An Open-Label, Phase 2 Efficacy Study of Temozolomide (TMZ) In Advanced Succinate Dehydrogenase (SDH)-Mutant/Deficient Gastrointestinal Stromal Tumor (GIST)

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Study Chair (Sponsor-Investigator)
Adam M. Burgoyne, MD, PhD
Department of Medicine
University of California, San Diego
Moores Cancer Center
3855 Health Sciences Drive #0987
La Jolla, CA 92093
Phone: 858-246-0674
E-mail: aburgoyne@health.ucsd.edu

Research Coordinating Center
UCSD Moores Cancer Center
3855 Health Sciences Drive #0698
La Jolla, CA 92093-0698

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IND Holder Name: Adam M Burgoyne, MD PhD

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LIST OF INVESTIGATORS

UCSD Moores Cancer Center

PRINCIPAL INVESTIGATOR

Adam M. Burgoyne, MD, PhD
Assistant Professor
Division of Hematology-Oncology
Department of Medicine
University of California, San Diego
Moores Cancer Center
3855 Health Sciences Drive #0987
La Jolla, CA 92093-0987
Phone: 858-246-0674
Fax: 858-246-0284
E-mail: aburgoyne@health.ucsd.edu

SUB-INVESTIGATORS

Jason K. Sicklick, MD
Associate Professor
Division of Hematology-Oncology
Department of Medicine
University of California, San Diego
Moores Cancer Center
3855 Health Sciences Drive #0987
La Jolla, CA 92093-0987
Phone: 858-822-3967
E-mail: jsicklick@health.ucsd.edu

Paul T. Fanta, MD
Associate Professor
Division of Hematology-Oncology
Department of Medicine
University of California, San Diego
Moores Cancer Center
3855 Health Sciences Drive #0987
La Jolla, CA 92093-0997
Phone: (858) 822-7973
E-mail: pfanta@health.ucsd.edu

Hitendra Patel, MD
Associate Professor
Division of Hematology-Oncology
Department of Medicine
University of California, San Diego
Moores Cancer Center
3855 Health Sciences Drive #0987
La Jolla, CA 92093-0997
Phone: 858-822-3115
E-mail: hip003@health.ucsd.edu

Aaron M. Miller, MD, PhD
Assistant Professor
Division of Hematology-Oncology
Department of Medicine
University of California, San Diego
Moores Cancer Center
3855 Health Sciences Drive #0987
La Jolla, CA 92093-0997
Phone: 858-822-3092
E-mail: ammiller@health.ucsd.edu

TRIAL SITE LOCATIONS

1. University of Miami
2. Dana-Farber Cancer Institute
3. Fox Chase Cancer Center
4. Oregon Health & Science University

Biostatistician:

Karen Messer, PhD
Professor
Department of Family Medicine and Public Health
University of California, San Diego
Moores UCSD Cancer Center
3855 Health Sciences Drive #0901
La Jolla CA, 92093-0901
Phone: 858-822-6823
E-mail: kmesser@health.ucsd.edu

Radiologist:

Michael Hahn, MD
Assistant Professor
Department of Radiology
University of California, San Diego
200 W. Arbor Drive #8756
San Diego, CA 92103-8756
Phone: 619-543-6768
Fax : 619-543-3781
E-mail : mehahn@health.ucsd.edu

Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

UCSD Principal Investigator/Study Chair

_____
Printed Name

_____ _____
Signature Date

Participating Site Principal Investigator

_____ _____
Printed Name Institution

_____ _____
Signature Date

INVESTIGATOR PROTOCOL AGREEMENT
Protocol # 180114

Title: An Open-Label, Phase 2 Efficacy Study of Temozolomide (TMZ) In Advanced Succinate Dehydrogenase (SDH)-Mutant/Deficient Gastrointestinal Stromal Tumor (GIST)

I confirm that my staff and I have carefully read and understand this protocol. I/we agree to comply with the procedures and terms of the clinical trial specified herein. In particular, I/we have agreed to:

- Abide by all obligations stated on the Form FDA 1572 and on other document(s) required by local regulatory authority.
- Comply with Good Clinical Practice (GCP) and all applicable regulatory requirements.
- Maintain confidentiality and assure security of the Sponsor (UCSD) confidential documents.
- Obtain Institutional Review Board (IRB) approval of the protocol, any amendment to the protocol, and periodic re-approval as required, and to keep the IRB informed of any adverse events and periodically report the status of the trial to the IRB.
- Not implement any deviations from or changes to the protocol without agreement from the Sponsor and prior review and written approval from the IRB, except where necessary to eliminate an immediate hazard to the patients or for administrative aspects of the trial (where permitted by all applicable regulatory requirements).
- Assure that each patient enrolled into the trial has read, understands, and has signed the informed consent.
- Ensure that I and all persons assisting me with the trial are adequately informed and trained about the trial treatment and of their trial-related duties and functions as described in the protocol.
- Make prompt reports of serious adverse events (SAEs) and deaths within 24 hours (1 business day) of becoming aware of the event to UCSD
- Assure access by the Sponsor and/or FDA to original source documents.
- Prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated in the investigation.
- Arrange for the transfer of appropriate data from case histories to case report forms for the collection and transmission of data to the Sponsor.
- Retain records and documents related to this trial for at least 3 years after the completion of the trial as confirmed by the sponsor.
- Cooperate fully with any trial-related GCP audit as performed by the assurance group specified by the Sponsor.
- Abide by the stipulations in the Confidentiality and Financial Disclosure sections and the manuscript preparation/authorship guidelines established at the outset of the trial.

Investigator's Printed Name: _____

Investigator' Signature: _____ Date: _____

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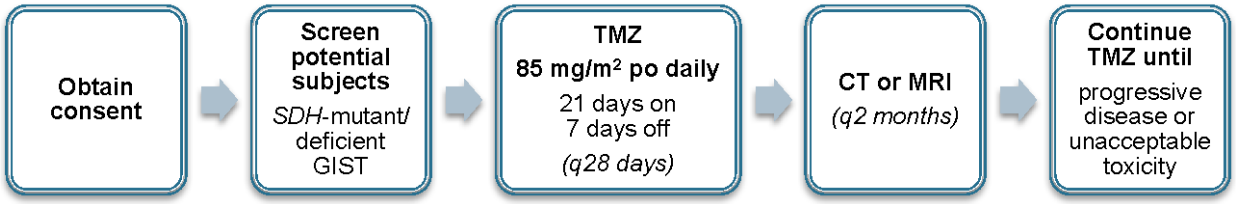
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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
AUC	Area under the curve
BCC	Basal Cell Cancer
BID	bis in diem/twice a day
CK	Creatinine Phosphokinase
Cmax	Maximum (peak) concentration of drug
Cmin	Minimum (peak) concentration of drug
CR	Complete Response
CRF	Case Report/Record Form; CRF can be applied to either EDC or Paper
CSS	Carney-Stratakis Syndrome
CT	Computed Tomography
CTCAE	Common Terminology Criteria Adverse Events
DTIC	Dacarbazine
DLT	Dose Limiting Toxicity
DS&E	Drug Safety and Epidemiology
DSMB	Data Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
FDG-PET	Fluorodeoxyglucose (^{18}F)-Positron Emission Tomography
GIST	Gastrointestinal stromal tumor
GPCR	G protein-couple receptor
HCV	Hepatitis C Virus
Hgb	Hemoglobin
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
OR	Objective Response
OS	Overall Survival
PCC	Pheochromocytoma
PD	Pharmacodynamics
PERCIST	Positron Emission Tomography Response Criteria in Solid Tumors
PFS	Progression Free Survival
PGL	Paraganglioma
Pgp	P-glycoprotein
PK	Pharmacokinetics
PMR	Partial Metabolic Response
p.o.	Per os/ by mouth/ orally
PR	Partial Response
QD	Quaque die/ once a day
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
SDH	Succinate Dehydrogenase

SGOT	Serum glutamic oxaloacetic transaminase; aspartate aminotransferase; AST
SGPT	Serum glutamic pyruvic transaminase; alanine aminotransferase; ALT
TKI	Tyrosine Kinase Inhibitor
TK	Toxicokinetics
Tmax	Median time of Cmax
TMZ	Temozolomide
Vss	Volume of distribution
WBC	White Blood cells

STUDY SCHEMA



SYNOPSIS

Gastrointestinal stromal tumor (GIST) is the most common sarcoma with approximately 1-in-13 cases occurring due to inherited mutations in succinate dehydrogenase (SDH) genes associated with Familial Paraganglioma/GIST Syndrome. Given the shared genomic alterations and inheritance patterns between *SDH*-mutant/deficient tumors, as well as reports of *SDHB*-mutant paraganglioma (PGL) sensitivity to Temozolomide (TMZ), a DNA alkylating agent, we hypothesize that these tyrosine kinase inhibitor (TKI)-resistant tumors share a conserved molecular phenotype that predicts sensitivity to TMZ. In this clinical trial, we aim to identify the response rate to TMZ in *SDH*-mutant/deficient GIST, and thereby improve patient outcomes.

