Onivyde (nanoliposomal irinotecan) and Metronomic Temozolomide for Patients With Recurrent Glioblastoma: A Phase IB/IIA Brown University Oncology Research Group Study

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1.0 OBJECTIVE

1.1 Primary Objective

1.1.1. To evaluate the maximum tolerated dose of nanoliposomal irinotecan with continuous low-dose temozolomide for patients with recurrent glioblastoma.

1.1.2 To assess the preliminary response rate and progression free survival of nanaliposomal irinotecan with continuous low-dose temozolomide in patients with recurrent glioblastoma.

1.2 Secondary Objectives

1.2.1 To evaluate the safety of nanoliposomal irinotecan with continuous low-dose temozolomide.

2.0 BACKGROUND

Glioblastoma: There are approximately 14,000 new cases of malignant brain tumors diagnosed each year in the United States.[1] Glioblastomas account for approximately 60 to 70% of malignant gliomas.[1] They are the most aggressive form of primary brain tumors and are characterized by areas of microvascular proliferation, necrosis, or both.[2] Patients with high-grade glioma typically present with subacute and progressive neurologic signs and symptoms that vary according to the location of the tumor within the brain. Headache is the most common presenting symptom, which is present in over half of patients at time of diagnosis.[3]

Temozolomide and Radiation is the Standard First-Line Treatment for GBM: High-grade gliomas are rapidly progressive tumors that are best managed with a combined modality approach, incorporating maximal surgical resection, adjuvant postoperative radiation therapy, and adjuvant chemotherapy.[3] In a phase III study by the European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) compared standard radiation alone to radiation and temozolomide. Temozolomide was administered daily throughout radiation then continued as a maintenance for 5 consecutive days of a 28-day cycle. There was an increase in median survival (14.6 months vs 12.1 months, $p < 0.0001$) with the addition of temozolomide to radiation as compared to radiation alone.[4] Furthermore, there was an improvement in 2-year survival with temozolomide and radiation as compared to radiation alone, 26.5% vs 10.4%, respectively. [4]

Metronomic Temozolomide For Recurrent GBM: Relapse after first line therapy is inevitable. Rechallenge with dose-dense TMZ schedules such as continuous dose (metronomic) schedules for recurrent GBM is recommended for patients who relapse on standard maintenance temozolomide.[5,6] Continuous therapy with metronomic regimens may inhibit tumor angiogenesis through the suppression of tumor endothelium regeneration and MGMT depletion of the tumor endothelium.[7-9]

Multiple studies have demonstrated modest benefit with continuous low-dose TMZ and this has become a standard treatment in recurrent GBM.[10,11] In a phase II study by Wick et al, 90 patients with recurrent GBM received temozolomide weekly, 1 week on and 1 week off. The median survival time from diagnosis of progression was 38 weeks (95% CI, 30 to 46 weeks), and the 1-year survival rate from progression was 23%.[11] O6-methylguanine DNA methyltransferase (MGMT) gene promoter methylation in the tumor tissue

was not associated with longer PFS (log-rank P = .37) implying that continuous TMZ is also active in patients with tumors lacking MGMT gene promoter methylation.

Woo et al administered TMZ daily at 50 mg/m^2/day in 30 patients with recurrent GBM. The median progression-free survival was 2 months (range, 0.5–16). At 6 months, PFS was 20%. The median overall survival from the start of therapy to death was 6 months (95% CI : 5.1–6.9).[12] The response rate is approximately 5-10%. This continuous low dose daily regimen (metronomic schedule) is probably the most commonly utilized regimen across the country and the standard practice within the Brown University Oncology Research Group affiliated hospitals.

More Effective Agents in Combination with Metronomic TMZ are needed. While metronomic TMZ is commonly used in GBM, the benefits are very modest and more effective agents are needed. Unfortunately, the addition of bevacizumab to continuous low-dose TMZ was not superior to temozolomide alone in terms of progression-free or overall survival.[13]

Irinotecan In GBM: Irinotecan has modest activity in GBM. In a study by Friedman et al, 9 of 60 patients (16%) with progressive or recurrent GBM had a partial response to irinotecan.[14] A randomized study of 167 patients evaluated the efficacy of bevacizumab, alone and in combination with irinotecan in patients with recurrent glioblastoma.[15] In the bevacizumab-alone and the bevacizumab-plus-irinotecan groups, estimated 6-month progression-free survival rates were 42.6% and 50.3%, respectively; objective response rates were 28.2% and 37.8%, respectively; and median overall survival times were 9.2 months and 8.7 months.

The nanoliposomal irinotecan More Effectively Crosses the Blood Barrier: Irinotecan has modest activity in glioblastoma. The blood brain barrier markedly reduces drug absorption preventing irinotecan the opportunity to reach its target in the brain.[16] Nanoliposomal irinotecan is a nanoliposomal encapsulation of irinotecan. A nanoliposome, or submicron bilayer lipid vesicle, is a new technology for the encapsulation and delivery of bioactive agents. Nanoliposomes improve the solubility and bioavailable of irinotecan markedly increasing the ability of irinotecan to cross the blood brain barrier. For example Noble et el, evaluated a nanoliposomal irinotecan as an intravenous treatment in an intracranial U87MG brain tumor model in mice, and irinotecan and SN-38 levels were analyzed in malignant and normal tissues.[17] Tissue analysis demonstrated favorable properties for nanoliposomal irinotecan, including a 10.9-fold increase in tumor AUC for drug compared with free irinotecan and 35-fold selectivity for tumor versus normal tissue exposure.[17]

Onivyde is FDA Approved in Advanced Pancreatic Cancer: The NAPOLI-1 trial randomized 417 patients with metastatic pancreatic adenocarcinoma that progressed after treatment with gemcitabine-based chemotherapy. Patients received either the nanoliposomal irinotecan (Onivyde) as a single agent, in combination with 5-Fluorouracil and leucovorin (5-FU/LV), or 5-FU/LV alone (control arm). The median survival in the combination therapy arm with Onivyde/5-FU/LV was

(6.1 vs 4.2 months; unstratified hazard ratio [HR], 0.67 [95% confidence interval

(CI), 0.49-0.92]; P = 0.012).[18] There was also an improvement in PFS to a median of 3.1 months with the irinotecan liposomal plus 5-FU/LV group as compared with 1.5 months for those receiving 5-FU/LV alone.[18] These results led to FDA approval for Onivyde.

Rationale for Combining nanoliposomal irinotecan and Temozolomide: Multiple in-vitro and clinical trials support the rationale for combining a topoisomerase I inhibitor such as irinotecan and an alkylating agent such as temozolomide.[19-21] The principle mechanism of action of a topoisomerase I inhibitor is mainly S phase specific inhibiting DNA replication. In contrast an alkylating agent directly damages DNA. The combination of a topoisomerase inhibitor with an alkylating agent is a rational, established strategy for increasing tumor-cell kill.[19-21]

Protocol Rationale: New treatments are greatly needed for patients with recurrent glioblastoma. Metronomic temozolomide is a standard treatment option but has, at best, modest activity. The nanoliposomal irinotecan may be much more active than the parent compound irinotecan since nanoliposomal irinotecan's ability to cross the blood brain barrier is improved. The combination of a topoisomerase inhibitor and an alkylating agent has strong preclinical and clinical rationale. This phase I study will establish the MTD of the combination of nanoliposomal irinotecan in combination with temozolomide and preliminary clinical efficacy of the combination of nanoliposomal irinotecan and metronomic temozolomide.

3.0 PATIENT ELIGIBILITY

3.1 Conditions for Patient Eligibility

3.1.1 Histologically confirmed glioblastoma multiforme (gliosarcoma also eligible), Pathology report to be sent to BrUOG.

3.1.2 Progression or recurrence after at least one line of therapy. Patient must have received temozolomide and radiation but it is not required that they were given concurrently. This does not include clinical progression.

3.1.3 Age ≥18 years

3.1.4 Karnofsky performance score ≥ 60

3.1.5 Life expectancy >12 weeks as noted by treating investigator

3.1.6 Laboratory results requirements

- Absolute neutrophil count (ANC) ≥ 1500/mm3.
- Platelets (Plt) ≥ 100,000/mm3
- Hemoglobin (Hgb) ≥ 9.0 g/dL
- Total bilirubin ≤ 1x ULN
- Albumin levels ≥ 3.0 g/dL
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN
- Serum creatinine ≤ 1.5 x ULN

3.1.7 . Not pregnant and not nursing. Women of child bearing potential must have a negative serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 7 days prior to Day 1 of treatment. Post-menopausal women (surgical menopause or lack of menses ≥12 months) do not need to have a pregnancy test, please document status.

3.1.8. Confirmation of informed consent.

3.1.9 . Men and women of childbearing potential enrolled in this study must agree to use adequate barrier birth control measures during the course of the study and for at least 2 months after the last treatment on study.

3.1.10 Recovered (≤ grade 1) from clinically significant effects of any prior surgery, radiotherapy or other anti-neoplastic therapy, except alopecia or hematological laboratory values (see 3.1.6 for required values for the trial).
3.1.11 Stable corticosteroid dose at least 7 days prior to day 1
3.1.12 Patient must have assessable (measurable) disease at baseline by brain MRI. Must be contrast enhancing. The tumor size will be measured in millimeters and is the largest cross-sectional area using perpendicular measurements of contrast enhancing abnormality.
3.2.13 Patient must be able to tolerate brain MRI with contrast

3.2 Exclusion Criteria

3.2.1 Non-GBM primary invasive malignant neoplasm that is considered by treating investigator to likely cause death in the next 5 years.
3.2.3 Radiation therapy or cytotoxic chemotherapy or biologics or immunotherapy within previous three weeks from day 1 of drug (no anticancer treatment of any kind within 3 weeks of day 1 of drug- steroids are acceptable if stable dose per 3.1.11).
3.2.4 Patient not to be receiving any cancer therapy or investigational anti-cancer drug.
3.2.5 Evidence of an active infection requiring intravenous antibiotic therapy
3.2.6 Any medical condition that in the opinion of the Investigator may interfere with a subject's participation in or compliance with the study. Must receive confirmation in writing from treating MD.
3.2.7 Pregnant or breast feeding; females of child-bearing potential must test negative for pregnancy at the time of enrollment based on serum pregnancy test.
3.2.8 Unwillingness or inability to follow the procedures required in the protocol, site to have documentation to confirm at time of registration that this is not the case.
3.2.9 Patient with a history of Gilbert's disease or known UGT1A1*28 allele. (Assessment for the UGT1A1*28 allele is not required for protocol entry.) Documentation required at time of study entry by treating MD.
3.2.10 myocardial infarction, unstable angina pectoris, stroke within 6 months of study registration.
3.2.11 NYHA Class III or IV congestive heart failure
3.2.12 Known hypersensitivity to any of the components of nanoliposomal irinotecan , other liposomal products, or temozolomide. Must be documented by treating MD.
3.2.13 Investigational anticancer therapy administered within 4 weeks of day 1 (the first scheduled day of dosing in this study). Site must submit all prior investigational agents with last dose administered and half-life for BrUOG review.
3.2.14 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, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines and are not allowed. All recent vaccines (within 30 days) to be listed on conmed log and submitted to BrUOG.
3.2.15 Use of strong CYP3A4 inducers is not allowed and patients must be off any of these exclusionary products for ≥ 2 weeks from day 1. The use of strong CYP3A4 inducers (rifampin, phenytoin, carbamazepine, rifabutin, rifapentine, phenobarbital, St. John's wort, nevirapine, fosphenytoin, pentobarbital, primidone, enzalutamide, lumacaftor, mitotane, apalutamide, quinine) should not be used during the trial. If possible, substitute non-enzyme inducing therapies at least 2 weeks prior to treatment day 1.

