Phase I/II Study of RAD001 in Combination with Temozolomide in Patients with Advanced Pancreatic Neuroendocrine Tumors

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Table of Contents

List of abbreviations

4E-BP1	4E-binding protein
ADR	Adverse Drug Reaction
AE	adverse event
ALT/SGPT	alanine aminotransferase/glutamic pyruvic transaminase/Serum glutamic-pyruvic transaminase
AST/SGOT	aspartate aminotransferase/glutamic oxaloacetic transaminase/Serum glutamic-oxaloacetic transaminase
ATC	Anatomical Therapeutic Chemical classification system
AUC	Area under the plasma-concentration time curve
BAC	Bronchoalveolar carcinoma
Cmax	Maximum plasma concentration
CR	Clinical research
CRF	Case report/Record form
CRO	Contract Research Organization
CT	Computer tomography
CTC	Common toxicity criteria
CV	Coefficient of Variation
CYP3A4	CytochromeP450 3A4 isoenzyme
DLT	Dose limiting toxicity
ECG	Electrocardiogram
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
eIF-4E	Eucariotic Initiation Factor 4E
EPR	Early progression rate
FDG-PET	Fluorine-18-2-fluoro-Deoxy-D-Glucose Positron Emission Tomography
FKBP-12	FK506-binding protein 12
GF	Growth factor
HDL	High-density lypoproteins
HER	Human Epidermal Receptor
HUVECS	human umbilical endothelial cells
IC50	Inhibitory concentration at 50%
IEC	Independent Ethics Committee
IGF1-R	Insulin-like Growth Factor 1 Receptor
IHC	immunohistochemistry
INN	International Non-proprietary Name

INR	International Normal Ratio
IRB	Institutional Review Board
LC-MS	liquid chromatography method with mass spectrometry
LDL	Low-density lypoproteins
LLOQ	Lower limit of quantification
MAPK	Mitogen Activated Protein Kinase
mRNA	messenger Ribonucleic acid
mTOR	mammalian Target of Rapamycin
NIH/NCI	National Institutes of Health/National Cancer Institute
nM	nano-molar
NSCLC	Non-small cell lung cancer
OS	overall survival
P-AKT	phosphor-AKT
PD	Pharmacodynamics
PET	Proton emission tomography
PFS	progression free survival
P-gp	P-glycoprotein
PI3K	Phosphoinositide 3-kinase
PK	Pharmacokinetics
PK/PD model	Pharmacokinetic/pharmacodynamic model
PT/PTT	prothrombin time
PTEN	Phosphatase and Tensin homolog deleted on chromosome 10
RBC	red blood cell count
REB	Research Ethics Board
RR	response rate
S6K1	S6 kinase 1
SAE	serious adverse event
SCLC	Small cell lung cancer
STAT3	Signal Transducer and Activator of Transcription 3
TK	Tyrosine kinase
TSC2	Tuberous Sclerosis Complex 2
TUNNEL	Terminal deoxynucleotidyl transferase (TdT)-mediated dUTP-biotin Nick End Labeling
ULN	upper limit of normal
VEGF	Vascular Endothelial Growth Factor
WBC	total white blood cell count
WHO	World Health Organization

1 Introduction

1.1 Overview of pancreatic neuroendocrine tumors

Pancreatic neuroendocrine tumors comprise about 1-2% of pancreatic tumors (Barakat, Meeran, and Bloom, 2004). The annual incidence of pancreatic neuroendocrine tumors is approximately 3.5 to 4 per million population. At the time of diagnosis, many patients have disease that is either unresectable or metastatic. In a study of 83 patients with pancreatic neuroendocrine tumor, median survival from the time of diagnosis was approximately 7.5 years for all patients; among patients with liver metastases, median survival was 4 years (Tomassetti, et al, 2005). In recent studies of patients receiving chemotherapy for pancreatic neuroendocrine tumors, the median survival has been 2 to 3 years.

Patients with unresectable or metastatic neuroendocrine tumors currently have few treatment options. The efficacy of standard cytotoxic chemotherapy in the treatment of patients with metastatic neuroendocrine tumors has not been clearly established. In the 1980s and early 1990s, regimens containing the combination of streptozocin and doxorubicin were considered standard based on a response rate of 69% and a survival benefit reported by Moertel et al (Moertel et al, 1992). However, the high reported response rates in this study have been questioned and are likely the result of the use of non-standard response criteria. Two subsequent retrospective analyses of patients receiving this regimen reported objective radiologic response rates using modern response criteria of less than 10% (Cheng et al, 1999, McCollum et al, 2004). Furthermore, while various combinations of streptozocin, 5-fluororuacil, doxorubicin, have been reported to result in tumor responses, these regimens have also been associated with significant toxicity. Only a single drug, streptozocin, is approved for use in pancreatic neuroendocrine tumors. However, streptozocin-based therapy can be associated with significant hematologic and renal toxicity; its use in pancreatic neuroendocrine tumors, particularly in the first-line setting, is not universally accepted. Novel treatment strategies are therefore clearly needed for this disease.

1.2 Temozolomide

Dacarbazine (DTIC) has been evaluated as a potential alternative to streptozocin-based therapy in pancreatic endocrine tumors. One phase II study of DTIC in 50 patients with advanced pancreatic islet cell carcinoma reported an objective response rate of 34%(Ramanathan, Cnaan et al. 2001). However, toxicity was a concern, with a significant proportion of patients developing nausea and/or vomiting. DTIC is therefore rarely used currently as a treatment for neuroendocrine tumors.

Temozolomide, a cytotoxic alkylating agent, was specifically developed as an oral and less toxic alternative to DTIC(Stevens, Hickman et al. 1987). Temozolomide and dacarbazine appear to have identical mechanisms of action: both agents are metabolized to the active agent MTIC, an inhibitor of nucleoside incorporation. The cytotoxicity of MTIC is thought to be

primarily due to alkylation at the O^6 position of guanine (Stevens, Hickman et al. 1987) with additional alkylation also occurring at the N^7 and N^3 positions. Temozolomide does not require metabolic activation; it undergoes spontaneous chemical degradation to MTIC at physiologic pH. Temozolomide has demonstrated clinical antitumor activity and a relatively well-tolerated and acceptable safety profile in phase I and II trials in patients with a broad range of solid tumors (Hammond, Eckardt et al. 1999; Danson and Middleton 2001). Temozolomide has been shown to be effective in prolonging progression-free survival in adult patients with recurrent high-grade gliomas, and has also demonstrated clinically meaningful activity in patients with anaplastic astrocytoma (van den Bent, Taphoorn et al. 2003; Chang, Prados et al. 2004).

Based on early evidence that dacarbazine has activity in neuroendocrine tumors, as well as the fact that thalidomide may contribute to antitumor activity through antiangiogeneic mechanisms, we recently explored a combination of temozolomide in combination with thalidomide (Kulke, Stuart et al. 2006). A total of 29 patients with metastatic carcinoid, pancreatic or pheochromocytoma neuroendocrine tumors were treated with temozolomide, administered at a dose of 150 mg/m^2 for 7 days, followed by a 7-day rest, together with thalidomide administered at doses of 50–400 mg daily without interruption. Objective responses (by RECIST) were seen in 45% of the 11 patients with pancreatic neuroendocrine tumor. The 29 enrolled patients received a median of 7.3 months of therapy (range 1-23 months). Neuropathy, a known toxicity of thalidomide, developed in 11 patients (38%). In six patients (21%), neuropathy persisted for more than 3 weeks despite withholding thalidomide treatment, and resulted in treatment discontinuation. The median time to treatment discontinuation for neuropathy was 10.8 months (range, 7.7 to 11.5 months). Grade 2 or 3 thrombocytopenia occurred in four patients (14%), resulting in their treatment discontinuation. Other toxicities resulting in treatment discontinuation included rash (one patient), neutropenia (one patient), and infection (four patients).

A total of eleven patients developed infections while receiving study treatment. The infections included three opportunistic infections: one case of *Pneumocystis carinii* pneumonia, one case of disseminated varicella zoster virus, and one case of cutaneous herpes zoster limited to one dermatome. These three patients had all received more than 6 months of therapy and all developed grade 3 or grade 4 lymphopenia. Grade 3 to 4 lymphopenia developed in 69% of the patient population. Lymphopenia generally developed in the absence of significant leukopenia or neutropenia: grade 3 or 4 leukopenia developed in only four patients, and grade 3 or 4 neutropenia occurred in only two patients during study treatment. Based on the development of these opportunistic infections, prophylaxis with trimethoprim-sulfamethoxasole was recommended for future patients receiving prolonged treatment courses with temozolomide.

Results from a subsequent phase II study of temozolomide and bevacizumab in patients with metastatic neuroendocrine tumors further confirmed the activity of temozolomide-based therapy in pancreatic neuroendocrine tumors (Kulke, Stuart et al. 2006). A partial response to

therapy was observed in 24% of patients with pancreatic neuroendocrine tumors; stable disease was observed in 71% of the patients. All patients received prophylaxis with trimethoprim-sulfamethoxasole, and no opportunistic infections were observed.

An analysis of 76 patients with neuroendocrine tumors treated with temozolomide based regimens at our institutions revealed that temozolomide-based therapy was associated with an overall response rate of 31% in pancreatic neuroendocrine tumors. Expression of the *MGMT* (O6-methylguanine-DNA-methyltransferase) gene has been associated with response to temozolomide and other alkylating agents. The *MGMT* gene encodes a DNA-repair enzyme that removes alkyl groups from the O6 position of guanine. In our study, loss of expression of *MGMT*, as assessed by immunohistochemistry, was associated with response to temozolomide (Kulke, Frauenhoffer et al. 2007). Loss of MGMT was observed only in pancreatic neuroendocrine tumors and not in carcinoid tumors.

These findings suggest that temozolomide was primarily responsible for the antitumor activity observed in pancreatic neuroendocrine tumors with the temozolomide/thalidomide and temozolomide/bevacizumab combination regimens. They further suggest that temozolomide is an active and appropriate first-line treatment option for patients with neuroendocrine tumors, and that further studies building on temozolomide in this setting are warranted.

Although we estimate the response rate for temozolomide-based therapy to be approximately 30%, this is not known for certain. A retrospective analysis conducted in Europe of temozolomide as monotherapy for patients with advanced malignant neuroendocrine tumors from various gastrointestinal and thoracic sites demonstrated an objective radiographic response rate of 14% (Ekeblad et al, 2007). As above, two prospective phase II studies of temozolomide-based therapy have been conducted at DF/HCC in patients with advanced neuroendocrine tumors (carcinoid tumor or pancreatic neuroendocrine tumor). The first study combined temozolomide and thalidomide; among patients with pancreatic neuroendocrine tumors, objective responses were seen in 5/11 patients (RR 45%, 95% CI 16%-75%). The second study combined temozolomide and bevacizumab; among patients with pancreatic neuroendocrine tumors, objective responses were seen in 4/17 patients (RR 24%, 95% CI 3%-44%). Additionally, in a retrospective analysis of patients with neuroendocrine tumors treated at DF/HCC with temozolmide-based therapy, some of whom received therapy as participants in these two phase II trials, objective responses to therapy were seen in 11/35 patients wtih pancreatic neuroendocrine tumors (RR 31%, 95% CI 18-44%).

Given the wide confidence intervals associated with these response rates and the uncertainty regarding the true response rate of temozolomide in this patient population, we believe that the future regimens including temozolomide would be worthy of further study if a 20% response rate is demonstrated.

1.3 RAD001 (everolimus)

RAD001 (everolimus) is a novel derivative of rapamycin. RAD001 has been in clinical development since 1996 as an immunosuppressant in solid organ transplantation. Since 2003, RAD001 has been approved in Europe (trade name: Certican®) via the Mutual Recognition Procedure (MRP) for the prevention of organ rejection in patients with renal and cardiac transplantation. Certican® is also approved in Australia, South Africa, the Middle East, Central and South America, the Caribbean and some Asian countries.

At the cellular and molecular level, RAD001 acts as a signal transduction inhibitor. It selectively inhibits mTOR (mammalian target of rapamycin), a key protein kinase that regulates cell growth, proliferation and survival. The mTOR is mainly activated via the PI3 kinase pathway through AKT/PKB and the tuberous sclerosis complex (TSC1/2). Mutations in these components or in PTEN, a negative regulator of PI3 kinase, may result in their dysregulation. Abnormal functioning of various components of the signaling pathways contributes to the pathophysiology of numerous human cancers. Various preclinical models have confirmed the role of this pathway in tumor development (Cohen, 2005).

1.3.1 Preclinical studies

RAD001 inhibits the proliferation of a range of human tumor cell lines *in-vitro* including lines originating from lung, breast, prostate, colon, melanoma and glioblastoma. IC50s range from sub/low nM to μM. RAD001 also inhibits the proliferation of human umbilical vein endothelial cells (HUVECS) *in vitro*, with particular potency against VEGF-induced proliferation suggesting that RAD001 may also act as an anti-angiogenic agent. The anti-angiogenic activity of RAD001 was confirmed *in vivo*. RAD001 selectively inhibited VEGF-dependent angiogenic response at well tolerated doses. Mice with primary and metastatic tumors treated with RAD001 showed a significant reduction in blood vessel density when compared to controls.

The potential of RAD001 as an anti-cancer agent was shown in rodent models. RAD001 is orally bioavailable, residing longer in tumor tissue than in plasma in an s.c mouse xenograft model, and demonstrating high tumor penetration in a rat pancreatic tumor model. The pharmacokinetic profile of RAD001 indicates sufficient tumor penetration, above that needed to inhibit the proliferation of endothelial cells and tumor cell lines deemed sensitive to RAD001 *in vitro*.

RAD001 administered daily p.o. was a potent inhibitor of tumor growth, at well tolerated doses, in 11 different mouse xenograft models (including pancreatic, colon, epidermoid, lung and melanoma) and two syngeneic models (rat pancreatic, mouse orthotopic melanoma). These models included tumor lines considered sensitive and “relatively resistant” *in vitro*. In general, RAD001 was better tolerated in mouse xenograft models than standard cytotoxic agents (i.e., doxorubicin and 5-fluorouracil), while possessing similar anti-tumor activity. Additionally, activity in a VEGF-impregnated s.c. implant model of angiogenesis and reduced vascularity (vessel density) of RAD001-treated tumors (murine melanoma) provided evidence of *in vivo* effects of angiogenesis.

It is not clear which molecular determinants predict responsiveness of tumor cells to RAD001. Molecular analysis has revealed that relative sensitivity to RAD001 *in vitro* correlates with the degree of phosphorylation (activation) of the AKT/PKB protein kinase and the S6 ribosomal protein; in some cases (i.e., glioblastoma) there is also a correlation with PTEN status.

In vivo studies investigating the anti-tumor activity of RAD001 in experimental animal tumor models showed that RAD001 monotherapy typically reduced tumor cell growth rates rather than produced regressions or stable disease. These effects occurred within the dose range of 2.5 mg to 10 mg/kg, p.o. once a day.

In preclinical models, the administration of RAD001 is associated with reduction of protein phosphorylation in target proteins downstream of mTOR, notably phosphorylated (p)-S6 (p-S6) and p-4E-BP1, and occasionally with an increase in phosphorylated AKT, a protein upstream of mTOR signaling pathway. Study CRAD001A2107 explored MPD (molecular pharmacodynamic) changes in tumor at different doses and schedules of RAD001 (weekly 20 mg, 50 mg and 70 mg or daily 5 mg and 10 mg).

All significant adverse events observed in toxicology studies with RAD001 in mice, rats, monkeys and mini-pigs were consistent with its anticipated pharmacological action as an anti-proliferative and immunosuppressant and at least in part reversible after a 2 or 4-week recovery period with the exception of the changes in male reproductive organs, most notably testes.

1.3.2 Clinical experience

1.3.2.1 Phase I and II oncology studies

Data are available from phase I clinical studies of RAD001 given as a single agent to 147 patients with advanced solid tumors. Such studies included various doses and schedules (weekly dosing, range 5-70 mg and daily dosing 5-10 mg). Approximately, 46% of patients reported rash or erythema and 40% of the patients presented with stomatitis/mucositis. The most frequent adverse events suspected to be drug-related observed in three studies using RAD001 as a single agent are listed in Table 1-1.

Table 1-1 Adverse events suspected to be drug-related in ≥10% of patients with advanced cancers reported in Phase I RAD001 monotherapy studies (C2101, C2102 and 2107)

	Weekly			Daily		
	5-30 mg n=30	50 mg n=18	70 mg n=38	5mg n=16	10 mg n=45	Total n=147
No. Pts with AEs						
Any event	23 (1)	17 (2)	38 (10)	14 (1)	43 (14)	135 (28)
By event						
- Rash	5	8	18	10	27 (1)	68 (1)
- Stomatitis/mucositis	6	8 (2)	16 (2)	6 (1)	23 (3)	59 (8)
- Fatigue	8	7 (1)	14 (1)	1	17 (1)	47 (3)
- Nausea	5	4	8	2	18 (1)	37 (1)
- Anorexia	1	6	10	3	15	35
- Diarrhea	1	7	7	-	9	24
- Vomiting	4	5	5	-	10	24
- Headache	7	4	6	6	4	20
- Pruritus	2	1	6	3	4	16
- Infections[1]	1	3	3 (1)	1	6 (2)	14 (3)
- Constipation	-	1	2	2	9	14

The numbers of patients (by dose level and dose schedule) who have reported grade ≥3[1] toxicities is given in brackets.

1. events included in brackets reached no more than grade 3 severity
2. Infections noted as drug-related included:
   - Herpes simplex: 5 pts (1 at 50 mg/wk; 1 at 5mg/d; 3 at 10 mg/d)
   - Oral candidiasis: 5 pts (1 at 50 mg/wk; 3 at 70 mg/wk, 1 at 10 mg/d)
   - Pneumonia (gr3) 1 pt (10 mg/d)
   - Pustular rash 1 pt (20 mg/wk)
   - Rhinitis 2 pts (50 mg/wk)
   - URT Infection 1 pt (50 mg/wk
   - Urinary Tract Infect 1 pt (50 mg/wk)

Reduced blood cell counts at the initiation of treatment are frequent but remain mostly within the normal range or limited to grade 1 although a grade 3 neutropenia was a DLT in one patient as was a grade 3 thrombocytopenia in a patient receiving RAD001 with letrozole where pharmacodynamic interaction is unlikely. This suggest that some patients may be particularly sensitive to the myelosuppressive effect of RAD001 making it necessary to monitor carefully blood cell counts at initiation of treatment.

Metabolic changes (hyperlipidemia and hyperglycemia) may be observed during treatment with RAD001. Both events may be medically managed. Hyperlipidemia has been reported as an adverse reaction in 10% of patients although review of the laboratory values suggests that as many as a quarter of patients develop grade 1-2 hyperlipidemia on treatment, mostly hypercholesterolemia. Hyperglycemia has been reported as an adverse event in 7% of patients. Grade 3 hyperglycemia has been observed, especially in diabetics receiving RAD001 treatment. Therefore, patients with diabetes should have their blood glucose monitored carefully and their medications adjusted, as needed, to maintain adequate control of their blood glucose levels.

In Novartis-sponsored clinical trials, symptomatic non-infectious pneumonitis has been reported as a serious adverse event in less than 1% of patients out of approximately 1000 cancer patients treated with RAD001 as of April 30, 2006. This adverse event has been noted in the Investigators' Brochure (IB, Edition 4 dated November 11, 2005). Corticosteroids were often administered to the patients with symptomatic pneumonitis.

Novartis has recently received reports of low-grade non-infectious pneumonitis in cancer patients treated with RAD001. Most of these reports involve patients with no respiratory symptoms (CTC grade 1 pneumonitis: radiographic findings only) or mild severity (CTC grade 2: symptomatic, not interfering activities of daily living), and were from two investigator-sponsored (private IND) trials, as follows:

- In a study of patients with advanced renal cell carcinoma receiving 10 p.o. mg/day, 15/20 patients reviewed by an independent radiologist were noted to have lung infiltrates consistent with pneumonitis on routine chest CT scans performed to follow the patients' thoracic metastases.
- In a study of patients with advanced breast cancer, 7/18 patients treated with RAD001 10 mg/d and 2/16 patients treated with RAD001 70 mg/week, had findings consistent with pneumonitis. In this study, two patients, one on the daily RAD arm and one on the weekly RAD001 arm, developed severe (grade 3) pneumonitis that resolved after RAD001 was discontinued.

