Cover Page:

Title: Tofacitinib: Suppressing Tumor Invasion in GBM Patients

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UTSouthwestern Harold C. Simmons Comprehensive Cancer Center | NCI Designated Comprehensive Cancer Center

SCCC: STU-2021-1029 Protocol v4.0

Tofacitinib: Suppressing Tumor Invasion in GBM Patients

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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.

Amendment/Version #_____

Tofacitinib in GBM Patients
Tofacitinib: Suppressing Tumor Invasion in GBM Patients

Principal Investigator (PI) Name: **___Michael Youssef, MD_____**

PI Signature: _____

Date: _____

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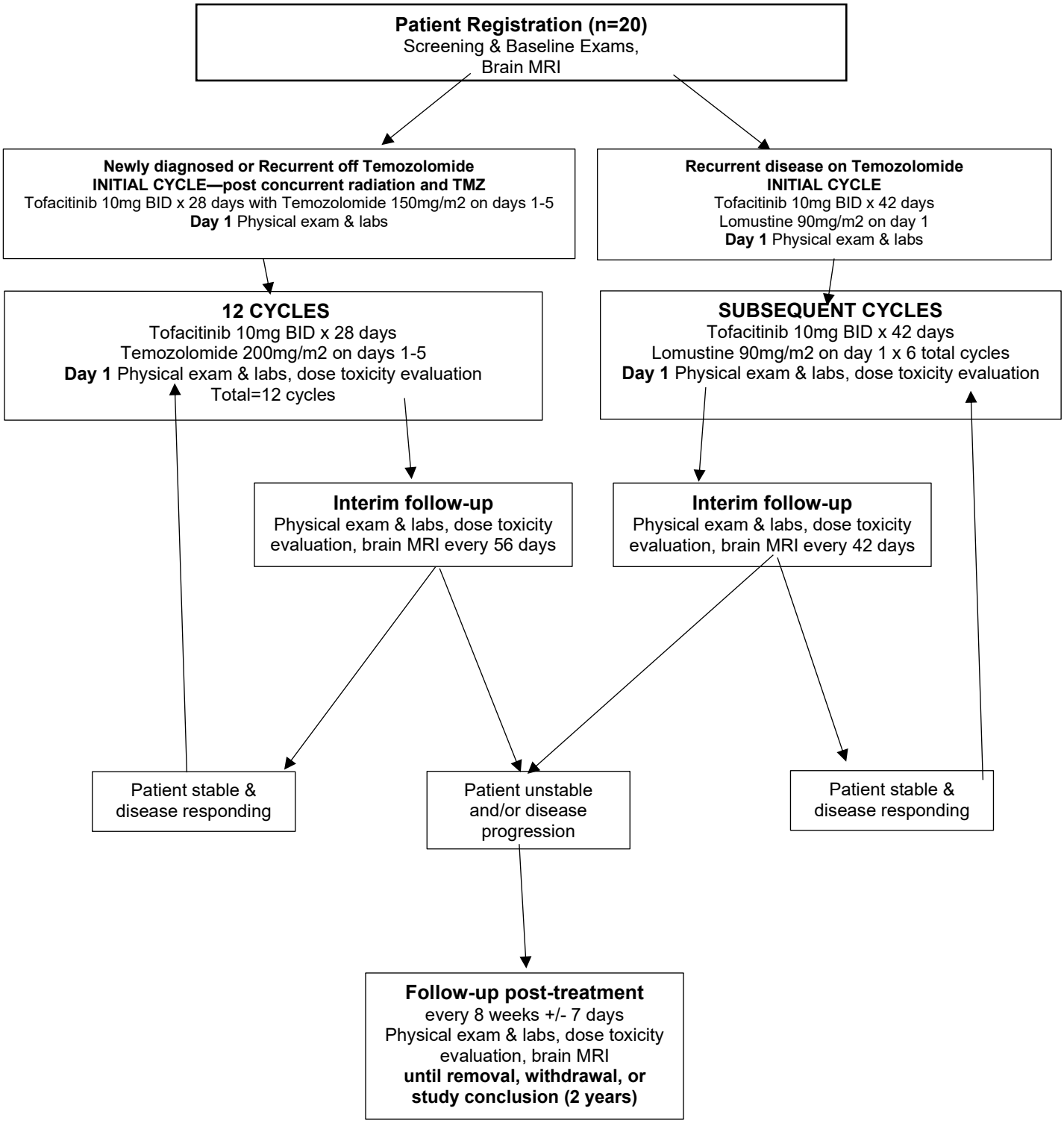
LIST OF ABBREVIATIONS

AE	Adverse Events
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
ANC	Absolute Neutrophil Count
AS	Ankylosing Spondylitis
AST	Aspartate Aminotransferase
BIN3	Bridging Integrator 3, a cytoskeletal protein
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CDK4/6	Cycline-dependent kinases 4 and 6
CFR	Code of Federal Regulations
CMP	Complete Metabolic Panel
CNS	Central nervous system
CR	Complete Response (RANO Response Criteria)
COI	Conflict of Interest
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Effects
CUH	Clements University Hospital
DLT	Dose Limiting Toxicity
DOT	Disease Oriented Team
DSMB	Data Safety and Monitoring Board
ECG	Electrocardiogram
EGFR	Epidermal growth factor receptor
EMR	Electronic Medical Record
FDA	U.S. Food & Drug Administration
GBM	Glioblastoma
GCP	Good Clinical Practice
GI	gastrointestinal
H&P	History & Physical Exam
HB-EGF	Heparin-binding epidermal growth factor
HHS	U.S. Health & Human Services
HRPP	Human Research Protections Program
HUD	Humanitarian use device
JAK	Janus kinases, a family of non-receptor tyrosine kinases
IB	Investigator's Brochure
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IDH WT	IDH wildtype
IHC	Immunohistochemistry
ILD	Interstitial Lung Disease
IV (or iv)	Intravenously
JIA	Juvenile Idiopathic Arthritis
KPS	Karnofsky Performance Score
LC-MS	Liquid chromatography-mass spectrometry
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NMSC	Non-melanoma skin cancer
ORR	Overall response rate
OS	Overall survival
PD	Progressive Disease (RANO Response Criteria)
PDX	Patient-derived xenograft
PFS	Profession-free survival
PK	Pharmacokinetics

PR	Partial Response (RANO Response Criteria)
p.o.	Per os/by mouth
QAC	Quality Assurance Coordinator
RA	Rheumatoid arthritis
RANO	Response Assessment in Neuro-Oncology
SAE	Serious Adverse Event
SD	Stable Disease
TEAE	Treatment-emergent adverse effects
TGFα	Transforming growth factor alpha
UADE	Unanticipated adverse device effects
ULN	Upper limit of normal
UTSW	University of Texas Southwestern
UPIRSO	Unanticipated Problems Involving Risks to Subjects or Others
VTE	Venous Thromboembolism
WBC	White Blood Cells

STUDY SCHEMA



STUDY SUMMARY

Title	Tofacitinib: Suppressing Tumor Invasion in Glioblastoma Patients
Short Title	Tofacitinib in Glioblastoma Patients
Protocol Number	**Tofacitinib in Glioblastoma Patients Protocol v4.0**
Phase	Pilot study
Methodology	2-arm, non-randomized, open-label trial
Study Duration	2 years
Study Center(s)	Single center: UT Southwestern Medical Center
Objectives	Primary Objective: • To determine the progression-free survival (PFS) of the study cohort. Secondary Objectives: • To determine the overall survival (OS) of the study cohort. • To assess the safety and tolerability of Tofacitinib in GBM patients. • To determine the radiographic responses of the patients in the study cohort by RANO criteria. • To determine predictive and pharmacodynamic biomarkers of JAK inhibitor therapy.
Number of Subjects	20
Diagnosis and Main Inclusion Criteria	Newly diagnosed or recurrent glioblastoma patients whose tumors have EGFR amplification and low levels of HB-EGF and TGFα loss of CDKN2A/B or gain or amplification of CDK4/6
Study Product(s), Dose, Route, Regimen	Tofacitinib (Xeljanz – Pfizer) 10 mg given orally twice daily
Duration of administration	Until evidence of progression, intolerance of treatment, withdrawal of consent, or death
Reference therapy	Historical controls; no established chemotherapy options in recurrent GBM patients have been proven to show survival benefit
Statistical Methodology	Kaplan-Meier curves will be fit to estimate the median PFS and OS, as well as the corresponding 95% confidence intervals. EGF receptor and EFGR ligands will be compared between those subjects who respond to Tofacitinib and those who do not using two-sample t-tests when appropriate and Mann-Whitney U tests otherwise. Receiver operating characteristic curves will be fit to determine the ability of these measures to predict treatment response and optimal cut-points for prediction.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background

Glioblastoma (GBM) is the most common malignant primary adult brain cancer. It is a devastating and fatal disease because of its highly invasive nature that results in extension of the tumor into the normal brain tissue. Although signaling pathways that drive GBM invasion have been reported, no signaling pathway or drug that actively suppresses invasion is known. Thus, the identification of a targetable mechanism that specifically inhibits invasion would be of enormous interest to scientists, clinicians, and patients. We have identified the N-Bar domain protein containing cytoskeletal protein BIN3 (bridging integrator 3) as a key suppressor of GBM invasion. BIN3 suppresses activation of a DOCK7-Rho GTPase pathway that is required for GBM invasion. Importantly, Tofacitinib (Xeljanz) upregulates BIN3 and suppresses invasion in multiple mouse intracranial models. We have found that Tofacitinib is more effective in a subset of GBMs that have low levels of EGFR ligand. We have extensive preclinical data describing the BIN3 mediated pathway that suppresses invasion and Tofacitinib mediated suppression of invasion. The scientific report of these data was submitted to Nature Cell Biology, and we are currently working on an invited revision.