3.3 Re-Screening:
Re-screening is defined in this protocol as screening a patient for this trial, once they have been found to not meet study eligibility criteria, outside of the 28-day screening window. While in the 28 day screening window, the patient may be screened multiple times (i.e. labs may be drawn and re-drawn), however, if a patient signs consent and then screen fails (does not meet the eligibility criteria) and the treating MD requests that the patient be re-screened outside of the 28 day screening window, sites are to contact BrUOG who will assess patients on a case by case basis. Depending on many diverse factors including the conditions that are being evaluated, the reasons why patient initially screen failed, and the nature of the initial results, re-screening may or may not be medically/scientifically appropriate. BrUOG should be made aware of such a situation with at least 72 hours and provided with information on screen-failure.

4.0 TREATMENT
Cycle = 2 weeks (14 days)

Temozolomide: 50mg/m^2/day until disease progression. Even though temozolomide will be given continuously, data will be captured by cycle with study drug. See section 5.3 for dose reduction information. Patients to receive enough TMZ pills for 2 cycles at a time (with refills on the prescription) and to align with the standard manner in which TMZ is prescribed. However, in order for research staff to confirm drug compliance and that a new cycle can begin, patients are encouraged to bring in TMZ and drug diary at the beginning of each new cycle. If a patient requires a reduced dose of TMZ in the middle of their prescription (prior to a new 28 day supply being written), the treating physician and research staff will communicate the dose reduction and manner in which the patent must take their pills for the remaining days of the drug supply.

	Dose Level -1	Dose Level 1
Temozolomide	25mg/m2/day	50mg/m2/day

Nanoliposomal irinotecan :
Dose Level 1 50mg/m^2 IV every 2 weeks
Dose Level 2 70 mg/m^2 IV every 2 weeks
Dose Level 3 80mg/m^2 IV every 2 weeks

	Dose Level -1	Dose Level 1	Dose Level 2	Dose Level 3
Nanoliposomal irinotecan	43 mg/m2, day 1	50 mg/m2, day 1	70 mg/m2, day 1	80 mg/m2, day 1

Doses do not need to be re-calculated unless there is a 10% change in weight or at the discretion of the treating physician if done more frequently.

(If nanoliposomal irinotecan dose level 1 exceeds the definition of maximum tolerated dose, as described below, then dose level -1 of nanoliposomal irinotecan, 43mg/m^2 IV every 2 weeks with temozolomide 50mg/m^2/day will be investigated.)

Nanoliposomal irinotecan will be administered by IV infusion over approximately 90 minutes. One cycle is 14 days, subsequent doses should be administered on the first day of each cycle +/- 3 days. An additional 1 day is provided for a holiday.

Three patients will be accrued to level 1. If no dose limiting toxicities are observed following completion of 4 weeks (2 cycles) of treatment then accrual to dose level 2 will proceed (patients must be evaluated prior to their cycle 3 treatment and this will be used to confirm DLTs). If a DLT is observed in one of the first 3 patients in a dose level, then accrual for that level will be expanded to 6 patients. Accrual will continue in this way until the MTD of nanoliposomal irinotecan with temozolomide 50mg/m^2/day is determined. Two or more instances of DLT in a cohort of 6 patients will result in the preceding dose level being defined as the MTD. If two or more instances of DLT in a cohort of 6 patients occurs in dose level 1 then dose level -1 of nanoliposomal irinotecan will be investigated. After determination of the MTD, the final cohort will be expanded so that a total of 25 patients are treated on study. The final cohort will be treated at the MTD.

If a patient is unable to receive 4 weeks of treatment (2 cycles) for reasons other than dose limiting toxicity, they will be replaced in a cohort.

Premedication

All patients must be premedicated prior to nanoliposomal irinotecan infusion with standard doses of dexamethasone and a 5-HT3 antagonist or other anti-emetics as per standard institutional practices for irinotecan administration. Atropine may be prescribed prophylactically for patients who experienced acute cholinergic symptoms in previous cycles.

Premedication prior to temozolomide is not required and may be administered as per institutional standard of care.

5.0 TOXICITIES, DOSE MODIFICATIONS, AND MANAGEMENT

Toxicities will be recorded as adverse events on the Adverse Event case report form and must be graded using The National Cancer Institute's Common Toxicity Criteria (CTCAE) version 4.03 (Appendix C).

5.1 Treatment Delay

A new course of treatment (cycle) with nanoliposomal irinotecan and temozolomide should not begin until the following criteria are met.

- Platelets $\geq$ 100,000x10^9/L (100,000/mm^3)
- Granulocytes (ANC) $\geq$1.5x10^9/L (1,500/mm^3)
- Recovery from other clinically significant, treatment related non-hematologic toxicities to $\leq$ Grade 2

*please refer to section 5.2 for events that require dose reductions cycles 3-on*The treating physician may decide to hold treatment secondary to other toxicities even if deemed not related to treatment if the physician feels it is in the patient's best interest. This must be documented and submitted to BrUOG on treatment form and AE log.

If the patient does not meet these criteria at the start of a scheduled cycle, treatment should be delayed until these requirements are met.

Patients who require a treatment delay of more than 4 weeks due to toxicity will be removed from protocol treatment. Patients who require a treatment delay of more than 8 weeks not due to toxicity will be removed from protocol treatment.

If a patient is unable to receive 4 weeks of treatment (2 cycles) for reasons other than a dose limiting toxicity, they will be replaced in a cohort.

5.2 Definition of Dose Limiting Toxicities:

Dose limiting toxicities will be defined as the following toxicities occurring during the first 2 cycles (28 days) of therapies. If however a patient experiences one of the below toxicities after cycle 2 they will be dose reduced (both drugs), even though it will no longer be defined as a DLT.

- Grade 4 neutropenia (ANC < 500/mm^3) for > 7 days
- ANC <1000/mm^3 with fever or infection
- Platelets <25,000/mm^3
- Platelets <50,000/mm^3 requiring transfusion
- Grade 3 or 4 treatment related non-hematologic toxicities excluding alopecia.
    - Grade 3 nausea, vomiting or diarrhea will only be considered a dose limiting toxicity if it occurs for greater than 72 hours despite maximal medical support.
    - Grade 3 electrolyte abnormalities will not be considered dose limiting toxicities if the electrolyte disorder can be corrected to grade 2 or less within 72 hours.
    - A grade 4 electrolyte abnormality will be considered a DLT.
- Delay of treatment for > 2 weeks due to toxicity (do not score a second DLT for a treatment delay caused by the same event)

Patients can resume treatment post a dose limiting toxicity (with a dose level reduction to both drugs), once they have recovered from treatment related non-hematologic toxicities to ≤ grade 2 and their platelets count is ≥ 100,000x10^9/L (100,000/mm^3) and their ANC count is ≥1.5x10^9/L (1,500/mm^3). A patient is required to be removed from protocol treatment if treatment is held in cycles 1 or 2 for a DLT >4 weeks. Patient's removed from treatment for this reason would undergo off study assessments, followed by 30 day assessments and would be followed as per section 6.

Of note when a patient experiences a DLT both drugs must be held and then both must be reduced, but they may be reduced at different times if a patient is found to experience a DLT mid-cycle. If this occurs, the TMZ will be held until patient's toxicities resolve to criteria above, after-which the dose of TMZ will be reduced for the remainder of the cycle and then at the start of the next cycle the nanoliposomal irinotecan will be reduced.

Example 1: If prior to day 1 of a cycle a patient experiences a DLT, dosing will be held until criteria for treatment are met. Both drugs will then be reduced.

Example 2: If a patient meets dosing criteria day 1 the cycle will begin and patient will be treated day 1 with both drugs. Since TMZ is given on a continuous basis if a patient experiences a DLT on day 5 TMZ will be held until patient meets criteria for treatment and then TMZ will be dose reduced for the remainder of the cycle. Nanoliposomal irinotecan will be dose reduced at the next cycle.

5.3 Dose Modifications

Dose limiting toxicities are defined in the first two cycles of treatment. Patients experiencing a toxicity defined above in section 5.2 at any time on protocol treatment, will have a 1 dose level reduction of nanoliposomal irinotecan **and** temozolomide. Patients experiencing a second dose limiting toxicity will be removed from protocol treatment.

For patients whose treatment is held for grade 3 or 4 non-hematologic adverse events not related to treatment (which would be at treating physician's discretion and not required per study), dose reductions are not required when treatment is resumed.

Patients can resume treatment once they have recovered from other clinically significant, treatment related non-hematologic toxicities to ≤ Grade 2, their platelets count is ≥ $100{,}000 \times 10^9$/L ($100{,}000/mm^3$) and their ANC count is ≥1.5×10^9/L ($1{,}500/mm^3$). Patients can resume treatment post a dose limiting toxicity (with a dose level reduction to both drugs), once they have recovered from treatment related non-hematologic toxicities to ≤ grade 2 and their platelets count is ≥ $100{,}000 \times 10^9$/L ($100{,}000/mm^3$) and their ANC count is ≥1.5×10^9/L ($1{,}500/mm^3$). A patient is required to be removed from protocol treatment if treatment is held in cycles 1 or 2 for a DLT >4 weeks. Patient's removed from treatment for this reason would undergo off study assessments, followed by 30 day assessments and would be followed as per section 6.

If a patient experiences an event outlined in 5.2 after cycle 2, they will need to be dose reduced (both drugs), even though it will no longer be defined as a DLT.

Treatment:

Nanoliposomal irinotecan 1 cycle = 14 days

	Dose Level -1	Dose Level 1	Dose Level 2	Dose Level 3
Nanoliposomal irinotecan	43 mg/m2, day 1	50 mg/m2, day 1	70 mg/m2, day 1	80 mg/m2, day 1

Temozolomide: Daily x 14 days = 1 cycle

	Dose Level -1	Dose Level 1 (Starting dose level all)
Temozolomide	25mg/m2/day	50mg/m2/day

Patients who require more than one dose reduction will be removed from protocol treatment.

5.4 Management of nanoliposomal irinotecan Infusion Reactions

Infusion reactions will be defined according to the National Cancer Institute CTCAE (Version 4.03)

Grade 1: Mild transient reaction; infusion interruption not indicated; intervention not indicated

Grade 2: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic

medications indicated for <=24 hrs

Grade 3: Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae

Grade 4: Life-threatening consequences; urgent intervention indicated

Study site policies or the following treatment guidelines may be used (not required) for the management of infusion reactions.

Grade 1

- Slow infusion rate by 50%
- Monitor patient every 15 minutes for worsening of condition

Grade 2

- Stop infusion
- Administer diphenhydramine hydrochloride 50 mg IV, acetaminophen 650 mg orally, and oxygen
- Resume infusion at 50% of the prior rate once infusion reaction has resolved
- Monitor patient every 15 minutes for worsening of condition
- For all subsequent infusions, consider premedicating with diphenhydramine hydrochloride 25-50 mg IV

For patients who experience a Grade 1 or Grade 2 infusion reaction, future infusions may be administered at a reduced rate (over 120 minutes), at the discretion of the Investigator.

For patients who experience a second grade 1 or 2 infusion reaction, it is suggested but not required that you administer dexamethasone 10 mg IV. It is suggested that subsequent infusions should be premedicated with diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, and acetaminophen 650 mg orally.

