Title: Capecitabine and Temozolomide for Treatment of Recurrent Pituitary Adenomas
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Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from WCMC.

List of

Abbreviations

All abbreviations used throughout the protocol must be defined.

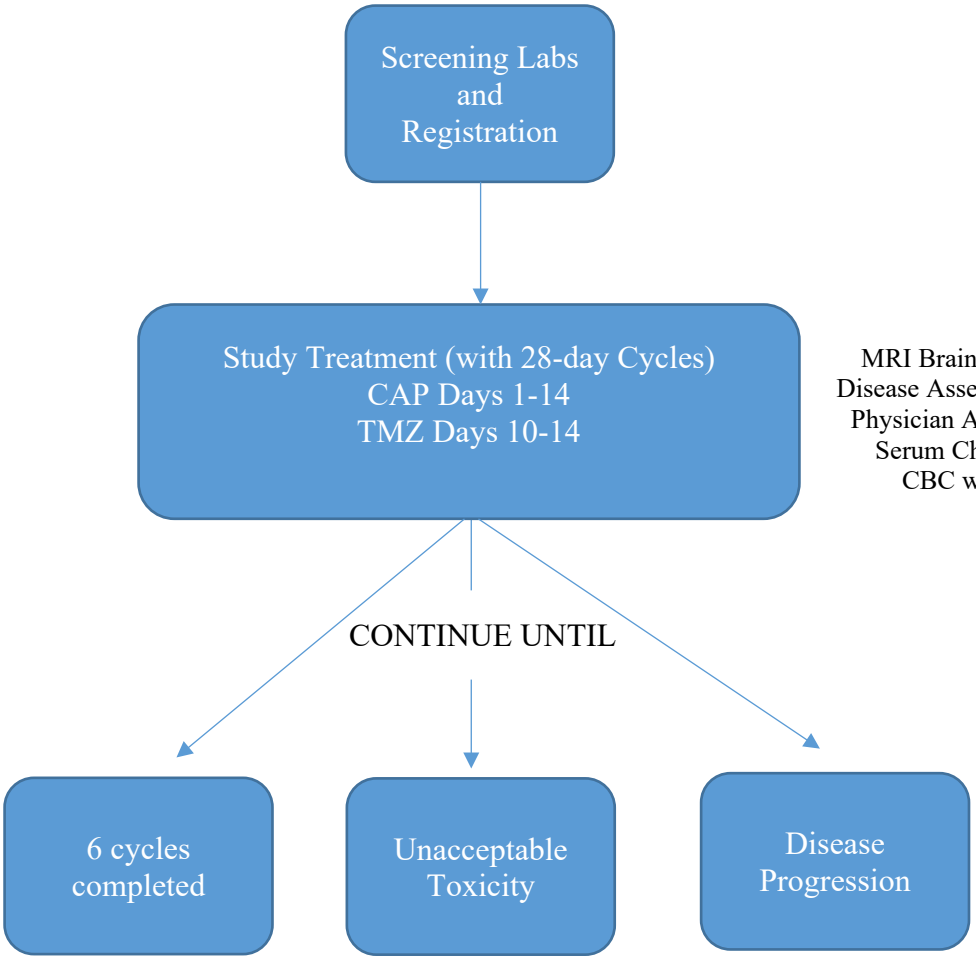
AE	Adverse Event
CFR	Code of Federal Regulations
CRF	Case Report Form
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HRBFA	Human Research Billing Analysis Form
ICF	Informed Consent Form
IND	Investigational New Drug
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
UAP	Unanticipated Problem
WCMC	Weill Cornell Medical College

Protocol Summary

Full Title:	Capecitabine and Temozolomide for Treatment of Recurrent Pituitary Adenomas
Short Title:	CAP and TMZ for Pituitary Adenomas
Clinical Phase:	Phase II (with safety run-in)
Principal Investigator:	Rajiv Magge MD
Sample Size:	N=21
Accrual Ceiling:	This study will enroll 21-33 subjects (based on results of safety-run)
Study Population:	Patients with residual or recurrent pituitary adenomas with relatively good performance status.
Accrual Period:	36 months.
Study Design:	This is an open label study to assess the efficacy of capecitabine (CAP) and temozolomide (TMZ) in recurrent pituitary adenomas. There will be a safety run-in of at least three patients to establish any DLT. Enrolled patients (sample size N=21 to 33) will receive treatment in 28-day cycles: capecitabine 1500mg/m2 per day (divided into two doses with maximum daily dose of 2500mg) on days 1 through 14 and oral temozolomide 150 to 200 mg/m2 on days 10 through 14. This will be followed by 14 days off treatment. MRI imaging will be completed after every two cycles. Treatment repeats every 28 days for up to 6 cycles in the absence of disease progression or unacceptable toxicity.
Study Duration:	After completion of 6 cycles, patients achieving a complete or partial tumor response may continue to receive capecitabine temozolomide at the investigator's discretion in the absence of disease progression or unacceptable toxicity. Patients will be monitored for six months after they come off the study (either after

	completing 6 cycles or in setting of disease progression or unacceptable toxicity).
Study Agent/ Intervention Description:	Capecitabine, Temozolomide 1) Capecitabine (oral 5-Fluorouracil) 1500mg/m2 orally per day (divided into two doses with maximum daily dose of 2500mg) on days 1 through 14. 2) Temozolomide (second generation alkylating agent) 150 to 200 mg/m2 orally on days 10 through 14.
Primary Objective:	To assess the radiographic response rate of capecitabine and temozolomide in patients with recurrent pituitary adenomas.
Secondary Objectives:	To assess the effect of capecitabine and temozolomide on pituitary adenoma hormone secretion in patients with residual or recurrent functioning pituitary adenomas; To assess the effect of capecitabine and temozolomide on pituitary function in these patient; To assess the overall safety and tolerability of combination treatment with capecitabine and temozlomide.
Exploratory Objectives:	Further clarify the role of Ki67 nuclear labelling index, p53 expression, MGMT expression/methylation status, and additional molecular profiling as indicators of tumor aggressiveness and invasiveness.
Endpoints:	Primary endpoints is tumor response assessed by the RECIST criteria. Secondary endpoints include biochemical control as assessed by measurement of hormones secreted in excess by the pituitary at baseline, pituitary function (assessed by standard pituitary function tests), and any change in tumor invasiveness (graded by Knosp classification system to quantify cavernous sinus invasion), and safety and tolerability of the combined CAP and TMZ regimen (as assessed by NCI CTCAE v4.0).