In both studies, most patients had radiological changes with mild or no symptoms and have continued RAD001 treatment without developing symptoms. The reason for an increased rate of reported low-grade pneumonitis among oncology patients in these studies is unclear. Both studies included serial chest CT scans allowing prolonged, detailed evaluation of the lung parenchyma; the dosage and drug exposure in these phase 2 trials is generally longer than in the phase 1 experience. In addition, the dosage of RAD001 used in the treatment of cancer patients is substantially higher than that given routinely in the organ transplant setting. Everolimus (RAD001) is approved at a daily dose of 0.75 mg twice a day guided by therapeutic drug monitoring (3-8 ng/ml) in combination with cyclosporine microemulsion in many regions of the world for renal and cardiac transplantation. In phase 3 trials investigating everolimus in renal and cardiac transplantation, the overall reported rate of pneumonitis ranged from 0.0 to 1.4%. The spontaneous reporting rate for pneumonitis following exposure to commercially available everolimus in transplantation is very low (0.08% or 84.4 events/100,000 patient-years). Refer to the latest version of the RAD001 Investigator's Brochure and safety letters (Investigator Notifications) for the most up to date information available.

Two phase I studies combining RAD001 with systemic cytotoxic chemotherapy (paclitaxel, gemcitabine) have been performed.

In the phase I study of gemcitabine and RAD001, RAD001 was administered orally at a dose of 20 mg/week, without interruption, in combination with weekly gemcitabine, 600 mg/m2 on days 1,8,15 of each 27-day cycle. Successive cohorts were to be defined by the dosage of gemcitabine, beginning with 600 mg/m2, which would have been increased to 800 mg/m2 and

1000 mg/m2 if feasible. 5/8 patients in the 600 mg/m2 cohort experienced a dose limiting toxicity in the first cycle (≥ grade 2 neutropenia, ≥ grade 1 thrombocytopenia). All patients had some evidence of myelosuppression (≥ 1 or more grade 1 levels of neutropenia, thrombocytopenia, or anemia). Due to the high rate of DLT at the first dose level, no dose escalation was undertaken in this study. The high frequency of DLT in the lowest-dose cohort was attributed to the antiproliferative activity of RAD002, increasing the direct myelotoxic effect of gemcitabine and/or delaying post-cytotoxic recovery.

In a separate phase I study combining RAD001 (15 mg and 30 mg /week orally) with paclitaxel (80 mg/m^2 on days 1,8,15 of each 21 day cycle) among patients with advanced solid tumors, the combination was found to be well tolerated. No dose limiting toxicities among the 16 treated patients were observed. (Dose limiting toxicity was defined as any grade 4 toxicity, grade 3 non-hematological toxicity despite preventive therapy, or ≥ grade 2 neutropenia or thrombocytopenia failing to revert to grade ≤ 1 (level at which cytotoxic treatment is permitted) within two weeks.) For further details, please refer to Investigator's Brochure, section 5.3.3.

1.3.2.2 Phase II studies of RAD001 in neuroendocrine tumors

A recent phase II clinical trial examined the combination of RAD001 5 mg per day and depot octreotide (Sandostatin LAR depot) in patients with advanced neuroendocrine tumors (Yao, Phan et al. 2006). Thirty patients who were treated were classified as follows: 17 patients had carcinoid, and 13 had pancreatic neuroendocrine tumor. All were evaluabe for response. Four patients were reported to have partial response (3 verified by independent radiologic review), 22 had stable disease, and 4 had progressive disease by RECIST criteria. Responses appeared to be durable; at last analysis, responses were ongoing in 3 patients at 12, 9, and 6 months on treatment, and the fourth patient progressed at 9 months on treatment. A partial response to therapy was seen in 2 of 11 patients with pancreatic neuroendocrine tumor who were evaluable for response. Of the 17 patients whose tumors had documented radiological progression prior to study entry, 13 (76%) were progression-free at 12 weeks and 11 (65%) were progression-free at 12 weeks and 11 (65%) were progression free at 24 weeks. Nineteen of the 30 evaluable patients had elevated chromogranin A at baseline. Eleven (37% of all patients or 58% of those with elevated chromogranin A at baseline) had >50% reductions in chromogranin A.

The combination of RAD001 5 mg per day and Sandostatin LAR Depot 30 mg every 28 days appears to have been well tolerated. The most common toxicity reported was mild aphthous ulceration. CTC Grade 3/4 toxicities reported included those previously reported for RAD001 alone (anemia, thrombocyotpenia, aphthous ulcer, diarrhea, edema, fatigue, hypoglycemia, nausea, pain, and rash). Only one patient discontinued treatment because of drug-related toxicities. When grade 3 toxicities occurred, RAD001 was held until toxicity resolved to grade 1, and RAD001 was resumed at the initial dose of 5 mg per day.

In phase I clinical studies of RAD001 as a monotherapy agent in oncology patients, the side-effect profile is essentially mild to moderate adverse events with a low frequency of DLT at the daily dose of 10 mg/d (see Table 1-1). Based on the PK/PD model, a daily dose of 10mg RAD001 is assumed to provide a persistently high degree of target inhibition in the tumor [Investigators' Brochure-Section 5.3.1.1]. In addition, preliminary data from phase 1 studies, in which changes in molecular characteristics of tumor induced by treatment with RAD001 at the doses of 5 and 10 mg/d were investigated, confirm the pharmacodynamic activity predicted previously by PK/PD modeling [Investigators' Brochure-Section 5.3.1.1]. Therefore, a dose of 10 mg/d should ensure adequate drug target inhibition for most patients, taking into consideration the known inter-patient variability in drug levels (CV of approx 50%).

The efficacy and safety of RAD001 at a dose of 10 mg per day, alone and in combination with Sandostatin LAR, currently is being evaluated in an ongoing multi-institutional phase II clinical trial.

1.5 Study Rationale

Given the single-agent activity demonstrated with both temozolomide and RAD001 in patients with neuroendocrine tumors, evaluation of a combination of these two agents in neuroendocrine tumors is warranted. The activity of temozolomide appears to be limited primarily to patients with pancreatic neuroendocrine tumors, based on our recent clinical experience. We therefore propose a phase I/II study to evaluate the efficacy and safety of RAD001 in combination with temozolomide in patients with metastatic pancreatic neuroendocrine tumors.

Although the combination of RAD001 and gemcitabine was associated with toxicity, RAD001 has been studied in combination with paclitaxel without evidence of synergistic toxicity. This data, as well as the markedly different mechanisms of action of RAD001 and temozolomide, suggest that combining these two agents at standard doses, with appropriate safety monitoring, may be feasible. However, to ensure that we do not miss unexpected toxicities, we will initiate treatment at a dose level below the anticipated phase II dose. Three patients will be treated with RAD001 orally at a dose of 5 mg daily, in combination with temozolomide at a standard dose (150 mg/m^2 daily for 7 days, followed by a 1 week break). Patients will be observed for toxicity. If no dose limiting toxicity is observed in this first cohort, subsequent patients will receive the full anticipated phase II dose of RAD001 10 mg daily, in combination with temozolomide 150 mg/m^2 daily for 7 days, every other week. To minimize the risk of lymphopenia-related opportunistic infections, temozolomide therapy will be limited to a maximum of 6 months, and all patients will receive PCP prophylaxis.

2 Study objectives

Primary

- To determine the objective response rate of RAD001 in combination with temozolomide in patients with advanced (unresectable or metastatic) pancreatic neuroendocrine tumors.

Secondary

- To determine the duration of response to the combination of RAD001 and temozolomide in patients with advanced pancreatic neuroendocrine tumors.
- To determine the safety and tolerability of the combination or RAD001 and temozolomide in patients with advanced pancreatic neuroendocrine tumors.
- To determine the progression free survival and overall survival of patients receiving the combination of RAD001 and temozolomide.

3 Investigational plan

3.1 Overall study design

This is an open-label phase I/II study to evaluate the efficacy and safety of RAD001 in combination with temozolomide in patients with advanced pancreatic neuroendocrine tumor.

Patients on study therapy may be at risk for temozolomide-related selective lymphopenia and opportunistic infections. To reduce the risk of opportunistic infections, patients will receive prophylaxis with Bactrim DS, 1 tablet by mouth every Monday, Wednesday, and Friday beginning after the first month of treatment. Patients allergic to Bactrim should be initiated on an alternate, standard PCP prophylaxis regimen. Previous infections associated with temozolomide-induced lymphopenia in neuroendocrine tumor patients have developed after more than 6 months of treatment. Treatment with temozolomide in this study will therefore be limited to a maximum duration of 6 months.

3.2 Basic Design Characteristics

Up to 44 patients with locally advanced or metastatic pancreatic neuroendocrine tumors who meet eligibility criteria will be enrolled sequentially into three cohorts.

3.2.1 Cohort 1

The first cohort will consist of a minimum of three patients who will receive an oral dose of 5 mg of RAD001 administered daily and an oral dose of temozolomide of 150 mg/m^2 daily for

7 days every other week beginning on Day 1 of RAD001 administration. The patients will be treated for a 28-day Treatment Period and then observed over a 7-day observation period for signs of treatment-emergent toxicity. Patients will not receive treatment with either RAD001 or temozolomide during the 7-day observation period. If these patients do not exhibit disease progression or a dose limiting toxicity (DLT), as defined in section 3.3, they will receive subsequent 28-day cycles of treatment without additional 7-day observation periods. Patients in this cohort may be treated simultaneously without requiring previously enrolled patients to complete their first cycle of treatment and observation.

If a dose limiting toxicity (DLT), as defined in section 3.3, is observed in 1 of the first 3 patients, 3 additional patients will be enrolled at that same dose level. If no additional DLT is observed after all patients have completed the first cycle of treatment and 7-day observation period, the trial will continue to enroll the second cohort of patients.

If a DLT is observed in 2 or more of the first 3 patients or of the total 6 patients during Cycle 1 of treatment, accrual to the trial will be suspended pending review of the events and revision of the protocol.

3.2.2 Cohort 2

Once the first cohort of patients completes the initial 35-day cycle without experiencing a DLT, the second cohort of patients will begin enrollment. The second patient cohort will consist of at least 3 patients who will receive an oral dose of 10 mg of RAD001 administered daily and an oral dose of temozolomide of 150 mg/m^2 daily for 7 days every other week beginning on Day 1 of RAD001 administration. The patients will be treated for a 28-day Treatment Period and then observed over a 7-day observation period for signs of treatment-emergent toxicity. Patients will not receive treatment with either RAD001 or temozolomide during the 7-day observation period. If patients do not exhibit disease progression or a dose limiting toxicity (DLT), as defined in section 3.3, they will receive subsequent 28-day cycles of treatment without additional 7-day observation periods. Patients in this cohort may be treated simultaneously without requiring previously enrolled patients to complete their first cycle of treatment and observation.

If a DLT is observed in 1 of the first 3 patients, 3 additional patients will be enrolled at that same dose level. If no additional DLT is observed after all patients have completed the first cycle of treatment and observation period, the trial will continue to enroll the third cohort of patients. If additional DLTs are observed, enrollment to the trial will be stopped and the study will be re-evaluated.

If a DLT is observed in 2 or more of the first 3 patients or of the total 6 patients during Cycle 1 of treatment, accrual to the trial will be suspended pending review of the events and revision of the protocol.

3.2.3 Cohort 3

Once the second cohort of patients completes the initial 35-day cycle without experiencing a DLT, the third cohort of patients will begin enrollment. The third patient cohort will consist of 32 patients who will receive an oral dose of the maximum tolerated dose of RAD001 administered daily and an oral dose of temozolomide of 150 mg/m^2 daily for 7 days every other week beginning on Day 1 of RAD001 administration. The patients will be treated for a 28-day Treatment Period. Patients who complete the initial cycle of therapy without evidence of significant treatment-emergent toxicity or progressive disease may receive additional 28-day cycles of treatment until the appearance of significant treatment-emergent toxicities or disease progression.

3.3 Definition of dose limiting toxicity (DLT) and maximum tolerated dose (MTD)

Dose limiting toxicity is defined as drug-related toxicity according to the NCI CTCAE v3.0 during the first cycle of treatment leading to the following:

- Grade 3 or higher non-hematologic toxicity (excluding nausea and/or vomiting).
- Grade 3 or higher nausea/vomiting uncontrolled by aggressive antiemetic support.
- Grade 3 or higher neutropenia or thrombocytopenia failing to revert to grade ≤ 2 (level at which cytotoxic treatment is permitted) in three weeks
- Febrile neutropenia
- Inability of the patient to take > 75% of the planned chemotherapy dose during the treatment period.
- Clinically significant treatment related toxicity

The maximum tolerated dose (MTD) is defined as the highest dose level at which less than 33% of the patients experience a DLT.

If a DLT is observed in 2 or more of the first 3 patients or of the total 6 patients in a dose level during cycle 1 of treatment, that dose level will be considered to be above the maximum tolerated dose (MTD). The dose one level lower will be declared as the MTD, if a DLT is observed in 1 or less patient of the total 6 patients in the dose level. If 2 or more patients have experienced a DLT at the first dose level, the investigator, medical monitor, and Sponsor may discuss to add a dose level at 50% of the first level.

3.4 Study population

3.4.1 Patient population

The target population is comprised of adult patients with histologically-confirmed, advanced pancreatic neuroendocrine tumor. The study will enroll up to 44 patients. Patients must have

baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. Results of all baseline evaluations, which assure that all inclusion and exclusion criteria have been satisfied, must be reviewed by the Principal Investigator or his/her designee prior to enrollment of that patient. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

Inclusion criteria

1. Locally unresectable or metastatic pancreatic neuroendocrine tumor.
   - Radiologic, operative, or pathology reports should document a pancreatic location of tumor.
   - Patients must have confirmed low-grade or intermediate-grade neuroendocrine carcinoma.
   - Patients with poorly differentiated neuroendocrine carcinoma, high-grade neuroendocrine carcinoma, adenocarcinoid, goblet cell carcinoid, and small cell carcinoma are not eligible.
2. Patients must have at least one measurable site of disease according to RECIST criteria that has not been previously irradiated. If the patient has had previous radiation, chemoembolization, or cryotherapy to the marker lesion(s), there must be evidence of progression since the radiation.
3. Age ≥ 18 years.
4. Minimum of two weeks since any major surgery, completion of radiation, or completion of all prior systemic anticancer therapy (adequately recovered from the acute toxicities of any prior therapy).
5. Prior treatment with chemotherapy is allowed, with the exception of prior treatment with temozolomide or dacarbazine.
6. No prior therapy with RAD001 or any other mTOR inhibitor.
7. ECOG performance status ≤ 2.
8. Life expectancy 12 weeks or more.
9. Adequate bone marrow function as shown by: ANC ≥ 1.5 x 10^9/L, Platelets ≥ 100 x 10^9/L, Hgb > 9 g/dL.
10. Adequate liver function as shown by: serum bilirubin ≤ 1.5 x upper limit of normal (ULN), and serum transaminases activity ≤ 3 x ULN, with the exception of serum transaminases (< 5 x ULN) if the patient has liver metastases.
11. Adequate renal function as shown by serum creatinine ≤ 1.5 x ULN.
12. Fasting serum cholesterol ≤ 300 mg/dL OR ≤ 7.75 mmol/L AND fasting triglycerides ≤ 2.5 x ULN. NOTE: In cases where one or both of these thresholds are exceeded, the patient can only be included after initiation of appropriate lipid lowering medication, see Section 4.4.6.

13. Women of childbearing potential must have a negative serum pregnancy test within 14 days of the administration of the first study treatment. Women must not be lactating. Both men and women of childbearing potential must be advised of the importance of using effective birth control measures during the course of the study.
14. Signed informed consent to participate in the study must be obtained from patients after they have been fully informed of the nature and potential risks by the investigator (or his/her designee) with the aid of written information.

Exclusion criteria

1. Prior treatment with any investigational drug within the preceding 4 weeks.
2. Chronic treatment with systemic steroids or another immunosuppressive agent, with the exception of patients receiving physiologic steroid replacement for adrenal insufficiency or other similar conditions.
3. Patients should not receive immunization with attenuated live vaccines during study period or within 1 week of study entry.
4. Uncontrolled brain or leptomeningeal metastases, including patients who continue to require glucocorticoids for brain or leptomeningeal metastases.
5. Other malignancies within the past 3 years except for adequately treated carcinoma of the cervix or basal or squamous cell carcinomas of the skin.
6. Patients who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:
   - Unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction ≤ 6 months prior to first study treatment, serious uncontrolled cardiac arrhythmia
   - Severely impaired lung function
   - Any active (acute or chronic) or uncontrolled infection/ disorders.
   - Nonmalignant medical illnesses that are uncontrolled or whose control may be jeopardized by the treatment with the study therapy
   - Liver disease such as cirrhosis, chronic active hepatitis or chronic persistent hepatitis
   - A known history of HIV seropositivity
   - Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of RAD001 (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome or small bowel resection)
7. Women who are pregnant or breast feeding, or women/men able to conceive and unwilling to practice an effective method of birth control. (Women of childbearing potential must have a negative serum pregnancy test within 14 days prior to administration of RAD001). Oral, implantable, or injectable contraceptives may be affected by cytochrome P450 interactions, and are therefore not considered effective for this study.
8. Patients who have received prior treatment with an mTOR inhibitor or temozolomide.
9. Patients with a known hypersensitivity to RAD001 (everolimus) or other rapamycins (sirolimus, temsirolimus) or to its excipients

10. History of noncompliance to medical regimens
11. Patients unwilling to or unable to comply with the protocol

4 Treatment Program

4.1 Study Treatment

The investigational study drugs used in the course of this trial are RAD001 and temozolomide:

- Cohort 1: Patients will receive an oral dose of 5 mg of RAD001 administered daily and an oral dose of temozolomide of 150 mg/m^2 daily for 7 days every other week beginning on Day 1 of RAD001 administration. Temozolomide will be administered for a maximum of 6 months; RAD001 may be administered until treatment progression, unacceptable or dose limiting toxicity, withdrawal of consent, or other reason for treatment discontinuation.

- Cohort 2: Patients will receive an oral dose of 10 mg of RAD001 administered daily and an oral dose of temozolomide of 150 mg/m^2 daily for 7 days every other week beginning on Day 1 of RAD001 administration. Temozolomide will be administered for a maximum of 6 months; RAD001 may be administered until treatment progression, unacceptable toxicity, withdrawal of consent, or other reason for treatment discontinuation.

- Cohort 3: Patients will receive an oral dose of RAD001 administered daily at the MTD as established in the phase I component of the study (Cohorts 1 and 2) and an oral dose of temozolomide of 150 mg/m^2 daily for 7 days every other week beginning on Day 1 of RAD001 administration. Temozolomide will be administered for a maximum of 6 months; RAD001 may be administered until treatment progression, unacceptable toxicity, withdrawal of consent, or other reason for treatment discontinuation.

Patients on study therapy may be at risk for temozolomide-related selective lymphopenia and opportunistic infections. To reduce the risk of opportunistic infections, patients will receive prophylaxis with Bactrim DS, 1 tablet by mouth every Monday, Wednesday, and Friday beginning after the first month of treatment. Patients allergic to Bactrim should be initiated on an alternate, standard PCP prophylaxis regimen. Previous infections associated with temozolomide-induced lymphopenia in neuroendocrine tumor patients have developed after more than 6 months of treatment. Treatment with temozolomide in this study will therefore be limited to a maximum duration of 6 months.

Novartis will supply RAD001, and Schering-Plough will provide temozolomide free of charge for study participants.

4.2 Interruption or discontinuation of treatment

For patients who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to keep the patient on study drug. If administration of RAD001 or temozolomide must be interrupted because of unacceptable toxicity, drug dosing will be interrupted or modified according to rules described in Section 4.4. Toxicity will be assessed using the NIH-NCI Common Terminology Criteria for Adverse Events, version 3.0 (CTCAEv3.0, (http://ctep.cancer.gov/forms/CTCAEv3.pdf)).

All interruptions or changes to study drug administration must be recorded.