Grade 3

- Stop infusion and disconnect infusion tubing from patient
- Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, bronchodilators for bronchospasm, and other medications or oxygen as medically necessary
- No further treatment with nanoliposomal irinotecan will be permitted

Grade 4

- Stop the infusion and disconnect infusion tubing from patient
- Administer epinephrine, bronchodilators or oxygen as indicated for bronchospasm
- Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV
- Consider hospital admission for observation

- No further treatment with nanoliposomal irinotecan will be permitted

See section 9.1.5 for Toxicity Considerations with nanoliposomal irinotecan

6.0 SCHEDULE OF EVALUATIONS / STUDY CALENDAR*The day an assessment (PE, labs, scan etc) is completed is day 0 for counting for example labs drawn on Friday can be used for Monday dosing as this is within 3 days*

Parameter	Pre-study (to be sent to BrUOG prior to registration)	Within 3days prior to Day 1 of Each Cycle (Every 2 weeks) [C]	Every 2 months during treatment	Off study (post completion of final cycle)+ 1 week	30 days post last dose of drug (+1 week)	FU[D]
Informed Consent (within 30 days of day 1) *pts are to be re-consented if ICF will be outside 30 day window	X					
History , Demographics (baseline only)	X					
Concomitant medication log	X	X		X		
Physical examination	X	X	X	X	X[G]	X
Weight	X	X	X	X		
Vital signs	X	X	X	X		
Toxicity Assessment	X	X	X	X	XF	
Performance Status	X	X	X	X	X[G]	
CBC, diff, platelet count	X (within 14 days)	X		X		
Na, K, BUN, Cr	X (within 14 days)	X				
AST, ALT, Bili, Albumin	X (within 14 days)	X				
Serum Pregnancy[E]	X (within 7 days of drug)					
MRI brain with contrast	X[A](within 28 days)		XH	X (not required for patients who had an MRI completed in prior 2 months)		X
EKG[B]	X					

Survival and Disease status			X		X	X

[A]- Brain MRI with contrast for disease assessment should be performed within 28 days of study entry. Each time: Report required to be sent to BrUOG.
[B]- EKG within 8 weeks of study entry. Report required.
[C] It is appropriate to use labs from screening for cycle 1 day 1, if labs are within 14 days (pregnancy must be within 7 days of drug day 1 as noted above for applicable patients). A physical exam within 7 days prior to cycle 1 day 1 may be utilized. Weight, vitals, PS, AE and conmed assessment can be used from screening for cycle 1 day 1 if within 14 days. Labs and physical exam (with weight, vitals, PS and AEs) for all subsequent cycles can be within 3 days prior to day 1 of treatment cycle (another 1 day is given for holiday).
[D]- For patients removed from protocol treatment due to toxicity(or other reason), without progression, follow-up until disease progression will include brain MRI, disease free and overall survival and physical approximately every 3 months (+/- 1 month). For patients who come off study for progression, overall survival is to be reported approximately every 3months (+/- 1 month). Follow-up will be for 2 years.
[E] post-menopausal women (surgical menopause or lack of menses $\geq$12 months) do not need to have a pregnancy test, document status
[F] Adverse event evaluation, inclusive of SAE evaluation, and Performance status assessment will be done 30 days (+1 week) post last dose of drug . SAEs occurring outside this 30 day window must be reported if the event is considered to be possibly related to the study drug. If a patient begins a new treatment, AE evaluation will be stopped unless the patient experiences an event that is thought to be possibly related to the study drug. SAE evaluation will not be stopped if patient begins a new treatment.
[G] Physical and performance status assessment to be done in coordination with 30 day toxicity assessment (+ 1 week allowed).
[H] MRI of brain with contrast to be done every 2 months (approximately after every 4 cycles) +1 month window.. More frequent MRI imaging is allowed per treating MD but all information must be sent to BrUOG.

7.0 RESPONSE ASSESSMENT:

7.1 Response Definition:

Response and progression will be evaluated in this study using standard criteria for patients with malignant gliomas. A major difference in response criteria for patients with brain tumors from measuring response in other solid tumors is the requirement that patients be on a stable or decreasing dose of corticosteroids when evaluating for response because of the potentially confounding impact of corticosteroids on contrast enhancement during brain tumor imaging. The tumor size will be measured in millimeters and is the largest cross-sectional area using perpendicular measurements of contrast enhancing abnormality.

Complete Response (CR): Complete disappearance of all enhancing tumor on MRI scans while, off corticosteroids, and neurologically stable or improved.

Partial Response (PR): $\geq$ 50% decrease in size of enhancing tumor on MRI scans, corticosteroids stable or reduced, and neurologically stable or improved.

Stable Disease (SD): Does not qualify for CR, PR, or PD.

Progression: $\geq$ 25% increase in the size of enhancing tumor or any new tumor; or neurologically worse, and steroids stable or increased.

Best Radiographic Response: The best response will be defined as the best radiographic response (CR, PR, SD, or PD) for patients evaluable for radiographic response while on study.

7.2 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).

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

7.3 Overall Survival and Progression Free Survival:
Overall survival and progression free survival will be measured from registration until death and time to progression, respectively (or time of withdrawal if patient withdraws consent).

8.0 PATIENT REGISTRATION

All patients will be registered through the Brown University Oncology Research Group Central Office. Eligibility Checklist with supporting documentation, On Study Form and the signed Patient Consent Form must be faxed to the BrUOG Central Office, Fax: (401) 863-3820, at the time of registration and prior to patient treatment.

Details of patient's study participation should be documented in clinic/file notes. The Brown University Oncology Research Group will provide case report forms, included in the appendix, for the recording and collection of data. In the event of corrections, each correction will be initialed and dated by the person making the correction. The investigator will sign the case reports to indicate that, to his/her knowledge, they are complete and accurate. Case report forms, flow sheets, off-study forms and follow-up forms should be mailed / faxed to:

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Phone: 401-863-3000
BrUOG @brown.edu

All support data must be sent in with the corresponding BrUOG forms. It is the treating physician's responsibility to review all data submitted to the BrUOG Central Office for accuracy and completeness and he/she must sign the off study form. Sites must confirm each element of inclusion and exclusion criteria and also provide support for all "pre-study" assessments on the schedule of evaluations table.

It is the treating physician's responsibility to review all data submitted to the BrUOG Central Office for accuracy and completeness.

9.0 PHARMACEUTICAL INFORMATION

9.1 Nanoliposomal irinotecan (Please note the label may reference the following: irinotecan liposome injection, MM-398, Onyvide). Onyvide=nanoliposomal irinotecan injection

9.1.1 Description of nanoliposomal irinotecan

MM-398 is irinotecan hydrochloride (also known as CPT-11) encapsulated in a nanoliposomal drug delivery system. It will be supplied as a sterile solution containing 4.3 mg/ml of irinotecan on the free base basis (equivalent to 5.0 mg/ml of irinotecan hydrochloride trihydrate) encapsulated in liposomes. Prior to administration, irinotecan liposome injection Injection drug product must be diluted in 5% Dextrose Injection or Normal Saline to a suitable volume for infusion. .Nanoliposomal irinotecan will be supplied by Ipsen Pharmaceuticals. Ipsen will be sending commercial supply of drug and the pharmacy will be required to label the drug with BrUOG 329 and a "for investigational use only" label.

9.1.2 Storage and Handling of nanoliposomal irinotecan

Nanoliposomal irinotecan must be stored refrigerated at 2 to 8°C, with protection from light. Light protection is not required during infusion. Nanoliposomal irinotecan must not be frozen. Responsible individuals should inspect vial contents for particulate matter before and after they withdraw the drug product from a vial into a syringe. They must contact the Sponsor or its designee if they notice a problem with the study drug. All emails should be sent to Ipsen and BrUOG for drug shipment issues, temperature excursions, expired drug, drug orders and anything else pertaining to the drug handling/storage.

Nanoliposomal irinotecan must be diluted prior to administration in 5% Dextrose Injection or Normal Saline (0.9% Sodium Chloride Injection) to a suitable volume for infusion. The diluted solution is physically and chemically stable for 6 hours at room temperature (15-30°C), but it is preferred to be stored at refrigerated temperatures (2-8°C), and protected from light. The diluted solution must not be frozen. Because of possible microbial contamination during dilution, it is advisable to use the diluted solution within 24 hours if refrigerated (2-8°C), and within 4 hours if kept at room temperature (15-30°C).

Drug order: There is no drug order form for this trial, an email from the Investigational pharmacist is required to be sent to Ipsen (and cc BrUOG) to order drug. The pharmacist may order as many vials as needed. It is noted that cartons may also be ordered. There are 20 vials in each carton.

It is required that with each drug order email the most up to date IRB approval letter be included or the drug order will not be processed.

Emails: Contact BrUOG at BrUOG@brown.edu for the most up to date email address and/or method to order drug for BrUOG 329

9.1.3 Packaging and Labeling of nanoliposomal irinotecan (Please note the label may reference the following: Onivyde, irinotecan liposome injection, MM-398)

The individual vials, as well as the outside of the cardboard container, will be labeled in accordance with local regulatory requirements. Ipsen will be sending commercial product and the pharmacy will be required to label the drug with a BrUOG 329 and a "for investigational use only" label.

Nanoliposomal irinotecan will be administered by IV infusion over approximately 90 minutes (this time frame may be extended secondary to an infusion reaction and as per information in section 5.4) as per the dose level the patient was assigned at the time of registration and until disease progression or withdrawal

Cycle duration is 2 weeks. The first cycle Day 1 is a fixed day; subsequent doses should be administered on the first day of each cycle +/- 3 days (an additional day is given for a holiday).

Prior to administration, the appropriate dose of nanoliposomal irinotecan) must be diluted in 5% Dextrose Injection solution (D5W) to a final volume of 500mL. Care should be taken not to use in-line filters or any diluents other than D5W. Nanoliposomal irinotecan can be administered using standard PVC-containing intravenous administration bags and tubing.

The actual dose of nanoliposomal irinotecan to be administered will be determined by baseline calculation of the patient's body surface area. Dose only needs to be re-calculated if there is a 10% change in weight or at the discretion of the treating MD. A +/- 5% variance in the calculated total dose will be allowed for ease of dose administration. Since nanoliposomal irinotecan vials are single-use vials, site staff must not store any unused portion of a vial for future use and they must discard unused portions of the product.

9.1.4 Premedication

All patients must be premedicated prior to nanoliposomal irinotecan infusion with standard doses of dexamethasone and a 5-HT3 antagonist or other anti-emetics as per standard institutional practices for irinotecan administration. Atropine may be prescribed prophylactically for patients who experienced acute cholinergic symptoms in the previous cycles.

9.1.5 Toxicity Considerations with nanoliposomal irinotecan

Data from previous nanoliposomal irinotecan studies does not show any unexpected toxicity when compared to the active ingredient, irinotecan, which has been studied extensively. The warnings and precautions for the use of irinotecan and the treatment procedures for managing those toxicities are provided below as applicable to nanoliposomal irinotecan.

Diarrhea

Irinotecan can induce both early and late forms of diarrhea that appear to be mediated by different mechanisms. Early diarrhea (occurring during or shortly after infusion of irinotecan) is cholinergic in nature. It is usually transient and only infrequently severe. It may be accompanied by symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyper-peristalsis that can cause abdominal cramping. For patients who experienced early cholinergic symptoms during the previous

cycle of nanoliposomal irinotecan,prophylactic administration of atropine will be given at the discretion of the investigator.