SCHEMA


Screening Labs and Registration
Study Treatment (with 28-day Cycles)
CAP Days 1-14
TMZ Days 10-14
MRI Brain/Pituitary x8 weeks
Disease Assessment labs x8 weeks
Physician Assessment x4 weeks
Serum Chemistry x2 weeks
CBC w/ Diff. x1 week
CONTINUE UNTIL
6 cycles completed
Unacceptable Toxicity
Disease Progression

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1. STUDY OBJECTIVES

1.1. Primary Objectives

- To assess the radiographic response rate of capecitabine and temozolomide in patients with residual or recurrent pituitary adenomas.

1.2 Secondary Objectives

- To assess the effect of capecitabine and temozolomide on pituitary adenoma hormone secretion in patients with residual or recurrent functioning pituitary adenomas
- To assess the effect of capecitabine and temozolomide on pituitary function in these patients.
- To assess the overall safety and tolerability of combination treatment with capecitabine

1.3 Exploratory Objectives

- To clarify the role of Ki67 nuclear labelling index, p53 expression, MGMT expression/methylation status, and additional tumor genetic profiling as indicators of tumor aggressiveness and invasiveness.

2.0 BACKGROUND

2.1 Disease

Pituitary adenomas are relatively common, representing 10-15% of all intracranial tumors [1-3]. Although generally considered benign, these tumors can have significant morbidity due to their sensitive location. Symptoms may be related to compression of cranial nerves and adjacent structures, particularly loss of vision and headaches. In addition to mass effect, some of these adenomas are invasive. A reported 25-55% of pituitary adenomas invade surrounding structures including the cavernous sinus and sphenoid sinus[3-6]. Criteria such as the Hardy and Knosp classification systems have been used to quantify the extent of tumor invastion (Hardy system focusing on bony invasion, while the Knosp system evaluates cavernous sinus invasion).

Unfortunately, a subset of pituitary adenomas are also pathologically aggressive, which is distinct from their potential invasiveness. Several factors including high mitotic activity, elevated MIB-1/Ki67, and increased p53 expression have been used to assess aggressiveness on pathology evaluation. Although not fully standardized, it has been shown that a Ki67 index of ≥3% is a predictor of tumor aggressiveness and may also indicate probable invasiveness[6]. Similarly, strong p53 immunoreactivity has been found in large, aggressive pituitary adenomas[7,8]. Further, elevated levels of EGFR, VEGFR, and FGFR have been associated with more aggressive tumors[9,10]. Unfortunately, there is still limited knowledge regarding the genetic causes of pituitary tumorigenesis and/or transition to more aggressive phenotypes.

Another complication is that a subset of these tumors may be functional and secrete

excess levels of pituitary hormones such as prolactin, adrenocorticotrophic hormone (ACTH), and growth hormone (GH) as well as less commonly thyroid stimulating hormone (TSH), follicle-stimulating hormone (FSH) and luteinizing hormone (LH) [1]. This hormonal dysfunction can contribute to significant systemic medical illness, including Cushing's disease and acromegaly with ACTH and GH-secreting tumors, respectively. Initial treatment of pituitary adenomas is specific for each type.

Initial treatment is variable and can be dependent on the specific tumor type (and whether it is functioning or non-functioning). Prolactinomas are typically first treated with dopamine agonist therapy, while surgery is usually preferred for adenomas that are non-functioning or produce GH or ACTH. Full resection may be limited by neoplastic invasion into surrounding structures. Radiotherapy is also considered for residual tumor present after surgery as well as on occurrence. Occasionally, pituitary adenomas behave aggressively and progress even after multiple treatment approaches including surgery, proton beam radiation therapy, stereotactic radiosurgery (SRS) and pharmacologic treatment[11,12]. As the goal of these treatments is often palliative, chemotherapy has been trialed in hopes of shrinking or stabilizing these tumors.

2.2 Investigational Agent or Device

2.2.1 Capecitabine (Xeloda)

Capecitabine (CAP) is an antimetabolite that is enzymatically converted to 5-fluorouracil (5-FU) which is then converted to active metabolites 5-fluoro-2-deoxyuridinemonophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP). Cytoxicity is mediated by two mechanisms. With folate cofactor N 5-10-methylenetetrahydrofolate, FdUMP binds to thymidylate synthase, forming a complex that inhibits thymidylate formation, which is necessary for DNA synthesis. Lack of thymidylate leads to blocking of cell division. Secondly, FUTP can be incorporated in place of uridine triphosphate during RNA synthesis, which causes an error that prevents proper RNA processing and protein synthesis.

CAP has been shown to be effective in several malignancies, and is often used for treatment of metastatic breast and colorectal cancers[13,14] as well as neuroendocrine tumors in combination with temozolomide (discussed below). FDA-approved dosage, based on several studies, is 1250mg/m^2 orally twice daily (total daily dose: 2500 mg/m^2) at the end of meal for two weeks followed by one to two week rest period.

<u>Significant adverse affects:</u>

• Bone marrow suppression: Bone marrow suppression may occur, hematologic toxicity is more common when used in combination therapy.

• Cardiotoxicity: Cardiotoxicity has been observed with capecitabine, including myocardial infarction, ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, ECG changes, and cardiomyopathy. These adverse events may be more common in patients with a history of coronary artery disease.

• Dermatologic toxicity: Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN) have been reported.

• Gastrointestinal toxicity: May cause diarrhea (may be severe); median time to first occurrence of grade 2 to 4 diarrhea was 34 days and median duration of grades 3 or 4 diarrhea was 5 days. Necrotizing enterocolitis (typhlitis) has been reported.

• Hand-and-foot syndrome: May cause hand-and-foot syndrome (palmar-plantar erythrodysesthesia or chemotherapy-induced acral erythema); characterized by numbness, dysesthesia/paresthesia, tingling, painless or painful swelling, erythema, desquamation, blistering, and severe pain. The median onset is 79 days (range: 11 to 360 days).

• Hepatotoxicity: Grade 3 and 4 hyperbilirubinemia have been observed (median onset: 64 days). Transaminase and alkaline phosphatase elevations have also been reported.

