dose.
			If symptoms persist for >5 days despite supportive management, reduce by 1 dose level.[b]
	2nd Appearance	Interrupt until resolved (Grade 0-1); start symptomatic treatment if possible	If recovered ≤5 days, reduce dose by 1 dose level.
			If symptoms persist for >5 days despite supportive management, discontinue permanently.
	3rd Appearance	Discontinue permanently; start symptomatic treatment if possible	N/A
Non-Hematologic Grade 4 (excluding trans-aminase increases)	1st Appearance	Interrupt until resolved (Grade 0-1); start symptomatic treatment if possible	If recovered <5 days, reduce by 1 dose level.
			If symptoms persist for ≥5 days despite supportive management, discontinue permanently.
	2nd Appearance	Discontinue permanently; start symptomatic treatment if possible	N/A

ANC = absolute neutrophil count; INR = international normalized ratio; N/A = not applicable; PLT = platelet; T = temperature; ULN = upper limit of normal

[a] Except for cases of Grade 3 emesis.

[b] Except in cases of Grade 3 symptomatic rash.

Dose interruptions for Grade 2 non-hematologic toxicity for up to 1 week can be implemented at the discretion of the treating physician to manage intolerable or clinically significant toxicity. No dose reduction is required when resuming treatment.

Table 4: Dose Modification Guidelines for Liver Function Abnormalities

Toxicity Grade CTCAE v4.0	Initial Action	Outcome	Action
ALT or AST Grade 2 (>3-5 × ULN); No increase in bilirubin[a]	Re-check ALT and AST immediately Hold study drug Monitor weekly[b] Check for changes to medications and for symptoms	Resolution to Grade 0–1 or baseline (no bilirubin increase)	Restart on resolution Grade 0–1 or baseline at 1 dose lower (reduce by one 200 mg capsule)
Grade 3 ALT or AST increase (>5-20 × ULN); No increase in bilirubin[a]	Re-check ALT and AST immediately Hold study drug Monitor 2x/week[b] Check for changes to medications and for symptoms	Resolution to Grade 0–1 or baseline (no bilirubin increase) within 14 days	Restart on resolution to Grade 0–1 or baseline at 1 dose lower (reduce by one 200 mg capsule)
		ALT and AST not decreasing within 14 days of holding study drug	Proceed to liver evaluation as outlined in Table 5. Restart only on resolution to Grade 0-1/baseline at 1 dose lower (reduce by one 200 mg capsule); For max AST or ALT >8 × ULN, consult with medical monitor prior to re-start
Grade 4 ALT or AST (>20 × ULN)	Discontinue treatment Monitor 2x/week until resolution to Grade 2 Follow-up until resolution Grade 0–1 or baseline Check for changes to medications and for symptoms	All outcomes	Discontinue treatment; Proceed to liver evaluation as outlined in Table 5. If clear confirmed alternate cause, restart on resolution to Grade 0–1 or baseline at 1 dose lower (reduce by one 200 mg capsule)
Any grade ALT or AST increase[a] with any bilirubin increase or signs of hypersensitivity	Discontinue treatment Monitor 2x/week until resolution to Grade 2 Follow-up until resolution Grade 0-1 or baseline Check for changes to medications and for symptoms	All outcomes	Discontinue treatment; Proceed to liver evaluation as outlined in Table 5. If clear confirmed alternate cause, restart on resolution to Grade 0–1 or baseline at 1 dose lower (reduce by one 200 mg capsule)

ALT = alanine aminotransferase; AST = aspartate aminotransferase;
CTCAE = Common Terminology Criteria for Adverse Events; ULN = upper limit of normal

[a] An increase in bilirubin is defined as all of the following: total bilirubin >ULN, total bilirubin >20% above baseline, and direct bilirubin is >ULN. If all of these conditions are met, then bilirubin is considered increased and should be immediately re-checked. Pexidartinib treatment should be immediately discontinued for increased bilirubin unless and until there is a clear, confirmed alternate cause.

[b] If ALT, AST, or bilirubin worsens during the monitoring period, follow the applicable guidance for the worst toxicity grade.

Table 5: Additional Liver Evaluation

Evaluation	Comments
Increase frequency of testing liver chemistries to twice per week, including INR, and continue until liver chemistries have stabilized, and then reduce to weekly until liver chemistries return to normal or baseline.	Investigational treatment may be started after liver function tests recover to Grade 0 to 1 or baseline level, and in consultation with Medical Monitor.
Detailed history focusing on medications and substances used: alcohol, change in medication dosages, new medications added, attention to use of acetaminophen, OTC medication use, and recreational drug use. Check for change in diet or use of dietary supplements, with particular attention to dose and duration of any herbal product.	Suspect medications will be discontinued or substituted for if possible.
Detailed medical history and physical examination seeking new abnormalities.	Evaluate abnormalities found.
Full serological evaluation for hepatitis A, B, C, and E (IgG and IgM). Check for autoimmune hepatitis with serological laboratory studies.	If viral hepatitis or autoimmune hepatitis suggested, have patient evaluated by hepatologist.
Liver ultrasound performed to evaluate liver and biliary tree.	Evaluate any abnormalities found.
Check history for exposure to chemical agents.	Remove chemical exposure and have patient seen by hepatologist.
Obtain hepatology consult if liver function continues to rise beyond 14 days.	Contact Medical Monitor.
We request that cases be discussed with the Medical Monitor as defined in the protocol whenever investigational product is being held for liver function test abnormality.	

Ig = Immunoglobulin; INR = international normalized ratio; OTC = over-the-counter

For suspected cases of cholestatic liver injury (eg, aminotransferase increase concurrent with hyperbilirubinemia, or liver biopsy suggesting cholestasis and/or ductopenia), patients will be followed to assess long-term outcome. Additional diagnostic and follow-up procedures might be implemented as appropriate to fully assess the event.

13.15 Discontinuation of Treatment, Patient Withdrawal, and Replacement

The reasons a patient may discontinue or be withdrawn from the study include, but are not limited to, adverse event, disease progression, patient request, investigator decision, protocol violation, patient noncompliance, and study termination by the Sponsor. When a patient discontinues or is withdrawn, the investigator will notify the Sponsor and should perform the procedures indicated in the End of Rx column in the trial flow chart within 30 days after discontinuation of study drug and prior to initiation of any therapy. After discontinuation of study drug, patients and/or their families will continue to be monitored by telephone every 6 months for OS.

Patients withdrawn from the study for reasons other than toxicity or disease progression (e.g. protocol violation or noncompliance) may be replaced at the discretion of the medical monitor and the investigator. Study drug administration may be discontinued for an adverse event or at the discretion of the investigator.

13.16 Stopping Rules

The Plexxikon Medical Monitor will monitor safety data throughout the course of the study. The Medical Monitor will review SAEs within timeframes mandated by company procedures and will review trends, laboratory analytes, and adverse events at periodic intervals and provide for interim safety analyses if appropriate. Safety data across all study patients will be reviewed at planned bimonthly teleconferences with all participating sites.

For Phase 1 dose escalation, a dose level will be considered unacceptable if 2 or more patients of the 6 eligible patients experience a DLT (see below). Should all 7 patients in the Cohort be analyzable for adverse events, only the first 6 will be considered in the determination of DLTs. A patient who misses more than 7 days of PLX3397 administration during the 7-week dosing period of Cycle 1 (4 weeks) and Cycle 2 (3 weeks) for reasons other than having had a DLT will be replaced. If 2 or more patients in a Cohort experience a DLT, no patients in the Cohort will be replaced.

If 2 or more of the first 6 patients in Cohort -2 (400 mg/day of PLX3397) experience a protocol-defined DLT, the combination will be considered too toxic and the study will be discontinued.

After approximately 50% of the planned Phase 2 patients have been completed their concurrent radiation therapy, an overall interim safety summary will be reviewed by the Medical Monitor and principal investigators to ensure that the potential clinical benefit outweighs the observed clinical risk to date. If the safety observations do not warrant continued enrollment, the study will be discontinued.

14.0 STUDY DRUG

14.1 Study Drug Administration

PLX3397 will be dosed orally using a capsule formulation (200 mg per capsule), twice daily in the fasting state with 240 mL (8 oz) of room-temperature water. The PLX3397 daily dose should be divided and administered twice daily approximately 12 hours apart. When the dose cannot be evenly divided, the higher of the two doses should be administered in the morning. For example, the PLX3397 1000 mg daily dose should be divided 600/400 AM/PM. For each dose, the patient should fast at least 1 hour before and 1 hour after administration. Patients will be permitted to eat a low-fat snack (e.g., crackers, toast, tea) during the fasting period if needed.

Temozolomide will be administered once daily, either in the morning or evening, also in the fasting, as noted in Section 16, either before or after PLX3397.

Study drug should be taken at approximately the same times of day, approximately 12 hours apart. On PK collection days, the morning dose of PLX3397 will be given at the clinical site; patients should be instructed NOT to take the study drug at home the morning of the clinic visit. The time of dosing will be recorded; patients will then take the evening dose at home. Between clinic visits, patients will take the study drug at home and record dosing information on the dosing diary. Missed doses (generally outside of a + 2 hour dosing window) should be skipped and not administered as a double dose at the next administration. Patients who vomit their dose should be instructed to NOT to make up that dose.

14.2 Packaging and Labeling

PLX3397-HCl capsules (200 mg strength of the active free base of PLX3397) are manufactured, packaged, and labeled according to GMP and GCP at the following address:

Catalent Pharma Solutions
10245 Hickman Mills Drive
Kansas City, MO 64137

14.3 Storage and Stability

PLX3397-HCl capsules will be stored at the clinical site, as indicated on the study drug label, i.e., room temperature (15-30°C).

Patients will be requested to store the study drug at the recommended storage conditions noted on the label, out of the reach of children or other cohabitants.

14.4 Study drug Accountability, Reconciliation, and Return

The investigator is accountable for all study drug supplied by the Sponsor. The designated copies of the completed dispensing and inventory record will be returned to the Sponsor after the Sponsor has performed accountability procedures. Returned and unused study drug should be destroyed and documented at the investigative site in accordance with GCP, after the study monitor has performed drug accountability.

14.5 Study Drug Compliance

At each clinic visit, patients will be questioned about their compliance with study drug administration, and their dosing diary should be reviewed.

15.0 RADIATION THERAPY

15.1 Dose Specifications and Schedule

Intensity Modulated RT (IMRT) is allowed, but the modality chosen at registration must be used for the entire course of treatment. Proton beam therapy is not allowed. For both IMRT and 3D-CRT plans, one treatment of 2 Gy will be given daily 5 days per week for a total of 60 Gy over

approximately 6 weeks. All portals shall be treated during each treatment session, for each course/sub-course of therapy, i.e. for the initial and boost phases. Doses are specified such that at least 95% of the Planning Target Volume (PTV) shall receive 100% of the prescribed dose; Dose Volume Histograms (DVHs) are necessary to make this selection.

15.2 Technical Factors

Treatment shall be delivered with megavoltage machines with a minimum energy of 6 MV photons. Selection of the appropriate photon energy/energies should be based on optimizing the radiation dose distribution within the target volume and minimizing dose to non-target normal tissue. Source skin distance for SSD techniques or source axis distance for SAD techniques must be at least 80 cm. Treatment with electrons or brachytherapy is not permissible.

15.3 Localization, Simulation, and Immobilization

The patient shall be treated in the supine or other appropriate position for the location of the lesion. A head-holding device to ensure adequate immobilization during therapy and ensure reproducibility is strongly recommended. Simulation may include a dedicated radiotherapy simulator or a virtual simulation using a treatment planning CT. Fusion with MR images is strongly recommended, whenever feasible.

For patients accrued to the protocol, treatment verification and documentation should be carried out, at least for the first treatment fraction, and more frequently, based on institutional policy; weekly verification is common. We suggest orthogonal images for documenting isocenter setup accuracy for the first fraction. These orthogonal images can be obtained with film or EPID. Other imaging techniques are possible, for example, the BrainLab ExacTrac system that uses two orthogonal imaging panels irradiated with KV x-rays. Another example is the volume images obtained with cone-beam CT, or helical tomotherapy or any other CT capability that is integrated with the treatment unit. For units with built-in or “on-rail” MR capabilities, if the weekly imaging is performed with MR images, these must be fused with the baseline planning CT for purposes of verification.

15.4 Treatment Planning/Target Volumes

Treatment plans may include opposed lateral fields, a wedge pair of fields, rotation, or multiple field techniques. Intensity-modulated inverse-planned approaches are permitted. Any of the methods of IMRT (including tomotherapy and volumetric arc-modulated techniques) may be used, subject to protocol localization and dosimetry constraints. CT-based treatment planning is necessary to assure accuracy in the selection of field arrangements. MRI-fusion for accurate target delineation is strongly recommended.

15.4.1 Initial Target Volume

Target volumes will be based upon postoperative-enhanced MRI. Preoperative imaging may be used for correlation and improved identification as clinically necessary and relevant. Two

planning target volumes (PTV) will be defined, as outlined below. The initial gross tumor volume (GTV1) will be defined by either the T2 or the FLAIR abnormality on the post-operative MRI scan In addition to the T2 and FLAIR volume, GTV1 must also include all postoperative MRI enhancement, and the surgical cavity. The initial clinical target volume (CTV1) will be the GTV plus a margin of 2 cm. If no surrounding edema is present, or the GTV1 volume is identical to the GTV2 volume, the initial planning target volume (PTV1) should include the contrast-enhancing lesion (and should include the surgical resection cavity) plus a 2.5-cm margin. The CTV1 margin may be reduced to as little as 0.5 cm around natural barriers to tumor growth such as the skull, ventricles, falx, etc, and also to allow sparing of the optic nerve/chiasm, or other critical structures, if necessary. The initial planning target volume (PTV1) is an additional margin of 3 to 5 mm, depending upon localization method and reproducibility, at each center. PTV margins account for variations in set-up and reproducibility. Reducing PTV margins to modify organ at risk (OAR) dose(s) is not generally permissible. However, OAR must be defined, along with a planning risk volume (PRV) for each OAR. Each PRV will be its OAR plus 3 mm. In the event that an OAR is in immediate proximity to a PTV such that dose to the OAR cannot be constrained within protocol limits, a second PTV (PTVoverlap), defined as the overlap between the PTV1 and the particular PRV of concern, may be created. Dose to the PTVoverlap must be as close as permissible to 46 Gy while not exceeding the OAR dose limit.

