STATUS PAGE

PROTOCOL **09-261**

Closed To New Accrual

Closure Effective Date: 09/30/10

No new subjects may be enrolled in the study as described above. Any questions regarding this closure should be directed to the study's Principal Investigator

Date Submitted: ***08/24/2010***
Date Posted: ***September 14, 2010***

Alert Page

DF/HCC Protocol #: 09-261

Safety / Drug (includes preparation, administration, dose modifications, equations)

Please see pages 69-71 for new drug diary

Protocol Clarifications (non-drug related e.g. eligibility criteria, study assessments)

Under Table 10.1 Study Calendar, chemistry labs must be repeated if they are outside of the 3 day window. In the case of a dosing delay, chemistry labs must fall within 3 days before dosing and should be repeated on delayed cycles if they are outside this window.

Protocol Version Date: 6/20/11

Local Protocol #:DFHCC 09-261

Title: A Phase 2 Study of ABT-888 and Temozolomide for Metastatic Breast Cancer

Principal Investigator:
Steven Isakoff, MD, PhD
Massachusetts General Hospital
55 Fruit St, LH306
Boston, MA 02114
Phone: 617-726-4920
Fax: 617-643-0589
Pager: 617-726-1818
sisakoff@partners.org

Coordinating Center: N/A

Co-Investigators:
Beth Overmoyer
Dana-Farber Cancer Institute
44 Binney Street
Boston, MA, 02115
Phone: 617-632-5351
Fax 617-632-1930
bovermoyer@partners.org

Nadine Tung, MD
Beth Israel Deaconess Medical Center
330 Brookline Avenue
Boston, MA, 02215
Phone: 617-667-7082
Fax 617-975-5665
ntung@caregroup.harvard.edu

Statistician:
Rebecca Gelman, PhD
Dana-Farber Cancer Institute
44 Binney Street
Boston, MA, 02115
Phone: 617-632-3629
Fax: 617-632-2444
gelman@jimmy.harvard.edu

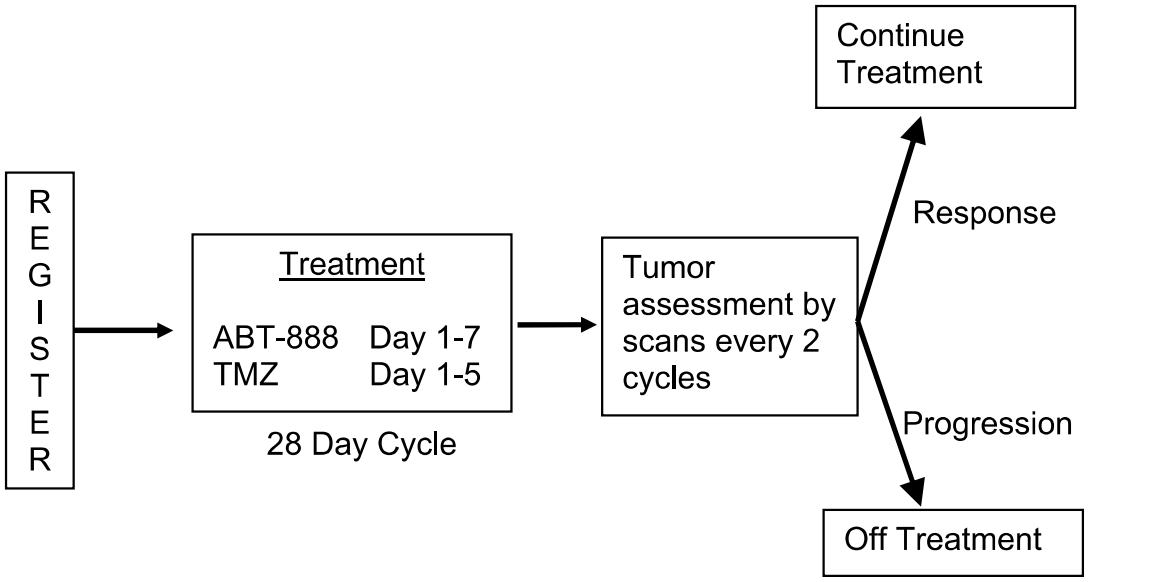
Study Coordinator: Kate Harrington
Massachusetts General Hospital
32 Fruit Street, Yawkey 9A, Room 9750
Boston, MA 02114
Phone: 617-724-8305
KEHarrington@partners.org

Responsible Research Nurse: Karleen Habin, RN
Massachusetts General Hospital
55 Fruit St, Yawkey 9A
Boston, MA 02114
Phone: 617-726-1922
khabin@partners.org

Responsible Data Manager: N/A

Agent(s): ABT-888 (IND#106078) – Supplier: Abbott Pharmaceuticals
Temozolomide – Supplier: Abbott Pharmaceuticals

1. SCHEMA



Eligibility
Stage 4 breast cancer
Measurable Disease
Archived tumor

Endpoints
Primary: Objective Response Rate
Secondary: Clinical Benefit Rate
PFS
Safety/Tolerability

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2. OBJECTIVES

The overall objective of this study is to evaluate whether there is sufficient anti-tumor activity of ABT-888 and temozolomide (TMZ) in subjects with metastatic breast cancer to pursue further testing of this combination, and to describe any associated toxicities with a larger sample size than in the phase 1 studies. This study will test the hypothesis that the combination of the novel PARP inhibitor ABT-888 in combination with TMZ is active in this population.

2.1. Study Design

This is a single arm, single stage phase II study to evaluate the efficacy of oral ABT-888 in combination with TMZ for the treatment of metastatic breast cancer. Subjects will receive ABT-888, 30mg PO/dose, every 12 hours on days 1 through 7 of each 28 day cycle. For cycle 1, TMZ will be started at a dose of 150mg/m2/day PO, daily on days 1 through 5 of a 28 day cycle. Measurable tumor will be assessed for response every 8 weeks by standard Response Evaluation Criteria In Solid Tumors. Additional study endpoints include safety assessment and evaluation of clinical benefit rate (CR+PR+SD>16 weeks) and progression free survival. Exploratory correlative studies will also be conducted as described in section 9.1.

This study will be conducted within the Dana-Farber/Harvard Cancer Center only.

A total enrollment of 41 patients is planned. However, patients who enter the study but do not complete 1 cycle of study drugs will not count towards this accrual goal of 41, so a few more patients may be entered.
The study is intended to complete accrual in approximately 18 months with an accrual rate of 2.5 subjects per month.

An expansion cohort of 20 patients with BRCA1 or BRCA2 mutations is planned. Patients who enter the study but do not complete 1 cycle of study drugs will not count towards this accrual goal of 20, so a few more patients may be entered. The expansion cohort is intended to complete accrual in approximately 4 months with an accrual rate of 5 patients per month.

2.2. Primary Objectives (for the primary study and an expansion cohort of BRCA1/2 positive patients)

- To determine the objective response rate (ORR) of ABT-888 and TMZ in metastatic breast cancer.

2.3. Secondary Objectives (for the primary study and an expansion cohort of BRCA1/2 positive patients)

- To further characterize the safety and tolerability of ABT-888 and TMZ in patients with metastatic breast cancer
- To evaluate progression free survival
- To evaluate the clinical benefit rate (CR+PR+SD>16 wks).

2.4. Exploratory Objectives (for the primary study except as noted)

- To explore the objective response rate in subgroups of breast cancer (hormone receptor positive, triple negative, and HER2 positive patients)
- To describe the CNS-specific progression free survival in patients with known brain metastases
- To determine the BRCA mutation status, the BRCA methylation status, and the BRCA expression level in archived tumors and to characterize the correlation with response
- To evaluate the Circulating Tumor Cell level and explore the correlation with response (in the primary study and the expansion cohort)
- To characterize the oncogene mutation status of a panel of known oncogenes in archived tumors (in the primary study and expansion cohort).

3. BACKGROUND

3.1. Study Disease

Breast Cancer

Breast cancer is diagnosed in over 1.3 million women worldwide each year and accounts for over 500,000 deaths making it the leading cause of cancer related death in women [1]. In the United States, breast cancer is the most common cancer in women and the second leading cause of cancer death with over 180,000 new cases and 40,000 deaths each year [2]. Despite recent advances in breast cancer treatment, metastatic breast cancer remains incurable. Although the number of agents approved for the treatment of metastatic breast cancer continues to increase, overall survival has changed relatively little and median survival remains in the range of 2-3 years.

With the development of gene expression array technology, the heterogeneity of breast cancer has become clearer and the identification of novel cancer subtypes has reinvigorated the search for more specific and effective therapies. Hierarchical clustering of genomic expression data from breast cancer specimens has demonstrated several distinct tumor subgroups with unique expression profiles including a HER2-positive subgroup, an estrogen receptor (ER)-positive group, and a subgroup termed the "basal-like or “basaloid” tumors.

Triple Negative Breast Cancer
The basal-like tumors have a poor prognosis relative to other subtypes [3], even with the best available chemotherapy. A common feature of tumors in the basal-like subgroup is the lack of expression of ER, PgR, and HER2 resulting in the description “triple-negative breast cancer” (TNBC). Although not all triple-negative breast cancers are basal-like, the classification of triple-negative tumors based on immunohistochemical staining is a clinically useful surrogate for the majority of basal-like breast cancer. Approximately 15% of women are diagnosed with TNBC, accounting for nearly 30,000 women in the US, with a disproportionate distribution in younger women, minority populations, and BRCA1

mutation carriers. Because TNBC does not express HER2 or endocrine receptors, trastuzumab and endocrine therapy are not effective. Therefore, conventional chemotherapy remains the only option for these patients. Little progress has been made in identifying specific molecular pathways associated with these refractory cancers that may be effectively targeted for therapeutic purposes [4, 5]. Thus, no proven, specific therapy exists for this tumor subtype.

Hormone Receptor Positive Breast Cancer
Approximately 75% of breast cancer are hormone receptor positive (HR+) and express either the estrogen receptor (ER+) and/or progesterone receptor (PgR+). Endocrine therapy with either aromatase inhibitors (AI) or the selective estrogen receptor modulator (SERM) tamoxifen is effective as initial therapy in over 2/3 of patients with advanced HR+ breast cancer, although first line therapy with AI appear superior to tamoxifen [6-8]. Treatment of HR+ breast cancer often involves sequencing of successive lines of endocrine therapy. However, up to 1/3 of patients are primarily resistant to endocrine therapy, and most patients who initially respond to endocrine therapy will eventually become resistant. Therefore, the vast majority of HR+ advanced breast cancer patients will receive chemotherapy during the course of their disease.

HER2 positive Breast Cancer
Approximately 20-25% of breast cancer contains HER2 gene amplification. [9] HER2 positive breast cancer has traditionally been considered an aggressive subtype of breast cancer. The development of HER2 directed targeted therapy has changed the natural history of this subtype of breast cancer. Adjuvant therapy with trastuzumab has consistently shown up to 50% reductions in risk of recurrence compared to non-trastuzumab based therapy. [10] In metastatic HER2 positive breast cancer, Trastuzumab therapy results in improved survival when used in combination with paclitaxel chemotherapy compared to paclitaxel alone. [11] Second line therapy with the small molecule anti HER2 agent lapatinib in combination with capecitabine showed an improved progression free survival compared to capecitabine alone. [12] Despite these dramatic advances, most patients eventually progress and metastatic HER2 positive breast cancer is still considered incurable. There is no standard therapy following second line therapy.

Poly(ADP-ribose) Polymerase (PARP) Activity
Poly(ADP-ribose) polymerase is a nuclear enzyme that recognizes DNA damage and facilitates DNA repair. [13-15] Activation of PARP enzymes is an essential step in the recognition of DNA damage that results in the poly(ADP-ribosyl)ation of many nuclear target proteins, including those that facilitate DNA repair of both single-stranded and double-stranded DNA breaks. Inactive PARPs 1 and 2 bind to damaged DNA, which leads to their auto-activation. The resulting activated PARP then poly(ADP-ribosyl)ates many nuclear target proteins, including those that facilitate DNA repair of both single-stranded and double-stranded DNA breaks. Higher expression of PARP in cancer cells compared to normal cells has been linked to drug resistance and the overall ability of cancer cells to sustain genotoxic stress. [16-19] Therefore, PARP inhibitors are proposed as sensitizing agents for a variety of DNA-damaging agents. Consequently, PARP inhibitors are proposed as sensitizing agents for a variety of DNA-damaging agents including alkylators (e.g., TMZ, BCNU, cyclophosphamide), platinums (e.g., cisplatin, oxaliplatin, carboplatin), topoisomerase inhibitions (e.g., irinotecan and topotecan), and radiation therapy.

DNA damaging agents including cytotoxic chemotherapy and radiation therapy remain a mainstay of treatment for many subjects with cancer. Since cancer cells are genetically unstable, often exhibiting complex karyotypes that include large deletions, insertions, and unbalanced translocations of

chromosomal material, these cells are more susceptible than normal tissues to cytotoxicity induced by DNA damaging agents. [20, 21] Of these, deficiencies in mismatch repair and homologous recombination are associated with the largest number of malignancies. These deficiencies render cells more dependent on PARP for DNA repair, and hence more sensitive to PARP inhibition. [22] Cancer cells with the ability to recognize and repair injury caused by chemotherapy and radiation therapy may recover and survive.

The therapeutic potential of PARP inhibitors was suggested by two clinical trials evaluating PARP inhibition in breast cancer and one in ovarian cancer. In patients with metastatic triple negative breast cancer who received no more than 2 prior regimens, the addition of a PARP inhibitor to gemcitabine and carboplatin chemotherapy improved the response rate, time to progression, and overall survival from 12% to 52%, 87 days to 211 days, and 169 days to >254 days, respectively.[23] A single arm trial evaluated a PARP inhibitor in metastatic breast cancer in patients with BRCA 1/2 mutations and demonstrated single agent activity with an overall response rate of 38% in heavily pretreated patients.[24] A similar trial in BRCA mutation carriers with metastatic ovarian cancer showed a response rate of 33%.[25] Together, these results validate the proof of concept that PARP inhibition is an attractive therapeutic target in breast and other cancers.

3.2. Study Agents

3.2.1. ABT-888

A detailed discussion of the pre-clinical toxicology, metabolism, and pharmacology can be found in the Information for Investigator's Brochure. [26]

ABT-888 Activity and Pharmacokinetic Profile
ABT-888 is a potent PARP inhibitor that delays the repair of DNA damage induced by chemotherapeutics. ABT-888 increased sensitivity of tumor cells to damaging agents in vitro, and demonstrated PARP inhibition in murine tumors in vivo and human peripheral blood mononuclear cells *ex vivo*.