We would like to undertake a clinical trial to examine the effects of Tofacitinib in patients with newly diagnosed or recurrent GBM in combination with standard of care therapy (temozolomide or lomustine). We have identified BIN3 as a critical suppressor of GBM invasion. Tofacitinib, a JAK inhibitor, increases levels of BIN3 and has been reported to cross the blood-brain barrier. We have extensive evidence from preclinical mouse models that treatment with Tofacitinib blocks GBM invasion, resulting in smaller tumors and increased survival. We have very compelling evidence from preclinical models that Tofacitinib improves survival in mouse models of GBM.

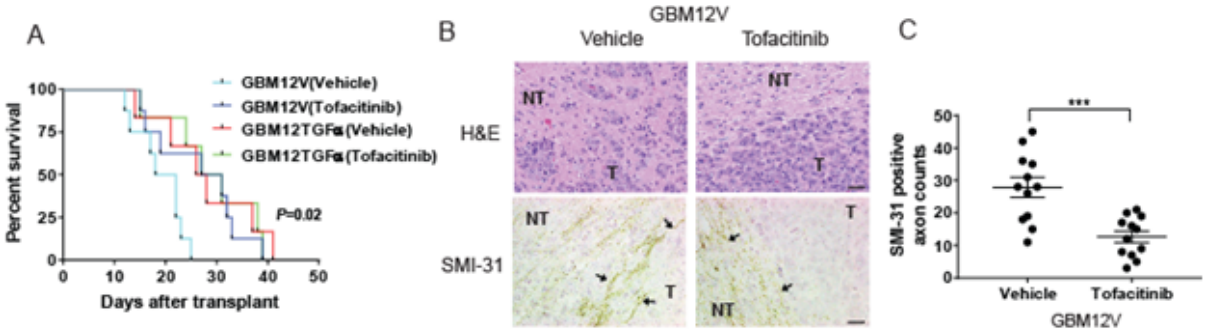
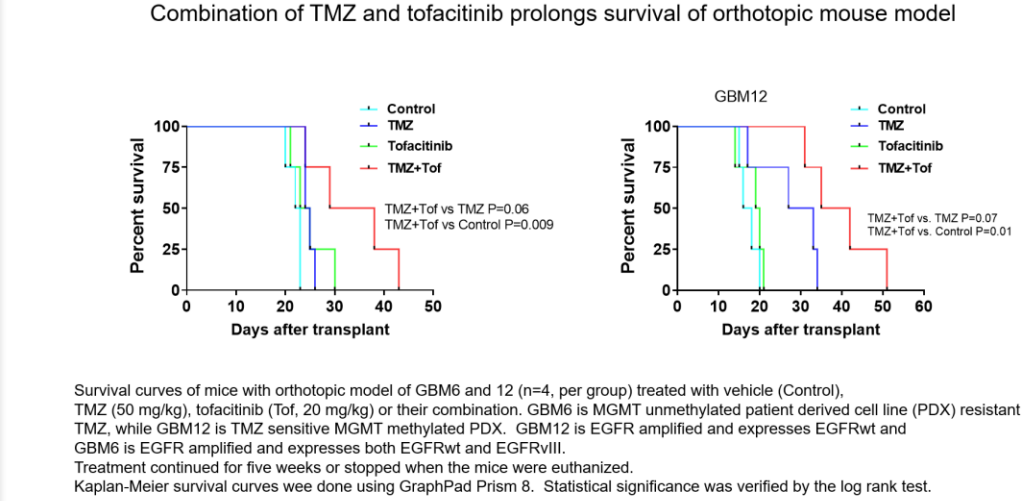


Figure 1. (A) Kaplan-Meier survival curves of mice with orthotopic xenotransplant model of GBM12V and GBM12TGFα treated with vehicle or Tofacitinib 20mg/kg/day (n=8 in GBM12TGFα groups, n=6 in GBM12V groups), P=0.02 vehicle vs Tofacitinib in GBM12TGFα groups. **(B)** Representative H&E staining and immunostaining for SMI-31 showing invasiveness in GBM12 orthotropic tumor from vehicle vs Tofacitinib treated mice, scale bar: 25 μM. **(C)** Quantification of SMI-31 counts in tumor tissue (SMI-31 is a mouse neurofilament that becomes disrupted as human tumor cells spread through normal brain and this can be quantitated.)

In this experiment, a patient-derived xenograft (PDX) GBM12V (expressing empty vector) or expressing a growth factor TGFα, were implanted in the mouse brain and the mice were monitored for neurological symptoms. The mice were sacrificed when they developed neurological symptoms. This experiment demonstrated that Tofacitinib improved survival in EGFR ligand-poor GBMs (about 50% of all GBMs). Furthermore, Tofacitinib clearly suppressed invasion in this experimental model.



Survival curves of mice with orthotopic model of GBM6 and 12 (n=4, per group) treated with vehicle (Control), TMZ (50 mg/kg), tofacitinib (Tof, 20 mg/kg) or their combination. GBM6 is MGMT unmethylated patient derived cell line (PDX) resistant to TMZ, while GBM12 is TMZ sensitive MGMT methylated PDX. GBM12 is EGFR amplified and expresses EGFRwt and GBM6 is EGFR amplified and expresses both EGFRwt and EGFRvIII.
Treatment continued for five weeks or stopped when the mice were euthanized.
Kaplan-Meier survival curves wee done using GraphPad Prism 8. Statistical significance was verified by the log rank test.

In addition an additional experiment was conducted combining tofacitinib with an alkylating agent in an orthotopic model showing a cumulative effect of tofacitinib when combined with alkylating chemotherapy. Additionally, by adding tofacitinib to the above chemotherapies, it is thought that it will act to inhibit the NF-kB pathway, which is a commonly found driver of growth in glioblastoma. NF is found to be mutated in 13-14% of glioblastoma patients. Given the limited amount of patients with mutations readily found, it is thought that a combination of traditional chemotherapy along with this more targeted therapy will present a benefit regarding PFS and OS when compared to chemotherapy alone.

1.2 Study Agent(s)/Therapy(ies) Background and Associated Known Toxicities

Tofacitinib is a potent, selective inhibitor of the Janus kinase (JAK) family of kinases with a high degree of selectivity against other kinases in the human genome.[1] In kinase assays, tofacitinib inhibits JAK1, JAK2, JAK3, and to a lesser extent, tyrosine kinase 2 (TyK2). Human pharmacokinetic activity of this drug is characterized by rapid absorption and elimination, with a time to peak concentration of 30 minutes and a half-life of 3 hours. The oral bioavailability of Tofacitinib is approximately 74%, with a clearance mechanism largely reliant on hepatic metabolism (70%) and partially on renal excretion (30%).

Summary of Safety Findings from In Vivo Studies

Tofacitinib is approved for the treatment of rheumatoid arthritis (RA), psoriatic arthritis, and ulcerative colitis and is currently being investigated for use in juvenile idiopathic arthritis (JIA) and Ankylosing Spondylitis (AS). Tofacitinib has been extensively studied in humans for safety and tolerability endpoints (see attached Tofacitinib Investigator Brochure) for both formulations, immediate and modified release, available on the market, with more than 50 Phase 2, Phase 3, and long-term extension studies performed.

Tolerability data from these studies showed that the drug was well tolerated, and adverse events (AEs) were similar between immediate and modified release formulations. In Phase 1 studies, the reported AEs within Tofacitinib-treated vs placebo-treated healthy volunteers, respectively, included gastrointestinal disorders (13.9% vs 8.3%), nervous system disorders (12.6% vs 10.7%), musculoskeletal and connective tissue disorders (4.0 vs 3.3%), and skin disorders (3.5% vs 1.7%). The most commonly reported AEs were headaches (10.7%), nausea & vomiting (6.1%), and diarrhea (2.5%), all mild in severity.

Due to its mechanism of action, potential safety risks for the patient treated with Tofacitinib include serious opportunistic infections. Treatment-related infections featured in approximately 25% of patients aggregated from multiple prior studies. In 45 completed oral Phase 2 and Phase 3 studies, all causality AEs occurring with a frequency of ≥ 5% were: nasopharyngitis, upper respiratory tract infections, urinary tract infections, bronchitis, diarrhea, herpes zoster, influenza, nausea, backpain, elevated blood creatine phosphokinase, hypertension, arthralgia, and headaches; and, with a frequency of ≥ 4% but <5%, were: cough, sinusitis, gastroenteritis, RA, bacterial infections, hypercholesterolemia, anemia, and falls.