Late diarrhea (generally occurring more than 24 hours after administration of irinotecan) can be life threatening since it may be prolonged and may lead to dehydration, electrolyte imbalance, or sepsis. Late diarrhea should be treated promptly with loperamide, and octreotide should be considered if diarrhea persists after loperamide. Loss of fluids and electrolytes associated with persistent or severe diarrhea can result in life threatening dehydration, renal insufficiency, and electrolyte imbalances, and may contribute to cardiovascular morbidity. The risk of infectious complications is increased, which can lead to sepsis in patients with chemotherapy-induced neutropenia. Patients with diarrhea should be carefully monitored, given fluid and electrolyte replacement if they become dehydrated, and given antibiotic support if they develop ileus, fever, or severe neutropenia as per institutional standard practice

Neutropenia

Deaths due to sepsis following severe neutropenia have been reported in patients treated with irinotecan. Neutropenic complications should be managed promptly with antibiotic support. Patients, who are known to have experienced Grade 3 or 4 neutropenia while receiving prior anti-neoplastic therapy, should be monitored carefully and managed as outlined in the section on dose modifications and as per institutional standard practice.

Hypersensitivity

Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have been observed. Suspected drugs should be withheld immediately and aggressive therapy should be given if hypersensitivity reactions or infusion reactions occur as outlined in section 5.4 .

Colitis/Ileus

Cases of colitis complicated by ulceration, bleeding, ileus, and infection have been observed. Patients experiencing ileus should receive prompt antibiotic support as per institutional standard practice.

Thromboembolism

Thromboembolic events have been observed in patients receiving irinotecan- containing regimens; the specific cause of these events has not been determined.

Pregnancy

The pregnancy category of irinotecan is D. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with irinotecan. If a pregnancy is reported, treatment should be discontinued. The patient should be withdrawn from the study, and the pregnancy should be followed until the outcome becomes known as per SAE section.

Care of Intravenous Site

Care should be taken to avoid extravasation, and the infusion site should be monitored for signs of inflammation. Should extravasation occur, flushing the site with sterile saline and applications of ice are recommended.

Patients at Particular Risk

In clinical trials of the weekly schedule of irinotecan, it has been noted that patients with modestly elevated baseline serum total bilirubin levels (1.0 to 2.0 mg/dL) have had a significantly greater likelihood of experiencing first-cycle grade 3 or 4 neutropenia than those with bilirubin levels that were less than 1.0 mg/dL (50.0% [19/38] versus 17.7% [47/226]; $p < 0.001$). Patients with abnormal glucuronidation of bilirubin, such as those with Gilbert's syndrome, may also be at greater risk of myelosuppression when receiving therapy with irinotecan.

Acute Infusion Associated Reactions

Acute infusion-associated reactions characterized by flushing, shortness of breath, facial swelling, headache, chills, back pain, tightness of chest or throat, and hypotension have been reported in a small number of patients treated with liposome drugs. In most patients, these reactions generally resolve within 24 hours after the infusion is terminated. In some patients, the reaction resolves by slowing the rate of infusion. Most patients who experienced acute infusion reactions to liposome drugs are able to tolerate further infusions without complications.

Other Toxicity Potential

Nanoliposomal irinotecan, the new liposome formulation of irinotecan is different from irinotecan in unencapsulated formulation, so there is a potential for toxicities other than those caused by irinotecan. All patients should be monitored closely for signs and symptoms indicative of drug toxicity, particularly during the initial administration of treatment.

9.2 Temozolomide

9.2.1 Temozolomide dose:
Temozolomide: 50mg/m2/day (or per dose modification table) until disease progression or withdrawal. Dose only needs to be re-calculated if there is a 10% change in weight or at the discretion of the treating MD. Patients to receive enough TMZ pills for 2 cycles at a time (with refills on the prescription) to be in alignment with the standard prescribing of TMZ (28 day intervals).

Formulation:
Formulation: Temozolomide is supplied in white opaque, preservative-free, two-piece, hard gelatin capsules of the following p.o. dosage strengths: 5 mg, 20 mg, 100 mg, and 250 mg. Each capsule contains drug substance in combination with lactose, anhydrous NF, colloidal silicon dioxide NF, sodium starch glycolate NF, tartaric acid NF, and stearic acid NF. The capsule shells contain gelatin NF, titanium dioxide USP, and sodium lauryl sulfate NF.

Other Names: Temodar, methazolastone.

Mode of Action: Alkylating agent of imidazotetrazinone class.

Supply:
Temozolomide is manufactured by Schering-Plough and is commercially available.
Storage and Stability:
The capsules are packaged in 30 cc, 28 mm, 48 Type I amber glass bottles (30 capsules / bottle) and should be stored between 2 and 30 degrees centigrade. Capsules are stable for at least 30 months when stored in amber glass bottles at this temperature.

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

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

Metabolism and Elimination:
Temozolomide is spontaneously hydrolyzed at physiologic pH to the active species, 3-methyl-(triazen-1-yl) imidazole-4-carboxamide (MTIC) and to temozolomide acid metabolite. MTIC is further hydrolyzed to 5-amino-imidazole-4-carboxamide (AIC), which is known to be an intermediate in purine and nucleic acid biosynthesis and to methylhydrazine, which is believed to be the active alkylating species. Cytochrome P450 enzymes play only a minor role in the metabolism of temozolomide and MTIC. Relative to the AUC of temozolomide, the exposure to MTIC and ACI is 2.4% and 23%, respectively. About 38% of the administered temozolomide total radioactive dose is recovered over 7 days; 37.7% in urine and 0.8% in feces. The majority of the recovery of radioactivity in urine is as unchanged temozolomide (5.6%), AIC (12%), temozolomide acid metabolite (2.3%), and unidentified polar metabolites(s) (17%). Overall clearance of temozolomide is about 5.5 L/hr/m^2.

Special Populations

- *Creatinine Clearance:* Population pharmacokinetic analysis indicates that creatinine clearance over the range of 36-130 mL/min/m^2 has no effect on the clearance of temozolomide after oral administration. The pharmacokinetics of temozolomide have not been studied in patients with severely impaired renal function (CLcr < 36 mL/min/m^2).
Caution should be exercised when temozolomide is administered to patients with severe renal impairment. Temozolomide has not been studied in patients on dialysis.

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

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

- *Age:* Population pharmacokinetic analysis indicates that age (range 19-78 years) has no influence on the pharmacokinetics of temozolomide. In the anaplastic astrocytoma study population, patients 70 years of age or older had a higher incidence of Grade 4 neutropenia and Grade 4 thrombocytopenia in the first cycle of therapy than patients under 70 years of age. In the entire safety database, however, there did not appear to be a higher incidence in patients 70 years of age or older.

Drug-Drug Interactions:
In a multiple dose study, administration of temozolomide with ranitidine did not change the C_{max} or AUC values for temozolomide or MTIC.

Population Analysis indicates that administration of valproic acid decreases the clearance of temozolomide by about 5%. The clinical implication of this effect is not known.

Population analysis failed to demonstrate any influence of co-administered dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H_2-receptor antagonists, or phenobarbital on the clearance of orally administered temozolomide.

Known Potential Adverse Events
Hematologic: Thrombocytopenia, leukopenia, lymphocytopenia
Gastrointestinal: Nausea, vomiting, anorexia
Hepatic: Elevated liver enzymes (reversible)
Skin: Rash, alopecia
Other: Constipation, diarrhea, stomatitis, fatigue, decreased performance status, headache Pneumocystis carinii pneumonia

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

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

Pregnancy Category D: Temozolomide may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with temozolomide.

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

10.0 AGENT ACCOUNTABILITY

Investigational Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all nanoliposomal irinotecan using a Drug Accountability Record Form. Sites may utilize the NCI drug accountability form. Sites must track lot numbers, expiration dates, dosing dates and doses per patients and overall inventory. Sites must submit to BrUOG accountability logs during the study, at the end of the study and prior to destruction. To be able to destroy drug, sites must contact BrUOG who will obtain approval from Ipsen prior to destruction.

10.1 Treatment Compliance

Records of nanoliposomal irinotecan used, dosages administered, and intervals between visits will be recorded during the study. Drug accountability will be noted.

All drugs will be administered to eligible patients under the supervision of the investigator or identified sub-investigator(s). The pharmacist will maintain records of drug receipt drug preparation, and dispensing, including the applicable lot numbers. Any discrepancy between the calculated dose and dose administered and the reason for the discrepancy must be recorded in the source documents.

11.0 ADVERSE DRUG REACTION (ADR) REPORTING

BrUOG considers the SAE reporting period to begin when the subject signs the study specific informed consent.

This study will utilize the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 for grading all adverse events. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

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

During clinical trials, adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more adverse events.)

Adverse events (AEs) will be recorded in the case report form for the duration of the trial, regardless of whether or not the event(s) are considered related to trial medication. All AEs considered related to trial medication will be followed until resolution even if this occurs post-trial.

11.1 Definitions

An adverse event is any new, undesirable medical experience or change of an existing condition that occurs during or after treatment, whether or not considered product-related.

Serious adverse event (SAE)

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition **such as the need for inpatient drug administration for observation or difficulties in transportation**
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent **This must be documented and submitted to BrUOG**
    - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition

The definition of serious adverse event (experience) also includes *important medical event*. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug

abuse. A new diagnosis of cancer during the course of treatment should be considered an important medical event.

The definition of "related" being that there is a reasonable possibility that the drug caused the adverse experience**.**

Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event. **Sites to inform BrUOG of a visit with confirmation that treating MD or PI has confirmed that ER visit does not meet above criteria, including an important medical event.**

Unexpected adverse event
An adverse event that is not mentioned in the Investigator's Brochure or package insert or the specificity or severity of which is not consistent with the investigator's brochure or package insert.

Life-threatening
Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more severe form, might have caused death.

11.2 Monitoring of Adverse Events and Period of Observation
Adverse events, both serious and non-serious, and deaths that occur during the patient's study participation will be recorded in the source documents. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

11.3 BRUOG ADVERSE EVENT REPORTING REQUIREMENTS
Investigators are required by Federal Regulation to report adverse drug reactions. Questions regarding drugs as used in this study should be directed to the Brown University Oncology Research Group (BrUOG) Central Office, Phone: (401) 863-3000 Fax (401) 863-3820, which will in turn notify the Principal Investigator.

Intensity for each adverse event will be scored using CTCAE Version 4.03. A copy of the CTCAE Version 4.03 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov). All appropriate treatment areas have access to a copy of the CTCAE Version 4.03. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

11.3.1 Pregnancies

Pregnancies
To ensure patient safety, each pregnancy in a patient on study treatment must be reported to BrUOG by the site within 24 hours (1 business day) of learning of its occurrence and BrUOG will report to Ipsen within 2 business days and up to 5 business days of learning of its occurrence and once BrUOG has received the formal documentation from the site via final signed Medwatch 3500A and

Pregnancy Report Form (080479-FOR). The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on Medwatch 3500A and 080479-FOR form and reported by the investigator to BrUOG, who will then report to the Ipsen Drug Safety department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Ipsen study treatment of any pregnancy outcome.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Pregnancies must be reported to BrUOG (who will report to Ipsen and the FDA) through 2 months post the last treatment (temozolomide or Nanoliposomal irinotecan, whichever is last). If a pregnancy is reported, it must be followed through birth, termination or miscarriage as noted above.

11.3.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study treatment (Nanoliposomal irinotecan and temozolomide), whatever is the last date of treatment), or until the subject withdraws consent from study participation (declines participation) or at the time patient becomes a screen failure, whichever occurs first, must be reported by the site (within 5 business days of being made aware of the event) to BrUOG who will in turn report the SAE to Ipsen within 2 business days and up to 5 business days of learning of its occurrence by receipt of final signed Medwatch 3500A from the site.