STUDY SUMMARY

Title	An Open-Label, Phase 2 Efficacy Study Of Temozolomide (TMZ) In Advanced Succinate Dehydrogenase (SDH)-Mutant/Deficient Gastrointestinal Stromal Tumor (GIST)
Short Title	Phase 2 Study of TMZ in SDH-Mutant/Deficient GIST
Phase	2
Study Sites	Multi Center University of California, San Diego University of Miami Dana-Farber Cancer Institute Fox Chase Cancer Center Oregon Health & Science University
Methodology	Open-label, single arm study of TMZ in patients with advanced or metastatic GIST
Study Duration	4 years
Objectives	<u>Primary Objective:</u> To determine overall response rate by 6 months for TMZ therapy in patients with *SDH*-mutant/deficient GIST <u>Secondary Objectives:</u> 1. To determine progression-free survival. 2. To determine overall survival. 3. To determine safety and tolerability of TMZ. <u>Exploratory Objectives:</u> 1. To determine effect of TMZ therapy on serum succinate/fumarate ratio. 2. To determine effect of TMZ therapy on tumor metabolism.
Number of Subjects	23
Inclusion Criteria	1. Patient has the ability to understand and the willingness to sign a written informed consent. 2. Patient is ≥ 12 years of age. 3. Patient has pathologically confirmed *SDH*-mutant/deficient GIST. 4. Has recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy. 5. Patient has an ECOG Performance Status of 0-2. 6. Patient has adequate hematologic, hepatic and renal function. 7. Female patient of childbearing potential has a negative serum or urine pregnancy within 72 hours prior to receiving the first dose of study medication. 8. Female patient of childbearing potential agrees to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication. 9. Male patient with a partner of childbearing potential agrees to use an adequate method of contraception starting with

	the first dose of study therapy through 120 days after the last dose of study therapy. 10. Has measurable or evaluable disease as per RECIST v1.1 (Appendix B). 11. Life expectancy of >12 weeks.
Exclusion Criteria	1. Patients who have had major surgery within 4 weeks of initiation of study medication. 2. Patients who are receiving other concurrent anti-neoplastic therapy (e.g., chemotherapy, targeted therapy, immunotherapy, or radiotherapy) at the start of study treatment. 3. Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events. 4. Evidence of severe or uncontrolled systemic diseases [e.g., unstable or uncompensated respiratory, cardiac (including life threatening arrhythmias)]. 5. Unresolved toxicity ≥ CTCAE Grade 2 from previous anti-cancer therapy except alopecia (if applicable) unless agreed that the patient can be entered after discussion with the Medical Monitor. 6. Presence of cardiac impairment class III and IV definitions; OR history of myocardial infarction/active ischemic heart disease within one year of study entry; OR uncontrolled dysrhythmias; OR poorly controlled angina. 7. Pregnant or breast-feeding females. 8. Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient. 9. Any concurrent condition which in the investigator's opinion makes it undesirable for the subject to participate in this trial or which would jeopardize compliance with the protocol. 10. Patients who cannot swallow oral formulations of the agent.
Study Product(s), Dose, Route, Regimen	TMZ 85 mg/m^2 mg orally once for 21 days followed by 7 days without treatment.
Duration of administration	Advanced, metastatic setting – up to 6 months (option to continue if benefiting)
Reference therapy	Historical control (observation)
Statistical Methodology	**Endpoints** <u>Primary Endpoint:</u> 1) Overall response (PR + CR) according to RECIST v1.1 at 6 months from onset of TMZ administration. <u>Secondary Endpoints:</u>

	1) Progression-free survival. 2) Overall survival. 3) Adverse events related to TMZ (description, grade [CTCAE v5.0], and seriousness). <u>Exploratory Endpoints:</u> 1) Fold-change of serum succinate/fumarate ratio. 2) Change in tumor metabolism profile. **Study Populations** The safety population will consist of all patients who have received at least one dose of TMZ. The Intention-to-Treat (ITT) population will consist of all patients who have been consented to the study. The Disease-Free Survival Efficacy-Evaluable (DFSEE) population will consist of patients with confirmed *SDH*-mutant/deficient GIST and who have received at least one dose of TMZ in the metastatic setting.

SCHEDULE OF EVENTS

Procedures[14]	Screening		Day 1	Day 15	Days 29, 57, 85, 113, 141	End of Tx Visit*	Follow Up
Visit Window (days)	**Day -30 to Day -1**	**Day -10 to Day -1**	**0**	**±3**	**±3**	±7	±7
Informed Consent	X						
Medical History		X					
Demographics		X					
Eligibility Criteria		X					
Concomitant Medications [1]		X	X	X	X	X	
Adverse Events [2]		X	X	X	X	X	
Vital Signs [3]		X		X	X	X	
Weight, height		X					
Physical Exam [4]		X		X	X	X	
ECOG Performance Status		X		X	X	X	
Hematology [5]		X		X	X	X	
Serum Chemistries [6]		X		X	X	X	
PT/PTT [7]		X		X	X	X	
Miscellaneous blood sample [8]		X		X	X	X	
Pregnancy Test [9]		X					
TMZ Administration [10]			X	X	X		
Pill Diary Review					X	X	
CT or MRI Scans[11]	X				X		
Biopsy [12]	X						
FU: Survival Contacts [13]							X

1. Concomitant medications: to be collected for any subject being followed for a Serious Adverse Event (SAE) occurring up to 30 days after last dose of study drug until resolution of the SAE.
2. Adverse events: to be collected once patient signs consent form and throughout the study until at least 4 weeks after the last dose of study drug and followed until resolution or stabilization. See Section 6 for more information.
3. Vital signs: consist of temperature, heart rate, respiration and blood pressure.
4. Physical exam: consists of a total body examination.
5. Hematology: hemoglobin, platelets, total white blood cell count, and differential.
6. Serum chemistries: Creatinine phosphokinase, magnesium, phosphorus and comprehensive metabolic panel (glucose, BUN, creatinine, sodium, potassium, chloride, bicarbonate, calcium, total protein, albumin, AST/sGOT, ALT/sGPT, alkaline phosphatase, and total bilirubin).
7. Coagulation: Prothrombin time (PT) and INR.

8. Miscellaneous blood sample collection: 10 mL of venous blood in lavender top (EDTA anticoagulant) vacutainer tube(s). The tubes should be inverted approximately 8-10 times to mix the EDTA. Refrigerate sample until shipping.
9. Pregnancy Test: A serum or urine pregnancy test is required for all females of childbearing potential.
10. TMZ Administration: See Section 4.2 for instructions on daily administration of oral TMZ. Temozolomide (TMZ) administered per package insert daily (85 mg/m^2) if all of the following conditions are met: absolute neutrophil count is > 1.5 X 10^9/L, platelet count > 100 X 10^9/L, and NCI-CTCAE, Version 5.0 non-hematological toxicity is ≤ Grade 1 (except for alopecia, nausea, and vomiting). No dose reductions are recommended during Concomitant Treatment; however, TMZ should be interrupted or discontinued during Concomitant Treatment according to the hematological and non-hematological toxicity criteria (see Table 4-1).
11. CT or MRI of chest/abdomen/pelvis performed for screening purposes may be done within 4 weeks prior to starting study treatment. Additional CT or MRI of chest/abdomen/pelvis will be performed after every 2 cycles (56 days) of treatment with TMZ.
12. Biopsy: Biopsy of GIST tissue for diagnostic confirmation of disease, including SDHB immunohistochemistry is only needed if it has not yet been previously performed.
13. Survival contacts: to occur via medical record review, telephone call, or review of the Social Security Index every 3-6 months from the end of treatment visit until death or lost to follow-up.

* End of Treatment (Tx) Visit: The last visit will occur approximately 28 days after the last dose of the study drug.

14. Alternative methods for informed consent and safety assessments (e.g., phone contact, virtual visit, alternative location for assessment, including local labs or imaging centers) may be implemented when necessary (e.g. COVID-19 pandemic) and feasible

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Gastrointestinal stromal tumor (GIST) is the most common sarcoma with ≈3,000 new malignant cases in the U.S. annually. The treatment of GIST provided proof-of-principle for precision oncology as oncogenic driver mutations in the KIT gene were identified and effectively targeted with imatinib, a tyrosine kinase inhibitor (TKI). GIST is not a single, homogeneous disease.[1,2] Historically tumors were only sub-classified based on histology, with distinctions made between tumors with epithelioid, spindle or mixed morphologies. More recently, GISTs have been characterized based on genomic alterations. Approximately 60–70% of GISTs are caused by gain-of-function somatic mutations in *KIT*, while another 15-20% are caused by somatic genomic alterations in *PDGFRA, RAS, BRAF, NF1, ETV6-NTRK3*, and *FGFR1*.[1,3-9] **Additionally, 5-7.5% of GISTs (i.e., 150-225 new cases per year in the U.S.) occur due to inherited germline mutations in the succinate dehydrogenase (*SDH*) A, B, C, and D genes** (i.e., Carney-Stratakis Syndrome or CSS; aka Familial Paraganglioma and GIST Syndrome). These *SDHA/B/C/D* mutations or *SDHC* promoter hypermethylation lead to loss of a functional SDH complex. In turn, these tumors are SDH-deficient and lack protein expression of SDHB.[2] This appears to be an autosomal dominant syndrome with incomplete penetrance and variable manifestations. Affected patients develop paraganglioma (PGL), GIST or the dyad of both.[10-12] Patients may also develop pheochromocytoma (PCC) and/or renal cell carcinoma (RCC). *SDH*-mutant/deficient GIST often occurs in young people (including children, adolescents, and young adults). Frequent lymph node and distant metastases characterize most *SDH*-mutant/deficient GISTs.[13] Moreover, since this syndrome is inherited, multiple generations of family members are affected. These *SDH*-mutant/deficient GISTs differ from GIST with somatic driver mutations not only in terms of genetics, but also in terms of clinical features, patient outcomes, and TKI-responsiveness. Despite these significant distinctions, all FDA-approved anti-GIST therapies use a “one size fits all” approach and have limited efficacy for treating *SDH*-mutant/deficient GIST. Thus, more effective agents are needed for treatment.

Despite the fact that imatinib (which targets mutant KIT and PDGFRA) significantly improves survival in many GIST patients, there remains a subset of patients who do not benefit from this or other FDA-approved anti-KIT TKIs, such as sunitinib or regorafenib. Moreover, drugs like linsitinib and vandetanib, which inhibit pathways reportedly upregulated in *SDH*-mutant/deficient GIST have failed to show benefit in this disease. As such, other traditional chemotherapeutic agents have been studied in patients with GIST. To date, two studies have evaluated the efficacy of temozolomide (TMZ), an oral alkylating agent, in GIST patients without reported genomic data.[14,15] The objective response rates were 0% in both studies of 18 patients each, suggesting that TMZ is ineffective in unselected GIST patients. On the other hand, a French study of 15 patients with PGL and PCC demonstrated that 50% of *SDHB*-mutant patients had partial responses (PR) and 40% had stable disease (SD), whereas in *SDHB* wild-type patients, 60% had SD and 40% had progressive disease (PD).[16] **Thus, *SDH* mutations were a biomarker for TMZ sensitivity in humans.** Moreover, DTIC is frequently used in the clinical care of PGL patients in combination with other chemotherapeutic agents. Given that *SDH*-mutant/deficient GIST, PGL and PCC have common underlying genomic alterations and inheritance patterns, we hypothesize that *SDH*-mutant/deficient GIST share a conserved molecular phenotype and chemosensitivity profile with other *SDH*-mutant/deficient tumors that respond to TMZ. This study is proposed to yield innovative

approaches to targeting TKI-resistant *SDH*-mutant/deficient cancers and thereby may significantly improve patient outcomes.