Further risks include venous thromboembolism (VTE) & pulmonary embolism (PE), potential for malignancies including lymphoma, gastrointestinal (GI) perforations, and interstitial lung disease (ILD). Treated patients may also be at increased risk for non-melanoma skin cancer (NMSC). There is nonclinical evidence showing that the drug has teratogenic effects and therefore should not be administered to pregnant and lactating women.

1.3 Other Agents

This study will use other agents in conjunction to Tofacitinib (Xeljanz). If the patient is newly diagnosed, patients will receive Temozolomide, which is the current standard of care medication, along with Tofacitinib. In recurrence, patients will receive temozolomide if they had progression while not taking temozolomide (i.e progressed on imaging surveillance), or they will receive lomustine if progression occurred while on temozolomide. All patients will prophylactic therapy with Trimethorpim/Sulfamethoxazole (Bactrim DS) while on therapy due to the increased immunosuppression from dual agent therapy.

1.4 Rationale

The highly invasive nature of GBM has been a major barrier to effective treatment. Thus, the identification of a drug that can inhibit GBM invasion would be highly beneficial. We have identified the cytoskeletal protein BIN3 as a protein that suppresses GBM invasion in cell culture as well in experimental mouse models. In a screen for drugs that upregulate BIN3, we identified Tofacitinib, as a drug that upregulates BIN3 and suppresses GBM in cell culture as well as mouse models of GBM. Thus, tofacitinib improves survival and reduces tumor size in mouse models of GBM. We would like to test whether tofacitinib is effective in recurrent GBM, a condition for which there is no effective treatment. In addition we would like to test the addition of Tofacitinib to temozolomide in the newly diagnosed population, as the current standard of care (Temozolomide alone) has shown limited response over time with the overall prognosis of GBM being less than 24 months.

1.5 Correlative Studies

Our preliminary data indicate that certain subsets of GBM are likely to be more responsive to tofacitinib. In particular, EGFR ligand poor GBMs are more likely to respond to tofacitinib. The epidermal growth factor receptor (EGFR) is amplified in about

45% of GBMs. In addition, seven EGFR ligands are expressed in GBM. Thus, determination of the EGFR level is of key importance and would be done by NGS—currently being done for almost all GBMs resected at UTSW. The EGFR ligands are not part of the NGS panel and would be determined by RT-PCR for paraffin embedded tissue. Other markers of interest include other receptors that are activated by the EGFR such as Met and Axl. In addition, downstream EGFR signaling would be determined by examination of canonical signals such ERK, Akt and STAT3 in paraffin embedded tissue by immunohistochemistry.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

2.1.1 To determine the progression-free survival (PFS) of the study cohort.

2.2 Secondary Objectives

2.2.1 To determine the overall survival (OS) of the study cohort.

2.2.2 To assess the safety and tolerability of Tofacitinib in recurrent GBM patients.

2.2.3 To determine the radiographic responses of the patients in the study cohort by RANO criteria.

2.2.4 To determine predictive and pharmacodynamic biomarkers of JAK inhibitor therapy.

2.3 Exploratory Objectives

2.3.1 To determine predictive and pharmacodynamic biomarkers of JAK inhibitor therapy

2.4 Endpoints

2.4.1 **Primary Endpoint**

Median progression-free survival from initiation of Tofacitinib until disease progression as defined by the RANO criteria, unacceptable toxicity, withdrawal of consent, or discontinuation from the trial for any other reason.

2.4.2 **Secondary Endpoints**

Median time from initiation of tofacitinib until death

Toxicities and adverse events according to CTCAE v.5.0

2.4.3 **Correlative Study Endpoints**

To determine predictive and pharmacodynamic biomarkers of JAK inhibitor therapy.

3.0 Subject ELIGIBILITY

3.1 Eligibility waivers are not recommended; however, if warranted, prior approvals are required per Section 11.6.1. Subjects must meet all inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered. Once registered, a subject is still required to meet all inclusion and exclusion criteria on the first day of treatment, prior to treatment. Inclusion Criteria

3.1.1 For newly diagnosed patients: Completion of concurrent radiation therapy and temozolomide therapy.

3.1.2 Histologically confirmed WHO Grade 4 Glioblastoma (2021 WHO CNS brain tumor classification criterion used) at new diagnosis or first, second, third, or fourth recurrence after concurrent chemoradiotherapy. Patients with an initial diagnosis of a lower-grade glioma are eligible if a subsequent biopsy determined the progressive tumor to be GBM.

3.1.3 For recurrent patients: Imaging confirmation of first, second, third, or fourth tumor progression or regrowth as defined by the Response Assessment in Neuro-Oncology (RANO) criteria. A minimum of 12 weeks must have elapsed from the completion of radiotherapy to study entry to minimize the potential for MRI changes related to radiation necrosis that might be misdiagnosed as progression of disease, unless there is a new lesion outside the radiation field or unequivocal evidence of viable tumor on histopathological sampling.

3.1.4 Karnofsky Performance Status (KPS) ≥ 60%.

3.1.5 Patients must be willing and able to provide written informed consent and to comply with the study protocol as judged by the investigator.

3.1.6 Age ≥ 18 years.

3.1.7 Patients must be able to swallow oral medications.

3.1.8 For women who are of child-bearing potential and who are sexually active and who are not surgically sterile (absence of ovaries and/or uterus): to use an adequate method of contraception (oral contraceptives, intrauterine contraceptive device, barrier method of contraception in conjunction with spermicidal jelly) during the treatment period and for at least 6 months after last dose of study drug. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. For male patients who are partners of premenopausal women: agreement to use a barrier method of contraception during the treatment period and for at least 6 months after the last dose of study drug.

3.1.8.1 A female of child-bearing potential is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- Has not undergone a hysterectomy or bilateral oophorectomy; or
- Has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

3.1.9 Patients who have undergone recent surgery for recurrent or progressive tumor are eligible provided that:

3.1.9.1 Surgery must have confirmed the diagnosis or recurrence of Glioblastoma.

3.1.9.2 A minimum of 28 days must have elapsed from the day of surgery to study entry. For core or needle biopsy, a minimum of 7 days must have elapsed prior to study entry.

3.1.9.3 Craniotomy or intracranial biopsy site must be adequately healed and free of drainage or cellulitis, and the underlying cranioplasty must appear intact at the time of randomization.

3.1.10 Patients must have recovered (Common Terminology Criteria for Adverse Events CTCAE version 6] Grade ≤1) from the acute effects of chemotherapy except for residual alopecia or Grade 2 peripheral neuropathy prior to randomization. Minimum times from prior therapies include:

3.1.10.1 Greater than or equal to 28 days elapsed from the administration of any investigational agent.

3.1.10.2 Greater than or equal to 28 days elapsed from the administration of any prior cytotoxic agents, except ≥ 42 days from nitrosoureas.

NOTE: Prior treatment with Novo-TTF therapy is allowed at initial diagnosis but must be discontinued prior to study entry.

3.1.11 GBMs of the study patients must have EGFR gene amplification, which will be detected by next generation sequencing of tumor tissue from resected sample.

3.1.12 Prior use of bevacizumab is allowed, however patient must be off of this medication for 180 days.

3.1.13 Patients must have adequate organ and marrow function as defined by the following criteria listed on Table 1:

Table 1. Laboratory Value Guidance to Establish Adequate Organ Function

System	Laboratory Value
Hematologic	
ANC	≥1.5 × 10^9/L
ALC	≥1.0 × 10^9/L
Platelets	≥100 × 10^9/L
Hemoglobin	≥8 g/dL
	Note: Patients may receive erythrocyte transfusions to achieve this hemoglobin level at the discretion of the investigator. Initial treatment must not begin earlier than the day after the erythrocyte transfusion.
Hepatic	
Total bilirubin	≤1.5 × ULN Patients with Gilbert's syndrome with a total bilirubin ≤2.0 times ULN and direct bilirubin within normal limits are permitted.
ALT and AST	≤3 × ULN

3.2 Exclusion Criteria

3.2.1 Prior treatment with an EGFR or JAK inhibitor.

3.2.2 Subjects may not be receiving any other investigational agents for the treatment of the cancer under study.

3.2.3 Patients unable to undergo brain MRI scans with IV gadolinium contrast.

3.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to Tofacitinib

3.2.5 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that, in the opinion of the investigator, would limit compliance with study requirements.

3.2.6 Subjects must not be pregnant or nursing due to the potential for congenital abnormalities and the potential of this regimen to harm nursing infants.

3.2.7 Prior history of hypertensive crisis, hypertensive encephalopathy, or inadequately controlled hypertension (defined as systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg while on antihypertensive medication).

3.2.8 Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product, or previous significant gastrointestinal resection that would preclude adequate absorption of the trial medications.

3.2.9 History of another malignancy in the previous 3 years, with a disease-free interval of < 3 years. Patients with prior history of in situ cancer or basal or squamous cell skin cancer are eligible.