Any SAEs experienced after this 30 days period should only be reported to BrUOG if the investigator suspects there may be a causal relationship to the study treatment (combination) or the study drug.

Information about all SAEs are to be collected and recorded by the site (submitted to BrUOG) on the MedWatch 3500A and all applicable sections of the form will be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete MedWatch 3500A in English, within 5 business days of being made aware of the event and BrUOG will then send the completed 3500A form to the oncology Ipsen Call Center within 2 business days and up to 5 business days (from time of BrUOG being in receipt of the signed site submitted Medwatch 3500A). For pregnancies or suspected pregnancies SAEs must be sent to BrUOG by the site within 24 hours (1 business day) of being made aware of the event. For SAEs that resulted in death see below guidance.

The original copy of the MedWatch 3500A and the email confirmation sheet must be kept with the case report form documentation at BrUOG. The email is: DrugSafety.USA@ipsen.com

Follow-up information: The Medwatch 3500A must state that this is a follow-up to the previously reported SAE. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event. The follow-up information should describe whether the event

has resolved or continues and whether the patient continued or withdrew from study participation. It is required that sites submit a follow-up SAE to report discharge from the hospital.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Ipsen study treatment, The Ipsen Call Center may urgently require further information from the investigator for Health Authority reporting. Ipsen may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

11.3.3 Expedited Reporting by Investigator to Ipsen

Serious adverse events (SAE) are defined above. All events must be reported, by FAX or email, to the Brown University Oncology Research Group who must inform Ipsen in writing using a Medwatch 3500A form (provided in a completed manner, inclusive of physician signature and date by the site), within 2 business days and up to 5 business days of receipt of completed final signed 3500A form. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document discharge from hospital is required. A copy of the fax transmission confirmation of the SAE report to Ipsen should be attached to the SAE and retained with the study records at BrUOG.

This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. **All deaths during treatment or within 30 days following completion of active protocol therapy (nanoliposomal irinotecan or temozolomide), whatever is the last date of treatment) must be reported to BrUOG within 5** business **days of the site being made aware of the event, or as soon as the investigator is made aware of the event. If the death is thought to be related to the study drug, deaths must be reported to BrUOG within 24 hours (1 business day) of the investigator being made aware of the event.**

Any serious adverse event occurring after the patient has provided informed consent and until 4 weeks (30 days) after the patient has stopped study participation/treatment (nanoliposomal irinotecan or temozolomide), whatever is the last date of treatment), or until the subject withdraws consent from study participation (declines participation) or at the time the patient becomes a screen failure, whichever occurs first, must be reported to BrUOG within 5 business days of the investigator being made aware of the event. This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication).

Serious adverse events occurring more than 4 weeks (30 days) after study discontinuation (nanoliposomal irinotecan or temozolomide), whatever is the last date of treatment) need only be reported if a relationship to the Ipsen study drug (or therapy) or combination treatment is suspected.

For Comparator Drugs/Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer by the investigator.

11.4 Reporting requirements and procedures depend upon:

1. Whether investigational agents are suspected of causing toxicity;
2. Whether the possibility of such a toxicity was reported in the protocol, consent form, or manufacturer's literature (Expected toxicity); and
3. The severity of grade of the toxicity.

11.5 Assessing Causality:

Investigators are required to assess whether there is a reasonable possibility that treatment caused or contributed to an adverse event. The following general guidance may be used:

Yes: if the temporal relationship of the clinical event to treatment administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

No: if the temporal relationship of the clinical event to treatment administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

11.6 Types of Report: For sites:

Telephone report: For SAE notification contact BrUOG Central Office (401) 863-3000 (or via email), immediately upon learning of the event (within 24 hours). For follow-up SAEs please inform BrUOG within 24 hours of sending in follow-up SAE reports. Provide BrUOG 24 hour notification prior to submitting a SAE (initial or follow-up).

Written report: Send the copy of the Medwatch 3500A form, within 5 business days of being made aware of the event to the BrUOG Central Office by email, scan or Fax:

Brown University Oncology Research Group
Phone: (401) 863-3000, Fax: (401) 863-3820
Emails: BrUOG@brown.edu

All deaths during treatment or within 30 days following completion of active protocol therapy (nanoliposomal irinotecan or temozolomide) whatever is the last date of treatment) must be reported within 5 business days of being made aware of the event or as soon as the investigator is made aware of the event. If the death is thought to be related to the study drug, deaths must be reported to BrUOG **within 24 hours (1 business day)** of the investigator being made aware of the event. Pregnancies or suspected pregnancies must be reported **within 24 hours (1 business day)** of the investigator being made aware of the event. For pregnancies a Medwatch 3500A and Pregnancy Report Form (080479-FOR) are required to be completed by the site and sent to BrUOG.

MedWatch 3500A Reporting Guidelines:

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Patient number, initials, age, sex, weight
- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)
- Lot number

- **Description of event, severity, treatment, and outcome, if known. Please be sure to differentiate events which are serious vs non-serious.**
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication **must reference relationship to BOTH nanoliposomal irinotecan and temozolomide
- MedWatch Reports are to be typed
- *It is required that the following are written on the Medwatch 3500A for tracking: BrUOG 329 & MM398_15_2016

A final report to document SAE (such as discharge from hospital) is required.

Follow-up information:

For any follow-up SAE report, submit a new MedWatch 3500A report; do not resubmit the initial report with any additions. The follow-up report must be submitted to BrUOG with subject identifiers (subject number, initials, and date of birth), protocol description and number (BrUOG 329 and MM398_15_2016), suspect drug, a brief summary of previously reported SAE information, and any new information, including modification of prior events, causality, new serious events, discharge date, etc.
A final report documenting discharge date from the hospital is required.

11.7 BrUOG Responsibility Regarding Reporting:
The BrUOG Central Office will notify by phone and/or fax all drug reaction reports to the FDA, the Principal Investigator, and the participating sites (who will in turn notify their local IRBs) as soon as possible but no later than 5 business days after initial receipt of the information from the reporting site via final signed Medwatch 3500A. BrUOG will alert Ipsen to an SAE within 2 business days and up to 5 business days, of being made aware of the event via receipt of final signed Medwatch 3500A from the site. If the study has an IND, SAEs will be reported as an amendment to the IND and it will be sent to the division fax, within 5 business days of sponsor notification. If the study is IND exempt, the SAE will be sent within the same time frame, to the Medwatch fax line. A copy of the form will be kept by the BrUOG Central Office.

BrUOG will document that for questions on the SAE Ipsen should contact the central office and BrUOG will route and handle all SAE queries.

Fax: 1-800-FDA-0178 (1-800-332-0178) For IND exempt study or for IND study the SAE will be sent to Center Drug Evaluation Division fax line that has responsibility for review of IND)

Mail: For IND studies BrUOG will send the SAE as an amendment to the IND as well

All SAEs will be emailed to: Ipsen

Ipsen email for SAE reporting: email is: DrugSafety.USA@ipsen.com
It is required that the following be listed on the Ipsen fax cover sheet: BrUOG 329 & Nanoliposomal irinotecan

11.8 Safety Reporting for IND Holders
In accordance with 21 CFR 212.32, Sponsor-Investigator of the study conducted under an IND must comply with following safety-reporting requirements:

a. Expedited IND Safety Reports:
BrUOG will fax reports to the FDA for IND Safety Reports: 1 (800) FDA – 0178, unless per the IND status BrUOG is to submit the SAEs to the Division Fax instead.

b. IND Annual Reports, for IND study only
If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The Annual Report should be filed in the study's Regulatory Binder, and a copy provided to nanoliposomal irinotecan as a supporter of this study.

11.9 Adverse event updates/IND safety reports External
Ipsen shall notify the Brown University Oncology Research Group (BrUOG) via an IND Safety Report of the following information:

- Any AE associated with the use of study drug in this study or in other studies that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

BrUOG will then notify the sites who shall notify their IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects as per their local policies.

12.0 REMOVAL OF PATIENTS FROM PROTOCOL THERAPY
Extraordinary medical circumstances or withdrawal of consent by the patient: If, at any time, the constraints of this protocol are detrimental to the patient's health, and/or the patient no longer wishes to continue protocol therapy, the patient shall be withdrawn from protocol therapy. Patients will also be withdrawn from study for the following reasons:

1. Disease Progression: Any patient with disease progression should be removed from study. Details and tumor measurements should be documented on flow sheets.
2. Patient is unable to tolerate the toxicity resulting from the study treatment, even with optimal supportive care, in the opinion of the Treating Physician. Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug.
3. The physician feels it is in the best interest of the patient to stop the treatment.
4. Inter current illness that would, in the judgment of the Investigator, affect assessment of clinical status to a significant degree or require discontinuation of study treatment
5. Non protocol chemotherapy or immunotherapy is administered during the study
6. Noncompliance with protocol or treatment—major violation
7. Pregnancies or Suspected Pregnancies(including positive pregnancy test)
8. Patient is lost to follow-up
9. Patient refuses to continue treatment (patient will continue to be followed for disease-free survival and overall survival)
10. Death

In this event notify:

Brown University Oncology Research Group (BrUOG) Central Office,
Phone: (401) 863-3000
Fax: (401) 860-3820
BrUOG@brown.edu

The BrUOG Central Office will in turn notify the Principal Investigator.

***Document the reason(s) for withdrawal on flow sheets. Follow the patient for survival with follow-up forms as dictated by the protocol**

13.0 FOLLOW-UP

All Subjects that discontinue treatment early for any reason (not including screen fails or patient with withdraw consent/decline study participation) as well as patients who complete therapy will be followed for survival (up to 2 years). At treatment discontinuation, subjects will undergo adverse event evaluation and again approximately 30 days post the last treatment (nanoliposomal irinotecan and temozolomide whatever is the last date of treatment). In addition off study evaluations will be done when treatment is discontinued -Section 6.0.

14.0 REGULATORY CONSIDERATIONS

This research study is sponsored by the Principal Investigator, Dr. Heinrich Elinzano, in collaboration with Brown University Oncology Research Group (BrUOG), which will serve as the central coordinating office for the study. This study is financially supported by Ipsen (the makers of nanoliposomal irinotecan).

14.1 Protection of Human Subjects

The Investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the Investigator and must include all elements required by CFR 21 Part 50.25 and the local IRB.

14.2 Compliance with the Protocol and Protocol Revisions:

The study must be conducted as described in this approved protocol.

All revisions to the protocol must be provided to Brown University Oncology Research Group, and Ipsen. The Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC and Ipsen of an Amendment, except where necessary to eliminate an immediate hazard(s) to study patients.

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to Brown University Oncology Research Group, and Ipsen . If the revision is an Administrative Letter, Investigators must inform their IRB(s)/IEC(s).

The Investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the Investigator and must include all elements required by CFR 21 Part 50.25 and the local IRB.

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

14.3 Protocol amendments or changes in study conduct:
Any change or addition (excluding administrative) to this protocol requires a written protocol amendment that must be reviewed and approved and created by Brown University Oncology Research Group, who will obtain approval by Ipsen and the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study require additional approval by the IRB at each study center. A copy of the written approval of the IRB must be provided to Brown University Oncology Research Group, and Ipsen .

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or by Brown University Oncology Research Group and Ipsen in the interests of preserving the safety of all patients included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented for safety reasons Brown University Oncology Research Group and Ipsen must be notified and the IRB at the center must be informed immediately. Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval but the IRB must be kept informed of such administrative changes.