1.2 Overview of Temozolomide (TMZ)

Temozolomide is a triazene analog of dacarbazine (DTIC) that functions as a cytotoxic alkylating agent. Temozolomide is not directly active but undergoes a rapid non-enzymatic conversion at physiologic pH to the short-lived reactive compound 5-(3-methyltriazen-1-yl)-imidazole-4-carboxamide (MTIC). The cytotoxicity of MTIC is due to methylation of DNA at the O^6 and N^7 positions of guanine, which results in inhibition of DNA replication. Unlike DTIC, which is metabolized to MTIC only in the liver, temozolomide is metabolized to MTIC at all sites. Temozolomide is administered orally.

1.2.1 Pharmacokinetics

- **Absorption:** Rapid and complete
- **Distribution:** Vd: Parent drug: 0.4 L/kg; penetrates blood brain barrier; CSF levels are ~35% to 39% of plasma levels.
- Protein binding: 15%
- Bioavailability: 100%
- **Time to peak, serum:** Empty stomach: 1 hour; with food (high-fat meal): 2.25 hours
- **Metabolism:** Prodrug, hydrolyzed to the active form, MTIC; MTIC is eventually eliminated as CO2 and 5-aminoimidazole-4-carboxamide (AID), a natural constituent of urine
- **Half-life elimination:** Mean: Parent drug: 1.8 hours
- **Excretion**: Urine (~38%; parent drug 6%); feces <1%
- **Clearance**: 1.45 L/hour

1.2.2 Drug Interactions

Valproic acid decreases oral clearance of TMZ.

1.2.3 Clinical Safety

Temozolomide is a generally well tolerated drug. The most commonly reported treatment emerging AEs experienced are: thrombocytopenia, nausea, vomiting, anorexia, and constipation. The most common adverse reactions across the cumulative TMZ experience were alopecia, nausea, vomiting, anorexia, headache, and constipation. Of patients treated with temozolomide, 49% reported one or more severe or life-threatening reactions, most commonly fatigue (13%), convulsions (6%), headache (5%), and thrombocytopenia (5%).

To date, no serious reactions have been reported with TMZ. However, safety will be assessed throughout the study by monitoring and recording adverse events, vital signs, clinical chemistry, and hematology studies. Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, v.5.0).

1.2.4 Clinical Efficacy

To date, very few studies have reported the treatment response rates of *SDH*-mutant/deficient GISTs. The standard of care for all FDA-approved therapies have limited efficacy for treating *SDH*-mutant/deficient GIST (**Table 1-1**). All FDA-approved anti-GIST therapies target the KIT oncoprotein, which is not a driver in *SDH*-mutant/deficient GIST. Therefore, these tumors are generally resistant to imatinib, while sunitinib and regorafenib have limited efficacy (<20% response rates), leading to disease progression and death.[17-21] Moreover, targeting pathways (e.g., VEGFR/EGFR/RET; IGF-1R) upregulated in *SDH*-mutant/deficient GISTs with vandetanib and linsitinib, respectively, have failed to show benefit in clinical trials.

Table 1-1. Clinical studies of TKI efficacy in SDH-mutant/deficient GIST.

Author	Journal	Year	Study	Imatinib	Nilotinib	Regorafenib	Sunitinib	Sorafenib
Boikos	*JAMA Oncology*	2016	Retrospective cohort study	1/49 (2.0%)			4/38 (10.5%)	
Ben Ami	*Annals of Oncology*	2016	GRID Study			2/6 (33.3%)		
Janeway	*Ped Blood Cancer*	2009	Treatment use protocol				1/7 (14.3%)	
Heinrich	*JAMA Oncology*	2017	SWOG Intergroup Trial S0033	1/12 (8.3%)				
Call	*CTOS* (abstract)	2017	Retrospective patient reported cohort study	6/41 (14.6)	1/7 (14.3)	1/9 (11.1%)	10/28 (35.7)	2/5 (40%)
			Combined	7.8%	14.3%	20.0%	20.5%	40.0%

The major impediment to the treatment of *SDH*-mutant/deficient GIST drug development is the lack of applicable models (i.e., cell lines, mouse models, patient-derived xenografts, or in silico models) that can be used to study the effects of anti-cancer compounds on *SDH*-mutant/deficient tumors. However, promising data in recent clinical studies has shown that non-GIST *SDH*-mutant/deficient tumors responds to TMZ.[22] Published data by Hadoux *et al*.[16] suggests that 50% of *SDHB*-mutant PCCs and PGLs respond to TMZ.[15, 16]

Taken together, TMZ may be a promising a single chemotherapeutic agent that merits further investigation for in the *SDH*-mutant/deficient GIST orphan disease population.

1.3 Rationale for the Study

The rationale for further exploration of TMZ chemotherapy is based on preliminary clinical data from UC San Diego. According to prior GIST studies not selected for *SDH*-mutation/deficiency [14,15], patient were dosed at 85 mg/m^2 PO for 21 days followed by 7 days. Five patients received oral TMZ for at least 2 cycles. **According to RECIST/PERCIST measurements, two patients had PRs (40%) and three patients had SD (60%) following progression on prior lines of systemic therapies. Thus, there was a 100% clinical benefit in this cohort.** Overall, these results warrant further investigation of TMZ in a clinical trial setting with a larger cohort of *SDH*-mutant/deficient GIST.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

1. To determine overall response rate by 6 months for TMZ therapy in patients with *SDH*-mutant/deficient GIST.

2.2 Secondary Objectives

1. To determine progression-free survival.
2. To determine overall survival.
3. To determine safety and tolerability of TMZ.

2.3 Exploratory Objectives

1. To determine effect of TMZ therapy on serum succinate/fumarate ratio.
2. To determine effect of TMZ therapy on tumor metabolism.

2.4 Endpoints

2.4.1 Primary Endpoint:

- Overall response (PR + CR) according to RECIST v1.1 at 6 months from onset of TMZ administration.

2.4.2 Secondary Endpoints:

- Progression-free survival.
- Overall survival.
- Adverse events related to TMZ (description, grade [CTCAE v5.0], and seriousness).

2.4.3 Exploratory Endpoints:

- Fold-change of serum succinate/fumarate ratio.
- Change in tumor metabolism profile.

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

Patients must meet all of the inclusion criteria to participate in this study.

1. Patient has the ability to understand and the willingness to sign a written informed consent.

2. Patient is ≥ 12 years of age.

3. Patient has pathologically confirmed GIST with loss of SDHB expression by immunohistochemistry and assessment of *SDHA/B/C/D gene* mutation(s) by next generation sequencing.

4. Patient has recurrent or refractory/unresectable or metastatic disease for which there is no known curative therapy. Patients with recurrent or progressive disease will be eligible. Newly diagnosed patients with resectable localized disease will not be eligible. Newly diagnosed patients with metastatic disease and newly diagnosed patients with residual tumor following surgical debulking will be eligible.

5. Prior Therapy:

- Prior therapy requirements: Because there are no standard therapy regimens known to be effective for SDH-mutant/deficient GIST, previously untreated participants are eligible. Patients previously treated with other therapies for GIST (i.e., imatinib, sunitinib, regorafenib, etc.) also will be eligible.

- Prior therapy wash-out period requirements: Patient has recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy.

  - Myelosuppressive chemotherapy: At least 3 weeks since completion.

  - Biologic (anti-neoplastic agent): At least 7 days since completion of therapy with a biologic agent.

- Radiation (XRT): ≥ 1 week must have elapsed from prior palliative XRT to non-target lesions.

6. Patient has an ECOG Performance Status of 0-2.

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

7. Patient has adequate organ function as defined below:

Test Name	*Laboratory Value*
Absolute Neutrophil Count	≥ 1000/mm3
Platelet count	≥ 50,000/ mm3 (transfusion independent for > 7 days)
Hemoglobin	≥ 8.0 g/dL (may receive transfusions)
Total bilirubin	≤ 2.0 x institution's upper limit of normal (ULN)
AST and ALT	≤ 5 x institutional ULN
Albumin	≥ 2 g/dL
Serum creatinine	≤ 1.5 x institutional ULN
Creatinine clearance	≥ 30 ml/min

8. Female patient of childbearing potential has a negative serum or urine pregnancy within 72 hours prior to receiving the first dose of study medication.

9. Female patient of childbearing potential agrees to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication (Reference Section 4.6.2). Note: Females of childbearing potential are those who have not been surgically sterilized or have not been free from menses for >1 year.

10. Male patient with a partner of childbearing potential agrees to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

11. Has measurable or evaluable disease as per RECIST v1.1 (Appendix B).

12. Life expectancy of > 12 weeks.

3.2 Exclusion Criteria

Patients meeting any of the exclusion criteria at baseline will be excluded from study participation.

1. Patients who have had major surgery within 4 weeks of initiation of study medication.

2. Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3. Evidence of severe or uncontrolled systemic diseases [e.g., unstable or uncompensated respiratory, cardiac (including life threatening arrhythmias)].

4. Unresolved toxicity ≥ CTCAE Grade 2 from previous anti-cancer therapy except alopecia (if applicable) unless agreed that the patient can be entered after discussion with the Medical Monitor.

5. Presence of cardiac impairment defined as:
    a. prior history of cardiovascular disease including heart failure that meets New York Heart Association (NYHA) class III and IV definitions; OR
    b. history of myocardial infarction/active ischemic heart disease within one year of study entry; OR
    c. uncontrolled dysrhythmias; OR
    d. poorly controlled angina.

6. Pregnant or breast-feeding females.

7. Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.

8. Any concurrent condition which in the investigator's opinion makes it undesirable for the subject to participate in this trial or which would jeopardize compliance with the protocol.

9. Patients who cannot swallow oral formulations of the agent(s).

3.3 Subject Withdrawal Criteria

Subjects will be removed from study therapy if any of the following occur:

- Occurrence of any toxicity which in the opinion of the investigator precludes ongoing protocol participation and/or the need for more than two dose reductions.
- Progression of the primary disease.
- Urgent need for alternative therapy (including but not limited to disease progression) incompatible with continuation of treatment.
- Any medical condition that in the opinion of the investigator precludes the safe continuation of the study.
- Patient request.
- Failure to adhere to significant protocol requirements as determined by the treating physician (non-compliance).