ABT-888 is a novel small molecule that is a potent PARP inhibitor (K_i of 5 nM and 3 nM for PARP-1 and PARP-2 enzymes, respectively) with a cellular EC_{50} of 2.4 nM. In vitro assays showed that ABT888 increased sensitivity of tumor cells to DNA damaging agents including TMZ, irinotecan, cyclophosphamide, BCNU, and cisplatin. In vivo pharmacology studies have demonstrated that ABT888 has enhanced the antitumor activities of DNA damaging agents that include alkylating/methylating agents (TMZ and cyclophosphamide), topoisomerase I inhibitors (irinotecan), crosslinking agents (cisplatin and carboplatin) and radiation. ABT-888 substantially increased the efficacy of cytotoxic therapies, when measured by either treated/control tumor volumes (%T/C) or by increased time for tumors to grow to a particular size (%ILS).

One of the most studied alkylating agents in combination with PARP inhibition is TMZ, which is used in the therapy of CNS tumors and melanoma. In preclinical studies ABT-888 potentiated cytotoxic therapy when administered either parenterally or orally. When administered parenterally via osmotic mini-pump in combination with TMZ, significant efficacy was observed at doses as low as 1mg/kg/day, and maximal efficacy was achieved at approximately 12.5 mg/kg/day corresponding to an ABT-888 steady state concentration of 70 ng/mL. When dosed orally, maximal potentiation was achieved at approximately 25 mg/kg/day divided twice daily (BID) achieving an $AUC_{0\text{-}24}$ of approximately 3.0 µg•hr/mL and plasma concentrations above 70 ng/mL for 8 hours per day (~4 hours/dose). No increased

toxicity was observed at any of these ABT-888 doses, either parenteral or oral. Projections of human PK indicate that an oral dose of 50 mg twice a day would achieve exposures greater than or equal to AUC_{0-24} of 3.0 μg•hr/mL and C_{max} of 0.21 μg/mL, consistent with the preclinically maximally efficacious dose.

The degree of PARP inhibition can be assessed by levels of PAR formation. Preclinically, significant inhibition of tumor PAR levels was observed at doses similar to those with anti-tumor effect; indicating that ABT-888 potentiation of DNA damaging agents was mediated through mechanistic inhibition of PARP. A facile enzyme-linked immunosorbent assay (ELISA) that can measure PAR formation has been developed, which allows measurement of the pharmacodynamic effect of ABT-888 in human clinical tissues including peripheral blood mononuclear cells (PBMCs) and tumor.

In rats and dogs, ABT-888 is primarily cleared in the urine as intact parent drug, with minor contributions from metabolism. The renal clearance and minimal metabolism observed in rats and dogs and the minimal metabolism observed in vitro in all species evaluated are consistent with the low molecular weight (246.31 g/mol) and good solubility of ABT-888. These data support the prediction that in the human, ABT-888 will be primarily cleared as intact parent in urine. ABT-888 is not a potent inhibitor of the major human cytochrome P450s (CYPs), suggesting a minimal potential for drug-drug interactions at the anticipated therapeutic concentrations.

Penetration of the Blood-Brain Barrier
The transplantable rat glioma cell line L9 produces orthotopic glioma in syngeneic Fisher 344 rats and can be used to assess the efficacy of a compound in an environment where drug must cross the blood-brain barrier. [27] In this experiment, rats were randomized to treatment with vehicle, TMZ (17.5 mg/kg/day, PO QD administered Days 4 to 8), and ABT-888 (5, 18, and 50 mg/kg/day, PO BID administered Days 3 to 13) with TMZ (17.5 mg/kg, PO QD). When combined with TMZ, ABT-888 significantly potentiated its antitumor activity. Tumor growth inhibition was dose-dependent. ABT-888 at 50 mg/kg/day in combination with TMZ reduced tumor volume compared to control as assessed by contrast-enhanced magnetic resonance imaging (MRI) on Day 14 by 63%, which was 44% better than TMZ alone ($p < 0.005$). After multiple doses of ABT-888 (50 mg/kg/day), the concentration of the compound 2 hours post dosing (near Cmax) was 1.36 ± 0.16 μg/mL, 0.72 ± 0.12 μg/g, and 3.00 ± 0.16 μg/g, in plasma, brain, and tumor tissues, respectively. Therefore, ABT-888 penetrates the blood-brain barrier and has activity in the CNS.

Preliminary Clinical Experience (Phase 0 Study)
A Phase 0 dose-ranging pharmacokinetic and pharmacodynamic study has been completed (NCI IND). [28, 29] In this trial, 13 subjects with various types of advanced cancer received a single dose of single-agent ABT-888 (10 mg, n = 3; 25 mg, n = 3; 50 mg, n = 7). The pharmacokinetic results from this study demonstrated that ABT-888 is orally bioavailable and primarily cleared through renal excretion, with a half-life of 4 to 5 hours. Additionally, this study provided proof of mechanism, as tumor PARP inhibition (> 90%) was demonstrated in 5 out of 6 human tumor biopsies that were obtained 3 to 6 hours after dosing with ABT-888. No serious adverse events, DLTs, or deaths were reported for this study.

ABT-888 Toxicology
In a 4-week repeat dose dog toxicity studies, the No-Observed-Adverse-Effect-Level (NOAEL) was 10 mg/kg/day (C_{max} of 1.68 μg/mL and AUC_{0-24} of 8.01 μg•hr/mL). The dose-limiting toxicity in this study was seizure observed at 30 mg/kg/day. Seizures were also noted a 2-week study, at dosages varying from 30 to 60 mg/kg/day. A dedicated EEG study in the conscious dog also determined that seizures

were observed at a dose of 30 mg/kg BID, with no evidence of abnormal cortical activity or seizures occurring at a lower dose of 20 mg/kg BID. Plasma exposure at the 30 mg/kg BID dose corresponded to a mean plasma exposure approximately 10-fold above the predicted clinical AUC_{0-24} of 3 μg•hr/mL. Therefore, preclinical dog studies determined an approximate 10-fold safety margin for seizure, when exposures were compared to anticipated therapeutic AUC_{0-24}.

In repeat-dose oral rat toxicity studies, the NOAEL was 25 mg/kg/day with key findings at higher exposures including decreased body weight, decreased white blood cell and erythro parameters, and testis degeneration. ABT-888 did not induce seizures at doses as high as 400 mg/kg/day. Additionally, ABT-888 did not induce seizures in a model of orthotopically implanted rat glioblastoma with a dose of up to 50 mg/kg. In safety pharmacology studies, ABT-888 did not affect the electronically induced seizure threshold, except for a small decrease at 30 mg/kg.

The secondary and safety pharmacology studies conducted with ABT-888 demonstrated minimal effects on the cardiovascular, pulmonary, and GI systems. In the anesthetized dog model, there was a trend towards delayed cardiac repolarization at plasma concentrations 21-fold higher than the predicted clinical C_{max}. In humans, QT_c prolongation is predicted to be less than 3 ms at a dose of 50 mg BID. ABT-888 produced no effect on heart rate or cardiac output at a concentration of 12.96 μg/mL in the dog (≈61-fold over predicted clinical exposure level) and no effect on pulmonary function at a plasma concentration of 5.82 μg/mL in the rat (≈28-fold over predicted clinical exposure level). ABT-888 was determined to unlikely be emetic or to elicit adverse GI effects at efficacious plasma concentrations.

In a separate study in rats in which ABT-888 was combined with TMZ, observed toxicities were consistent with exacerbation of known TMZ toxicity. Co-administration of TMZ at 16 mg/kg/day and ABT-888 at doses of 12.5 and 25 mg/kg/day (divided BID) resulted in increased toxicity over that observed with TMZ administration alone, affecting bone marrow (manifesting as decreased neutrophils, lymphocytes, and reticulocytes), lymphoid tissues, testes, and ovaries. Recovery of toxicologic findings was observed at the end of a 28-day recovery period (with the exception of the testes). At a higher dose of ABT-888 (75 mg/kg/day divided BID), there was watery diarrhea with histologic changes, including intestinal crypt necrosis, and dose-related hematologic toxicity. Limited exposure data for ABT-888 was obtained in this study as the majority of the plasma was utilized to evaluate the pharmacokinetic profile of TMZ. However, evaluation of selected pharmacokinetic time points was comparable to that noted in previous studies. In these previous preclinical toxicology studies, a dose of 25 mg/kg/day resulted in an exposure that exceeded anticipated clinical efficacious exposure by 1.3 to 4 fold in the male rat and 2.6 to 7 fold in the female rat.

ABT-888 resulted in a reversible and non-lethal exacerbation of TMZ hematologic toxicity in the rat at doses that, in previous studies, resulted in exposures that were similar to or greater than the maximally efficacious exposure (AUC) in the melanoma murine model. However, even in the most sensitive preclinical model (dog) seizures were not seen at exposures less than or equal to 8-fold above the preclinical efficacious exposure (AUC). Therefore, hematological toxicity is expected to be the dose-limiting toxicity in the clinic occurring at doses and exposures well below those at which seizures have been observed. Subjects in the clinic will be carefully monitored for hematologic abnormalities.

3.2.2. Temozolomide

One of the most studied alkylating agents in combination with PARP inhibition is TMZ. Temozolomide is a newer generation DNA-methylating agent that crosses the blood-brain barrier. It is used in the

therapy of CNS tumors and melanoma. TMZ is an oral agent with a broad spectrum of antitumor activity and relatively little toxicity. TMZ is a prodrug of the active alkylating agent 5-(3methyltrizen-1-yl)imidazole4-carbozimide (MTIC). Adverse events associated with TMZ observed in previously conducted studies in glioblastoma include myelosuppression with grade 3 or 4 neutropenia (reported as adverse event or laboratory abnormality) observed in 8% of subjects and grade 3 or 4 thrombocytopenia (reported as adverse event or laboratory abnormality) was observed in 14% of subjects. For additional information regarding TMZ, please refer to the Temodar® package insert. [30]

Few clinical studies have evaluated TMZ in breast cancer. In vitro studies using primary human breast tumors demonstrated a potent cytotoxic effect at clinically meaningful doses. [31] A phase II trial in 19 patients with MBC evaluated TMZ monotherapy using 150mg/m2 on days 1-7 and 15-21 of a 28 day cycle. [32] TMZ was well tolerated, but in 18 evaluable patients no objective responses were seen and 3 patients had stable disease. TMZ in combination with cisplatin was evaluated in patients with brain metastases and resulted in 6 of 15 patients with breast cancer achieving a partial response in both the brain and extra-cranial sites. [33] The study conducted by the Hellenic Cooperative Oncology Group used TMZ 150mg/m2 days 1-5 and cisplatin 75mg/m2 day 1 of a 28 day cycle. However, a previous study by the same group evaluated TMZ monotherapy in patients with brain metastases and there were no responses in the 4 breast cancer patients in that study. [34] A second phase II study of TMZ monotherapy in patients with brain metastases showed no responses in 10 patients with breast cancer, but 4 patients had stable disease in the brain for 8 weeks. [35]

3.3. Rationale

ABT-888 is an orally bioavailable PARP inhibitor that possesses an excellent efficacy and pharmacokinetic profile, and enhances the antitumor activity of DNA-damaging agents such as TMZ. The feasibility of inhibiting target PARP in the clinic has been demonstrated in the Phase 0 study described above. The large unmet medical need in advanced breast cancer, and the potential for the broad use of this compound in combination with numerous chemotherapeutic regimens renders ABT-888 an attractive agent for clinical development.

PARP inhibition and TMZ

Inhibiting PARP-1 through the use of PARP inhibitors has been shown to increase the activity of DNA-damaging chemotherapy in a variety of in vitro models [14, 36-38], including breast cancer models. [39] In particular, a role for PARP inhibition alone has been suggested for breast cancers with deficient homologous recombination such as those in BRCA1- and 2-mutation carriers, and in TNBC, which are more likely to overexpress PARP.[40, 41]

TMZ treatment results in several DNA methylation products including N7-methylguanine (N7-MeG), N3-methyladenine (N7-MeA), and O6-methylguanine (O6-MeG). N7-MeG and N3-MeA account for nearly 80-90% of the total alkylating events. Although present in lower amounts, O6-methylguanine is cytotoxic due to mispairing with thymine during replication. However, O6-MeG is efficiently repaired by removal of the methyl group by methylguanine-methyltransferase (MGMT). Many cancers have elevated levels of MGMT which may contribute to TMZ resistance by facilitating DNA repair caused by alkylating agents such as TMZ. [42, 43] Breast tumors contain high levels of MGMT which may contribute to TMZ resistance in breast cancer. Furthermore, deficiencies in the DNA mismatch repair system, which is common in many cancers, leads to a second mechanism of resistance to TMZ by inducing tolerance of O6-MeG. The more predominant N7-MeG and N3-MeA products are rapidly repaired by the base-excision repair pathway under normal conditions, and the base-excision repair pathway has been shown to be important in mediating TMZ resistance.[44] PARP-1 and -2 play a key role in the base-

excision repair pathway. This is supported by the increase in PARP activity in peripheral blood lymphocytes after TMZ treatment suggesting its importance in this pathway. [45] In this way, inhibition of PARP potentiates the activity of TMZ and other alkylators by rendering the normally insignificant production of N7-MeG and N3-MeA into lethal methyl-DNA adducts via interruption of the base excision repair pathway. (Reviewed in [46])

Several studies demonstrate that PARP inhibition potentiates the activity of TMZ.[22, 36, 47-53] For example, xenograft studies in athymic mice using a TMZ resistant medulloblastoma cell line demonstrate that inhibition of PARP inhibited tumor growth and induced some responses, whereas either TMZ or PARP inhibition alone had minimal effect.[48] Similar results were observed in two neuroblastoma xenograft models. [49] In mismatch repair deficient colon and ovarian cell lines, PARP inhibition potentiated the growth inhibition of TMZ treated cells, though the effect was less pronounced in mismatch repair proficient counterparts. [22] A phase 1 study evaluating TMZ and a tricyclic indole PARP inhibitor, AG014699, demonstrated the combination was well tolerated with expected neutropenia and thrombocytopenia as the main toxicities. No toxicity was attributable to the PARP inhibitor alone, and promising clinical activity was seen in melanoma and other cancers.[54]

