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TEMOZOLOMIDE AND BEVACIZUMAB THERAPY IN ADVANCED HEMANGIOPERICYTOMA/ SOLITARY FIBROUS TUMOR

Min S. Park

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by

Min S. Park, MD

APPROVED:

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Dejka M. Araujo, MD

_____
Karin Hahn, MD, MS

_____
Alexander Lazar, MD, PhD

_____
Dina C. Lev, MD

_____
Jonathan C. Trent, MD PhD

APPROVED:

_____
Dean, The University of Texas Health Science Center at Houston Graduate School of Biomedical Sciences

Temozolomide and bevacizumab therapy in advanced hemangiopericytoma/ solitary fibrous tumor

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Dedication

This thesis is dedicated to the patients with hemangiopericytoma and solitary fibrous tumor (HPC/SFT) who have struggled with their rare diseases. Their hope for better awareness, understanding, and therapies for HPC/SFT serve as my inspiration.

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Temozolomide and bevacizumab therapy in advanced hemangiopericytoma/ solitary fibrous tumor

Min S. Park, MD

Supervisory Professor: Jonathan C. Trent, MD, PhD

Tumors comprising the spectrum of hemangiopericytoma/ malignant solitary fibrous tumor (HPC/SFT) are thought to arise from fibroblasts and represent a small subset of soft tissue sarcomas. Surgery is typically the treatment of choice for localized disease, with reported 10-year overall survival rates of 54-89% after complete surgical resection. However, for the approximately 20% of HPC/SFT patients who eventually develop local recurrences and/or distant metastases, options for effective treatment are limited and are poorly defined. Alternative therapeutic options are therefore needed for improved palliation and disease control. We hypothesize that HPC/SFT are a spectrum of soft tissue tumors with unique clinical, pathological, and molecular makeup and clinical behavior. HPC/SFT respond to unique therapeutic agents that specifically target aberrations specific to these tumors.

We retrospectively reviewed the characteristics and the clinical outcomes for all HPC/SFT patients whose tumor specimens have been reviewed at the MD Anderson Cancer Center from January 1993 to June 2007 by a MD Anderson pathologist and were treated at the institution with available electronic medical records. We identified 128 patients, 79 with primary localized disease and 49 with recurrent and/or metastatic disease. For the 23 patients with advanced HPC/SFT

who received adriamycin-based, gemcitabine based, or paclitaxel chemotherapy as first- or second-line therapy, the overall RECIST response rate was 0%. Most patients achieved a brief duration of disease stabilization on chemotherapy, with median progression-free survival (PFS) period of 4.6 months. For the 14 patients with advanced HPC/SFT who received temozolomide and bevacizumab systemic therapy, the overall RECIST response rate was 14%, with the overall Choi response rate of 79%. The median PFS for the cohort was 9.7 months with a median 6-month progression free rate of 78.6%. The most frequently observed toxic effect of temzolomide-bevacizumab therapy was myelosuppression. We have designed a phase II study to evaluate the safety and efficacy of temozolomide-bevaciumab in locally advanced, recurrent, and metastatic HPC/SFT in a prospective manner.

Combination therapy with temozolomide and bevacizumab may be a potentially clinically beneficial regimen for advanced HPC/SFT patients.

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COMMONLY USED ABBREVIATIONS

BEV	Bevacizumab
CI	Confidence interval
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
GTR	Gross Total Resection
HPC/SFT	Hemangiopericytoma/ Solitary fibrous tumor
HPF	High-powered field
HU	Hounsfield unit
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression free survival
PR	Partial response
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Stable disease
TMZ	Temozolomide
TTP	Time to progression
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
XRT	Radiation therapy

Chapter 1

INTRODUCTION

Hemangiopericytoma and Solitary Fibrous Tumor. Tumors comprising the spectrum of hemangiopericytoma/ solitary fibrous tumor (HPC/SFT) are rare entities that represent a small subset of soft tissue sarcomas. Stout and Murray first described HPC in 1942 as a distinct vascular soft tissue tumor characterized by groups of endothelial-lined tubes and sprouts, featuring Zimmerman's pericytes. (1) Essential features of the diagnosis of HPC include the presence of well-developed branching "staghorn" thick-walled vessels surrounded by connective tissue sheath, moderate-to-high cellularity, and monotonous appearance under light microscopy examination. (2) Classically, HPC tumors express immunohistochemical (IHC) positivity for muscle-specific actin (HHF-35), smooth muscle actin (SMA), tropomyosin and CD34, and negativity for desmin and h-caldesmon. (2) However, only 10-20% of HPC display this classic expression pattern, with the majority showing non-specific patterns. (2) Solitary fibrous tumor (SFT) was first recognized as a unique neoplasm by Klemperer and Rabin in 1931. (Klemperer 1931) SFT demonstrate a wide variety of histological features under light microscopy: multinodular, partially sclerotic pattens; HPC-like patterns displaying many thin walled staghorn branching vessels; and hypocellular, fibrous areas alternating with a monotous, highly cellular "patternless pattern" are all seen. (3) Immunohistochemical reactivity for CD34, CD99, bcl-2, and vimentin in the setting

of negativity for desmin, cytokeratins, and S-100, is a key characteristic of SFT, but such patterns are variable across cases. (2)

The Hemangiopericytoma/ Solitary Fibrous Tumor (HPC/SFT) Spectrum: An Evolving Concept. Much confusion and debate exist regarding the exact cell of origin and a clear set of classification criteria for HPC and SFT. Because of the large overlap of morphologic and clinical features between HPC and SFT, the two entities have been frequently misdiagnosed for each other. In the most recent WHO classification of soft tisse sarcomas, the concept of HPC as a vascular, pericyte-derived tumor was abandoned in favor of a fibroblastic cell of origin, thus placing HPC more closely with SFT. (4) Therefore, the current paradigm has begun to view HPC and SFT as a spectrum of a *single* entity, a viewpoint which will be adopted in this study.

Natural history of HPC/SFT. HPC/SFT primarily occur in adults between ages 20-70, with an equal frequency between men and women. (5) SFT was first identified in the pleura and has classically been described as a neoplasm involving the serosal surfaces, i.e. pleural, pericardial, or peritoneal. However, as more cases of extrapleural SFT were reported, and as the diagnoses of HPC and SFT became more aligned with each other, HPC/SFT has been described as a malignancy affecting virtually every body site. (5-7) The most commonly affected sites include the lower extremities, abdomen/pelvic fossa, lung/pleura, and head and neck (especially the supratentorial meninges), with additional sites including breast,

greater omentum, peritoneum, liver, stomach, uterus, ovary and vagina also reported in literature. (5, 8-11)

HPC/SFT are often present for several years prior to diagnosis, and most patients present with symptoms related to local growth. A slow-growing mass or pain associated with locoregional pressure by the tumor are the most common. (5) Other symptoms related to the specific tumor site include urinary retention, constipation, (retroperitoneum and pelvic fossa), cough, dyspnea (lung and pleura), vomiting, headache (meninges), unitlateral varicose veins or telangiectasia of overlying skin (extremities). (5, 8) A small number of HPC/SFT patients exhibit Doege-Potter syndrome, hypoglycemia which is thought to be mediated by overexpression of insulin-like growth factors (IGFs) produced by the tumor. (12, 13) Resolution of hypoglycemia occurs after tumor resection.