15.4.2 Boost Target Volume

The boost gross tumor volume (GTV2) will be defined by the contrast-enhanced T1 abnormality on the post-operative MRI scan. This must also include the surgical cavity. The boost clinical target volume (CTV2) will be the GTV plus a margin of 2 cm. The CTV2 margin may be reduced to as little as 0.5 cm around natural barriers to tumor growth such as the skull, ventricles, falx, etc, and also to allow sparing of the optic nerve/chiasm, or other critical structures, if necessary. The boost planning target volume (PTV2) is an additional margin of 3 to 5 mm, depending upon localization method and reproducibility, at each center. PTV margins account for variations in set-up and reproducibility. Reducing PTV margins to modify organ at risk (OAR) dose(s) is not generally permissible. However, OAR must be defined, along with a planning risk volume (PRV) for each OAR. Each PRV will be its OAR plus 3 mm. In the event that an OAR is in immediate proximity to a PTV such that dose to the OAR cannot be constrained within protocol limits, a second PTV (PTVoverlap), defined as the overlap between the PTV2 and the particular PRV of concern, may be created (the overlap is the intersection between the PTV1 and the PRV). Dose to the PTVoverlap must be as close as permissible to 14 Gy while not exceeding the OAR dose limit.

15.4.3 Dose Guidelines

The initial target volume will be treated to 46 Gy in 23 fractions. After 46 Gy, the conedown or boost volume will be treated to a total of 60 Gy, with seven additional fractions of 2 Gy each (14 Gy boost dose).

Isodose distributions for the initial target volume (PTV1) and the conedown target volume (PTV2) are required on all patients. A composite plan is required showing the respective target volumes. The inhomogeneity within the target volume shall be kept to ± 10% of the prescribed dose.

The minimum dose to the target volume should be kept within 10% of the prescribed. Doses are specified such that at least 95% of the PTV shall receive 100% of the prescribed dose; DVHs are necessary to make this selection.

15.4.4 Dose Limitations and Critical Structures

In addition to the above defined GTVs, CTVs and PTVs the lenses of both eyes, both retinae, both optic nerves, the optic chiasm, and the brainstem must be defined. The maximum point (defined as a volume greater than 0.03 cc) doses permissible to the structures are listed in the table below.

Table 6: Maximum Doses Permissible for Critical Structures

Critical Structure	Maximum Dose
Lenses	8 Gy
Retinae	50 Gy
Optic Nerves	56 Gy
Optic Chiasm	56 Gy
Brainstem	61 Gy

15.5 Compliance Criteria

For all patients, as mentioned above, two PTV prescriptions, PTV1 and PTV2 will be used and the prescription isodose (46 Gy for PTV1 and 14 Gy for PTV2) must cover >95% of the PTV volume; therefore, the total dose in the PTV2 volume will be 60 Gy. The minimum acceptable dose within PTV1 will be 41.4 Gy (90% of 46 Gy), and in the PTV2 volume, it will be 54 Gy (90% of 60 Gy). This minimum dose must cover 100% of the PTV. If the minimum dose falls below these parameters, an unacceptable deviation will be assigned. The maximum dose for the PTV2 should not exceed 66 Gy (110% of 46 Gy). If the maximum doses exceed these parameters, an unacceptable deviation will be assigned.

Up to 5 days of treatment interruption are permitted for any reason. Interruptions of 6 to 7 treatment days will be considered an acceptable protocol deviation. For interruptions of 8 days or greater, continuation of patients in the study should be discussed with the medical monitor.

15.6 Radiation Therapy Adverse Events

15.6.1 Acute

Expected acute radiation-induced toxicities include hair loss, fatigue, and erythema or soreness of the scalp. Potential acute toxicities include nausea and vomiting as well as temporary aggravation of brain tumor symptoms such as headaches, seizures, and weakness. Reactions in the ear canals and on the ear should be observed and treated symptomatically; these reactions could result in short-term hearing impairment. Dry mouth or altered taste have been occasionally reported.

15.6.2 Early Delayed

Possible early delayed radiation effects include lethargy and transient worsening of existing neurological deficits occurring 1-3 months after radiotherapy treatment.

15.6.3 Late Delayed

Possible late delayed effects of radiotherapy include radiation necrosis, endocrine dysfunction, and radiation-induced neoplasms. In addition, neurocognitive deficits, which could lead to mental slowing and behavioral change, are possible. Permanent hearing impairment and visual damage are rare. Cataracts can be encountered.

16.0 TEMOZOLOMIDE THERAPY

16.1 Temozolomide During Concomitant Radiation Therapy

Temozolomide will be administered continuously from day 1 of radiotherapy to the last day of radiotherapy at a daily oral dose of 75 mg/m^2 for a maximum of 49 days. The drug will be administered orally 1 hour before each session of radiotherapy during weekdays (Monday through Friday). During weekends without radiotherapy (Saturday and Sunday), the drug will be taken in the morning.

The dose will be determined using actual body surface area (BSA) as calculated in square meters at the beginning of the concomitant treatment. The BSA will be calculated from the height obtained at the pretreatment visit and the weight obtained at the visit immediately before the first day of treatment. Capsules of temozolomide are available in 5, 20, 100, 140, 180, and 250 mg. The daily dose will be rounded to the nearest 5 mg. If the investigator does not want to prescribe the temozolomide 5 mg unit strength, he/she should round off the dose to the closest 10 mg. For example, for a 1.7 m^2 subject, the 75 mg/m^2 dose would be 127.5 mg and the dose would be rounded off to 120 mg. For the same subject, the 150 mg/m^2 dose would be 255 mg and the dose would be rounded off to 260 mg. The exact dose administered should be recorded in the CRF. Each daily dose should be given with the least number of capsules.

Patients will be instructed to swallow the capsules whole, in rapid succession, without chewing them. If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed

before the next scheduled dose. The capsules should be taken on an empty stomach, therefore a minimum of 2 hours after eating and with no food consumption for at least 1 hour after temozolomide administration. Although, nightly administration just before bedtime has been reported to improve tolerance, the low daily dose administered during radiation is very well tolerated and administration in the morning before radiation dosing is required for this protocol. Administration of the higher dosing regimen during the adjuvant phase of the protocol should be performed using the nightly administration.

Antiemetic prophylaxis is usually not required for the continuous daily dosing schedule (during radiation). However, prophylaxis with a 5-HT3 antagonist is recommended prior to administration of the first few temozolomide doses and should be administered orally 30 to 60 minutes before temozolomide treatment. Most patients report optimal nausea control with the use of a 5-HT3 antagonist. Routine use of antiemetics is recommended during the adjuvant phase of treatment. Additionally, pneumocystis carinii prophylaxis is at the discretion of the Investigator during the radiation phase.

During the 4-week break after completion of radiotherapy, neither temozolomide nor study drug will be administered.

16.2 Post-Radiation Temozolomide

Patients will receive up to 12 cycles of adjuvant temozolomide at a dose of 150-200 mg/m^2 Days 1-5 of a 28-day cycle and along with PLX3397. Temozolomide will be administered orally once per day for 5 consecutive days (Days 1-5) of a 28-day cycle. The starting dose for the first cycle will be 150 mg/m^2/day, with a single dose escalation to 200 mg/m^2/day in subsequent cycles if no treatment-related adverse events >Grade 2 are noted.

The start of the first cycle will be scheduled 28 days ± 7 days after the last day of radiotherapy. The start of all subsequent cycles (2-12) will be scheduled every 4 weeks (28 days ± 7 days) after the first daily dose of temozolomide of the preceding cycle.

The dose will be determined using the BSA calculated at the beginning of each treatment cycle. The BSA will be calculated from the height obtained at the pretreatment visit and from the weight obtained at the visit immediately before each cycle. Capsules of temozolomide are available in 5, 20, 100, 140, 180, and 250 mg. The daily dose will be rounded to the nearest 5 mg. If the investigator does not want to prescribe the temozolomide 5 mg unit strength, he/she should round off the dose to the closest 10 mg. For example for a 1.7 m^2 subject, the 75 mg/m^2 dose would be 127.5 mg and the dose would be rounded off to 120 mg. For the same subject, the 150 mg/m^2 dose would be 255 mg and the dose would be rounded off to 260 mg. The exact dose administered should be recorded in the CRF. Each daily dose should be given with the least number of capsules.

Patients will be instructed to fast at least 2 hours before and 1 hour after temozolomide administration. Water is allowed during the fast period. Patients will be instructed to swallow the capsules whole, in rapid succession, without chewing them. Treatment should be given at night.

If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose.

Antiemetic prophylaxis with a 5-HT3 antagonist is strongly recommended and should be administered 30 to 60 minutes before temozolomide administration.

Dose reductions of temozolomide during the adjuvant period should be made according to the prescribing information, as summarized below.

Table 7: Temozolomide Dose Levels for Maintenance Treatment

Dose Level	Dose (mg/m^2/day)	Remarks
-1	100	Reduction for prior toxicity
0	150	Dose during Cycle 1
1	200	Dose during Cycles 2-6 in absence of toxicity

Table 8: Temozolomide Dose Reduction or Discontinuation During Maintenance Treatment

Toxicity	Reduce TMZ by 1 Dose Level[a]	Discontinue TMZ
Absolute Neutrophil Count	$<1.0 \times 10^9$/L	See footnote[b]
Platelet Count	$<50 \times 10^9$/L	See footnote[b]
CTC Non-hematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 3	CTC Grade 4[b]

TMZ = temozolomide; CTC = Common Toxicity Criteria

[a] TMZ dose levels are listed in Table 7.

[b] TMZ is to be discontinued if dose reduction to <300 mg/m^2 is required or if the same Grade 3 nonhematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction.

16.3 Temozolomide Prescribing Information

Full temozolomide prescribing information is located in Attachment 4. Key features are highlighted below.

16.3.1 Storage and Stability

The capsules are packaged in amber glass bottles and should be stored at 25°C. Temperature excursions between 15 and 30°C are permissible. Refer to the commercially labeled bottles for expiration dating.

16.3.2 Pharmacokinetics

Temozolomide is rapidly and completely absorbed after oral administration; peak plasma concentrations occur in 1 hour. Food reduces the rate and extent of temozolomide absorption. Mean peak plasma concentration and AUC decreased by 32% and 9%, respectively, and T_{max} increased 2-fold (from 1.1 to 2.25 hours) when temozolomide was administered after a modified high-fat breakfast.

Temozolomide is rapidly eliminated with a mean elimination half-life of 1.8 hours and exhibits linear kinetics over the therapeutic dosing range. Temozolomide has a mean apparent volume of distribution of 0.4 L/kg (%CV=13%). It is weakly bound to human plasma proteins; the mean percent bound of drug-related total radioactivity is 15%.

16.3.3 Metabolism and Elimination

Temozolomide is spontaneously hydrolyzed at physiologic pH to the active species, 3-methyl-(triazen-1-yl)imidazole-4-carboxamide (MTIC) and to temozolomide acid metabolite. MTIC is further hydrolyzed to 5-amino-imidazole-4-carboxamide (AIC), which is known to be an intermediate in purine and nucleic acid biosynthesis and to methylhydrazine, which is believed to be the active alkylating species. Cytochrome P450 enzymes play only a minor role in the metabolism of temozolomide and MTIC.

16.3.4 Special Populations

Creatinine Clearance

Caution should be exercised when temozolomide is administered to patients with severe renal impairment. Temozolomide has not been studied in patients on dialysis.

Hepatically Impaired Patients

In a pharmacokinetic study, the pharmacokinetics of temozolomide in patients with mild to moderate hepatic impairment (Child's-Pugh Class I-II) were similar to those observed in patients with normal hepatic function. Caution should be exercised when temozolomide is administered to patients with severe hepatic impairment.

Gender

Population pharmacokinetic analysis indicates that women have an approximately 5% lower clearance (adjusted for body surface area) for temozolomide than men. Women have higher incidences of Grade 4 neutropenia and thrombocytopenia in the first cycle of therapy than men.

Age

Population pharmacokinetic analysis indicates that age (range 19-78 years) has no influence on the pharmacokinetics of temozolomide.

16.3.5 Drug-Drug Interactions

In a multiple dose study, administration of temozolomide with ranitidine did not change the C_{max} or AUC values for temozolomide or MTIC. Population analysis indicates that administration of valproic acid decreases the clearance of temozolomide by about 5%. The clinical implication of this effect is not known. Population analysis failed to demonstrate any influence of co-administered dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H_2-receptor antagonists, or phenobarbital on the clearance of orally administered temozolomide.

16.3.6 Adverse Events

- Hematologic: Thrombocytopenia, leukopenia, myelodysplastic syndrome
- Gastrointestinal: Nausea, vomiting, anorexia
- Hepatic: Elevated liver enzymes (reversible). Additional information regarding hepatic toxicity can be found in Attachment 4.
- Skin: Rash
- Neurologic: Convulsions, weakness on one side of the body, abnormal coordination, paralysis
- Other: Constipation, diarrhea, stomatitis, fatigue, decreased performance status, headache

16.3.7 Special Handling and Precautions

Capsules should not be opened or damaged. Rigorous precautions should be taken to avoid capsule contents having contact with skin or mucous membranes. Capsule contents may be irritating to skin and eyes. Mutagenic and prolonged exposure may cause serious health effects (outside of prescribed dosage in this trial).

Temozolomide is potentially mutagenic and should be handled with appropriate precautions by both staff and patients. Capsules should not be opened. If capsules are accidentally opened or damaged, rigorous precautions should be taken with the capsule contents to avoid inhalation or contact with the skin or mucous membranes. Procedures for proper handling and disposal of anticancer drugs should be considered.

16.3.8 Contraindications

Temozolomide is contraindicated in patients who have a history of a hypersensitivity reaction to any of its components or to DTIC.

16.3.9 Pregnancy Category D

Temozolomide may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the

potential hazard to the fetus. **Women of childbearing potential should be advised to avoid becoming pregnant during therapy with temozolomide.**

Treatment of a man with temozolomide may increase the risk of birth defects if he causes a woman to become pregnant while he is taking temozolomide. Men treated with temozolomide may have difficulty causing a woman to become pregnant after their treatment is completed. Men receiving temozolomide should be directed to use effective contraception while they are being treated. There is insufficient data to know what the risk of subsequent problems with fertility will be. Similarly, women who are treated with temozolomide may have difficulty becoming pregnant in the future and may at be at increased risk of having children with birth defects. There is insufficient evidence to determine what the risk of these complications will be.

16.3.10 Supply

Commercially available.

17.0 MEASURES TO MINIMIZE/AVOID BIAS

Each patient will be assigned a unique number and will keep this number for the duration of the study. Patient numbers will not be reassigned or reused for any reason. Patients should be identified to the Sponsor only by their assigned number, initials, date of birth, and sex. The investigator must maintain a patient master log.

18.0 SAFETY EVALUATION

Routine safety and tolerability will be evaluated from the results of reported signs and symptoms, scheduled physical examinations, vital sign measurements, 12-lead ECGs (including QTcF intervals), and clinical laboratory test results.