ABT-888 and TMZ were evaluated in a xenograft mouse models using 2 breast cancer cell lines, MX-1 and MDA-231. Either agent alone had minimal activity. The combination induced a dose dependent inhibition of tumor growth. At the higher doses, 5 of 10 tumors in the MX-1 model had no residual tumor by H&E (Abbott, unpublished data). Further support for the combination of TMZ and a PARP inhibitor in breast cancer comes from a study that evaluated 3 breast cancer cell lines including 2 ER positive lines (MCF-7 and T47D) and a triple negative line (MDA-231). TMZ induce growth inhibition was potentiated by addition of either of 2 classes of PARP inhibitors in all 3 cell lines.[50]

Phase 1 Study of ABT-888 and TMZ

A Phase 1 multiple-dose study of ABT-888 in combination with TMZ in subjects with nonhematologic malignancies and metastatic melanoma is ongoing (Abbott IND). Study M06-862 is a dose-escalation study designed to assess the safety, tolerability, and pharmacokinetic profile of ABT-888 in combination with TMZ. A dosing cycle in Study M06-862 consists of 7 days on ABT-888 (Days 1 through 7) and 5 days on TMZ (Days 1 through 5) with a subsequent 21-day rest period. As of 21 April 2009[55], 29 subjects have enrolled into the M06-862 study (10 mg BID n = 3; 20 mg BID n = 3; 40 BID mg n = 3, 80 mg BID n=3, 60 mg BID n=3, and 40 mg BID n=14 in an MTD expansion cohort). No DLTs were reported for the first 3 dose cohorts (10 mg BID, 20 mg BID and 40 mg BID). At doses higher than 40 mg BID, DLTs were observed. At 80 mg BID, 2 of 3 subjects enrolled experienced grade 4 thrombocytopenia or neutropenia. At 60 mg BID, 2 of 3 subjects enrolled experienced grade 4 thrombocytopenia or grade 3 hematemesis. In the 40mg BID MTD expansion cohort, 1 of 14 subjects had Grade 4 thrombocytopenia and neutropenia. Most common adverse events (>20%) seen in this study were thrombocytopenia, neutropenia, leucopenia, anemia, nausea, fatigue, vomiting, anorexia, constipation, diarrhea, headache, abdominal pain, fever, and dyspnea. Of 20 patients evaluated for efficacy, 1 had a partial response (hepatocellular carcinoma) and 10 had stable disease including 2 subjects with breast cancer[55]. Preliminary ABT-888 pharmacokinetic results following doses of 10, 20, or 40 mg ABT-888 BID were consistent with those seen following single doses of 10, 25, or 50 mg ABT-888 in Phase 0. Therefore, the dose level of 40 mg ABT-888 BID, which achieved the steady-state exposure (AUC) that was effective in murine efficacy models was initially selected as the ABT-888 dose to be given in this study. To reduce the risk of hematological toxicity, the dose was modified to 30mg ABT-888 BID. Based on safety pharmacology, toxicology, metabolism, and pharmacokinetic data it can be concluded that ABT-888 has been adequately characterized to support the initiation of this

Phase 2 clinical trial in breast cancer subjects.

Conclusion
Together, the above supports the hypothesis that the combination of ABT-888 and TMZ may have clinical activity in breast cancer and justifies testing in this phase II trial.

Specifically, the following points support the use of this combination in breast cancer:

- Based on phase I data, the combination is safe and well tolerated at the doses used in this trial.
- In vitro studies demonstrate potent activity of TMZ against some breast cancer cell lines.
- TMZ is one of the most well-studied alkylating agents in combination with PARP inhibitors.
- TMZ and ABT-888 are both oral agents allowing for ease of home administration
- In vitro and xenograft models suggest that breast cancer, can be rendered particularly sensitive to TMZ when combined with ABT-888.
- The demonstrated penetration of TMZ and ABT-888 into the CNS suggests that breast cancer brain metastases may also be a target of this combination, and TMZ monotherapy has shown some evidence of disease stabilization in the CNS.
- Few if any patients will have had prior exposure to TMZ, thereby minimizing any confounding effects of prior TMZ treatment.
- The preclinical data indicates that the mechanism of action of TMZ potentiation by PARP inhibition occurs in hormone receptor positive breast cancer and triple negative breast cancer, and is therefore not specific to particular subtypes of breast cancer.

The above data support the use of the combination of TMZ and ABT-888 in this phase II clinical study in all subtypes of breast cancer.

Rationale for the expansion cohort
In the first 41 patients that were enrolled in the phase 2 study, a preliminary analysis revealed 8 patients with known positive BRCA mutation status, 7 patients with normal BRCA1/2 status, 25 patients who have not been tested, and 1 patient with a BRCA1 variation of unknown significance. Among the 8 BRCA1/2 mutation carriers, as of April 11, 2010 there have been 4 patients with a partial or complete response (response rate 50%, 3 with PR, 1 with CR), 1 patient with stable disease (12.5%) for greater than 16 weeks, and 3 patients with progressive disease (37.5%) as their best response. The clinical benefit rate in the BRCA1/2 carriers is 62.5%. Among the 33 patients with normal or unknown BRCA1/2 status, there are 2 patients with stable disease and no responders. Therefore, the BRCA1/2 subgroup has demonstrated potentially significant response rate.

The most common grade 3/4 toxicities were expected thrombocytopenia and neutropenia. Of 12 patients who experienced grade 3/4 thrombocytopenia (8 grade 4, 4 grade 3) only 1 was a BRCA mutation carrier. Of 10 patients who experienced grade 3/4 neutropenia (3 grade 4, 7 grade 3), 3 were BRCA mutation carriers. There were no reported episodes of bleeding or febrile neutropenia. Based on the higher than expected rate of hematological toxicity observed in the primary study, the dose of ABT888 was reduced from 40mg to 30mg BID. There have not been any additional episodes of grade 3/4 heme toxicity after this change and in conjunction with protocol-specified dose reductions in TMZ. However, all patients in the primary study received 40mg BID of ABT888 for the first cycle. Therefore, the heme toxicity in patients starting at the 30mgBID dose of ABT888 is not clear from our primary study.

Based on the above preliminary data, an expansion cohort of 20 patients with known deleterious mutations in BRCA1/2 will be accrued in order to further characterize the activity and safety of ABT888 and TMZ. The data obtained from this expansion cohort will be used to support follow up phase 2 and phase 3 studies limited to BRCA1/2 mutation carriers.

4. PARTICIPANT SELECTION

4.1. Eligibility Criteria

Participants must meet the following criteria on screening examination to be eligible to participate in the study:

4.1.1. Participants must have histologically or cytologically confirmed breast cancer that is metastatic (Stage IV) or unresectable and for which standard curative or palliative measures do not exist or are no longer effective (i.e. patients have progressed on their most recent anticancer therapy).

4.1.2. Participants must have measurable disease by Response Evaluation Criteria In Solid Tumors (RECIST). (See Section 11 for the definition of measurable disease.)

4.1.3. All immunohistochemical subtypes of breast cancer (Estrogen receptor +/-, progesterone receptor +/-, and HER2+/-) are eligible. HER2 positive breast cancer (HER2 3+ by immunohistochemistry or amplification by FISH > 2) must have progressed on prior standard HER2 therapy or have a contraindication to anti-HER2 therapy.

4.1.4. Participants must have at least 1 prior chemotherapy regimen for metastatic disease, with no limit on total number of lines of prior therapy. EXPANSION COHORT ONLY: Participants may have any number of prior chemotherapy regimens for metastatic disease, with no limit on total number of lines of prior therapy. This also includes participants with no prior chemotherapy for metastatic disease.

4.1.5. Age $\geq$ 18 years

4.1.6. Life expectancy $\geq$ 12 weeks.

4.1.7. ECOG performance status $\leq$2 (see Appendix A)

4.1.8. Participants must have normal organ and marrow function as defined below:

- Leukocytes $\geq$ 3,000/mm^3
- Absolute neutrophil count $\geq$ 1,500/mm^3
- Platelets $\geq$ 100,000/mm^3

- total bilirubin ≤ 1.5X the upper limit of institutional normal limits(subjects with Gilbert's Syndrome may have a bilirubin ≥ 1.5 X the upper limit of institutional normal limit if no evidence of biliary obstruction exists)
- AST (SGOT)/ALT (SGPT) ≤ 2.5 X institutional upper limit of normal (or ≤ 5 X institutional upper limit of normal if significant liver involvement of tumor is present)
- creatinine ≤ 2mg/dL or creatinine clearance ≥ 50 mL/min/1.73 m^2 for subjects with creatinine levels above institutional normal.

4.1.9. Archived tissue block or 25 unstained slides (from primary and/or metastatic tumor) if available for correlative exploratory studies. Absence of available tissue will not exclude subjects from participating.

4.1.10. CNS metastases are allowed if they are clinically stable without current evidence of symptomatic progression and do not require steroids (except for patients who recently completed brain radiation and are on stable or tapering doses of steroids), whole brain radiation therapy, or stereotactic radiosurgery (gamma/cyber knife). This may include brain metastases not previously treated or previously treated if they are clinically stable as described above. Note: CNS metastases in a location that the treating physician believes to be at high risk for causing symptoms in the very near future are encouraged to receive treatment first. Patients receiving brain radiation may start treatment 1 week after completing radiation and such patients may continue steroids.

4.1.11. The effects of ABT-888 on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

4.1.12. Women of childbearing potential must have a negative pregnancy test within 14 days of registration.

4.1.13. Ability to understand and the willingness to sign a written IRB approved informed consent document.

4.1.14. Patients enrolled in the expansion cohort must have confirmed BRCA1 or BRCA2 status with a pre-existing genetic report from a laboratory certified to carry out clinical genetic testing. Patients must have a BRCA1/2 mutation known to cause loss of gene function (clinical deleterious or suspected deleterious mutation).

4.2. Exclusion Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study, with exceptions as noted.

4.2.1. Participants who have had chemotherapy, biologic therapy, small molecule targeted therapy or radiotherapy within 14 days prior to entering the study or those who have not recovered from adverse events due to agents administered more than 2 weeks earlier. Anti-cancer hormonal therapy must be stopped 24 hours prior to starting study treatment.

4.2.2. Participants may not be receiving any other investigational agents.

4.2.3. Prior therapy with TMZ is allowed except if participant has a history of allergic reactions attributed to TMZ, or if therapy was discontinued due to intolerance of or toxicity from TMZ.

4.2.4. Prior therapy with an investigational or approved single agent PARP inhibitor is allowed except if participant has a history of allergic reactions attributed to the compound or, if therapy was discontinued due to intolerance of or toxicity from the PARP inhibitor. Prior combination therapy with a PARP inhibitor and chemotherapy is not allowed. EXPANSION COHORT ONLY: Prior therapy with an investigational or approved PARP inhibitor (alone or with combination therapy) is allowed except if participant has a history of allergic reactions attributed to the compound or, if therapy was discontinued due to intolerance of or toxicity from the PARP inhibitor.

4.2.5. Leptomeningeal disease. EXPANSION COHORT ONLY: Leptomeningeal disease may be permitted with approval of the study chair for patients who meet the following criteria: a) ECOG PS=0 or 1; b) "clinically stable" leptomeningeal disease defined by no progressive symptoms for the past 30 days and no concurrent use of steroids for the treatment of leptomeningeal disease; and c) standard non-CNS RECIST measurable disease is present.

4.2.6. CNS involvement requiring steroids (except for patients who recently completed brain radiation and are on stable or tapering doses of steroids).

4.2.7. Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, recent myocardial infarction, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements, or other comorbid condition the investigator believes may compromise participant's safe and effective participation in the trial.

4.2.8. Inability to comply with requirements of the trial.

4.2.9. Concurrent radiation therapy is not permitted while on study

4.2.10. Concurrent anti-cancer therapy (hormonal therapy, chemotherapy, biologic therapy, targeted therapy) is not permitted on trial.

4.2.11. Pregnant women are excluded from this study because ABT-888 and TMZ are chemotherapy agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk of adverse events in nursing infants secondary to treatment of the mother, breastfeeding should be discontinued if the mother is treated with ABT-888 or TMZ.

4.2.12. History of uncontrolled seizure disorder

4.2.13. Individuals with a history of other malignancies are eligible if they meet the following criteria:

- The other malignancy was treated with curative intent and is deemed by the investigator to be at low risk for recurrence, AND
- A metastatic lesion has been histologically confirmed as breast cancer, AND
- Patient has at least 1 RECIST measurable lesion thought to be breast cancer.
- Individuals with the following cancers are eligible if diagnosed and treated: cervical cancer *in situ*, and basal cell or squamous cell carcinoma of the skin.

4.3. Inclusion of Women, Minorities and Other Underrepresented Populations

This study is open to women and men. This study is open to participants of all ethnic and cultural groups. No specific recruitment efforts are planned for traditionally underrepresented populations.

5. REGISTRATION PROCEDURES

5.1. 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.

5.2. 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 situations 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.

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.

6. TREATMENT PLAN

Treatment will be administered on an outpatient basis. Expected toxicities and potential risks as well as dose modifications for ABT-888 and TMZ are described in Section 7 (Expected Toxicities and Dosing Delays/Dose Modifications). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

A summary of the treatment plan is provided in Table 6.1 below.

A summary of on study evaluation is provided in the study calendar in Table 10.1.

In summary, all subjects who sign informed consent, enroll in the study, and meet the pre-treatment requirements will receive study drugs. Subjects will self administer ABT-888, 30mg, every 12 hours PO on days 1-7 of each 28 day cycle. Subjects will self administer TMZ, 150-200mg/m^2, orally once daily on days 1-5 ONLY of each cycle. The dose of TMZ will be 150mg/m^2 for CYCLE 1, and will increase to 200mg/m^2 for CYCLE 2 and higher, per section 6.2.2. The intention is for both drugs to be administered concurrently and ABT-888 and TMZ should begin on the same day. If a delay in dosing of either drug is required for any reason, both drugs should be delayed until the subject is eligible to receive both drugs as scheduled concurrently. If for any reason the subject is permanently taken off either ABT-888 or TMZ, the subject will be off study treatment. Refer to Section 6.2 for details of administration of each agent.