Patients who discontinue treatment will receive no further treatment with TMZ. Thereafter, they will be monitored for efficacy, safety and scored for toxicity and followed for the planned course of observation.

Patients who receive at least one dose of TMZ will be monitored for safety for the duration of the study and will be included in all safety and efficacy analyses (intent-to-treat population).

4.0 TREATMENT PLAN

4.1 Study Design

This is an open label, phase 2 study in patients with *SDH*-mutant/deficient GIST treated with TMZ. Twenty-three patients will participate in this study to determine objective response rate by 6 months. Secondary objectives include progression-free survival, overall survival, and adverse events and toxicity. Exploratory objectives include serum succinate/fumarate ratios and characterization of tumor metabolism.

All patients providing informed consent will be screened for eligibility. Adequate tumor biopsy tissue or completed SDHB tumor immunostaining and *SDHA/B/C/D* mutation analysis must be available for participation. Baseline assessments will include vital signs, physical exam, blood hematology and chemistries, ECOG Performance Status evaluation, and tumor imaging. Extra samples of blood will be collected before, during, and after treatment for correlative metabolism studies.

Temozolomide 85 mg/m^2 will be administered orally for 21 days followed by 7 days without treatment in 28 day cycles.

Agent	**Dose**	**Route**	**ReRx**
Temozolomide (TMZ) (TEMODAR®)	85 mg/m^2	PO	Every 28 days

Treatment will continue for 6 months (with option to continue if benefiting treatment) or until disease progression or unacceptable toxicity (whichever occurs first). All patients will have regular evaluations for assessment of safety parameters. Temozolomide dose may be held and/or modified for the management of adverse treatment effects according to

pre-specified criteria. Patients will have radiographic imaging (CT or MRI) every 8 weeks to assess tumor resection.

An end of treatment visit for clinical evaluations and safety assessments will be performed approximately 28 days (± 7 days) after the last dose of study drug. Patients discontinuing study treatment will be followed every 3-6 months for disease recurrence and survival.

4.2 Treatment Dosage and Administration

4.2.1 Preparation and Administration of Temozolomide

Temozolomide will be administered on an outpatient basis, 85 mg/m^2 orally for 21 days and the dosing should be based on actual body weight. Temozolomide capsules should be taken with up to 200 mL of water on an empty stomach one hour before or two hours after food. Capsules should not be opened or chewed but swallowed whole with a glass of water. Temozolomide may be administered on an empty stomach to reduce nausea and vomiting. Bedtime administration may be advised. Do not repeat if vomiting occurs after dose is administered, wait until the next scheduled dose.

4.2.2 Monitoring of Dose Administration

Patients will be monitored during and after the administration with assessment of vital signs at the times specified in the Schedule of Events.

Patients will be monitored for the presence of drug-related reactions.

4.2.3 Criteria for Starting Subsequent Cycles

A cycle may be repeated every 28 days if the patient is without ongoing Grade 3 non-hematologic or Grade 4 hematologic toxicities attributable to TMZ.

4.3 Toxicities and Dosing Delays

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the NCI Common Toxicity Criteria for Adverse Events (NCI-CTCAE), version 5.0.

Adverse events (both non-serious and serious) associated with temozolomide exposure 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 temozolomide dosage calculations based on body surface area (BSA) (see **Table 4-2)**. Temozolomide must be withheld for drug-related toxicities and severe or life-threatening AEs as per **Table 4-1** below. See Section 4.5.1 for supportive care guidelines.

Table 4-1. Guidelines for Drug-Related Adverse Events

Toxicity	TMZ Interruption*	TMZ Discontinuation
Absolute Neutrophil Count	≥ 0.5 and < 1.5 x 10^9/L	< 0.5 x 10^9/L
Platelet Count	≥ 10 and < 100 x 10^9/L	<10 x 10^9/L
CTC Non-hematological Toxicity (except for alopecia, nausea, vomiting)	Grade 2	Grade 3 or 4

AST, ALT, or Increased	Grade 3 or 4	Toxicity does not resolve within 12 weeks of last dose.
Bilirubin	Grade 3 or 4	Permanently discontinue
Hypertension	Grade 2	Grade 3 or 4
Drug reaction	Grade 3 or 4	Permanently discontinue
* Treatment with TMZ could be continued when all of the following conditions are met: Absolute Neutrophil Count ≥1.5 x 10^9/L; platelet count ≥100 x 10^9/L; CTC non-hematological toxicity less than or equal to Grade 1 (except for alopecia, nausea, vomiting). TMZ=Temozolomide; CTC=Common Toxicity Criteria. Patients with intolerable or persistent AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.		

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Patients should be placed back on study therapy within 4 weeks of the scheduled interruption. The reason for interruption should be documented in the patient's study record.

Table 4-2. Daily Temozolomide Dosage Calculations by Body Surface Area (BSA)

Total BSA (m^2)	85 mg/m^2 (mg daily)
1.0	8.5
1.1	93.5
1.2	102
1.3	110.5
1.4	119
1.5	127.5
1.6	136
1.7	144.5
1.8	153
1.9	161.5
2.0	170
2.1	178.5
2.2	187
2.3	195.5
2.4	204
2.5	212.5

4.4 Concomitant Medications/Vaccinations

Concomitant medication also includes all prescription, over-the-counter (OTC), herbal supplements, blood transfusions, and IV medications and fluids. The patient needs to notify the investigational site about any new medications he/she takes after the start of the study drug.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded in the patient's medical record. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs as defined in Section 7.8.

4.4.1 Permitted concomitant therapy

Medications required for treating adverse events and managing cancer symptoms, concurrent stable disease (e.g., controlled hypertension) and supportive care agents such as anti-emetics, erythropoietin, granulocyte growth factors, or blood transfusion, and pain medications are allowed. The patient needs to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug must be recorded in the patient's medical record.

4.4.2 Prohibited concomitant therapy

Patients are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy.
- Immunotherapy not specified in this protocol.
- Chemotherapy not specified in this protocol.
- Investigational agents other than temozolomide.
- Radiation therapy.
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.

Patients who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the treatment portion of the study. Patients may receive other medications that the investigator deems to be medically necessary.

4.5 Rescue Medications and Supportive Care

4.5.1 Supportive Care Guidelines

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator.

Myelosuppression has been found to be the dose-limiting toxicity. Grade 3 thrombocytopenia occurred in 6% of patients and grade 4 in 1%. Grade 3 and grade 4 lymphopenia occurred in 55% of patients. Leukopenia, lymphopenia, thrombocytopenia and anemia usually occur 2-8 weeks after initiation of treatment. Monitor CBC carefully and report any significant changes to MD. Instruct patient to report signs/symptoms of infection, unusual bruising and bleeding to health care team.

Advise patient that a mild-moderate rash may be experienced. Fatigue may be experienced and work with patient in energy conserving lifestyle. Remind patient that drug

needs to be taken on an empty stomach with a full glass of water. Drug should not be crushed, chewed, opened, or dissolved. Nausea and vomiting are common. Teach patient to self-medicate with anti-emetics as directed by their healthcare provider. Assess for effectiveness. If vomiting occurs, do not repeat dose. Wait until next scheduled dose. Constipation can occur. Encourage patient to increase fluid intake. Administer stool softeners or laxatives if ordered and monitor for their effectiveness.

Headache may be seen. Assess for more serious condition (i.e. cerebral bleed, disease progression) first and then treat symptomatically and monitor for effectiveness.

4.6 Other Considerations

4.6.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

4.6.2 Contraception

Temozolomide may have adverse effects on a fetus *in utero*. Furthermore, it is not known if temozolomide has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥ 45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be 2 barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Patients should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study drug.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Patients should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in Section 7.6.2 Pregnancy and Lactation. If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

4.6.3 Use in Pregnancy

If a patient inadvertently becomes pregnant while on treatment with temozolomide, the patient will immediately be removed from the study. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the PI and to the Sponsor without delay and within 24 hours to the PI and within 2 working days to the Sponsor if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the principal investigator. If a male patient impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the principal investigator and to the Sponsor and followed as described above and in Section 7.12.1 and 7.12.2.

4.6.4 Use in Nursing Women

It is unknown whether temozolomide is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

4.7 Patient Withdrawal/Discontinuation from Study Treatment

In the absence of treatment delays due to adverse events, metastatic study treatment may continue until:

- The patient completes 6 months of treatment with temozolomide
  Note: Patients who are benefitting at 6 months may have the option to continue treatment with temozolomide;
- The patient or legal representative withdraws consent;
- The patient exhibits radiographic disease progression, unless the patient is clinically stable or clinically improved or the investigator believes continued study treatment is in the best interest of the patient;
- The patient experiences unacceptable adverse event(s) or those events listed in the dose modification guidelines that require discontinuation;
- The patient exhibits an inter-current illness that prevents further administration of study treatment,
- The patient has a confirmed positive serum pregnancy test;
- The patient is noncompliant with trial treatment or procedure requirements;
- The patient is lost to follow-up;
- The patient dies;
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator;
- Administrative reasons.

4.8 End of Study Treatment and Follow Up

After the last dose of study treatment, each patient will be followed for 28 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.8). Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

Patients who discontinue for reasons other than recurrent disease will have post-treatment follow-up approximately every 3-6 months or disease status until disease recurrence, initiation of a non-study cancer treatment, withdrawal of consent or lost to follow-up.

After documented disease recurrence, each patient will be followed approximately every 3-6 months by review of medical records, telephone, or review of the Social Security Index for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

4.9 Patient Withdrawal/Discontinuation from Study Criteria

Patients may be removed from study participation for the following reasons:

- The patient or legal representative withdraws consent for follow-up;
- The patient is lost to follow-up;
- The patient dies;
- It is the decision of the investigator.

5.0 STUDY PROCEDURES

Refer to the study Schedule of Events for procedures.

All patients will be closely monitored for safety and tolerability during all cycles of therapy, at study treatment completion/early study treatment discontinuation, and during the follow-up period.