Pharmacokinetics:

Absorption
- Bioavailability: readily absorbed (bioavailability data lacking)
- Effect of food: reduces rate and extent of absorption

Distribution
- Protein binding: less than 60% (35% bound to human albumin)

Metabolism
- Hepatic: extensive
- 5-fluorouracil: active
- 5'-deoxy-5-fluorocytidine (5-DFCR): active
- 5'-deoxy-5-fluorouridine (5-DFUR): active
- 5-fluoro-2'-deoxyuridine monophosphate (FdUMP): active
- 5-fluorouridine triphosphate (FUTP): active

Excretion
- Renal: 95.5% (3% as unchanged drug)
- Fecal: 2.6%

Elimination Half Life

- Capecitabine: 38 to 45 minutes

(*from Micromedex*)

2.2.2 Temozolomide (Temodar)

TMZ is an alkylating agent which interferes with cell division. It is rapidly converted to its active form MTIC, which alkylates DNA (at the O6 and N7 positions of guanine) causing DNA double strand breaks and subsequent apoptosis.

TMZ has become standard-of-care for treatment of glioblastoma based on the landmark trial by Stupp et al[15]. In glioblastoma, a dose of 75 mg/m^2 orally is given daily concurrent with radiation. In the adjuvant setting, the first cycle 150mg/m^2 daily x 5 days followed by 23 days without treatment (starting 4 weeks after the TMZ + RT phase). The dose is escalated to 200mg/m^2 per day for five days, again followed by 23 days off treatment, if there is not significant hematologic toxicity.

<u>Significant adverse affects:</u>

- Bone marrow suppression: Myelosuppression may occur; may require treatment interruption, dose reduction and/or discontinuation; monitor blood counts. An increased incidence has been reported in geriatric and female patients. Prolonged pancytopenia resulting in aplastic anemia has been reported (may be fatal); concurrent use of temozolomide with medications associated with aplastic anemia (eg, carbamazepine, co-trimoxazole, phenytoin) may obscure assessment for development of aplastic anemia.

- Gastrointestinal toxicity: Temozolomide is associated with a moderate emetic potential (Dupuis 2011; Roila 2010); antiemetics are recommended to prevent nausea and vomiting.

- Hepatotoxicity: Hepatotoxicity has been reported; may be severe or fatal. Postmarketing reports of hepatotoxicity have included liver function abnormalities, hepatitis, hepatic failure, cholestasis, hepatitis cholestasis, jaundice, cholelithiasis, hepatic steatosis , hepatic necrosis, hepatic lesion, and hepatic encephalopathy (Sarganas 2012).

- Pneumonia: Pneumocystis jirovecii pneumonia (PCP) may occur; risk is increased in those receiving steroids or longer dosing regimens. Monitor all patients for development of PCP (particularly if also receiving corticosteroids).

- Secondary malignancies: Rare cases of myelodysplastic syndrome and secondary malignancies, including myeloid leukemia, have been reported.

Pharmacokinetics:

Absorption

- Oral: Rapid and complete

Distribution

- Vd: Parent drug: 0.4 L/kg; penetrates blood-brain barrier; CSF levels are ~35% to 39% of plasma levels (Yung 1999)Protein binding:15%

Metabolism

- Prodrug, hydrolyzed to the active form, MTIC; MTIC is eventually eliminated as CO2 and 5-aminoimidazole-4-carboxamide (AIC), a natural constituent in urine; CYP isoenzymes play only a minor role in metabolism (of temozolomide and MTIC)

Bioavailability

- Oral: 100%

Half-life elimination

- Mean: Parent drug: Adults: 1.6-1.8 hours

Time to peak

- Oral:
  - Empty stomach: 1 hour
  - With food (high-fat meal): 2.25 hours

Excretion:

- Urine (~38%; parent drug 6%)
- Feces <1%

Clearance

- 5.5 L/hour/m2; women have a ~5% lower clearance than men (adjusted for body surface area)

(*from Micromedex*)

2.3 Rationale for combination of CAP and TMZ

Temozolomide, a second-generation alkylating agent, has emerged as a promising treatment for aggressive pituitary adenomas. It kills tumor cells through methylation of DNA at the O^6 position of guanine, which mispairs with thymine during the subsequent cycle of DNA replication[16]. Based on several case series, the overall clinical and radiological response rate with temozolomide is about 60% in aggressive pituitary adenomas[3,11,17-19].Losa et al. completed a one-year prospective study of TMZ in atypical pituitary adenoma. Five patients were treated with TMZ treatment, with two demonstrating response, two with stable disease, and two stopping treatment at 3 and 6 months, respectively, due to disease progression[20]. Low expression of 6-O-methylguanine-DNA methyltransferase (MGMT), a DNA repair enzyme that reverses the effects of temozolomide, may correlate with better outcomes with chemotherapy.

Both temozolomide and capecitabine penetrate the blood-brain barrier. Several studies have shown the efficacy of combination treatment with capecitabine and temozolomide in neuroendocrine tumors[21-23]. Based on this literature, Robert Fine et al. utilized this regimen in four patients with aggressive refractory ACTH-producing adenomas, and reported prolonged antitumor response[24]. The capecitabine (oral 5-fluorouracil) may have synergistic antitumor effects with the temozolomide, by contributing to thymidine depletion which may increase temozolomide-induced toxicity on tumor cells. To our knowledge, the efficacy of temozolomide and/or capecitabine in recurrent pituitary adenomas has not been assessed in a controlled clinical trial, and with the encouraging anecdotal data this deserves further investigation.

2.4 Risk/Benefit Assessment

Unfortunately, treatment for recurrent/residual pituitary adenomas is limited, and for some patients the tumors remain or progress even after multimodality treatment. Chemotherapy is not often used in these type of tumors due to limited clinical evidence, but it may play a key role in treatment. This study would clarify, in a standardized fashion, whether chemotherapy with temozolomide and capecitabine demonstrates activity in recurrent pituitary adenomas. Additionally, it will provide significant information regarding tolerability of chemotherapy in these patients.

2.5 Correlative Studies Background

No correlative studies are planned.

3.0 SUBJECT SELECTION

3.1 Study Population

The study population will include patients 18 years of age and older with relatively good functional status who have a diagnosis of pituitary adenoma (both secreting and non-functioning) that has recurred (or with residual disease) after at least one prior treatment (such as with surgery, radiation and/or medical therapy).

3.2 Inclusion Criteria

1. Male or female ≥ 18 years of age.

2. Patients with nonfunctioning tumors must have histologically confirmed pituitary adenoma. Patients with functioning tumors do not require surgery if there is clear diagnosis of functioning pituitary adenomas established based on endocrine evaluation.