Table 6.1 Treatment Descriptions

*** CYCLE 1 ONLY ***					
Agent	**Instructions**	**Dose**	**Route**	**Schedule**	**Cycle length**
ABT-888	Take AM dose at same time as TMZ	30mg q 12 hrs	PO	Days 1-7	28 days
TMZ	Take without food	150mg/m2 QD	PO	Days 1-5	
*** CYCLE 2 and HIGHER ***					
Agent	**Instructions**	**Dose**	**Route**	**Schedule**	**Cycle length**
ABT-888	Take AM dose at same time as TMZ	30mg q 12 hrs	PO	Days 1-7	28 days
TMZ	Take without food	200mg/m2 QD	PO	Days 1-5	

6.1. Pre-treatment Criteria

After a patient has been determined to be eligible for this study and has provided signed written informed consent, a pre-study baseline evaluation is required as indicated in Table 10.1 prior to initiation of cycle 1. This evaluation must be completed within 1 week prior to starting therapy, except as indicated (imaging may be up to 4 weeks prior). Confirmation that adequate tissue sample is available to be sent to MGH for correlative studies should be obtained prior to enrollment, but tissue may be sent after enrollment. Inability to confirm tissue, however, is not an exclusion to eligibility nor a cause for delay in dosing if other pre-study criteria are met.

6.2. Agent Administration

6.2.1. ABT-888

Dosing

Total daily dose will be 30mg every 12 hours (unless modified according to dose modification instructions below) given on days 1-7 every 28 days.

ABT-888 will be supplied as 10mg capsules. Subjects will be instructed to take 3 (three) 10mg capsules to achieve the 30mg dose.

Subjects will self-administer the morning and evening doses of ABT-888 orally, approximately 12 hours apart in the same calendar day.

On days when TMZ will also be coadministered (days 1-5), the morning dose of ABT-888 and TMZ can be taken at around the same time, but the study drugs should be taken under fasting conditions to reduce the chance of nausea and vomiting per TMZ label recommendation (no food for at least 1 hour before and after dose; water and regular medications are OK). The evening dose of ABT-888 may be taken with or without food.

The following guidelines shall be used regarding missed doses of ABT-888:

- It is recommended that if a subject misses a scheduled dose of ABT-888 and less than 6 hours have passed since the scheduled dosing time, the dose should be taken immediately.
- It is recommended that if more than 6 hours have passed since the scheduled dosing time, the subject should not take the missed dose of ABT-888, but should wait and take the next regularly scheduled dose.
- If the subject vomits within 15 minutes of taking ABT-888, another dose of ABT-888 will be administered. The dose may only be repeated once.
- If the subject vomits and more than 15 minutes have passed from the time of oral dosing of ABT-888 then no additional doses of ABT-888 will be taken.
- For situations not otherwise clearly described above, the principal investigator or designee will provide appropriate instructions for subjects who miss a dose of study drug.

Criteria to treat
There are no known direct clinically significant toxicities due to ABT-888 monotherapy for which dose dependent modification of ABT-888 are necessary. Criteria to treat will be based on the criteria to treat with TMZ, described in Section 6.2.2.

Documentation of dosing
A record of ABT-888 supplied to each subject must be maintained in the source documents.

Each subject will receive a drug diary (Appendix G) to record the date, time and amount of drug taken.

Subjects will be instructed to return their drug diary and all study drug bottles (empty, partially filled or full) to the study site personnel prior to each cycle and at the Final Visit. The study coordinator will document the bottles returned and the number of capsules per bottle per institutional policy. The bottle(s) will be returned to the Institutional research pharmacy for disposal.

6.2.2. Temozolomide

Dosing
TMZ will be administered orally once a day for 5 consecutive days on days 1-5 and repeated every 28 days.

The dose administered will be determined using the body surface area (BSA) calculated at the beginning of each cycle. The BSA will be calculated from the height obtained at the baseline evaluation and from the weight obtained at the beginning of each cycle. The chart in Appendix B may be used to determine the dose of TMZ based on known BSA. A maximum BSA of 2.5 for TMZ dose calculation will be used for subjects with BSA>2.5.

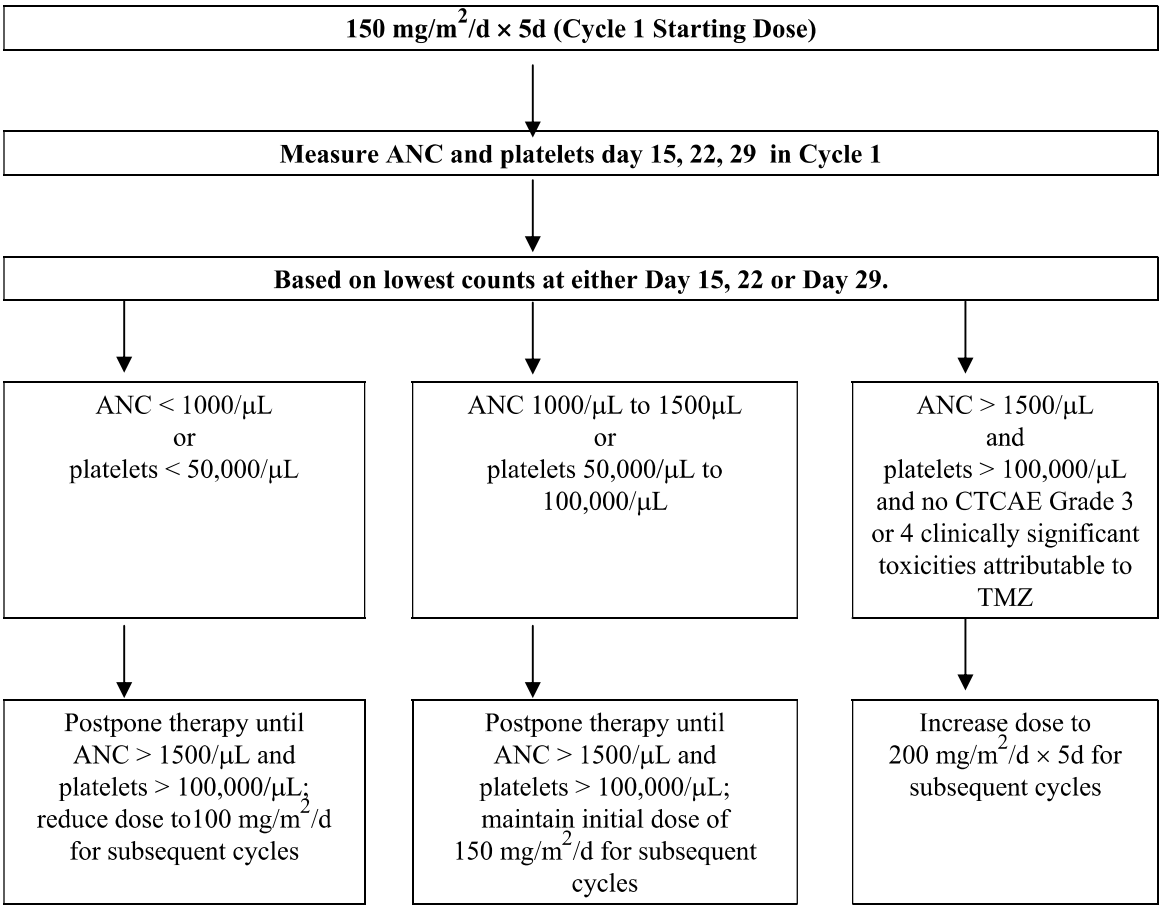
TMZ dosing will be as follows, shown schematically in Table 6.2:

Cycle 1 Only:
The dose for the first cycle of TMZ is 150 mg/m2/day. Blood counts will be monitored day 15 and 22 for cycle 1.

Cycle 2 and higher:
The dose for cycle 2 and higher will be determined as follows:

- If during the first cycle, all clinically significant CTCAE non-hematological toxicity attributable to TMZ observed was Grade ≤ 2 (except for alopecia) and with platelets ≥ 100,000/ul and ANC ≥ 1500/ul then TMZ dose should be escalated to 200 mg/m2/day and this dose should be used as the starting dose for subsequent cycles.
- If treatment after cycle 1 has to be delayed because of ongoing clinically significant non-hematological toxicity of CTCAE grade > 2, then no escalation is possible. If subject does not meet the criteria for dose escalation then the subject should remain at the 150mg/m2/day dose.
- If during the first cycle the subject experiences platelets < 50,000/ul and/or ANC < 1000/ul and/or a clinically significant non-hematologic toxicity > grade 3 then subject should postpone therapy until ANC > 1500/ul and platelets >100,000/ul and reduce dose to 100mg/m2/day pas per dose reduction in Section 7.
- If the dose was not escalated at cycle 2 then the dose should not be escalated in further cycles.

Table 6.2 TMZ Dosing Modification For Cycle 2



The start of the each cycle will be scheduled 28 days ± 3 days after the last day of the previous cycle.

Capsules of TMZ are available in 5, 20 and 100 mg strengths. The daily dose will be rounded to the nearest 5 mg. However, for patient convenience the dose may be rounded up or down no more than 5% from calculated dose in order to minimize the number of pills per dose. The exact dose administered should be recorded in the CRF. Each daily dose should be given with the least number of capsules. Appendix C may be used to assist in calculating to capsule combinations to achieve the desired dose. Subjects will be instructed to fast for at least one hour before and one hour after administration of TMZ. Water is allowed during the fast period. Subjects should be told to swallow the whole capsules in rapid succession without chewing them. If vomiting occurs during the course of treatment, no re-dosing of the subject with TMZ is allowed before the next scheduled dose. Missed doses will not be made up. For situations not otherwise clearly described above, the principal investigator or designee will provide appropriate instructions for subjects who miss a dose of study drug.

Please see Section 7 for dose modification guidelines.

Criteria to Treat
Prior to each 5-day treatment with TMZ a complete blood count (CBC) must be obtained (within -3 days prior to dosing, except for cycle 1 which may be -7 days). Blood counts will be evaluated again day 15

and 22 for cycle 1 and on day 22 for cycle 2 and higher. Within -3 days prior to first dose of each 5-day TMZ treatment the subject must have an ANC ≥ 1500/ul and platelet count ≥ 100,000/ul. On day 1 of each cycle (within -3 days) all clinically significant treatment related non-hematological toxicity grade 3 or 4 (except for alopecia) must have resolved (CTCAE grade ≤ 1). If toxicity persists, treatment should be delayed by about one week for up to 3 consecutive weeks. If after 3 weeks of delay all clinically significant treatment related toxicity has still not resolved then subject should be discontinued from study treatment.

Documentation of dosing
A record of TMZ supplied to each subject must be maintained in the source documents.

Each subject will receive a drug diary (Appendix G) to record the date, time and amount of drug taken.

Subjects will be instructed to return their drug diary and all study drug bottles (empty, partially filled or full) to the study site personnel prior to each cycle and at the Final Visit. The study coordinator will document the bottles returned and the number of capsules per bottle per institutional policy. The bottle(s) will be returned to the Institutional research pharmacy for disposal.

6.3. General Concomitant Medication and Supportive Care Guidelines

Antiemetics
The prophylactic use of a 5-HT3-antagonsist is strongly recommended before the TMZ administration. Additional standard antiemetics are permitted as required.

CYP450 Interactions
Neither ABT-888 nor TMZ are known to have significant cytochrome P450 interactions. However, because there is a potential for interaction of ABT-888 or TMZ with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies.

Hematopoietic growth factors
Use of colony stimulating factors (GCSF) is permitted at the discretion of the treating physician if they believe it to be in the subject's best interest. Because the population of subjects eligible in this study may have significant prior therapy, it is possible that the study treatment may result in leucopenia. Standard erythropoiesis stimulating agents may be used at the treating physician's discretion. Transfusions of RBC are permitted at physician discretion.

Bisphosphonates
Use of standard bisphosphonates such as zoledronic acid is permitted.

Anticancer therapy
Concomitant medications (hormonal therapy, chemotherapy, biologic therapy, targeted therapy) intended to treat the underlying cancer are not permitted.

Glucocorticoid steroids
Use of steroids for the treatment of progressive brain metastases will be considered evidence of clinical progression.

Other medications

Investigators may prescribe other concomitant medications or treatments deemed necessary to provide adequate supportive care except as noted in Section 6.3.

6.4. Duration of Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse events, treatment may continue indefinitely or until one of the following criteria applies:

- Disease progression (note: see Section 6.6 for CNS-only progression),
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Participant decides to withdraw from the study,
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator, or
- Study drug becomes unavailable due to manufacturer or other causes.

6.5. Duration of Follow Up

Participants will be followed for two years after removal from study. . Participants removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Patients will be followed off study by their primary treating physician. At the time of informed consent, patients will be asked for permission to contact the patient or their family in the future after coming off therapy to determine patient outcome or if any relevant follow up issues arise from the clinical or exploratory endpoints.

6.6. Criteria for Removal from Study

Participants will be removed from study when any of the criteria listed in Section 6.4 applies. The reason for study removal and the date the participant was removed must be documented in the study-specific case report form (CRF). Alternative care options will be discussed with the participant.

In the event of unusual or life-threatening complications, participating investigators must immediately notify the Principal Investigator Steven Isakoff at 617-726-1818.

NOTE: Participants without evidence of progression of visceral disease who develop CNS progression (isolated new brain metastases or progression of brain metastases) treatable with radiation as their only site of progression may be allowed to continue to receive protocol based therapy. Such participants may continue on protocol therapy until either they experience systemic progression of their non-CNS disease and/or further progression in the brain (by investigator assessment). Such participants are advised not to initiate radiation within 14 days of last dose of study drug (unless clinical care requires more urgent initiation of radiation), and the next cycle of study drug should not resume until ≥ 7 days after radiation is complete. A delay of up to 9 weeks is permitted to allow for radiation therapy. Participants must have ECOG performance status ≤2 when resuming study drug, and restaging CT scans

(chest/abd/pelvis) should be obtained ≤4 weeks of restarting study drug and will serve as the new baseline to assess non-CNS response.

7. EXPECTED TOXICITIES AND DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made using the following recommendations. Toxicity assessments will be done using NCI Common Terminology Criteria for Adverse Events (CTCAE v3.0) which is available at http://ctep.cancer.gov/reporting//ctc.html).

If possible, symptoms should be managed symptomatically. In the case of toxicity, appropriate medical treatment should be used (including anti-emetics, anti-diarrheals, etc.).

All adverse events experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit. Participants continuing to experience toxicity at the off study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

Dose may be delayed as described in Section 7.2.

A list of the adverse events and potential risks associated with the agents administered in this study appear below and will determine whether dose delays and modifications will be made or whether the event requires expedited reporting **in addition** to routine reporting.