It will be documented whether or not each patient completed the clinical study. If for any patient either study treatment or observations were discontinued the reason will be recorded. Reasons that a patient may discontinue participation in a clinical study are considered to constitute one of the following:

1. adverse event(s)
2. abnormal laboratory value(s)
3. abnormal test procedure result(s)
4. disease progression
5. protocol violation
6. subject withdrew consent
7. lost to follow-up
8. administrative problems
9. death

4.3 Monitoring of suspected toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value suspected to be related to RAD001 or temozolomide must be followed at least weekly until the adverse event or abnormal laboratory resolves or returns to grade 1. If a patient requires a dose delay of > 21 days from the intended day of the next scheduled dose, then the patient must be discontinued from the study.

4.4 Dose Modification

4.4.1 RAD001 dose adjustments

Three RAD001 dose levels are defined for dose adjustment: 10 mg daily, 5 mg daily, and 5 mg every other day.

Table 4.1.1 : Dose Reduction Schedule for RAD001 – Cohort 1

Dose Level	Dose and schedule	Days per cycle (cycle length = 28 days)
0	5 mg daily	Continuous
Decrease 1 dose level	5 mg every other day	Continuous
Decrease 2 dose levels	Discontinue therapy	

Table 4.1.2 : Dose Reduction Schedule for RAD001 – Cohort 2

Dose Level	Dose and schedule	Days per cycle (cycle length = 28 days)
0	10 mg daily	Continuous
Decrease 1 dose level	5 mg daily	Continuous
Decrease 2 dose levels	5 mg every other day	Continuous
Decrease 3 dose levels	Discontinue therapy	

4.4.2 Temozolomide dose adjustments

Three temozolomide dose levels are defined for dose adjustment: 150 mg/m^2 daily, 100 mg/m^2 daily, and 50 mg/m^2 daily, administered on days 1-7 and days 15-21 of each cycle.

Table 4.2 : Dose Reduction Schedule for Temozolomide

Dose Level	Dose and schedule	Days per cycle (cycle length = 28 days)
0	150 mg/m^2 daily	Days 1-7; 15-21
Decrease 1 dose level	100 mg/m^2 daily	Days 1-7; 15-21
Decrease 2 dose levels	50 mg/m2 daily	Days 1-7; 15-21
Decrease 3 dose levels	Discontinue therapy	

4.4.3 Dose reductions for hematologic toxicity

Cohort 1: If the ANC is <1,000 or the platelet count is <50,000 during study therapy, RAD001 and temozolomide will be delayed. If RAD001 or temozolomide cannot be administered on the scheduled day of dosing, the CBC will be repeated weekly for up to and including 3 weeks until the ANC is ≥ 1000/mm^3 and the platelet count ≥ 50,000mm^3. At that time, temozolomide will be reinitiated at one reduced dose level (100 mg/m^2 daily, see Tables 4.1-4.2). The dose of RAD001 will remain at 5 mg daily. For subsequent dose reductions, both temozolomide and RAD001 will be reduced by one dose level. If treatment is held more than 3 weeks, the patient should be taken off protocol therapy.

Cohort 2: If the ANC is <1,000 or the platelet count is <50,000 during study therapy, RAD001 and temozolomide will be delayed. If RAD001 or temozolomide cannot be administered on the scheduled day of dosing, the CBC will be repeated weekly for up to and including 3 weeks until the ANC is ≥ 1000/mm^3 and the platelet count ≥ 50,000mm^3. At that time, RAD001 and temozolomide will be reinitiated at one reduced dose level (see Tables 4.1-4.2). If treatment is held more than 3 weeks, the patient should be taken off protocol therapy.

Growth factors cannot be used to induce elevations in neutrophil count for the purposes of administration of RAD001 and temozolomide on the scheduled dosing OR to allow treatment. Administration of erythropoietin is allowed.

4.4.4 Dose reductions for non-hematologic toxicity

Both RAD001 and temozolomide should be held for all clinically significant drug related toxicities that are grade 3 or higher and not specified in the drug-specific toxicities below. All drug related CTCAE Grade 3 and 4 toxicities must have resolved to at least CTCAE Grade 1 prior to repeat dosing. For patients with baseline grade 2 elevations in transaminases or bilirubin or alkaline phosphatase, transaminase, bilirubin, or alkaline phosphatase levels must have resolved to the level defined by the Inclusion Criteria prior to repeat dosing.

Once toxicities have resolved to at least grade 1, RAD001 and temozolomide will be reinitiated at one reduced dose level per Table 4.3. If treatment is held more than 3 weeks, the patient should be taken off protocol therapy.

If multiple toxicities are seen, the dose administered should be based on the dose reduction required for the most severe grade of any single toxicity observed. If unacceptable toxicity occurs, therapy should be discontinued.

Table 4.3 Criteria for dose-modification of RAD001 and temozolomide for non-hematologic toxicity

Toxicity	Actions
Grade 2 (except pneumonitis [refer to Table 4.4] and mucositis)	**If the toxicity is tolerable to the patient, maintain the same dose. If the toxicity is intolerable to patient, interrupt RAD001 and temozolomide until recovery to grade ≤1. Then reintroduce RAD001 and temozolomide at one lower dose level.**
Grade 2 mucositis	**If the toxicity is tolerable to the patient, maintain the same dose. If the toxicity is intolerable to patient, interrupt RAD001 and temozolomide until recovery to grade ≤1. Then reintroduce RAD001 at one lower dose level and continue same dose of temozolomide. See section 4.4.5 for further details.**
Grade 3 (except hyperlipidemia and hyperglycemia and mucositis and pneumonitis)	**Interrupt RAD001 and temozolomide until recovery to grade ≤1. Then reintroduce both RAD001 and temozolomide at one lower dose level.**
Grade 3 hyperlipidemia	**Grade 3 hyperlipidemia (hypercholesterolemia and/or hypertriglyceridemia) should be managed using medical therapies, per section 4.4.6. Dose reduction of RAD001 or temozolomide can be considered but is not required.**
Grade 3 hyperglycemia	**Grade 3 hyperglycemia should be managed using medical therapies, per section 4.4.6. . Dose reduction of RAD001 or temozolomide can be considered but is not required.**
Grade 3 mucositis	**For Grade 3 mucositis, interrupt RAD001 and temozolomide until recovery to grade ≤1. Then reintroduce RAD001 at one lower dose level and continue temozolomide at same dose. See section 4.4.5 for further details.**
Grade 3 pneumonitis	**Please refer to Table 4.4.**
Grade 4	**Discontinue protocol therapy**
Any non-hematological toxicity requiring interruption for > 3 weeks	**Discontinue protocol therapy**

4.4.5 Management of stomatitis/oral mucositis/mouth ulcers

Stomatitis/oral mucositis/mouth ulcers are common toxicities associated with RAD001 and should be treated using local supportive care. Please note that investigators in earlier trials have described the oral toxicities associated with RAD001 as mouth ulcers, rather than mucositis or stomatitis. If your examination reveals mouth ulcers rather than a more general inflammation of the mouth, please classify the adverse event as such. Dose modification of RAD001 for stomatitis/oral mucositis/mouth ulcers is described in Section 4.4.4. Additionally, please follow the paradigm below for treatment of stomatitis/oral mucositis/mouth ulcers:

1. For mild toxicity (grade 1), use conservative measures such as non-alcoholic mouth wash or salt water (0.9%) mouth wash several times a day until resolution.
2. For more severe toxicity (grade 2 in which case patients have pain but are able to maintain adequate oral alimentation, or grade 3 in which case patients cannot maintain adequate oral alimentation), the suggested treatments are topical analgesic mouth treatments (i.e., local anesthetics such as, benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®).
3. Agents containing hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents.

Antifungal agents must be avoided unless a fungal infection is diagnosed. In particular, systemic imidazole antifungal agents (ketoconazole, fluconazole, itraconazole, etc.) should be avoided in all patients due to their strong inhibition of RAD001 metabolism, therefore leading to higher RAD001 exposures. Therefore, topical antifungal agents are preferred if an infection is diagnosed. Similarly, antiviral agents such as acyclovir should be avoided unless a viral infection is diagnosed.

4.4.6 Management of hyperlipidemia and hyperglycemia

Treatment of ***hyperlipidemia*** is recommended but not required as part of study therapy, and should take into account the patient's underlying condition and the relative risk/benefit ratio of treatment. Treatment of hyperlipidemia should take into account the pre-treatment status and dietary habits. For patients with grade 2 hypercholesterolemia (>300 mg/dL or 7.75 mmol/L) or grade 2 hypertriglyceridemia (>2.5 x upper normal limit) consideration should be given to treatment with a statin or appropriate lipid-lowering medication, in addition to diet. Patients should be monitored clinically and through serum biochemistry for the development of rhabdomyolysis and other adverse events as required in the product label/data sheets for HMG-CoA reductase inhibitors.

Note: Concomitant therapy with fibrates and an HMG-CoA reductase inhibitor is associated with an increased risk of a rare but serious skeletal muscle toxicity manifested by rhabdomyolysis, markedly elevated creatine kinase (CPK) levels and myoglobinuria, acute

renal failure and sometimes death. The risk versus benefit of using this therapy should be determined for individual patients based on their risk of cardiovascular complications of hyperlipidemia.

Grade 3 ***hyperglycemia*** has been observed in patients receiving RAD001 therapy. In almost all cases the affected patients had an abnormal fasting glucose at baseline. Based on this finding, we suggest that optimal glucose control should be achieved before starting a patient on RAD001 and should be monitored during RAD001 therapy. For patients who develop clinically significant hyperglycemia while on therapy, initiation of oral hypoglycemic or insulin therapy should be considered.

4.4.7 Management of non-infectious pneumonitis

Both asymptomatic radiological changes (grade 1) and symptomatic non-infectious pneumonitis (grade 2 = not interfering with activities of daily living or grade 3 = interfering with activities of daily living and oxygen indicated) have been noted in patients receiving RAD001 therapy. Non-infectious pneumonitis has been associated with RAD001 and other mTOR inhibitors (Atkins, 2004). In order to monitor for asymptomatic (grade 1) pulmonary infiltrates, a chest X-ray is required if a CT scan of chest is not used for bi-monthly disease evaluations. Additional chest X-rays/CT scans may be done, when clinically necessary. If non-infectious pneumonitis develops, consultation with a pulmonologist should be considered. Management of non-infectious pneumonitis suspected to be associated with RAD001 and dose modifications instructions are provided in Table 4.4.

Table 4.4 Management of non-infectious pneumonitis

Worst Grade Pneumonitis	Required Investigations	Management of Pneumonitis	Actions
Grade 1	**CT scans with lung windows.**	**No specific therapy is required**	**Administer 100% of RAD001 and temozolomide doses.**
Grade 2	**CT scan with lung windows. Consider pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat each subsequent Cycle until return to within normal limits. Consider a bronchoscopy.**	**Symptomatic only. Prescribe corticosteroids if cough is troublesome.**	**Discontinue study therapy until recovery to ≤ grade 1. Study therapy may also be interrupted if symptoms are troublesome. If recovered, resume treatment with RAD001 and temozolomide at one lower dose level. Patients will be withdrawn from the study if they fail to recover to ≤ grade 1 within 3 weeks.**
Grade 3	**CT scan with lung windows and pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest.; Repeat each subsequent Cycle until return to within normal limits. Bronchoscopy is**	**Prescribe corticosteroids if infective origin is ruled out. Taper as medically indicated.**	**Hold RAD001 and temozolomide until recovery to ≤ grade 1. May restart RAD001 and temozolomide within 2 weeks at a reduced dose (by one level) if evidence of clinical benefit.**

Worst Grade Pneumonitis	Required Investigations	Management of Pneumonitis	Actions
	recommended.		
Grade 4	**CT scan with lung windows and required pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Repeat each subsequent Cycle until return to within normal limits. Bronchoscopy is recommended.**	**Prescribe corticosteroids if infective origin is ruled out. Taper as medically indicated.**	**Discontinue RAD001 and temozolomide.**

***** Patients will be removed from study if there is a repeat episode of pneumonitis or if pneumonitis does not resolve within 2 weeks.

4.5 Treatment Plan

4.5.1 Investigational therapy

The investigational therapy used in the course of this study is RAD001 in combination with temozolomide. Study medication will be administered by the patients themselves. Patients are provided with a diary to document date, time, dose and any symptoms they experience while taking study medications. During the study, RAD001 will be administered orally as a once daily dose continuously from study day 1 until progression of disease or unacceptable toxicity. Patients in cohort 1 will receive RAD001 at a dose of 5 mg per day in combination with temozolomide 150 mg/m^2/day on days 1-7 and 15-21 of each 28-day treatment cycle. Patients will be monitored for 7 days after their first cycle of therapy. They will not receive therapy during this observation period. Patients in cohort 2 will receive RAD001 at a dose of 10 mg per day in combination with temozolomide 150 mg/m^2/day on days 1-7 and 15-21 of each 28-day treatment cycle. Patients will be monitored for 7 days after their first cycle of therapy. They will not receive therapy during this observation period. Patients in cohort 3 will receive RAD001 at the maximum tolerated dose in combination with temozolomide 150 mg/m^2/day on days 1-7 and 15-21 of each 28-day treatment cycle.

Medication labels will comply with US legal requirements and be printed in English. They will supply no information about the patient. The storage conditions for study drug will be described on the medication label.

4.5.1.1 RAD001

RAD001 will be provided by Novartis. RAD001 is formulated as tablets for oral administration of 5mg strength. Tablets are blister-packed under aluminum foil in units of 10 tablets, which should be opened only at the time of administration as drug is both hygroscopic and light-sensitive.

RAD001 should be taken by the patient in a fasting state or with no more than a light fat-free meal. Vomited doses and missed doses should not be repeated. Dietary habits around the time of RAD001 intake should be as consistent as possible throughout the study.

4.5.1.2 RAD001 pharmacokinetics

The pharmacokinetic characteristics of RAD001 have been extensively investigated in the context of the drug's development as an immunosuppressant in solid organ transplantation where RAD001 was administered twice daily as a part of an immunosuppressant, multi-drug regimen consistently including cyclosporin A and glucocorticoids. Recent Phase I studies provide steady-state pharmacokinetics for both the weekly and daily schedules at varying dose levels in patients with advanced cancers.

RAD001 is rapidly absorbed after oral administration, with a median time to peak blood levels (t_{max}) of 1-2 hours postdose. The extent of absorption is estimated at above 11%. The area under the blood concentration-time curve (AUC) is dose-proportional over the dose range tested while maximum blood concentration C_{max} appears to plateau at dose levels higher than 20 mg. The terminal half-life in cancer patients averaged 30 hours, which is similar to that in healthy subjects. Inter-patient variability is moderate with the coefficient of variation (CV) of approximately 50%. A high-fat meal altered the absorption of RAD001 with 1.3 hour delay in $t_{max,}$ a 60% reduction in C_{max} and a 16% reduction in AUC. In whole blood, approximately 80% of RAD001 is contained in red blood cells. Of the fraction of drug contained in plasma, 74% is protein-bound. The apparent distribution volume (Vz/F) after a single dose was 4.7 L/kg. RAD001 is eliminated by metabolism, mainly by hydroxylation, then excreted into the feces >80%.

RAD001 is mainly metabolized by CYP3A4 in the liver and to some extent in the intestinal wall. RAD001 is also a substrate of P-glycoprotein (P-gp). Therefore, absorption and subsequent elimination of systematically absorbed RAD001 may be influenced by medicinal products that interact with CYP3A4 and/or P-glycoprotein. *In vitro* studies showed that RAD001 is a competitive inhibitor of CYP3A4 and of CYP2D6 substrates, potentially increasing the concentrations of medicinal products eliminated by these enzymes. In two phase III clinical trials in patients following kidney transplantation, strong inhibitors of CYP3A4 (azoles, antifungals, cyclosporine, erythromycin) have been shown to reduce the clearance of RAD001 therapy thereby increasing RAD001 blood levels. Similarly, Rifampin, a strong inducer of CYP3A4, increases the clearance of RAD001 thereby reducing RAD001 blood levels. Caution should be exercised when co-administering RAD001 with CYP3A4 inhibitors or inducers.

Pharmacokinetic drug to drug interactions with cancer agents are being evaluated in ongoing phase Ib studies. Based on currently available results, gemcitabine (study 2101 part 2) and paclitaxel (study 2104) did not alter RAD001 pharmacokinetics to a clinically relevant extent whereas imatinib notably increased RAD001 exposure with a mean increase in AUC by a multiple of 3.7 for RAD001 administered weekly and two-fold for RAD001 administered daily (study 2206). Exposure to RAD001 in the presence of letrozole did not exceed that in monotherapy (study 2108). Co-administration of RAD001 did not influence pharmacokinetics of gemcitabine, imatinib or letrozole. Exposure to paclitaxel in the presence of RAD001 was slightly decreased (average by 23%).

RAD001 pharmacokinetics in transplant patients was investigated in special populations such as subjects with hepatic or renal impairment, various ethnic groups and pediatric renal transplant patients. In subjects with mild–moderate hepatic impairment, mean AUC to RAD001 is increased by 3-fold whilst renal impairment does not affect the pharmacokinetics

of RAD001. Age, weight (both over the adult range) and gender do not affect the pharmacokinetics of RAD001 to a clinically relevant extent. Also, pharmacokinetics does not alter in Japanese or Asian patients whereas black patients have 21% higher clearance compared to non-blacks. In children, the apparent clearance of RAD001 increases linearly with body surface. The clearance per square meter of body surface area is 12-fold higher compared with adult patients.

The pharmacokinetic parameters derived for RAD001 given weekly are summarized in Table 4.5.

Table 4-5 Steady-state RAD001 pharmacokinetics (weekly dosing)

Parameter	5 mg	10 mg	20 mg	30 mg	50 mg	70 mg
N	4	4	2	5	5	6
Tmax ()	1 (1-2)	1 (1)	1 (1)	2 (1-2)	1 (1-2)	1 (1)
C_{max} (ng/mL)	32 ± 15	69 ± 8	94 ± 0	88 ± 20	163 ± 63	174 ± 49
C_{max}/Dose Ng/mL/mg	6.5 ± 3.1	6.9 ± 0.8	4.7 ± 0.0	2.9 ± 0.7	3.3 ± 1.2	2.5 ± 0.7
AUC ^{ss} (ng-h/mL)	283 ± 48	573 ± 258	1001 ± 301	1798 ± 827	2621 ± 633	3615 ± 1497
AUC ^{ss}/Dose (ng-h/mL/mg)	57 ± 10	57 ± 27	50 ± 15	60 ± 28	52 ± 13	52 ± 21
$t_{1/2}$ (h)	26 ± 3	38 ± 14	31 ± 12	37 ± 6	27 ± 7	26 ± 2

Values are median (range) for tmax and mean ± standard deviation for all others.
Reference: RAD001 Investigator's Brochure 2005

Cmax was achieved by 1 to 2 hours post dose. While Cmax rose in roughly dose proportional manner from 5 to 20 mg/week, it appeared to increase less than proportionally at higher doses.

4.5.1.3 RAD001 Pharmacodynamic studies

Pharmacokinetic/pharmacodynamic modeling based on inhibition in a peripheral biomarker (S6 kinase inhibition in peripheral blood mononuclear cells) suggests that 5-10 mg daily should be an adequate dose to produce a high-degree of sustained target inhibition. Furthermore, molecular pharmacodynamic (MPD) studies using IHC in biopsied tumor tissue assessed the degree of inhibition and its duration (for p-S6, p-4E-BP1 and p-Akt expression) with the daily and weekly dosing. The pathologist was blinded for the biopsy sequence. There was almost complete inhibition of p-S6 at all doses and schedules studied (p=0.001). Preliminary results suggest a dose-related decrease in p-4E-BP1 and increase in p-Akt expression with maximal effect at 10 mg daily and ≥ 50 mg weekly. The study results are provided in Table 4-6.

Table 4-6 p-S6, p-4E-BP1 and p-Akt expression at various doses of RAD001

Dose of RAD001	p-S6 inhibition (mean %)	p-4E-BP1 inhibition (mean %)	p-Akt activation (mean %)

Daily 5 mg (n=3)	100.0	48.0	22.2
Daily 10 mg (n=6)	92.5	58.2	45.5
Weekly 20 mg (n=5)	96.7	5.9	32.7
Weekly ≥ 50 mg (n=6)	100.0	63.8	63.1
Reference: RAD001 Investigator's Brochure 2005			

4.5.1.4 Temozolomide

Temozolomide is available in 5mg, 20mg, 100mg, and 250mg capsules which are supplied in amber glass bottles with child-resistant polypropylene caps. The capsules should not be opened or chewed. They should be swallowed whole with a glass of water. Procedures for handling and disposal of anticancer drugs should be considered.