3. Karnofsky performance status ≥ 70%.

4. Life expectancy of greater than six months.

5. Residual or recurrent pituitary adenoma ≥1cm in maximal diameter on MRI Brain; patient must have received at least one prior therapy, such as surgery, radiation and/or medical therapy.

6. Patients must have normal organ and marrow function as defined below. NOTE: Laboratory values must be taken within 7 days prior to chemotherapy administration. Transfusions and/or growth factor support may not be used to meet this criteria):

    a. Platelet count ≥ 100×10^9/L.
    b. Hemoglobin ≥ 9 g/dL.
    c. WBC ≥ 3×10^9/L
    d. Absolute neutrophil count (ANC) ≥ 1.5×10^9/L.
    e. Serum bilirubin ≤ 1.5 × upper limit of normal (ULN) or ≤ 3 x ULN if Gilbert's disease is documented.
    f. Aspartate transaminase (AST) ≤ 2.5 ULN.
    g. Alanine transaminase (ALT) ≤ 2.5 ULN.
    h. Serum creatinine ≤ 1.5 × ULN OR creatinine clearance≥60mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.

7. Patients must be able to undergo a MRI Brain/Pituitary

8. For women of child-bearing potential and for men with partners of child-bearing potential, subject must agree to take contraceptive measures for duration of treatment and at least 6 months after the last dose of chemotherapy.

9. Patients must have the ability to understand and the willingness to sign a written informed consent document.

3.3 Exclusion Criteria

1. Prior temozolomide and/or capecitabine therapy for treatment of the pituitary tumor.

2. Other active malignancy outside of nonmelanoma skin cancer (patients in remission and with prior treatment more than two years ago will be accepted into trial).

3. Clinically significant renal, hematologic or hepatic abnormalities.

4. Use of Vitamin K antagonists such as warfarin (concentrations may be altered by concomitant use of capecitabine)

5. Uncontrolled concurrent illness including, but not limited to, ongoing or active infection requiring IV antibiotics & psychiatric illness/social situations that would limit compliance with study requirements

6. History of deficient dihydropyrimidine dehydrogenase activity.

7. History of immunodeficiency.

8. Patients who are taking any other concurrent investigational therapy.

9. Patients who are pregnant or breastfeeding.

10. Patients who have had prior radiation treatment in the last six months

11. Patients who have had prior pituitary surgery within the last two months

4.0 REGISTRATION PROCEDURES

4.1 Patient Registration

Patients will be centrally registered with Weill Cornell Medicine, Joint Clinical Trials Office, Cancer Clinical Trials Operations. To register a patient, completed the web-based

demographic, enrollment pages and the following documents and email to the Joint Clinical Trials Office.

- WCMC Patient Registration Form
- First and last page of the fully executed informed consent form, plus additional pages if with subject's markings
- Fully executed HIPAA research authorization form (if separate from the consent document)
- Eligibility checklist signed and dated by investigator and second study team member
- Documentation of any eligibility waivers granted

5.0 STUDY PROCEDURES

5.1 Overview

This is an open label study to assess the efficacy of capecitabine (CAP) and temozolomide (TMZ) in recurrent pituitary adenomas. There will be a safety run-in of at least three patients to establish any DLT. Enrolled patients (sample size N=21 to 33) will receive treatment in 28-day cycles: capecitabine 1500mg/m2 per day (divided into two doses with maximum daily dose of 2500mg) on days 1 through 14 and oral temozolomide 150 to 200 mg/m2 on days 10 through 14. This will be followed by 14 days off treatment. MRI imaging will be completed after every two cycles. Treatment repeats every 28 days for up to 6 cycles in the absence of disease progression or unacceptable toxicity.

After completion of 6 cycles, patients achieving a complete or partial tumor response may continue to receive capecitabine temozolomide at the investigator's discretion in the absence of disease progression or unacceptable toxicity. Patients will be monitored for six months after they come off the study (either after completing 6 cycles or in setting of disease progression or unacceptable toxicity).

5.2 Table of Assessments

	Screening	Each Treatment Cycle				EOT	Follow Up
		Day 1	Day 8	Day 15	Day 22		
Agent Administration		X	X	X	X		
Informed consent	X						
Demographics	X						
Medical history	X						
Physical exam	X	X				X	
Karnofsky Performance Status	X						
Vital signs	X	X				X	
Height	X						
Weight	X	X				X	
CBC w/diff	X	X	X	X	X	X	
Serum chemistry (including LFTs)[a]	X	X		X		X	
B-HCG	X[b]						

Serum prolactin, GH, IGF-1, ACTH, cortisol +/- Dexamethasone level, FSH, LH, testosterone/estradiol, TSH, free T4, free T3, 24h urine free cortisol, creatinine, midnight salivary cortisol	X	X[c]				X	
EKG	X						
MRI Brain/Pituitary	X[d]	To be performed every 8 weeks according to institutional standards					
Adverse Event Review		X	X	X	X	X	
Conmed Review		X	X	X	X	X	
Survival Phone Call							X

a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT[AST], SGPT[ALT], sodium, ALK, and Liver Function Tests.
b: Serum pregnancy test (women of childbearing potential).
c: Only labs that are abnormal at baseline need to be checked every 8 weeks (on Day 1 of even cycles)
d: to be completed within 6 weeks of enrollment on trial, according to institutional standards

5.3 Screening Visit

Labs must be completed within three weeks of study consent

- Informed consent
- Medical history
- Medication history
- Physical exam
- KPS
- Vital Signs
- Height
- Weight
- CBC w/diff, platelets
- Serum chemistry with liver function tests
- Serum prolactin, GH, IGF-1, ACTH, cortisol +/- Dexamethasone level, FSH, LH, testosterone/estradiol, TSH, free T4, free T3, 24h urine free cortisol, creatinine, midnight salivary cortisol
- B-HCG if woman of childbearing age
- EKG
- Radiologic evaluation with MRI Brain or MRI Pituitary for baseline tumor measurements and Knosp classification grading (to be completed within 14 days of study enrollment)

5.4 Treatment Phase

(1 cycle=28 days)

CAP will be taken twice daily Days 1-14 with the addition of TMZ Days 10-14 followed by 14 days off treatment. Prior to each cycle, ANC must be ≥1,500/mm3 and platelets ≥100,000/mm3 or treatment will be held.