Clinical management of HPC/SFT. For localized disease, complete surgical resection is often the treatment of choice. Retrospective analyses of the outcomes of HPC/SFT patients who had undergone initial surgery show that favorable long-term outcomes can be achieved after complete surgical resection, with estimated 5-year overall survival rates of 79-100%. (10, 14, 15) Patients with incomplete surgical resection of their primary disease, however, have worse long-term prognosis, with an estimated 10-yr overall survival of 50%.

Approximately 15-20% of primary HPC/SFT recur, either locally or distally, after initial surgical resection. Factors that are associated with an increased risk of developing disease recurrence include larger tumor size (>10 cm), non-extremities

primary tumor location, and the presence of “malignant” histology. (10, 14, 15) Histological features of “malignant” HPC/SFT tumors include a high number of mitotic figures (≥ 4/10 mitoses/HPF), cellular atypia, and the presence of necrosis and/or hemorrhage, and tumors lacking such features are classified as “benign”. (2) Malignant histology alone, however, does not always predict aggressive clinical behavior. Likewise, the clinical behavior and the prognosis of “benign” tumors also cannot be reliably predicted. (2, 4) Given this lack of clear prognostic indicators, all HPC/SFT patients should undergo long-term follow-up, since late recurrences (more than 20 years) can occur. (5)

Management of recurrent HPC/SFT is challenging, since no clearly effective strategies are known. Additional surgeries should be attempted for isolated local and/or distant lesions, but they are not always feasible nor successful. (9, 10) Palliative radiation therapy has some role in controlling symptomatic lesions. Stereotactic radiosurgery in recurrent, unresectable HPC/SFT of the central nervous system may also produce some degree of durable disease control. (16)

Limited published data regarding the effectiveness of systemic chemotherapy in HPC/SFT are available. Doxorubicin- and/or ifosfamide-based regimens have most often been used, as well as gemcitabine-docetaxel. (10, 17-19) Systemic chemotherapy seems to be ineffective in the management of advanced HPC/SFT. A recent single-institution retrospective analysis of 13 HPC/SFT patients treated with doxorubicin- or ifosfamide-based therapy showed that only 1 of 9 (11%) and 4 of 4 (0%) patients, respectively, had response. (18) The exact efficacy of standard of

care chemotherapy regimens in advanced HPC/SFT, however, is yet poorly defined.

Potential role of antiangiogenic therapy in HPC/SFT. HPC/SFT are highly vascular tumor tumors, and agents that modulate or inhibit angiogenesis, therefore, are rational and attractive therapeutic possibilities in treatment of HPC/SFT. Case reports of advanced HPC/SFT patients who were treated with IFN-α and/or thalidomide showed durable disease stabilization for 16-41 months. (20, 21) Recently, several inhibitors of the vascular endothelial growth factor (VEGF) pathway, the key mediator of angiogenesis, have been evaluated in soft tissue sarcoma in phase II trials. A small number of HPC/SFT patients underwent treatment with sunitinib, sorafenib, or pazopanib -- vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors – and a few patients demonstrated durable stable disease up to 22 months. (22-25) These cases thus suggest that angiogenesis may play a major role in HPC/SFT tumorigenesis, and that targeting the VEGF-VEGFR pathway may produce clinically effective outcomes in HPC/SFT patients.

Temozolomide (TMZ) and bevacizumab (BEV) combination therapy is another regimen that offers therapeutic promise in HPC/SFT. TMZ is an oral cytotoxic alkylating agent whose active metabolite, monomethyltriazenoimidazole carboxamide is identical to that of dacarbazine, which has known antitumor activity against soft tissue sarcomas. (26, 27) BEV is a recombinant monoclonal antibody that targets VEGF. BEV has shown antitumor activity when combined with a

number of cytotoxic chemotherapeutic agents, such that its use in combination therapy has been approved for the treatment of metastatic colorectal, non-small cell lung, and HER2-negative breast cancers. (28-30)

TMZ was initially approved for the treatment of recurrent high grade glioma at a dose of 150-200 mg/m2/day for 5 consecutive days in a 28-day cycle. (31, 32) Subsequently, alternative dosing regimens using higher cumulative concentrations were developed in advanced high grade glioma patients. In one phase I study, 32 subjects with solid malignancies were sequentially enrolled into the following dose cohorts: 50, 75, 100, 125, 150, and 175 mg/m2/day using a 7-days-on/7-days-off ("dose-dense") schedule. (33) TMZ was administered PO, in the morning of days 1 through 7 and days 15 through 21 per cycle. Treatment cycles were repeated every 28 days. TMZ was rapidly absorbed and eliminated following PO administration. The MTD dose of 150 mg/m2 determined for this study. In a phase II study of TMZ at 150 mg/m2/d on days 1 through 7 and 15 through 21 every 28 days, 90 patients with recurrent gliomas were treated, achieving a 6-month PFS rate clinically meaningful and statistically superior than that achieved with convenetional 5-day TMZ dosing. (34) Major toxicities seen in this study, while more frequent than those of conventional TMZ dosing regimens, were acceptable: CTCAE grade 4 hematotoxicity was only observed in 2.6% of patients, with grade 4 lymphopenia in 12% of patients. No opportunistic infections were seen. Thrombocytopenia was the next most frequently observed toxicity, with CTCAE grade 3 and 4 toxcities observed in 8.5% and 1.9%, respectively.

In clinical practice, BEV is used in combination with cytotoxic chemotherapy in doses ranging from 5 mg/kg to 15 mg/kg. The maximum tolerated dose of BEV has not been determined. However, recruitment into the 20 mg/kg every-2-weeks dose group of a BEV monotherapy study in patients with metastatic breast cancer was prematurely suspended due to severe headache associated with nausea and vomiting occurring in 4 of 16 patients (25%) in this dose group. This is the highest dose tested in humans. The ideal biologically effective dose of BEV is unknown. The most serious adverse events associated with BEV treatment are gastrointestinal perforations, fistulae, hemorrhage (including tumor-associated, mucocutaneous and intracranial), arterial and venous thromboembolic events and wound healing complications. Increased rates of severe neutropenia, febrile neutropenia, or infection with severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus BEV in comparison to chemotherapy alone. Hypertension and proteinuria are also associated with BEV therapy, and there is some evidence from the dose-finding Phase II trials that they are likely to be dose-dependent. Information from marketing experience identified hypertensive encephalopathy and reversible posterior leukoencephalopathy syndrome as rare events associated with BEV treatment. (Avastin IB)

The antitumor activity of TMZ combined with BEV is currently being studied in a number of different dosing schedules in several phase II and III trials in glioblastoma and malignant melanoma patients. (35) Two recently published Phase II studies explored the safety and efficacy of TMZ in a conventional 5-day dosing

and in a lose-dose, metronomic dosing (50 mg/m2/day for 21 days in a 28-day cycle) combinbed with BEV 10 mg/kg with expected side effect profiles. (36, 37)

In May 2005, a patient with a recurrent meningeal HPC that was refractory to multiple surgical resections, radiotherapy, and chemotherapy was empirically treated with TMZ and BEV at our institution. He subsequently achieved a radiologically evident reduction in tumor size as well as palliation of tumor-related symptoms. This anecdotal evidence led us to treat additional patients who had locally advanced, recurrent, or metastatic HPC/SFT not amenable to surgery with TMZ-BEV regimen. We hypothesized that HPC/SFT patients treated with TMZ-BEV would achieve at least similar degree of disease control, if not superior, as standard of care chemotherapy regimens.