5.1 Definitions of Study Assessments

a. Medical history

A medical history and details regarding the disease for which the patient has enrolled in this study will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Any clinically significant changes from Screening (e.g. worsening severity or abnormal findings) are considered to be adverse events (AEs).

b. Demographics

The patient's demographic profile of date of birth, gender, race, and ethnicity will be obtained unless the patient declines.

c. Review of eligibility criteria

Review of eligibility criteria as described in Section 3 to ensure patient qualification for study entry and metastatic study treatment.

d. Concomitant Medication

All concomitant therapy, including anesthetic agents, vitamins, homeopathic/herbal remedies, nutritional supplements, received by patients from five days prior to the first day of study treatment until 28 days after the last study dose (or until the start of a new treatment, whichever comes first) will be recorded in the patient's medical record. If a reportable adverse event deemed related to study intervention (see Section 7) occurs within 28 days after last study dose and the patient has not started a new treatment, recording of concomitant medications related to the treatment of that adverse event should continue until resolution of the adverse event.

e. Physical exam

The investigator or qualified designee will perform a complete physical examination during screening, which should include the evaluation of general appearance; evaluation of head, eyes, ears, nose, and throat (HEENT); and cardiovascular, pulmonary, abdominal, musculoskeletal, skin, lymph nodes, neurological, and genitourinary systems. Subsequent exams may be directed as appropriate.

Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as adverse events if clinically significant.

f. Vital Signs and height

Vital signs should include temperature, pulse, blood pressure and weight. Height will only be collected at screening.

g. Performance status

Performance status is evaluated by the Eastern Cooperative Oncology Group (ECOG) scale.

h. Adverse event assessment

Baseline assessment of subject status for determining adverse events. See Section 7 for Adverse Event monitoring and reporting.

i. Laboratory Assessments

Laboratory tests for hematology, chemistry, and others are specified in Table 5-1.

Table 5-1. Laboratory tests

Hematology	• Complete Blood Count (CBC) with differential
	  ○ hemoglobin,
	  ○ hematocrit,
	  ○ platelet count,
	  ○ white blood cell count,
	  ○ percentage or absolute differential count

Chemistry	• Comprehensive metabolic panel (CMP)
	  ○ albumin
	  ○ alkaline phosphatase
	  ○ aspartate aminotransferase (ALT)
	  ○ alanine aminotransferase (AST)
	  ○ bicarbonate (CO_2)
	  ○ blood urea nitrogen (BUN)
	  ○ calcium
	  ○ chloride
	  ○ creatinine
	  ○ glucose
	  ○ potassium
	  ○ sodium
	  ○ total protein
	  ○ total bilirubin
	• Thyroid stimulating hormone (TSH)

Pregnancy Test	• Urine human chorionic gonadotropin (HCG) or serum βHCG

j. Blood collection for correlative studies

See Section 5.5 for details.

k. Tumor assessment
Radiologic assessment is performed by MRI or CT of chest, pelvis and abdomen. The same radiographic technique should be used throughout the study. However, a patient who develops a contraindication to undergo an MRI scan during study treatment may remain on study and undergo contrast enhanced CT scans.

l. Tumor biopsy and tissue collection
See Section 5.5 for details.

5.2 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 30 days prior to registration unless otherwise stated. The screening procedures include:

- Written informed consent *(within 30 days)*.
- Review of inclusion and exclusion criteria.
- Complete medical/oncology history.
- Demographics.
- Documentation of concomitant medications.
- Complete physical examination, including vital signs and height.
- Performance status assessment.
- Laboratory tests *(within 10 days)*
- Blood collection for correlative studies.
- Documentation of tumor staging with baseline CT or MRI of chest/abdomen/pelvis

5.3 Procedures during Treatment

5.3.1 Day 1 *(D1)*

- Documentation of concomitant medications
- Adverse events.
- Temozolomide administration.
- Pregnancy test

5.3.2 Day15 *(D15 ±3)*

- Documentation of concomitant medications
- Adverse events.
- Physical Exam, ECOG Performance, Coagulation (PT,PTT), CBC and CMP
- Blood collection for correlative studies.

5.3.3 Day29 *(D22 ±3)*

- Documentation of concomitant medications
- Adverse events.
- Vital Signs, Physical Exam, ECOG Performance, Coagulation (PT,PTT), CBC and CMP
- Blood collection for correlative studies.
- Temozolomide administration.

- Pill Diary

5.3.4 Imaging *(8 weeks)*

- Radiographic imaging with CT or MRI of chest/abdomen/pelvis to measure lesions selected for response assessment.
- Tumor imaging assessment when clinically indicated every 2 months following Cycle 1 Day 1.

5.3.5 End of Treatment Visit *(28 days after last dose, ± 7 days)*

- Documentation of concomitant medications
- Adverse events.
- Physical exam, vital signs.
- ECOG assessment.
- CBC, CMP, Coagulation (PT,PTT)
- Blood collection for correlative studies.
- Pill Diary

5.4 Follow-up Procedures (±7 days)

Patients discontinuing study treatment will be followed every 3-6 months after the last dose of study treatment until death with:

- Tumor assessments if they discontinued from study treatment without disease recurrence- until disease recurrence or initiation of a new anti-cancer therapy, and
- Survival contacts via medical record review, telephone call, or review of the Social Security Index.

5.5 Correlative Studies

The goal of the planned laboratory correlative studies is to further characterize the biology of SDH-mutant/deficient GIST, to gain a better understanding of the impact of TMZ on the tumor's metabolism, and explore potential biomarkers (e.g., serum succinate/fumarate ratio), which may correlate with response.

5.5.1 Sample Collection Guidelines

Specimens should be collected as outlined below and ALL samples should be labeled with the following:

- Protocol number
- Institution
- Patient's de-identified study number

5.5.1.1 Tumor tissue from prior biopsy or surgical resection

Tumor tissue for research will be collected from only material in excess of that needed for routine clinical care as determined by a staff pathologist.

Depending on the amount of tissue available, tissue should be collected for research in the following order of preference:

1. Ten (10) unstained sections (4-5 micron slices) and one (1) 20 micron roll-ups from FFPE tissue.
2. 10 unstained sections from fresh frozen tissue.

Fresh frozen samples should be stored in liquid nitrogen and FFPE samples at room temperature until shipment.

5.5.1.2 Tumor tissue from subsequent clinical care *(optional)*

Additional tissue obtained as part of clinical care following relapse on TMZ but prior to additional cancer-directed therapy will be collected when possible similar to previously described tumor tissue as appropriate.

5.5.1.3 Miscellaneous blood sample collection

Blood samples will be collected in one EDTA [lavender] top tube (approximately 10 ml each) and one serum separating [gold] top tube (approximately 10 ml each)

- Prior to study treatment at screening (may be collected at the same time as blood drawn for routine laboratory tests).

- End of every 28 days cycle.
- At the end of treatment or at the time of disease progression.

The blood sample tubes should be inverted approximately 8-10 times to mix the EDTA. Samples will be flash frozen and stored at -80°C at the UC San Diego Biorepository until correlative studies are performed.

Specimens must be labelled with the protocol number, patient ID, patient initials, sample type (whole blood) and collection date & time.

5.5.2 Specimen Banking

Patient samples collected for this study will be retained in the UCSD Moores Cancer Center Biorepository for analysis and future cancer research.

Attn: Sharmeela Kaushal
Moores Cancer Center, 3345/3G, GG
3855 Health Sciences Drive
La Jolla, CA 92093-0819
Phone: 858-822-7661

Specimens will be stored indefinitely or until they are used up. Samples will be labeled with the protocol number, subject's de-identified study number and collection date. The link between study number and medical record number will be viewed over a password secured encrypted server-client.

The study research coordinator at each local site will review their subject's medical record for demographic and clinical information pertaining to the subject's general medical history, diagnosis, and outcomes of any treatments received. This information will be transmitted to and retained by the Coordinating Site UCSD. Samples and data extracted from the subject's medical record will be coded with a de-identified study number so that the subject's name and identifying information will be removed. A log that links the subject's name and identifiers to the study number will be maintained in a secure database distinct from the secure database into which the subject's clinical information will be entered by study personnel.

Dissemination of specimens for research is at the discretion of the Dr Burgoyne. Potential

research collaborators outside of UCSD who approach the Moores Cancer Center for clinical specimens will be required to complete an agreement (Material Transfer Agreement or recharge agreement) stating that the specimens will only be released for use in disclosed research, and any specimen left over from research will either be returned to the Cancer Center or destroyed. Any data obtained from the use of clinical specimen will be the property of UCSD for publication and any licensing agreement will be strictly adhered to. These outside collaborators may include for-profit biotechnology corporations interested in collaborating with UCSD investigators in research diagnostic, prognostic assays and drug development.

The specimens, DNA, and their derivatives may have significant therapeutic or commercial value. The Informed Consent form contains this information and informs the subject that there is the potential for financial gain by UCSD, the investigator or a collaborating researcher or entity.

If patients later decide they do not want their specimens collected to be used for future research, they may tell this to the local site principal investigator, who will inform the Dr Burgoyne. Dr. Burgoyne will use his best efforts to stop any additional studies and to destroy the specimens. Samples stored in the Biorepository will be destroyed; for samples that have been disseminated outside of the Biorepository, Dr. Burgoyne will contact the recipient to notify them of the need to halt further research and destroy specimens.

6.0 SOLID TUMOR STUDY ASSESSMENTS

6.1 Efficacy Assessments

Tumor response will be determined for all subjects with measurable lesions using RECIST version 1.1 guidelines [23] (*see Appendix A*).

The assessments will be made at baseline, at the end of cycle 2, then every other cycle, or more frequently if indicated.

7.0 ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the investigational agent, is also an AE.

Progression of the cancer under study or events which are unequivocally due to disease progression should not be reported as an AE during the study (unless it is considered to be drug related by the investigator).

7.1 Expected Adverse Events

The following adverse events may be present/absent and the severity graded, at baseline and for each cycle of treatment.