The dose of Temozolomide will be based on baseline BSA +/- 5%. The dose of temozolomide should be rounded down to the nearest dose available through combination of appropriate capsules. To facilitate patient administration of temozolomide, a simpler combination of pills is acceptable if the total dose is within +/- 5% of the calculated dose based on BSA. The exact dose administered will be recorded in the case report form (CRF). The dose of temozolomide will be recalculated when BSA changes >5% or <5% from baseline.

Temozolomide should be given with approximately 8 ounces of water over as short a time as possible. Patients should be instructed to swallow capsules whole and in rapid succession and to not chew capsules. If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. Missed doses should not be repeated. It is recommended that patients take Temozolomide at bedtime and fast for 2 hours before each dose and continue fasting for 1 hour after each dose. Water is allowed during the fasting period.

4.5.2 Concomitant therapy

1. Patients on study therapy may be at risk for temozolomide-related selective lymphopenia and opportunistic infections. To reduce the risk of opportunistic infections, patients will receive prophylaxis with Bactrim DS, 1 tablet orally every Monday, Wednesday, and Friday. Patients allergic to Bactrim should be initiated on an alternate, standard PCP prophylaxis regimen. Prophylaxis will begin for all patients after completing their first cycle of therapy (approximately one month after beginning therapy).

2. Temozolomide may be emetogenic, and it is suggested that patients take compazine 10 mg po prior to each dose while beginning their treatment regimen. Other antiemetics may be utilized at the discretion of the treating physician. If patients appear to tolerate Temozolomide without nausea, the routine prophylactic use of compazine may be

discontinued. If refractory nausea develops, the use of prophylactic odansetron should be considered.

3. All patients should be maintained on the same medications throughout the study period, as medically feasible.

4. The investigator should instruct the patient to notify the study staff about any new medications he/she takes after the start of the study drug. All medications (other than study drug/s) and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug/s must be recorded.

4.5.3 Prohibited medications

1. Growth factors cannot be used to induce elevations in neutrophil count for the purposes of administration of Temozolomide on the scheduled dosing interval or to allow treatment with Temozolomide at a higher dose.

2. Use of erythropoietin is allowed.

3. No other investigational drugs will be allowed during the study.

4. Patients must be instructed not to take any additional medications (including over-the-counter products) during the trial without prior consultation with the investigator. All medications taken within 30 days of screening should be recorded. If concomitant therapy must be added or changed, the reason and name of the drug/therapy should be recorded.

5. In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient are allowed, including drugs given prophylactically (e.g. antiemetics +/- steroids), with the following exceptions:
   - no other investigational therapy should be given to patients
   - no chronic treatment with systemic steroids or another immunosuppressive agent
   - no anticancer agents other than the study medications administered as part of this study protocol should be given to patients. If such agents are required for a patient then the patient must first be withdrawn from the study.
   - leukocyte growth factors (e.g.G-CSF and GM-CSF) are not to be administered systematically but may be prescribed by the investigator for severe neutropenia if this is thought to be appropriate.
   - no live vaccines should be administered to patient due to immunosuppressant potential of RAD001.
   - drugs or substances known to be inhibitors or inducers of the isoenzyme CYP3A (Table 4.7) cannot be administered in association with RAD001 as these can alter

metabolism. Strong inhibitors or inducers of the isoenzyme CYP3A cannot be administered as systemic therapy.

Table. 4.7 Clinically relevant drug interaction: substrates, inducers and inhibitors of isoenzyme CYP3A

Substrates	
Antibiotics: **clarithromycin** **erythromycin** **NOT azithromycin** **telithromycin** Anti-arrhythmics: **quinidine** Benzodiazepines: **alprazolam** **diazepam** **midazolam** **triazolam** Immune Modulators: **cyclosporine** **tacrolimus (FK506)** HIV Protease Inhibitors: **indinavir** **ritonavir** **saquinavir** Prokinetic: **cisapride** Antihistamines: **astemizole** **chlorpheniramine**	Calcium Channel Blockers: **amlodipine** **diltiazem** **felodipine** **nifedipine** **nisoldipine** **nitrendipine** **verapamil** HMG CoA Reductase Inhibitors: **atorvastatin** **cerivastatin** **lovastatin** **NOT pravastatin** **simvastatin** Miscellaneous: **aripiprazole** **buspirone** **gleevec** **haloperidol (in part)** **methadone** **pimozide** **quinine** **NOT rosuvastatin** **sildenafil** **tamoxifen** **trazodone** **vincristine**

Inducers		
Carbamazepine **Phenobarbital** **Phenytoin**	**Rifabutin** **Rifampin**	**St John's wort** **Troglitazone**

Inhibitors		
Amiodarone **Cimetidine** **Clarithromycin** **Diltiazem** **Erythromycin**	**Fluvoxamine** **Grapefruit juice** **Seville orange juice or product** **Indinavir** **Itraconazole** **Ketoconazole**	**Mibefradil** **Nefazodone** **Nelfinavir** **Ritonavir** **Troleandomycin** **Verapamil**

Reference to published literature: http://www.medicine.iupui.edu/flockhart/clinlist.htm as of July 13, 2006

4.5.4 Treatment compliance

Records of study medication used, dosages administered, and intervals between visits will be recorded during the study. Drug accountability will be noted and patients will be asked to return all unused study medication.

5 Visit schedule and assessments

5.1 Visit schedule and assessments

5.1.1 Pretreatment evaluation

Tests to be performed within 28 days prior to initiation of therapy (if day 28 falls on a weekend or holiday the deadline may be extended to the next working day):

- Radiologic assessment of tumor burden by CT scan within 28 days prior to initiation of therapy.
- Assessment of secretory proteins within 28 days prior to initiation of therapy. All patients will undergo an initial assessment of chromogranin A. Measurement of gastrin, VIP, or other secretory proteins will also be performed depending on tumor type.

Tests to be performed within 14 days prior to initiation of therapy (if day 14 falls on a weekend or holiday, the deadline may be extended to the next working day):

- All patients will be assessed by history and physical examination, including height, weight, vital signs, and performance status within 14 days prior to initiation of therapy.
- Baseline hematological and biochemical profiles, including CBC with differential, platelets, and serum chemistries: fasting glucose, sodium, potassium, chloride, bicarbonate, creatinine, blood urea nitrogen, albumin, total protein, SGOT (AST), SGPT (ALT), total bilirubin, alkaline phosphatase, calcium, magnesium, phosphate.
- Serum pregnancy test for women of childbearing potential

5.1.2 Evaluations during treatment

5.1.2.1 Day 1 of every cycle

- Physical examination
- Toxicity assessment
- Vital signs
- Weight
- Serum chemistries

- CBC with differential

5.1.2.2 Day 15 of cycles 1 through 6 only

- Physical examination
- Toxicity assessment
- Vital signs
- Weight
- CBC with differential

5.1.2.3 Data to be obtained following every 2 cycles of treatment (time of restaging):

- Radiologic assessment of tumor burden by CT scan
- Assessment of serum chromogranin A and other secretory proteins (if applicable).

5.1.3 Post-treatment evaluation

Data to be obtained at completion of study:

- Physical examination
- Toxicity assessment
- Vital signs
- Weight
- Serum chemistries
- CBC with differential
- Radiologic assessment of tumor burden by CT scan. All sites of tumor progression or metastases will be noted
- Progression-free and overall survival will be determined

Patients who have an ongoing Grade 4 or serious adverse event at the time of discontinuation from study drug treatment will continue to be followed at monthly intervals, until resolution of toxicity to < Grade 2.

5.1.3.1 Table of required data

Table 5.1. Evaluation and visit schedule

Examination	Screening		Every Cycle	Cycles 1- 6	Every 2 cycles	End
	-28 days	-14 days	Day 1	Day 15		
Screening [a]		X				
History		X	X*	X		X
Physical Exam		X	X*	X		X
Vital Signs		X	X*	X		X
Height		X				
Weight		X	X*	X		X
ECOG PS		X	X*			X
Pregnancy Test [b]		X				
Hematology [c]		X	X*	X		X
Serum Chemistry [d]		X	X*			X
Serum Lipid Profile [e]		X			X	X
Radiologic Assessment of Tumor Burden [f]	X				X	X
Secretory proteins, serum chromogranin [g]	X				X	X
Prior/concomitant medication		X	continuous ----------			
Adverse events		X	continuous ----------			

* Screening tests do not need to be repeated for cycle 1.

[a] Screening includes review of: demography/informed consent, inclusion/exclusion criteria, relevant medical history/concomitant medications, diagnosis and extent of cancer

[b] For women of child-bearing potential: Women of childbearing potential must have a negative serum pregnancy test within 14 days of enrollment. Acceptable contraception should be used while on study and for at least 30 days after the last dose of RAD001.

[c] Hematology must include: hemoglobin, hematocrit, platelets, total white blood cell count (WBC) and differential

[d] Serum chemistry should be performed while fasting and include: fasting glucose, sodium, potassium, chloride, bicarbonate, creatinine, blood urea nitrogen, albumin, total protein, SGOT (AST), SGPT (ALT), total bilirubin, alkaline phosphatase, calcium, magnesium, phosphate.

[e] Fasting serum lipid profile (repeated every three months) must include: total cholesterol, triglycerides, LDL, and HDL

[f] Screening radiologic tests include abdominal and pelvic CT or MRI and must be done within 28 days of first RAD001 and temozolomide dose. Radiological scans documenting target lesions should be repeated every two months. If an initial observation of a partial or complete response is made, a confirmation scan should be done no sooner than 4 weeks and no more than 6 weeks after the initial observation. The same type of scan should be used at each evaluation.

[g] Assessment of secretory proteins will be performed within 28 days prior to initiation of therapy.

6 Efficacy assessments

The primary efficacy endpoint is objective response rate as determined by radiology review. Important secondary endpoints are response duration and progression-free survival.

6.1 Criteria for response

The Response Evaluation Criteria in Solid Tumors (RECIST) guidelines will be employed in this study. For the purposes of this study, target lesions are defined as metastatic lesions that are bidirectionally measurable with one diameter measuring at least 2 cm (or 1 cm with spiral CT scan). All lesions up to a maximum of 10 lesions representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or

clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

Measurable disease: lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$ 20mm with conventional techniques or as $\geq$ 10mm with spiral CT scan.

Non-measurable disease: all other lesions, including small lesions (longest diameter < 20mm with conventional techniques or < 10mm with spiral CT scan).

Complete response (CR): complete disappearance of all target lesions, confirmed by repeat assessments at no less than 4 weeks after the criteria for response are first met.

Partial response (PR): at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter. This must be confirmed by repeat assessment at no less than 4 weeks after the criteria for response are first met.

Progressive disease (PD): at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions.

Stable Disease (SD): neither sufficient decrease to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started.

Non-target Lesions: all other lesions (or sites of disease) not included in the "target disease" definition should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present" or "absent".

Complete Response: Disappearance of all non-target lesions.

Non-complete response/Non-progression: Persistence of one or more non-target lesions.

Progression: Appearance of one or more new lesions. Unequivocal progression of existing non-target lesions.

Cytology and Histology: if the measurable disease is restricted to a solitary lesion, its neoplastic nature should ideally be confirmed by cytology or histology. These techniques can be used to differentiate between PR and CR in rare cases.

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response, stable disease, and progressive disease

Evaluation of Best Overall Response: the best overall response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note:
Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

6.2 Guidelines for Evaluation of Measurable Disease

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial (e.g. skin nodules, palpable lymph nodes). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

Chest X-ray. Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT scan is preferable.

CT scan. Conventional CT scan should be performed with cuts of 10mm or less in slice thickness contiguously. Spiral CT scan should be performed using a 5mm contiguous reconstruction algorithm. This applies to the chest, abdomen, and pelvis. Head & neck and extremeties usually require specific protocols.

Ultrasound. Ultrasound should not be used to measure tumor lesions that are clinically not easily accessible when the primary endpoint of the study is objective response evaluation. It is a possible alternative to clinical measurements of superficial palpable nodes, subcutaneous lesions, and thyroid nodules. Ultrasound may also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

6.3 Confirmation Measurement/Duration of Response

Confirmation: To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat studies that should be performed no less than 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks.

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

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

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

Progression Free Survival (PFS): PFS is defined as the time from the date of first study treatment to the date of the first documented disease progression or death due to any cause. If a patient has not progressed or died at the date of the analysis cut-off or when he/she receives any further anti-cancer therapy, PFS is censored at the time of the last tumor assessment before the cut-off or the anti-cancer therapy date.

7 Safety assessments

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology, blood chemistry and urine values, regular measurement of vital signs and the performance of physical examinations.

These assessments should be performed within ±2 days of the scheduled day of assessment except for adverse events that will be evaluated continuously through the study. Safety and tolerability will be assessed according to the NIH/NCI CTCAE http://ctep.cancer.gov/forms/CTCAEv3.pdf.

7.1 Adverse events

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. the severity grade (mild, moderate, severe) or (grade 1-4)
2. its relationship to the study drug(s) (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. whether it constitutes a serious adverse event (SAE)

All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the [Investigators' Brochure] or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

7.1.1 Serious adverse events

Information about all serious adverse events will be collected and recorded. To ensure patient safety each serious adverse event must also be reported to Novartis within 24 hours of learning of its occurrence. A serious adverse event is an undesirable sign, symptom or medical condition which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect

- 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 (specify what this includes)
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - 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
  - 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

Lymphopenia is an expected toxicity of this regimen and is not life threatening. Patients are prescribed prophylactic Bactrim and do not receive more than 6 months of treatment with Temozolomide to minimize the effects of this toxicity. Grade 3-4 lymphopenia will not be considered a Serious Adverse Event. Information regarding this toxicity will be collected although reporting of each instance of grade 3-4 lymphopenia will not be required.

7.1.2 Novartis instructions for rapid notification of serious adverse events

The principal investigator has the obligation to report all serious adverse events to the FDA, IRB, and Novartis Pharmaceuticals Clinical Safety and Epidemiology Department (CS&E).

All events reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form).

All events must be reported, by FAX (888-299-4565), to Novartis Pharmaceuticals CS&E Department within 24 hours of learning of it's occurrence. 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 must be reported within 5 working days.

Any serious adverse event occurring after the patient has provided informed consent and until 4 weeks after the patient has stopped study participation must be reported. 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 after study discontinuation need only be reported if a relationship to the Novartis study drug (or therapy) is suspected.

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

7.2 Pregnancies

Any pregnancy that occurs during study participation should be reported. To ensure patient safety each pregnancy must also be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications.

7.3 Evaluations

7.3.1 Hematology

Hematology must include hemoglobin, hematocrit, platelets, total white blood cell count (WBC) and differential.

7.3.2 Blood chemistry

Blood chemistry must be performed in a fasting state and include: fasting glucose, sodium, potassium, chloride, bicarbonate, creatinine, blood urea nitrogen, albumin, total protein, SGOT (AST), SGPT (ALT), total bilirubin, alkaline phosphatase, calcium, magnesium, phosphate. Serum lipid profile (triglycerides, total cholesterol, HDL and LDL) will be checked after every two cycles of therapy.

Because accurate serum glucose and lipid measurements are required, patients should be fasting at the time of the blood sampling.

Assessment of secretory proteins will be performed at baseline. All patients will undergo an initial assessment of chromogranin A. Measurement of gastrin, VIP, or other secretory proteins will also be performed depending on tumor type.

7.3.3 Vital signs

Vital sign assessment consists of height (first visit), pulse, blood pressure, respiration rate, temperature and weight. Blood pressure, pulse and respiration rate should be measured on patients after at least 3 minutes in the sitting position

7.3.4 Physical examination

Physical examination will be performed which must comprise a total body examination (general appearance, skin, neck, including thyroid, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and basic nervous system).

Significant findings made after the start of study drug which meet the definition of an Adverse Event must be recorded.

7.3.5 Performance status

Performance status will be assessed using the Eastern Cooperative Oncology Group (ECOG) perfomance status scale, as follows:

Grade	Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

7.3.6 Drug levels and pharmacokinetic assessments

Drug level and pharmacokinetic assessments will not be measured.

8 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 by Novartis 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. All amendments must be reviewed by the DFCI IRB. A copy of the written approval of the IRB must be provided to Novartis. Examples of amendments requiring such approval are:

1. increases in drug dose or duration of exposure of subjects,
2. significant changes in the study design (e.g. addition or deletion of a control group),
3. increases in the number of invasive procedures,
4. addition or deletions of a test procedure required for monitoring of safety.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or by Novartis 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 Novartis 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. Examples of administrative changes not requiring formal protocol amendments and IRB approval include:

1. changes in the staff used to monitor trials
2. minor changes in the packaging or labeling of study drug.

9 Data management

9.1 Data collection

The DF/HCC QACT will develop a set of electronic case report forms (eCRFs). These forms are designed to collect data for each study. The CRCs designated at each institution will enter data on the eCRFs, and data will be reviewed by the Overall PI.

10 Statistical methods

10.1 Sample size and power calculation

The study is designed with a total accrual goal of up to 44 patients (up to 12 in Cohorts 1/2 and up to 32 in Cohort 3). If no toxicity is observed in the first two cohorts of patients, a total of 32 patients in Cohort 3 will be treated at the full dose of each drug (RAD001 at the MTD plus temozolomide).

A two-stage design will be employed for the patients treated at the full doses of each drug: 17 patients in the first stage and 15 patients in the second stage. The research plan incorporates anticipated response rate into the early stopping rule. At the end of the first stage of accrual (17 patients) data will be reviewed to decide if the study should be terminated due to inactivity of the treatment. Thus, the design protects patients from inappropriate treatment. The investigators would wish to conclude that the regimen is worthy of further pursuit if the clinical response rate is 20% or greater, and conclude that the regimen is not worthy of pursuit if the response rate is 5% or less (Please refer to Section 1.2). The proposed design is based on the following criteria:

1. In the first stage, 17 patients will be treated
2. If there are 0 responses, the study will be terminated
3. If there are 1 or more responses, the study will proceed to the second stage, accruing an additional 15 patients to a total of 32
4. If the second stage is completed with a total of 3 or more responses, then it will be concluded that the treatment deserves further study
5. Conversely, it the responses total 2 or fewer, then the treatment will not be recommended for further study.

With this design, the probability of terminating the study after 17 patients is 0.42 if the true but unknown response rate is 5%, but 0.02 if the true but unknown response rate is 20%. The study will have overall power of 0.95, and overall type I error of 0.18. Allowing for a 5% rate of ineligibility, the overall accrual goal will be 32 patients.

10.2 Statistical analysis

For the primary objective, we will estimate the response rate and provide the associated 95% confidence interval. For the secondary objectives, we will use the Kaplan-Meier method to estimate the distributions of time to response and progression-free survival. We will apply multivariate analysis to further examine effects of factors that are potentially related to these outcomes.

11 Registration Procedures

11.1 General Guidelines for DF/HCC and DF/PCC Institutions

Institutions will register eligible participants with the DF/HCC Quality Assurance Office for Clinical Trials (QACT) central registration system. Registration must occur prior to the initiation of therapy. Any participant not registered to the protocol before treatment begins will be considered ineligible and registration will be denied.

A member of the study team will confirm eligibility criteria and complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol treatment. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a participant does not receive protocol therapy following registration, the participant's protocol status must be changed. Notify the QACT Registrar of participant status changes as soon as possible.

11.2 Registration Process for DF/HCC and DF/PCC Institutions

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situation when a participant must begin treatment during off-hours or holidays, call the QACT registration line at 617-632-3761 and follow the instructions for registering participants after hours. Registrations received after 5pm EST aren't processed until the next business morning.

The registration procedures are as follows:

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.

2. Complete the protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical/research record. **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist.**

   Reminder: Confirm eligibility for ancillary studies at the same time as eligibility for the treatment study. Registration to both treatment and ancillary studies will not be completed if eligibility requirements are not met for all studies.

3. Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at 617-632-2295.