Hypotheses and Specific Aims. I hypothesized that HPC/SFT are a spectrum of soft tissue tumors with unique clinical, pathological, and molecular makeup and clinical behavior. HPC/SFT respond to unique therapeutic agents that specifically target aberrations specific to these tumors. To test my hypothesis I designed the following specific aims:

1. To estimate the overall response rate (ORR) and progression-free survival (PFS) of advanced HPC/SFT patients who were treated systemic chemotherapy, especially those with doxorubicin-based, gemcitabine-based or paclitaxel-based chemotherapy.

2. To describe the activity of TMZ-BEV therapy in advanced HPC/SFT and identify potential clinicopathological factor(s) that correlate with response to therapy and outcome.
3. To design a prospective phase II trial to determine the efficacy of TMZ-BEV regimen in locally advanced, recurrent, and metastatic HPC/SFT.

Chapter 2

METHODS

AIM 1: To estimate the overall response rate (ORR) and progression-free survival (PFS) of advanced HPC/SFT patients who were treated systemic chemotherapy, especially those with doxorubicin-based, gemcitabine-based or paclitaxel-based chemotherapy.

Patient selection:

Patient identification. The study was approved by the University of Texas M.D. Anderson Cancer Center institutional review board, and a waiver of consent was granted for the proposed patient record review. All patients were initially identified from the soft tissue tumor pathology database at the M. D. Anderson Cancer Center. For all patients whose tumor specimens have been reviewed at the M. D. Anderson Cancer Center from January 1993 to June 2007 by a M. D. Anderson pathologist, the pathology reports containing the terms “hemangiopericytoma” or “solitary fibrous tumor” within the body of the text were identified. The start time period was chosen to reflect the time period at which the patient records were available electronically. The pathology reports were then reviewed by me to identify those patients whose pathologic diagnosis met the following categories: 1) HPC, 2) SFT, 3) HPC/SFT, 4) unclassified spindle cell neoplasm/tumor, mesenchymal cell tumor/neoplasm, or fibrosarcoma with additional comment by the pathologist subsequently identifying the tumor as HPC and/or SFT. Patients whose pathology

reports included HPC and/or SFT in the differential diagnosis but were ultimately determined to have another diagnosis were excluded.

The clinical records of the selected patients were then reviewed using the institutional electronic medical records database (ClinicStation™). All clinical encounters available in the database, as well as all available outside records which had been scanned into the system, were reviewed. Patients who only had pathology reports in the system without clinical notes were excluded. Patients who had pathology reports and were seen only at their initial visit without subsequent follow up visits at M. D. Anderson were also excluded. Pediatric patients, defined as age at diagnosis < 18, were also excluded.

Clinicopathological Variables:

Patient demographic characteristics consisting of age at diagnosis, sex, race, and vital status as of April 1, 2010 were collected. Primary tumor characteristics consisting of histologic diagnosis (HPC, SFT), site, size, histologic classification (benign, malignant, or unknown), and the presence of metastases, if any, were collected. Site of primary tumor were categorized as central nervous system (CNS), head & neck, lung/pleura, abdomen/pelvis, extremities, or other. Tumor site and size were determined using pathology reports, operative reports, and/or radiologic examinations. Available pathology reports were examined for the presence of a high number of mitotic figures (≥ 4/10 mitoses/HPF), cellular atypia, and the presence of necrosis and/or hemorrhage in the tumor. Tumors containing one or more of these features were classified as malignant, and tumors lacking these

features were classified as benign. Tumors whose pathology report did not describe these histologic features were classified as unknown.

For patients who were initially evaluated at the MD Anderson Cancer Center with primary localized disease, the dates and the resection status of the primary tumor were recorded; dates of surgery, gross total resection status and/or microscopic margin involvement were gathered from operative reports, clinical reports, and/or pathology reports. Neo/ adjuvant radiation treatment status and neo/ adjuvant chemotherapy status was recorded. Variables related to clinical outcome that were collected included the development of local recurrence and/or distant metastases, sites of recurrence, time to disease recurrence from initial diagnosis and overall survival.

For patients who were initially evaluated at the MD Anderson Cancer Center with locally recurrent disease or metastatic disease, treatment information regarding the surgical resection, neo/ adjuvant radiation, and neo/ adjuvant chemotherapy was gathered in the same fashion as the treatment of the primary tumor. Time to disease progression from their initial treatment at MD Anderson Cancer Center and overall disease-specific survival were also calculated.

For patients with unresectable disease who received systemic chemotherapy, the chemotherapy regimen used, the number of cycles, the best response reached (for patients with measurable disease only), date of disease progression, and reasons for discontinuing therapy were collected. For patients whose radiologic scans were available, information regarding the best response and

disease progression was collected from direct measurement of the radiology report, if scans were available for measurements; radiology reports, or clinic reports.

For all missing dates, all missing days of the month were coded as the 1st of the month, and all missing months of the year were coded as January.

Radiologic Response Assessment:

All patients who had received systemic therapy were evaluated for having their radiologic scans at baseline, during, and after treatment available in the institution's radiology archives. Radiologic response to treatment were assessed using Response Evaluation Criteria In Solid Tumors (RECIST) v.1.1 (38) using available images. For the patients whose CT and/or MRIs were in the institution's picture archiving and communication systems (PACS), their radiologic response to treatment were assessed using Response Evaluation Criteria In Solid Tumors (RECIST) v.1.1 and the Choi criteria. (39)

Statistical Analysis:

Patient characteristics were summarized using medians and ranges for continuous variables and frequencies and percentages for categorical variables. The response rates and the 95% confidence interval (CI) were calculated from variance estimates. Fisher's exact test was used to assess the association between patient or tumor characteristics and best response. Time to best radiologic response was measured from the initiation of systemic therapy to development of Choi complete response or Choi partial response (Choi criteria) or to development

of RECIST complete response or RECIST partial response (RECIST). Progression-free survival time (PFS) was defined as the time interval between the start of systemic therapy and radiologic evidence of disease progression (PD) as defined by either the Choi response criteria or RECIST, or death from any cause. Survival data were updated on April 1, 2010 and the patients' data were censored at that point. Kaplan-Meier method was used to estimate the PFS and overall survival (OS). All statistical analyses were carried out in S-plus 8.0 (TIBCO Software Inc., Somerville, MA).