CTCAE v5.0 Term	CTCAE v5.0 System Organ Class (SOC)
Nausea	Gastrointestinal
Fatigue	General Disorders
Constipation	Gastrointestinal
Platelet Count decrease	Investigations
Anorexia	Metabolism and Nutrition Disorders
Neutrophil count decreased	Investigations
Diarrhea	Gastrointestinal

7.2 Common known potential toxicities, > 10%:

- **Cardiovascular:** Peripheral edema (11%)
- **Central nervous system:** Fatigue (34% to 61%), headache (23% to 41%), seizure (6% to 23%), hemiparesis (18%), fever (13%), dizziness (5% to 12%), coordination abnormality (11%)
- **Dermatologic:** Alopecia (55%), rash (8% to 13%)
- **Gastrointestinal:** Nausea (49% to 53%; grades 3/4: 1% to 10%), vomiting (29% to 42%; grades 3/4: 2% to 6%), constipation (22% to 33%), anorexia (9% to 27%), diarrhea (10% to 16%)
- **Hematologic:** Lymphopenia (grades 3/4: 55%), thrombocytopenia (grades 3/4: adults: 4% to 19%), neutropenia (grades 3/4: adults: 8% to 14%), leukopenia (grades 3/4: 11%)
- **Miscellaneous:** Viral infection (11%)

7.3 Less common known potential toxicities, 1% - 10%:

- **Central nervous system:** Amnesia (10%), insomnia (4% to 10%), somnolence (9%), ataxia (8%), paresis (8%), anxiety (7%), memory impairment (7%), depression (6%), confusion (5%)
- **Dermatologic:** Pruritus (5% to 8%), dry skin (5%), radiation injury (2% maintenance phase after radiotherapy), erythema (1%)
- **Endocrine & metabolic:** Hypercorticism (8%), breast pain (females 6%)
- **Gastrointestinal:** Stomatitis (9%), abdominal pain (5% to 9%), dysphagia (7%), taste perversion (5%), weight gain (5%)
- **Genitourinary:** Incontinence 98%), urinary tract infection (8%), urinary frequency (6%)
- **Hematologic:** Anemia (grades 3/4: 4%)
- **Neuromuscular & skeletal:** Paresthesia (9%), back pain (8%), abnormal gait (6%), arthralgia (6%), myalgia (5%)
- **Ocular:** Blurred vision (5% to 8%), diplopia (5%), vision abnormality (visual deficit/vision changes 5%)
- **Respiratory:** Pharyngitis (8%), upper respiratory tract infection (8%), cough (5% to 8%), sinusitis (6%), dyspnea (5%)
- **Miscellaneous:** Allergic reaction (up to 3%)

7.4 Rare toxicities <1%:

Alkaline phosphatase increased, alveolitis, anaphylaxis, aplastic anemia, emotional lability, erythema multiforme, febrile neutropenia, flu-like syndrome, hallucination, hematoma, hemorrhage, herpes simplex, herpes zoster, hyperglycemia, hypokalemia, interstitial pneumonia/pneumonitis, myelodysplastic syndrome, opportunistic infection (e.g., PCP), oral candidiasis, pancytopenia, peripheral neuropathy, petechiae, pneumonitis, pulmonary fibrosis, secondary malignancies (including myeloid leukemia), Stevens-Johnson syndrome, toxic epidermal necrolysis and liver damage which may cause yellowing of eyes and skin, swelling and may result in liver failure.

7.5 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care.

As far as possible, each adverse event should be evaluated to determine:

- duration (start and end dates)
- severity (grade)
- seriousness
- relationship to study agent
- action taken (i.e., none, study agent modification, medical intervention)
- outcome (i.e., resolved without sequelae, resolved with sequelae, ongoing)

All adverse events (AE) must be recorded in the adverse event record of the subject's case report form (CRF). The information recorded should be based on the signs or symptoms detected during the physical examination and clinical evaluation of the subject.

All patients experiencing an adverse event at least possibly related to study treatment will be monitored until:

1. the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
2. any clinically significant abnormal laboratory values have returned to baseline;
3. there is a satisfactory explanation other than the study drug for the changes observed; or
4. death.

7.6 Severity

All adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The CTCAE v5.0 is available at http://ctep.cancer.gov/reporting/ctc.html

If no CTCAE grading is available, the severity of an AE is graded as follows:

Mild (grade 1): the event causes discomfort without disruption of normal daily activities; intervention not indicated.

Moderate (grade 2): the event causes discomfort that affects normal daily activities; minimal, local or noninvasive intervention indicated.

Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status; intervention indicated.

Life-threatening (grade 4): the patient was at risk of death at the time of the event; urgent intervention indicated.

Fatal (grade 5): the event caused death.

7.7 Seriousness

A "serious" adverse event is defined in regulatory terminology as any untoward medical occurrence that:

1. **Results in death.**
   If death results from (recurrence of) the disease, the disease should be reported as event (SAE) itself.
2. **Is life-threatening.**
   (the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).
3. **Requires in-patient hospitalization or prolongation of existing hospitalization**. Note: Hospitalization (including hospitalization for an elective procedure) for a preexisting condition which has not worsened does not constitute a serious adverse event.
4. **Results in persistent or significant disability or incapacity**. Substantial disruption of one's ability to conduct normal life functions.
5. **Is a congenital anomaly/birth defect.**
6. **Is an important medical event.**
   Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".
   For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization;

development of drug abuse or drug dependency.

7.8 Relationship

Attribution categories for adverse events in relationship to protocol therapy are as follows:

Definite – The AE *is clearly related* to the study treatment.
Probable – The AE *is likely related* to the study treatment.
Possible – The AE *may be related* to the study treatment.
Unlikely – The AE *is doubtfully related* to the study treatment.
Unrelated – The AE *is clearly NOT related* to the study treatment.

The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the AE based upon the available information.

The following components are to be used to assess the relationship between temozolomide and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely temozolomide caused the AE:

Exposure: Is there evidence that the subject was actually exposed to the product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

Time course: Did the AE follow in a reasonable temporal sequence from administration of TMZ? Is the time of onset of the AE compatible with a drug-induced effect?

Likely cause: Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors?

Dechallenge: Was temozolomide discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge.
Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; or (2) the AE resolved/improved despite continuation of temozolomide.

Rechallenge: Was the subject re-exposed to temozolomide in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge.
Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability.

7.9 Prior experience

Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is <u>not</u> listed in the current known adverse events listed in the agent clinical experience section of this protocol or the current Investigator's Brochure.

7.10 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report

forms/worksheets and reported within 24 hours to the PI and within 2 working days to the Sponsor . Events of clinical interest for this trial include:

7.10.1 Overdose of Temozolomide

For purposes of this trial, an overdose of TMZ will be defined as any dose of 2,000 mg per day for 5 days. No specific information is available on the treatment of overdose of temozolomide. In the event of overdose, the patient should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an AE is associated with ("results from") the overdose of TMZ, the AE is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of temozolomide meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

7.10.2 Pregnancy and Lactation

Although pregnancy and lactation are not considered AEs, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a patient (spontaneously reported to them), including the pregnancy of a male patient's female partner that occurs during the trial or within 120 days of completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All patients and female partners of male patients who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

7.10.3 Elevated Lab Values

The purpose of the following elevated lab value criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology:

- AST or ALT ≥ 10X the institutional ULN
- Total bilirubin ≥ 5X the institutional ULN
- Alkaline phosphatase ≥ 5X the institutional ULN

7.11 Expedited Reporting Requirements for Adverse events

Serious adverse events, or a follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study requires expedited reporting as described below.

7.11.1 Expedited Reporting to Site Principal Investigator

The Study Chair and Site Principal Investigator must be notified within 24 hours of learning of any serious adverse events (SAEs).

7.11.2 Expedited Reporting to Regulatory Authorities

A. The **Institutional Review Board (IRB) of each site** must be notified by the site principal investigator according to their local policies.

B. The **UCSD Human Research Protections Program (HRPP)** and **Moores Cancer Center Data and Safety Monitoring Board (DSMB)** must be notified within 10 business days of "any unanticipated problems involving risk to subjects or others" (UPR).

The following events meet the definition of UPR:

1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.
5. Any breach in confidentiality that may involve risk to the subject or others.
6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

C. The **FDA** must be notified by the PI according to the following timelines:

- within 7 calendar days of any unexpected fatal or life-threatening adverse event with possible relationship to study drug, and
- within 15 calendar days of any event that is considered: 1) serious, 2) unexpected, and 3) at least possibly related to study participation.

7.12 Routine Reporting Requirements for Adverse events

A. The **IRB of each site** must be notified by the site principal investigator according to their local policies.

B. The **UCSD HRPP** must be notified of any adverse events that are not unanticipated problems involving risk to subjects or others (non-UPRs) at the time of the annual Continuing Review.

C. The **FDA** must be notified by the PI of all non-serious adverse events annually at the time of the annual report.

8.0 AGENT INFORMATION

8.1 TEMOZOLOMIDE

Please refer to the Product Label and Investigator's Brochure for more comprehensive information.

Other Names: TEMODAR®

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.

Availability: Clinical supplies are provided by a commercial supplier and will be affixed

with a clinical label in accordance with regulatory requirements.

Dosage Forms and Strengths:
Temozolomide 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 temozolomide Capsules are as follows: temozolomide 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). Temozolomide 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).

Preparation:
Temozolomide will be prepared according to the product label unless otherwise directed in the Pharmacy Manual.

Storage and stability:
- Store Temozolomide Capsules at room temperature 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Route of administration for this study: Oral.