More frequent safety evaluations may be performed if clinically indicated or at the discretion of the investigator. All AEs will be recorded from the time the patient receives the first dose of study drug up to 28 days after the last dose.

As this is an open label study, ongoing safety will be continuously and rigorously monitored by the Sponsor. Additionally, biweekly teleconferences are planned to review in detail the safety across all study sites.

18.1 Physical Examination

Complete and symptom-directed physical examinations (including neurological exam) will be performed by a licensed physician (or physician's assistant or nurse practitioner).

18.2 Vital Signs

Vital signs (blood pressure, respiratory rate, pulse rate and temperature) will be obtained in the sitting position. Patients should be sitting for 3-5 minutes prior to obtaining vital signs.

18.3 Electrocardiograms

Patients should rest in the supine position for at least 5 minutes before each 12-lead ECG recording is started. The ECGs should be reviewed, signed, and dated by a qualified physician (or qualified physician's assistant or nurse practitioner) and any clinically important finding recorded on the appropriate eCRF. The investigator is responsible for providing the interpretation of all ECGs. The results will include heart rate, respiratory rate (RR), PR interval, QRS interval, QT interval, and QTcF interval. Fridericia's formula is required.:
$QTcF = (QT)/\sqrt[3]{(RR)}$

18.4 Safety Laboratory Determinations

Laboratory evaluations will be performed as noted in the flow chart. Please see Attachment 1 for the specific laboratory tests to be performed.

19.0 BIOMARKER SAMPLES

Blood samples for PD biomarkers will be obtained as noted in the flow chart. Samples will be collected and processed by LabCorp according to the study-specific laboratory manual. LabCorp will perform the MGMT analyses. For all patients, archival tumor samples will be obtained. Please see Attachment 1 for the specific laboratory tests to be performed on both plasma and tissue samples.

20.0 PHARMACOKINETIC EVALUATION

20.1 Blood Collection

For each PK sample, blood should be collected as noted in the flow chart. Samples will be collected, processed, stored, and shipped according to the study-specific laboratory manual.

Blood samples for PK analysis should be collected at the requested time but within a ±15 minute window. The exact actual time of collection should be noted in the source documents and eCRFs.

The total amount of blood to be collected from each patient is <30 mL during screening, <60 mL during Cycle 1, and <30 mL for subsequent cycles.

20.2 Bioanalytical Methodology

The plasma and tissue samples will be analyzed for PLX3397 by using a validated method (high performance liquid chromatography (HPLC) with tandem quadrupole mass spectrometric detection) of appropriate specificity and sensitivity.

21.0 STATISTICAL ANALYSIS

21.1 General Statistical Considerations

21.1.1 Phase 1b Portion

The objective of the Phase 1b portion of this study is to determine the recommended Phase 2 dose (RP2D) of PLX3397 when combined with concurrent radiation therapy and temozolomide. Two expected dose levels are specified for testing, with one or more lower doses to be evaluated if the starting dose of 800 mg/day is above the MTD. For each dose level, 7 patients will be accrued to assure that there will be 6 patients eligible for evaluation of toxicity. A patient registered to the study who is found retrospectively not to meet the study eligibility criteria, who does not receive any PLX3397, or who is considered non-evaluable during the toxicity evaluation period for reasons not related to study drug will be excluded from evaluation of DLT and replaced.

Patient accrual will be suspended after each dose cohort is enrolled until there is sufficient information collected to make a decision relative to dose escalation. A dose level for PLX3397 will be considered acceptable if no more than 2 patients of the 6 eligible patients experience a DLT. Should all 7 patients be analyzable for adverse events, only the first 6 will be considered in the determination of DLTs. If the current level is considered acceptable, then dose escalation will occur and the protocol will be reopened. Otherwise, the preceding acceptable dose level will be declared the MTD. The Sponsor, together with the study investigators, will evaluate the safety of each cohort prior to dose escalation.

21.1.2 Phase 2 Portion

For Part 2 (Phase 2 portion), the primary objective is the comparison of median Progression Free Survival (PFS) to historical control. Secondary objectives include the evaluation of overall survival (OS), pharmacokinetics (PK), correlative imaging studies, safety, and the exploratory endpoint of pharmacodynamic (PD) effects of PLX3397.

21.2 Sample Size and Power

For the primary endpoint of median PFS, based on a one-sided log rank test with a significance level of 0.1 and power of 80%, 22 events (death or progression) in approximately 31 patients would be required to detect a 50% relative hazard reduction in progression-free survival due to the addition of PLX3397 compared to the recent historical control median PFS of 5.5 months (RTOG 0525). Assuming a ~30% rate of non-evaluability, approximately 37 patients are planned to be enrolled in the Phase 2 portion of the study, which when combined with the 7 patients treated at that dose level in the Phase 1 portion of the study will yield approximately 44 patients.

21.3 Analysis Populations

The primary population for efficacy and safety will consist of the modified ITT population, i.e., patients who receive at least one dose of study drug and have any follow-up data. A per protocol

efficacy population will consist of all patients who fulfill the inclusion/exclusion criteria and receive at least 4 weeks of treatment with study drug as well as at least 90% of the planned radiation therapy.

21.4 Efficacy Analysis

Response to treatment will evaluated using the Response Assessment in Neuro-Oncology (RANO) criteria (Wen 2010). The response criteria are summarized in Attachment 3. All patients who are eligible for efficacy analyses will be evaluable for PFS, calculated for each subject as the number of days from the first day of treatment (C1D1) to the date of the first documented disease progression or date of death, whichever occurs first. The Kaplan-Meier method will be used to estimate the median PFS.

Statistical modeling will be used to match the experimental group to the RTOG 0525 historical group for expected prognosis based on both clinical and molecular factors, importantly the level of MGMT methylation in the tumor tissue.

For each subject with a response to therapy, duration of response will be calculated. The duration of response is defined as number of days from the date of initial response to the date of first documented disease progression or death, whichever occurs first. The Kaplan-Meier method will be used to estimate median duration of response. In the event no disease progression or death is documented prior to study termination, analysis cutoff, or the start of confounding anticancer therapy, PFS and duration of response will be censored at the date of last evaluable tumor assessments. The median duration will be compared to the historical control PFS of 5.5 months. The secondary endpoint of OS will be analyzed in a similar fashion.

Additional secondary analysis of efficacy will include patient-specific biomathematical modeling of tumor growth (Baldock 2013) to allow quantification of the degree of deflection of the tumor off of its growth curve related to the therapy (Neal 2013a; Neal 2013b; Adair 2014). The patient-specific model will be tuned to the pre-treatment MRIs. The degree of deflection of the tumor off of its growth curve will be measured as Days Gained and as Radial Treatment Response as in (Neal 2013a; Neal 2013b; Adair 2014). Briefly, patient-specific simulations of predicted tumor growth will be compared with followup MRIs in terms of a temporal delay of imageable tumor growth (Days Gained) or as a delay of tumor growth in terms of size (Radial Treatment Response). These metrics will be correlated with PFS and OS through correlative and Kaplan-Meier analyses to connect treatment response with outcomes. In addition, relationships between treatment response, PFS, PD biomarkers, and tissue prognostic markers will be explored.

21.5 Safety Analysis

Safety variables to be analyzed are AEs, laboratory test results (hematology and clinical chemistry), ECG, weight, and vital signs.

Adverse event terms recorded on the eCRFs will be mapped to preferred terms using the Medical Dictionary for Drug Regulatory Activities (MedDRA®) version 10.1 or later. All AEs will be summarized according to the system organ class and preferred term within the organ class. Adverse events will be tallied for overall frequency (number and percentage of subjects), worst reported severity, and relationship to study drug for each preferred term per subject. Serious adverse events will be similarly summarized. Listings of deaths, SAEs, and AEs leading to early termination of study treatment or premature withdrawal from study will also be provided.

Laboratory variables will be examined using mean change in value from baseline to scheduled time points. Laboratory values will also be categorized according to their CTCAE (version 4) toxicity grade and tabulated by worst on-study toxicity grade. The baseline value of a variable is defined as the last value obtained on or before the date and time of the first PLX3397 dose.

ECG, weight, and vital signs will also be summarized by changes from baseline to scheduled time points using descriptive statistics.

21.6 Pharmacokinetic Analysis

For the Phase 1b portion of the study, a partial AUC (AUC_{0-6}) will be calculated using samples collected from C1D8 (pre-temozolomide) and C1D15 (concurrent temozolomide). Values for C_{max} and T_{max} will be determined from the concentration-time profile.

A formal PK statistical analysis plan will be created for this protocol, and a separate formal PK report will be written for inclusion in the final study report.

21.7 Pharmacodynamic Analysis

21.7.1 Central histopathologic review and tissue requirements

At least 20 unstained FFPE slides from a representative block of tumor tissue (0.5 cm diameter) should be submitted on all participants in the study. One slide will be H&E stained at the central site to confirm diagnosis and determine eligibility for further study. The remaining slides will be utilized for MGMT methylation assessment, biomarker analysis, and correlation of treatment effect with genotype and phenotype.

21.7.2 Tissue Evaluation

The rationale for evaluation of tumor tissue is two-fold: 1) to analyze prognostic molecular factors to be able to compare the data vs. historical control data, and 2) to conduct exploratory evaluation of biomarkers of Fms inhibition, as well as correlation of clinical outcomes with response and tumor parameters. Because of the importance of this tumor tissue evaluation, surgical samples are required, and biopsy-only samples are not allowed.

Planned biomarkers are listed in Attachment 1. The staining patterns will be semi-quantitatively and manually scored and correlated with other measures for number of TAMs and their morphology and location within the tumor.

No formal statistical analysis of PD endpoints will be performed. PD data from each assay will be listed, and possible relationships between clinical response and PD variables will be explored. Any biological activity will be described.

21.7.3 Serum biomarker analysis

Serum biomarkers will also be assayed at a central laboratory. Please consult the laboratory manual for shipping and handling instructions.

22.0 PRECAUTIONS

Although major adverse events are not anticipated, the investigator must proceed with utmost caution. Equipment, supplies, and properly skilled medical personnel must be immediately available for emergency use in the event of an unexpected reaction. Patients must be carefully selected and closely monitored.

For a complete description of preclinical and clinical studies of PLX3397, please refer to the PLX3397 Investigator's Brochure.

23.0 ADVERSE EVENTS

For safety information on PLX3397, refer to the most recent version of the Investigator's Brochure.

23.1 Definitions

An **adverse event** (AE) is any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, or laboratory or physiologic observations occurring in a person given a study drug in a clinical study. The event does not need to be causally related to the study drug. An AE includes, but is not limited to, the following:

- Any clinically significant worsening of a preexisting condition.
- An AE occurring from overdose (i.e., a dose higher than that indicated in the protocol) of a study drug, whether accidental or intentional.
- An AE occurring from abuse (e.g., use for nonclinical reasons) of a study drug.
- An AE that has been associated with the discontinuation of the use of a study drug.

Any treatment-emergent abnormal laboratory result which is clinically significant, i.e., meeting one or more of the following conditions, should be recorded as a single diagnosis on the adverse event page in the eCRF:

- Accompanied by clinical symptoms
- Leading to a change in study medication (e.g., dose modification, interruption or permanent discontinuation)

- Requiring a change in concomitant therapy (e.g., addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment)

A **serious adverse event** is an AE that:

- Results in death (NOTE: death is an outcome, not an event)
- Is life-threatening.
- Requires inpatient hospitalization or prolongation of an existing hospitalization.
- Results in a persistent or significant disability or incapacity.
- Results in a congenital anomaly or birth defect.
- Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Clear progression of neoplasia should not be reported as an adverse event or serious adverse event. Findings that are clearly consistent with the expected progression of the underlying cancer should not be reported as an adverse event, and hospitalizations due to the progression of cancer do not necessarily qualify for a serious adverse event. Sudden and unexplained death should be reported as an SAE. If there is any uncertainty about a finding being due solely to progression of neoplasia, the finding should be reported as an adverse event or serious adverse event as appropriate.

Life-threatening refers to immediate risk of death as the event occurred per the reporter. A life-threatening experience does not include an experience, had it occurred in a more severe form, which might have caused death, but as it actually occurred, did not create an immediate risk of death. For example, hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though hepatitis of a more severe nature can be fatal. Similarly, an allergic reaction resulting in angioedema of the face would not be life-threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.

Hospitalization is official admission to a hospital. Hospitalization or prolongation of a hospitalization constitutes criteria for an AE to be serious; however, it is not in itself considered a serious adverse event (SAE). In absence of an AE, a hospitalization or prolongation of a hospitalization should not be reported as an SAE. This is the case in the following situations:

- The hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol. Day or night survey visits for biopsy or surgery required by the protocol are not considered serious.

- The hospitalization or prolongation of hospitalization is part of a routine procedure followed by the center (e.g., stent removal after surgery). This should be recorded in the study file.
- Hospitalization for survey visits or annual physicals falls in the same category.

In addition, hospitalizations planned before the start of the study, for a preexisting condition that has not worsened, do not constitute an SAE. An emergency room visit is not considered a hospitalization unless it results in a hospitalization.

Disability is defined as a substantial disruption in a person's ability to conduct normal life functions.

If there is any doubt about whether the information constitutes an SAE, the information is treated as an SAE.

Relatedness to study medication will be graded as either "probably", "possibly", or "not related", as follows:

Probably – The adverse event

- Follows a reasonable temporal sequence from drug administration
- Abates upon discontinuation of the drug
- Cannot be reasonably explained by the known characteristics of the patient's clinical state

Possibly – The adverse event

- Follows a reasonable temporal sequence from drug administration
- Could have been produced by the patient's clinical state or by other modes of therapy administered to the patient

Not Related – The adverse event

- Does not follow a reasonable sequence from drug administration
- Is readily explained by the patient's clinical state or by other modes of therapy administered to the patient

A **protocol-related adverse event** is an AE occurring during a clinical study that is not related to the study drug, but is considered by the investigator or the medical monitor (or designee) to be related to the research conditions, i.e., related to the fact that a patient is participating in the study. For example, a protocol-related AE may be an untoward event occurring during a washout period or an event related to a medical procedure required by the protocol.

Other **Reportable Information**: certain information, although not considered an SAE, must be recorded, reported, and followed up as indicated for an SAE. This includes:

- A case involving a pregnancy exposure to a study drug, unless the product is indicated for use during pregnancy e.g., prenatal vitamins. Information about use in pregnancy encompasses the entire course of pregnancy and delivery and perinatal and neonatal outcomes, even if there were no abnormal findings. If a pregnancy is confirmed, study drug must be discontinued immediately. All reports of pregnancy must be followed for information about the course of the pregnancy and delivery, as well as the condition of the newborn. When the newborn is healthy, additional follow-up is not needed. Pregnancies occurring up to 6 months after completion of the study treatment must also be reported to the investigator.
- Overdose (e.g., a dose higher than that indicated in the protocol) with or without an AE.
- Abuse (e.g., use for nonclinical reasons) with or without an AE.
- Inadvertent or accidental exposure with or without an AE.
- Device malfunction with or without an AE.