AIM 2: To describe the activity of TMZ-BEV therapy in advanced HPC/SFT and identify potential clinicopathological factor(s) that correlate with response to therapy and outcome

Patient selection:

The medical records of all patients with the histologic diagnoses of HPC or SFT treated with the temozolomide-bevacizumab combination therapy at The University of Texas M. D. Anderson Cancer Center through June 2007 were retrospectively reviewed. All patients were initially identified from the soft tissue tumor pathology database at the M. D. Anderson Cancer Center. The clinical records of the selected patients were then reviewed using the institutional electronic medical records database (ClinicStation™). All clinical encounters available in the database, as well as all available outside records which had been scanned into the

system, were reviewed. Patients for whom radiologic scans were unavailable for radiologic response assessment were excluded from the analysis. The following data on patient and disease characteristics were collected: age, sex, and ethnicity; disease characteristics, including primary tumor site and extent of disease; previous treatment and responses; toxic effects of temzolomide and bevacizumab; and survival. This study was approved by our institutional review board.

Radiologic Assessment:

Baseline radiologic studies had been performed up to 4 weeks prior to the initiation of chemotherapy and follow-up scans had been performed every 8 to 12 weeks. Contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI), was used at the discretion of the treating physician. Radiologic tumor response was determined as described below.

Tumor size. The longest cross-sectional dimension for each measurable lesion was measured at the start of therapy and on each follow-up study. The sum of the longest selected measurable lesions at each timepoint was computed for each patient. Radiologic response was then determined by calculating the absolute and percentage change from the baseline sum.

Tumor density (CT attenuation coefficient). In patients whose responses were assessed with contrast-enhanced CT scans, the tumor density of each lesions was measured in Hounsfield units (HU) by drawing a region of interest around the margin of the entire lesion. In patients who had CTs with triphasic techniques, tumor density was measured on scans obtained in the portal venous phase. The mean

baseline tumor density was compared with the mean tumor density on the subsequent studies.

Response Assessment:

Using the Choi response criteria, a complete response (CR) was defined as the disappearance of all lesions without the appearance of new lesions. A Choi partial response (PR) was defined as a ≥10% decrease in the sum of the target lesions or a ≥15% decrease in tumor density in the absence of new lesions or obvious progression of nonmeasurable disease. Choi progressive disease (PD) was defined as a ≥10% increase in tumor size in the absence of favorable tumor density change required to achieve Choi PR. Patients whose disease did not meet the criteria for Choi CR, PR, or PD and who did not have tumor-related symptomatic deterioration were classified as having stable disease (SD). Only the best response for each patient was used in determining response rate. Response was also assessed using Response Evaluation Criteria in Solid Tumors (RECIST) to compare to Choi responses.

Pathology Review:

All tumor specimens had been reviewed by an M. D. Anderson sarcoma pathologist who established the diagnoses of HPC or SFT at the time of the patients' initial presentation to our institution. For the purpose of this study, two sarcoma pathologists who were blinded to the patients' outcome re-reviewed all the available specimens to confirm the diagnoses. Histopathologic variables including

size, number of mitoses, cellularity, pleomorphism, and presence of necrosis and/or hemorrhage, were noted during the re-review if possible. Tumors were sub-categorized as benign, malignant, or unknown and classified according to the 2002 WHO disease classification criteria for sarcomas.

Statistical Analysis:

Patient characteristics were summarized using medians and ranges for continuous variables and frequencies and percentages for categorical variables. The response rates and the 95% confidence interval (CI) were calculated from variance estimates. Fisher's exact test was used to assess the association between patient or tumor characteristics and best response. Time to best radiologic response was measured from the initiation of temozolomide and bevacizumab therapy to development of Choi complete response or Choi partial response. Progression-free survival time (PFS) was defined as the time interval between the start of temozolomide and bevacizumab therapy and radiologic evidence of PD as defined by either the Choi response criteria or the RECIST criteria, or death from any cause. Survival data were updated on October 15, 2009 and the patients' data were censored at that point. Kaplan-Meier method was used to estimate the PFS and overall survival (OS). All statistical analyses were carried out in S-plus 8.0 (TIBCO Software Inc., Somerville, MA).

AIM 3: To design a prospective phase II trial to determine the efficacy of TMZ-BEV regimen in locally advanced, recurrent, and metastatic HPC/SFT.

The protocol was written in the format of National Cancer Institute's Cancer Therapy Evaluation Program (CTEP) Phase II Protocol Submission form and modified . Templates can be found at http://ctep.cancer.gov/forms.

Primary Objectives:

1) To better estimate the overall response rate (ORR) for patients with unresectable or metastatic HPC/SFT receiving the combination of temozolomide and bevacizumab using the Choi criteria.

2) To assess the safety and tolerability of the combination of temozolomide and bevacizumab in patients with unresectable or metastatic HPC/SFT.

Secondary Objectives:

1) To better estimate the ORR and disease control rate (DCR) for patients with unresectable or metastatic HPC/SFT receiving the combination of temozolomide and bevacizumab using RECIST.

2) To determine the time to progression (TTP) in patients with unresectable or metastatic HPC/SFT receiving the combination of temozolomide and bevacizumab using the Choi criteria and RECIST.

3) To determine the relationship between best response and TTP, as assessed by Choi and RECIST.

Primary Endpoints:

1) Overall response rate (ORR), defined as the sum of complete response (CR) and partial response (PR) rates as assessed by the Choi criteria.

2) Safety and toxicity profile, as assessed by NCI CTCAE version 4.

Secondary Endpoints:

1) Overall response rate (ORR) as assessed by RECIST.

2) Disease control rate (DCR), defined as the sum of complete response (CR), partial response (PR), and stable disease (SD) for the period of 6 months, assessed using RECIST.

3) Time to progression (TTP), as assessed by the Choi criteria.

4) Time to progression (TTP), as assessed by RECIST.

Patient Selection:

Inclusion criteria:

1. Disease characteristics:
    a. Diagnosis of HPC/SFT, histologically confirmed by a central pathologist at M. D. Anderson Cancer Center:
        i. unresectable disease, primary or recurrent
        ii. metastatic disease

b. Measurable disease, defined as at least one lesion that can be measured in at least one dimension as ≥ 20 mm (or ≥ 10 mm of the CT slice thickness is ≥ 5 mm)
    i. measurable lesion must not have been irradiated ≤ 6 months before start of therapy.
c. Must have 1 paraffin block of primary tumor and/or metastatic tissue available prior to starting therapy

2. Prior treatment characteristics:
    a. Prior surgical resection is allowed, if measurable residual disease is present.
3. Patient characteristics:
    a. Age ≥ 18 years and life expectancy of ≥ 6 months
    b. ECOG performance status of 0-2
    c. ANC ≥ 1,500 cells/microliter, Hgb ≥ 9 g/dl, Platelet count ≥ 125,000 cells/microliter
    d. Serum creatinine ≤ 1.5 mg/dl, serum ALT, AST, total bilirubin ≤ 1.5 x ULN
    e. Signed informed consent approved by IRB prior to patient entry
    f. If sexually active, patients must take contraceptive measures for the duration of treatments