15.0 DATA MONITORING / QUALITY ASSURANCE/ RECORD RETENTION
15.1 Good Clinical Practice: The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and in the US Code of Federal Regulations. The investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

15.2 Patient Confidentiality: In order to maintain patient privacy, all data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The investigator will grant monitor(s) and auditor(s) from Ipsen or its designees and regulatory authority (ies) access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

15.3 Protocol Compliance: The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Changes to the protocol will require approval from Ipsen and written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authority (ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB/IEC. The investigator will submit all protocol modifications to Ipsen and the regulatory authority (ies) in accordance with the governing regulations.

Any departures from the protocol must be fully documented in the source documents.

15.4 On-site Audits: Regulatory authorities, the IEC/IRB and/or Ipsen clinical quality assurance group may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

15.5 Drug Accountability: Accountability for the drug at all study sites is the responsibility of the principal investigator. The investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records indicating the drug's delivery date to the site (if applicable), inventory at the site (if applicable), use by each patient, and disposal of the drug (if applicable and if approved through BrUOG by Ipsen) will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates (if applicable), and patient numbers.

All material containing Nanoliposomal irinotecan will be treated and disposed of as hazardous waste in accordance with governing regulations.

15.6 Premature Closure of the Study: This study may be prematurely terminated, if in the opinion of the investigator or Ipsen , there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Ipsen by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend or discontinue the development of the drug
- Should the study be closed prematurely, all study materials must be destroyed as per approved pharmacy standard operating procedure .

15.7 Record Retention:

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

The Brown University Oncology Research Group, as coordinator of this study, is responsible for ensuring proper conduct of the study with regard to protocol adherence and the validity of the data recorded on the case report forms. The Principle Investigator (Heinrich Elinzano, M.D.) and Brown University Oncology Research Group will monitor this study. The case report forms will be monitored against the submitted documents for accuracy, completeness, adherence to the protocol and regulatory compliance.

U.S. FDA regulations (21CFR312.62[c] require all records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consents forms, laboratory test results and medication inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the investigation is discontinued and the FDA and the applicable local health authorities are notified. Amgen will notify the Principle Investigator if an application is filed.

16.0 DATA SAFETY AND MONITORING BOARDS

All trials initiated by the Brown University Oncology Research Group (BrUOG) are subject to oversight by the Data Safety Monitoring Board (DSMB). This board meets two times per year with any additional meetings scheduled when needed. The responsibilities are as follows:

- Familiarize themselves with the research protocol (s)
- The DSMB reviews trial performance information such as accrual information.
- Review interim analyses of outcome data and cumulative toxicity data summaries to determine whether the trial should continue as originally designed, should be changed, or should be terminated based on these data.
- The DSMB also determines whether and to whom outcome results should be released prior to the reporting of study results.
- All adverse events are reviewed by the committee, with assurances that these have been in fact sent for review to all pertinent IRBs.
- Review of reports of related studies to determine whether the monitored study needs to be changed or terminated.
- Review major proposed modifications to the study prior to their implementation (e.g., termination, dropping an arm based on toxicity results or other reported trial outcomes, increasing target sample size).
- Following each DSMB meeting, provide the study leadership with written information concerning findings for the trial as a whole related to cumulative toxicities observed and any relevant recommendations related to continuing, changing, or terminating the trial.

The study leadership will provide information on cumulative toxicities and relevant recommendations to the local principal investigators to be shared with their IRB's.

17.0 STATISTICS

SAMPLE SIZE AND STATISTICAL DESIGN

Three patients will be accrued to level 1. If no dose limiting toxicities are observed following completion

of 4 weeks of treatment (2 cycles) then accrual to dose level 2 will proceed. If a DLT is observed in one of the first 3 patients in a dose level, then accrual for that level will be expanded to 6 patients. Accrual will continue in this way until the MTD is determined. Two or more instances of DLT in a cohort of 6 patients will result in the preceding dose level being defined as the MTD. After determination of the MTD, the final cohort will be expanded so that a total of 25 patients are treated on study. The final cohort will be treated at the MTD.

If a patient is unable to receive 4 weeks of treatment (2 cycles) for reasons other than a dose limiting toxicity, they will be replaced in a cohort. Patients who require a treatment delay of more than 8 weeks not due to toxicity will be removed from protocol treatment.

If two or more instances of DLT in a cohort of 6 patients occurs in dose level 1 then dose level -1 of nanoliposomal irinotecan will be investigated.

Definition of Dose Limiting Toxicities

- Grade 4 neutropenia (ANC < 500/mm^3)
- ANC <1000/mm^3 with fever (temp > 101) or infection
- Grade 4 thrombocytopenia: Platelets <25,000/mm^3
- Platelets <50,000/mm^3 requiring transfusion
- Grade 3 or 4 treatment related non-hematologic toxicities excluding alopecia.
    - Grade 3 nausea, vomiting or diarrhea will only be considered a dose limiting toxicity if it occurs for greater than 72 hours despite maximal medical support.
    - Grade 3 electrolyte abnormalities will not be considered dose limiting toxicities if the electrolyte disorder can be corrected to grade 2 or less within 72 hours.
    - A grade 4 electrolyte abnormality will be considered a DLT.
- Delay of treatment for > 2 weeks due to toxicity

Second Primary Objective: Preliminary Efficacy

The secondary objective is to assess the preliminary response rate and progression free survival of nanoliposomal irinotecan with continuous low-dose temozolomide in patients with recurrent glioblastoma.

Activity will be defined as a complete, partial response as defined by the via Macdonald criteria these criteria incorporating corticosteroid dosage and clinical status in addition to imaging findings.[28]

We will differentiate between a 10% level of activity and a 30% level of activity. Specifically, the hypothesis which will be tested is:

H_1: $p \leq 0.1$ versus H_1: $p \geq 0.3$

Interim Analysis

Twenty-five patients with recurrent glioblastoma will be accrued to this study. A Simon two-stage design will be used in this study. The first 13 evaluable patients treated at the MTD will be assessed for response. The trial will be terminated early if 0 or 1 responses are observed in these patients, and it will be concluded that the true response rate is unlikely to be > 10%. If at least 2 responses are observed, accrual

will continue until a total of 25 evaluable patients are enrolled to the study. Preliminary efficacy will be assessed collectively in the 25 patients entered to the respective dose levels. If 4 or fewer patients of 25 with glioblastoma do not have a response, the null hypothesis will be accepted and it will be concluded that there is not sufficient activity to merit further investigation of the regimen. Otherwise, it will be concluded that the treatment regimen has sufficient activity to warrant further investigation.

The characteristics of this study design are as follows:

The probability of erroneously concluding that the treatment is active ($p \geq 0.3$) when it is actually ineffective ($p \leq 0.1$) is less than 0.098, i.e. $\alpha = 0.098$.

Overall survival and time to progression will be determined by the Kaplan Meier method (from the time of study enrollment).

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APPENDIX A **Agreement to Participate in a Research Study**
And Authorization for Use and Disclosure of Information

Onivyde (nanoliposomal irinotecan) and Metronomic Temozolomide for Patients With Recurrent Glioblastoma:
A Phase IB/IIA Brown University Oncology Research Group Study

You are being asked to take part in a research study. All research studies at <INSERT HOSPITAL NAME> hospitals follow the rules of the state of <INSERT STATE>, the United States government and <INSERT HOSPITAL NAME>. Before you decide whether to be in the study, you and the researcher will engage in the "informed consent" process. During this process, the researcher will explain the purpose of the study, how it will be carried out, and what you will be expected to do if you participate. The researcher will also explain the possible risks and benefits of being in the study, and will provide other information. You should feel free to ask any questions you might have. The purpose of these discussions is for you to decide whether participating in the study is the best decision for you.

If you decide to be in the study, you will be asked to sign and date this form in front of the person who explained the study to you. This form summarizes the information you discussed. You will be given a copy of this form to keep.

Nature and Purpose of the Study

Your doctors are participating in this research study sponsored by the Principal Investigator, Dr. Heinrich Elinzano, in collaboration with Brown University Oncology Research Group (BrUOG), which will serve as the central coordinating office for the study. The study is financially supported by Ipsen Pharmaceuticals, the makers of the drug nanoliposomal irinotecan (Onivyde).

You are being asked to take part in this study because you have a type of brain tumor called a glioblastoma. You have previously received standard radiation therapy and the standard chemotherapy drug temozolomide but your cancer has become worse.

This study will evaluate the drug nanoliposomal irinotecan with temozolomide for patients with recurrent glioblastoma. Nanoliposomal irinotecan consists of the chemotherapy drug called irinotecan that is placed in a tiny covering called a nanoliposome which may improve the ability of irinotecan to penetrate inside brain tumors. Nanoliposomal irinotecan is approved by the United States Food and Drug Administration (FDA) for the treatment of pancreatic cancer, but it is not approved, and is experimental, for the treatment of glioblastoma. Temozolomide is FDA approved for the treatment of glioblastoma. The combination of nanoliposomal irinotecan and temozolomide in patients with glioblastomas is investigational.

The purpose of this study is to determine the highest tolerable dose of nanoliposomal irinotecan that can be given safely with daily temozolomide. The other main purpose is to study the efficacy (positive response) of the combination of nanoliposomal irinotecan and temozolomide in patients with recurrent glioblastoma brain tumors.

We expect to enroll approximately 25 patients into this study.

Explanation of Procedures

What will happen if I take part in this research study?

If you take part in this study, you will have exams, tests and procedures to show if you can be in the study, and if you choose to take part, then you will need the following tests and procedures, while on the study:

Baseline tests prior to starting treatment:

- Medical history
- Physical examination, including weight, vitals (Blood pressure, temperature, heart rate, and respiration rate), performance status (a scale used by physicians to assess how your disease affects your daily living abilities), toxicity assessment (an assessment by the physician or research nurse to determine how well you are tolerating the drug and to assess and side effects you may be having from study treatment), review of other medications you may be taking, demographics
- Blood tests - approximately 3 tablespoons of blood. If you are a female of child-bearing potential you will also have a pregnancy test (via blood).
- MRI of the brain
- EKG.

Tests while you receive study treatment with nanoliposomal irinotecan and temozolomide:

- Physical examination, including weight, vitals, performance status, toxicity assessment, review of other medications you may be taking, every 2 weeks.
- Blood tests, approximately 3 tablespoons of blood, every 2 weeks.
- MRI of the brain approximately every 2 months

Follow-up:

Once you complete the study treatment, you will have an off study visit. During this visit the following will occur:

- Physical examination, including weight, vitals, performance status, toxicity assessment
- Blood tests, approximately 3 tablespoons of blood
- You will also undergo a toxicity assessment, physical, performance status assessment approximately 30 days after your last treatment

You will then see your study doctor approximately every 3 months for approximately 2 years. During that time the following will occur:

- MRI of the brain approximately every 3 months
- Survival and disease status approximately every 3 months

How is the Study Treatment Given?

A cycle of treatment is defined as being approximately 2 weeks long.

You will receive nanoliposomal irinotecan intravenous (by vein) over approximately 90 minutes every 2 weeks in the outpatient clinic. Prior to nanoliposomal irinotecan you may receive medications to prevent nausea as per your institution's standard practice. You will receive temozolomide daily as a pill. You will continue to receive nanoliposomal irinotecan and temozolomide as long as your cancer does not become worse and you do not have severe side effects.

All people on the trial will receive the standard dose of daily temozolomide (50mg/m2/day). Depending on how you are doing on the study, the dose of daily temozolomide may be reduced. This study will determine the safest dose of nanoliposomal irinotecan to administer with daily temozolomide.