23.2 Recording and Reporting

A patient's AE or SAE can occur from the time the patient receives the first dose of study drug up to 28 days after the last dose.

The investigator must follow-up on all drug-related AEs, SAEs, and other reportable information until the events have subsided, returned to baseline, the patient has initiated any other anticancer treatment, or in case of permanent impairment, until the condition stabilizes. Pregnancies and overdoses are not considered AEs but must be reported to the Sponsor.

All AE and SAEs must be recorded on source documents and collected in TEMPO. All AEs and SAEs for patients who are not screen failures will be recorded in the eCRFs.

AEs should be based on the signs or symptoms detected during the physical examination and on clinical evaluation of the patient. In addition to the information obtained from those sources, the patient should be asked the following nonspecific question: "How have you been feeling since your last visit?" Signs and symptoms should be recorded using standard medical terminology.

Any unanticipated risks to the patients must be reported promptly to the IRB/IEC.

23.3 Serious Adverse Event Reporting

All SAEs, other reportable information, and follow-up information must be reported within 24 hours of learning of the event by completing the SAE form within the eCRF. As a back-up, the site may fax a completed serious adverse event form to the fax number indicated in the Emergency Contacts section and confirming by phone or e-mail that the fax was received. Plexxikon (or designee) will process and evaluate all SAEs as soon as the reports are received. For each SAE received, Plexxikon will make a determination as to whether the criteria for expedited reporting have been met.

Plexxikon (or designee) is responsible for reporting relevant SAEs to the relevant regulatory authorities and participating investigators, in accordance with FDA regulations 21 CFR 312.32, ICH guidelines, European Clinical Trials Directive (Directive 2001/20/EC), and/or local regulatory requirements.

Reporting of SAEs by the investigator to the Institutional Review Board (IRB) or Ethics Committee (EC) will be done in accordance with the standard operation procedures and policies of the IRB/EC. Adequate documentation must be maintained showing that the IRB/EC was properly notified.

24.0 STUDY SUSPENSION, TERMINATION, AND COMPLETION

The Sponsor may suspend or terminate the study or any part of the study at any time for any reason. If the investigator suspends or terminates the study, the investigator will promptly inform the Sponsor and the IRB/IEC and provide them with a detailed written explanation. The investigator will also return all study drug, containers, and other study materials to the contract distribution center, or destroy the materials at the investigative site. Upon study completion, the investigator will provide the Sponsor, IRB/IEC, and regulatory agency with final reports and summaries as required by regulations. For IND studies, the investigator must submit a written report to the Sponsor and the IRB/IEC within 3 months after the completion or termination of the study.

25.0 INFORMED CONSENT

The investigator will provide for the protection of the patients by following all applicable regulations. These regulations are available upon request from the Sponsor. The informed consent form used during the informed consent process must be reviewed by the Sponsor and approved by the IRB/IEC.

Before any procedures specified in the protocol are performed, a patient must:

- Be informed of all pertinent aspects of the study and all elements of informed consent.
- Be given time to ask questions and time to consider the decision to participate.
- Voluntarily agree to participate in the study.
- Sign and date an IRB/IEC approved informed consent form.

26.0 PROTOCOL AMENDMENTS

Any significant change in the study requires a protocol amendment. An investigator must not make any changes to the study without IRB/IEC and Sponsor approval except when necessary to eliminate apparent immediate hazards to the patients. A protocol change intended to eliminate an apparent immediate hazard to patients may be implemented immediately, but the change must then be documented in an amendment, reported to the IRB/IEC within 5 working days, and

submitted to the appropriate regulatory agency in the required time frame. All protocol amendments must be reviewed and approved following the same process as the original protocol.

27.0 QUALITY CONTROL AND ASSURANCE

The Sponsor performs quality control and assurance checks on all clinical studies that it sponsors. Before enrolling any patients in this study, Sponsor personnel and the investigator review the protocol, the investigator's brochure, the eCRFs and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs. A qualified representative of the Sponsor will monitor the conduct of the study. During these site visits, information recorded in the eCRFs is verified against source documents.

28.0 DIRECT ACCESS, DATA HANDLING, AND RECORD KEEPING

28.1 Investigator

The investigator will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and documents.

All study-related information will be recorded on source documents. All required data will be recorded in the eCRFs. All eCRF data must be submitted to the Sponsor throughout and at the end of the study.

If an investigator retires, relocates, or otherwise withdraws from conducting the study, the investigator must notify the Sponsor to agree upon an acceptable storage solution. Regulatory agencies will be notified with the appropriate documentation.

All laboratory and clinical data gathered in this protocol will be stored in a password-protected database. All patient information will be handled using anonymous identifiers. Linkage to patient study data is only possible after accessing a password-protected database. Access to the database is only available to individuals directly involved in the study.

Patient personal health information that is accessed for this study will not be reused or disclosed to any other person or entity, or for other research.

28.2 Sponsor

The data will be checked for completeness and correctness by real-time online checks as it is entered into the electronic data capture system [Tempo] used to collect the data. Off-line checks will also be run to perform any additional data review required. Discrepancy reports will be generated accordingly and transferred to the study center for resolution by the investigator or designee.

29.0 PRE-STUDY DOCUMENTATION

The investigator must provide the Sponsor with the following documents BEFORE enrolling any patients:

- Completed and signed form 1572.
- All applicable country-specific regulatory forms.
- Current signed and dated curricula vitae for the investigator, subinvestigators, and other individuals having significant investigator responsibility who are listed on the Form 1572 or equivalent, or the clinical study information form.
- Copy of the IRB/IEC approval letter for the protocol and informed consent. All advertising, recruitment, and other written information provided to the patient must be approved by the IRB/IEC. Written assurance of continuing approval (at least annually) as well as a copy of the annual progress report submitted to the IRB/IEC must also be provided to the Sponsor.
- Copy of the IRB/IEC-approved informed consent document to be used.
- Where applicable, a list of the IRB/IEC members or a FWA/DHHS number.
- Copy of the protocol sign-off page signed by the investigator.
- Copy of the current medical license of the principal Investigator and any subinvestigators.
- Fully executed Clinical Trial Agreement.
- Where applicable, a financial disclosure form for the investigator, subinvestigators, and other individuals who have significant investigator responsibility and are listed on the Form 1572.
- A written document containing the name, location, certification number, and date of certification of the laboratory to be used for laboratory assays and those of other facilities conducting tests. This document should be returned along with the lab director's curriculum vitae and active medical license. The Sponsor must be notified if the laboratory is changed or if any additional laboratory is to be used.
- List of normal laboratory values and units of measure for all laboratory tests required by the protocol. This is required for each laboratory to be used during the study. The Sponsor must be notified if normal values or units of measurement change.

30.0 RECORDS RETENTION

The investigator shall retain and preserve 1 copy of all data generated in the course of the study, specifically including but not limited to those defined by GCP as essential, for the longer of: (i) 2 years after the last marketing authorization for the study drug has been approved or the Sponsor has discontinued its research with respect to such drug or (ii) such longer period as required by applicable global regulatory requirements. At the end of such period, the investigator shall notify the Sponsor in writing of its intent to destroy all such material. The Sponsor shall

have 30 days to respond to the investigator's notice, and the Sponsor shall have a further opportunity to retain such materials at the Sponsor's expense.

31.0 REFERENCES

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ATTACHMENT 1: LABORATORY TESTS

Hematology

Hemoglobin and hematocrit
White blood cell count with differential
Platelet count

Serum Chemistry

Sodium
Potassium
Chloride
CO_2
Calcium
Phosphorus
Glucose
Blood urea nitrogen
Creatinine
Uric acid
Total protein
Albumin
Total and direct bilirubin
Aspartate aminotransferase (AST)
Alanine aminotransferase (ALT)
Alkaline phosphatase (AP)
Lactate dehydrogenase (LDH)

Serum pregnancy test (β-HCG): women of child-bearing potential

Blood Response Biomarkers:

- CSF-1
- Biomarkers of kinase inhibition and myeloid cell recruitment
- CD14/CD16 mononuclear cells

Tissue Response Biomarkers in Formalin-Fixed Surgical Tissue

- MGMT methylation
- CSF1R and CSF1
- Tumor-associated macrophages
- Other prognostic markers as appropriate

Because the identification of new response prediction or early response biomarkers of disease activity is a rapidly developing field, the definitive list of analyses remains to be determined, and may include additional markers of macrophage activity, in addition to anti-tumor biomarkers that may be related to PLX3397 treatment.

ATTACHMENT 2: STRONG CYP3A4 INHIBITORS AND INDUCERS

Strong Inhibitors	Strong Inducers
Protease inhibitors • Ritonavir • Indinavir • Nelfinavir Macrolide antibiotics • Erythromycin • Telithromycin • Clarithromycin Azole antifungals • Fluconazole • Ketoconazole • Itraconazole Chloramphenicol (antibiotic) Nefazodone (antidepressant) Bergamottin (constituent of grapefruit juice) Aprepitant (antiemetic) Verapamil (calcium channel blocker)	Anticonvulsants, mood stabilizers • Phenytoin • Carbamazepine • Oxcarbazepine Non-nucleoside reverse transcriptase inhibitors • Efavirenz • Nevirapine • Etravirine Phenobarbital (barbiturate) Rifampicin (bactericidal) Modafinil (stimulant) Hyperforin (constituent of St Johns Wort) Cyproterone (antiandrogen, progestin)

ATTACHMENT 3: RANO RESPONSE CRITERIA

Patients with measurable disease (bidimensional measurements) will be assessed by the RANO (radiographic assessment in neurooncology) criteria. For the purposes of this study, patients should be re-evaluated every 8 weeks with a contrast-enhanced cranial MRI scan. The response will be determined as outlined in the RANO criteria below.

Complete Response (requires all of the following):

a) Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.

b) No new lesions.

c) All measurable and non-measurable lesions must be assessed using the same techniques as baseline.

d) Patients must be on no steroids.

e) Stable or improved non-enhancing (T2/FLAIR) lesions.

f) Stable or improved clinically.

Note: Patients with non-measurable disease cannot have a complete response. The best response possible is stable disease.

Partial Response (requires all of the following):

a) Greater than or equal to 50% decrease compared to baseline in the sum of products of perpendicular diameters (bi-dimensional measurements) of all measurable enhancing lesions sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.

b) No progression of non-measurable disease.

c) No new lesions.

d) All measurable and nonmeasurable lesions must be assessed using the same techniques as baseline.

e) The steroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan.

f) Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan.

g) Stable or improved clinically.

Note: Patients with non-measurable disease cannot have a partial response. The best response possible is stable disease.

Stable Disease (requires all of the following):

a) Does not qualify for CR, PR, or progression.

b) The designation of stable disease requires a minimum of 4-week duration.

c) All measurable and non-measurable sites must be assessed using the same techniques as baseline.

d) Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan. In the event that the corticosteroid dose has been increased, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.

e) Stable clinically.

Progressive Disease (defined by any of the following):

a) >25% increase in sum of the products of perpendicular diameters (bi-dimensional measurements) of enhancing lesions (over baseline if no decrease) on stable or increasing doses of corticosteroids. and/or

b) Significant increase in T2/FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared to baseline scan or best response following initiation of therapy, not due to co-morbid events (radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects).

c) Any new lesion.

d) Clear clinical deterioration not attributable to other causes apart from the tumor (e.g., seizures, medication side effects, complications of therapy, cerebrovascular events, infection, etc.). The definition of clinical deterioration is left to the discretion of the treating physician, but it is recommended that a decrease in 20% of KPS or from any baseline to 50% or less be considered, unless attributable to comorbid events.

e) Failure to return for evaluation due to death or deteriorating condition.

Assessment of Response (Efficacy)

Timing of the Evaluation of Response: Assessment of response will begin with the previous MRI. All scans are to be compared to the smallest measurement scan to date.

ATTACHMENT 4: TEMOZOLOMIDE PRESCRIBING INFORMATION

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TEMODAR safely and effectively. See full prescribing information for TEMODAR.

TEMODAR® (temozolomide) Capsules
TEMODAR® (temozolomide) for Injection
administered via intravenous infusion
Initial U.S. Approval: 1999

----------INDICATIONS AND USAGE----------
TEMODAR is an alkylating drug indicated for the treatment of adult patients with:
- Newly diagnosed glioblastoma multiforme (GBM) concomitantly with radiotherapy and then as maintenance treatment. (1.1)
- Refractory anaplastic astrocytoma patients who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine. (1.2)

----------DOSAGE AND ADMINISTRATION----------
- Newly Diagnosed GBM: 75 mg/m^2 for 42 days concomitant with focal radiotherapy followed by initial maintenance dose of 150 mg/m^2 once daily for Days 1-5 of a 28-day cycle of TEMODAR for 6 cycles. (2.1)
- Refractory Anaplastic Astrocytoma: Initial dose 150 mg/m^2 once daily for 5 consecutive days per 28-day treatment cycle. (2.1)
- The recommended dose for TEMODAR as an intravenous infusion over 90 minutes is the same as the dose for the oral capsule formulation. Bioequivalence has been established only when TEMODAR for Injection was given over 90 minutes. (2.1, 12.3)

----------DOSAGE FORMS AND STRENGTHS----------
- 5-mg, 20-mg, 100-mg, 140-mg, 180-mg, and 250-mg capsules. (3)
- 100-mg powder for injection. (3)

----------CONTRAINDICATIONS----------
- Known hypersensitivity to any TEMODAR component or to dacarbazine (DTIC). (4.1)

----------WARNINGS AND PRECAUTIONS----------
- Myelosuppression — monitor Absolute Neutrophil Count (ANC) and platelet count prior to dosing and throughout treatment. Geriatric patients and women have a higher risk of developing myelosuppression. (5.1)
- Cases of myelodysplastic syndrome and secondary malignancies, including myeloid leukemia, have been observed. (5.2)
- *Pneumocystis carinii* pneumonia (PCP) – prophylaxis required for all patients receiving concomitant TEMODAR and radiotherapy for the 42-day regimen for the treatment of newly diagnosed glioblastoma multiforme. (5.3)
- All patients, particularly those receiving steroids, should be observed closely for the development of lymphopenia and PCP. (5.4)
- Complete blood counts should be obtained throughout the treatment course as specified. (5.4)
- Fetal harm can occur when administered to a pregnant woman. Women should be advised to avoid becoming pregnant when receiving TEMODAR. (5.5)
- As bioequivalence has been established only when given over 90 minutes, infusion over a shorter or longer period of time may result in suboptimal dosing; the possibility of an increase in infusion-related adverse reactions cannot be ruled out. (5.6)

---------- ADVERSE REACTIONS ----------
- The most common adverse reactions (≥10% incidence) are: alopecia, fatigue, nausea, vomiting, headache, constipation, anorexia, convulsions, rash, hemiparesis, diarrhea, asthenia, fever, dizziness, coordination abnormal, viral infection, amnesia, and insomnia. (6.1)
- The most common Grade 3 to 4 hematologic laboratory abnormalities (≥10% incidence) that have developed during treatment with temozolomide are: lymphopenia, thrombocytopenia, neutropenia, and leukopenia. (6.1)
- Allergic reactions have also been reported. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
- Valproic acid: decreases oral clearance of temozolomide. (7.1)

---------- USE IN SPECIFIC POPULATIONS ----------
- Nursing mothers: Not recommended. (8.3)
- Pediatric use: No established use. (8.4)
- Hepatic/Renal Impairment: Caution should be exercised when TEMODAR is administered to patients with severe renal or hepatic impairment. (8.6, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 06/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Newly Diagnosed Glioblastoma Multiforme

TEMODAR® (temozolomide) is indicated for the treatment of adult patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as maintenance treatment.