Days 1, 8, 15, and 22 of Every Cycle (± 3 days):

- CBC w/diff, platelets

Days 1 and 15 of every cycle (± 3 days):

- Serum chemistry with liver function tests

Day 1 of every cycle (± 5 days):

- Physical exam
- Vital Signs
- Adverse Event and Conmed Review
- Physical Exam
- Vital Signs

Day 1 of every even cycle (± 5 days)

- Serum prolactin, GH, IGF-1, ACTH, cortisol +/- Dexamethasone level, FSH, LH, testosterone/estradiol, TSH, free T4, free T3, 24h urine free cortisol, creatinine, midnight salivary cortisol (*only labs that are abnormal at baseline need to be checked every eight weeks)
- MRI Brain/Pituitary with tumor measurements and Knosp classification grading

*Continue as above with imaging and pituitary function tests after completion of every even chemotherapy cycle (i.e. 2, 4, 6, 8, 10, 12) unless toxicity preventing further chemotherapy and/or progression on imaging.

5.5 End of Study Visit

- Physical exam
- Vital Signs
- CBC w/diff, platelets
- Serum chemistry with liver function tests
- Serum prolactin, GH, IGF-1, ACTH, cortisol +/- Dexamethasone level, FSH, LH, testosterone/estradiol, TSH, free T4, free T3, 24h urine free cortisol, creatinine, midnight salivary cortisol (*only labs that are abnormal at baseline need to be checked again at end of study)
- Radiologic evaluation with MRI Brain or MRI Pituitary

6.0 TREATMENT ADMINISTRATION

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications for *Investigational Agent or Device* are described in Section 6.

1) Capecitabine 1500mg/m2 orally per day (divided into two doses with maximum daily dose of 2500mg) on days 1 through 14.

   Doses should be taken with water within 30 minutes after a meal. The tablets should be swallowed whole (should not be cut or crushed).

2) Temozolomide 150mg/m2 orally per day on days 10 through 14 (dose will be escalated to 200mg/m2 on Cycle #2 if well-tolerated without significant hematologic toxicity on first cycle).

   Patient will take odansetron 4mg on empty stomach, and 20 minutes later take the temozolomide dose. The capsules should be swallowed whole with a glass of water. Capsules should not be opened or chewed, and patients should avoid contact with skin or mucous membranes if capsules are accidentally opened or damaged.

6.1 Dose De-escalation Schema (for Safety Run-in component in case of DLT)

6.1.1 Inter-patient De-escalation

Dose level	Capecitabine	Temozolomide
-2	750mg/m2 orally per day in two divided doses on Days 1-14	100mg/m2 once daily on Days 10-14 for all subsequent cycles
-1	1000mg/m2 orally per day in two divided doses on Days 1-14	150mg/m2 once daily on Days 10-14 for all subsequent cycles
0	1500mg/m2 orally per day in two divided doses on Days 1-14	150mg/m2 once daily on Days 10-14 for cycle 1, 200mg/m2 once daily on Days 10-14 (for cycles 2-12 if no significant toxicity on first cycle)

6.1.2 Criteria for Dose De-escalation

Cohorts of 3 to 6 patients will be treated with capecitabine and temozolomide at dose level 0. If a minimum of three patients who are evaluable for toxicity have completed first cycle of treatment at this dose level without evidence of dose-limiting toxicity (DLT) (section 5.3.3), the study may be proceeded to the phase II component with subsequent patients being enrolled at the same dose level.

If DLT is observed in 1 patient from the initial cohort of 3 patients at dose level 0 (1/3 with DLT), an additional 3 patients will be enrolled at dose level 0.

If DLT is observed in 1 patient from the 6 patients at dose level 0 (1/6 with DLT), then dose level 0 will be the dose level for phase II component, and we may proceed to the phase II component with subsequent patients being enrolled at dose level 0.

If 2 or more patients have DLT at dose level 0 from the first 3 patients (>= 2/3 with DLT) or 2 or more patients with DLTs are observed in 6 patients (>= 2/6 with DLT), three more patients will be enrolled at one lower dose level.

The dose level for the phase 2 component will be the dose below the one where two or more patients in a group of 6 experience a DLT.

6.2 Definition of Dose Limiting Toxicity (DLT) (Criteria for entire study)

Dose-limiting toxicity (DLT) is defined as the occurrence of any of the following AEs using NCI-CTCAE (v 4.03) that are possibly, probably or definitely attributed to capecitabine or temozolomide during the FIRST CYCLE of treatment:

1) Any Grade 4 non-hematologic toxicity (excluding alopecia, nausea/vomiting) including palmar-plantar erythrodysesthesia (Hand-Foot Syndrome).
2) Any >= Grade 3 neurologic toxicity
3) Grade 4 thrombocytopenia
4) Grade 4 neutropenia

6.3 General Concomitant Medication and Supportive Care Guidelines

Capecitabine: CAP is a strong inhibitor of CYP2C9. It may increase the anticoagulant effects of warfarin leading to bleeding events, including death. Use of Vitamin K antagonists is contraindicated with CAP. It may also interfere with the concentrations of other drugs metabolized by CYP2C9.

Temozolomide: Due to moderate risk of nausea/vomiting, preventative anti-emetic is taken before every dose of TMZ (Odansetron 4mg orally 20 minutes before administration of TMZ capsules).

6.4 Duration of Therapy and Criteria for Removal from Study

In the absence of treatment delays due to adverse event(s), treatment may continue for 12 cycles or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,

- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator,.

6.6 Duration of Follow Up

Patients will be followed every two months for six months after removal from study. If possible, MRI imaging will be completed every two months to continue monitoring of the pituitary adenoma (according to institutional practice). Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

7.0 DOSING DELAYS/DOSE MODIFICATIONS

*Prior to treatment for each cycle, ANC must be ≥1,500/mm3 and platelets ≥100,000/mm3. If those values are not met, treatment will be held until they reach the respective threshold.

Capecitabine:
Normal Dosage: 1500mg/m2 orally per day (divided into two doses with maximum daily dose of 2500mg) on Days 1-14 of a 28-day treatment cycle.