Patients will be treated in groups of 3-6 patients to determine the highest safe dose of nanoliposomal irinotecan. Your doctor will discuss with you the dose of nanoliposomal irinotecan that you will receive. The dose of nanoliposomal irinotecan you receive depends on when you take part in the study. Neither you nor your doctor can choose which dose you will receive and your dose will not be increased. Only after 3-6 patients have completed treatment at a dose level, and the dose level is determined to be safe, will 3-6 additional patients start a higher dose level of nanoliposomal irinotecan. Once the highest safe dose level is found, more patients will be treated at the determined dose so that a total of 25 patients are treated on the study.

How long will I be in the study?

You will receive nanoliposomal irinotecan IV every 2 weeks and daily temozolomide by pill as long as your cancer does not become worse and you don't have severe side effects. You will then be followed by your doctors approximately every 3 months for survival and disease status for approximately 2 years

You may not have any Temodar wafers (a treatment where small wafers are placed at the tumor site that deliver chemotherapy) placed prior to enrollment in the study or during study treatment.

Costs for participating in this study

Some of the services you will receive are being performed only because you are participating in this research study. Examples of these 'research only' services include the drug nanoliposomal irinotecan, which will be provided at no charge by Ipsen Pharmaceuticals, the maker of the drug.

Other services you will receive during this research study are considered "routine clinical services" that you would have received even if you were not in the research study. Examples are; all study doctor visits, blood tests, the temozolomide pills, drugs used to reduce side effects from chemotherapy, MRIs, EKG. These services will be billed to your health insurance company, but you will be responsible for paying any deductibles, co-payments, or co-insurance that are a normal part of your health insurance plan. If you do not have health insurance, you will be responsible for those costs.

Contact Information: If you have any questions regarding this study, you may contact your site Principal Investigator, <INSERT CONTACT>, MD at <INSERT NUMBER>

Discomforts and Risks

You may have side effects while on this study. We will monitor everyone in the study for any side effects. Contact your study doctor if you experience a side effect or have any questions about possible side effects.

Side effects may be mild or serious. We may give you medicines to help lessen side effects. Some side effects will go away as soon as you stop taking the drug. In some cases, side effects can be serious, long-lasting, or may never go away. There is a small risk of death.

Taking part in this study may lead to time away from work.

NANOLIPOSOMAL IRINOTECAN :

Risks and side effects related to the Nanoliposomal irinotecan include those which are:

Likely (>10%)

- Low levels of blood cells (neutropenia and leukopenia), which could lead to an increased risk of infection or weakness
- Diarrhea (loose or watery and frequent stools)
- Nausea and vomiting
- Pain in the stomach or in the gut area
- Loss of weight
- Loss of appetite
- Loss of body fluid (dehydration)
- Unusual hair loss
- Tiredness
- Fever
  Generalized weakness

Less Likely (1-10%)

- Infections- for example, fungal infections in the mouth (oral candidiases), fever with low counts of white blood cells (febrile neutropenia), infections related to the administration of the product into a vein
- Inflammation of the stomach and the guts (gastroenteritis)
- Systemic body inflammation, caused by infection (sepsis)
- Thromboembolic event (formation of a blood clot that breaks loose and plugs a vessel).

Rare but serious (<1%)

- Systemic body inflammation, caused by infection of the gall bladder and bile ducts (billiary sepsis)
- Allergic reaction to nanoliposomal irinotecan
- Diminished availability of oxygen to the body tissues
- Inflammation of the esophagus (food pipe)
- Inflammation of the lining of the rectum (the end of the large intestine)
- Type of rash, characterized by the appearance of a flat, red area on the skin covered with bumps (maculo-papular rash)
- Change in the color of the nail plates

Serious side effects may occur

- Infections (particularly if your white blood cells are low). Symptoms of infection may include fever, chills, dizziness, or shortness of breath. Blood cell counts will be monitored periodically by your study doctor during treatment.
- Diarrhea. Diarrhea can be early (beginning within 24 hours of receiving nanoliposomal irinotecan) or late (beginning more than 24 hours after nanoliposomal irinotecan administration). Symptoms of severe diarrhea may include persistent diarrhea; discolored stools (black, green or bloody); or symptoms of dehydration such as lightheadedness, dizziness, or faintness. Your study doctor may treat diarrhea with anti-diarrhea medicines
- Lung problems (interstitial lung disease). Symptoms of interstitial lung disease include new onset of cough or difficulty breathing and fever.
- Allergic reaction (hypersensitivity). Seek immediate medical attention for signs of severe reaction such as chest tightness; shortness of breath; wheezing; dizziness or faintness; or swelling of the face, eyelids, or lips when receiving or during the 24 hours after receiving nanoliposomal irinotecan.

TEMOZOLOMIDE:

Likely (>20%)

- Decreased blood counts, especially white cells, which can result in infection. Platelet counts can be reduced which can result in bleeding or easy bruising.
- Nausea and vomiting.
- Weakness and dehydration.
- Decreased appetite
- Headache
- Constipation
- Drowsiness/fatigue

Less Likely (1-20%)

- Decrease in blood counts that may cause infection, bleeding, and bruising
- Diarrhea
- Fever
- Sores in your mouth
- Rash
- Elevated liver enzymes
- Swelling in your arms and legs
- Memory loss
- Confusion
- Itchiness
- Increased need to urinate
- Weakness

- Back pain
- Dizziness
- Tingling/burning in your arms and legs
- Anxiety
- Depression
- Stomach pain
- Blurred vision
- Hair loss
- Temporary abnormalities in liver function tests, which may cause fatigue and skin discoloration

Rare but Serious (<1%)

- Decreased ability to carry out daily activities
- Convulsions
- Weakness on one side of your body
- Abnormal coordination
- Paralysis
- Myelodysplastic syndrome (problem with the bone marrow that causes decreased production of red cells, white cells, or platelets that can sometimes turn into blood cancer)

Risk of Secondary Cancers or Leukemia: Chemotherapy drugs (such as nanoliposomal irinotecan and temozolomide) may increase the risk of other cancers or leukemia (a blood cancer).

Reproductive Risks

Chemotherapy may decrease the sperm count. This is usually temporary but is infrequently permanent, which would result in sterility. Because the drugs in this study can affect an unborn baby, you should not become pregnant while on this study Ask your study doctor for more information regarding preventing pregnancy during the study treatments. You should not nurse your baby while on this study. If you are premenopausal, your periods are likely to stop temporarily and may stop permanently due to the study treatments, which may lead to symptoms of menopause, such as hot flashes, and the inability to become pregnant, which may be permanent. If you are concerned about this, ask your study doctor about options for preserving your reproductive choices, which may include referral to a specialist in this field.

If you decide to take part in this study, you must agree to use medical doctor-approved contraception throughout the study, and for 2 months after your last dose of study drug. If you become pregnant during the study you must tell the study doctor right away. If this happens, your participation in this study will be discontinued (stopped). If you become pregnant within 2 months after taking your last dose of study drug you must tell the study doctor right away. The study doctor will follow you and your pregnancy to birth.

Males: If you have a partner of childbearing age, you must agree to use a medical doctor-approved form of contraception throughout the study, and should avoid fathering a child for 2 months after your last dose of study drug. If your partner becomes pregnant during the study or within 2 months after you took your last dose of study drug, you must tell the study doctor right away.

By signing this document you are acknowledging that you understand and agree to the information presented in this reproductive risk section.

Antiemetics (anti-nausea medications): Various medications used to prevent nausea and vomiting may cause drowsiness, dry mouth, diarrhea, constipation, headache, restlessness, agitation, anxiety, dizziness, involuntary tremors, skin rash, and possible allergic reaction.

You will receive pre-medication to reduce the risk of infusion/injection reactions on your treatment days. Overall, the pre-medications you will be given are well tolerated.

Venipuncture (inserting a needle into a vein to obtain blood or give medication): May cause inflammation, pain, bruising, bleeding, or infection.

When you receive chemotherapy by vein, there is a slight risk that some of the drug may leak out around the needle at the injection site. A skin burn may result. Most skin burns are treatable and heal well.

In order to monitor the side effects, your physician will examine you frequently and obtain laboratory tests to determine the effects of your treatment and alter the drug dosages if necessary.

Risk of MRI imaging:

Rarely MRI has been associated with kidney damage.

Your doctors will be carefully monitoring your condition to minimize any possible risks to you. If your doctors feel that the side effects are too severe in your particular case, they will lower the dose of the medications or even stop them.

There may be other side effects that have not been reported. If you have any unusual symptoms, you should report them immediately to your doctor or nurse.

Benefits

The goal of this study is to determine the safest dose and side effects of the addition of nanoliposomal irinotecan to standard temozolomide. The goal is also to determine how well nanoliposomal irinotecan and temozolomide are in treating glioblastoma. The treatment may not be effective and may not be of help in treating your cancer. We hope the information learned from this study will benefit other patients with cancer in the future.

Alternative Therapies

What other choices do I have if I do not take part in this study?

- Getting treatment for your glioblastoma with daily temozolomide alone
- Getting treatment with other anticancer drugs such as bevacizumab
- You should discuss with your doctor whether there is a role for more radiation or surgery.
- Taking part in another study
- Getting no treatment

Talk to your doctor about your choices before you decide if you will take part in this study.

Refusal/Withdrawal

It is up to you whether you want to be in the study. You are not required to enroll or participate. If you decide to participate, you can always change your mind and quit at any time. If you decide not to be in the study, or if you quit later, you will still be able to get the health care services you normally get. If you join, but later on the researcher or your doctor feels being in the study is no longer good for you, they may choose to take you out of the study before it is over. If new information becomes available that might change your mind about whether you want to stay in the study the researcher will share this information with you as soon as possible.

If you decide to withdraw from this study (stop taking study medication) for any reason, you will be asked to sign a form indicating whether you give your permission for your doctor and the research staff to continue to collect and submit follow-up information on your health status from your physicians and medical record. After signing the form, you still have the right to change your mind, at any time, regarding follow-up after withdrawal.

You have the right to change your mind at any time regarding follow-up after withdrawal. If you decide to quit the study please tell your site Principal Investigator <INSERT NAME>, MD by calling <INSERT PHONE NUMBER>

Medical Treatment/Payment in Case of Injury

A research injury is any physical or mental injury or illness caused by being in the study. If you are injured by a medical treatment or procedure you would have received even if you were not in the study that is not a research injury. To help avoid research injury and added medical expenses, it is very important to follow all study directions carefully. If you do experience a research injury, <INSERT HOSPITAL NAME> or the study doctor can arrange medical treatment for you. Such treatment will be paid for as described below.

If you have insurance and have a research injury that is not covered by the study, it is possible that some or all of the cost of treating you could be billed to your insurer. If your health insurance will not cover such costs, it is possible you would have to pay out of pocket. In some cases, <INSERT HOSPITAL NAME> might be able to help you pay if you qualify for free care under <INSERT HOSPITAL NAME> policy. However, <INSERT HOSPITAL NAME> has no policy to cover payment for such things as lost wages, expenses other than medical care, or pain and suffering.

Neither Dr. Heinrich Elinzano, the sponsor of the study, nor BrUOG, the coordinating center, nor Ipsen Pharmaceuticals have money set aside to reimburse you for medical bills from treatment of a research related injury or otherwise compensate you in the event of a study-related injury.