<u>Exclusion criteria:</u>

1. Prior treatment characteristics:

a. Prior history of systemic chemotherapy
b. Prior radiation treatment ≤ 6 months prior to starting therapy

2. Patient characteristics:
    a. Known history of hypersensitivity to dacarbazine
    b. History of HIV infection
    c. Pregnant or breastfeeding
    d. Active infection requiring IV antibiotics or antifungal medications
    e. Inadequately controlled hypertension
    f. Any prior history of hypertensive crisis/ hypertensive encephalopathy
    g. ≥ Grade II New York Heart Association congestive heart failure
    h. History of myocardial infarction/ unstable angina < 6 months prior to enrollment
    i. Serious cardiac arrhythmia (i.e. ventricular arrhythmia, high-grade atrioventricular block) that requires medication during the study, interferes with regularity of the study treatment, or is uncontrolled by medications
    j. History of stroke/ TIA < 6 months prior to study enrollment
    k. Significant vascular disease
    l. Symptomatic peripheral vascular disease
    m. Evidence of bleeding diathesis/ coagulopathy with INR > 1.5
    n. Major surgical procedure, open biopsy, significant traumatic injury < 4 weeks prior to enrollment

o. Core biopsy/ other minor surgical procedure, excluding placement of vascular access device < 7 days prior to enrollment
p. History of abdominal fiscula, GI perforation, intra-abdominal abscess < 6 months prior to enrollment
q. Serious, non-healing wound, active peptic ulcer or non-healing bone fracture
r. Proteinuria ≥ 2+ by urine dipstick OR urine protein > 1g by 24-hour urine collection
s. History of other primary tumors within the past 5 years, except adequately controlled limited basal cell or squamous cell skin cancer or carcinoma in situ of the cervix.
t. Presence of frequent vomiting or any other pre-existing medical condition that would preclude swallowing and/or absorption of oral medication.
u. Evidence of any psychological dysfunction, psychiatric disorder, giving reasonable suspicion of a disease or condition that contraindicates the use of therapy, or that may affect patient compliance with study routines, or places the patient at high risk from treatment-related complications.

Treatment Plan:

This protocol will utilize a single arm, phase II design. All patients will receive temozolomide orally at 150 mg/m2 daily on days 1-7 and 15-22 on a 1 week-on, 1

week-off schedule in a 28-day cycle. Bevacizumab will be delivered intravenously at 10 mg/kg on days 8 and 22. Patients will continue on treatment until disease progression, severe toxicity, or if the patient's physician felt that it was not in the patient's best interest to continue. A patient may discontinue treatment for an intercurrent illness that prevented further treatment administration, if the patient decides to withdraw from the study.

The dosing schema and route are illustrated below:

Table 1. Temozolomide-bevacizumab administration schema

REGIMEN DESCRIPTION				
Agent	**Dose**	**Route**	**Schedule**	**Cycle Length**
Temozolomide	150 mg/m^2 in tablets	PO in the a.m.	Days 1-7, 15-21	4 weeks (28 days)
Bevacizumab	5 mg/kg	IV over 90, then 60 minutes	Days 8, 22	

Dose reductions in temozolomide are allowed, and will occur in the following manner:

Table 2. Dose reduction guidelines for temozolomide therapy

Toxicity	**Reduce TMZ by 1 Dose Level**	**Discontinue TMZ**
Absolute Neutrophil Count	< 1.0 x 10^9/L	See below
Platelet Count	< 50 x 10^9/L	See below
CTC non-hematolotical toxicity (except for alopecia, nausea, vomiting)	CTC grade 3	CTC grade 4

Dose Level	Temozolomide Dose (mg/m2/day)	Remarks
-2	75	Second reduction for toxicity
-1	125	Reduction for toxicity
0	150	Initial dose

TMZ is to be discontinued if dose reduction to < 75 mg/m^2 is required or if the same Grade 3 non-hematological toxicity (except for alopecia, nausea, vomiting) recurs after dose reduction. For the treatment of nausea and vomiting associated with temozolomide, patients will be prescribed antiemetic agents as necessary for symptom control. Pain medications will also be prescribed as needed. In the cases of grade 3 or 4 hematological toxicities, the use of hematopoietic growth factors will be determined on an individual case base by the Principle Investigator.

Pretreatment Evaluation:

Evaluation before initiating treatment with temozolomide and bevacizumab will include the following:

- Complete history and physical examination, including documentation of all measurable disease as well as signs, symptoms, concurrent medications, and performance status.
- Laboratory studies: CBC with differential, sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, magnesium, albumin, alkaline phosphatase, total bilirubin, SGOT[AST], SGPT[ALT], PT/PTT, urinalysis, serum pregnancy test (women of childbearing potential).

- 12-lead EKG within 28 days prior to starting treatment.
- Radiologic evaluation of measurable disease
- Optional serum samples for evaluation of angiogenesis-related markers, including but not limited to VEGF, IL-8, IL-12, PIGF, bFGF, PDGF, and hypoxia-inducible factor at the start of treatment.
- Patient must sign IRB-approved informed consent prior to any study-specific procedures unless such procedures are part of the standard of care.

Evaluation During Study:

Evaluation once after initiating treatment will include the following (see also the previous table):

- Physical examination (including vital signs, weight, performance status): before week 1 of each cycle prior to starting the next cycle.
- Labs prior to day 1 1 of each cycle: CBC with differential, sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, magnesium, albumin, alkaline phosphatase, total bilirubin, SGOT [AST], SGPT [ALT]. Urinalysis prior to day 1 of each cycle.
- Radiologic evaluations will be repeated after 2 cycles of treatment. The same radiologic method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

- For the patients who underwent pretreatment serum studies, additional serum will be analyzed during weeks 8-12 of treatment, then at the time of disease progression or at the end of the treatment, whichever is earlier.

Table 3. Study calendar: TMZ-BEV therapy

	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Schedule repeated until an endpoint is met	Off Study[c]
Temozolomide		T		T		T		T		T		T			
Bevacizumab			B		B		B		B		B		B		
Informed consent	X														
Demographics	X														
Medical history	X														
Concurrent meds	X	X----------X													
Physical exam	X	X				X				X					X
Vital signs	X	X				X				X					X
Height	X														
Weight	X	X				X				X					X
Performance status	X	X				X				X					X
CBC w/diff, plts	X	X				X				X					
Serum chemistry[a]	X	X				X				X					
EKG (as indicated)	X														
Adverse event evaluation		X----------X													X
Tumor measurements	X	Tumor measurements are repeated every 8 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease.													X[c]
Radiologic evaluation	X	Radiologic measurements should be performed every 8 weeks.													X[c]
B-HCG	X[b]														

A: *CTEP IND Agent*: Dose as assigned; *administration schedule*
B: *Other Agent(s)*: Dose as assigned*; administration schedule*
a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
b: Serum pregnancy test (women of childbearing potential).
c: Off-study evaluation.