3.2.10 Concurrent use of Bevacizumab.

3.2.11 Creatine Clearance less than or equal to 50mL/min.

3.2.12 Positive Quantiferon Gold

3.2.13 Active hepatitis B or C infection (as indicated by positive Hepatitis B or C surface antigen)

4.0 TREATMENT PLAN

4.1 Treatment Dosage and Administration

Any subject who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events table. Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 5.0. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

The trial treatments in this study are outlined below on Table 5. The treatments will be administered in the outpatient setting. Patients will also undergo treatment with concurrent temozolomide or lomustine at the standard of care dosing schedule.

4.1.1 Dosing Instructions for Tofacitinib, Temozolomide, and Lomsustine

Study patients will be instructed to take the doses of Tofacitinib twice daily at approximately the same times every day. If the patient vomits or misses a dose, the patient is instructed to take the next dose at the next scheduled time. Patients are not to chew, crush, or split Tofacitinib tablets before swallowing. Patients are not to ingest the tablets if they are broken, cracked, or otherwise not intact. Trial patients will complete the Study Medication Diary.
Temozolomide will be dosed at 150mg/m2/day on days 1-5 of the 28 day cycle for cycle 1, then increased to 200mg/m2/day for cycles 2-12. Lomustine will be dosed at 90mg/m2

on day 1 of the 42 day cycle and will complete up to 6 cycles. Patients will complete a Study medication diary for their chemotherapy separate from the tofacitinib study medication diary.

Table 2. Study Regimen

TOFACITINIB REGIMEN					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Tofacitinib	None.	10 mg bid	PO twice daily	Twice daily continuously	4 weeks (28 days)
Temozolomide	Ondansetron 8mg	150-200mg/m2/day	PO	Days 1-5 of the 28 day cycle	4 weeks (28 days)
Lomustine	ondansetron 8mg	90mg/m2	PO	day 1 of 42	6 weeks (42 days)

4.2 Toxicities and Dose Modifications

Any subject who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to Table 5. Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 5.0. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

Dose adjustments for temozolomide and lomustine will be done per treating physician judgement according to the standard of care practices. In the event of grade 3 of higher myelosuppression, or active infection, tofacitinib will be held until toxicity is resolved.

Table 3. Non-Hematological Toxicity Dose Reductions

Event	Action
Liver toxicity: AST, ALT elevation	
Grade 2	Dose reduction to half: tofacitinib 5mg BID & recheck at next lab draw.
Grade 3	Hold all remaining doses of current cycle & recheck; physician to consider restarting consequent cycle at half-dose.

Grade 4	Discontinue tofacitinib and monitor.
Renal toxicity: CK elevation	
Grade 1-2	Dose reduction to half: tofacitinib 5mg BID & recheck at next lab draw.
Grade 3	Hold all remaining doses of current cycle & recheck; physician to consider restarting consequent cycle at half-dose.
Grade 4	Discontinue tofacitinib and monitor.
Hyperlipidemia: LDL elevation	
Grade 1-2	Allow attempt at control, e.g. with statin agents.
Grade 3	Hold all remaining doses of current cycle & recheck; physician to consider restarting consequent cycle at half-dose.
Grade 4	Discontinue tofacitinib and monitor.
Active infection	
Grade 1-2	Hold dose until resolution of infection; treat with appropriate antimicrobials.
Grade 3	Discontinue tofacitinib and monitor; treat with appropriate antimicrobials.
Grade 4	Discontinue tofacitinib and monitor; treat with appropriate antimicrobials.
Thromboembolic event	
Grade 1-2	Hold all remaining doses of current cycle & reassess; allow attempt at treatment & prophylaxis with anticoagulants. Physician to consider restarting consequent cycle at half-dose with adjuvant anticoagulation.
Grade 3	Discontinue tofacitinib and monitor.
Grade 4	Discontinue tofacitinib and monitor.

Table 4. Hematological Toxicity Dose Reductions

Event	Action
Neutropenia	
Grade 1-2	Dose reduction to half: tofacitinib 5mg BID & recheck at next lab draw.
Grade 3	Hold all remaining doses of current cycle & recheck; physician to consider restarting consequent cycle at half-dose.
Grade 4	Discontinue tofacitinib and monitor.
Lymphopenia	
Grade 1-2	Dose reduction to half: tofacitinib 5mg BID & recheck at next lab draw.
Grade 3	Hold all remaining doses of current cycle & recheck; physician to consider restarting consequent cycle at half-dose.
Grade 4	Discontinue tofacitinib and monitor.
Anemia	
Grade 1-2	Continue treatment unless symptomatic; if symptomatic, physician may opt to correct with transfusion.
Grade 3	Correct with transfusion & monitor; consider dose reduction to half.
Grade 4	Hold all remaining doses of current cycle & recheck; physician to consider restarting consequent cycle at half-dose vs discontinuation.

4.3 Concomitant Medications/Treatments

Since Tofacitinib is metabolized by CYP3A4, interaction with drugs that inhibit or induce CYP3A4 is likely. Tofacitinib exposure is increased when co-administered with potent CYP3A4 inhibitors (e.g., clarithromycin, ketoconazole, voriconazole) or when administration of one or more concomitant medications results in both moderate Inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g. fluconazole). Thus, avoid co-administration of such drugs and drugs in similar classes. Tofacitinib exposure is decreased when co-administered with potent CYP3A4 inducers (e.g. carbamazepine, phenytoin, rifampin), and thus must avoid such drugs or drugs in similar classes. Inhibitors of CYP2C19 or P-glycoprotein are unlikely to alter the pharmacokinetics of tofacitinib.

If patient is currently taking a medication that is a strongCYP3A4 inhibitor OR dual moderate CYP3A4 inhibitor(s), they will be dosed at 5mg BID. If toxicity is seen they will be reduced to 5mg once daily.

Given the increased likelihood of immunosuppression while on therapy, patients will be prescribed and instructed to take Bactrim DS (Trimethoprim/sulfmethoxazole) three times weekly while on therapy.

4.3.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medications will be recorded on the case report form (CRF) including all prescription, over the counter, herbal supplements, and IV medications. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

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. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs as defined in Section 7.
Recurrent glioblastoma patients are also permitted to receive concurrent re-irradiation if deemed necessary or advantageous by the treating physician.

4.3.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Chemotherapies not specified in this protocol
- Investigational agents other than Tofacitinib
- 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, Bacillus Calmette–Guérin, and typhoid vaccines.

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

4.4 Duration of Therapy

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

- Disease progression
  - Two MRI scans approximately 4 weeks apart are required to determine tumor progression in order to prevent removal of therapy due to pseudoprogression. The patient should be placed on therapeutic dose of dexamethasone for 4 weeks prior to second MRI to adequately prove progression of disease.
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Subject decides to withdraw from the study, **OR**
- General or specific changes in the patient's condition render the subject unacceptable for further treatment in the judgment of the investigator.

4.5 Duration of Follow Up

Subjects will be followed for **2 years** after removal from treatment or until death, whichever occurs first. Subjects removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Trial follow up

after study removal will be with clinic visits as indicated and with a phone call every 3 months if the patient is no longer being seen.

4.6 Removal of Subjects from Protocol Therapy

Subjects will be removed from therapy when any of the criteria listed in Section 5.5 apply. Notify the Principal Investigator and document the reason for treatment discontinuation and the date of discontinuation. The subject should be followed-up per protocol.

4.7 Subject Replacement

If a patient is enrolled but does not receive Tofacitinib for any reason, they may be replaced with another trial participant. Also, patients that receive less than 4 weeks of Tofacitinib may be replaced with another trial participant.

4.8 Subject Withdrawal / Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.0

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression
  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved; please see Section 11.5.
- Unacceptable adverse experiences
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Administrative reasons

5.0 STUDY PROCEDURES

5.1 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. The screening procedures include:

5.1.1 Informed Consent

5.1.2 Medical history

Complete medical and surgical history, history of infections. Any ongoing sign/symptoms at registration should be assessed and graded per CTCAE, and followed as per section 7

5.1.3 Demographics

Age, gender, race, ethnicity

5.1.4 Review subject eligibility criteria

5.1.5 Review previous and concomitant medications

5.1.6 Physical exam including vital signs, height and weight

Vital signs (temperature, pulse, respirations, blood pressure), height, weight

5.1.7 Performance status

Karnofsky Performance Score (KPS) prior to initiation of study.

5.1.8 Labs

5.1.8.1 Serum chemistries

Comprehensive metabolic panel (CMP) to include: albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, creatinine, electrolytes (sodium, potassium, calcium, chloride, bicarbonate), glucose, and total bilirubin.