1.2 Refractory Anaplastic Astrocytoma

TEMODAR is indicated for the treatment of adult patients with refractory anaplastic astrocytoma, i.e., patients who have experienced disease progression on a drug regimen containing nitrosourea and procarbazine.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing and Dose Modification Guidelines

The recommended dose for TEMODAR as an intravenous infusion over 90 minutes is the same as the dose for the oral capsule formulation. Bioequivalence has been established only when TEMODAR for Injection was given over 90 minutes *[see Clinical Pharmacology (12.3)]*. Dosage of TEMODAR must be adjusted according to nadir neutrophil and platelet counts in the previous cycle and the neutrophil and platelet counts at the time of initiating the next cycle. For TEMODAR dosage calculations based on body surface area (BSA) see **Table 5**. For suggested capsule combinations on a daily dose see **Table 6**.

Patients with Newly Diagnosed High Grade Glioma: *Concomitant Phase:* TEMODAR is administered at 75 mg/m^2 daily for 42 days concomitant with focal radiotherapy (60 Gy administered in 30 fractions) followed by maintenance TEMODAR for 6 cycles. Focal RT includes the tumor bed or resection site with a 2- to 3-cm margin. No dose reductions are recommended during the concomitant phase; however, dose interruptions or discontinuation may occur based on toxicity. The TEMODAR dose should be continued throughout the 42-day concomitant period up to 49 days if all of the following conditions are met: absolute neutrophil count greater than or equal to 1.5 x 10^9/L, platelet count greater than or equal to 100 x 10^9/L, common toxicity criteria (CTC) nonhematological toxicity less than or equal to Grade 1 (except for alopecia, nausea, and vomiting). During treatment a complete blood count should be obtained weekly. Temozolomide dosing should be interrupted or discontinued during concomitant phase according to the hematological and nonhematological toxicity criteria as noted in **Table 1**. *Pneumocystis carinii* pneumonia (PCP) prophylaxis is required during the concomitant administration of TEMODAR and radiotherapy, and should be continued in patients who develop lymphocytopenia until recovery from lymphocytopenia (CTC Grade less than or equal to 1).

TABLE 1: Temozolomide Dosing Interruption or Discontinuation During Concomitant Radiotherapy and Temozolomide

Toxicity	TMZ Interruption*	TMZ Discontinuation
Absolute Neutrophil Count	greater than or equal to 0.5 and less than 1.5 x 10^9/L	less than 0.5 x 10^9/L
Platelet Count	greater than or equal to 10 and less than 100 x 10^9/L	less than 10 x 10^9/L
CTC Nonhematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 2	CTC Grade 3 or 4

*Treatment with concomitant TMZ could be continued when all of the following conditions were met: absolute neutrophil count greater than or equal to 1.5 x 10^9/L; platelet count greater than or equal to 100 x 10^9/L; CTC nonhematological toxicity less than or equal to Grade 1 (except for alopecia, nausea, vomiting).

TMZ=temozolomide; CTC=Common Toxicity Criteria.

Maintenance Phase:

Cycle 1: Four weeks after completing the TEMODAR+RT phase, TEMODAR is administered for an additional 6 cycles of maintenance treatment. Dosage in Cycle 1 (maintenance) is 150 mg/m^2 once daily for 5 days followed by 23 days without treatment.

Cycles 2-6: At the start of Cycle 2, the dose can be escalated to 200 mg/m^2, if the CTC nonhematologic toxicity for Cycle 1 is Grade less than or equal to 2 (except for alopecia, nausea, and vomiting), absolute neutrophil count (ANC) is greater than or equal to 1.5 x 10^9/L, and the platelet count is greater than or equal to 100 x 10^9/L. The dose remains at 200 mg/m^2 per day for the first 5 days of each subsequent cycle except if toxicity occurs. If the dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles.

Dose Reduction or Discontinuation During Maintenance: Dose reductions during the maintenance phase should be applied according to **Tables 2** and **3**.

During treatment, a complete blood count should be obtained on Day 22 (21 days after the first dose of TEMODAR) or within 48 hours of that day, and weekly until the ANC is above 1.5 x 10^9/L (1500/µL) and the platelet count exceeds 100 x 10^9/L (100,000/µL). The next cycle of TEMODAR should not be started until the ANC and platelet count exceed these levels. Dose reductions during the next cycle should be based on the lowest blood counts and worst nonhematologic toxicity during the previous cycle. Dose reductions or discontinuations during the maintenance phase should be applied according to **Tables 2** and **3**.

TABLE 2: Temozolomide Dose Levels for Maintenance Treatment

Dose Level	Dose (mg/m^2/day)	Remarks
-1	100	Reduction for prior toxicity
0	150	Dose during Cycle 1
1	200	Dose during Cycles 2-6 in absence of toxicity

TABLE 3: Temozolomide Dose Reduction or Discontinuation During Maintenance Treatment

Toxicity	Reduce TMZ by 1 Dose Level*	Discontinue TMZ
Absolute Neutrophil Count	less than 1.0 x 10^9/L	See footnote†
Platelet Count	less than 50 x 10^9/L	See footnote†
CTC Nonhematological Toxicity (except for alopecia, nausea, vomiting)	CTC Grade 3	CTC Grade 4†

*TMZ dose levels are listed in **Table 2**.

†TMZ is to be discontinued if dose reduction to less than 100 mg/m^2 is required or if the same Grade 3 nonhematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction.

TMZ=temozolomide; CTC=Common Toxicity Criteria.

Patients with Refractory Anaplastic Astrocytoma: For adults the initial dose is 150 mg/m^2 once daily for 5 consecutive days per 28-day treatment cycle. For adult patients, if both the nadir and day of dosing (Day 29, Day 1 of next cycle) ANC are greater than or equal to 1.5 x 10^9/L (1500/µL) and both the nadir and Day 29, Day 1 of next cycle platelet counts are greater than or equal to 100 x 10^9/L (100,000/µL), the TEMODAR dose may be increased to 200 mg/m^2/day for 5 consecutive days per 28-day treatment cycle. During treatment, a complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until the ANC is above 1.5 x 10^9/L (1500/µL) and the platelet count exceeds 100 x 10^9/L (100,000/µL). The next cycle of TEMODAR should not be started until the ANC and platelet count exceed these levels. If the ANC falls to less than 1.0 x 10^9/L (1000/µL) or the platelet count is less than 50 x 10^9/L (50,000/µL) during any cycle, the next cycle should be reduced by 50 mg/m^2, but not below 100 mg/m^2, the lowest recommended dose (see **Table 4**). TEMODAR therapy can be continued until disease progression. In the clinical trial, treatment could be continued for a maximum of 2 years, but the optimum duration of therapy is not known.

TABLE 4: Dosing Modification Table

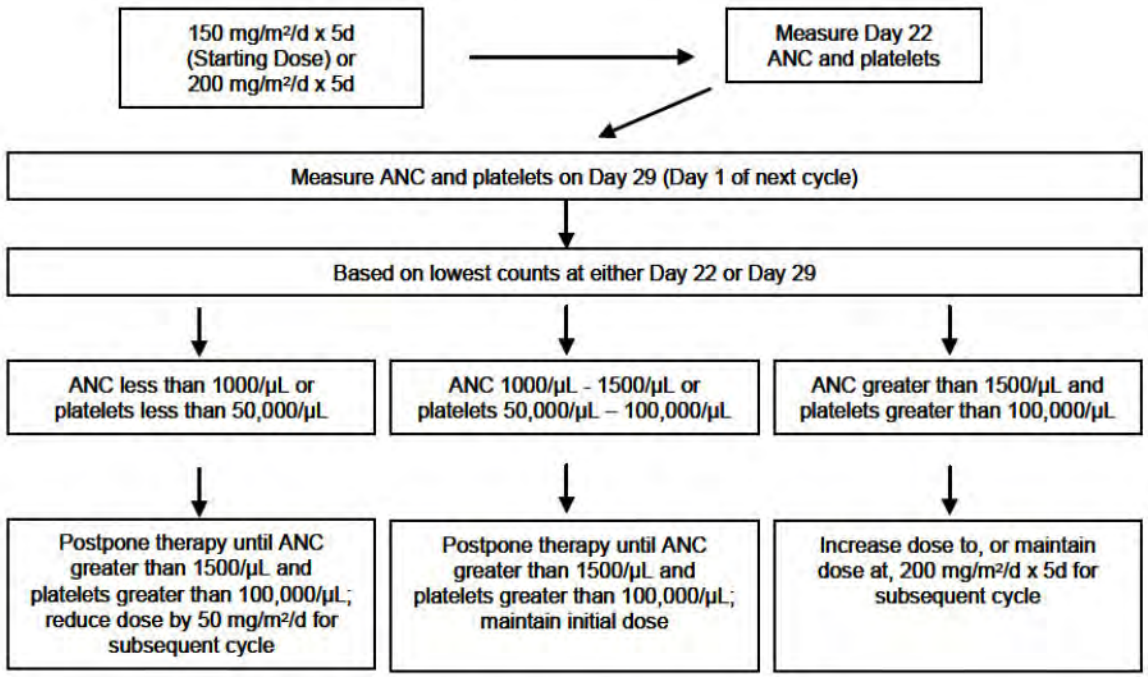


TABLE 5: Daily Dose Calculations by Body Surface Area (BSA)

Total BSA (m^2)	75 mg/m^2 (mg daily)	150 mg/m^2 (mg daily)	200 mg/m^2 (mg daily)
1.0	75	150	200
1.1	82.5	165	220
1.2	90	180	240
1.3	97.5	195	260
1.4	105	210	280
1.5	112.5	225	300
1.6	120	240	320
1.7	127.5	255	340
1.8	135	270	360
1.9	142.5	285	380
2.0	150	300	400
2.1	157.5	315	420
2.2	165	330	440
2.3	172.5	345	460
2.4	180	360	480
2.5	187.5	375	500

TABLE 6: Suggested Capsule Combinations Based on Daily Dose in Adults

Number of Daily Capsules by Strength (mg)						
Total Daily Dose (mg)	**250 mg**	**180 mg**	**140 mg**	**100 mg**	**20 mg**	**5 mg**
75	0	0	0	0	3	3
82.5	0	0	0	0	4	0
90	0	0	0	0	4	2
97.5	0	0	0	1	0	0
105	0	0	0	1	0	1
112.5	0	0	0	1	0	2
120	0	0	0	1	1	0
127.5	0	0	0	1	1	1
135	0	0	0	1	1	3
142.5	0	0	1	0	0	0
150	0	0	1	0	0	2
157.5	0	0	1	0	1	0
165	0	0	1	0	1	1
172.5	0	0	1	0	1	2
180	0	1	0	0	0	0
187.5	0	1	0	0	0	1
195	0	1	0	0	0	3
200	0	1	0	0	1	0
210	0	0	0	2	0	2
220	0	0	0	2	1	0
225	0	0	0	2	1	1
240	0	0	1	1	0	0
255	1	0	0	0	0	1
260	1	0	0	0	0	2
270	1	0	0	0	1	0
280	0	0	2	0	0	0
285	0	0	2	0	0	1
300	0	0	0	3	0	0
315	0	0	0	3	0	3
320	0	1	1	0	0	0
330	0	1	1	0	0	2
340	0	1	1	0	1	0
345	0	1	1	0	1	1
360	0	2	0	0	0	0
375	0	2	0	0	0	3
380	0	1	0	2	0	0
400	0	0	0	4	0	0
420	0	0	3	0	0	0
440	0	0	3	0	1	0
460	0	2	0	1	0	0
480	0	1	0	3	0	0
500	2	0	0	0	0	0

2.2 Preparation and Administration

TEMODAR Capsules: In clinical trials, TEMODAR was administered under both fasting and nonfasting conditions; however, absorption is affected by food *[see Clinical Pharmacology (12.3)]*, and consistency of administration with respect to food is recommended. There are no dietary restrictions with TEMODAR. To reduce nausea and vomiting, TEMODAR should be taken on an empty stomach. Bedtime administration may be advised. Antiemetic therapy may be administered prior to and/or following administration of TEMODAR.

TEMODAR (temozolomide) Capsules should not be opened or chewed. They should be swallowed whole with a glass of water.

If capsules are accidentally opened or damaged, precautions should be taken to avoid inhalation or contact with the skin or mucous membranes *[see How Supplied/Storage and Handling (16.1)]*.

TEMODAR for Injection: Each vial of TEMODAR for Injection contains sterile and pyrogen-free temozolomide lyophilized powder. When reconstituted with 41 mL Sterile Water for Injection, the resulting solution will contain 2.5 mg/mL temozolomide. Bring the vial to room temperature prior to reconstitution with Sterile Water for Injection. The vials should be gently swirled and not shaken. Vials should be inspected, and any vial containing visible particulate matter should not be used. Do not further dilute the reconstituted solution. After reconstitution, store at room temperature (25°C [77°F]). Reconstituted product must be used within 14 hours, including infusion time.

Using aseptic technique, withdraw up to 40 mL from each vial to make up the total dose based on **Table 5** above and transfer into an empty 250 mL infusion bag {2}. TEMODAR for Injection should be infused intravenously using a pump over a period of 90 minutes. TEMODAR for Injection should be administered only by intravenous infusion. Flush the lines before and after each TEMODAR infusion.

TEMODAR for Injection may be administered in the same intravenous line with 0.9% Sodium Chloride injection only.