7.1. Anticipated Toxicities

7.1.1. ABT-888

Preliminary safety data are available for 24 subjects from Study M06-862, a dose ranging phase 1 study of ABT 888 and TMZ. [26] Twenty-two of the 24 subjects (91.7%) experienced at least 1 adverse event. The most common adverse events, reported in > 30% of the subjects, were nausea (66.7%), fatigue (58.3%), thrombocytopenia and vomiting (54.2% each), anorexia (45.8%), neutropenia (37.5%), and constipation (33.3%). Among adverse events considered possibly or probably related to ABT-888, the most common were nausea (58.3%); fatigue (54.2%); thrombocytopenia (50.0%); and neutropenia, vomiting, and anorexia (37.5% each). Additional adverse events reported by at least 2 subjects and considered possibly or probably related to ABT-888 included anemia, leukopenia, abdominal pain, constipation, diarrhea, pyrexia, dizziness, headache, alopecia, petechiae, and rash; in addition, clinically significant events of febrile neutropenia and stomatitis also were seen in 1 patient each. [26]

Eight of 24 subjects (33.3%) experienced a serious adverse event in Study M06-862. The most commonly reported serious adverse event was vomiting (3 subjects, 12.5%). Additional serious adverse events considered possibly or probably related to ABT-888 were neutropenia and nausea (2 subjects each, 8.3%), and febrile neutropenia, leukopenia, thrombocytopenia, gastrointestinal hemorrhage, hematemesis, pyrexia, pneumonia, and dehydration (1 subject each, 4.2%). No dose relationship has been established for these events. [26]

No subject has died during Study M06-862, and no pregnancies have been reported.

As with any medication, allergic reactions are a possibility. Problems and side effects may occur with the use of ABT-888 that are not expected or are unknown at this time.

7.1.2. Temozolomide

Known potential toxicities of TMZ are hematological toxicities (leucopenia, lymphopenia, thrombocytopenia, and anemia), renal insufficiency, nausea and vomiting, liver enzyme abnormalities, lethargy, rash, headache, alopecia, constipation, fatigue/malaise, anorexia, hyperglycemia and diarrhea are known toxicities. Refer to the package insert[30] (http://www.spfiles.com/pitemodar.pdf) for additional information on adverse events observed to date. Rats given TMZ in recent multidose toxicity studies have developed adenocarcinoma of the breast, fibrosarcomas, malignant Schwannomas (a variant of fibrosarcoma), keratoacanthomas and basal cell adenomas. Similar studies conducted in dogs did not reveal any similar findings. The significance of this finding for humans is not known presently. The expected toxicities of the combination of TMZ and ABT-888 are described above in Section 7.1.1.

7.2. Dose Modifications/Delays

Blood counts will be evaluated within -3 days prior to day 1 of each cycle. Subject must have an ANC ≥ 1500/ul and platelet count ≥ 100,000/ul within -3 days of day 1 of each cycle. On day 1 of each cycle (within -3 days) all clinically significant treatment related **non-hematological** toxicity grade 3 or 4 (except for alopecia) must have resolved (CTCAE grade ≤ 1 or baseline). If toxicity persists, treatment should be delayed for up to 3 consecutive weeks. If after 3 weeks of delay all clinically significant treatment related toxicity has still not resolved then any further treatment with TMZ and ABT-888 should be stopped (subject is off treatment). Study drug interruptions for events that are clearly not related to the study drug, e.g., underlying cancer, planned surgical procedures or acute viral illnesses, should not necessitate a dose reduction and treatment may be delayed as necessary beyond 3 weeks.

Dose reductions:
ABT-888 Dose Reduction and Delay
The following are guidelines for dose reduction, delay and discontinuation of ABT-888.

- ABT-888 dose reduction and delay guidelines are summarized in Table 7.2.1.
- ABT-888 should be discontinued at the same time of discontinuation of TMZ.
- For any subject who experiences Grade 3/4 toxicity which is not attributable to TMZ or the underlying disease, the ABT-888 dose will be discontinued until the toxicity resolves to Grade 1 or lower or to baseline if Grade 2 at the time of study entry. The dose of ABT-888 will be reduced to a dose of 20 mg every 12 hours. Only one ABT-888 dose reduction is allowed. If a subject experiences a second Grade 3/4 toxicity which is not attributable to TMZ or the underlying disease and is thought (by the treating physician with consultation of the principal investigator as needed) to be related to the ABT-888, subject must discontinue study treatment.

- Any event of seizure, regardless of grade or attribution, requires interruption of ABT-888 and discussion with the Principal Investigator regarding the decision to resume treatment, and the Abbott Oncology Safety Desk (Section 12.5.1) should be notified.

Temozolomide Dose Reduction and Delays
Clinically significant hematological toxicities should result in TMZ dose reduction or delay. During treatment, CBCs should be monitored and the next cycle of therapy should not be started unless the ANC is > 1500/uL and platelet count is > 100,000/uL. For any Grade 3/4 toxicities attributable to TMZ, dose reduction and/or delay guidelines should be followed per Table 7.2.1. Dose reductions in the next cycle should be based on lowest blood counts and worst non-hematologic toxicity observed in the previous cycle. The 75 mg/m^2/day dose is the lowest dose of TMZ that is allowed in this study. Subjects must stop TMZ and ABT-888 if they are at the 75 mg/m^2/day dose level of TMZ and require an additional dose reduction (per Table 7.2.1) due to toxicities. Temozolomide dose levels to be used for dose reductions are summarized in Table 7.2.2.

For TMZ dosage calculations based on body surface area please refer to Appendix B.

Important:
- If the dose was **reduced or delayed** for toxicity, there will **be no dose re-escalation.**
- Any event of seizure that was clearly attributable to ABT-888 requires discontinuation of ABT-888.

Table 7.2.1 ABT-888 and TMZ Dose Reduction or Delay

	Adverse Event	Dose Reduction
Hematologic Toxicity attributable to TMZ	ANC < 1000/μL* and/or Platelets < 50,000/μL*	1. Hold TMZ and ABT-888. Check CBC weekly until recovery to: ANC > 1500/μL **and** platelets > 100,000/μL **and** 2. Reduce TMZ dose by 1 dose level at the next cycle***
	ANC 1000/μL* to 1500/μL* Platelets 50,000/μL* to 100,000/μL*	1. Hold TMZ and ABT-888. Check CBC weekly until recovery to ANC > 1500/μL **and** platelets > 100,000/μL **and** 2. Maintain Current TMZ Dose at the next cycle
	Adverse Event	**Dose Reduction**
Non-hematologic Toxicity attributable to TMZ	Nausea/Vomiting CTC ≥ Grade 3 despite optimal antiemetic therapy	1. Delay cycle until Grade 1 (or Grade 2 if present at baseline) **and** 2. Reduce TMZ dose by 1 dose level for the next cycle***
	Fatigue, constipation, anorexia or headaches CTC ≥ Grade 3	
	Any other CTC ≥ Grade 3 deemed to be clinically significant by PI	
	Adverse Event	**Dose Reduction****
Attributable to ABT-888	Any Grade 3 or 4 toxicity which is not attributable to TMZ or underlying disease	1. Delay cycle until Grade 1 (or Grade 2 if present at baseline) **and** 2. Reduce ABT-888 dose to 20 mg q12 hrs . **and** 3. Reduce TMZ dose by 1 dose level for the next cycle

* Regardless of attribution.

** There will only be one ABT-888 dose reduction allowed.

*** TMZ dose cannot be reduced below 75 mg/m^2/day.

Table 7.2.2 Temozolomide Dose Level Definition Summary

Dose Level	Temozolomide Dose
1	200 mg/m^2/day
2	150 mg/m^2/day
3	100 mg/m^2/day
4	75 mg/m^2/day

8. DRUG FORMULATION AND ADMINISTRATION

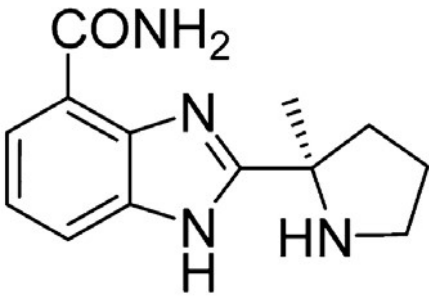
8.1. ABT-888

Additional information regarding ABT-888 can be found in the Investigator's Brochure.

8.1.1. Description

Chemical Name:	2-[(*R*)-2-methylpyrrolidin-2-yl]-1*H*-benzimadazole-4-carboxamide
Associated Name(s):	ABT-888, A-861695.0
Generic Name:	Not applicable
INN (International Nonproprietary Name):	Not applicable
USAN (United States Adopted Name):	Not applicable
Molecular Formula:	$C_{13}H_{16}N_4O$
Molecular Weight:	244.29

Structure:



8.1.2. Pharmacokinetics

Preliminary pharmacokinetic results are available from 13 subjects in CTEP Study 7675 (A06-161). The ABT-888 formulation that was used in this study was powder for oral solution. The ABT-888 powder was reconstituted with compounded excipient (sorbitol crystalline, citric acid anhydrous, citric acid monohydrate, distilled water) at the clinical site to a final concentration of 5 mg/mL. ABT-888 oral solution was prepared the day of administration and was used only that same day. The formulated solution was supplied to subjects in oral syringes for dosing.

The ABT-888 pharmacokinetic parameters following single oral doses administered in CTEP Study 7675 are presented in Figure 7.1. The absorption of ABT-888 after oral dosing was relatively rapid, with average time to maximum observed plasma concentration (T_{max}) ranging from 1 to 2 hours across dose

levels. The maximum observed plasma concentration (C_{max}) and the area under the plasma concentration curve from time zero to infinity (AUC_{∞}) of ABT-888 were approximately dose-proportional across the dose range studied. The apparent volume of distribution (V/F) of ABT-888 was large, and oral clearance was rapid. The average terminal half-life of ABT-888 ranged from 4 to 5 hours across dose levels. The coefficients of variation in dose-normalized C_{max} and AUC_{∞} were 36% and 22%, respectively. Recovery of the dose as parent drug in the urine over 24 hours after dosing averaged 78% (N = 6).

Figure 7.1

Preliminary ABT-888 Pharmacokinetic Parameters Following Single-Dose Oral Administration of ABT-888 in CTEP Study 7675

	ABT-888 mg dose		
Parameter	**10**	**25**	**50**
N	3	3	7
C_{max} (ng/mL)	81 ± 34	150 ± 37	260 ± 69
T_{max} (h)	0.7 ± 0.3	1.8 ± 1.0	1.0 ± 0.9
AUC_{∞} (ng•h/mL)	422 ± 99	852 ± 47	1775 ± 424
V/F (L)	134 ± 33	166 ± 26	250 ± 122
CL/F (L/h)	24.6 ± 6.0	29.4 ± 1.6	29.8 ± 8.2
Elimination $t_{1/2}$ (h)[a]	3.5 ± 2.3	3.9 ± 0.4	5.3 ± 1.2

Data are expressed as mean ± SD.

a. Harmonic mean ± pseudo–standard deviation.

Description: White to light yellow solid

Solubility: A-861695.0 is slightly soluble in aqueous media.

Optical Isomerism: A-861695.0 contains 1 chiral center and is manufactured as the (*R*)-isomer.

Dosage Form: Immediate release capsules

Strength: 10 and 50 mg

Components: Microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate, gelatin, sodium lauryl sulfate, and titanium dioxide

Manufacturer: Abbott Pharmaceuticals

8.1.3. Storage and Stability

Study drug in this study is defined as ABT-888. Study drug and clinical supplies must be stored in a secure place until they are dispensed for subject use or are destroyed by pharmacy per institutional guidelines.

Investigational products are for investigational use only, and are to be used only within the context of this study. The clinical supplies supplied for this study must be maintained under adequate security and stored under conditions specified on the label.

US Storage: ABT-888 must be stored at 15-25°C (59-77°F). Excursions are permitted up to 30°C (86°F). In cases where excursions occur beyond permitted limit, Abbott can be notified and replacement drug may be arranged.

8.1.4. Compatibility

The compatibility of coadministration of oral ABT-888 and TMZ was demonstrated in a phase I study.

8.1.5. Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.1.6. Availability

ABT-888 is an investigational agent and will be supplied free-of-charge from Abbott.

8.1.7. Administration

ABT-888 will be packaged in bottles containing 16 capsules per bottle of the 10 mg capsules. Labeling of the bottles containing the capsules will be done in accordance with the local procedures (as required by law).

8.1.8. Accountability

The investigator, or a responsible party designated by the investigator, will maintain a careful record of the inventory and disposition of the ABT-888 using the Institutional Drug Accountability Record Form or another comparable drug accountability form.

8.2. Temozolomide

8.2.1. Description

Generic name: Temozolomide (TMZ)

Commercial name: Temodar®

Chemical names: 3,4-dihydro-3-methyl-4-oxoimidazo[5,1-d]-*as*-tetrazine-8 carboxamide

Empirical Formula: $C_6H_6N_6O_2$

Molecular weight:	194.15
Appearance:	White to light tan/light pink powder
Melting point:	Decomposes at 206ºC
How Supplied:	Provided by Abbott Pharmaceuticals
Stability:	The molecule is stable at acidic pH (<5), and labile at pH >7, hence Temodar® can be administered orally. The prodrug, TMZ, is rapidly hydrolyzed to the active 5-(3-methyltriazen-1-yl)imidazole-4-carboxamide (MTIC) at neutral and alkaline pH values, with hydrolysis taking place even faster at alkaline pH. The product label recommends storage at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).
Half life:	TMZ is rapidly eliminated with a mean elimination half-life of 1.8 hours

8.2.2. Handling

TMZ is potentially mutagenic and should be handled with appropriate precautions by both staff and subjects. Subjects with known or suspected hypersensitivity to TMZ should not be treated with TMZ. There are no data available on the effect or management of TMZ overdose.

8.2.3. Packaging, dispensing and storage

Temodar® Capsules will be supplied in 5-mg, 20-mg, and 100-mg strengths. The capsules contain a white capsule body with a color cap and the colors vary based on the dosage strength. The 5-mg, 20-mg and 100-mg will be supplied in 5-count packages The product label recommends Storage at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). Labeling of the packages containing the capsules will be done in accordance with the local procedures (as required by law). According to the dosing, the hospital pharmacist delivers the TMZ dosage for a complete cycle to the subject.

8.3. Ordering Study Medications

The investigator or those named as subinvestigators on the Statement of Investigator Form 1572 agree to supply study drugs only to those subjects enrolled in the study. The investigator or designee will keep a current and accurate inventory of all clinical drug supplies provided by Abbott Laboratories. The study site will maintain a dispensing log. Compliance with the assigned treatment regimen will be calculated at the site from this information at each visit. Compliance below 80% will require consultation with the study investigator and potential removal from study for continued non-compliance as judged by the investigator.

Each participating site should order its own inventory to be shipped directly to that site. A fax will be sent to Abbott from each site to order study drugs according to the Manual for Procedures to be provided by Abbott.