Evaluation of Toxicity

Toxicities will be described according to the NCI-CTCAE Version 4.0. Dose limiting toxicity (DLT) was defined as any grade 3 or 4 non-hematologic toxicity as defined in the NCI CTC v4.0, even if expected and believed related to the study medications

(except nausea and vomiting responsive to appropriate regimens or alopecia), any Grade 4 hematologic toxicity lasting 2 weeks or longer (as defined by the NCI-CTCAE), despite supportive care; any Grade 4 nausea or vomiting > 5 days despite maximum anti-nausea regimens, and any other Grade 3 non-hematologic toxicity including symptoms/signs of vascular leak or cytokine release syndrome; or any severe or life-threatening complication or abnormality not defined in the NCI-CTCAE that is attributable to the therapy.

Criteria for Response

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response, i.e. CR or PR as defined by the Choi criteria.

Response and progression will be evaluated in this study using the Choi criteria. (39) Like the RECIST criteria, changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used to calculate change in size. In addition, changes in CT attenuation coefficient (density) of the tumor will be evaluated in Hounsfield Units (HU). A mean HU for each tumor density will be used to calculate percent changes in CT density. The definition for CR, PR, SD, and PD for Choi criteria for best response assessment is illustrated in Table 4:

Table 4. Summary of the Choi criteria definitions

Response	Definitions
CR	Disapperance of all lesions No new lesions
PR	A decrease in size of ≥ 10% or a decrease in tumor density (HU) ≥ 15% on CT No new lesions No obvious progression of nonmeaserable disease
SD	Does not meet the criteria for CR, PR, or PD No symptomatic deterioration attributed to tumor progression
PD	All increase in tumor size of ≥ 10% and does not meet criteria of PR by tumor by tumor density (HU) on CT New lesions New intratumoral nodules or increase in the size of the existing intratumoral nodules

Response and progression will also be assessed in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee. (38) Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria.

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

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 or progressive disease is objectively documented.

The duration of disease control response (DCR) is measured from the time measurement criteria are met for CR, PR, or SD (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). This will be considered censored if the patient is lost to follow-up or dies of a cause unrelated to the disease under study prior to the ascertainment of progressive disease.

Stable disease (SD) 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. This will be considered censored if the patient is lost to follow-up or dies of a cause unrelated to the disease under study prior to the ascertainment of progressive disease

Time to progression (TTP) is defined as the duration of time from start of treatment to time of disease progression, death secondary to disease or toxicity of treatment, or date of last follow-up. Patients who have not demonstrated progressive disease or have died because of disease or toxicity will be considered censored for this outcome at the last contact.

Criteria for Removal from Study

Patients will be discontinued from treatment on the study for any of the following events:

- Progression of disease per Choi criteria as described previously.
- The development of unacceptable toxicity.
- Physician recommendation for patient removal.
- Patient elects to discontinue further treatment on the study medications.

Statistical Considerations:

Any patient who completes two (2) or more cycles of therapy and demonstrates CR or PR as per the Choi criteria will be considered for evaluation of the primary efficacy endpoint of Choi ORR. Patients who demonstrate CR or PR as assessed by the Choi criteria after cycle 2 and beyond will be considered as "responders" for the purposes of the evaluation rule below. All other response-evaluable patients will be considered "non-responders". Patients who are removed from protocol therapy prior to cycle 2 because of toxicity will be considered non-responders for the purposes of the study endpoint. Patients who are removed from protocol therapy prior to cycle 2 for reasons other than disease progression or toxicity will be replaced.

Any patient who completes at least four cycles of therapy and demonstrates RECIST CR, RECIST PR, or maintains SD through cycle 4 will be considered for evaluation of the primary efficacy endpoint of disease control rate (DCR). Patients who demonstrate RECIST CR, RECIST PR, or maintains SD through cycle 4 will be

considered as “responders”. Patients who experiences PD before the fourth cycle of therapy also will be considered and will be considered as “non-resonders” All other patients will be considered non-responders. Time to progression will be calculated using both the RECIST and the Choi criteria. Time to progression (RECIST) and time to progression (Choi) will then be analyzed according to the responders and the non-responders, as previously defined by each criteria. Kaplan-Meier curves will be constructed for each of the outcome measures. (40)

A minimum of 8 patients and a maximum of 30 patients will be enrolled. We will monitor the trial continuously using Bayesian methodology. Denote the overall response rate (ORR) by p_R and the toxicity rate by p_T. We consider an overall response rate of less than 35% not clinically meaningful and an overall response rate of 50% or greater would warrant further development. Therefore, we assume *a priori* that the ORR has a mean of 0.35 and $p_R \sim$ Beta(0.7, 1.3). The expected toxicity rate is 20% and thus $p_T \sim$ Beta(0.4, 1.6) which has a mean of 0.2. A toxicity rate of 30% or greater is considered unacceptable. We will stop the trial for lack of activity if $Pr(p_R < 0.5 \mid \text{data}) < 0.99$. That is, if it is very unlikely that we have reached the target response rate of 50% then we will stop the trial for lack of activity. We will stop the trial for excessive toxicity if $Pr(p_T > 0.3 \mid \text{data}) > 0.8$. The resulting stopping rules are provided in Tables 5 and 6.

In order to obtain the design’s operating characteristics the trial was simulated and the results are provided in Table 7. The goal of the design is to have a high likelihood of stopping when a drug is too toxicity or has a low ORR. The scenarios listed in red indicated that the drug is either too toxic or has a lack of

activity. In scenario 1, the ORR is 60% and the toxicity is 20% and there is only at 10% chance that we will incorrectly stop the trial. However, in scenario 6 the ORR is 25% and the toxicity rate is 30% and due to the lace of activity and unacceptable toxicity rate the trial is stopped early 88% of the time and on average 15 patients are enrolled. In general, the lower the ORR or the higher the toxicity rate the more likely it is that the trial will be stopped early.

Table 5: Response stopping boundaries

The following are less-than-or-equal boundaries: a pair (n, m) means to stop if the number of responses after treating m patients is less than or equal to n.

n (# responses)	m (# patients)
0	8
1	9
2	12
3	15
4	18
5	20
6	23
7	26
8	28
9	30

Table 6: Toxicity stopping boundaries

The following are greater-than-or-equal boundaries: a pair (n, m) means to stop if the number of toxicities after treating m patients is greater than or equal to n.

n (# toxicities)	m (# patients)
8	8
7	8
6	8
5	8
4	8
5	10
6	12
6	13
7	15
7	16
8	18
8	19
9	21
9	22
10	24
10	25
11	27
11	28
12	30

Table 7: TMZ-BEV study: simulation results

Response rates in bold have indicate scenarios where the ORR has failed to reach an acceptable level and true toxicity rates in red indicate scenarios where the toxicity rate is too high.