Because no data are available on the compatibility of TEMODAR for Injection with other intravenous substances or additives, other medications should not be infused simultaneously through the same intravenous line.

3 DOSAGE FORMS AND STRENGTHS

- TEMODAR (temozolomide) Capsules for oral administration
  - 5-mg capsules have opaque white bodies with green caps. The capsule body is imprinted with two stripes, the dosage strength, and the Schering-Plough logo. The cap is imprinted with "TEMODAR."
  - 20-mg capsules have opaque white bodies with yellow caps. The capsule body is imprinted with two stripes, the dosage strength, and the Schering-Plough logo. The cap is imprinted with "TEMODAR."
  - 100-mg capsules have opaque white bodies with pink caps. The capsule body is imprinted with two stripes, the dosage strength, and the Schering-Plough logo. The cap is imprinted with "TEMODAR."
  - 140-mg capsules have opaque white bodies with blue caps. The capsule body is imprinted with two stripes, the dosage strength, and the Schering-Plough logo. The cap is imprinted with "TEMODAR."
  - 180-mg capsules have opaque white bodies with orange caps. The capsule body is imprinted with two stripes, the dosage strength, and the Schering-Plough logo. The cap is imprinted with "TEMODAR."
  - 250-mg capsules have opaque white bodies with white caps. The capsule body is imprinted with two stripes, the dosage strength, and the Schering-Plough logo. The cap is imprinted with "TEMODAR."
- TEMODAR (temozolomide) is available as 100-mg/vial powder for injection. The lyophilized powder is white to light tan/light pink.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

TEMODAR (temozolomide) is contraindicated in patients who have a history of hypersensitivity reaction (such as urticaria, allergic reaction including anaphylaxis, toxic epidermal necrolysis, and Stevens-Johnson syndrome) to any of its components. TEMODAR is also contraindicated in patients who have a history of hypersensitivity to dacarbazine (DTIC), since both drugs are metabolized to 5-(3-methyltriazen-1-yl)-imidazole-4-carboxamide (MTIC).

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Patients treated with TEMODAR may experience myelosuppression, including prolonged pancytopenia, which may result in aplastic anemia, which in some cases has resulted in a fatal outcome. In some cases, exposure to concomitant medications associated with aplastic anemia, including carbamazepine, phenytoin, and sulfamethoxazole/trimethoprim, complicates assessment. Prior to dosing, patients must have an absolute neutrophil count (ANC) greater than or equal to 1.5 x 10^9/L and a platelet count greater than or equal to 100 x 10^9/L. A complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until the ANC is above 1.5 x 10^9/L and platelet count exceeds 100 x 10^9/L. Geriatric patients and women have been shown in clinical trials to have a higher risk of developing myelosuppression.

5.2 Myelodysplastic Syndrome

Cases of myelodysplastic syndrome and secondary malignancies, including myeloid leukemia, have been observed.

5.3 *Pneumocystis carinii* Pneumonia

For treatment of newly diagnosed glioblastoma multiforme: Prophylaxis against *Pneumocystis carinii* pneumonia (PCP) is required for all patients receiving concomitant TEMODAR and radiotherapy for the 42-day regimen.

There may be a higher occurrence of PCP when temozolomide is administered during a longer dosing regimen. However, all patients receiving temozolomide, particularly patients receiving steroids, should be observed closely for the development of PCP regardless of the regimen.

5.4 Laboratory Tests

For the concomitant treatment phase with RT, a complete blood count should be obtained prior to initiation of treatment and weekly during treatment.

For the 28-day treatment cycles, a complete blood count should be obtained prior to treatment on Day 1 and on Day 22 (21 days after the first dose) of each cycle. Blood counts should be performed weekly until recovery if the ANC falls below 1.5 x 10^9/L and the platelet count falls below 100 x 10^9/L *[see Recommended Dosing and Dose Modification Guidelines (2.1)]*.

5.5 Use in Pregnancy

TEMODAR can cause fetal harm when administered to a pregnant woman. Administration of TEMODAR to rats and rabbits during organogenesis at 0.38 and 0.75 times the maximum recommended human dose (75 and 150 mg/m^2), respectively, caused numerous fetal malformations of the external organs, soft tissues, and skeleton in both species *[see Use in Specific Populations (8.1)]*.

5.6 Infusion Time

As bioequivalence has been established only when TEMODAR for Injection was given over 90 minutes, infusion over a shorter or longer period of time may result in suboptimal dosing. Additionally, the poss bility of an increase in infusion-related adverse reactions cannot be ruled out.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Newly Diagnosed Glioblastoma Multiforme: During the concomitant phase (TEMODAR+radiotherapy), adverse reactions including thrombocytopenia, nausea, vomiting, anorexia, and constipation were more frequent in the TEMODAR+RT arm. The incidence of other adverse reactions was comparable in the two arms. The most common adverse reactions across the cumulative TEMODAR experience were alopecia, nausea, vomiting, anorexia, headache, and constipation (see **Table 7**). Forty-nine percent (49%) of patients treated with TEMODAR reported one or more severe or life-threatening reactions, most commonly fatigue (13%), convulsions (6%), headache (5%), and thrombocytopenia (5%). Overall, the pattern of reactions during the maintenance phase was consistent with the known safety profile of TEMODAR.

TABLE 7: Number (%) of Patients with Adverse Reactions: All and Severe/Life Threatening (Incidence of 5% or Greater)

	Concomitant Phase RT Alone (n=285)				Concomitant Phase RT+TMZ (n=288)*				Maintenance Phase TMZ (n=224)			
	All		Grade ≥3		All		Grade ≥3		All		Grade ≥3	
Subjects Reporting any Adverse Reaction	**258**	**(91)**	**74**	**(26)**	**266**	**(92)**	**80**	**(28)**	**206**	**(92)**	**82**	**(37)**
Body as a Whole — General Disorders												
Anorexia	25	(9)	1	(<1)	56	(19)	2	(1)	61	(27)	3	(1)
Dizziness	10	(4)	0		12	(4)	2	(1)	12	(5)	0	
Fatigue	139	(49)	15	(5)	156	(54)	19	(7)	137	(61)	20	(9)
Headache	49	(17)	11	(4)	56	(19)	5	(2)	51	(23)	9	(4)
Weakness	9	(3)	3	(1)	10	(3)	5	(2)	16	(7)	4	(2)
Central and Peripheral Nervous System Disorders												
Confusion	12	(4)	6	(2)	11	(4)	4	(1)	12	(5)	4	(2)
Convulsions	20	(7)	9	(3)	17	(6)	10	(3)	25	(11)	7	(3)
Memory Impairment	12	(4)	1	(<1)	8	(3)	1	(<1)	16	(7)	2	(1)
Disorders of the Eye												
Vision Blurred	25	(9)	4	(1)	26	(9)	2	(1)	17	(8)	0	
Disorders of the Immune System												
Allergic Reaction	7	(2)	1	(<1)	13	(5)	0		6	(3)	0	
Gastrointestinal System Disorders												
Abdominal Pain	2	(1)	0		7	(2)	1	(<1)	11	(5)	1	(<1)
Constipation	18	(6)	0		53	(18)	3	(1)	49	(22)	0	
Diarrhea	9	(3)	0		18	(6)	0		23	(10)	2	(1)
Nausea	45	(16)	1	(<1)	105	(36)	2	(1)	110	(49)	3	(1)
Stomatitis	14	(5)	1	(<1)	19	(7)	0		20	(9)	3	(1)
Vomiting	16	(6)	1	(<1)	57	(20)	1	(<1)	66	(29)	4	(2)
Injury and Poisoning												
Radiation Injury NOS	11	(4)	1	(<1)	20	(7)	0		5	(2)	0	
Musculoskeletal System Disorders												
Arthralgia	2	(1)	0		7	(2)	1	(<1)	14	(6)	0	
Platelet, Bleeding and Clotting Disorders												
Thrombocytopenia	3	(1)	0		11	(4)	8	(3)	19	(8)	8	(4)
Psychiatric Disorders												
Insomnia	9	(3)	1	(<1)	14	(5)	0		9	(4)	0	
Respiratory System Disorders												
Coughing	3	(1)	0		15	(5)	2	(1)	19	(8)	1	(<1)
Dyspnea	9	(3)	4	(1)	11	(4)	5	(2)	12	(5)	1	(<1)
Skin and Subcutaneous Tissue Disorders												
Alopecia	179	(63)	0		199	(69)	0		124	(55)	0	
Dry Skin	6	(2)	0		7	(2)	0		11	(5)	1	(<1)
Erythema	15	(5)	0		14	(5)	0		2	(1)	0	
Pruritus	4	(1)	0		11	(4)	0		11	(5)	0	
Rash	42	(15)	0		56	(19)	3	(1)	29	(13)	3	(1)
Special Senses Other, Disorders												
Taste Perversion	6	(2)	0		18	(6)	0		11	(5)	0	

*One patient who was randomized to RT only arm received RT+temozolomide.
RT+TMZ=radiotherapy plus temozolomide; NOS=not otherwise specified.
Note: Grade 5 (fatal) adverse reactions are included in the Grade ≥3 column.

Myelosuppression (neutropenia and thrombocytopenia), which is a known dose-limiting toxicity for most cytotoxic agents, including TEMODAR, was observed. When laboratory abnormalities and adverse reactions were combined, Grade 3 or Grade 4 neutrophil abnormalities including neutropenic

reactions were observed in 8% of the patients, and Grade 3 or Grade 4 platelet abnormalities, including thrombocytopenic reactions, were observed in 14% of the patients treated with TEMODAR.

Refractory Anaplastic Astrocytoma: **Tables 8** and **9** show the incidence of adverse reactions in the 158 patients in the anaplastic astrocytoma study for whom data are available. In the absence of a control group, it is not clear in many cases whether these reactions should be attributed to temozolomide or the patients' underlying conditions, but nausea, vomiting, fatigue, and hematologic effects appear to be clearly drug-related. The most frequently occurring adverse reactions were nausea, vomiting, headache, and fatigue. The adverse reactions were usually NCI Common Toxicity Criteria (CTC) Grade 1 or 2 (mild to moderate in severity) and were self-limiting, with nausea and vomiting readily controlled with antiemetics. The incidence of severe nausea and vomiting (CTC Grade 3 or 4) was 10% and 6%, respectively. Myelosuppression (thrombocytopenia and neutropenia) was the dose-limiting adverse reaction. It usually occurred within the first few cycles of therapy and was not cumulative.

Myelosuppression occurred late in the treatment cycle and returned to normal, on average, within 14 days of nadir counts. The median nadirs occurred at 26 days for platelets (range: 21-40 days) and 28 days for neutrophils (range: 1-44 days). Only 14% (22/158) of patients had a neutrophil nadir and 20% (32/158) of patients had a platelet nadir, which may have delayed the start of the next cycle. Less than 10% of patients required hospitalization, blood transfusion, or discontinuation of therapy due to myelosuppression.

In clinical trial experience with 110 to 111 women and 169 to 174 men (depending on measurements), there were higher rates of Grade 4 neutropenia (ANC less than 500 cells/µL) and thrombocytopenia (less than 20,000 cells/µL) in women than men in the first cycle of therapy (12% vs. 5% and 9% vs. 3%, respectively).

In the entire safety database for which hematologic data exist (N=932), 7% (4/61) and 9.5% (6/63) of patients over age 70 experienced Grade 4 neutropenia or thrombocytopenia in the first cycle, respectively. For patients less than or equal to age 70, 7% (62/871) and 5.5% (48/879) experienced Grade 4 neutropenia or thrombocytopenia in the first cycle, respectively. Pancytopenia, leukopenia, and anemia have also been reported.

TABLE 8: Adverse Reactions in the Anaplastic Astrocytoma Trial in Adults (≥5%)

	No. (%) of TEMODAR Patients (N=158)	
	All Reactions	**Grade 3/4**
Any Adverse Reaction	**153 (97)**	**79 (50)**
Body as a Whole		
Headache	65 (41)	10 (6)
Fatigue	54 (34)	7 (4)
Asthenia	20 (13)	9 (6)
Fever	21 (13)	3 (2)
Back pain	12 (8)	4 (3)
Cardiovascular		
Edema peripheral	17 (11)	1 (1)
Central and Peripheral Nervous System		
Convulsions	36 (23)	8 (5)
Hemiparesis	29 (18)	10 (6)
Dizziness	19 (12)	1 (1)
Coordination abnormal	17 (11)	2 (1)
Amnesia	16 (10)	6 (4)
Insomnia	16 (10)	0
Paresthesia	15 (9)	1 (1)
Somnolence	15 (9)	5 (3)
Paresis	13 (8)	4 (3)
Urinary incontinence	13 (8)	3 (2)
Ataxia	12 (8)	3 (2)
Dysphasia	11 (7)	1 (1)
Convulsions local	9 (6)	0
Gait abnormal	9 (6)	1 (1)
Confusion	8 (5)	0
Endocrine		
Adrenal hypercorticism	13 (8)	0
Gastrointestinal System		
Nausea	84 (53)	16 (10)
Vomiting	66 (42)	10 (6)
Constipation	52 (33)	1 (1)
Diarrhea	25 (16)	3 (2)
Abdominal pain	14 (9)	2 (1)
Anorexia	14 (9)	1 (1)
Metabolic		
Weight increase	8 (5)	0
Musculoskeletal System		
Myalgia	8 (5)	
Psychiatric Disorders		
Anxiety	11 (7)	1 (1)
Depression	10 (6)	0
Reproductive Disorders		
Breast pain, female	4 (6)	
Resistance Mechanism Disorders		
Infection viral	17 (11)	0
Respiratory System		
Upper respiratory tract infection	13 (8)	0
Pharyngitis	12 (8)	0
Sinusitis	10 (6)	0
Coughing	8 (5)	0
Skin and Appendages		
Rash	13 (8)	0
Pruritus	12 (8)	2 (1)
Urinary System		
Urinary tract infection	12 (8)	0
Micturition increased frequency	9 (6)	0
Vision		
Diplopia	8 (5)	0
Vision abnormal*	8 (5)	

*Blurred vision; visual deficit; vision changes; vision troubles

TABLE 9: Adverse Hematologic Effects (Grade 3 to 4) in the Anaplastic Astrocytoma Trial in Adults

	TEMODAR*
Hemoglobin	7/158 (4%)
Lymphopenia	83/152 (55%)
Neutrophils	20/142 (14%)
Platelets	29/156 (19%)
WBC	18/158 (11%)

*Change from Grade 0 to 2 at baseline to Grade 3 or 4 during treatment.