9. CORRELATIVE/SPECIAL STUDIES

9.1. Exploratory Objectives

- To determine the BRCA mutation status, the BRCA methylation status, and the BRCA expression level in archived tumors and to characterize the correlation with response
- To evaluate the Circulating Tumor Cell level and explore the correlation with response
- To characterize the oncogene mutation status in archived tumors

9.1.1. BRCA1/2 mutation, mRNA expression, and promoter methylation.
Deficiencies in the DNA repair pathways may render cancer cells more susceptible to DNA damaging agents such as alkylating agents. BRCA1 and 2 are important in repairing DNA damage. Cancer cells with impaired function of BRCA1/2 may be particularly reliant on the base excision repair pathway to survive. PARP inhibition effectively inhibits BER and has shown promising activity in cells known to be deficient in BRCA1 or 2 and in phase 2 clinical trials. [24, 25] BRCA1/2 harbors inactivating mutations in approximately 5% of breast cancer with a higher frequency in certain populations. In addition, another mechanism to phenocopy BRCA1/2 mutation is to decrease expression by promoter methylation and resultant decreased mRNA expression. Therefore, in order to explore whether BRCA1/2 mutation or suppression is important in this population, we will use archived tumors to determine the BRCA1/2 mutation status, the mRNA level as a marker of expression, and the promoter methylation as a marker of gene silencing.

Whole genome DNA will be extracted from pretreatment blood and mutation detection will be performed using the Exon Grouping Analysis (EGAN) method or in collaboration with Myriad Genetics. EGAN is based on Conformation Specific Gel Electrophoresis (CSGE). [56, 57] All coding exons and surrounding intronic sequences in any gene of interest are amplified and analyzed on four ABI 3730XL capillary sequencers in the laboratory. PCR fragments with aberrant mobility are sequenced. This method has been compared directly to standard sequencing using a blinded patient set and has shown a sensitivity of 97.4% in detecting *BRCA1* and *BRCA2* sequence changes (A. Miron, manuscript in preparation). Benefits of the EGAN method include sensitivity of mutation detection despite high levels of contamination of tumor DNA with normal cell DNA as is typical for many breast tumor samples and significantly less expense than solid sequencing methods. The process is completely automated using a Tecan robotic system in the laboratory. Software has been developed in-house for both automated PCR primer selection as well as downstream EGAN analysis.

Blood samples should be shipped as follows:

DFHCC Samples
Two Purple Top (EDTA) Tubes (7-10 ml each) will be sent. Samples should be sent prior to initiation of protocol therapy and ideally may be drawn at the same time as regularly scheduled blood draws. Samples should be shipped with a requisition form (See Appendix D). An email notification should be sent to *kmfoley@partners.org* and *pmiron1@partners.org* to alert them to expect the shipment

(Shipment tracking number should be included). Samples may be drawn Monday through Thursday, but not on Fridays or the day before a holiday, unless prior arrangements have been made with the coordinating center and samples can be sent by same day courier.

Blood samples should be shipped or transported at room temperature by same day or overnight courier directly to:

Kathleen Foley
Dana-Farber Cancer Institute
Smith Building, Room 1056
1 Jimmy Fund Way
Boston, MA 02115
(617) 632-5232

Abbott Samples
Two Purple Top (EDTA) Tubes (7-10 ml each) will be sent. Samples should be sent prior to initiation of protocol therapy and ideally may be drawn at the same time as regularly scheduled blood draws. Samples should be immediately inverted 8-10 times to reduce the likelihood of clot formation. Samples should then be centrifuged 1100-1300 x g for 15 minutes using a refrigerated centrifuge at 2 to 8 degrees Celsius. Within 15 minutes, plasma should be transferred to 4 separate 2 mL Cryovials labeled with study drug number, sample type (plasma), assay type (proteomic), protocol number, subject number, and time point (baseline). Samples should then be stored immobile and upright at -70^{o}C or colder until shipped frozen to Abbott. If a-70^{o}C freezer is not available, samples should be shipped monthly. Otherwise they can be shipped quarterly or at study completion. Samples should be shipped with a requisition form (See Appendix D).

Blood samples should be shipped frozen by overnight courier directly to:

Evelyn McKeegan
Abbott Laboratories
200 Abbott Park Rd
Dept R4CD., Bldg AP10
Room 1-114
Abbott Park, IL 60004
(847) 935-1969 or (847) 937-6278

Archived tumor tissue should be shipped as follows:

Tissue will be processed under the direction of Dr. Leif Ellisen, Director of the Translational Research Laboratory at MGH. At the time of consent, patients will be informed that the portion of the tumor block used for this study will become the property of DFHCC institutions for correlative studies. Patients will be informed that their specimens may be used for research by investigators at the MGH, DFCI, BWH, the DF/HCC or sent to other academic and industrial institutions, including for-profit corporations, with which we may collaborate. Shared specimens will be identified with a sample ID number and all patient identifying material will be removed. The remainder of the tumor block will be

returned to the originating institution. Patients will be asked for their permission to retain a portion of the tumor for future exploratory studies related to this trial or others. If paraffin blocks are available but are unable to be shipped due to institutional regulations, a minimum of 25 unstained paraffin embedded slides (4-8 micron) may be sent instead. However, where possible, paraffin blocks are preferred. Tissue should be sent within 60 days of enrollment.

Paraffin blocks or slides from original tumor samples should be shipped with a requisition form (See Appendix F) at room temperature via FedEx. Unstained fresh cut slides should be shipped within 24 hours of being cut.

Tissue samples should be shipped or transported to:

Massachusetts General Hospital
Translational Research Laboratory
Attention: Darrell Borger, Ph.D.
GRJ 10th Floor 1008
55 Fruit Street
Boston, MA 02114
Phone: 617-724-9889

9.1.2. Circulating Tumor Cells

An experimental method for following response to therapy is to measure microscopic tumor burden, manifested as circulating tumor cells. With the use of immunohistochemical and PCR-based strategies, it is possible to detect rare circulating tumor cells (1 in 1 million to 1 in 100 million) in women with advanced breast cancer. Circulating tumor cells (CTC) as detected by such assays have the potential of being a sensitive measure of tumor response or progression and can be measured in samples of blood that are easily obtained from subjects. [58] Moreover, CTCs can be probed using immunohistochemical, RNA, or genomic methods to assess characteristics of the CTC that may correlate with response. For these reasons, there is widespread clinical interest in examining the usefulness of these methods in subjects being treated on clinical trials in order to see whether more sensitive correlates of tumor response can be identified.

Because CTC analysis is exploratory, if an individual subject's CTC collection is not completed no violation will have occurred.

Samples should be shipped with a requisition form (See Appendix E). Samples are to be collected in CellSave preservative tube (8mls) and should be shipped at room temperature for same day or overnight delivery. Samples will be collected at baseline, the first day of cycle 2, the first day of cycle 3, and at the time of progression or off study (or up to 1 week prior). If patients are due for a CTC blood draw (due to progression) within 3 weeks of prior CTC blood draw, a new sample does not need to be sent. It is recommended that email notification be sent to Dr. Ian Krop at ***ikrop@partners.org*** and ***ludmila_flores@dfci.harvard.edu*** to alert them to expect the shipment. Samples may be drawn Monday through Friday but not the day before a holiday (unless prior arrangements to receive the sample have

been made). Samples should be labeled with indelible marker with the study identification number, patient case number, and date of collection.

People of interest (e.g. those having high CTC count) may be asked to provide another 10-15 mls of whole blood collected in EDTA purple top tubes at their next visit, or additional samples may be requested at other visits.

Samples should be shipped or transported by same day courier or overnight parcel directly to:

Dr. Ian Krop
Attention: Ludmila Flores
Dana Farber Cancer Institute
44 Binney St
Dana 804
Boston, MA 02115
(617) 632- 5958

9.1.3. Oncogene mutation status

Recent studies have identified that a significant fraction of breast cancer tumors harbor one or more activating mutations in a number of oncogenes. The PI3 Kinase (PI3K) catalytic subunit p110alpha is mutated in over 25% of breast cancer cases, for example. Additional proto-oncogenes that may contain oncogenic mutations include p53, KRAS, and BRAF.

Archived samples of diagnostic tumor will be analyzed in the Translation Research Laboratory at MGH to evaluate for the presence of oncogenic mutations. The analysis will be exploratory to describe the spectrum of mutations in this population. Samples for this correlative study will be allocated from the total tissue samples collected in Section 9.1.1 above by the DFCI Pathology Core (Dr. Richardson).

10. STUDY CALENDAR

Table 10.1shows a study calendar.

Baseline evaluations are to be conducted within 1-week prior to start of protocol therapy, except as noted on the Study Calendar Table 10.1. Pre-study evaluations completed within 1 week of Cycle 1 Day 1 may serve as the Cycle 1 Day 1 assessment. Scans must be done $\leq$4 weeks prior to the start of therapy. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

All assessments must be performed prior to administration of any study medication. All study assessments and medications should be administered within $\pm$ 3 days of the protocol-specified date, unless otherwise noted.

TABLE 10.1 STUDY CALENDAR

	Pre-Study[m]	Day 1 each cycle	Day 22 each cycle	Day 15 cycle 1 and 2 only[n]	Every 2 Cycles	Off Study
Informed consent	X					
Study Agent(s)						
ABT-888[a]		X				
Temozolomide[b]		X				
History and Physical						
History	X	X				
Physical exam[c]	X	X				X
Concurrent meds	X	X				
Performance Status (ECOG)	X	X				X
Laboratory						
CBC with diff, platelets[d]	X	X	X	X		
Serum chemistry [e]	X	X				
Tumor markers[f]	X	X				
Serum pregnancy test [g]	X					
Tissue sample collection[h]	X					
Blood for correlative studies[i]	X					
CTC Blood collection[j]	X					X
Assessments						
CT Scan (chest/abd/pelv) or PET/CT (+/- MRI)[k]	X				X	X
Adverse Event evaluation[l]		X				X

All assessments must be performed prior to administration of any study medication. All study assessments and medications should be administered within +/- 3 days of the protocol-specified date, unless otherwise noted.

a- See protocol for details. ABT-888 to be administered days 1-7 each cycle
b- See protocol for details. Temozolomide to be administered days 1-5 each cycle
c- Physical exam should include standard directed relevant physical exam, standard vital signs and weight. Baseline height may be used throughout study. BSA should be calculated for day 1 each cycle per Section 6.2.2
d- Day 15 and 22 CBC can be obtained locally. Day 1 of cycle CBC should be done at Study Site (up to 3 days prior to Day 1 of Cycle 2 and higher, and up to 7 days prior to Cycle 1). CBC should include Total WBC, Absolute Neutrophil Count (neutrophils plus bands), % Neutrophils, % lymphocytes, Hematocrit, Hemoglobin, and PLT.
e- Chemistry includes: Sodium, potassium, Chloride, BUN, Cr, Glucose, Total bilirubin, AST, ALT, Alk Phos, Albumin, Calcium, Magnesium, Phosphorus

f- CA15-3 (or CA27-29) and CEA should be drawn at baseline. Subsequent tumor markers need only be drawn in subjects with elevated baseline values.
g- For women of child bearing potential; samples may be obtained up to 14 days prior to registration and do not need to be repeated prior to cycle 1.
h- Archived tissue should be collected as described in Section 9.1.1. If tissue is unavailable this is not considered an exclusion criteria. Available tissue should be collected in a reasonable period (<60 days) and sent with a Tissue Shipment Form in Appendix F to: Dr. Darrell Borger, Ph.D., Massachusetts General Hospital Translational Research Laboratory GRJ 10th Floor 1008, 55 Fruit Street, Boston, MA 02114, (P): 617-724-9889
i- Baseline blood should be collected as described in Section 9.1.1 and sent with a Research Blood Collection Form in Appendix D to : 1) Vanessa Sem, Dana-Farber Cancer Institute Smith Building, Room 1056, 1 Jimmy Fund Way, Boston, MA 02115 and 2) Evelyn McKeegan, Abbott Laboratories, 200 Abbott Park Rd, Dept R4CD., Bldg AP10,Room 1-114, Abbott Park, IL 60004
j- CTC samples (3 tubes for each time point) should be collected pre-study, on Cycle 2 day 1, on Cycle 3, Day 1 and off study/progression as described in Section 9.1.2 and sent with a CTC Requisition Form in Appendix E to: Dr. Ian Krop, Attn: Ludmila Flores, Dana Farber Cancer Institute, 44 Binney St, Dana 804, Boston, MA 02115
k- Subjects with known brain metastases should have baseline and follow up brain imaging. Bone scans are not required. Scans should be completed every 2 cycles. Scans include chest, abdomen, and pelvis CT. Follow up scans should be completed and reviewed 0-14 days prior to each odd numbered cycle (3,5,7, etc) to determine whether to proceed on study. Pre-study scan may be up to 4 weeks prior to cycle 1. Timing of scans should be adjusted accordingly to account for any dose delays. The use of MRIs to follow measurable lesions is acceptable, where appropriate, but required CT scans should still be performed. Patients taken off study treatment for concern for clinical progression (by exam or tumor markers) and who have not had scans within 14 days should have scans, if possible, to document radiological progression.
l- Adverse events should be monitored continuously during the study.
m-Baseline evaluation should be done $\leq$ 1 week of C1 except as noted (Scans may be $\leq$4 weeks prior to C1)
n- If day 15 ANC is <1500/ul or platelets <100,000/ul, then day 15 CBC is recommended to be monitored for all subsequent cycles.

11. MEASUREMENT OF EFFECT

Objective response rate is the primary endpoint of this trial. Participants with measurable disease will be assessed by RECIST v1.1. For the purposes of this study, participants should be reevaluated every 2 cycles. In addition to a baseline scan, confirmatory scans should also be obtained no less than 4 weeks following initial documentation of an objective response.

The study requires evaluation by scan every 2 cycles. However, a confirmatory scan may be obtained at investigator discretion prior to required scans, but after 4 weeks to confirm a response.

11.1. Antitumor Effect– Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee version 1.1 (RECIST v1.1).[59]

11.1.1. Definitions

- Evaluable for toxicity. All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

- Evaluable for objective response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression or die prior to the end of cycle 1 will also be considered evaluable.)