Scenario	True p_R	True p_T	Pr (Stop Early)	Avg. # Pts.	Avg. # of Responses	Avg. # Toxicity	Avg. Trial Duration (Months)
1	0.60	0.20	0.09	28	17	6	21.2
2	0.50	0.20	0.14	28	14	6	20.9
3	0.50	**0.30**	0.40	23	11	7	17.7
4	**0.35**	0.20	0.47	23	8	5	17.7
5	**0.35**	**0.30**	0.63	20	7	6	15.3
6	**0.25**	**0.30**	0.88	15	4	5	8.4
7	**0.20**	**0.30**	0.96	13	3	4	7.1

Chapter 3

RESULTS

AIM 1: To estimate the overall response rate (ORR) and progression-free survival (PFS) of advanced HPC/SFT patients who were treated systemic chemotherapy, especially those with doxorubicin-based, gemcitabine-based or paclitaxel-based chemotherapy

Patient and Disease Characteristics

Five hundred and fifty-three patients with the diagnosis of HPC/SFT whose pathology specimens were evaluated that The University of Texas MD Anderson Cancer Center between January 1993 to June 2007 were identified. They were then evaluated for available clinical medical records at MD Anderson. Four hundred twenty-three patients were excluded, and the remaining 128 patients were analyzed. (Figure 1) The patients' characteristics are summarized in Table 8. Patients were analyzed based on the disease status at which they first presented at MD Anderson. Patient characteristics of all patients who presented with primary localized HPC/SFT are summarized in Table 9. Patient characteristics of all patients who presented with locally recurrent and/or metastatic HPC/SFT are summarized in Table 13.

Figure 1. Evaluation schema for identification of evaluable HPC/SFT patients

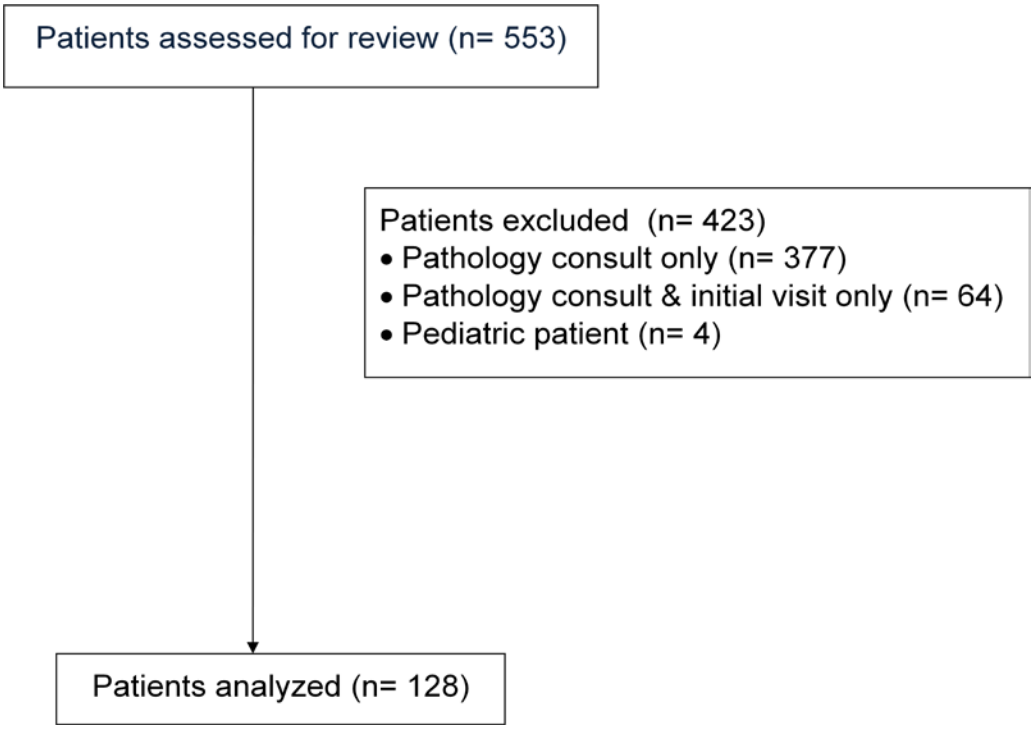


Table 8. HPC/SFT patient characteristics: all patients

Characteristic	**(N=128)**	**(%)**
Age at First MDACC registration		
median	54 years	
range	19 – 88 years	
Gender		
male	71	55.5
female	47	44.5
Ethnicity		
White	101	78.9
Hispanic	17	13.3
Black	4	3.1
Asian	6	4.7
Primary tumor site		
CNS/meninges	39	30.5
Head/neck	13	10.2
lung/pleura	17	13.3
Abdomen/pelvis	36	28.1
Extremities	15	11.7
Other	6	4.7

HPC/SFT – Primary Localized Disease

Seventy-nine patients who presented to MD Anderson with primary localized disease were analyzed. Consistent with reports in the literature, the sites of primary disease were divided evenly throughout diverse body sites, with the abdominopelvic cavity as the most common site. Almost all patients received surgical resection as their initial therapy. For the seventy-two patients who received surgery, most patients had gross total resection (GTR) of their primary disease. Thirty-six (46%) patients also received additional radiation therapy either as neoadjuvant or adjuvant therapy. Ten (13%) patients also received chemotherapy either in neoadjuvant or adjuvant fasion. For the seven patients who were not deemed surgically resectable, they received palliative radiation therapy (n=1), chemotherapy (n=1), or both (n=5). The treatment histories are summarized in Table 10.

Table 9. HPC/SFT patient characteristics: primary localized HPC/SFT

Variable	Median (range)	N (%)
N		**79**
Age	51 (19 - 86)	
Sex		
Male		34 (43)
Female		45 (57)
Primary Tumor Site		
CNS/meninges		20 (25)
Head and Neck		12 (15)
Lung/Pleura		10 (13)
Abodmen/Pelvis		23 (29)
Extremities		12 (15)
Other		2 (3)

Table 10. Treatment: primary localized HPC/SFT

	N = 79	%
Initial Treatment - surgery		
No	7	9
Yes	72	91
Complete resection		
GTR	26	33
R0	37	47
R1	6	7
Incomplete resection (R2)	3	4
Unknown	7	9
Initial Treatment - Radiation Therapy		
Neoadjuvant Rx	14	18
Adjuvant Rx	22	28
Initial Treatment - Chemotherapy		
Neoadjuvant Rx	8	10
Adjuvant Rx	2	3

The majority of the HPC/SFT patients had a favorable clinical course, similar to previously described cases in the literature. (Table 11) The median follow-up period for the cohort following surgical resection was 45.4 months (range, 0.1 – 198.8 months). Fifty-three (67%) patients were recurrence-free at the time of this analysis. Median recurrence free survival for the cohort was 126 months, or 10.5 years (Figure 2) Univariate analysis showed that age and tumor size were the only significant variables for predicting recurrence-free survival (RFS). (Table 12)

Table 11. Clinical outcome: primary localized HPC/SFT

	N = 79	%
Disease recurrence (for resected pts)		
Yes		
Local	12	15
Metastatic	13	16
Local & Metastatic	3	4
No		
Median Recurrence Free Survival (months)	126	
Median Overall survival (months)	155	