TEMODAR for injection delivers equivalent temozolomide dose and exposure to both temozolomide and 5-(3-methyltriazen-1-yl)-imidazole-4-carboxamide (MTIC) as the corresponding TEMODAR capsules. Adverse reactions probably related to treatment that were reported from the 2 studies with the intravenous formulation (n=35) that were not reported in studies using the TEMODAR capsules were: pain, irritation, pruritus, warmth, swelling, and erythema at infusion site as well as the following adverse reactions: petechiae and hematoma.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of TEMODAR. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the drug exposure.

TEMODAR Capsules: allergic reactions, including anaphylaxis, have been reported. Erythema multiforme has been reported, which resolved after discontinuation of TEMODAR and, in some cases, recurred upon rechallenge. Cases of toxic epidermal necrolysis and Stevens-Johnson syndrome have been reported.

There have been reported cases of hepatotoxicity, including elevations of liver enzymes, hyperbilirubinemia, cholestasis, and hepatitis.

Opportunistic infections including *Pneumocystis carinii* pneumonia (PCP) have also been reported. Cases of interstitial pneumonitis/pneumonitis, alveolitis, and pulmonary fibrosis have been reported. Prolonged pancytopenia, which may result in aplastic anemia, has been reported, and in some cases has resulted in a fatal outcome.

7 DRUG INTERACTIONS

7.1 Valproic Acid

Administration of valproic acid decreases oral clearance of temozolomide by about 5%. The clinical implication of this effect is not known *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D. See Warnings and Precautions section.

TEMODAR can cause fetal harm when administered to a pregnant woman. Five consecutive days of oral temozolomide administration of 0.38 and 0.75 times the highest recommended human dose (75 and 150 mg/m^2) in rats and rabbits, respectively, during the period of organogenesis caused numerous malformations of the external and internal soft tissues and skeleton in both species. Doses equivalent to 0.75 times the highest recommended human dose (150 mg/m^2) caused embryolethality in rats and rabbits as indicated by increased resorptions. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with TEMODAR.

8.3 Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants and tumorigenicity shown for temozolomide in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of TEMODAR to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established. TEMODAR Capsules have been studied in 2 open-label studies in pediatric patients (aged 3-18 years) at a dose of 160 to 200 mg/m^2 daily for 5 days every 28 days. In one trial, 29 patients with recurrent brain stem glioma and 34 patients with recurrent high grade astrocytoma were enrolled. All patients had recurrence following surgery and radiation therapy, while 31% also had disease progression following chemotherapy. In a second study conducted by the Children's Oncology Group (COG), 122 patients were enrolled, including patients with medulloblastoma/PNET (29), high grade astrocytoma (23), low grade astrocytoma (22), brain stem glioma (16), ependymoma (14), other CNS tumors (9), and non-CNS tumors (9). The TEMODAR toxicity profile in pediatric patients is similar to adults. **Table 10** shows the adverse reactions in 122 children in the COG study.

TABLE 10: Adverse Reactions Reported in the Pediatric Cooperative Group Trial (≥10%)

	No. (%) of TEMODAR Patients (N=122)*	
Body System/Organ Class Adverse Reaction	**All Reactions**	**Grade 3/4**
Subjects Reporting an AE	**107 (88)**	**69 (57)**
Body as a Whole		
Central and Peripheral Nervous System		
Central cerebral CNS cortex	22 (18)	13 (11)
Gastrointestinal System		
Nausea	56 (46)	5 (4)
Vomiting	62 (51)	4 (3)
Platelet, Bleeding and Clotting		
Thrombocytopenia	71 (58)	31 (25)
Red Blood Cell Disorders		
Decreased Hemoglobin	62 (51)	7 (6)
White Cell and RES Disorders		
Decreased WBC	71 (58)	21 (17)
Lymphopenia	73 (60)	48 (39)
Neutropenia	62 (51)	24 (20)

*These various tumors included the following: PNET-medulloblastoma, glioblastoma, low grade astrocytoma, brain stem tumor, ependymoma, mixed glioma, oligodendroglioma, neuroblastoma, Ewing's sarcoma, pineoblastoma, alveolar soft part sarcoma, neurofibrosarcoma, optic glioma, and osteosarcoma.

8.5 Geriatric Use

Clinical studies of temozolomide did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

In the anaplastic astrocytoma study population, patients 70 years of age or older had a higher incidence of Grade 4 neutropenia and Grade 4 thrombocytopenia (2/8; 25%, *P*=0.31 and 2/10; 20%, *P*=0.09, respectively) in the first cycle of therapy than patients under 70 years of age *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

In newly diagnosed patients with glioblastoma multiforme, the adverse reaction profile was similar in younger patients (<65 years) vs. older (≥65 years).

8.6 Renal Impairment

Caution should be exercised when TEMODAR is administered to patients with severe renal impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

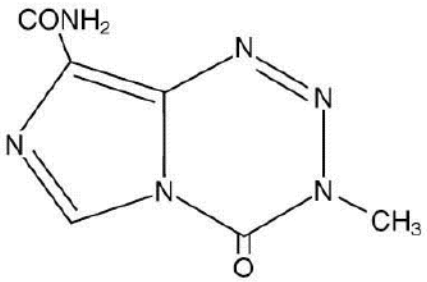
Caution should be exercised when TEMODAR is administered to patients with severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Doses of 500, 750, 1000, and 1250 mg/m^2 (total dose per cycle over 5 days) have been evaluated clinically in patients. Dose-limiting toxicity was hematologic and was reported with any dose but is expected to be more severe at higher doses. An overdose of 2000 mg per day for 5 days was taken by one patient and the adverse reactions reported were pancytopenia, pyrexia, multi-organ failure, and death. There are reports of patients who have taken more than 5 days of treatment (up to 64 days), with adverse reactions reported including bone marrow suppression, which in some cases was severe and prolonged, and infections and resulted in death. In the event of an overdose, hematologic evaluation is needed. Supportive measures should be provided as necessary.

11 DESCRIPTION

TEMODAR contains temozolomide, an imidazotetrazine derivative. The chemical name of temozolomide is 3,4-dihydro-3-methyl-4-oxoimidazo[5,1-d]-*as*-tetrazine-8-carboxamide. The structural formula is:



The material is a white to light tan/light pink powder with a molecular formula of $C_6H_6N_6O_2$ and a molecular weight of 194.15. The molecule is stable at acidic pH (<5) and labile at pH >7; hence TEMODAR can be administered orally and intravenously. The prodrug, temozolomide, is rapidly hydrolyzed to the active 5-(3-methyltriazen-1-yl) imidazole-4-carboxamide (MTIC) at neutral and alkaline pH values, with hydrolysis taking place even faster at a kaline pH.

TEMODAR Capsules:

Each capsule for oral use contains either 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, or 250 mg of temozolomide.

The inactive ingredients for TEMODAR Capsules are as follows:

TEMODAR 5 mg: lactose anhydrous (132.8 mg), colloidal silicon dioxide (0.2 mg), sodium starch glycolate (7.5 mg), tartaric acid (1.5 mg), and stearic acid (3 mg).

TEMODAR 20 mg: lactose anhydrous (182.2 mg), colloidal silicon dioxide (0.2 mg), sodium starch glycolate (11 mg), tartaric acid (2.2 mg), and stearic acid (4.4 mg).
TEMODAR 100 mg: lactose anhydrous (175.7 mg), colloidal silicon dioxide (0.3 mg), sodium starch glycolate (15 mg), tartaric acid (3 mg), and stearic acid (6 mg).
TEMODAR 140 mg: lactose anhydrous (246 mg), colloidal silicon dioxide (0.4 mg), sodium starch glycolate (21 mg), tartaric acid (4.2 mg), and stearic acid (8.4 mg).
TEMODAR 180 mg: lactose anhydrous (316.3 mg), colloidal silicon dioxide (0.5 mg), sodium starch glycolate (27 mg), tartaric acid (5.4 mg), and stearic acid (10.8 mg).
TEMODAR 250 mg: lactose anhydrous (154.3 mg), colloidal silicon dioxide (0.7 mg), sodium starch glycolate (22.5 mg), tartaric acid (9 mg), and stearic acid (13.5 mg).
The body of the capsules is made of gelatin, and is opaque white. The cap is also made of gelatin, and the colors vary based on the dosage strength. The capsule body and cap are imprinted with pharmaceutical branding ink, which contains shellac, dehydrated alcohol, isopropyl alcohol, butyl alcohol, propylene glycol, purified water, strong ammonia solution, potassium hydroxide, and ferric oxide.
TEMODAR 5 mg: The green cap contains gelatin, titanium dioxide, iron oxide yellow, sodium lauryl sulfate, and FD&C Blue #2.
TEMODAR 20 mg: The yellow cap contains gelatin, sodium lauryl sulfate, and iron oxide yellow.
TEMODAR 100 mg: The pink cap contains gelatin, titanium dioxide, sodium lauryl sulfate, and iron oxide red.
TEMODAR 140 mg: The blue cap contains gelatin, sodium lauryl sulfate, and FD&C Blue #2.
TEMODAR 180 mg: The orange cap contains gelatin, iron oxide red, iron oxide yellow, titanium dioxide, and sodium lauryl sulfate.
TEMODAR 250 mg: The white cap contains gelatin, titanium dioxide, and sodium lauryl sulfate.
TEMODAR for Injection: Each vial contains 100 mg of sterile and pyrogen-free temozolomide lyophilized powder for intravenous injection. The inactive ingredients are: mannitol (600 mg), L-threonine (160 mg), polysorbate 80 (120 mg), sodium citrate dihydrate (235 mg), and hydrochloric acid (160 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Temozolomide is not directly active but undergoes rapid nonenzymatic conversion at physiologic pH to the reactive compound 5-(3-methyltriazen-1-yl)-imidazole-4-carboxamide (MTIC). The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA. Alkylation (methylation) occurs mainly at the O^6 and N^7 positions of guanine.

12.3 Pharmacokinetics

Absorption: Temozolomide is rapidly and completely absorbed after oral administration with a peak plasma concentration (C_{max}) achieved in a median T_{max} of 1 hour. Food reduces the rate and extent of temozolomide absorption. Mean peak plasma concentration and AUC decreased by 32% and 9%, respectively, and median T_{max} increased by 2-fold (from 1-2.25 hours) when temozolomide was administered after a modified high-fat breakfast.
A pharmacokinetic study comparing oral and intravenous temozolomide in 19 patients with primary CNS malignancies showed that 150 mg/m^2 TEMODAR for injection administered over 90 minutes is bioequivalent to 150 mg/m^2 TEMODAR oral capsules with respect to both C_{max} and AUC of temozolomide and MTIC. Following a single 90-minute intravenous infusion of 150 mg/m^2, the geometric mean C_{max} values for temozolomide and MTIC were 7.3 mcg/mL and 276 ng/mL, respectively. Following a single oral dose of 150 mg/m^2, the geometric mean C_{max} values for temozolomide and MTIC were 7.5 mcg/mL and 282 ng/mL, respectively. Following a single 90-minute intravenous infusion of 150 mg/m^2, the geometric mean AUC values for temozolomide and MTIC were 24.6 mcg·hr/mL and 891 ng·hr/mL, respectively. Following a single oral dose of 150 mg/m^2, the geometric mean AUC values for temozolomide and MTIC were 23.4 mcg·hr/mL and 864 ng·hr/mL, respectively.
Distribution: Temozolomide has a mean apparent volume of distribution of 0.4 L/kg (%CV=13%). It is weakly bound to human plasma proteins; the mean percent bound of drug-related total radioactivity is 15%.
Metabolism and Elimination: Temozolomide is spontaneously hydrolyzed at physiologic pH to the active species, MTIC and to temozolomide acid metabolite. MTIC is further hydrolyzed to 5-amino-imidazole-4-carboxamide (AIC), which is known to be an intermediate in purine and nucleic acid biosynthesis, and to methylhydrazine, which is believed to be the active alkylating species. Cytochrome P450 enzymes play only a minor role in the metabolism of temozolomide and MTIC. Relative to the AUC of temozolomide, the exposure to MTIC and AIC is 2.4% and 23%, respectively.
Excretion: About 38% of the administered temozolomide total radioactive dose is recovered over 7 days: 37.7% in urine and 0.8% in feces. The majority of the recovery of radioactivity in urine is unchanged temozolomide (5.6%), AIC (12%), temozolomide acid metabolite (2.3%), and unidentified polar metabolite(s) (17%). Overall clearance of temozolomide is about 5.5 L/hr/m^2. Temozolomide is rapidly eliminated, with a mean elimination half-life of 1.8 hours, and exhibits linear kinetics over the therapeutic dosing range of 75 to 250 mg/m^2/day.
Effect of Age: A population pharmacokinetic analysis indicated that age (range: 19-78 years) has no influence on the pharmacokinetics of temozolomide.
Effect of Gender: A population pharmacokinetic analysis indicated that women have an approximately 5% lower clearance (adjusted for body surface area) for temozolomide than men.
Effect of Race: The effect of race on the pharmacokinetics of temozolomide has not been studied.
Tobacco Use: A population pharmacokinetic analysis indicated that the oral clearance of temozolomide is similar in smokers and nonsmokers.
Effect of Renal Impairment: A population pharmacokinetic analysis indicated that creatinine clearance over the range of 36 to 130 mL/min/m^2 has no effect on the clearance of temozolomide after oral administration. The pharmacokinetics of temozolomide have not been studied in patients with severely impaired renal function (CLcr <36 mL/min/m^2). Caution should be exercised when TEMODAR is administered to patients with severe renal impairment *[see Use in Special Populations (8.6)]*. TEMODAR has not been studied in patients on dialysis.
Effect of Hepatic Impairment: A study showed that the pharmacokinetics of temozolomide in patients with mild-to-moderate hepatic impairment (Child-Pugh Class I - II) were similar to those observed in patients with normal hepatic function. Caution should be exercised when temozolomide is administered to patients with severe hepatic impairment *[see Use in Specific Populations (8.7)]*.
Effect of Other Drugs on Temozolomide Pharmacokinetics: In a multiple-dose study, administration of TEMODAR Capsules with ranitidine did not change the C_{max} or AUC values for temozolomide or MTIC.
A population analysis indicated that administration of valproic acid decreases the clearance of temozolomide by about 5% *[see Drug Interactions (7.1)]*.
A population analysis did not demonstrate any influence of coadministered dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H_2-receptor antagonists, or phenobarbital on the clearance of orally administered temozolomide.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Temozolomide is carcinogenic in rats at doses less than the maximum recommended human dose. Temozolomide induced mammary carcinomas in both males and females at doses 0.13 to 0.63 times the maximum human dose (25-125 mg/m^2) when administered orally on 5 consecutive days every 28 days for 6 cycles. Temozolomide also induced fibrosarcomas of the heart, eye, seminal vesicles, salivary glands, abdominal cavity, uterus, and

prostate, carcinomas of the seminal vesicles, schwannomas of the heart, optic nerve, and harderian gland, and adenomas of the skin, lung, pituitary, and thyroid at doses 0.5 times the maximum daily dose. Mammary tumors were also induced following 3 cycles of temozolomide at the maximum recommended daily dose.