5.1.8.2 Pregnancy test (for females of child bearing potential)

See section 3.1.7.1 for definition. At screening visit, serum pregnancy test will be performed **within 7 days** prior to registration

5.1.8.3 Hematology

Hgb, platelets, white blood cells, red blood cells, differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils (% or absolute)

5.1.8.4 Coagulation studies

PT, PTT, INR

5.1.8.5 Urinalysis

Macroscopic panel (dipstick) (color, total bilirubin, blood, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen)
Microscopic panel (RBC, WBC, casts, crystals, bacteria, epithelial cells)

5.1.8.6 ECG

A standard 12 lead ECG should be used for assessments as clinically indicated

5.1.9 Tumor Assessment

To be performed using the RANO criteria according to Table 6

5.2 Procedures During Treatment

Study evaluations will be performed according to the visit schedule (Table 5). Once consented and registered, eligible patients will commence **Cycle 1** and be assessed on **Cycle 1 Day 1**, which includes blood draws for CBC and CMP. An entire cycle will be 28 days of continuous Tofacitinib dosing and 5 days of Temozolomide dosing in the temozolomide arm, and will be 42 days of continuous tofacitinib dosing and 1 day of lomustine dosing in the lomustine arm. The patient will once again be assessed on **Cycle 1 Day 22**, this time including toxicity evaluations, blood draws, and urine sampling.

An **interim follow-up** will be done after the second cycle, during which the patient will undergo a brain MRI for tumor measurements along with all other assessments (including blood draws and urine sampling). Subsequent cycles will continue as prior, with subject assessments and toxicity evaluations every 4 weeks and brain MRI every 8 weeks. Each subject may receive a maximum of 12 cycles when treated with temozolomide and 6

cycles when treated with lomustine. Treatments will stop upon evidence of disease progression, unacceptable toxicity, or if the physician deems it unsafe for the subject to continue in the study. Subjects may also withdraw their consent at any time. Trial follow up after study removal will be with clinic visits as indicated and with a phone call every 3 months if the patient is no longer being seen.

Table 5. Trial Visit Evaluations and Schedule

ASSESSMENT	Screening (D1 to D21)	CYCLE 1-2 Day 1 (within 21 days of Screening +/- 3 days)	CYCLES 3+ Day 1 (+/- 3 days)	Every 8 weeks after Cycle 3 (7 days +/- 3 days)	End of Treatment visit (disease progression, withdrawal, removal of treatment)
Pathology Review	X				
Informed Consent	X				
History, Physical Exam (including Neurologic exam)	X	X	X	X	X
Performance Status (KPS)	X	X	X	X	X
Toxicity (include DLT) Evaluation			X	X	X
MRI Brain w/wo contrast	X		X (every 8 weeks)		
Tumor Measurements on MRI	X		X (coincide with MRI Brain)	X	X
Concomitant medications (including steroid and anticonvulsant doses)	X	X	X	X	X
CBC with differential[1]	X	X (every 7 days)	X (every 7 days)	X(every 7 days)	X
CMP[2]	X	X	X	X	X
PT/PTT/INR[3]	X				
Urinalysis	X		X	X	X
Serum Pregnancy test (if applicable)[4]	X				
ECG	X				
Hepatitis B and Hepatitis C surface antigen	X				
Quantiferon Gold	X				

[1] CBC (Complete Blood Count) includes WBC, Hgb, ANC, and Platelet count
[2] CMP (Complete Metabolic Profile) includes total bilirubin, alkaline phosphatase, SGOT (AST), glucose, sodium, potassium, calcium, and creatinine

[3] All patients will have PT/PTT/INR at baseline. Patients on full-dose therapeutic anticoagulant medications are eligible provided the patient has been on a stable dose for at least 2 weeks and has an INR range of 2 to 3. For these patients, repeat PT/PTT/INR weekly for first 4 weeks and then as clinically indicated.
[4] For women of childbearing potential only. Testing must be done ≤ 7 days prior to registration.

5.3 Removal of Subjects from Study

Subjects can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

5.4.1 Subject voluntarily withdraws from treatment (follow-up permitted)

5.4.2 Subject withdraws consent (termination of treatment and follow-up)

5.4.3 Subject is unable to comply with protocol requirements

5.4.4 Subject demonstrates disease progression (unless continued treatment with study drug/treatment is deemed appropriate at the discretion of the investigator)

5.4.5 Subject experiences toxicity that makes continuation in the protocol unsafe

5.4.6 Treating physician determines continuation on the study would not be in the subject's best interest

5.4.7 Subject becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event)

5.4.8 Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study

5.4.9 Lost to follow-up.
If a research subject cannot be located to document survival after a period of 2 years, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented and approved by the Data Monitoring Committee.

6.0 Measurement of Effect

6.1 Tumor Measurements

Tumor response will be assessed using contrast and non-contrast brain magnetic resonance imaging (MRI) with assessments based on the international criteria proposed by the Response Assessment in Neuro-Oncology (RANO) Working Group [30], until progression of disease. For patients who do not progress or die, PFS will be censored at the last adequate radiologic assessment.

6.1.1 Definitions

Evaluable for toxicity. All subjects will be evaluable for toxicity from the time of their first treatment with study therapy.

Evaluable for objective response. Only those subjects who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These subjects will have their response classified according to the definitions stated below.

6.1.2 Disease Parameters

Measurable Disease: Measurable lesions are defined as bi-dimensionally contrast-enhancing lesions with clearly defined margins by MRI, with two perpendicular diameters of at least 10 mm, visible on 2 or more axial slices which are preferably at most 5 mm apart with 0 mm skip. In the event there are inter-slice gaps, this also needs to be considered in determining the size of measurable lesions at baseline.

Non-measurable disease: All other lesions that are uni-dimensionally measurable lesions, masses with margins not clearly defined, or lesions with maximal perpendicular diameters <10 mm. Tumor lesions around a cyst or surgical cavity are considered non-measurable unless there is a nodular component measuring at least 10 mm in diameter. The cystic or surgical cavity should not be measured in determining response.

Target lesions: All measurable lesions up to a maximum of five lesions should be identified as target lesions and recorded and measured (sum of the products of the perpendicular diameters) at baseline. Target lesions should be selected based on their size lesions with the longest diameters) and their suitability for accurate repeated measurements by imaging techniques. Occasionally, the largest lesions may not be suitable for reproducible measurements and the next largest lesions, which can be measured reproducibly, should be selected.

Non-target lesions. For patients with recurrent disease who have multiple lesions of which only one or two are increasing in size, the enlarging lesions should be considered the target lesions for evaluation of response. The other lesions will be considered non-target lesions and should also be recorded. Rarely, unequivocal progression of a non-target lesion requiring discontinuation of therapy, or development of a new contrast-enhancing lesion may occur even in the setting of stable disease (SD) or partial response (PR) in the target lesions. These changes would qualify as progression. Non-target lesions also include measurable lesions that exceed the maximum number of 5. Measurements of these lesions are not required but the presence or absence of each should be noted throughout follow-up.

6.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and not more than 14 days before the beginning of the treatment cycles.

Conventional MRI: Conventional brain MRI with contrast is required; CT is not acceptable. 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. These techniques should be performed with cuts of 5 mm or less in slice thickness contiguously

6.1.4 Response Criteria

The responses in this study will be determined according to the RANO criteria described below.

6.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Requires all of the following:

a. Complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks
b. No new lesions
c. Stable or improved non-enhancing (T2/FLAIR) lesions
d. Patients must be off corticosteroids
e. Stable or improved clinically

Partial Response (PR): Requires all the following:
a. ≥50% decrease compared to baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks
b. No progression of non-measurable disease
c. No new lesions
d. Stable or improved non-enhancing (T2 FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan
e. The corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of the baseline scan
f. Stable or improved clinically

Progressive Disease (PD): Requires any of the following:
a. ≥25% increase in the sum of products of perpendicular diameters of enhancing lesions compared to the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids
b. Significant increase in T2 FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared to baseline scan or best response following initiation of therapy, not due to co-morbid events (e.g. radiation therapy, demyelination, ischemic injury, infection, seizures, post-operative changes, or other treatment effects).
c. Any new lesion
d. Clear clinical deterioration not attributable to other causes apart from the tumor (e.g. seizures, medication side effects, complications of therapy, cerebrovascular events, infection, etc.) or changes in corticosteroid dose
e. Failure to return for evaluation due to death or deteriorating condition
f. Clear progression of non-measurable disease

Stable Disease (SD): Requires all the following:
a. Does not qualify for complete response, partial response, or progression
b. Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared to baseline scan. In the event that the corticosteroid dose had been increased, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose
c. Clinical stability

6.1.4.2 Evaluation of Best Overall Response

If there is uncertainty regarding whether there is progression, the patient may continue on treatment and remain under close observation. If subsequent evaluations suggest that the patient is progressing, the date of progression should be the time point at which this issue was initially raised. Patient will discontinue from the study if s/he meets the study discontinuation criteria. According to these criteria, patients with

progression in some instances are allowed to remain on study therapy. The RANO Response Criteria are summarized in Table X.

Table 6. Summary of RANO Response Criteria

	CR	PR	SD*	PD
T1-Post Contrast Enhancement	None	≥ 50% Decrease	< 50% Decrease, < 25% Increase	≥ 25% Increase
T2 FLAIR	Stable or Decreased	Stable or Decreased	Increased	Stable or Decreased
New Lesion	None	None	Present	None
Corticosteroids	None	Stable or Decreased	N/A	Stable or Decreased
Clinical Status	Stable or Improved	Stable or Improved	Stable or Improved	Worsened
Requirement for Response	All	All	All	Any

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease
N/A: Increase in corticosteroids alone will not determine progressive disease in the absence of persistent clinical deterioration

6.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or 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 since the treatment started). The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Note that be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed at least 4 weeks after the criteria for response are first met.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

6.1.6 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression.