   Exception: DF/PCC Affiliate sites must fax the entire signed consent form including HIPAA Privacy Authorization and the eligibility checklist to the Network Affiliate Office. The Network Affiliate Office will register the participant with the QACT.

4. The QACT Registrar will (a) validate eligibility, (b) register the participant on the study, and (c) randomize the participant when applicable.

5. The QACT Registrar will send an email confirmation of the registration and/or randomization to the person initiating the registration immediately following the registration and/or randomization. Treatment can not be initiated until after receipt of registration confirmation.

11.3 Registration Process for Other Participating Institutions

Please see section 5.7 in DSMP, Appendix B

12 Data and Safety Monitoring

12.1 Data Reporting

12.1.1 Method

The QACT will collect, manage, and monitor data for this study.

12.1.2 Data Submission

The schedule for completion and submission of case report forms (paper or electronic) to the QACT is as follows:

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration with QACT
On Study Form	Within 14 days of registration
Baseline Assessment Form	Within 14 days of registration
Treatment Form	Within 10 days of the last day of the cycle
Adverse Event Report Form	Within 10 days of the last day of the cycle
Response Assessment Form	Within 10 days of the completion of the cycle required for response evaluation
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

12.2 Safety Meetings

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team.

The DSMC will meet quarterly and/or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days for Phase I or II protocols; for gene transfer protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives

designated by the Principal Investigator (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

13 References

Adjei A, Hidalgo M (2006) Intracellular signal transduction pathway proteins as targets for cancer therapy. J Clin Oncol; 23, 5386-5403.

Adlard J, Richman S, Seymour M, et al. (2002) Prediction of the response of colorectal cancer to systemic therapy. The Lancet; 3, 75-82.

Atkins MB, Hidalgo M, Stadler WM, et al. (2004) Randomized phase II study of multiple dose levels of CCI-779, a novel mammalian target of rapamycin kinase inhibitor, in patients with advanced refractory renal cell carcinoma. J Clin Oncol; 22, 909-918.

Atkinson EN, Brown BW (1985) Confidence limits for probability of response in multistage phase II clinical trials. Biometrics: 41, 741-744.

Barakat MT, Meeran K, Bloom SR (2004) Neuroendocrine tumors. Endocrine-related Cancer 11: 1-18.

Bjornsti MA, Houghton PJ. (2004) The TOR pathway: a target for cancer therapy. Nat Rev Cancer; 4, 335-48.

Chang, S. M., M. D. Prados, et al. (2004). "Phase II study of neoadjuvant 1, 3-bis (2-chloroethyl)-1-nitrosourea and temozolomide for newly diagnosed anaplastic glioma: a North American Brain Tumor Consortium Trial." Cancer 100(8): 1712-6.

Cheng, P. and L. Saltz, Failure to confirm major objective antitumor activity ofr streptozocin and doxorubicin in the treatment of patients with advanced islet cell carcinoma. Cancer, 1999. 86: p. 944-8.

Cohen SJ, Cohen RB, Meropol N (2005) Targeting signal transduction pathways in colorectal cancer – more than skin deep. J Clin Oncol; 23, 5374-5385.

Clopper CJ, Pearson ES (1934) The use of confidence or fiducial Limits illustrated in the case of the binomial. Biometrika; 26, 404-413.

Cunningham D, Humblet Y, Siena S, et al. (2004) Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med; 351, 337-345.

Danson, S. J. and M. R. Middleton (2001). "Temozolomide: a novel oral alkylating agent." Expert Rev Anticancer Ther 1(1): 13-9.

Ekeblad S, Sundin A, Janson ET, et al. (2007) Temozolomide as monotherapy is effective in treatment of advanced malignant neuroendocrine tumors. Clin Cancer Res; 13, 2986-91.

Frattini M, Signoroni S, Pilotti S, et al. (2005) Letter to the Editor: Phosphatase protein homologue to tensin expression and phosphatidylinositol-3 phosphase kinase mutations in colorectal cancer. Cancer Res; 65, 11227.

Goel A, Arnold CN, Niedzwiecki D, et al. (2004) Frequent inactivation of PTEN by promoter hypermethylation in microsatellite instability-high sporadic colorectal cancers. Cancer Res; 64, 3014-3021.

Grothey, A, Sarge D, Goldberg RM, et al. (2004) Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. J Clin Oncol; 22, 1209-1214.

Hammond, L. A., J. R. Eckardt, et al. (1999). "Phase I and pharmacokinetic study of temozolomide on a daily-for-5-days schedule in patients with advanced solid malignancies." J Clin Oncol 17(8): 2604-13.

Hurwitz H, Fehrenbacher L, Novotny W, et al. (2004) Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med.; 23, 2335-42.

Ikenoue T, Kanai F, Hikiba Y, et al. (2005) Functional analysis of PIK3CA Gene Mutations Cancer Res; 65, 4562-5467.

Kaper F, Dornhoefer N, Giaccia A. (2006) Mutations in the PI3K/PTEN/TSC2 pathway contribute to mammalian target of rapamycin activity and increased translation under hypoxic conditions. Cancer Res; 66, 1561-1569.

Khaleghpour K, Li Y, Banville D, et al (2004) Involvement of the PI 3-kinase signaling pathway in progression of colon adenocarcinoma. Carcinogenesis; 25, 241-8.

Kianoush K, Li Y, Banville D, et al. (2004) Involvement of the PI 3-kinase signaling pathway in progression of colon adenocarcinoma. Carinogenesis; 25, 241-248.

Kulke, M., C. Frauenhoffer, et al. (2007). "Loss of MGMT Expression Predicts Responses to Temozolomide-based Therapy in Patients with Advanced Neuroendocrine Tumors." ASCO Annual Meeting.Proceedings.

Kulke, M., K. Stuart, et al. (2006). "A phase II study of temozolomide and bevacizumab in patients with advanced neuroendocrine tumors." Journal of Clinical Oncology, 2006 ASCO Annual Meeting Proceedings 24(18S): A 4044.

Kulke, M. H., K. Stuart, et al. (2006). "Phase II study of temozolomide and thalidomide in patients with metastatic neuroendocrine tumors." J Clin Oncol 24(3): 401-6.

McCollum, A.D., et al., Lack of efficacy of streptozocin and doxorubicin in patients with advanced pancreatic endocrine tumors. Am J Clin Oncol, 2004. 27(5): p. 485-8.

Moertel, C., et al., Streptozocin-doxorubicin, stretpozocin-fluorouracil, or chlorozotocin in the treatment of advanced islet-cell carcinoma. N Engl J Med, 1992. 326: p. 519-23.

Morrow C, Gray A, Dive C. (2005) Comparison of phosphatidylinositol-3-kinase signaling within a panel of human colorectal cancer cell lines with mutant or wild-type PIK3CA. FEBS Letters; 579, 5123-5128.

Oberg, K. and B. Eriksson, Medical treatment of neuroendocrine gut and pancreatic tumors. Acta Oncol, 1989. 28: p. 425-431.

Peeters M, Cutsem EV, Siena S, et al. (2006) A phase III, multicenter, randomized controlled trial (RCT) of panitumumab plus best supportive care (BSC) vs BSC alone in patients (pts) with metastatic colorectal cancer (mCRC). Proc Amer Assoc Cancer Res; 47.

Ramanathan, R. K., A. Cnaan, et al. (2001). "Phase II trial of dacarbazine (DTIC) in advanced pancreatic islet cell carcinoma. Study of the Eastern Cooperative Oncology Group-E6282." Ann Oncol 12(8): 1139-43.

Simon R (1989) Optimal two-stage designs for phase II clinical trials. Controlled Clinical Trials; 10, 1-10.

Stevens, M. F., J. A. Hickman, et al. (1987). "Antitumor activity and pharmacokinetics in mice of 8-carbamoyl-3-methyl-imidazo[5,1-d]-1,2,3,5-tetrazin-4(3H)-one (CCRG 81045; M & B 39831), a novel drug with potential as an alternative to dacarbazine." Cancer Res 47(22): 5846-52.

Tomassetti P, Campana D, Piscitelli L, et al (2005) Endocrine pancreatic tumors: factors correlated with survival. Ann Oncol 16:1806-1810.

van den Bent, M. J., M. J. Taphoorn, et al. (2003). "Phase II study of first-line chemotherapy with temozolomide in recurrent oligodendroglial tumors: the European Organization for Research and Treatment of Cancer Brain Tumor Group Study 26971." J Clin Oncol 21(13): 2525-8.

Velho S, Oliveira C, Ferreira A, et al. (2005) The prevalence of PIK3CA mutations in gastric and colon cancer. Eur J Cancer; 41, 1649-54.

Wang, L., A. Ignat, et al. (2002). "Differential expression of the PTEN tumor suppressor protein in fetal and adult neuroendocrine tissues and tumors: progressive loss of PTEN expression in poorly differentiated neuroendocrine neoplasms." Appl Immunohistochem Mol Morphol 10(2): 139-46.

Weber WA, Petersen V, Schmidt B, et al. Positron emission tomography in non-small-cell lung cancer: prediction of response to chemotherapy by quantitative assessment of glucose use. J Clin Oncol 2003;21:2651-2657.

Yao, J., T. Phan, et al. (2006). "Phase II study of RAD001 (everolimus) and depot octreotide (Sandostatin LAR) in patients with advanced low grade neuroendocrine carcinoma." J Clin Oncology, 2006 ASCO Annual Meeting Proceedings 24: A4042.

14 Procedures and instructions

14.1 Publication of results

Any formal presentation or publication of data from this trial may be published after review and comment by Novartis and prior to any outside submission. Novartis must receive copies of any intended communication in advance of publication (at least fifteen working days for presentational materials and abstracts and thirty working days for manuscripts). These requirements acknowledge Novartis' responsibility to provide peer input regarding the scientific content and conclusions of such publications or presentations. Principal Investigation/Institution shall have the final authority to determine the scope and content of its publications, provided such authority shall be exercised with reasonable regard for the interests of Novartis and, in accord with the trial contract and shall not permit disclosure of Novartis confidential or proprietary information.

14.2 Disclosure and confidentiality

The investigator agrees to keep all information provided by Novartis in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents provided by Novartis (investigators' brochures and other material) will be stored appropriately to ensure their confidentiality. The information provided by Novartis to the investigator may not be disclosed to others without direct written authorization from Novartis, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

14.3 Discontinuation of study

Novartis reserves the right to discontinue any study under the conditions specified in the clinical trial agreement.

14.4 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and the principles of Good Clinical Practice, as described in Novartis standard operating procedures and:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
3. Declaration of Helsinki and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects).

The investigator agrees to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

14.4.1 Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB). A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. Any amendments to the protocol, other than administrative ones, must be reviewed by Novartis approved by this committee.

14.4.2 Informed consent

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.

The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with it for IRB/IEC/REB approval.

14.4.3 Declaration of Helsinki

The investigator must conduct the trial in accordance with the principles of the Declaration of Helsinki. Copies of the Declaration of Helsinki and amendments will be provided upon request or can be accessed via the website of the World Medical Association at http://www.wma.net/e/policy/17-c_e.html.

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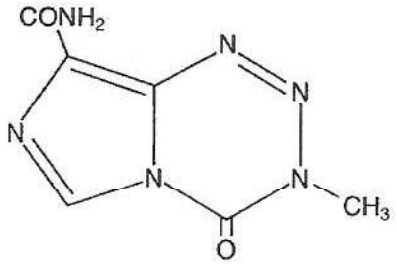
PRODUCT INFORMATION

TEMODAR®
(temozolomide)
CAPSULES

DESCRIPTION

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



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

Each capsule contains either 5 mg, 20 mg, 100 mg, or 250 mg of temozolomide. The inactive ingredients for TEMODAR Capsules are lactose anhydrous, colloidal silicon dioxide, sodium starch glycolate, tartaric acid, and stearic acid. Gelatin capsule shells contain titanium dioxide. The capsules are white and imprinted with pharmaceutical ink.

TEMODAR 5 mg: green imprint contains pharmaceutical grade shellac, anhydrous ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, ammonium hydroxide, titanium dioxide, yellow iron oxide, and FD&C Blue #2 aluminum lake.

TEMODAR 20 mg: brown imprint contains pharmaceutical grade shellac, anhydrous ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, purified water, ammonium hydroxide, potassium hydroxide, titanium dioxide, black iron oxide, yellow iron oxide, brown iron oxide, and red iron oxide.

TEMODAR 100 mg: blue imprint contains pharmaceutical glaze (modified) in an ethanol/shellac mixture, isopropyl alcohol, n-butyl alcohol, propylene glycol, titanium dioxide, and FD & C Blue #2 aluminum lake.

TEMODAR 250 mg: black, imprint contains pharmaceutical grade shellac, anhydrous ethyl alcohol, isopropyl alcohol, n-butyl alcohol, propylene glycol, purified water, ammonium hydroxide, potassium hydroxide, and black iron oxide.

CLINICAL PHARMACOLOGY

Mechanism of Action: Temozolomide is not directly active but undergoes rapid nonenzymatic conversion at physiologic pH to the reactive compound MTIC. The cytotoxicity of MTIC is thought to be primarily due to alkylation of DNA. Alkylation (methylation) occurs mainly at the O^6 and N^7 positions of guanine.

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 AIC 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 metabolite(s) (17%). Overall clearance of temozolomide is about 5.5 L/hr/m^2.

Special Populations: *Age* Population pharmacokinetic analysis indicates that age (range 19 to 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 (see **PRECAUTIONS**).

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 (see **ADVERSE REACTIONS**).

Race The effect of race on the pharmacokinetics of temozolomide has not been studied.

Tobacco Use Population pharmacokinetic analysis indicates that the oral clearance of temozolomide is similar in smokers and nonsmokers.

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 TEMODAR Capsules are administered to patients with severe renal impairment. TEMODAR 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.

Drug-Drug Interactions In a multiple-dose study, administration of TEMODAR Capsules 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% (see **PRECAUTIONS**).
Population analysis failed to demonstrate any influence of coadministered dexamethasone, prochlorperazine, phenytoin, carbamazepine, ondansetron, H_2-receptor antagonists, or phenobarbital on the clearance of orally administered temozolomide.

CLINICAL STUDIES

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

At the time of disease progression, TEMODAR was administered as salvage therapy in 161 patients of the 282 (57 %) in the RT alone arm, and 62 patients of the 277 (22%) in the TEMODAR + RT arm.
The addition of concomitant and maintenance TEMODAR to radiotherapy in the treatment of patients with newly diagnosed GBM showed a statistically significant improvement overall survival compared radiotherapy alone. (Figure 1) The hazard ratio (HR) for overall survival was 0.63 (95 % CI for HR=0.52-0.75) with a log-rank p <0.0001 in favor of the TEMODAR arm. The median survival was increased by 2 ½ months in the TEMODAR arm.

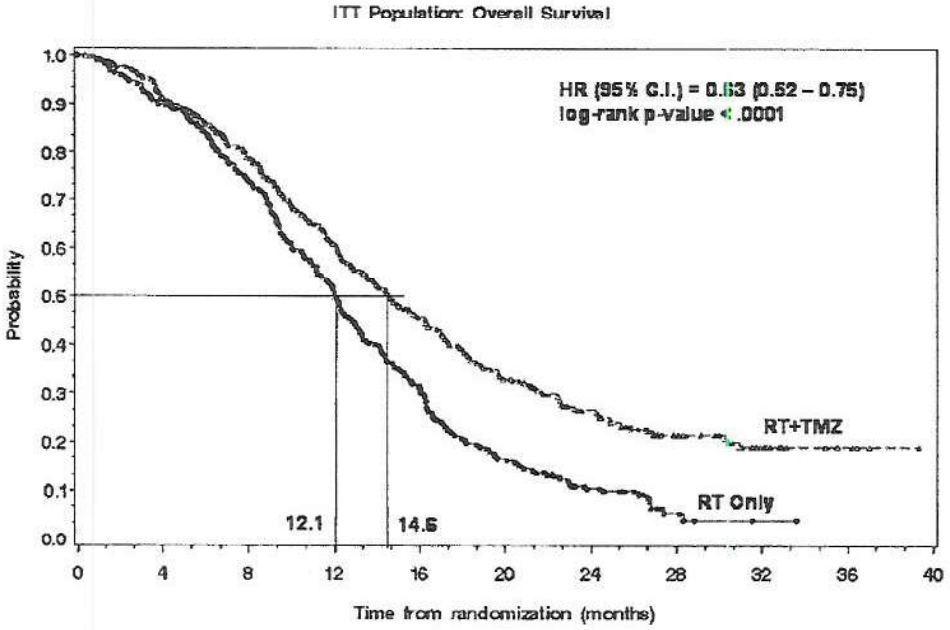


Figure 1 Kaplan-Meier Curves for Overall Survival (ITT Population)

Refractory (Anaplastic Astrocytoma)

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

underwent a subtotal resection and 27% underwent a gross total resection. Eighteen percent of patients had surgery at the time of first relapse. The median time from initial diagnosis to first relapse was 13.8 months (4.2 to 75.4).

TEMODAR Capsules were given for the first 5 consecutive days of a 28-day cycle at a starting dose of 150 mg/m^2/day. If the nadir and day of dosing (Day 29, Day 1 of next cycle) absolute neutrophil count was >1.5 x 10^9/L (1,500/µL) and the nadir and Day 29, Day 1 of next cycle, platelet count was >100 x 10^9/L (100,000/µL), the TEMODAR dose was increased to 200 mg/m^2/day for the first 5 consecutive days of a 28-day cycle.

In the refractory anaplastic astrocytoma population the overall tumor response rate (CR + PR) was 22% (12/54 patients) and the complete response rate was 9% (5/54 patients). The median duration of all responses was 50 weeks (range of 16 to 114 weeks) and the median duration of complete responses was 64 weeks (range of 52 to 114 weeks). In this population, progression-free survival at 6 months was 45% (95% confidence interval 31% to 58%) and progression-free survival at 12 months was 29% (95% confidence interval 16% to 42%). Median progression-free survival was 4.4 months. Overall survival at 6 months was 74% (95% confidence interval 62% to 86%) and 12-month overall survival was 65% (95% confidence interval 52% to 78%). Median overall survival was 15.9 months.

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

TEMODAR (temozolomide) Capsules are contraindicated in patients who have a history of hypersensitivity reaction to any of its components. TEMODAR is also contraindicated in patients who have a history of hypersensitivity to DTIC, since both drugs are metabolized to MTIC.

WARNINGS

Patients treated with TEMODAR Capsules may experience myelosuppression. Prior to dosing, patients must have an absolute neutrophil count (ANC) $\geq$1.5 x 10^9/L and a platelet count $\geq$100 x 10^9/L. A complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until the ANC is above 1.5 x 10^9/L and platelet count exceeds 100 x10^9/L.Geriatric patients and women have been shown in clinical trials to have a higher risk of developing myelosuppression. Very rare cases of myelodysplastic syndrome and secondary malignancies, including myeloid leukemia have also been observed.

For treatment of newly diagnosed glioblastoma multiforme: Prophylaxis against *Pneumocystis carinii* pneumonia is required for all patients receiving concomitant TEMODAR and radiotherapy for the 42 day regimen.
There may be a higher occurrence of PCP when temozolomide is administered during a longer dosing regimen. However, all patients receiving temozolomide, particularly patients receiving steroids should be observed closely for the development of PCP regardless of the regimen.

Pregnancy: Temozolomide may cause fetal harm when administered to a pregnant woman. Five consecutive days of oral administration of 75 mg/m^2/day in rats and 150 mg/m^2/day in rabbits during the period of organogenesis (3/8 and 3/4 the maximum recommended human dose, respectively) caused numerous malformations of the external organs, soft tissues, and skeleton in both species. Doses of 150 mg/m^2/day in rats and rabbits also caused embryolethality as indicated by increased resorptions. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with TEMODAR Capsules.

PRECAUTIONS

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

Drug Interaction: Administration of valproic acid decreases oral clearance of temozolomide by about 5%. The clinical implication of this effect is not known.

Patients with Severe Hepatic or Renal Impairment: Caution should be exercised when TEMODAR Capsules are administered to patients with severe hepatic or renal impairment (see **Special Populations**).