Dose modification for CAP-related toxicity (including renal, hematologic, hepatic):

Toxicity Grades	**During course of therapy**	**Dose adjustment for NEXT cycle**
Grade 1	Maintain dose level	Maintain dose level
Grade 2		
1st appearance	Interrupt until resolved to grade 0 to 1	No change
2nd appearance	Interrupt until resolved to grade 0 to 1	750mg/m2 daily dose (max 1250mg daily dose)
3rd appearance	Discontinue CAP	(may still continue with TMZ monotherapy if toxicity presumed fully related to CAP)
Grade 3 or 4		
1st appearance	Discontinue CAP	(may still continue with TMZ monotherapy if toxicity presumed fully related to CAP)

Temozolomide Normal Dosage:
Cycle 1: 150 mg/m2 once daily on Day 10-14 of 28-day treatment cycle

Cycles 2 to 12: Increase to 200 mg/m2 once daily on Day 10-14 of 28 day treatment cycle, IF ANC ≥1,500/mm3, platelets ≥100,000/mm3, and non-hematologic toxicities for Cycle 1 are ≤grade 2 (excludes alopecia, nausea/vomiting)

Dosage modification for TMZ-related toxicity:

If patient experiences ANC <1,000/mm3, platelet count <50,000/mm3, or grade 3 non-hematologic toxicity (excluding alopecia, nausea/vomiting) during previous cycle:

- Decrease dose by 1 dose level (by 50 mg/m2/day)
- If dose has already been lowered to 100 mg/m2/day, then discontinue therapy.

Patients should come off trial if any of the following conditions are met:

- If dose reduction <100 mg/m2/day is required
- Patient experiences a grade 4 nonhematologic toxicity (excluding alopecia, nausea/vomiting)
- Patient previously had a dose reduction, but the same grade 3 non-hematologic toxicity occurs after dose reduction

8.0 ADVERSE EVENT REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug or device under investigation. Safety will be monitored by evaluation of adverse events reported by patients or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, x-rays, electrocardiographs, etc.

8.1 Adverse Event Definition

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

8.1.1 Investigational Agent or Device Risks

Capecitabine: Potential adverse reactions related to capecitabine include (but are not limited to) myelosuppression, fatigue/weakness, hand and foot syndrome, dermatitis, diarrhea, mucositis, abdominal pain, anorexia, hyperbilirubinemia, paresthesias, and peripheral sensory neuropathy.

Temozolomide: Generally well-tolerated but side effects include myelosuppression, moderate nausea/vomiting (reduced by taking on empty stomach), anorexia, constipation, headache, fatigue and alopecia. MDS and secondary malignancies have been reported but are extremely rare.

8.1.2 Adverse Event Characteristics and Related Attributions

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **Attribution** of the AE:
  - 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.

8.1.3 Recording of Adverse Events

All adverse events will be recorded on a patient specific AE log. The AE log will be maintained by the research staff and kept in the patient's research chart and Redcap database.

8.1.4 Reporting of AE to WCMC IRB

All AEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

8.2 Definition of SAE

SAE's include death, life threatening adverse experiences, hospitalization or prolongation of hospitalization, disability or incapacitation, overdose, congenital anomalies and any other serious events that may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.2.1 Reporting of SAE to IRB

All SAEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link: http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

8.2.2 Reporting of SAE to FDA

If an SAE occurs on this study, the event will be filed on a MedWatch form with the FDA. The investigator must notify the FDA of any SAE's as soon as possible but no later than 7 calendar days after the initial receipt of the information

CDER-only Biologic INDs:
Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biologic Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

8.2.3 AE/SAE Follow Up

All SAEs and AEs reported during this study will be followed until resolution or until the investigator confirms that the AE/SAE has stabilized and no more follow-up is required. This requirement indicates that follow-up may be required for some events after the patient discontinues participation from the study.

9. PHARMACEUTICAL INFORMATION

9.1 Investigational Agent

Capecitabine: CAP is an antimetabolite that is enzymatically converted to 5-FU in tumors which induces cytotoxicity. It is a commonly used chemotherapy in breast cancer, colorectal cancer and neuroendrocrine tumors. It undergoes extensive hepatic metabolism and is mostly excreted by the kidney with elimination half life of 38-45 minutes. It is available in 150mg and 500mg tablets. It is considered a hazardous neoplastic agent, and NIOSH recommends single gloving for administration of intact tablets.

Temozolomide: Temozolomide is a second generation alkylating agent that inhibits DNA replication and cell division. It is used as standard-of-care chemotherapy for

glioblastoma. About 38% is eliminated in the urine with an elimination half-life of 1.6-1.8 hours. It is available in 5, 20, 100, 140, 180 and 250mg capsules. It is considered a hazardous neoplastic agent, and NIOSH recommends single gloving for administration of intact capsules.

9.2 Availability

Both Capecitabine and Temozolomide are available through any specialty pharmacy that provides chemotherapy.

9.3 Agent Ordering

Not applicable.

9.4 Agent Accountability

Not applicable.

10. CORRELATIVE/SPECIAL STUDIES

10.1 Pathology Evaluation/Molecular Profiling

To be performed if tissue sample available; this will not be necessary for enrollment.

The exact mechanisms for pituitary tumorigenesis and transformation to a more aggressive phenotype are still not known. Both Ki67 nuclear labelling index and p53 expression are possible indicators of pituitary tumor invasiveness and aggressiveness. Further, low expression of 6-O-methylguanine-DNA methyltransferase (MGMT), a DNA repair enzyme that reverses the effects of temozolomide, may correlate with better outcomes with chemotherapy.

On enrollment, we will request 20 unstained tumor tissue slides from the institution where surgery was performed (if available) for evaluation of MGMT expression, MGMT methylation status, p53 expression, and Ki67 nuclear labelling index. In addition, we will attempt to acquire extended genetic profiling of these pituitary tumors via testing with Foundation Medicine. Specific somatic mutations within the tumor may contribute to tumorigenesis, aggressiveness and invasiveness. These tumor samples will be encouraged but are NOT necessary for enrollment in the trial.

11 MEASUREMENT OF EFFECT

Although not fully validated for pituitary tumors, the RECIST criteria [25] will be used to assess response of pituitary adenoma to the chemotherapy regimen of CAP and TMZ.

11.1 **Definitions**

11.1.1 Measurable

Pituitary tumor: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10mm by MRI scan.

11.1.2 Non-measurable

This may be irrelevant for the pituitary tumors, if metastatic probably carcinomas.

All other lesions, including small lesions (longest diameter <10 mm) as well as truly non-measurable lesions (such as leptomeningeal disease).

11.1.3 Special considerations regarding lesion measurability

Cystic lesions:

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

Lesions with prior local treatment:

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

11.2 **Response Criteria**

11.2.1 Evaluation of Target lesions:

Complete Response (CR):
Disappearance of all target lesions.