6.1.7 Overall Survival

Overall survival (OS) is defined as the time from randomization until death from any cause.

6.2 Safety/Tolerability

Response analyses will be performed for all subjects having received at least one dose of study therapy. The study will use the CTCAE version 5.0 for reporting of adverse events. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

7.0 ADVERSE EVENTS

7.1 Experimental Therapy

For the most recent safety update, please refer to the current Investigator's Brochure for tofacitinib.

7.1.1 Contraindications

- Pregnancy
- Active infection
- Significant history for and/or active thromboembolic events (e.g. DVT, PE, or strokes)
- Significant history for coagulopathy
- Live vaccines should not be given while patient is on tofacitinib
- Biological DMARDs such as JAK antagonists, IL-1R antagonists, IL-6R antagonists, anti-CD20 monoclonal antibodies, IL-17 antagonists, IL-12/23 antagonists, anti-integrins, selective co-stimulation modulators, and potent immunosuppressant such as azathioprine, 6-mercaptopurine, tacrolimus (Prograf), and cyclosporines

7.1.2 Special Warnings and Precautions for Use

- Use caution with patients who are concomitant medications that might predispose them for opportunistic infections (e.g. corticosteroids), as well as those with similar preexisting conditions (e.g. diabetes).
- Patients should be tested for latent or active tuberculosis infection prior to initiation. Active tuberculosis should be treated before initiation of tofacitinib.
- Viral reactivation has been reported in a handful of tofacitinib studies (e.g. herpes zoster virus).
- DVTs are very common. Ensure proper prophylaxis is present for patients who are being treated with tofacitinib.
- Use tofactinib with caution in patients who are at increased risk of GI perforation (e.g. patients with a history of diverticulitis). New-onset abdominal symptoms after initiation of tofacitinib warrants immediate evaluation.
- Tofacitinib has been shown to modestly reduce vaccine antibody responses. Use with caution when patients are receiving vaccination.

7.1.3 Interaction with other medications

- Tofacitinib exposure is increased when co-administered with potent CYP3A4 inhibitors (e.g. clarithromycin, ketoconazole, voriconazole) or when administration of one or more concomitant medications results in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g. fluconazole).
- Tofacitinib exposure is decreased when co-administered with potent CYP3A4 inducers (e.g. carbamazepine, phenytoin, rifampin).

7.1.4 Adverse Reactions

In rheumatoid arthritis studies, the most commonly reported adverse reactions during the first 3 months were: headache, upper respiratory tract infections, nasopharyngitis, hypertension, nausea, and diarrhea. The proportion of patients who stopped treatment due to any adverse reaction during the first 3 months was 3.8%, with the most common infections resulting in therapy discontinuation being herpes zoster and pneumonia. (For a detailed list of adverse reactions collated from clinical trials on tofacitinib, please refer to the Investigator's Brochure, Table 7.2).

7.2 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. Adverse events are assessed 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 subject safety and care.

All subjects experiencing an adverse event, regardless of its relationship to study therapy, will be monitored until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline or is stable in the opinion of the investigator
- there is a satisfactory explanation other than the study therapy for the changes observed; or
- death.

7.2.1 Definitions

An adverse event is defined as any untoward or unfavorable medical occurrence in a human research study participant, including any abnormal sign (for example, abnormal physical exam, imaging finding or clinically significant laboratory finding), symptom, clinical event, or disease, temporally associated with the subject's participation in the research, whether or not it is considered related to the subject's participation in the research.

Adverse events encompass clinical, physical, and psychological harms. Adverse events occur most commonly in the context of biomedical research, although on occasion, they can occur in the context of social and behavioral research. Adverse events may be expected or unexpected.

Acute Adverse Events

Adverse events occurring in the time period from the signing of the informed consent, through 28 days post treatment will be considered acute adverse events.

Severity

Adverse events will be graded by a numerical score according to the defined NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0. Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined below.

- Grade 1: Mild
- Grade 2: Moderate

- Grade 3: Severe or medically significant but not immediately life threatening
- Grade 4: Life threatening consequences
- Grade 5: Death related to the adverse event

Serious Adverse Events

OHRP and UTSW HRPP define serious adverse events as those events, occurring at any dose, which meets any of the following criteria:

- results in death
- is life-threatening (places the subject at immediate risk of death from the event as it occurred)
- results in inpatient hospitalization[1,2] or prolongation of existing hospitalization
- results in a persistent or significant disability/incapacity
- results in a congenital anomaly/birth defect; or
- based upon appropriate medical judgment, may jeopardize the subject's health, and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Note: A "Serious adverse event" is by definition an event that meets ***any*** of the above criteria. Serious adverse events may or may not be related to the research project. A serious adverse event determination does not require the event to be related to the research. That is, both events completely unrelated to the condition under study and events that are expected in the context of the condition under study may be serious adverse events, independent of relatedness to the study itself. As examples, a car accident requiring ≥24 hour inpatient admission to the hospital would be a serious adverse event for any research participant; likewise, in a study investigating end-stage cancer care, any hospitalization or death which occurs during the protocol-specified period of monitoring for adverse and serious adverse events would be a serious adverse event, even if the event observed is a primary clinical endpoint of the study.

[1]Pre-planned hospitalizations or elective surgeries are not considered SAEs. Note: If events occur during a pre-planned hospitalization or surgery, that prolong the existing hospitalization, those events should be evaluated and/or reported as SAEs.

[2] NCI defines hospitalization for expedited AE reporting purposes as an inpatient hospital stay equal to or greater than 24 hours. Hospitalization is used as an indicator of the seriousness of the adverse event and should only be used for situations where the AE truly fits this definition and NOT for hospitalizations associated with less serious events. For example: a hospital visit where a patient is admitted for observation or minor treatment (e.g. hydration) and released in less than 24 hours. Furthermore, hospitalization for pharmacokinetic sampling is not an AE and therefore is not to be reported either as a routine AE or in an expedited report.

7.2.2 Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs):

The phrase "unanticipated problems involving risks to subjects or others" is found, but not defined in the HHS regulations at 45 CFR 46, and the FDA regulations at 21 CFR 56.108(b)(1) and 21 CFR 312.66. For device studies, part 812 uses the term unanticipated adverse device effect, which is defined in 21 CFR 812.3(s). Guidance from the regulatory agencies considers unanticipated problems to include any incident, experience, or outcome that meets ALL three (3) of the following criteria:

- Unexpected in terms of nature, severity or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research

protocol and informed consent document; and (b) the characteristics of the subject population being studied

AND

- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research)

AND

- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

Follow-up

All adverse events will be followed up according to good medical practices.

7.3 Steps to Determine If a Serious Adverse Event Requires Expedited Reporting to the SCCC DSMC

Step 1: Identify the type of adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE v5).

Step 2: Grade the adverse event using the NCI CTCAE v5.

Step 3: Determine whether the adverse event is related to the protocol therapy. Attribution categories 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 *may NOT be related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported as indicated in the sections below.

Step 4: Determine the prior experience of the adverse event. Expected events are those that have been previously identified as resulting from administration of the treatment. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol (if applicable)
- the drug package insert (if applicable)
- the current Investigator's Brochure (if applicable)
- the Study Agent/Therapy Background and Associated Known Toxicities section of this protocol

7.3.1 Reporting SAEs and UPIRSOs to the Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC)

SAEs and UPIRSOs at all sites, which occur in research subjects on protocols for which the SCCC is the DSMC of record require reporting to the DSMC regardless of whether IRB reporting is required. All SAEs occurring during the protocol-specified monitoring

period and all UPIRSOs should be submitted to the SCCC DSMC within 5 business days of the study team members awareness of the event(s). In addition, for participating centers other than UTSW, local IRB guidance should be followed for local reporting of serious adverse events or unanticipated problems.

The UTSW study PI is responsible for ensuring SAEs/UPIRSOs are submitted to the SCCC DSMC Coordinator. This may be facilitated by the IIT project manager, study team, sub-site or another designee. Hardcopies or electronic versions of the eIRB Reportable Event report; FDA Form #3500A forms, or other sponsor forms, if applicable; and/or any other supporting documentation available should be submitted to the DSMC Coordinator. The DSMC Coordinator forwards the information onto the DSMC Chairman who determines if immediate action is required. Follow-up eIRB reports, and all subsequent SAE or UPIRSO documentation that is available are also submitted to the DSMC Chair who determines if further action is required. *(See Appendix III of the SCCC DSMC Plan for a template Serious Adverse Event Form which may be utilized).*

If the event occurs on a multi-institutional clinical trial coordinated by the UTSW Simmons Comprehensive Cancer Center, the IIT Project Manager or designee ensures that all participating sites are notified of the event and resulting action, according to FDA guidance for expedited reporting. DSMC Chairperson reviews all SAEs and UPIRSOs upon receipt from the DSMC Coordinator. The DSMC Chairperson determines whether action is required and either takes action immediately, convenes a special DSMC session (physical or electronic), or defers the action until a regularly scheduled DSMC meeting.