Geriatrics: Clinical studies of temozolomide did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Caution should be exercised when treating elderly patients.
In the anaplastic astrocytoma study population, patients 70 years of age or older had a higher incidence of Grade 4 neutropenia and Grade 4 thrombocytopenia (2/8; 25%, p=.31 and 2/10; 20%, p=.09, respectively) in the first cycle of therapy than patients under 70 years of age (see **ADVERSE REACTIONS**).
In newly diagnosed patients with glioblastoma multiforme the adverse event profile was similar in younger patients (<65 years) vs older (≥65 years).

Laboratory Tests: For the concomitant treatment phase with RT a complete blood count should be obtained weekly.
For the 28 day treatment cycles, a complete blood count should be obtained on Day 22 (21 days after the first dose). Blood counts should be performed weekly until recovery if the ANC falls below 1.5 x 10^9/L and the platelet count falls below 100 x 10^9/L.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Standard carcinogenicity studies were not conducted with temozolomide. In rats treated with 200 mg/m^2 temozolomide (equivalent to the maximum recommended daily human dose) on 5 consecutive days every 28 days for 3 cycles, mammary carcinomas were found in both males and females. With 6 cycles of treatment at 25, 50, and 125 mg/m^2 (about 1/8 to 1/2 the maximum recommended daily human dose), mammary carcinomas were observed at all doses and fibrosarcomas of the heart, eye, seminal vesicles, salivary glands, abdominal cavity, uterus, and prostate; carcinoma of the seminal vesicles, schwannoma of the heart, optic nerve, and harderian gland; and adenomas of the skin, lung, pituitary, and thyroid were observed at the high dose.
Temozolomide was mutagenic *in vitro* in bacteria (Ames assay) and clastogenic in mammalian cells (human peripheral blood lymphocyte assays).
Reproductive function studies have not been conducted with temozolomide. However, multicycle toxicology studies in rats and dogs have demonstrated testicular toxicity (syncytial cells/immature sperm, testicular atrophy) at doses of 50 mg/m^2 in rats and 125 mg/m^2 in dogs (1/4 and 5/8, respectively, of the maximum recommended human dose on a body surface area basis).

Pregnancy Category D: See **WARNINGS** section.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from TEMODAR Capsules, patients receiving TEMODAR should discontinue nursing.

Pediatric Use:
TEMODAR effectiveness in children has not been demonstrated. TEMODAR Capsules have been studied in 2 open label Phase 2 studies in pediatric patients (age 3-18 years) at a dose of 160-200 mg/m^2 daily for 5 days every 28 days. In one trial conducted by the Schering Corporation, 29 patients with recurrent brain stem glioma and 34 patients with recurrent high grade astrocytoma were enrolled. All patients had failed surgery and radiation therapy, while 31% also failed chemotherapy. In a second Phase 2 open label study conducted by the Children's Oncology Group (COG), 122 patients were enrolled, including medulloblastoma/PNET(29), high grade astrocytoma (23), low grade astrocytoma (22), brain stem glioma (16), ependymoma (14) other CNS tumors (9) and non-CNS tumors (9). The TEMODAR toxicity profile in children is similar to adults. Table 1 shows the adverse events in 122 children in the COG Phase 2 study.

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Table 1

Adverse Events Reported in Pediatric Cooperative Group Trial (≥10%)		
	No. (%) of TEMODAR Patients (N=122)[a]	
Body System/Organ Class Adverse Event	**All Events**	**Gr 3/4**
Subjects Reporting an AE	**107 (88)**	**69 (57)**
Body as a Whole		
Central and Peripheral Nervous System		
Central cerebral CNS cortex	22 (18)	13 (11)
Gastrointestinal System		
Nausea	56 (46)	5 (4)
Vomiting	62 (51)	4 (3)
Platelet, Bleeding and Clotting		
Thrombocytopenia	71 (58)	31 (25)
Red Blood Cell Disorders		
Decreased Hemoglobin	62 (51)	7 (6)
White Cell and RES Disorders		
Decreased WBC	71 (58)	21 (17)
Lymphopenia	73 (60)	48 (39)
Neutropenia	62 (51)	24 (20)

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

292 **ADVERSE REACTIONS IN ADULTS**
293 **Newly Diagnosed Glioblastoma Multiforme**
294
295 During the concomitant phase (Temodar + radiotherapy), adverse events including
296 thrombocytopenia, nausea, vomiting, anorexia and constipation, were more frequent
297 in the TEMODAR + RT arm the RT arm. The incidence of other adverse events
298 was comparable in the two arms. The most common adverse events across the
299 cumulative TEMODAR experience were alopecia, nausea, vomiting, anorexia,
300 headache, and constipation (see **Table 2**). Forty-nine percent (49%) of patients
301 treated with TEMODAR reported one or more severe or life-threatening events, most
302 commonly fatigue (13%), convulsions (6%), headache (5%) and thrombocytopenia
303 (5%). Overall, the pattern of events during the maintenance phase was consistent
304 with the known safety profile of TEMODAR.
305

306 **Table 2 Number (%) of Patients with Adverse Events: All and Severe/Life**
307 **Threatening (Incidence of 5% or Greater)**
308

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

	Concomitant Phase RT Alone (n=285)		Concomitant Phase RT+TMZ (n=288)*		Maintenance Phase TMZ (n=224)	
	All	Grade ≥ 3	All	Grade ≥ 3	All	Grade ≥ 3
Skin and Subcutaneous Tissue Disorders						
Alopecia	179 (63)	0	199 (69)	0	124 (55)	0
Dry Skin	6 (2)	0	7 (2)	0	11 (5)	1 (<1)
Erythema	15 (5)	0	14 (5)	0	2 (1)	0
Pruritus	4 (1)	0	11 (4)	0	11 (5)	0
Rash	42 (15)	0	56 (19)	3 (1)	29 (13)	3 (1)
Special Senses Other, Disorders						
Taste Perversion	6 (2)	0	18 (6)	0	11 (5)	0

*One patient who was randomized to RT only arm received RT + Temozolomide

RT+TMZ=radiotherapy plus temozolomide; LT=life threatening; SGPT = serum glutamic pyruvic transaminase (=alanine aminotransferase [ALT]); NOS=not otherwise specified.

Note: Grade 5 (fatal) adverse events are included in the Grade ≥ 3 column.

Myelosuppression, (neutropenia and thrombocytopenia), which are known dose limiting toxicities for most cytotoxic agents, including TEMODAR, were observed. When laboratory abnormalities and adverse events were combined, Grade 3 or Grade 4 neutrophil abnormalities including neutropenic events were observed in 8% of the patients and Grade 3 or Grade 4 platelet abnormalities, including thrombocytopenic events were observed in 14% of the patients treated with TEMODAR.

Refractory anaplastic astrocytoma

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

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

In clinical trial experience with 110 to 111 women and 169 to 174 men (depending on measurements), there were higher rates of Grade 4 neutropenia (ANC < 500 cells/μL) and thrombocytopenia (< 20,000 cells/μL) in women than men in the first cycle of therapy: (12% versus 5% and 9% versus 3%, respectively).
In the entire safety database for which hematologic data exist (N=932), 7% (4/61) and 9.5% (6/63) of patients over age 70 experienced Grade 4 neutropenia or thrombocytopenia in the first cycle, respectively. For patients less than or equal to age 70, 7% (62/871) and 5.5% (48/879) experienced Grade 4 neutropenia or thrombocytopenia in the first cycle, respectively. Pancytopenia, leukopenia, and anemia have also been reported.

Table 3

Adverse Events in the Anaplastic Astrocytoma Trial in Adults(>5%)

	No. (%) of TEMODAR Patients (N=158)	
	All Events	**Grade 3/4**
Any Adverse Event	**153 (97)**	**79 (50)**
Body as a Whole		
Headache	65 (41)	10 (6)
Fatigue	54 (34)	7 (4)
Asthenia	20 (13)	9 (6)
Fever	21 (13)	3 (2)
Back pain	12 (8)	4 (3)
Cardiovascular		
Edema peripheral	17 (11)	1 (1)
Central and Peripheral Nervous System		
Convulsions	36 (23)	8 (5)
Hemiparesis	29 (18)	10 (6)
Dizziness	19 (12)	1 (1)
Coordination abnormal	17 (11)	2 (1)
Amnesia	16 (10)	6 (4)
Insomnia	16 (10)	0
Paresthesia	15 (9)	1 (1)
Somnolence	15 (9)	5 (3)
Paresis	13 (8)	4 (3)
Urinary incontinence	13 (8)	3 (2)
Ataxia	12 (8)	3 (2)
Dysphasia	11 (7)	1 (1)
Convulsions local	9 (6)	0
Gait abnormal	9 (6)	1 (1)
Confusion	8 (5)	0
Endocrine		
Adrenal hypercorticism	13 (8)	0
Gastrointestinal System		
Nausea	84 (53)	16 (10)
Vomiting	66 (42)	10 (6)
Constipation	52 (33)	1 (1)
Diarrhea	25 (16)	3 (2)
Abdominal pain	14 (9)	2 (1)
Anorexia	14 (9)	1 (1)
Metabolic		
Weight increase	8 (5)	0

Musculoskeletal System		
Myalgia	8 (5)	
Psychiatric Disorders		
Anxiety	11 (7)	1 (1)
Depression	10 (6)	0
Reproductive Disorders		
Breast pain, female	4 (6)	
Resistance Mechanism Disorders		
Infection viral	17 (11)	0
Respiratory System		
Upper respiratory tract infection	13 (8)	0
Pharyngitis	12 (8)	0
Sinusitis	10 (6)	0
Coughing	8 (5)	0
Skin and Appendages		
Rash	13 (8)	0
Pruritus	12 (8)	2 (1)
Urinary System		
Urinary tract infection	12 (8)	0
Micturition increased frequency	9 (6)	0
Vision		
Diplopia	8 (5)	0
Vision Abnormal*	8 (5)	

*Blurred vision, visual deficit, vision changes, vision troubles.

Table 4
Adverse Hematologic Effects (Grade 3 to 4) in the Anaplastic Astrocytoma Trial in Adults

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

[a]Change from Grade 0 to 2 at baseline to Grade 3 or 4 during treatment.

In addition, the following spontaneous adverse experiences have been reported during the marketing surveillance of TEMODAR Capsules: allergic reactions, including rare cases of anaphylaxis. Rare cases of erythema multiforme have been reported which resolved after discontinuation of TEMODAR and, in some cases, recurred upon rechallenge. Rare cases of opportunistic infections including *Pneumocystis carinii* pneumonia (PCP) have also been reported.

OVERDOSAGE

Doses of 500, 750, 1,000, and 1,250 mg/m ^{2} (total dose per cycle over 5 days) have been evaluated clinically in patients. Dose-limiting toxicity was hematologic and was reported with any dose but is expected to be more severe at higher doses. An overdose of 2,000 mg per day for 5 days was taken by one patient and the adverse events reported were pancytopenia, pyrexia, multi-organ failure and death. There are reports of patients who have taken more than 5 days of treatment (up to 64 days) with adverse events reported including bone marrow suppression, which in some cases was severe and prolonged, and infections and resulted in death. In the

event of an overdose, hematologic evaluation is needed. Supportive measures should be provided as necessary.

Handling and Disposal: TEMODAR causes the rapid appearance of malignant tumors in rats. 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[1-7]. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

HOW SUPPLIED

TEMODAR (temozolomide) Capsules are supplied in amber glass bottles with child resistant polypropylene caps containing the following capsule strengths:
TEMODAR (temozolomide) Capsules 5 mg: 5 and 20 capsule bottles.
5 count - NDC 0085-1248-01
20 count - NDC 0085-1248-02

TEMODAR (temozolomide) Capsules 20 mg: 5 and 20 capsule bottles.
5 count - NDC 0085-1244-01
20 count - NDC 0085-1244-02
TEMODAR (temozolomide) Capsules 100 mg: 5 and 20 capsule bottles.
5 count - NDC 0085-1259-01
20 count - NDC 0085-1259-02
TEMODAR (temozolomide) Capsules 250 mg: 5 and 20 capsule bottles.
5 count - NDC 0085-1252-01
20 count - NDC 0085-1252-02

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).
[See USP Controlled Room Temperature]

REFERENCES

1. Recommendations for the Safe Handling of Parenteral Antineoplastic Drugs, NIH Publication No. 83-2621. For sale by the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402.
2. AMA Council Report, Guidelines for Handling Parenteral Antineoplastics. *JAMA*. 1985; 2.53(11):1590-1592.
3. National Study Commission on Cytotoxic Exposure – Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.
4. Clinical Oncological Society of Australia, Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. *Med J Australia*. 1983; 1:426-428.
5. Jones RB, et al. Safe Handling Of Chemotherapeutic Agents: A Report from the Mount Sinai Medical Center. CA - *A Cancer Journal for Clinicians*. 1983 ;(Sept/Oct):258-263.
6. American Society of Hospital Pharmacists Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. *Am J Hosp Pharm*. 1990; 47:1033-1049.
7. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice Guidelines), *Am J Health-Syst Pharm*. 1996;53:1669-1685.

Schering Corporation
Kenilworth, NJ 07033 USA

Rev 3/05 B-XXXXXXXX

PHARMACIST:

Tear at perforation and give to patient.

Temodar®
[temozolomide]
Capsules

PHARMACIST INFORMATION SHEET

IMPORTANT DISPENSING INFORMATION

IMPORTANT DISPENSING INFORMATION
For every patient, TEMODAR must be dispensed in a separate vial or in its original glass bottle making sure each container lists the strength per capsule and that patients take the appropriate number of capsules from each bottle or vial.
Please see the dispensing instructions below for more information.

What is TEMODAR?

TEMODAR® (temozolomide) is an oral alkylating agent for the treatment of newly diagnosed glioblastoma multiforme and refractory anaplastic astrocytoma.

How is TEMODAR dosed?

The daily dose of TEMODAR Capsules for a given patient is calculated by the physician, based on the patient's body surface area (BSA). The resulting dose is then rounded off to the nearest 5 mg. An example of the dosing may be as follows: the initial daily dose of TEMODAR in milligrams is the BSA multiplied by mg/m^2/day, (a patient with a BSA of 1.84 is 1.84 x 150 = 276, or 275 mg/day). The dose for subsequent cycles may be adjusted according to nadir neutrophil and platelet counts in the previous cycle and at the time of initiating the next cycle.

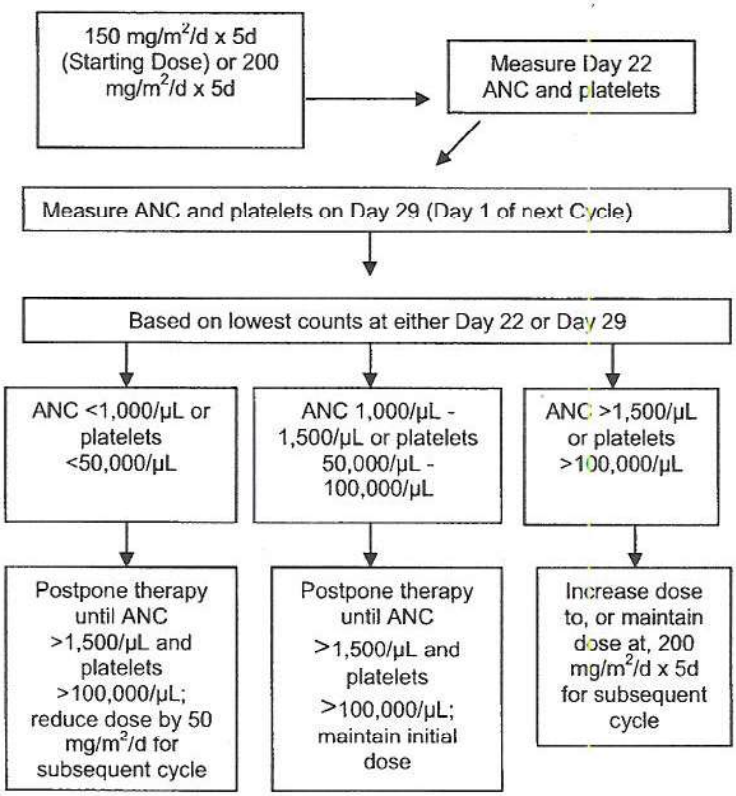
How might the dose of TEMODAR be modified for Refractory Anaplastic Astrocytoma?

Dosage of TEMODAR must be adjusted according to nadir neutrophil and platelet counts in the previous cycle and neutrophil and platelet counts at the time of initiating the next cycle. The initial dose is 150 mg/m^2 orally once daily for 5

consecutive days per 28-day treatment cycle. If both the nadir and day of dosing (Day 29, Day 1 of next cycle) absolute neutrophil counts (ANC) are $\geq 1.5 \times 10^9$/L (1,500/µL) and both the nadir and Day 29, Day 1 of next cycle platelet counts are $\geq 100 \times 10^9$/L (100,000/µL), the TEMODAR dose may be increased to 200 mg/m^2/day for 5 consecutive days per 28-day treatment cycle. During treatment, a complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until the ANC is above 1.5×10^9/L (1,500/µL) and the platelet count exceeds 100×10^9/L (100,000/µL). The next cycle of TEMODAR should not be started until the ANC and platelet count exceed these levels. If the ANC falls to $<1.0 \times 10^9$/L (1,000/µL) or the platelet count is $<50 \times 10^9$/L (50,000/µL) during any cycle, the next cycle should be reduced by 50 mg/m^2, but not below 100 mg/m^2, the lowest recommended dose (see **Table 1** below).

TABLE 1

Dosing Modification Table for Refractory Anaplastic Astrocytoma



What is the TEMODAR® (temozolomide) Capsules treatment regimen?

TEMODAR is given for 5 consecutive days on a 28-day cycle. Patients should continue taking TEMODAR until their physician determines that their disease has progressed, up to 2 years, or until unacceptable side effects or toxicities occur. Physicians may alter the treatment regimen for a given patient.

Newly Diagnosed Concomitant Phase Treatment Schedule

TEMODAR is administered orally at 75 mg/m^2 daily for 42 days concomitant with focal radiotherapy (60Gy administered in 30 fractions), followed by maintenance TEMODAR for 6 cycles.No dose reductions are recommended, however, dose interruptions may occur based on patient tolerance. The TEMODAR dose can be continued throughout the 42 day concomitant period up to 49 days if all of the following conditions are met: absolute neutrophil count ≥ 1.5 x 10^9 /L platelet count ≥ 100 x10^9 /L common toxicity criteria (CTC) non-hematological toxicity ≤Grade 1 (except for alopecia, nausea and vomiting). During treatment a complete blood count should be obtained weekly. Temozolomide dosing should be interrupted or discontinued during concomitant phase according to the hematological and non-hematological toxicity criteria as noted in **Table 2.** PCP prophylaxis is required during the concomitant administration of Temodar and radiotherapy and should be continued in patients who develop lymphocytopenia until recovery from lymphocytopenia (CTC grade ≤ 1).

Table 2 Temozolomide Dosing Interruption or Discontinuation During Concomitant Radiotherapy and Temozolomide

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

a: Treatment with concomitant TMZ could be continued when all of the following conditions were met: absolute neutrophil count ≥1.5 x 10^9/L; platelet count ≥100 x 10^9/L; CTC non-hematological toxicity ≤Grade 1 (except for alopecia, nausea, vomiting)

TMZ = temozolomide; CTC = Common Toxicity Criteria.

Maintenance Phase Treatment Schedule

Four weeks after completing the TEMODAR + RT phase, TEMODAR is administered for an additional 6 cycles of maintenance treatment. Dosage in Cycle 1 (maintenance) is 150 mg/m^2 once daily for 5 days followed by 23 days without treatment. At the start of Cycle 2, the dose is escalated to 200 mg/m^2 , if the CTC non-hematologic toxicity for Cycle 1 is Grade ≤2 (except for alopecia, nausea and vomiting), absolute neutrophil count (ANC) is ≥ 1.5 x 10^9/L, and the platelet count is ≥ 100 x 10^9/L. If the dose was not escalated at Cycle 2, escalation should not be done in subsequent cycles. The dose remains at 200 mg/m^2 per day for the first 5 days of each subsequent cycle except if toxicity occurs.

During treatment a complete blood count should be obtained on Day 22 (21 days after the first dose) or within 48 hours of that day, and weekly until the ANC is above 1.5 x 10^9/L (1,500/µL) and the platelet count exceeds 100 x 10^9/L (100,000/µL). The next cycle of TEMODAR should not be started until the ANC and platelet count exceed these levels. Dose reductions during the next cycle should be based on the lowest blood counts and worst non-hematologic toxicity during the previous cycle. Dose reductions or discontinuations during the maintenance phase should be applied according to tables 3 **and 4**.