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

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

Stable Disease (SD):

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.2.2 Evaluation of non-target lesions

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

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

Non-CR/Non-PD:
Persistence of one or more non-target lesion(s)

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

11.2.3 Duration of Response

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

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

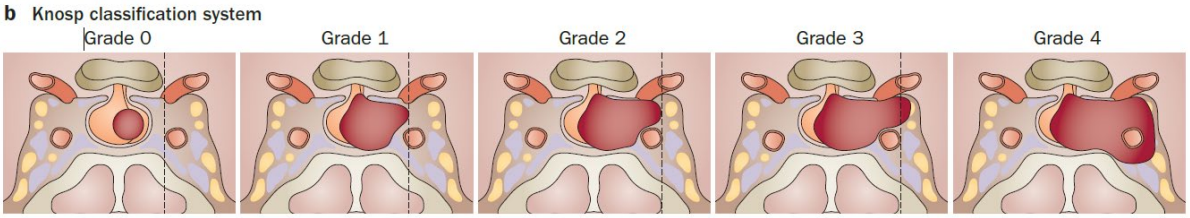
Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

11.3 **Other Response Parameters**

11.3.1 Knosp Classification[3]

We will use the Knosp classification system to quantify invasion of pituitary tumor into the cavernous sinus, which is clinically relevant and cannot be fully assessed by the measurements described under the RECIST criteria.

Grade 0: No cavernous sinus involvement
Grade 1: Pushes into medial wall of the cavernous sinus but not past hypothetical line extending between the centers of the two segments of the internal carotid artery
Grade 2: Extends past hypothetical line extending between the centers of the two segments of the internal carotid artery, but without passing a line tangent to the lateral margins of the artery itself
Grade 3: Tumor extends laterally to the internal carotid artery within the cavernous sinus
Grade 4: Total encasement of the intracavernous carotid artery



(from Di leva, A. et al. Nat. Rev. Endrocrinol. 10, 423-435 (2014)

11.3.2 Pituitary function testing

Will measure baseline serum prolactin, IGF-1, ACTH, FSH, LH and TSH and re-check every 8 weeks while patients are on study. Will assess any interval change in these levels after initiation of chemotherapy.

12 DATA REPORTING / REGULATORY CONSIDERATIONS

12.1 Data Collection

The data collection plan for this study is to utilize REDCap to capture all treatment, toxicity, efficacy, and adverse event data for all enrolled patients.

12.1.1 REDCap

REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool

for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

12.2 Regulatory Considerations

All protocol amendments and consent form modifications will be made by the Principal Investigator.

13 STATISTICAL CONSIDERATIONS

13.1 Analysis for Primary endpoint:

This is a single-stage phase II clinical trial with safety run-in. The primary endpoint of the study is the response rate in patients with recurrent pituitary adenoma treated with temozolomide and capecitabine, assessed by the RECIST criteria.

Safety run-in
In the safety run-in portion, a conventional 3+3 design is used. The initial starting dose of capecitabine and temozolomide will be dose level 0 in table 5.3.1. The total dose level will likely only be 1, with the possibility of 2 dose de-escalations. Cohorts of 3 to 6 patients will be treated per dose level. The recommended dose for the phase II part will be defined as the dose level immediately below the level at which 2 or more patients in a group of 6 experience a DLT. The safety run-in patients at the final recommended dose for the phase II part will be counted in the total accrual for Phase II part.

Phase II
Patients will be treated at the recommended dose for the phase II portion based on the safety run-in.

We consider that the effect of temozolomide and capecitabine on patients with recurrent pituitary adenomas to be clinically meaningful if the response rate is at least 20%, with the null hypothesis that a 5% response rate is seen with standard treatment. A total of 21 patients will be enrolled for the phase II part, including those in the safety run-in group who are treated at the recommended dose for the phase II part. The null hypothesis will be rejected if 3 or more responders are observed out of 21 evaluable patients. We assume that responses are binomially distributed. With a sample size of 21 patients, the power to detect a response rate of 0.2 is 82.1%, with a one-sided alpha of 8.5%.

(Sample size, accrual rate and enrollment time will be addressed later after the design, alternative and null hypothesis for the study have been decided.)

13.2 Sample Size/Accrual Rate

If none of the first 3 patients, or 1 out of the first 6 patients, at dose level 0 experience a DLT, the total sample size will be 21 patients.

If the toxicity is worse than expected, 3 patients will have de-escalated to dose level -1 prior to the decision to proceed to the phase II. If none of the first 3 patients or 1 out of the first 6 patients at dose level -1 experience a DLT, the sample size will be 24-27 patients.

If 2 or more of the first 6 patients at dose level -1 experiencing DLT, the dose level will be de-escalated to dose level -2, and the sample size will be 27 – 33 patients.

Hence, the minimum sample size is 21 patients, and the maximum could be 33.

13.3 Analysis for Secondary endpoints:

1. *Assess the effect of temozolomide on pituitary adenoma hormone secretion and on pituitary function in these patients.*

   Any change in pituitary hormone secretion during the study will be assessed by endocrine laboratory work-up (including serum prolactin, IGF-1, ACTH, FSH, LH and TSH levels) at baseline, every two months while receiving treatment, and at the end of study. Descriptive statistics will be provided, including any change from baseline. Linear mixed model will be utilized, as appropriate, to assess the effect of chemotherapy on pituitary adenoma hormone secretion over time. Statistical analysis for these endpoints will be considered exploratory.

2. *To assess the overall safety and tolerability of temozolomide and capecitabine in patients with recurrent pituitary adenomas.*

   The number and severity of all adverse events will be tabulated and summarized. The grade 3 or higher adverse events will also be summarized in a similar way. Summary tables of number and percentage of patients who experienced AEs as well as SAEs by severity (graded according to CTCAE version 4.0) and by relationship to temozolomide and/or capecitabine will also be provided. This will be based on the maximum grade of the specific AE experienced by a patient.

13.4 Exploratory analysis

1. *To clarify the role of Ki67 nuclear labelling index, p53 expression, MGMT*

expression/methylation status, and additional tumor genetic profiling as indicators of tumor aggressiveness and invasiveness.