11.1.2. Disease Parameters

Measurable disease. Measurable disease is the presence of at least one (1) lesion that can be accurately measured in at least one dimension with longest diameter ≥20 millimeters (mm) using conventional techniques (MR1, x-ray) or ≥10 mm with CT scan. Measurable lesions must be at least 2 times the slice thickness in mm. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

A lesion in a previously irradiated area is not eligible for measurable disease unless there is objective evidence of progression of the lesion prior to study enrollment. Lesions in previously irradiated areas must be clearly identified as such.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions (except as above), leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

Patients with brain metastases are eligible for this study. For the purposes of this study, brain metastases will not be considered measurable disease for determination of response.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and 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 repeated 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 the reference by which to characterize the objective tumor response.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted at each follow-up.

11.1.3. Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation, using a ruler, calipers, or digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial and >10 mm using calipers (e.g., skin nodules and 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 is preferable.

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

Ultrasound (US). When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

FDG PET and PET/CT. The acquisition of FDG PET and FDG PET/CT scans should follow the NCI Guidelines for using FDG PET as an indicator of therapeutic response [60] . Patients should avoid strenuous exercise and be on a low carbohydrate diet for 24 hours prior to the scan. Patients should fast for 4 hours or longer prior to the FDG injection and should have a serum glucose of less than 200 mg/dL at the time of FDG injection. A 10-20 mCi dose of FDG should be injected for typical adult patients. For longitudinal studies with multiple scans, particular attention should be paid to ensure consistent patient preparation and acquisition parameters between the follow-up scan and the baseline scan. When designing a study where PET scans are going to be utilized as one of the modalities to evaluate efficacy, it is important to consult with physicians in nuclear medicine in designing the appropriate criteria to be utilized.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained.

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response. Specific additional criteria for standardized usage of prostate-specific antigen (PSA) and CA-125 response in support of clinical trials are being developed.

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

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 or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

11.1.4. Response Criteria

11.1.4.1. Evaluation of Target Lesions

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

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

- Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions (new lesions must be > slice thickness). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

- Unknown (UN): Assessment of target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

Note: If tumor response data is missing, an overall assessment cannot be done. However, if there is missing or unevaluable data for non-target lesions, but data is available for all target lesions, the overall response for that time point will be assigned based on the sum LD of all target lesions. Additionally, the assessment of CR cannot be made if there is missing or unevaluable data for non-target lesions. In this case, the overall assessment would be PR.

11.1.4.2. Evaluation of Non-Target Lesions

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

  Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response

- Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesions and/or maintenance of tumor marker level above the normal limits.

- Progressive Disease (PD): Appearance of one or more new lesions (new lesions must be > slice thickness) and/or unequivocal progression of existing non-target lesions.

- Unknown (UN): Assessment of target lesions cannot be made due to insufficient or unevaluable data. In this case, a concise explanation must be given.

  Note: Although a clear progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed at a later time by review of the Principal Investigator (or Protocol Chair). Additionally, the cytological confirmation of the neoplastic origin of any effusion that appears or

worsens during treatment is mandatory to differentiate between stable or progressive disease status.

Note: Brain metastases or leptomeningeal disease that progress either by imaging, or by development of neurological symptoms, or that require intervention (with either steroids, radiation, surgery, or change in therapy) will be considered PD.

11.1.4.3. Evaluation of Best Overall Response

The best overall response is the best 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). The participant's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	≥4 wks confirmation
CR	Non-CR/Non-PD	No	PR	≥4 wks confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	Documented at least once ≥4 wks from baseline
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants 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.

11.1.5. Duration of Response

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

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

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.

11.1.6. Response Review

The DF/HCC Tumor Imaging Metric Core will provide independent radiological review to assess for response using standard RECIST version 1.1.

11.1.7. Non-CNS Response

Subjects with CNS-only progression will have an opportunity to remain on study treatment according to the criteria in Section 6.6. In such cases, the new baseline scans (chest/abd/pelvis) obtained prior to restarting study drug after treatment for CNS disease will serve as the new baseline scan for subsequent evaluation of non-CNS progression.

12. ADVERSE EVENT REPORTING REQUIREMENTS

12.1. General

Adverse event collection and reporting is a routine part of every clinical trial. This study will use the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0) that is available at http://ctep.cancer.gov/reporting//ctc.html.

Information on all adverse events, whether reported by the participant, directly observed, or detected by physical examination, laboratory test or other means, will be collected, recorded, followed and reported as described in the following sections.

Adverse events experienced by participants will be collected and reported from initiation of study medication, throughout the study, and within 30 days of the last dose of study medication. Participants who experience an ongoing adverse event or related to a study procedures and/or study medication beyond 30 days will continue to be contacted by a member of the study team until the event is resolved, stabilized, or determined to be irreversible by the participating investigator.

Participants should be instructed to report any serious post-study event(s) that might reasonably be related to participation in this study. The investigator should notify the IRB and any other applicable regulatory agency of any unanticipated death or adverse event occurring after a participant has discontinued or terminated study participation that may reasonably be related to the study.

12.2. Definitions

12.2.1. Adverse Event (AE)

An adverse event is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

12.2.2. Serious adverse event (SAE)

A serious adverse event is an undesirable sign, symptom, or medical condition which:

- is fatal or life-threatening;
- requires or prolongs inpatient hospitalization;
- results in persistent or significant disability/incapacity;
- constitutes a congenital anomaly or birth defect; or
- jeopardizes the participant and requires medical or surgical intervention to prevent one of the outcomes listed above.

Events **not** considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures
- elective or pre-planned treatment for a pre-existing condition that did not worsen
- emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission
- respite care

12.2.3. Expectedness

Adverse events can be 'Expected' or 'Unexpected.'

12.2.3.1. Expected adverse event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

Refer to Section 7.1 for a listing of expected adverse events associated with the study agent(s).

12.2.3.2. Unexpected adverse event

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

12.2.3.3. Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

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

12.3. Recording Adverse Events

Adverse event information will be obtained at each contact with the participant. All adverse events will be recorded on the appropriate study-specific case report forms (CRFs).

12.4. Reporting Adverse Events

Each adverse event will be assessed to determine if it meets the criteria for serious adverse event. If a serious adverse event occurs, expedited reporting will follow local policies, and federal guidelines and regulations as appropriate.

It is the responsibility of the participating investigator to notify the Principal Investigator, IRB, and others of all serious adverse events as required in the protocol.

The Principal Investigator will provide information with respect to adverse events and safe use of the study treatment (e.g., safety reports, Action Letters) to all participating investigators as soon as the information becomes available.

12.5. Manufacturer Notification by Investigator

12.5.1. Serious Adverse Event Reporting Requirements

All events meeting the criteria for Serious Adverse Event (see Section 12.2) that occur after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported as serious adverse events.

The participating investigator must report each serious adverse event, regardless attribution, to the Principal Investigator within 24 hours of learning of the occurrence. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone and facsimile on the Medwatch 3500A form to:

Oncology Group Safety Desk
Abbott Laboratories
Dept. R477, Bldg. AP30
200 Abbott Park Road
Abbott Park, IL 60064-6146

Office: (847) 935-2609
Fax: 1-866-254-3559 (toll-free North America only) or
(847) 938-0559
e-mail: oncology.safety@abbott.com

Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

12.5.2. Non-Serious Adverse Event Reporting Requirements

Non-serious adverse events will be reported to the Principal Investigator on the toxicity Case Report Forms.

All grade 3 and grade 4 non-serious adverse events will be reported on a quarterly basis to the Abbott in simple tabular form. Unless otherwise notified, this report should be sent to the Oncology Group Safety Desk above.

12.6. Institutional Review Board (IRB) Notification by Investigator

The participating investigator will report all adverse events and serious adverse events to the Principal Investigator (or Protocol Chair) and to the IRB according to the local IRB's policies and procedures in reporting adverse events.

12.7. Food and Drug Administration (FDA) Notification by Sponsor-Investigator

The Sponsor-Investigator will report to the FDA any adverse event that is serious, unexpected and reasonably related (i.e., possible, probable, definite) to the study treatment.

Unexpected fatal or life-threatening experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 7 calendar days after initial receipt of the information.

All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information.

Events will be reported to the FDA by telephone (1-800-FDA-1088) or by fax (1-800-FDA-0178) using Form FDA 3500A (Mandatory Reporting Form for investigational agents. Forms are available at http://www.fda.gov/medwatch/getforms.htm.

12.8. Hospital Risk Management Notification by Investigator

The participating investigator will report to the Principal Investigator (or Protocol Chair) and to local Risk Management any subject safety reports or sentinel events that require reporting according to institutional policy.

13. DATA AND SAFETY MONITORING

13.1. Data Reporting

13.1.1. Method

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

13.1.2. 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

13.2. 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; 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.

13.3. 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.

14. REGULATORY CONSIDERATIONS

14.1. Protocol Review and Amendments

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by a properly constituted IRB governing each study location.

Any changes made to the protocol must be submitted as amendments and must be approved by the IRB prior to implementation. Any changes in study conduct must be reported to the IRB. The Principal Investigator will disseminate protocol amendment information to all participating investigators.

All decisions of the IRB concerning the conduct of the study must be made in writing.

14.2. Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the

participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

14.3. Ethics and Good Clinical Practice (GCP)

This study is to be conducted according to the following considerations, which represent good and sound research practice:

- ICH Consolidated Good Clinical Practice: Guidelines (E6) www.fda.gov/cder/guidance/iche6.htm
- US Code of Federal Regulations (CFR) governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki
  - Title 21 Part 11 – Electronic Records; Electronic Signatures www.access.gpo.gov/nara/cfr/waisidx_02/21cfr11_02.html
  - Title 21 Part 50 – Protection of Human Subjects www.access.gpo.gov/nara/cfr/waisidx_02/21cfr50_02.html
  - Title 21 Part 54 – Financial Disclosure by Clinical Investigators www.access.gpo.gov/nara/cfr/waisidx_02/21cfr54_02.html
  - Title 21 Part 56 – Institutional Review Boards www.access.gpo.gov/nara/cfr/waisidx_02/21cfr56_02.html
  - Title 21 Part 312 – Investigational New Drug Application www.access.gpo.gov/nara/cfr/waisidx_02/21cfr312_02.html
- State laws
- Institutional research policies and procedures www.dfhcc.harvard.edu/clinical-research-support/clinical-research-operations-cro/policies-and-procedures

It is understood that deviations from the protocol should be avoided, except when necessary to eliminate an immediate hazard to a research participant. In such case, the deviation must be reported to the IRB according to the local reporting policy.

14.4. Study Documentation

The investigator must prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each research participant. This information enables the study to be fully documented and the study data to be subsequently verified.

Original source documents supporting entries in the case report forms include but are not limited to hospital records, clinical charts, laboratory and pharmacy records, recorded data from

automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

14.5. Records Retention

All study-related documents must be retained for the maximum period required by applicable federal regulations and guidelines or institutional policies.

14.6. Multi-center Guidelines

N/A

15. STATISTICAL CONSIDERATIONS

15.1. Study Design/Endpoints

This is a single arm, single stage phase II study to evaluate the response to the novel PARP inhibitor ABT-888 in combination with TMZ. Eligible subjects have unresectable or stage IV metastatic breast cancer with measureable disease according to RECIST. Subjects must have at least 1 prior therapy for metastatic disease, with no maximum. Subjects in the expansion cohort may have any number of prior chemotherapy regimens for metastatic disease, with no limit on total number of lines of prior therapy. All histologic subtypes of breast cancer are eligible. Subjects will receive study treatment with ABT-888 twice each day on days 1-7 and TMZ once each day on days 1-5 of each 28 day cycle. The primary endpoint of the study is the objective response rate. Secondary endpoints are the clinical benefit rate (CR+PR+stable disease > 16 weeks), progression free survival, and safety. Additional correlative exploratory endpoints will be carried out on archived tumor sample and blood.

There are only few small reports of TMZ for metastatic breast cancer. The reported response rate to TMZ monotherapy is poor, with 0 responses in 18 patients [32]. TMZ in combination with platinum in metastatic breast cancer with brain metastases was 6 of 15 patients [33], and 2 studies of TMZ monotherapy in breast cancer with brain metastases demonstrated no responses[34, 35]. A growing literature of preclinical studies of TMZ and ABT-888 (and other PARP inhibitors) provides strong support for the hypothesis that the combination will demonstrate significant clinical activity.

Primary Endpoint
The primary endpoint of this study is to determine the objective response rate (ORR) of ABT-888 and TMZ in metastatic breast cancer.

TMZ has no demonstrated monotherapy activity in breast cancer at this time. Therefore a true response rate of 20% associated with the combination of ABT-888 and TMZ in this heavily pretreated heterogeneous population would be considered to be of considerable clinical benefit worthy of further study. On the other hand, a true response rate of 5% to this combination would be considered to be of no clinical interest. The combination will be considered worthy of further research if at least 5 of the 41 subjects have a confirmed PR or CR. With this design, if the true response rate is 5% then there will be a 0.05 (alpha=0.05) chance of deeming the combination worthy of further research. If the true response rate is 20%, then there will be a 0.93 (beta=0.07) chance of deeming the combination worthy of further research.

A 90% confidence interval (CI) will be calculated for the true response rate. The 90% CI will be 5 to 24% if 5 of the 41 patients have a confirmed response; it will be 8 to 30% if 7 of the 41 have a confirmed response; it will be 12 to 35% if 9 of the 41 patients have a confirmed response.

Expansion Cohort
The primary endpoint of the expansion cohort is to further characterize the ORR of ABT-888 and TMZ in metastatic breast cancer in patients with known deleterious mutations in BRCA1 or BRCA2. Based on preliminary subset analysis from the primary study, among 41 patients enrolled there were 8 patients with known mutations in BRCA1 or BRCA2. The response rate among the 8 BRCA1 and BRCA2 mutation carriers was 50% (4/8; 1 CR, 3 PR) and the clinical benefit rate (CR+PR+SD>16 weeks) is 62.5% (5/8). The patient with SD has had continued reduction in tumor size from 8% to 24% at the 4th cycle and remains on study.

Based on the preliminary response data above, in the population of BRCA1 and BRCA2 carriers a true response rate of 45% would be considered of considerable clinical benefit. A true response rate of 15% in this population would be considered of little clinical interest. If at least 7 of the 20 subjects have a confirmed PR or CR the study will be deemed a success. With this design, if the true response rate is 15% then there will be a 0.025 (1-sided alpha=0.025) chance of deeming the combination worthy of further research. If the true response rate is 45%, then there will be a 0.87 (beta=0.13) chance of deeming the combination worthy of further research.

15.2. Sample Size/Accrual Rate

A total of 41 patients who receive at least one cycle of study drug will be enrolled.

Subjects who discontinue study participation after enrollment but before receiving one cycle of study drug will be replaced with an additional subject. Subjects who receive at least one cycle of study drugs but who never have follow-up tumor measurements done will be counted as non-responders.