Rights and Complaints

Signing this form does not take away any of your lawful rights. If you have any complaints about this study, or would like more facts about the rules for research studies, or the rights of people who take part in research studies you may contact<INSERT NAME> in the <INSERT HOSPITAL NAME> Office of Research Administration, at <INSERT CONTACT>

Confidentiality

Your research records will be treated as private health care records and will be protected according to <INSERT HOSPITAL NAME> privacy practices and policies that are based on state and federal law. In particular, federal law requires us to get your permission to use or disclose (release your information to someone outside of <INSERT HOSPITAL NAME>) your health information for research purposes. If you sign this form you agree to be in this research study and you permit the use and disclosure of your health information for the purpose of conducting the research, providing treatment, collecting payment and running the business of the hospital. This permission has no expiration date. You may withdraw from the study at any time. However, if you do not want the researchers to use or disclose any further information in this study you must cancel permission in writing and may do so at any time. If you cancel your permission, you will stop taking part in the study and no new information will be collected about you. However, if you cancel your permission, it will not apply to actions already taken or information already collected about you by the hospital or the researchers before you canceled your permission.

Generally, the entire research record and any medical records held by the hospital may be used and released for research purposes. The following people or businesses/companies/ might use, release, or receive such information:

- The researcher and their support staff;
- The study sponsor Dr. Heinrich Elinzano, BrUOG, the group coordinating the study and their affiliates, and Ipsen, the supplier of the drug, its authorized agents and financial supporter of this trial.
- Doctors, nurses, laboratories and others who provide services to you or the sponsor in connection with this study;
- The company or section of the U.S. government that is paying for the study and others they hire to oversee, administer, or conduct the research;
- The United States Food and Drug Administration, the Department of Health and Human Services, the Office of Inspector General, and the Office of Civil Rights; Governmental agencies in other countries where the study drug may be considered for approval
- People who volunteer to be patient advocates or research volunteer protectors;
- Members of the hospital's administrative staff responsible for reviewing, approving and administering clinical trials and other healthcare or research activities.
- Accrediting Organizations

The results of this research study , in which you agree to participate, will probably be shared with other people and may be published in scientific reports, but your name and the fact that you were in this study

will be kept confidential. Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality.

There are times when the law might require or permit <INSERT HOSPITAL NAME> to release your health information without your permission. For example, <INSERT STATE> law requires researchers and health care workers to report abuse or neglect of children to the Department of Children, Youth and Families (DCYF) and to report abuse or neglect of people age 60 and older to the Department of Elderly Affairs.

All researchers and health care providers are required to protect the privacy of your health care information. Other people and businesses/organizations that are not health care providers are not required by law to do that so it is possible they might re-release your information.

You have the right to refuse to sign this form and not participate in the research. Your refusal would have no affect on your treatment, charges billed to you, or benefits at any <INSERT HOSPITAL NAME> health care site. If you do not sign, you will not be able to enroll in the research study and will not receive treatment as a study participant.

If you decide to quit the study after signing this form (as described in Section 6) no new information will be collected about you unless you gave us permission to do so. However, the hospital or the researchers may continue to use information that was collected before you quit the study to complete analysis and reports of this research.

Additionally, a description of this clinical trial will be available on *http://www.ClinicalTrials.gov,* as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

For more detail about your privacy rights see the <INSERT HOSPITAL NAME> Joint Privacy Notice which has or will be given to you.

Consent for a Legally Authorized Representative

I being of sound mind willfully and voluntarily make known my desire that if I am unable to make decisions in the future due to my disease condition, I give permission to my legally authorized representative to make decisions on my behalf. ☐yes ☐ no

Please review the information below and make decisions on your participation in this clinical trial should you become unable to make decisions in the future due to your disease condition:

If I continue to meet all criteria for continuing treatment per the study:
☐ *I would like to continue treatment. I agree to participate in protocol-required procedures such as imaging scans, blood draws, doctor's visits, or any other procedure as required by the study AND I give my permission to continue to collect information about my health.*

OR

☐ *I would like to stop treatment.*

If I no longer meet all criteria for continuing treatment per the study, have completed treatment, or have indicated above that I would like to stop treatment:

☐ *I agree to participate in protocol-required follow-up procedures such as imaging scans, blood draws, doctor's visits, or any other procedure as required by the study AND I give my permission to continue to collect information about my health.*

OR

☐ *I agree to have follow-up information collected about my health, but I no longer wish to participate in protocol-required procedures such as imaging scans, blood draws, doctor's visits, or any other procedure that is not routine care.*

OR

☐ *I do not give my permission to continue to collect information about me in follow-up.*

SIGNATURE

I have read this informed consent and authorization form. ALL OF MY QUESTIONS HAVE BEEN ANSWERED, AND I WANT TO TAKE PART IN THIS RESEARCH STUDY.

By signing below, I give my permission to participate in this research study and for the described uses and releases of information. *I also confirm that I have been now or previously given a copy of the <INSERT HOSPITAL NAME> Privacy Notice*

This informed consent document expires on _____.

The Researcher is required to provide a copy of this consent to you.

_____ _____ _____
Signature of study volunteer/authorized representative* Date and Time when signed

I was present during the consent PROCESS AND signing of this agreement by the study volunteer or authorized representative

_____ _____
Signature of witness (required if consent is presented orally or at the request of the IRB) Date

_____ _____
Signature of Translator Date

_____ _____ _____
Signature of researcher or designate Date and Time when signed

* If signed by agent other than study volunteer, please explain below.

_____
_____

APPENDIX B: Checklist

Onivyde (nanoliposomal irinotecan) and Metronomic Temozolomide for Patients With Recurrent Glioblastoma:
A Phase IB/IIA Brown University Oncology Research Group Study

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Inclusion Criteria

_____(y/n) Histologically confirmed glioblastoma multiforme or gliosarcoma

_____(y/n) Progression after at least one line of therapy.

_____(y/n)Patient must have received temozolomide and radiation but it is not required that they were given concurrently.

_____(y/n) Voluntary, informed consent, Date signed_____

_____(y/n) Age ≥18

_____(y/n) All males and women of childbearing potential, must be willing to consent to use an adequate barrier birth control measure while on treatment and for at least 2 months after the last treatment on study

_____(y/n) Brain MRI completed with contrast

_____(y/n) Patient must be able to tolerate brain MRI with contrast

_____(y/n) EKG within 8 weeks study entry

_____(y/n) Life expectancy >12 weeks as noted by treating investigator

_____(y/n) Absolute neutrophil count ≥ 1,500/ul, Date_____

_____(y/n) Platelet ≥ 100,000/uL, Date_____

_____(y/n) Total bilirubin ≤1. 0 x ULN, Date_____

_____(y/n) AST≤ 2.5x ULN and ALT ≤ 2.5x ULN Institution

_____(y/n) Creatinine ≤1.5xULN

_____(y/n) HGB ≥ 9.0g/dL

_____(y/n) Albumin levels ≥ 3.0 g/dL

_____(y/n) Karnofsky performance score ≥ 60

_____(y/n) Recovered (≤ grade 1) from the effects of any prior surgery, radiotherapy or other anti-neoplastic therapy, except alopecia. See section 3.1.10

_____(y/n) Stable corticosteroid dose at least 7 days prior to day 1

_____(y/n) Patients must have assessable (measurable) disease at baseline by brain MRI. Must be contrast enhancing. The tumor size will be measured in millimeters and is the largest cross-sectional area using perpendicular measurements of contrast enhancing abnormality.

Exclusion Criteria:

_____(y/n) Non-GBM primary invasive malignant neoplasm that is considered by treating investigator to likely cause death in the next 5 years.
_____(y/n) Patient not to be receiving any cancer therapy or investigational anti-cancer drug.

_____(y/n) Radiation therapy or cytotoxic chemotherapy or biologics or immunotherapy within previous three weeks from day 1 of drug (no anticancer treatment of any kind within 3 weeks of day 1 of drug).
_____(y/n) Evidence of an active infection requiring intravenous antibiotic therapy
_____(y/n) Women of child bearing potential without a negative serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 7 days prior to Day 1 of treatment. Post-menopausal women (surgical menopause or lack of menses ≥12 months) do not need to have a pregnancy test, please document status.
_____(y/n) pregnant or breastfeeding
_____(y/n) Unwillingness or inability to follow the procedures required in the protocol, site to have documentation to confirm at time of registration.
_____(y/n) Patient with a history of Gilbert's disease or known UGT1A1*28 allele. (Assessment for the UGT1A1*28 allele is not required for protocol entry.)
_____(y/n) Myocardial infarction, unstable angina pectoris, stroke within 6 months of study registration.
_____(y/n) NYHA Class III or IV congestive heart failure
_____(y/n) Known hypersensitivity to any of the components of nanoliposomal irinotecan , other liposomal products, or temozolomide
_____(y/n) Investigational anticancer therapy administered within 4 weeks. See section 3.2.13
_____(y/n) Any medical condition that in the opinion of the Investigator may interfere with a subject's participation in or compliance with the study. Must receive confirmation in writing from treating MD.
_____(y/n) Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. See section 3.2.14

_____(y/n) Use of CYP3A4 enzyme-inducing anticonvulsants phenytoin and strong CYP3A4 inducers is not allowed. Conmed log to show patients has been off any of these exclusionary products for ≥ 2 weeks from day 1.

The support documentation, per the requirements under the study parameters section of this study, as well as the consent form and this checklist, must be faxed to the BrUOG Central Office at the time of registration. Please check if "Enclosed", state reason when "Not Enclosed," or check if "Not Applicable."

1) Eligibility Form Enclosed __Not Enclosed _____ Not Applicable __

2) Heme/Onc initial note Enclosed __Not Enclosed _____ Not Applicable __

3) Pathology Report(s) Enclosed __Not Enclosed _____ Not Applicable __

4) MRI/CT Report(s) Enclosed __Not Enclosed _____ Not Applicable __

5) Lab Source Document Enclosed __Not Enclosed _____ Not Applicable __

6) ICF signature page

7) Other documents, please list_____

IRB approval date of protocol: _____

Hospital where patient will be treated with Oncologist: _____

Date patient will begin treatment: _____ Primary Physician (Oncologist):_____

Your signature: _____

APPENDIX C

NCI CTC Version 4

Toxicity will be scored using NCI CTC Version 4 for toxicity and adverse event reporting. A copy of the NCI CTC Version 4can be downloaded from the CTEP homepage: (**http://ctep.info.nih.gov**). All appropriate treatment areas have access to a copy of the CTC Version 4

APPENDIX D

ECOG PATIENT PERFORMANCE STATUS

STATUS	KARNOFSKY	ZUBROD-ECOG-WHO	Description
No complaints	100	0	Normal activity
Able to carry on normal activities	90	1	Symptoms, but fully ambulatory
Normal activity with effort	80		
Cares for self. Unable to carry on normal activity or to do active work	70	2	Symptomatic, but in bed <50% of the day
Requires occasional assistance, but able to care for most of his needs	60		
Requires considerable assistance and frequent medical care	50	3	Needs to be in bed >50% of the day, but not bedridden
Disabled, requires special care and assistance	40		

Severely disabled. Hospitalization indicated though death non imminent	30	4	Unable to get out of bed
Very sick. Hospitalization Necessary. Active support treatment necessary	20		
Moribund	10		
Dead	0		

From: Minna J.D., Higgins G.A and Glapstein E.J. Cancer of the lung: In: DeVita V, Hellman S., Rosenberg S., (Eds.). Cancer: Principles and Practice of Oncology, Lippincott, Philadelphia, 1984, p. 536

APPENDIX E

CASE REPORT FORMS

Attached separately are the BrUOG Case Report Forms