Telephone reports to: **Michael Youssef MD** +1 (864) 421-7031 michael.youssef@utsouthwestern.edu
Written reports to: **Michael Youssef MD** Department of Neurology and Oncology Harold C. Simmons Cancer Center 2201 Inwood Road, Dallas TX 75390 +1 (214) 648-5842 Michael.youssef@utsouthwestern.edu UTSW SCCC Data Safety Monitoring Committee Coordinator Email: SCCDSMC@utsouthwestern.edu Fax: 214-648-5949 or deliver to BLB.306 UTSW Institutional Review Board (IRB) Submit a Reportable Event via eIRB with a copy of the final sponsor report as attached supporting documentation.

Reporting Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs) to the UTSW HRPP

UTSW reportable event guidance applies to all research conducted by or on behalf of UT Southwestern, its affiliates, and investigators, sites, or institutions relying on the UT Southwestern IRB. Additional reporting requirements apply for research relying on a non-UT Southwestern IRB.

According to UTSW HRPP policy, UPIRSOs are incidents, experiences, outcomes, etc. that meet **ALL three (3)** of the following criteria:

1. Unexpected in nature, frequency, or severity (i.e., generally not expected in a subject's underlying condition or not expected as a risk of the study; therefore, not included in the investigator's brochure, protocol, or informed consent document),AND
2. Probably or definitely related to participation in the research, AND
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. Note: According to OHRP, if the adverse event is serious, it would always suggest a greater risk of harm.

For purposes of this policy, UPIRSOs include unanticipated adverse device effects (UADEs) and death or serious injury related to a humanitarian use device (HUD).

UPIRSOs must be promptly reported to the UTSW HRPP within 5 working days of study team awareness.

For research relying on a non-UT Southwestern IRB (external, central, or single IRB):

Investigators relying on an external IRB who are conducting research on behalf of UT Southwestern or its affiliates are responsible for submitting **LOCAL** UPIRSOs to the UT Southwestern IRB within 5 working days of study team awareness. Investigators must report to their relying IRB according to the relying IRB's policy. In addition, the external IRB's responses or determinations on these local events must be submitted to the UT Southwestern IRB within 10 working days of receipt.

Events NOT meeting UPIRSO criteria:

Events that do NOT meet UPIRSO criteria should be tracked, evaluated, summarized, and submitted to the UTSW HRPP/IRB at continuing review.

For more information on UTSW HRPP/IRB reportable event policy, see https://www.utsouthwestern.edu/research/hrpp/quality-assurance/

7.4 Stopping Rules

The study medication will be stopped if one of the following are met:

- Disease progression on two subsequent MRI brain done at least 28 days apart
- Patient must be greater than 3 months from radiation therapy completion
- Unacceptable toxicity from the study medication

8.0 DRUG/TREATMENT INFORMATION

8.1 Tofacitinib

- Other names for the drug(s): Xeljanz
- Classification - type of agent: Kinase inhibitor
- Mode of action: Selective inhibitor of the Janus kinase (JAK) family of kinases
- Storage and stability: For specific storage instructions refer to the product label

- Protocol dose: 10 mg twice daily
- Preparation: Pfizer will provide a commercial supply of Tofacitinib to the UT Southwestern Simmons Cancer Center Pharmacy
- Route of administration for this study: Oral
- Incompatibilities: None
- Availability: Provided by sponsor (Pfizer)
- Side effects: Refer to the agent's package insert for a comprehensive list of adverse events.
- Nursing implications: Female patients are advised to not breastfeed while receiving Tofacitinib

8.1.1 Return and Retention of Study Drug

The study drug will be destroyed by the UT Southwestern designated investigational drug service pharmacy in accordance with institutional protocols. No patient returned drug will be re-assigned to other patients or diverted to another person.

8.1.2 Study Drug Compliance

Tofacitinib will be administered orally, with full documentation of administration in the medical record and study records.

9.0 CORRELATIVES/SPECIAL STUDIES

The goal of the planned laboratory correlative studies is to determine if the level of EGF receptor or EGFR ligands correlates with the response to tofacitinib. Submission of samples for correlative studies is mandatory.

9.1 Sample Collection Guidelines

Most patients with GBM get a surgical resection at the time of diagnosis. This study is focused on recurrent GBM patients who may or may not have a second surgical resection. We will use paraffin embedded tissue from the original resection to determine the level of EGFR and EGFR ligands. The slides will be obtained with help from Neuropathology and de-identified slides will be picked up by a technician from the Habib lab and delivered to Habib Lab (NL10.110K) for further analysis.

Samples will be collected at the following time points (+/- window):

We will use paraffin embedded tissue from the original resection. Thus, the samples have been collected prior to tofacitinib being administered.

In those cases, where a 2nd resection has been done at the time of recurrence, we will also examine paraffin embedded tissue from the 2nd resection to examine the same parameters (EGF receptor and ligands).

9.2 Planned Biospecimen Studies

Our preliminary data indicate that EGF receptor levels and EGFR ligand levels regulate the invasiveness of GBM. In GBMs that express a high level of EGFR, EGFR ligands suppress invasion and confer a better prognosis in preclinical models. Studies of tofacitinib in preclinical models suggest that tofacitinib suppresses invasion in GBMs that have low levels of EGFR ligand. Thus, we anticipate that tofacitinib will be more effective in EGFR ligand poor tumors. As noted, paraffin embedded tissues will be used to quantitate EGFR and EGFR ligands using quantitative real time PCR.

9.3 Specimen Banking

Paraffin embedded tissues are stored in the Department of Pathology and slides will be obtained for specific tumors. If unused for the studies, proposed studies, the slides will be discarded.
Amyn Habib (Associate Professor of Neurology at UT Southwestern) will be responsible for requesting clinical specimens from Dr. Kimmo Hatanpaa (Professor of Pathology at UT Southwestern). We do not anticipate requesting tissue from any other institution.

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

This is a 2-arm, non-randomized, open label pilot study.

10.1.1 Primary Objective

To determine the progression-free survival (PFS) of the study cohort.

10.1.2 Secondary Objectives

To assess the safety and tolerability of Tofacitinib in recurrent GBM patients.
To determine the overall survival (OS) of the study cohort.
To determine the radiographic responses of the patients in the study cohort by RANO criteria.

10.1.3 Correlative Study Objectives

To determine predictive and pharmacodynamic biomarkers of JAK inhibitor therapy.

10.2 Sample Size and Accrual

Sample size justification is not necessary due to the exploratory nature of the pilot study. The sample size of 20 patients was determined by the feasibility of the study.

10.3 Data Analyses All analyses will be performed in R (version 4.0.5 or newer). The analysis of PFS and OS will be performed using the survival package in R. Kaplan-Meier curves will be visualized using the survminer package in R.

The primary outcomes, PFS of the study cohort, a Kaplan-Meier curve will be fit to the (potentially right-censored) time to disease progression. Results of this analysis will include the estimated median PFS and corresponding 95% confidence interval. Similarly, to determine the OS of the study cohort, a Kaplan-Meier curve will be fit to the (potentially right-censored) time until death, resulting in an estimated median OS and corresponding 95% confidence interval.

To determine predictive and pharmacodynamic biomarkers of JAK inhibitor therapy, differences in EGF receptor and EFGR ligands between those who response versus those who do not respond to JAK inhibitor will be tested using a two-sample t-test when normality assumptions are verified and the Mann-Whitney U test otherwise. Additionally, receiver operating characteristic curves will be fit to determine optimal cut-points for the EGF receptor and EGFR ligands to distinguish between responders and non-responders. The resulting area under the curve and accuracy measures (e.g., sensitivity, specificity, positive predictive value, and negative predictive value) will be computed to determine the ability of the predictive and pharmacodynamic biomarkers to predict JAK inhibitory therapy response. To determine the predictive power of the cut-point on a sample of subjects used to estimate the sample (i.e., training sample), as well as a sample of subjects not included in the model estimation (i.e., testing sample), we will define a training set of 90% of subjects (18) and a testing set of 10% of subjects (2). That is, the optimal cut-point will be estimated based on 90% of the subjects and will then be used to predict treatment response in the remaining 10% of subjects. This process will be performed for all possible combinations of testing sample (190), and the resulting averages and standard deviations of the in-sample (i.e., based on the training sample) and out-of-sample (i.e., based on testing sample) measures of accuracy will be reported. The resulting optimal cut-points and their associated in-sample and out-of-sample predictive ability will be reported.

11.0 STUDY MANAGEMENT

11.1 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 by the UTSW COI Committee and IRB according to UTSW Policy on Conflicts of Interest. All investigators will follow the University conflict of interest policy.

11.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB must approve the consent form and protocol.

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 subject 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 subject and the investigator is assured that the subject understands the implications of participating in the study, the subject 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 subject and by the person who conducted the informed consent discussion.