Side effects:
Adverse Reactions Based on Clinical Data
Common known potential toxicities, > 10%:
Cardiovascular: Peripheral edema (11%)
Central nervous system: Fatigue (34% to 61%), headache (23% to 41%), seizure (6% to 23%), hemiparesis (18%), fever (13%), dizziness (5% to 12%), coordination abnormality (11%)
Dermatologic: Alopecia (55%), rash (8% to 13%)
Gastrointestinal: Nausea (49% to 53%; grades 3/4: 1% to 10%), vomiting (29% to 42%; grades 3/4: 2% to 6%), constipation (22% to 33%), anorexia (9% to 27%), diarrhea (10% to 16%)
Hematologic: Lymphopenia (grades 3/4: 55%), thrombocytopenia (grades 3/4: adults: 4% to 19%), neutropenia (grades 3/4: adults: 8% to 14%), leukopenia (grades 3/4: 11%)
Miscellaneous: Viral infection (11%)

Less common known potential toxicities, 1% - 10%:
Central nervous system: Amnesia (10%), insomnia (4% to 10%), somnolence (9%), ataxia (8%), paresis (8%), anxiety (7%), memory impairment (7%), depression (6%), confusion (5%)
Dermatologic: Pruritus (5% to 8%), dry skin (5%), radiation injury (2% maintenance phase after radiotherapy), erythema (1%)
Endocrine & metabolic: Hypercorticism (8%), breast pain (females 6%)
Gastrointestinal: Stomatitis (9%), abdominal pain (5% to 9%), dysphagia (7%), taste perversion (5%), weight gain (5%)
Genitourinary: Incontinence 98%), urinary tract infection (8%), urinary frequency (6%)
Hematologic: Anemia (grades 3/4: 4%)
Neuromuscular & skeletal: Paresthesia (9%), back pain (8%), abnormal gait (6%), arthralgia (6%), myalgia (5%)
Ocular: Blurred vision (5% to 8%), diplopia (5%), vision abnormality (visual deficit/vision

changes 5%)
Respiratory: Pharyngitis (8%), upper respiratory tract infection (8%), cough (5% to 8%), sinusitis (6%), dyspnea (5%)
Miscellaneous: Allergic reaction (up to 3%)

Rare toxicities <1%:
Alkaline phosphatase increased, alveolitis, anaphylaxis, aplastic anemia, emotional lability, erythema multiforme, febrile neutropenia, flu-like syndrome, hallucination, hematoma, hemorrhage, herpes simplex, herpes zoster, hyperglycemia, hypokalemia, interstitial pneumonia/pneumonitis, myelodysplastic syndrome, opportunistic infection (e.g., PCP), oral candidiasis, pancytopenia, peripheral neuropathy, petechiae, pneumonitis, pulmonary fibrosis, secondary malignancies (including myeloid leukemia), Stevens-Johnson syndrome, toxic epidermal necrolysis and liver damage which may cause yellowing of eyes and skin, swelling and may result in liver failure.

8.1.1 Study Drug Accountability and Disposition
The site Principal Investigators are responsible for ensuring accountability for the investigational agent, including reconciliation of materials and maintenance of drug records.

Dispensing and administration of Temozolomide will be recorded following institutional practices. An accurate accounting will be available for verification. Accountability records will include:
- Confirmation of delivery to the site
- Inventory at the site
- Dispensing for each patient
- Return or alternative disposition of unused study drug

Upon completion or termination of the study, all unused and/or partially used Temozolomide will be destroyed at each site per institutional policy. It is the Principal Investigators' responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

9.0 STATISTICAL CONSIDERATIONS
9.1 Sample Size and Power

The primary endpoint is the ORR as defined by the investigator according to RECIST v1.1 at 6 months from TMZ administration.

Available published data (excluding self-reported patient data, **Table 1-1**) for *SDH*-mutant/deficient GIST indicate an objective response rate of ~10%. To be conservative, we will assume a null response rate to standard-of-care of 15%. We anticipate that an ORR of 35% or greater from TMZ would be of clinical importance. Given the lack of good treatment options for this **orphan disease**, and the small number of available patients, we will use a statistical test with 10% alpha for this proof-of-concept study. A two stage Simon optimal design will be used, at 80% power and 10% type I error. In this case, the total

needed sample size is 23 subjects, and there will be an interim analysis after the first 9 subjects attain the primary endpoint.

9.1.1 Accrual

Over the past 2+ years, UC San Diego has seen 11 *SDH*-mutant/deficient GIST patients. This is an orphan disease so the number of patients will be low. Given these numbers, it would be feasible to enroll at least 1 patient per 2-3 months on study. Therefore, we anticipate this study would require 4 years for accrual of 23 subjects. **To boost enrollment, the three patient advocate groups, namely the GIST Life Raft Group, GIST Support International, and the SDH-Deficient GIST Research Advocates have all agreed to support recruitment and enrollment of patients from across the U.S.**

9.2 Analysis Populations

The Safety population will consist of all randomized patients who have received at least one dose of temozolomide.

The modified Intention-to-Treat (mITT) population will consist of all randomized patients who receive at least one dose of temozolomide (same as the Safety population).

The Intention-to-Treat (mITT) population will consist of all randomized patients.

The Disease-Free Survival Efficacy-Evaluable (DFSEE) population will consist of patients with confirmed gross disease resection. As enrollment of subjects occurs prior to salvage surgery, we cannot predict with absolute certainty that every subject will have a confirmed gross disease resection. Careful patient selection, however, will minimize the number of patients with gross disease to less than 10% of patients accrued.

If the endpoints for a subject cannot be assessed (for example, a subject is lost to follow-up prior to the 6-month assessment), it will be considered to be an event that does not favor the study therapy (e.g., disease recurrence for the primary outcome).

The primary population for all efficacy analyses is the mITT population, without imputation for missing values. The safety population will be used for analyses of safety endpoints.

9.3 Analysis of the primary endpoint

The primary endpoint is partial response as defined by the investigator according to RECIST v1.1 at 6 months from the end of TMZ treatment.

The primary hypothesis is that the ORR to Temozolomide will be at least 35%, tested using a one-sided test at 10% significance level, using a Simon optimal two-stage procedure, against the null hypothesis of a 15% response rate to standard-of-care. There will be an interim analysis after the first 9 subjects have reached the primary endpoint (see below). At the final analysis, 23 subjects will have reached the primary endpoint. The null hypothesis will be rejected if 6 or more subjects attain a OR at 6 months, and we will conclude the response rate to Temozolomide is greater than 15%.

The final efficacy analysis will calculate the UMVUE[24] estimate, p-value and 95% CI[25] for the response rates. The calculation will be performed using R *clinfun* package (www.r-project.org).

9.4 Secondary Efficacy Analyses

Secondary efficacy endpoints are progression free survival and overall survival. All primary and seconday efficacy endpoints will be presented for the DFSEE, ITT and mITT populations. We will also describe the PFS experience of patients with gross residual disease. We will estimate median survival times together with their 95% confidence intervals, and report number of events, as well as Kaplan Meier plots with 95% confidence bands.

9.5 Secondary Safety Analyses

Analyses will be performed for all patients having received at least one dose of study treatment. The proportion of subjects experiencing adverse events, serious adverse events, and treatment delays will be summarized. Tolerability will be assessed based on dosage delays and discontinuation due to adverse events.

All AEs will be listed, documenting the course, outcome, severity, and relationship to the study treatment. Incidence rates of AEs and the proportion of subjects prematurely withdrawn from the study due to AEs will be shown**.**

9.6 Interim analysis

An interim analysis for futility will be performed when the first 9 subjects have reached the primary endpoint. If 1 subjects or fewer have an OR (11% ORR), then the study will stop for futility. Otherwise the study will continue. This stopping rule has 60% chance to stop the study early if the true ORR is 15% or less.

The interim analysis will be documented in a formal study report by the Biostatistics team, in consultation with the study investigators.

Accrual will not be suspended pending the interim analysis because there are no effective standar of care therapies for this patient population. In addition, the toxicity profile of the study drug is well established with a low incidence of grade 3-4 adverse events. Accrual is expected to be slow. Thus, safety and tolerability are not expected to be a concern and patients on this trial are not forgoing other therapeutic options; we anticipate at most a few additional patients on study pending the interim analysis outcome.

10.0 STUDY MANAGEMENT

10.1 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed according to local institutional policies and the UCSD conflict of interest policy.

10.2 Institutional Review Board (IRB) Approval and Consent

The IRB of each study site should approve the consent form and protocol prior to any study-related activities. It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

10.3 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the UCSD Moores Cancer Center

- A copy of the official IRB approval letter for the protocol and informed consent.
- A copy of the IRB-approved consent form.
- CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation.
- CAP and CLIA Laboratory certification numbers and institution lab normal values.
- Executed clinical research contract.

10.4 Patient Registration

All patients must be registered with the UCSD Moores Cancer Center Clinical Trials Office before enrollment to the study. Prior to registration, eligibility criteria must be confirmed with the UCSD Study Coordinator. To register a patient, call (858) 822-6100 Monday through Friday, 8:00am-4:30pm Pacific Time. Study sites other than UCSD must fax informed consent documentation, completed eligibility checklist, and all source documentation for eligibility confirmation to the UCSD Clinical Trials Office (Fax: 858-822-5380).

Patients will be given a unique sequential study number at the time of enrollment. UCSD will fax the outside study site for confirmation of patient registration, the patient's study number, and ability to start study treatment.

10.5 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), subjects who have provided written informed consent must also sign a subject authorization to release medical information to the study Sponsor and allow a regulatory authority, or Institutional Review Board access to subject's medical information relevant to the study.

10.6 Data and Safety Monitoring/Auditing

In addition to adverse event monitoring and clinical oversight by the PI, site principal investigator and co-investigators, quality assurance of the study will be performed by the UCSD Moores Cancer Center Clinical Trials Office internal monitor. Monitoring intervals will be dependent upon the number of patients enrolled and the complexity of the study.

This study will also use the UCSD Moores Cancer Center Data Safety and Monitoring Board (DSMB) to provide oversight in the event that this treatment approach leads to unforeseen toxicities. Data from this study will be reported annually and will include:

1. the protocol title, IRB protocol number, and the activation date of the study.
2. the number of patients enrolled to date.
3. the date and site of patients' enrollment.
4. a summary of all adverse events regardless of grade and attribution.
5. a response evaluation for evaluable patients when available.
6. a summary of any recent literature that may affect the ethics of the study.

10.7 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, investigators are required to conduct their research according to the plans reviewed and approved by the IRB.

10.7.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate apparent immediate hazards/risks to trial subjects without prior IRB approval. Any such emergency modification implemented must be noted and reported to the IRB along the lines of a protocol deviation or violation, depending on the nature of the modification.

10.7.2 Protocol Violations

Any unplanned variance from an IRB approved protocol is considered a violation and must be reported to the IRB in a timely fashion. For the UCSD IRB:

A. Major violations must be reported to the IRB within 10 working days of awareness of the violation.
Major violations include:
- Instances that have harmed or increased the risk of harm to one or more research participants.
- Instances that have damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

B. Minor violations may be reported to the IRB at the time of the continuing review.
Minor violations have no substantive effect on the risks to participants or on the scientific integrity of the research plan or the value of the data collected.

10.8 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the PI. It should also be noted that when an amendment to the protocol

substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRBs at each site and submitted to the FDA by the PI for approval prior to implementation.