Table 3 Temozolomide Dose Levels for Maintenance Treatment

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

Table 4 Temozolomide Dose Reduction or Discontinuation During Maintenance Treatment

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

a: TMZ dose levels are listed in Table 3

b: TMZ is to be discontinued if dose reduction to <100 mg/m^2 is required or if the same Grade 3 non-hematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction.

TMZ = temozolomide; CTC = Common Toxicity Criteria.

How is TEMODAR taken?

Patients should take each day's dose with a full glass of water at the same time each day. Taking the medication on an empty stomach or at bedtime may help ease nausea. If patients are also taking antinausea or other medications to relieve the side effects associated with TEMODAR, they should be advised to take these medications 30 minutes before they take TEMODAR. Temozolomide causes the rapid appearance of malignant tumors in rats. Patients **SHOULD NOT** open or split the capsules. If capsules are accidentally opened or damaged, rigorous precautions should be taken with the capsule contents to avoid inhalation or contact with the skin or mucous membranes. The medication should be kept away from children and pets. The TEMODAR capsules should be swallowed whole and **NEVER CHEWED**.

What should the patient avoid during treatment with TEMODAR?

There are no dietary restrictions for patients taking TEMODAR. TEMODAR may affect testicular function, so male patients should exercise adequate birth control measures. TEMODAR may cause birth defects. Female patients should avoid becoming pregnant while receiving this drug. Women who are nursing prior to receiving TEMODAR should discontinue nursing. It is not known whether TEMODAR is excreted into breast milk.

What are the side effects of TEMODAR?

Nausea and vomiting are the most common side effects associated with TEMODAR. Noncumulative myelosuppression is the dose-limiting toxicity. Patients should be evaluated periodically by their physician to monitor blood counts.

Other commonly reported side effects reported by patients taking TEMODAR are fatigue, constipation, and headache.

How is TEMODAR supplied?

TEMODAR capsules are available in 250 mg, 100 mg, 20 mg, and 5 mg strengths. The capsules are white with color-coded printing according to strength.

TEMODAR Capsule Strength	Color
5 mg	Green Imprint
20 mg	Brown Imprint
100 mg	Blue Imprint
250 mg	Black Imprint

All capsule strengths are available in 5-count and 20-count packages.

How is TEMODAR dispensed?

Each strength of TEMODAR must be dispensed in a separate vial or in its original glass bottle (one strength per one container). Follow the instructions below:

Based on the dose prescribed, determine the number of each strength of TEMODAR capsules needed for the full 5 day cycle as prescribed by the physician. For example, 275 mg/day for 5 days would be dispensed as five 250-mg capsules, five 20-mg capsules and five 5-mg capsules. Label each container with the appropriate number of capsules to be taken each day. Dispense to the patient, making sure each container lists the strength (mg) per capsule and that he or she understands to take the appropriate number of capsules of TEMODAR from each bottle or vial to equal the total daily dose prescribed by the physician.

How can TEMODAR be ordered?

TEMODAR can be ordered from your wholesaler. Remember to order enough TEMODAR for a full five-day cycle. For example, a five-day course of 275 mg/day would require the following to be ordered:

1 5-count package of 250-mg capsules
1 5-count package of 20-mg capsules
1 5-count package of 5-mg capsules

TEMODAR Product	NDC Number
250-mg capsules (5 count)	0085-1252-01
250-mg capsules (20 count)	0085-1252-02
100-mg capsules (5 count)	0085-1259-01
100-mg capsules (20 count)	0085-1259-02
20-mg capsules (5 count)	0085-1244-01
20-mg capsules (20 count)	0085-1244-02
5-mg capsules (5 count)	0085-1248-01
5-mg capsules (20 count)	0085-1248-02

22571613 Rev. 3/05

Temodar®

[temozolomide]
Capsules

Patient Information Sheet
IMPORTANT INFORMATION
FOR THE PATIENT

Patient Package Insert

TEMODAR® (temozolomide) Capsules

What is TEMODAR?

TEMODAR (temozolomide) is used to treat certain cancerous tumors in the brain of adult patients for whom this tumor has recurred. Your doctor has prescribed TEMODAR (temozolomide) as part of your cancer treatment. TEMODAR is a drug you take by mouth that interferes with cell growth, especially in cells that are growing rapidly, such as cancerous cells. TEMODAR has been shown to help slow the growth of certain cancerous tumors. When given to patients with brain cancer, TEMODAR has been shown to reduce the size of the tumor in some patients.

Who should not take TEMODAR?

You should not take TEMODAR Capsules if you have had an allergic reaction to DTIC-Dome (dacarbazine), a different treatment for cancer. If you have had an allergic reaction before to drugs such as DTIC-Dome, be sure to tell your doctor before taking TEMODAR. If you are allergic to drugs similar to TEMODAR, you may also have an allergic reaction to TEMODAR.

How should I take TEMODAR?

Take each day's dose of capsules at one time, with a full glass of water. **DO NOT** open or split the capsules. If the capsules are accidentally opened or damaged, you should be extremely careful to avoid inhaling the powder in the capsules or getting it on your skin or mucous membranes (eg, in nose or mouth). Flush the area with water if contact occurs. The medication should be kept away from children and pets. They should be swallowed whole and **NEVER CHEWED**. If capsules are vomited do not take a second dose. New capsules should not be taken until the next planned dose. The medicine is used best by your body if you take it at the same time every day in relation to a meal. To reduce nausea, try to take TEMODAR on an empty stomach or at bedtime. Your doctor may also have prescribed antinausea or other medications to relieve the side effects associated with TEMODAR. Antinausea medications should be taken as directed by your doctor. It is important that you continue to see your doctor regularly to check your progress. Your doctor can uncover side effects of treatment that you might not notice.

Because TEMODAR (temozolomide) Capsules is a drug you take by mouth, you can take it at home. There are two different dosing schedules for taking TEMODAR. Be sure you follow the one that your doctor has prescribed for you. One schedule you may be prescribed is ,TEMODAR for 42 days (up to 49 days) with radiotherapy.. Another schedule should be taken for 5 consecutive days only, then you must **STOP** taking TEMODAR for the next 23 days. This total period of 5 days on TEMODAR and 23 days off TEMODAR is called one treatment cycle. Your dose is based on your height and weight, and the number of treatment cycles will depend on how you respond to and tolerate this treatment.

TEMODAR comes in different strength capsules (shown on the outer label in mg). Each strength has a different color band. Depending on the dose of TEMODAR that your doctor prescribes, you may have to take several capsules on each dosing day of a treatment cycle (Day 1 through Day 5, followed by 23 days with no capsules) or the 42 days (up to 49 days) of consecutive treatment schedule with radiotherapy.

- Be sure you understand exactly how many capsules you need to take of each strength. Ask your doctor or pharmacist to write down the number of each strength (include color) that you need to take each dosing day.
- Be sure you know exactly which days are your dosing days.
- Be sure to review the dose with your health care provider each time you start a new cycle. Sometimes the dose or the mix of capsules you need to take will be different from the last cycle.
- Once you take the medicine home, if you are confused or unsure about how to take your dose, contact your doctor or pharmacist immediately.

Your doctor may have prescribed a treatment regimen that is different from the one discussed in this information sheet. If so, make sure you follow the specific instructions given to you by your doctor. You should talk to your doctor about what to do if you miss a day. If you take more than the prescribed amount of medicine, contact your doctor right away. It is important that you understand your dosage regimen, it is also important that you do not take more than the amount of TEMODAR prescribed for you. Overdoses can lead to serious outcomes including severe low blood counts and possible death.

How is TEMODAR supplied?

TEMODAR® (temozolomide) Capsules are white with color-coded printing according to strength, each a different size. The capsules are available in four different strengths.

TEMODAR Capsule Strength	Color
5mg	Green Imprint
20mg	Brown Imprint
100mg	Blue Imprint
250mg	Black Imprint

What should I avoid while taking TEMODAR?
There are no limitations on what you may eat or drink while taking TEMODAR. However, to ease nausea, try to take TEMODAR on an empty stomach.

TEMODAR may cause birth defects. Therefore, male or female patients who take TEMODAR should use effective birth control. Female patients should avoid becoming pregnant while receiving this drug. You should not breast-feed an infant while taking TEMODAR. It is not known whether TEMODAR passes into breast milk. Because many drugs do pass into breast milk, there is the possibility of serious harm to nursing infants.

What are the possible or reasonably likely side effects of TEMODAR?
Nausea and vomiting are the most common side effects associated with TEMODAR. Your doctor can prescribe medicines that may help reduce some of these. Other common side effects include headache, feeling tired, and constipation.

TEMODAR also can reduce the number of certain types of blood cells, which can have serious effects. White blood cells are needed to fight infections. Lowering of white blood cells could result in a serious infection with a potential outcome of death. Platelets are needed in the normal course of blood clotting. Lowering of platelets does not allow your blood to clot normally, which can result in bleeding episodes. Therefore, it is important that your doctor check your blood periodically while you are taking TEMODAR to see if these side effects are occurring. Patients age 70 or older, women, and patients who have had chemotherapy or radiation therapy may be more likely to have their blood cells affected.

There are other side effects associated with TEMODAR. They are included in a longer, more technical information leaflet written for health care providers that you can get from your doctor or pharmacist.

General information about the use of prescription drug products.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Package Insert. You should contact your health care professional regarding any concerns you may have about using TEMODAR. TEMODAR should not be used for a condition for which it was not prescribed, and it should not be given to other persons.

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APPENDIX B

Dana-Farber/Harvard Cancer Center
Multi-Center Data and Safety Monitoring Plan

Table of Contents

1.0 INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for a DF/HCC Multi-Center research protocol.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center (DF/HCC) Multi-center protocol will comply with Federal regulations (21 CFR Part 11); Good Clinical Practice (GCP) Guidelines; and Health Insurance Portability and Accountability Act (HIPAA) requirements in accordance with the CTEP Multi-center Guidelines.

1.2 Multi-Center Data and Safety Monitoring Plan Components

The Multi-Center Data and Safety Monitoring Plan includes the following components:

DF/HCC Multi-center Protocol: One or more outside institutions collaborating with Dana-Farber/Harvard Cancer Center on a research protocol where DF/HCC is the Lead Institution. *Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates are not viewed as outside sites in this definition.*

Lead Institution: One of the Dana-Farber/Harvard Cancer Center sites (DFCI, MGH, BIDMC, CH, BWH) will be the Lead Institution and will be responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (CTEP, FDA, OBA etc.).

DF/HCC Contract Principal Investigator: Investigator located at the Lead Institution who will be charged with the responsibility of the administration of the DF/HCC Project. This most often will be the Protocol Chair, but occasionally this may be the overall grant or contract holder, as applicable.

Protocol Chair: The Protocol Chair is the Principal Investigator for the DF/HCC protocol submitted as the Lead Institution. For applicable protocols, the Protocol Chair will be the single liaison with any regulatory agencies (ie.CTEP Protocol and Information Office (PIO), FDA, OBA etc.).

Participating Institution: A participating institution is an institution that desires to collaborate with DF/HCC and commits to accruing participants to a DF/HCC protocol. The participating institution acknowledges the Protocol Chair as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: The Lead Institution is the Coordinating Center for the DF/HCC Multi-center Protocol. The Coordinating Center will provide the administrative support to the Protocol Chair in order that he/she may fulfill the responsibilities outlined in the DSMP and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines). In addition to the Lead Institution, the Quality Assurance Office for Clinical Trials (QACT) provides support services to

assist the Protocol Chair.

2.0 GENERAL ROLES AND RESPONSIBILITIES

In accordance with the CTEP Multi-center Guidelines, the Protocol Chair (DF/HCC Principal Investigator), Coordinating Center (Lead Institution or designee), and the Participating Institutions will all agree to the general responsibilities as follows (specific procedures for these general responsibilities are detailed in the DSMP):

2.1 Protocol Chair (DF/HCC Principal Investigator)

The Protocol Chair, Jennifer Ang Chan, MD will accept responsibility for all aspects of the Multi-Center Data and Safety Monitoring Plan to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Submit the Multi-Center Data and Safety Monitoring Plan as an inclusion to the protocol.
- Assure all participating institutions are using the correct version of the protocol.
- Monitor progress and overall conduct of the study at all participating institutions.
- Ensure all DFCI IRB, DF/HCC and other applicable (i.e. FDA)- reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with FDA (sponsor-investigator IND trials) , as applicable.

Identify participating institutions and obtain accrual commitments. The Protocol Chair will also submit a protocol attachment labeled as "Participating Investigators" to the DFCI IRB and if applicable, FDA,that provides the names and contact information for all participating institutions that perform the function of recruiting, enrolling, and treating participants for the protocol. The Coordinating Center (Lead Institution or designee) must be designated on the title page.

2.2 Coordinating Center (Lead Institution)

The Coordinating Center is the DF/HCC Lead Institution's study team or designee (i.e Medical Monitor, Clinical Research Organization). The DF/HCC Lead Institution will ensure that all participating sites within the Multi-Center Protocol demonstrate their intent and capability of complying with Federal Regulations, GCPs and Health Insurance Portability and Accountability Act (HIPAA) requirements. To assist the Protocol Chair in meeting his/her responsibilities as required by the DSMP, the DF/HCC Lead Institution's study team or designee will assume the following general responsibilities:

- Assist in protocol review.
- Maintain copies of Institutional Review Board (IRB) approvals from all participating institutions.
- Maintain updated roster of participants.
- Verify eligibility.
- Verify response.
- Collect data on protocol specific CRFs.
- Prepare all submitted data for review by the Protocol Chair.
- Maintain documentation of Serious Adverse Event (SAE) reports submitted by

Participating Institutions and submit to Protocol Chair for timely review.
- Distribute external Serious Adverse Event safety reports.
- Monitor and audit Participating Institutions either by on-site inspection of selected participant records and/or with submitted source documents and research records submitted to the Lead Institution.

In addition to the Lead Institution, the DF/HCC Quality Assurance Office for Clinical Trials provides the following support services to assist the Protocol Chair:

- Develop protocol specific case report forms (CRF/eCRFS).
- QA/QC data of protocol specific CRFs.
- Provide Central Participant Registration.
- Confirm eligibility and consent.
- Provide auditing services (funding and QACT approval required).

2.3 Participating Institution

The Participating Institution(s) will be identified on the title page for each protocol. In addition, each participating institution will provide to the Lead Institution or designee a list of the key personnel assigned to the role for oversight of data management at their site. All sites must have office space, office equipment, and internet access that meet HIPAA standards.
The general responsibilities for each participating institution are as follows:

- Commit to accrual to the Lead Institution's (DF/HCC) protocol.
- Submit protocol and/or amendments to their local IRB.
- Update Coordinating Center (Lead Institution or designee) with research staff changes on a timely basis.
- Register participants through the QACT.
- Submit source documents, research records, and CRFs per protocol specific submission guidelines to the Coordinating Center (Lead Institution or designee).
- Submit Serious Adverse Event reports directly to the Coordinating Center (Lead Institution or designee)..
- Submit deviations and violations to the Coordinating Center (Lead Institution or designee).
- For protocols using investigational agents, the participating institution will order their own investigational agents regardless of the supplier (i.e., pharmaceutical company).

3.0 DF/HCC QUALITY ASSURANCE OFFICE FOR CLINICAL TRIALS

The DF/HCC QACT is a unit that has been developed to collect, manage, and monitor data for DF/HCC trials. The DF/HCC QACT is located administratively in the office of the Senior Vice President for Clinical Research, at Dana-Farber Cancer Institute. The QACT uses DF/HCC computerized institutional databases for participant registrations and for the management of trial data as well as a set of quality assurance programs designed to monitor DF/HCC trials.

3.1 Organizational Structure

The DF/HCC Quality Assurance Office for Clinical Trials administrative structure consists of:

DF/HCC Quality Assurance Officer for Clinical Trials: Oversees the functions of the DF/HCC QACT.

QACT Assistant Director for Data: Provides direct oversight to the QACT Data Analysts assigned to CRF design, data collection and computerization for DF/HCC trials.

The DF/HCC QACT Data Analysts will be assigned on a protocol by protocol basis. Each protocol's data analyst is responsible for database management, data entry, data quality assurance, and protocol specific correspondence related to the collection and quality assurance of data.

QACT Assistant Director for Monitoring: Provides direct oversight to the QACT Protocol Registrars and Clinical Research Auditors.

The DF/HCC Protocol Registrars are responsible for the confirmation of each participant's eligibility and consent prior to protocol registration.

If funded and QACT approved, the DF/HCC Clinical Research Auditors may assist the Lead Institution in their auditing responsibilities for multi-center trials. The QACT auditor is responsible for systematically evaluating participant safety, protocol compliance, institutional SOPs, ICH GCP and Federal regulation compliance, data accuracy and investigational drug handling to assure a high standard of quality for DF/HCC trials.

4.0 PROTOCOL DEVELOPMENT

4.1 Activation of a Protocol

The Protocol Chair is responsible for the coordination, development, and approval of the protocol as well as its subsequent amendments, and reporting SAEs, violations and deviations per DFCI IRB guidelines and if applicable, FDA. Further, the Protocol Chair will be the single liaison with the FDA as applicable.

To meet these requirements, the Protocol Chair will be responsible for the following minimum standards:

- Inclusion of the DF/HCC Multi-Center Data and Safety Monitoring Plan in the protocol as an appendix.
- Identify participating institutions and obtain accrual commitments. The Protocol Chair will also submit a protocol attachment labeled as "Participating Investigators" to the DFCI IRB and if applicable FDA, that provides the names and contact information for

all participating institutions that perform the function of recruiting, enrolling, and treating participants for the protocol. The Coordinating Center (Lead Institution or designee) must be designated on the title page.

- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the Protocol Chair.
- Ensure that there is only one version of the Protocol and that all Participating Institutions use the correct version.
- Oversee the development of data collection forms (case report forms) that are of common format for use at all the Participating Institutions.

4.2 Coordinating Center Support Function

The DF/HCC Lead Institution's study staff or designee will provide administrative and clerical support to the Protocol Chair for the development and distribution of the protocol.

The tasks to be performed by the DF/HCC Lead Institution's study staff or designee include:

- Review of the protocol and consent to check for logistics, spelling, and consistency. Provide the Protocol Chair a list of queries related to any inconsistencies.
- Provide necessary administrative sections, including paragraphs related to registration logistics, data management schedules, and multi-center guidelines.
- Maintenance of contact list of all participating institutions in the DF/HCC Multi-center Protocol and the distribution of updates to the sites as needed.
- Derivation of the study calendar, if applicable.
- Assistance in preparation and maintenance of case report forms.
- Maintain and document communication with all participating institutions.

5.0 PROTOCOL MANAGEMENT

The Coordinating Center (Lead Institution of designee) is responsible for assuring that each Participating Institution in the DF/HCC Multi-center Protocol has the appropriate assurance on file with the Office of Human Research Protection (OHRP). Additionally, the Lead Institution or designee must maintain copies of all IRB approvals, for each participating institution.

5.1 Protocol Distribution

The Coordinating Center (Lead Institution or designee) will distribute the final approved protocol and any subsequent amended protocols to all Participating Institutions.

5.2 Protocol Revisions and Closures

The participating institutions will receive phone, fax, mail or e-mail notification of protocol

revisions from the Lead Institution or designee. It is the individual participating institution's responsibility to notify its IRB of these revisions.

Non life-threatening revisions: Participating institutions will receive written notification of protocol revisions regarding non life-threatening events from the Lead Institution or designee. Non-life-threatening protocol revisions should be implemented within 90 days from receipt of the notification.

Revisions for life-threatening Causes: Participating institutions will receive telephone notification from the Lead Institution or designee concerning protocol revisions required to protect lives with follow-up by fax, mail or e-mail. Life-threatening protocol revisions will be implemented immediately.

Protocol Closures and Temporary Holds: Participating institutions will receive fax, e-mail, or phone notification of protocol closures and temporary holds, with follow-up by mail from the Lead Institution or designee. Closures and holds will be effective immediately. In addition, the Lead Institution or designee will update the Participating institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

5.3 Informed Consent Requirements

The Principal Investigator (PI) at each participating site will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. It is DF/HCC policy that Nurses and Fellows cannot obtain consent to greater than minimal risk trials. All participating sites must follow this policy.