On enrollment, unstained tumor slides will be requested from the institution where surgery was completed, and below studies will be used for the exploratory analysis. These are NOT necessary for enrollment in the trial. We will evaluate Ki67 nuclear labelling index, p53 expression, MGMT expression/methylation status, and additional tumor genetic profiling. Descriptive statistics of Ki67 nuclear labelling index, p53 expression, MGMT expression/methylation status, and tumor genetic profiling of enrolled patients will be provided separately. Statistic modelling methods, if appropriate, such as Cox proportional hazard model, will be used to explore the relationship between these indicators and response to chemotherapy, time to progression, and tumor invasiveness (based on the Knosp criteria). Statistical analysis for these endpoints will be considered exploratory.

14 Data and Safety Monitoring Plan (DSMP)

This study will utilize the Weill Cornell Medical College (WCMC) Institutional Data Safety Monitoring Board (DSMB) and follow its policies and procedures for monitoring this study for safety concerns, with ongoing updates from the Study Chair on an ongoing basis.

Reports to the DSMB will include the following items for review:
1. Completed DSMB Periodic Review Form.
2. Synopsis of the study to date.
3. IRB approved consent form.
4. IRB current protocol.
5. Summary table of study results.
6. Adverse event table.
7. Data safety monitoring plan.

14.1 Stopping Rules

If at any time 5 or more patients have a grade 4+ event attributable to treatment then trial accrual will be halted to determine the safety of the regimen. A decision will be made with input from DSMB whether to (1) continue the trial as planned, (2) permanently halt the trial or, (3) modify the treatment protocol.

REFERENCES

1. Aflorei ED, Korbonits M. Epidemiology and etiopathogenesis of pituitary adenomas. *J Neurooncol.* 2014;117(3):379-394.
2. Asa SL, Ezzat S. The pathogenesis of pituitary tumors. *Annu Rev Pathol.* 2009;4:97-126.
3. Di Ieva A, Rotondo F, Syro LV, Cusimano MD, Kovacs K. Aggressive pituitary adenomas--diagnosis and emerging treatments. *Nat Rev Endocrinol.* 2014;10(7):423-435.
4. Meij BP, Lopes MB, Ellegala DB, Alden TD, Laws ER, Jr. The long-term significance of microscopic dural invasion in 354 patients with pituitary adenomas treated with transsphenoidal surgery. *J Neurosurg.* 2002;96(2):195-208.
5. Scheithauer BW, Kovacs KT, Laws ER, Jr., Randall RV. Pathology of invasive pituitary tumors with special reference to functional classification. *J Neurosurg.* 1986;65(6):733-744.
6. Thapar K, Kovacs K, Scheithauer BW, et al. Proliferative activity and invasiveness among pituitary adenomas and carcinomas: an analysis using the MIB-1 antibody. *Neurosurgery.* 1996;38(1):99-106; discussion 106-107.
7. Thapar K, Scheithauer BW, Kovacs K, Pernicone PJ, Laws ER, Jr. p53 expression in pituitary adenomas and carcinomas: correlation with invasiveness and tumor growth fractions. *Neurosurgery.* 1996;38(4):765-770; discussion 770-761.
8. George DH, Scheithauer BW, Kovacs K, et al. Crooke's cell adenoma of the pituitary: an aggressive variant of corticotroph adenoma. *Am J Surg Pathol.* 2003;27(10):1330-1336.
9. Mete O, Ezzat S, Asa SL. Biomarkers of aggressive pituitary adenomas. *J Mol Endocrinol.* 2012;49(2):R69-78.
10. LeRiche VK, Asa SL, Ezzat S. Epidermal growth factor and its receptor (EGF-R) in human pituitary adenomas: EGF-R correlates with tumor aggressiveness. *J Clin Endocrinol Metab.* 1996;81(2):656-662.
11. Heaney A. Management of aggressive pituitary adenomas and pituitary carcinomas. *J Neurooncol.* 2014;117(3):459-468.
12. Kaltsas GA, Nomikos P, Kontogeorgos G, Buchfelder M, Grossman AB. Clinical review: Diagnosis and management of pituitary carcinomas. *J Clin Endocrinol Metab.* 2005;90(5):3089-3099.
13. Bachelot T, Romieu G, Campone M, et al. Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study. *Lancet Oncol.* 2013;14(1):64-71.
14. Hong YS, Song SY, Lee SI, et al. A phase II trial of capecitabine in previously untreated patients with advanced and/or metastatic gastric cancer. *Ann Oncol.* 2004;15(9):1344-1347.
15. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med.* 2005;352(10):987-996.
16. Syro LV, Ortiz LD, Scheithauer BW, et al. Treatment of pituitary neoplasms with temozolomide: a review. *Cancer.* 2011;117(3):454-462.

17. McCormack AI, Wass JA, Grossman AB. Aggressive pituitary tumours: the role of temozolomide and the assessment of MGMT status. *Eur J Clin Invest.* 2011;41(10):1133-1148.
18. Ortiz LD, Syro LV, Scheithauer BW, et al. Temozolomide in aggressive pituitary adenomas and carcinomas. *Clinics (Sao Paulo).* 2012;67 Suppl 1:119-123.
19. Raverot G, Castinetti F, Jouanneau E, et al. Pituitary carcinomas and aggressive pituitary tumours: merits and pitfalls of temozolomide treatment. *Clin Endocrinol (Oxf).* 2012;76(6):769-775.
20. Losa M, Mazza E, Terreni MR, et al. Salvage therapy with temozolomide in patients with aggressive or metastatic pituitary adenomas: experience in six cases. *Eur J Endocrinol.* 2010;163(6):843-851.
21. Abbasi S, Kashashna A, Albaba H. Efficacy of capecitabine and temozolomide combination in well-differentiated neuroendocrine tumors: Jordan experience. *Pancreas.* 2014;43(8):1303-1305.
22. Fine RL, Gulati AP, Krantz BA, et al. Capecitabine and temozolomide (CAPTEM) for metastatic, well-differentiated neuroendocrine cancers: The Pancreas Center at Columbia University experience. *Cancer Chemother Pharmacol.* 2013;71(3):663-670.
23. Strosberg JR, Fine RL, Choi J, et al. First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. *Cancer.* 2011;117(2):268-275.
24. Zacharia BE, Gulati AP, Bruce JN, et al. High response rates and prolonged survival in patients with corticotroph pituitary tumors and refractory Cushing disease from capecitabine and temozolomide (CAPTEM): a case series. *Neurosurgery.* 2014;74(4):E447-455; discussion E455.
25. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45(2):228-247.