10.9 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

10.10 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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Appendix A. Response Evaluation Criteria in GIST Tumors (RECIST)

A1 MEASURABILITY OF TUMOR AT BASELINE

A1.1 Definitions

At baseline, tumor lesions will be categorized as follows:

A1.1.1 Measurable

Tumor lesions: must be accurately measured in at least one dimension (longest diameter in the plane of measurements is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measureable).
- 20 mm by chest X-ray.

Malignant lymph nodes: to be considered pathologically enlarged and measurable, a lymph node must be >= 15 mm in short axis when assessed by CT scan. At baseline and in follow-up, only the short axis will be measured and followed.

A1.1.2 Non-measurable

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with >= 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

A1.1.3 Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- ‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

A1.2 Specifications by methods of measurements

A1.2.1 Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

A1.2.2 Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and P10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

A2 TUMOR RESPONSE EVALUATION

A2.1 Baseline documentation of 'target' and 'non-target' lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of P15mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by GISTtumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis.

For example, an abdominal node which is reported as being 20mm· 30mm has a short axis of 20mm and qualifies as a malignant, measurable node. In this example, 20mm should be recorded as the node measurement. All other pathological nodes (those with short axis P10mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added

into the sum. The baseline sum diameters will be used as reference to further characterize any objective
tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

A2.2 Response criteria
This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

A2.2.1 Evaluation of target lesions
Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

A2.2.2 Special notes on the assessment of target lesions
Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion

has likely disappeared, the measurement should be recorded as 0mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned in this circumstance as well). This default value is derived from the 5mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible; therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5mm.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

A2.2.3 Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

A2.2.4 Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall

progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden.
Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e.an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

A2.2.5 New lesions
The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow- up:
If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

A2.3 Evaluation of best overall response
The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'. This is described further below.

A2.3.1 Time point response
It is assumed that at each protocol specified time point, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.
When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Table 1. Time point response: patients with target (+/- non-target) disease.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Inevaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Table 2. Time point response: patients with non-target disease only.

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	Inevaluable

Unequivocal PD	Yes or No	PD
Any	Yes	PD

A2.3.2 Missing assessments and inevaluable designation
When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

A2.3.3 Best overall response: all time points
The best overall response is determined once all the data for the patient is known.

Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 3.

Table 3. Best overall response when confirmation of CR and PR required.

Overall response First time point	**Overall response Subsequent time point**	**BEST overall response**
CR	CR	CR
CR	PR	SD, PD OR PR
CR	SD	SD provided minimum criteria for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	Inevaluable	SD provided minimum criteria for SD duration met, otherwise inevaluable
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD

PR	Inevaluable	SD provided minimum criteria for SD duration met, otherwise inevaluable
Inevaluable	Inevaluable	Inevaluable

A2.3.4 Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1–3.

Conditions that define 'early progression, early death and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

A2.4 Confirmatory measurement/duration of response

A2.4.1 Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error.

This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, i.e. in randomized trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

A2.4.2 Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

A2.4.3 Duration of stable disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

APPENDIX B DOSING DIARY

PATIENT MEDICATION DIARY - TEMOZOLOMIDE (to be completed by physician's office)	
Subject Number: _____ Cycle: ____ **Your Assigned Dose is 85 mg/m^2 daily by mouth.**	Cycle Start Date: ____ / _____ / _____ # of Capsules Dispensed: _____ DD MMM YYYY Cycle End Date: ____ / _____ / _____ # of Capsules Returned: _____ DD MMM YYYY

DOSING INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each week-period while you take temozolomide.
2. You will take your dose of temozolomide for 21 days and 7 days off.
3. If you have any comments or notice any side effects, please record them in the Comments column. If you make a mistake while you write, please cross it out with one line, put your initials next to it, and then write the corrected information next to your initials.
4. Please return this form to your physician when you go for your next appointment.
5. Take the study medication (temozolomide) once daily in the morning around the same time.
6. Swallow capsule(s) whole and do not chew or open.
7. Take the capsule(s) with a glass of water (approximately 8 ounces).
8. Avoid eating food for at least 1 hour after taking the study medication.
9. If you forget to take your dose in the morning, you make take it within six hours of the missed dose; otherwise you should skip that day's dose and continue the next day on schedule.
10. If vomiting occurs, do not try make up the dose. Take the next scheduled dose the following day.

DRUG STORAGE:

Please keep the study medication in the refrigerator.

STUDY VISITS:

1. Bring all of your study medication and this completed diary with you to the clinic at each visit.
2. You must return all study medication containers (including empty bottles) along with any unused medication at each visit.

DIARY INSTRUCTIONS:

1. Note the date and time of day you took the study dose.
2. In the comment section, please include any time you vomit or any time you are unable to complete the dosing instructions and why.

3. If you have any questions, please contact the study staff listed in your informed consent form.

STUDY DAY	DATE (DD-MON-YYYY)	TIME OF MORNING DOSE	NUMBER OF CAPSULES TAKEN	COMMENTS
Ex.	*17 March 2017*	*9:00 AM*	*1*	
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				

18				
19				
20				
21				
22 (if needed)				
23 (if needed)				
24 (if needed)				
25 (if needed)				
26 (if needed)				
27 (if needed)				
28 (if needed)				

APPENDIX C UCSD Moores Cancer Center Data Monitoring

Title: An Open-Label, Phase 2 Efficacy Study of Temozolomide (TMZ) In Advanced Succinate Dehydrogenase (SDH)-Mutant/Deficient Gastrointestinal Stromal Tumor (GIST)

Introduction

This data reporting plan outlines the routine monitoring reports that are to be generated by the study statistician or the study data manager, based on the data that have already been entered into the electronic data capture data base (VELOS).

The purposes of these reports are to monitor the progress of trials and the safety of participants, to assure data accuracy, data completeness and protocol compliance.

All the study personnel listed on the VELOS Clinical study information and personnel contact information page will receive these reports. (see Appendix A).

For an outline of the report see Appendix B.

I. Table of Contents

II. Executive Summary –

The Executive Summary will be an overarching description of the data analyzed.

III. Protocol Synopsis -

The Protocol will be an overarching description of the study.

(note: Study coordinator is to obtain this information from the research plan and the first page of IRB submission for this report. It may be also available on the VELOS study information page.)

IV. Study Data Report –

The Study Report will include the following Tables:

- Table 1: Overall Enrollment
- Table 2: Monthly Enrollment
- Table 3: Consent and Treatment Dates
- Table 4: Screen Failures
- Table 5: Off Treatment
- Table 6: Gender, Race, Ethnicity
- Table 7: Age (years)
- Table 8: Subjects Demographics
- Table 9: Deaths
- Table 10: All Adverse Events

- Table 11: Adverse Events Summary
- Table 12: Serious Adverse Events

Additional tables related to stopping rules will be added dependent on the study design.

Only, the Principal Investigator will received reports of outcome data and appendices that include treatment assessment, response assessment, baseline characteristics and data issues, as determined by study statistician.

Below has details for each of the tables/reports listed above. The frequencies of running the reports will be modified according to each study protocol.

1. Overall Enrollment - Table 1

- Purpose

To monitor enrollment; to ensure that accrual goals are met in a timely manner; to notify the team when accrual goal is nearing completion

- Components

Accrual (number of patients and percentages) by month. Protocol indicates a targeted enrollment of one patient per 2-3 months.

- Frequency: first two week data analysis, after interim analysis, semi-annually, annually

2. Study Status Report – Tables 2-5

- Purpose

To provide a summary of the status of study subjects.

- Components

1) Total number of accrual as of date; number of subjects who are on/off study; number of subjects who are still on study treatment (s); number of subjects who are still on study but off study treatment (s).

2) Listings of off study/off treatment with subject ID, date, week and reason.

- Frequency: first two week data analysis, after interim analysis, semi-annually, annually

3. Baseline Characteristics Report –Tables 6-8 and Appendix

- Purpose

To provide a summary of subjects' baseline characteristics

- Components

Baseline variables which are crucial to study design and analysis

For categorical variables frequency tables will be generated.

For continuous variables, mean (range) will be reported.

- Frequency: first two week data analysis, after interim analysis, semi-annually, annually

4. Toxicity/Adverse Event Report – Tables 9-12

- Purpose:

To monitor toxicities; to evaluate unexpected toxicities; to ensure that toxicity rates are acceptable. All participants receiving investigational agents will be evaluated for safety.

- Components: adverse events reported to the investigator by participants.

1) Listing of all deaths.

2) Frequency tables of all the signs and symptoms or laboratory toxicities by grade and across grades

3) Listing of all adverse events. The list will include patient study ID number, toxicity name, grade, relationship to study drug (probably related, unknown relationship, definitely not related), and date.

- Frequency: first two week data analysis, after interim analysis, semi-annually, annually

5. Stopping Rules (Interim Analysis)

- Components:

    1) Defined Response assessments

- Frequency: interim analysis, semi-annually, annually

6. Treatment and Dose Modifications Report (Treatment Form)

- Purpose: To monitor treatment and dose adjustment

- Components: Listings of study treatment (s) and their corresponding dosages, including treatment start date, treatment modification dates and off treatment date.

- Frequency: first two week data analysis, after interim analysis, semi-annually, annually

7. Issues with Data including Data Completeness Report (various data forms)

- Purpose:

To ensure that clinic visits and other endpoint-related visits are conducted according to schedule; that endpoint-related data are collected appropriately and in a timely manner; to correct the database; to make sites and site principal investigators (PIs) aware of specific problems and to ensure that the compliance rate for visits and sample acquisition is high enough to satisfy protocol objectives.

- Frequency: first two week data analysis, after each stopping rule milestone (if applicable), semi-annually, annually

Timeline for Reports

Date	Accrual*	Study Status	Baseline Characteristics *	Study Completeness	Toxicity/ Adverse Event	Treatment and Dose Modifications	Interim Analysis Response Assessment
x**	X	X	X	X	X	X	
Xxxxxx *** (Cohort Analysis)	X	X	X	X	X	X	X
x	X	X	X	X	X	X	
x	X	X	X	X	X	X	
x	X	X	X	X	X	X	
x	X	X	X	X	X	X	
x	X	X	X	X	X	X	
x	X	X	X	X	X	X	
x	X	X	X	X	X	X	
x	X	X	X	X	X	X	

*****Accrual and Baseline Characteristics Reports may be discontinued following closing the study to accrual
** The first data reports will be two weeks after the study opens or after the first subject
*** Cohort Analyses will be completed when necessary