Temozolomide is a mutagen and a clastogen. In a reverse bacterial mutagenesis assay (Ames assay), temozolomide increased revertant frequency in the absence and presence of metabolic activation. Temozolomide was clastogenic in human lymphocytes in the presence and absence of metabolic activation.

Temozolomide impairs male fertility. Temozolomide caused syncytial cells/immature sperm formation at 0.25 and 0.63 times the maximum recommended human dose (50 and 125 mg/m^2) in rats and dogs, respectively, and testicular atrophy in dogs at 0.63 times the maximum recommended human dose (125 mg/m^2).

13.2 Animal Toxicology and/or Pharmacology

Toxicology studies in rats and dogs identified a low incidence of hemorrhage, degeneration, and necrosis of the retina at temozolomide doses equal to or greater than 0.63 times the maximum recommended human dose (125 mg/m^2). These changes were most commonly seen at doses where mortality was observed.

14 CLINICAL STUDIES

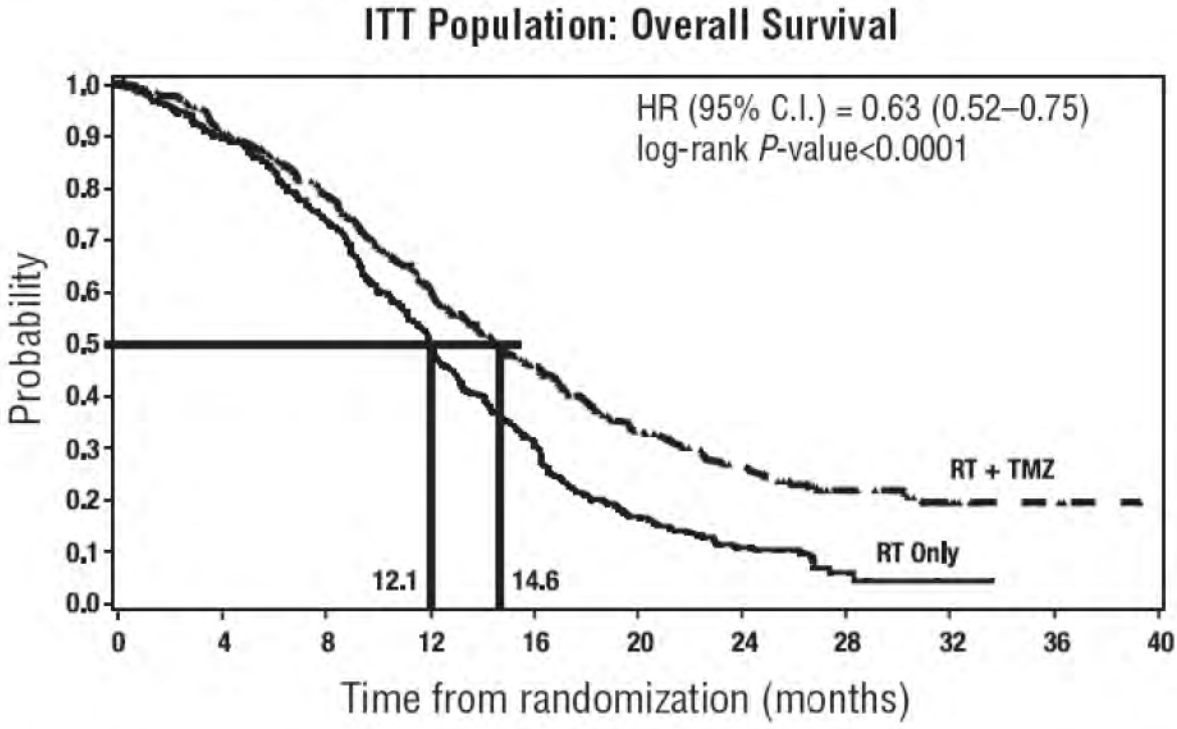
14.1 Newly Diagnosed Glioblastoma Multiforme

Five hundred and seventy-three patients were randomized to receive either TEMODAR (TMZ)+Radiotherapy (RT) (n=287) or RT alone (n=286). Patients in the TEMODAR+RT arm received concomitant TEMODAR (75 mg/m^2) once daily, starting the first day of RT until the last day of RT, for 42 days (with a maximum of 49 days). This was followed by 6 cycles of TEMODAR alone (150 or 200 mg/m^2) on Days 1 to 5 of every 28-day cycle, starting 4 weeks after the end of RT. Patients in the control arm received RT only. In both arms, focal radiation therapy was delivered as 60 Gy/30 fractions. Focal RT includes the tumor bed or resection site with a 2- to 3-cm margin. *Pneumocystis carinii* pneumonia (PCP) prophylaxis was required during the TMZ+RT, regardless of lymphocyte count, and was to continue until recovery of lymphocyte count to less than or equal to Grade 1.

At the time of disease progression, TEMODAR was administered as salvage therapy in 161 patients of the 282 (57%) in the RT alone arm, and 62 patients of the 277 (22%) in the TEMODAR+RT arm.

The addition of concomitant and maintenance TEMODAR to radiotherapy in the treatment of patients with newly diagnosed GBM showed a statistically significant improvement in overall survival compared to radiotherapy alone (**Figure 1**). The hazard ratio (HR) for overall survival was 0.63 (95% CI for HR=0.52-0.75) with a log-rank *P*<0.0001 in favor of the TEMODAR arm. The median survival was increased by 2.5 months in the TEMODAR arm.

FIGURE 1: Kaplan-Meier Curves for Overall Survival (ITT Population)



14.2 Refractory Anaplastic Astrocytoma

A single-arm, multicenter study was conducted in 162 patients who had anaplastic astrocytoma at first relapse and who had a baseline Karnofsky performance status of 70 or greater. Patients had previously received radiation therapy and may also have previously received a nitrosourea with or without other chemotherapy. Fifty-four patients had disease progression on prior therapy with both a nitrosourea and procarbazine, and their malignancy was considered refractory to chemotherapy (refractory anaplastic astrocytoma population). Median age of this subgroup of 54 patients was 42 years (19-76). Sixty-five percent were male. Seventy-two percent of patients had a KPS of >80. Sixty-three percent of patients had surgery other than a biopsy at the time of initial diagnosis. Of those patients undergoing resection, 73% underwent a subtotal resection and 27% underwent a gross total resection. Eighteen percent of patients had surgery at the time of first relapse. The median time from initial diagnosis to first relapse was 13.8 months (4.2-75.4).

TEMODAR Capsules were given for the first 5 consecutive days of a 28-day cycle at a starting dose of 150 mg/m^2/day. If the nadir and day of dosing (Day 29, Day 1 of next cycle) absolute neutrophil count was greater than or equal to 1.5 x 10^9/L (1500/µL) and the nadir and Day 29, Day 1 of next cycle platelet count was greater than or equal to 100 x 10^9/L (100,000/µL), the TEMODAR dose was increased to 200 mg/m^2/day for the first 5 consecutive days of a 28-day cycle.

In the refractory anaplastic astrocytoma population, the overall tumor response rate (CR+PR) was 22% (12/54 patients) and the complete response rate was 9% (5/54 patients). The median duration of all responses was 50 weeks (range: 16-114 weeks) and the median duration of complete responses

was 64 weeks (range: 52-114 weeks). In this population, progression-free survival at 6 months was 45% (95% CI: 31%-58%) and progression-free survival at 12 months was 29% (95% CI: 16%-42%). Median progression-free survival was 4.4 months. Overall survival at 6 months was 74% (95% CI: 62%-86%) and 12-month overall survival was 65% (95% CI: 52%-78%). Median overall survival was 15.9 months.

15 REFERENCES

1. OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999.
2. American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health-Syst Pharm.* 2006; 63:1172-1193.
3. NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.[3]
4. Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Safe Handling and Disposal

Care should be exercised in the handling and preparation of TEMODAR. Vials and capsules should not be opened. If vials or capsules are accidentally opened or damaged, rigorous precautions should be taken with the contents to avoid inhalation or contact with the skin or mucous membranes. The use of gloves and safety glasses is recommended to avoid exposure in case of breakage of the vial or capsules. Procedures for proper handling and disposal of anticancer drugs should be considered {1-4}. Several guidelines on this subject have been published.

16.2 How Supplied

TEMODAR Capsules: TEMODAR (temozolomide) Capsules are supplied in amber glass bottles with child-resistant polypropylene caps or child-resistant sachets containing the following capsule strengths:

TEMODAR Capsules 5 mg: have opaque white bodies with green caps. The capsule body is imprinted with two stripes, the dosage strength, and the Schering-Plough logo. The cap is imprinted with "TEMODAR".
They are supplied as follows:
Bottles:
5-count – NDC 0085-3004-02
14-count – NDC 0085-3004-01
Sachets:
5-count – NDC 0085-3004-03
14-count – NDC 0085-3004-04

TEMODAR Capsules 20 mg: have opaque white bodies with yellow caps. The capsule body is imprinted with two stripes, the dosage strength, and the Schering-Plough logo. The cap is imprinted with "TEMODAR".
They are supplied as follows:
Bottles:
5-count – NDC 0085-1519-02
14-count – NDC 0085-1519-01
Sachets:
5-count – NDC 0085-1519-03
14-count – NDC 0085-1519-04

TEMODAR Capsules 100 mg: have opaque white bodies with pink caps. The capsule body is imprinted with two stripes, the dosage strength, and the Schering-Plough logo. The cap is imprinted with "TEMODAR".
They are supplied as follows:
Bottles:
5-count – NDC 0085-1366-02
14-count – NDC 0085-1366-01
Sachets:
5-count – NDC 0085-1366-03
14-count – NDC 0085-1366-04

TEMODAR Capsules 140 mg: have opaque white bodies with blue caps. The capsule body is imprinted with two stripes, the dosage strength, and the Schering-Plough logo. The cap is imprinted with "TEMODAR".
They are supplied as follows:
Bottles:
5-count – NDC 0085-1425-01
14-count – NDC 0085-1425-02
Sachets:
5-count – NDC 0085-1425-03
14-count – NDC 0085-1425-04

TEMODAR Capsules 180 mg: have opaque white bodies with orange caps. The capsule body is imprinted with two stripes, the dosage strength, and the Schering-Plough logo. The cap is imprinted with "TEMODAR".
They are supplied as follows:
Bottles:
5-count – NDC 0085-1430-01
14-count – NDC 0085-1430-02
Sachets:
5-count – NDC 0085-1430-03
14-count – NDC 0085-1430-04

TEMODAR Capsules 250 mg: have opaque white bodies with white caps. The capsule body is imprinted with two stripes, the dosage strength, and the Schering-Plough logo. The cap is imprinted with "TEMODAR".
They are supplied as follows:
Bottles:
5-count – NDC 0085-1417-01
Sachets:
5-count – NDC 0085-1417-02

TEMODAR for Injection: TEMODAR (temozolomide) for Injection is supplied in single-use glass vials containing 100 mg temozolomide. The lyophilized powder is white to light tan/light pink.

TEMODAR for Injection 100 mg:

NDC 0085-1381-01

16.3 Storage

Store TEMODAR Capsules at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Store TEMODAR for Injection refrigerated at 2-8°C (36-46°F). After reconstitution, store reconstituted product at room temperature (25°C [77°F]). Reconstituted product must be used within 14 hours, including infusion time.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information).

17.1 Information for the Patient

Physicians should discuss the following with their patients:

- Nausea and vomiting are the most frequently occurring adverse reactions. Nausea and vomiting are usually either self-limiting or readily controlled with standard antiemetic therapy.
- Capsules should not be opened. If capsules are accidentally opened or damaged, rigorous precautions should be taken with the capsule contents to avoid inhalation or contact with the skin or mucous membranes.
- The medication should be kept away from children and pets.

TEMODAR Capsules

Manufactured by: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

TEMODAR for Injection

Manufactured for: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA

Manufactured by:
Baxter Oncology GmbH, Halle 33790, Germany

For patent information: www.merck.com/product/patent/home.html

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Action Letter

Attachment 4: Severe liver toxicity associated with temozolomide (Temodal ®) letter from MSD

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UK
Telephone Hoddesdon +44 (0)1992 467272
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MSD

12 December 2013

Severe liver toxicity associated with temozolomide (Temodal®)

Dear Healthcare Provider,

Merck Sharp & Dohme (MSD) in agreement with the European Medicines Agency (EMA) and Medicine and Healthcare Products Regulatory Agency (MHRA) would like to inform you of the following:

Summary

- **Cases of hepatic injury, including fatal hepatic failure, have been reported in patients receiving temozolomide.**
- **Liver toxicity may occur several weeks or more after initiation of treatment or after temozolomide discontinuation.**
- **Liver function tests should be performed**
  - **prior to treatment initiation. If abnormal, the decision to initiate temozolomide treatment should carefully consider the benefits and risks for the individual patient;**
  - **after each treatment cycle.**
- **For patients on a 42 day treatment cycle, liver function tests should be repeated midway during this cycle;**
- **For patients with significant liver function abnormalities the benefits and risks of continuing treatment should be carefully considered.**

Background

Temodal® is indicated for the treatment of:

- Adult patients with newly-diagnosed glioblastoma multiforme concomitantly with radiotherapy (RT) and subsequently as monotherapy treatment.
- Malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, showing recurrence or progression after standard therapy in children from the age of three years, adolescents and adult patients.

Safety concern

A review of serious, including fatal, cases of hepatotoxicity reported for temozolomide worldwide was recently performed. In total, 44 cases of hepatic injury, including fatal hepatic failure were

Action Letter

identified in patients receiving temozolomide. These cases of fatal hepatic failure were reported with an approximate onset of 42 to 77 days following initiation of treatment with temozolomide. Non-fatal cases of liver toxicity were also reported with variable times to onset up to 112 days. The product label for temozolomide already documents hepatotoxicity, but does not include fatal hepatocellular injury and hepatic failure, or specific recommendations for monitoring liver function.

As a consequence of this review, the product information for temozolomide (Temodal®) is being updated across the EU in line with the summary recommendations above.

Call for reporting
Please report suspected adverse events with the use of temozolomide in accordance with your national reporting system.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events with this product should also be reported to MSD (Tel: 01992467272).

Company contact point
If you have any questions or require additional information regarding the use of Temodal, please call MSD Medical Information services on 01992 467272. For all other queries regarding temozolomide please contact the relevant Marketing Authorisation Holder.

Yours sincerely,

[redacted]

[redacted]
Medical Director