5.4 IRB Documentation

The following must be on file with the DF/HCC Lead Institution or designee prior to participant registration:

- Approval Letter of the institution's IRB **(**An Expedited IRB first approval is NOT acceptable)
- IRB approval for all amendments

It is the individual institution's responsibility to notify its IRB of protocol revisions. Participating institutions will have 90days from receipt to provide the DH/HCC Lead Institution or designee their IRB approval for Major Amendments* to a protocol.

*** DF/HCC defines a Major Amendment** as: A substantive change in the study which may increase or decrease the risk to study participants. Major revisions require full IRB approval. The following criteria are examples of revisions to a protocol that are considered to be major amendments:

- Change of eligibility (inclusion/exclusion) criteria
- Change in design of protocol
- Change in statistical section
- Change in sample size/accrual (e.g., doubling the sample size)
- Change in informed consent
- Change of estimated dropout rate
- Change of treatment or intervention
- Change of device
- Change in primary objective evaluation process

5.5 IRB Re-Approval

Annual IRB re-approval from the Participating institution is required in order to register participants onto a protocol. There is no grace period for annual re-approvals.

Protocol registrations will not be completed if a re-approval letter is not received by the DF/HCC Lead Institution or designee from the Participating Institutions on or before the anniversary of the previous approval date.

5.6 Participant Confidentiality and Authorization Statement

The Health Insurance Portability and Accountability Act of 1996 contains, as one of its six major components, the requirement to create privacy standards for health care information that is used or disclosed in the course of treatment, payment or health care operations. The original Privacy Rule, as it has come to be known, was published in December 2000. The Final Rule was published on August 14, 2002, which has modified the privacy rule in significant ways vis-à-vis research.

In order for covered entities to use or disclose protected health information during the course of a DF/HCC Multi-Center Protocol the study participant must sign an Authorization. This Authorization may or may not be separate from the Informed Consent. The DF/HCC Multi-Center Protocol, with the approval from the DFCI IRB and if applicable NCI/CTEP, will provide an Informed Consent template, which covered entities (DF/HCC Multi-Center Protocol participating institutions) must use.

The DF/HCC Multi-Center Protocol will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected per National Cancer Institute requirements. These are the primary reasons why DF/HCC has chosen to use Authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

5.7 Participant Registration

To register a participant, the following documents should be completed by the DF/HCC Multi-

Center Protocol participating site and faxed to the Lead Institution's study coordinator at (617) 582-7988. :

- Copy of required laboratory tests [Hematology, Chemistry, Lipid Panel and Secretory Proteins]
- Signed informed consent form
- HIPAA authorization form (if separate from the informed consent document)
- Other appropriate forms including the Eligibility Screening Worksheet,and Pathology Report confirming diagnosis,)

The research DF/HCC Multi-center Protocol participating site will then call or e-mail the Lead Institution or designee to verify eligibility. To complete the registration process, the Lead Institution or designee will:

- Register the participant on the study with the DF/HCC Quality Assurance Office for Clinical Trials (QACT)
- Fax or e-mail the participant case number, and if applicable the dose treatment level, to the participating site
- Call the research nurse or data manager at the participating site and verbally confirm registration

5.8 DF/HCC Multi-center Protocol Case Number

Once eligibility has been established and the participant successfully registered, the participant is assigned a five digit protocol case number. This number is unique to the participant on this trial and must be used for QACT CRF/eCRF completion and written on all data and QACT correspondence for the participant.

5.9 DF/HCC Multi-center Protocol Registration Policy

5.9.1 Initiation of Therapy: Participants must be registered with the DF/HCC QACT before receiving treatment. Treatment may not be initiated until the site receives a faxed or e-mailed copy of the participant's Registration Confirmation memo from the DF/HCC QACT. Therapy must be initiated per protocol guidelines. The Protocol Chair and DFCI IRB must be notified of any exceptions to this policy**.**

5.9.2 Eligibility Exceptions: The DF/HCC QACT will make no exceptions to the eligibility requirements for a protocol without DFCI IRB approval. The DF/HCC QACT requires each institution to fully comply with this requirement.

5.9.3 Verification of Registration, Dose Levels, and Arm Designation: A registration confirmation memo for participants registered to DF/HCC Multi-Center Protocol will be faxed or emailed to the registering institution within one working day of the registration. Treatment may not be initiated until the site receives a faxed or e-mailed copy of the registration confirmation memo.

5.9.4 Confidentiality: All documents, investigative reports, or information relating to the participant are strictly confidential. Any participant specific reports (i.e. Pathology

Reports, MRI Reports, Operative Reports, etc.) submitted to the Lead Institution or designee must have the participant's full name & social security number "blacked out" and the assigned DF/HCC QACT case number and protocol number written in (with the exception of the signed informed consent document). Participant initials may only be included or retained for cross verification of identification.

5.10 Schedule of Data Submission

The DF/HCC QACT develops a set of either paper or electronic case report forms, (CRF/eCRFs) for use with the DF/HCC Multi-Center Protocol. These forms are designed to collect data for each study. The schedule for submission of case report forms to the DF/HCC QACT is generally specified in each protocol. When not specified in the protocol, the DF/HCC QACT will require the forms to be submitted as follows:

COMMON FORMS & REPORTS

- Eligibility Checklist, (Informed Consent/ Participant Authorization for the Release of Personal Health Information)
- On-study Form
- Baseline Assessment Form (Baseline disease assessment/measurement)
- Treatment Forms
- Adverse Event Forms
- Response Assessment Form (Follow-up disease assessment/Measurement)
- Off-Treatment/Off Study Form
- Follow-Up/Survival Forms

Note: It is necessary to send only ONE copy of all paper Case Report Forms.

Please see section 12.1.2 of the protocol for schedule of data submission.

5.10.1 Eligibility Checklist

Purpose - Outlines protocol-specific eligibility criteria and includes the following:

Participant Demographics (address, zip code, sex, race, ethnicity, initials, date of birth)

1) Parameters for eligibility
2) Parameters for exclusion
3) Parameters for stratifications

If a time frame is not specified in the protocol, tests must be completed as follows:

- Lab tests required for eligibility must be completed within 14 days prior to study enrollment by the QACT.
- For protocols requiring measurable disease, lab baseline measurements must be completed within 28 days prior to study enrollment by the QACT. Examples: tumor markers and hormones (Chromogranin A, Gastrin, VIP).
- Non-lab tests required for eligibility must be performed within 28 days prior to study entry. Example: radiological scans
-

- **Schedule for Submission -** Completed prior to participant registration. The Informed Consent/ Participant Authorization for the Release of Personal Health Information should be submitted with the Eligibility Checklist at the time of registration.

5.10.2 On-study Form

Purpose - documents the following items:

- Demographic data
- Prior therapy
- Past medical and surgical history
- Description of participant's physical status at protocol registration
- Disease site specific data

5.10.3 Baseline Assessment Form

Purpose – Documents objective and subjective disease status as defined by the protocol**.** Records all pertinent radiographic and laboratory measurements of disease utilized in determining response evaluations.

5.10.4 Treatment Form

Purpose - Records the following information related to the time the participant receives protocol treatment:

- Participant, Protocol, Affiliate information
- Protocol treatment and supportive therapy per treatment cycle
- Protocol specific laboratory values per treatment cycle
- All medications other than protocol chemotherapy agents used to treat concomitant diagnoses, if applicable

5.10.5Adverse Event Report Form

Purpose – Documents adverse events that occur while the participant is receiving treatment and for up to 30 days after the last dose of treatment. All adverse events are to be graded by number using the toxicity grading scale required by the protocol. *This form is not for IRB submission, but for recording the AE in the research database.*

5.10.6 Response Assessment Form

Purpose – Documents objective and subjective response as defined by the protocol. Records all pertinent radiographic and laboratory measurements of disease utilized in

determining response evaluations.

5.10.7 Off Treatment/Off Study Form

Purpose - The Off Treatment/Off Study Form is submitted when the participant is removed from the study or has completed all protocol treatment. Note: If the participant dies while on protocol**,** the Off Study Form is the last form submitted.

5.10.8 Follow up / Survival Form

Purpose - Summarizes participant status at a given point in time after being removed from treatment.

5.11 Data Form Review

When data forms arrive at the DF/HCC QACT, they are reviewed for:

Timeliness:
Did the form arrive on time as specified in the protocol?

Completeness:
Is all the information provided as required per protocol?

Participant Eligibility:
Does the participant meet the eligibility requirements for the study based on the demographic data, lab values and measurements provided?

Stratification:
Are the stratification parameters consistent with what was given at the time of registration?

Protocol Treatment Compliance:
Are the body surface area (BSA) and drug dosage calculations correct? The dose must be within 10% of the calculated protocol dose.

Adverse Events (Toxicities):
Did the participant experience adverse events (toxicities or side effects) associated with the treatment? Was the treatment delayed due to the adverse event? What was the most severe degree of toxicity experienced by the participant?

Notations concerning adverse events will address relationship to protocol treatment for each adverse event grade. All adverse events encountered during the study will be evaluated according to the NCI Common Toxicity Criteria assigned to the protocol and all adverse events

must be noted on the participant's Adverse Event (Toxicity) Forms.

Response:
Did the participant achieve a response? What level of response did they achieve? On what date did the participant achieve the response and how was the response determined?

Response criteria are defined in the protocol. A tumor assessment must be performed prior to the start of treatment and while the participant is on treatment as specified by the protocol.

Objective responses must have documentation such as physical measurements, x-rays, scans, or laboratory tests.

A subjective response is one that is perceived by the participant, such as reduction in pain, or improved appetite.

5.12 Missing and Deficient Memorandum

Data submissions are monitored for timeliness and completeness of submission. Participating institutions are notified of their data submission delinquencies in accordance with the following policies and procedures:

Incomplete or Questionable Data

If study forms are received with missing or questionable data, the submitting institution will receive a written query from the DF/HCC QACT Data Analyst. Responses to the query should be completed and returned within 14 days. Responses may be returned on the written query or on an amended case report form. In both instances the query must be attached to the specific data being re-submitted in response.

Missing Forms

If study forms are not submitted on schedule, the participating institution will receive a Missing Form Report from the DF/HCC QACT noting the missing forms. These reports are compiled by the DF/HCC QACT and distributed a minimum of three times a year.

6.0 REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is generally specified in the protocol.

Participating sites will be supplied the investigational agents by the DF/HCC Lead Institution. Participating sites will contact Lead Institutions Research Pharmacy by email or phone and drugs will be shipped overnight via FedEx to the shipment address provided by participating sites. Drug should be stored as specified in section 4.5 of the protocol. It is the responsibility of the Participating sites to contact Lead Institutions Research Pharmacy. A log should be kept of all investigational drug dispensed on the NCI drug accountability forms.
The local IRB should be kept informed of who will supply the agent (i.e., NCI or a pharmaceutical company) so that any regulatory responsibilities can be met in a timely fashion.

7.0 SAFETY ASSESSMENTS AND TOXICITY MONITORING

All participants receiving investigational agents will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported to the investigator by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria assigned to the protocol (CTCAE Version 3.0) and recorded prior to each course of therapy. Life-threatening toxicities should be reported immediately to the Protocol Chair and Institutional Review Board (IRB).

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

7.1 Serious Adverse Events

A serious adverse event (SAE) is any adverse drug experience at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions in a participant who has never had seizure activity in the past that do not result in inpatient hospitalization, or the development of drug dependency or abuse.

Unless otherwise specified in the protocol, the study will utilize the Cancer Therapy Evaluation Program (CTEP) Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 for Toxicity and Adverse Event reporting. A copy of the CTC or CTCAE Criteria can be downloaded from the CTEP home page (http://ctep.info.nih.gov).

7.2 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Serious Adverse Events (SAEs) will be followed as is delineated in the protocol.

In addition, the Participating Institutions must report the serious adverse events to the Protocol Chair and the Coordinating Center (Lead Institution) at the time SAEs are submitted.

The Lead Institution will maintain documentation of all Adverse Event Reporting and be responsible for communicating all SAEs to all Participating sites.

7.3 Guidelines for Processing IND Safety Reports

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent.

IND Safety Reports: The Protocol chair at the Lead Institution. will be sent a copy of expedited adverse events reports.. Within 7 business days of receipt of the notification, the Lead Institution or designee will forward the letters by email to the Participating sites with protocol specific instructions for IRB submissions, participant notifications, etc. For routine IND Safety Reports, that do not require an immediate revision to the protocol and/or model informed consent documents should be filed with their protocol and a copy of the report sent to theirIRB according to their local IRB's policies and procedures.

8.0 PROTOCOL VIOLATIONS AND DEVIATIONS

Neither the FDA nor the ICH GCP guidelines define the terms "protocol violation" or "protocol deviation." All DF/HCC Protocol Chairs must adhere to those policies set by the DFCI IRB, the definitions for protocol violation and deviation as described by the DFCI IRB will be applied for reporting purposes for all institutions participating in the DF/HCC Multi-center Protocol.

8.1 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol.

Protocol Violation: Any protocol deviation that was not prospectively approved by the IRB prior to its initiation or implementation.

8.2 Reporting Procedures

The Protocol Chair: is responsible for ensuring that clear documentation is available in the medical record to describe all protocol deviations and violations.
The Protocol Chair will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from DFCI IRB. The Participating institution must submit the deviation request to the Protocol Chair and Lead Institution or designee, who will submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation should be submitted to the participating site's own IRB, per its policy.
Protocol violations occurring at a participating institution will be submitted to that site's own IRB. A copy of the participating institution's IRB report and determination will be forwarded to the DF/HCC Lead Institution or designee by facsimile, within 10 business days after the original submission.

Coordinating Center: Upon receipt of the violation/deviation report from the participating

institution, the DF/HCC Lead Institution or designee will submit the report to the Protocol Chair for review. Subsequently, the participating institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines.

9.0 QUALITY ASSURANCE

1) The quality assurance process for a clinical trial research study requires verification of protocol compliance and data accuracy. As the Coordinating Center, the DF/HCC Lead Institution or designee with the aid of the QACT provides quality assurance oversight for the DF/HCC Multi-center Protocol.

9.1 Ongoing Monitoring of Protocol Compliance

All data submitted to the DF/HCC QACT will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion. The Lead Institution or designee and if applicable QACT Data Analysts assigned to the Protocol will perform the ongoing protocol compliance monitoring with the support of the participating institution's Coordinators, the Principal Investigators, and the Protocol Chair.

9.2 Evaluation of Participating Institution Performance

9.2.1 Eligibility Checklist: Eligibility criteria are checked on a protocol-specific eligibility checklist and faxed to the DF/HCC QACT prior to registration on protocol. The checklist and informed consent document are reviewed by a DF/HCC QACT Protocol Registrar before the participant can be registered on a protocol. The DF/HCC QACT cannot make exceptions to the eligibility requirements.

9.2.5 Accrual of Eligible Participants: Annual accrual rates for eligible participants enrolled onto therapeutic clinical trials is calculated for each institution. Institutions are expected to maintain the minimum annual average accrual as defined by the protocol grant or contract.

9.3 On-Site Auditing

9.3.1 DF/HCC Sponsored Trials

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For all DF/HCC sponsored protocols:
The participating institutions are required to submit subject source documents to the DF/HCC Lead Institution or designee for monitoring. Participating sites will be asked to submit material for the first patient after completion of 2 cycles. Thereafter, subjects will be selected at random for on-site monitoring conducted by the DF/HCC Lead Institution or designee. Participating sites will be notified 28 days prior to monitoring visit.

DF/HCC Lead Institution requires the participating site to submit all relevant source documentation after the frist patient is enrolled and has completed their 1st restaging scan.

9.3.2 Participating Institution

It is the participating institution's responsibility to notify the DF/HCC Lead Institution or designee of all scheduled audit dates and re-audit dates (if applicable), which involve the DF/HCC Multi-Center Protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the DF/HCC Lead Institution or designee within 12 weeks after the audit date.

9.3.3 Coordinating Center (Lead Institution or designee)

The Protocol Chair will review all DF/HCC Multi-Center Protocol Final Audit reports and corrective action plans if applicable. The Lead Institution or designee must forward these reports to the DF/HCC QACT per DF/HCC policy for review by the DF/HCC Audit Committee. Based upon the audit assessments the DF/HCC Audit Committee could accept or conditionally accept the audit rating and final report. Conditional approval could require the Protocol Chair to implement recommendations or require further follow-up. For unacceptable audits, the Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

9.4 Sub-Standard Performance

The Protocol Chair, DFCI IRB and the NCI for CTEP trials, is charged with considering the totality of an institution's performance in considering institutional participation in the DF/HCC Multi-Center Protocol.

9.4.1 Corrective Actions: Institutions that fail to meet the performance goals of accrual, submission of timely accurate data, and adherence to protocol requirements will be recommended for a six- month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Institutions that fail to demonstrate significant improvement will be considered by the Protocol Chair for revocation of participation.

07-325 RAD001 and Temozolomide

Name: **MRN:**

Cycle:

RAD001 Dose: **Temozolomide Dose:**

Temozolomide will be taken on a one week on, one week off schedule. It should be taken with 8 ounces of water and the tablets should be taken whole without chewing. It is recommended you take the Temozolomide at bedtime and fast for two hours before and one hour after dosing. You can drink water during the fasting period.If either drug is vomited or misse, do not take another dose that day; Do resume your regular dose the next day. Bring your study drugs and this diary to clinic each visit.

RAD001 is to be taken every day, in the morning, on an empty stomach, 1 hour before breakfast.

Day	Date	Drug	Dose	Time	Drug	Dose	Time	Symptoms
1		RAD001		: AM	Temozolomide		: PM	
2		RAD001		: AM	Temozolomide		: PM	
3		RAD001		: AM	Temozolomide		: PM	
4		RAD001		: AM	Temozolomide		: PM	
5		RAD001		: AM	Temozolomide		: PM	
6		RAD001		: AM	Temozolomide		: PM	
7		RAD001		: AM	Temozolomide		: PM	
8		RAD001		: AM				
9		RAD001		: AM				
10		RAD001		: AM				
11		RAD001		: AM				
12		RAD001		: AM				
13		RAD001		: AM				
14		RAD001		: AM				
15		RAD001		: AM	Temozolomide		: PM	
16		RAD001		: AM	Temozolomide		: PM	
17		RAD001		: AM	Temozolomide		: PM	
18		RAD001		: AM	Temozolomide		: PM	
19		RAD001		: AM	Temozolomide		: PM	
20		RAD001		: AM	Temozolomide		: PM	
21		RAD001		: AM	Temozolomide		: PM	
22		RAD001		: AM				
23		RAD001		: AM				
24		RAD001		: AM				
25		RAD001		: AM				
26		RAD001		: AM				
27		RAD001		: AM				
28		RAD001		: AM				

Patient's Signature: _____ Date: _____

07-325 RAD001 and Temozolomide

Name: _____ **MRN:** _____
Cycle: _____
RAD001 Dose: _____

RAD001 is to be taken every day, in the morning, on an empty stomach, 1 hour before breakfast
You will not make up any missed or vomited doses of drug. Do resume your regular dose the next day.
Bring your study drugs and this diary to clinic each visit.

Day	Date	Drug	Dose	Time	Symptoms
1		RAD001		: AM	
2		RAD001		: AM	
3		RAD001		: AM	
4		RAD001		: AM	
5		RAD001		: AM	
6		RAD001		: AM	
7		RAD001		: AM	
8		RAD001		: AM	
9		RAD001		: AM	
10		RAD001		: AM	
11		RAD001		: AM	
12		RAD001		: AM	
13		RAD001		: AM	
14		RAD001		: AM	
15		RAD001		: AM	
16		RAD001		: AM	
17		RAD001		: AM	
18		RAD001		: AM	
19		RAD001		: AM	
20		RAD001		: AM	
21		RAD001		: AM	
22		RAD001		: AM	
23		RAD001		: AM	
24		RAD001		: AM	
25		RAD001		: AM	
26		RAD001		: AM	
27		RAD001		: AM	
28		RAD001		: AM	

Patient's Signature: _____ Date: _____