Approximately 2-3 patients per month, minimally, are expected to accrue over 18 months for a total of 41 subjects. However, due to investigator and patient interest, accrual may be rapid between all DFHCC sites.

In the expansion cohort a total of approximately 20 patients are planned to be enrolled, with up to 22 allowed, in case of possible rapid accrual over a short period of time. This will allow patients who may have signed consent prior to formal administrative closure of the trial to enroll. Approximately 5 patients per month are expected to accrue over 4 months.

15.3. Analysis of Secondary Endpoints

Secondary Endpoints
All patients who receive at least 1 cycle of study drugs will be considered evaluable for clinical benefit analysis (CR+PR+SD>16wks); those who lack tumor measurements will be counted as non-responders. Patients who develop early disease progression, regardless of duration of study treatment, prior to response evaluation will be considered to have progressed on study. The 90% confidence interval will be calculated.

Progression free survival (PFS) will be defined as the time from enrollment until disease progression, death, or date of last patient contact. Patients alive and free from disease progression (including being free of CNS progression) will be considered censored. All other patients will be considered to have experienced an event. Risk for PFS-event will be estimated according to the method of Kaplan and Meier and confidence curves will be estimated by the Greenwood method.

Analysis for safety will be completed for all subjects who receive at least 1 dose of either ABT-888 and/or TMZ. Subject incidence rates of all adverse events will be tabulated organ system class, preferred term, and severity. Tables and/or narrative descriptions of deaths occurring while on trial and other serious adverse events and early withdrawals due to adverse events will be provided.

All reported AEs will be assigned to an organ system class and preferred term according to MedDRA AE preferred term dictionary. The number and percentage of subjects reporting adverse events (categorized as all, serious and related) will be tabulated.

Summary statistics for certain laboratory evaluations and other recorded findings will be generated. Summary statistics for recorded toxicities according to CTCAE 3.0 may be generated.

The DFHCC DSMC will also monitor this study as described in Section 13.2.

Exploratory Endpoints
Summary statistics will be presented for the total number of subjects in each of the following subgroups of breast cancer, and the number of subjects responding in each group: triple negative (<1% ER, <1%PR, and HER2 negative), HER2 positive (any ER/PR status, HER2 3+ by IHC or positive by FISH), or Endocrine positive (HER2 negative and ER positive and/or PgR positive).

Summary statistics will be presented for the total number of patients with brain metastases at baseline, the response of those patients having RECIST-measurable brain metastases, the response of non-CNS disease in those patients, and narrative descriptions of those patients.

The BRCA mutation status, the BRCA methylation status, and the BRCA expression level in archived tumors will be determined and presented as summary statistics.

Exploratory studies to evaluate the number of Circulating Tumor Cells at baseline and prior to cycle 2 will be presented in summary tables.

Summary tables describing the presence of any oncogene mutations identified with multiplex mutation analysis will be presented.

Patients who experience CNS-only progression and remain on study according to Section 6.6 will be coded as having a progression at the time of their CNS-only progression, but the amount of time they remain on treatment without further progression will be reported for descriptive purposes only.

15.4. Reporting and Exclusions

15.4.1. Evaluation of toxicity.

All subjects who receive at least one dose of study drug (ABT-888 and/or TMZ) will be considered evaluable for toxicity from the time of their first treatment.

Subjects who enroll but do not receive any study treatment will not be considered evaluable for toxicity.

15.4.2. Evaluation of response.

All subjects who register to participate in the study and receive at least one cycle of study drug will be assessed for response to treatment even if there are major protocol treatment deviations or if they are ineligible. Each participant should be assigned one of the following categories: 1) complete response, 2)

partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.

All participants who met the eligibility criteria, except those who received no study medication, will be included in the main analysis of the response rate. Participants in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Patients who did not receive any dose of study drug will not be included in the response evaluation.

16. PUBLICATION PLAN

At the conclusion of this study, results of the primary endpoint will be submitted for publication in a peer reviewed journal within 24 months of the date of completion. A full report of the data from this trial shall be made public within 36 months of the completion of the study. No publications or reporting of data shall be made prior by any coinvestigator without the acknowledgment and approval of the principal investigator. Abbott shall be provided any manuscripts or abstracts to be submitted for publication or presentation no less than 30 days prior to submission to review data and provide comments. Final approval of the submitted document will be made by the principal investigator.

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18. APPENDICES

18.1. Appendix A: Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Description	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

18.2. Appendix B- Temozolomide Daily Dose Calculations by Body Surface Area

Temozolomide Daily Dose Calculations by Body Surface Area**

Total BSA (m2)	75 mg/m2 (mg daily)	100 mg/m2 (mg daily)	150 mg/m2 (mg daily)	200 mg/m2 (mg daily)
1.0	75	100	150	200
1.1	82.5	110	165	220
1.2	90	120	180	240
1.3	97.5	130	195	260
1.4	105	140	210	280
1.5	112.5	150	225	300
1.6	120	160	240	320
1.7	127.5	170	255	340
1.8	135	180	270	360
1.9	142.5	190	285	380
2.0	150	200	300	400
2.1	157.5	210	315	420
2.2	165	220	330	440
2.3	172.5	230	345	460
2.4	180	240	360	480
2.5 *	187.5	250	375	500

* For subjects with BSA >2.5, the maximum BSA of 2.5 will be used.
** For patient convenience the dose may be rounded up or down up to 5% from calculated dose in order to minimize the number of pills per dose, per section 6.2.2.

18.3. Appendix C- Suggested Temozolomide Capsule Combinations

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

18.4. Appendix D: Research Blood Sample Shipment Form

DFHCC CORE LAB SHIPPING FORM
DF/HCC Protocol 09-261

1. Complete this requisition form and include with sample.
2. Label ALL tubes
3. Two Purple Top Tubes (7-10 ml each) will be sent.
4. All samples are to be shipped at room temperature to:

Kathleen Foley
Dana-Farber Cancer Institute
Smith Building, Room 956
1 Jimmy Fund Way
Boston, MA 02115
(617) 632-5232

Sample information

Patient Initials: _____

QACT Case Number: _____

Clinical Trial: 09-261

Date of Collection: _____

Time of Collection: _____

Contact Information

Name: _____

Telephone Number: _____

Address: _____

_____

_____

*An email notification should be sent to *kmfoley@partners.org* and *pmiron1@partners.org* to alert them to expect the shipment (Shipment tracking number should be included).

ABBOTT LABORATORIES SHIPPING FORM

DF/HCC Protocol 09-261

1. Complete this requisition form and include with sample.
2. Label ALL tubes
3. Two Purple Top Tubes (7-10 ml each) will be sent.
4. All samples are to be shipped frozen by overnight courier to:

Evelyn McKeegan
Abbott Laboratories
200 Abbott Park Rd
Dept R4CD., Bldg AP10
Room 1-114
Abbott Park, IL 60004
(847) 935-1969 or (847) 937-6278

Sample information

Patient Initials: _____

QACT Case Number: _____

Clinical Trial: 09-261

Date/Time of Collection: _____

Timepoint: BASELINE _____

Sample Type: Plasma for proteomics _____

Contact Information

Name: _____

Telephone Number: _____

Address: _____

_____

_____

Appendix E: CTC Requisition Form

Circulating Tumor Cell/ Circulating Endothelial Cell Studies

QACT Case Number _____
Sample Identifier/Number_____
Hospital/Institution Name_____
Collection Date_____**Collection Time** _____(both required)
Time Point collected: ☐ **Pre-treatment** ☐ **Pre-cycle 2** ☐ **Pre-cycle 3** ☐ **Progression**
☐ **Other**_____
Protocol Chair: Steven Isakoff, MD
Protocol name and number: DF/HCC Protocol 09-261

_____, M.D. ☐☐☐☐
FIRST LAST NAME **Physician's ID (if applicable)**
Print FULL NAME OF SUBMITTING PHYSICIAN
ALL FIELDS MUST BE LEGIBLY COMPLETED IN PEN (No pencil)
Submitted for: ☒ **Circulating tumor cell (CTC) enumeration**
☐ **Circulating endothelial cell (CEC) enumeration**
☐ **Collection with Profile kit**
☐ **Other special studies**_____

SAMPLE COLLECTION

1. Ensure that peripheral blood collection occurs prior to administration of i.v. therapy.
2. If the patient is on doxorubicin (Adriamycin), it is recommended to wait at least 7 days after administration before drawing a blood sample.
3. The blood samples must be collected in a CellSave preservative tube. Label the tube with the sample identifier/number, protocol number, and submitting investigator and date of collection.
4. Collect at least 7 ml of blood for best results. Gently invert the tube 8 times to prevent clotting immediately after filling the tube. Three (3) tubes should be collected for each time point.

SAMPLE STORAGE AND TRANSPORT

1. The blood sample can be transported and stored at room temperature (15-30C) until processing. Do NOT refrigerate or freeze the sample.
2. Samples must be processed within 72 hours of collection, but best results are obtained if the sample is processed as soon as possible.
3. Do not submit clotted samples.
4. Samples should be shipped by same day courier or overnight parcel directly to:
   Dr. Ian Krop
   Dana Farber Cancer Institute, Dana 804
   44 Binney Street
   Boston, MA 02114
5. Email notification should be sent to *ludmila_flores@dfci.harvard.edu* and *ikrop@partners.org* to alert them to expect the shipment.

18.5. Appendix F: Tissue Sample Shipment Form

DF/HCC Protocol 09-261

1. Complete this requisition form and include with sample (Do not ship samples on Fridays or Saturdays).
2. Label Paraffin Block or slides with local surgical specimen number (including block number) and DFHCC QACT case number.
3. Include a de-identified pathology report that is associated with the sample, where patient name, DOB and MRN are obliterated.
4. If slides are being sent, these should be sent out **within 24 hours** of being **cut**. All samples are to be shipped at room temperature to:

Massachusetts General Hospital
Translational Research Laboratory
Attention: Darrell Borger, Ph.D.
GRJ 10th Floor 1008
55 Fruit Street
Boston, MA 02114
Phone: 617-724-9889

Sample information

DFHCC QACT Case Number: _____ Date Shipped:_____

Surgical Specimen Number w/Block Number (local): _____

Date of Original Specimen Collection: _____

Organ Biopsied *if other than Breast*: _____

Indicate if primary of metastatic site: _____

Contact Information

Name: _____

Telephone Number: _____

Address: _____

_____

* Please send an email to Dr. Darrell Borger (dborger@partners.org) and Dr. Steven Isakoff (sisakoff@partners.org) to indicate this has been shipped.

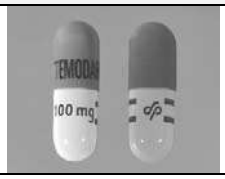
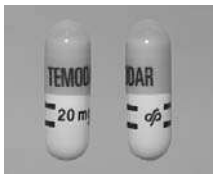
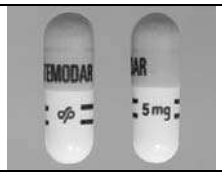
18.6. Appendix G: 09-261 Study Participant Self-Administration Drug Diary

09-261 ABT-888 and Temozolomide

Cycle Number:
_____ Study ID _____
Subject Name: _____ Date Disp _____
Unit Number: _____ Your MD _____
RN _____ Phone: _____
Phone _____

Please take the following number of capsules as listed in the table below

SPECIAL INSTRUCTIONS:
1. Take the morning dose of ABT-888 and then take the morning dose of Temozolomide.
2. Take the morning dose without food (1 hour before or after; water and other medications are OK).
3. Take the evening dose of ABT-888 without regard to meals.
4. If a dose of Temozolomide is vomited or missed, do not replace that dose; Do resume your next regular dose.
5. If a dose of ABT-888 is vomited within 15 minutes of taking, you may replace that dose.
6. If a dose of ABT-888 is missed, you may take the dose if less than 6 hours have passed.
7. Bring all empty drug bottles and this diary to each clinic visit
8. Store the study drugs at room temperature

# of capsules to take per dosing	Medication Picture	Description	Consecutive # of medication days
ABT-888			
Take ____10 mg Capsules daily twice per day		Capsule all white	Days 1-7
TEMOZOLOMIDE			
Take ___ **100 mg** capsules daily after ABT-888		Capsule white and peach	Days 1-5
Take ___ **20 mg** capsules daily after ABT-888		Capsule white and mustard (yellow)	Days 1-5
Take ___ **5 mg** capsules daily after ABT-888		Capsule white and lime green	Days 1-5

Day	Date	ABT 888 10 mg capsules	Time of Dose	Did you fast 1 hour before taking study medications	Did you fast 1 hour after taking study medications
Example	9/10/10	3 capsules	8:30 ▪ a.m 8:30 ▪ p.m	YES	YES
1			_____ □ a.m _____ □ p.m		
2			_____ □ a.m _____ □ p.m		
3			_____ □ a.m _____ □ p.m		
4			_____ □ a.m _____ □ p.m		
5			_____ □ a.m _____ □ p.m		
6			_____ □ a.m _____ □ p.m		
7			_____ □ a.m _____ □ p.m		

Day	Date	Temozolomide (TMZ) Capsules			Time of Dose	Did you fast 1 hour before taking study medications	Did you fast 1 hour after taking study medications
		100 mg	20 mg	5 mg			
Example	9/10/10	# X	# X	# X	8:30 □ a.m	YES	YES
1					_____ □ a.m		
2					_____ □ a.m		
3					_____ □ a.m		
4					_____ □ a.m		
5					_____ □ a.m		
6 ---------- NO Temozolomide Dose on Day 6 ----------							
7 ---------- NO Temozolomide Dose on Day 7 ----------							

Please indicate any symptoms that you may experience during your treatment.
Include the date that your particular symptom started and when it ended.

Please grade your symptoms according to the following scale:

Grade 1 = Minimal: you are aware of the symptoms, but it did not interfere with normal activities
Grade 2 = Mild: the symptom disrupted normal routine, but required activities were accomplished
Grade 3 = Moderate: the symptom prevented normal activities, but was manageable with prescribed therapies at home
Grade 4 = Severe: the symptom required you to seek further medical Intervention

Symptom Start Date End Date Grade

Symptom	Start Date	End Date	Grade (refer above)

Other Medications:

If you take any other mediations (prescribed or otherwise) please indicate the name of the drug, the dosage taken and the date taken. Please use one line per drug and indicate the start and stop dates under the "Dates Taken" section (i.e., 1/2/10 -2/4/10)

Drug	Dose	Dates Taken	Reason taken