11.3 Registration/Randomization Procedures

Prior to registration, eligibility criteria must be confirmed with the Study Coordinator. To register a subject, contact the Study Coordinator Monday-Friday 9am to 6pm.

New subjects will receive a number beginning with 001 upon study consent such that the first subject consented is numbered 001, the second subject consented receives the number 002, etc.

Upon confirmation of eligibility and enrollment as per the afore-mentioned instructions, the subject will be assigned a secondary number in the order of enrollment. For example, subject 001 will become 001-01 upon enrollment. If subject 002 screen fails, and subject 003 is the next subject enrolled, subject 003 will become 003-02 and so-on.

Each newly consented subject should be numbered using the schema provided above. Upon registration, the registrar will assign the additional registration/randomization code according to the numbering schema outlined above, which should then be entered as the patient study id in Velos upon updating the status to enrolled.

The numbering schema should clearly identify the site number; the sequential number of the subject enrolled as well as the status of the subjects enrolled so that the number of subjects consented versus the number of subjects actually enrolled may be easily identified.

11.4 Data Management and Monitoring/Auditing

REDCap is the UTSW SCCC institutional choice for the electronic data capture of case report forms for SCCC Investigator Initiated Trials. REDCap will be used for electronic case report forms in accordance with Simmons Comprehensive Cancer Center requirements.

Toxicity and dose escalation reviews will be performed through the duration of the trial. These reviews will be documented by the Clinical Research Office and the reports will be distributed to the SCC-DSMC, if needed.

The UTSW Simmons Comprehensive Cancer Center (SCCC) Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UTSW SCCC clinical trials. As part of that responsibility, the DSMC reviews all serious adverse events and UPIRSOs in real time as they are reported and reviews adverse events on a quarterly basis. The quality assurance activity for the Clinical Research Office provides for periodic auditing of clinical research documents to ensure data integrity and regulatory compliance. A copy of the DSMC plan is available upon request.

The SCCC DSMC meets quarterly and conducts annual comprehensive reviews of ongoing clinical trials, for which it serves as the DSMC of record. The Quality Assurance Coordinator (QAC) works as part of the DSMC to conduct regular audits based on the level of risk. Audit findings are reviewed at the next available DSMC meeting. In this way, frequency of DSMC monitoring is dependent upon the level of risk. Risk level is determined by the DSMC Chairman and a number of factors such as the phase of the study; the type of investigational agent, device or intervention being studied; and monitoring required to ensure the safety of study subjects based on the associated risks of the study. Protocol-specific DSMC plans must be consistent with these principles.

11.4.1 Trial Monitoring

Trial monitoring will be conducted according to the study-specific monitoring plan. For guidance on creating a monitoring plan, refer to the UTSW SCCC IIT Management Manual.

11.5 Adherence to the Protocol

Except for an emergency situation, in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.5.1 Exceptions (also called single-subject exceptions or single-subject waivers): include any departure from IRB-approved research that is *not due to an emergency* and is:

- intentional on part of the investigator; or
- in the investigator's control; or
- not intended as a systemic change (e.g., single-subject exceptions to eligibility [inclusion/exclusion] criteria)
- **Reporting requirement***: Exceptions are non-emergency deviations that require ***prospective*** IRB approval before being implemented. Call the IRB if your request is urgent. If IRB approval is not obtained beforehand, this constitutes a major deviation. For eligibility waivers, studies which utilize the SCCC-DSMC as the DSMC of record must also obtain approval from the DSMC prior to submitting to IRB for approval.

11.5.2 Emergency Deviations: include any departure from IRB-approved research that is necessary to:

- avoid immediate apparent harm, or
- protect the life or physical well-being of subjects or others
- **Reporting requirement***: Emergency deviations must be promptly reported to the IRB within 5 working days of occurrence.

11.5.3 Serious Noncompliance (formerly called **major deviations** or **violations**): include any departure from IRB-approved research that:

- Increase risk of harm to subjects; and/or

adversely affects the rights, safety, or welfare of subjects (any of which may also be an unanticipated problem); and/or

- adversely affects the integrity of the data and research (i.e., substantially compromises the integrity, reliability, or validity of the research)
- **Reporting requirement***: Serious Noncompliance must be promptly reported tothe IRB within 5 working days of discovery.

11.5.4 Continuing Noncompliance: includes a pattern of repeated noncompliance (in or more protocols simultaneously, or over a period of time) which continues **after** initial discovery, including inadequate efforts to take or implement corrective or preventive action within a reasonable time frame.

- **Reporting requirement***: Continuing Noncompliance must be promptly reported to the IRB within 5 working days of discovery.

11.5.5 Noncompliance (that is neither serious nor continuing; formerly called minor deviations) any departure from IRB-approved research that:

- Does not meet the definition of serious noncompliance or continuing noncompliance
- **Reporting requirement***: Noncompliance that is neither serious nor continuing should be tracked and summarized the next IRB continuing review, or the notice of study closure, whichever comes first.

*Reporting Requirements reflect UTSW HRPP/IRB guidelines; participating sites should follow the reporting guidelines for their IRB of record.

11.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. A summary of changes document outlining proposed changes as well as rationale for changes, when appropriate, is highly recommended. 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 IRB for approval prior to implementation.

11.7 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 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.

11.8 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 may 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.

12.0 REFERENCES

1. Karaman MW, Herrgard S, Treiber DK, et al. A quantitative analysis of kinase inhibitor selectivity. *Nat Biotechnol* 2008;26:127-32.

13.0 APPENDICES

APPENDIX A. KARNOFSKY PERFORMANCE STATUS SCALE RATING CRITERIA (%)

	100	Normal no complaints; no evidence of disease.
Able to carry on normal activity and to work; no special care needed.	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
	70	Cares for self; unable to carry on normal activity or to do active work.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	60	Requires occasional assistance but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
	40	Disabled; requires special care and assistance.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

APPENDIX B. STUDY MEDICATION PILL DIARY—Temozolomide and Tofacitinib

Please bring this medication diary and ALL BOTTLES of the study drug Tofacitinib (Including empty bottles) to each clinic visit.

INSTRUCTIONS

Take the doses of Tofacitinib twice daily at approximately the same times every day. If you vomit or miss a dose, take the next dose at the next scheduled time. Do **NOT** chew, crush, or split the Tofacitinib tablets before swallowing. Do **NOT** ingest the tablets if they are broken, cracked, or otherwise not intact. Avoid grapefruit and grapefruit juice. On the chemotherapy calendar, please also note when you have taken your chemotherapy.

Please contact Tammy Ricklefs, RN at Tammy.ricklefs@utsouthwestern.edu / +1 (214) 519-1716 if you have any questions or concerns about your treatment.

STUDY MEDICATION (Tofacitinib + Temozolomide) DIARY

Name: _____ Subject ID: _____Cycle Number: _____

DATE	DAY OF CYCLE	TIME TAKEN AM/PM	# OF TABLETS TAKEN*	REASON FOR MISSED DOSE	COMMENTS
_____	***Example***	***7:15 AM***	***1***	***Missed 2 because I forgot***	_____
	1				
	1				
	2				
	2				
	3				
	3				
	4				
	4				
	5				
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TEMOZOLOMIDE DIARY

Name: _____ Subject ID: _____Cycle Number: _____

DATE	DAY OF CYCLE	TIME TAKEN AM/PM	# OF TABLETS TAKEN*	REASON FOR MISSED DOSE	COMMENTS
_____	***Example***	***7:15 AM***	***1***	***Missed 2 because I forgot***	_____
	1				
	2				
	3				
	4				
	5				

APPENDIX C. STUDY MEDICATION PILL DIARY—Lomustine and Tofacitinib

Please bring this medication diary and ALL BOTTLES of the study drug Tofacitinib (Including empty bottles) to each clinic visit.

INSTRUCTIONS

Take the doses of Tofacitinib twice daily at approximately the same times every day. If you vomit or miss a dose, take the next dose at the next scheduled time. Do **NOT** chew, crush, or split the Tofacitinib tablets before swallowing. Do **NOT** ingest the tablets if they are broken, cracked, or otherwise not intact. Avoid grapefruit and grapefruit juice. On the chemotherapy calendar, please also note when you have taken your chemotherapy.

Please contact Tammy Ricklefs, RN at Tammy.ricklefs@utsouthwestern.edu / +1 (214) 519-1716 if you have any questions or concerns about your treatment.

STUDY MEDICATION (Tofacitinib) DIARY

Name: _____ Subject ID: _____Cycle Number: _____

DATE	DAY OF CYCLE	TIME TAKEN AM/PM	# OF TABLETS TAKEN*	REASON FOR MISSED DOSE	COMMENTS
_____	***Example***	***7:15 AM***	***1***	***Missed 2 because I forgot***	_____
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Lomustine DIARY

Name: _____ Subject ID: _____Cycle Number: _____

DATE	DAY OF CYCLE	TIME TAKEN AM/PM	# OF TABLETS TAKEN*	REASON FOR MISSED DOSE	COMMENTS
_____	***Example***	***7:15 AM***	***1***	***Missed 2 because I forgot***	_____
	1				