Figure 2. Recurrence-free survival curve: primary Localized HPC/SFT

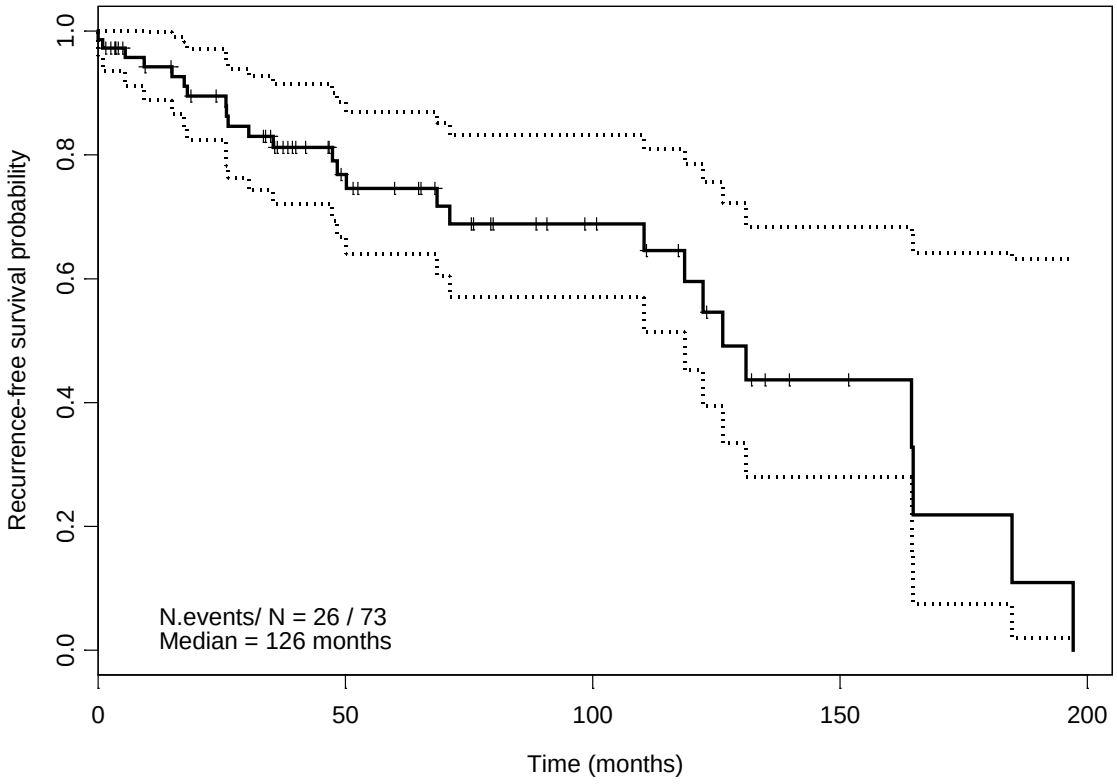


Table 12. Univariate analysis for RFS: Primary localized HPC/SFT

Variable	Coefficient	SE	Hazard Ratio	P-value
Age	0.03	0.01	1.03	**0.02**
Gender = Male (vs. Female)	-0.41	0.41	0.66	0.31
Tumor size (cm)	0.07	0.02	1.07	**0.002**
Tumor site = Extremities (vs. others)	-1.72	1.03	0.18	0.10
Tumor site = CNS (vs. others)	-0.37	0.49	0.69	0.45
Tumor site = Head & Neck (vs. others)	-1.18	0.76	0.31	0.12
Type of resection = R2 or unkonwn (vs. R0/R1/GTR)	0.20	1.04	1.23	0.85

HPC/SFT – Locally Recurrent and Metastatic Disease

The patient characteristics of the 49 HPC/SFT patients who presented to MD Anderson with locally recurrent and/or metastatic disease are summarized in Table 13. The most common site of metastases was liver (n=15), followed by bone (n=12) and lung (n=8). Surgical resection remained the initial treatment of choice for the majority of the patients, and the many of them were able to undergo successful surgical resection. The use of additional treatment modalities, i.e. radiation therapy and/r chemotherapy were noted more frequently, with 43% of patients undergoing systemic therapy either as adjuvant or neoadjuvant fashion. Despite these treatment, however, the duration of remission after their initial management at MD Anderson was relatively short, with the median PFS of 18 months. (Figure 3) Many patients subsequently underwent many additional courses of various therapies including additional surgical resection, radiation therapy, and/or systemic therapy, which is reflected by the relatively long median overall survival of 55 months (Figure 4), from the time of their initial treatment at MD Anderson.

Table 13. HPC/SFT patient characteristics: locally recurrent and metastatic HPC/SFT

HPC/SFT

	N = 49	%
Age at First MDACC Registration		
Median	56	
Range	19 - 76	
Sex		
male	25	51
female	24	49
Primary tumor site		
CNS/meninges	19	40
Head & Neck	1	2
Lung/pleura	7	15
Abodmen/pelvis	13	28
Extremities	3	6
Other	4	8
Locally Recurrent Disease	19	39
Metastatic Dieseas		
lung	8	16
liver	15	31
bone	12	24
Other	8	16

Table 14. Treatment: locally recurrent and metastatic HPC/SFT

	N = 49	**%**
Surgery		
Curative Intent		
complete resection (R0/R1/GTR/unknown)	43	87
Incomplete resection (R2)	6	13
Radiation Therapy		
Adjuvant/Neoadjuvant Rx	9	18
Palliative	2	4
Chemotherapy		
Adjuvant/Neoadjuvant Rx	21	43
Palliative	0	0
Median progression-free survival	18 months	

Figure 3. Progression-free survival curve from time of treatment: locally recurrent and metastatic HPC/SFT

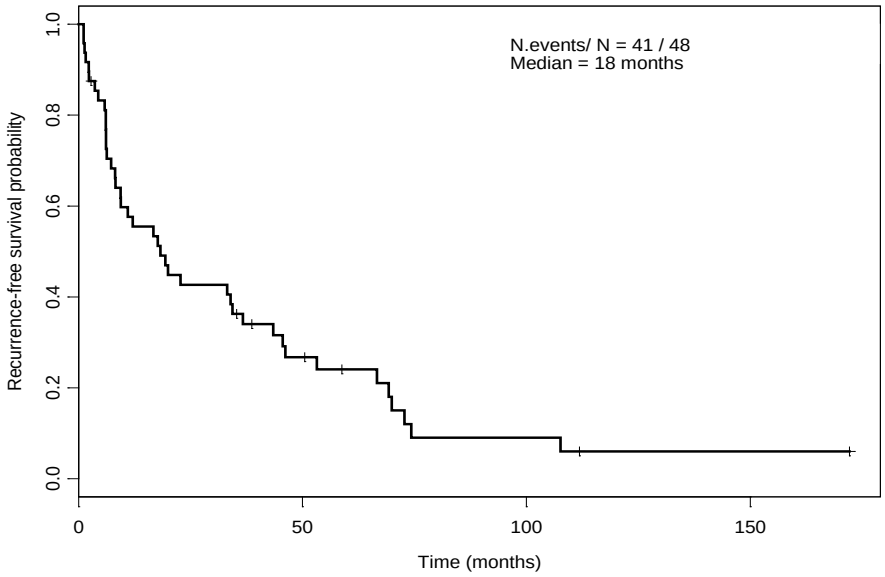
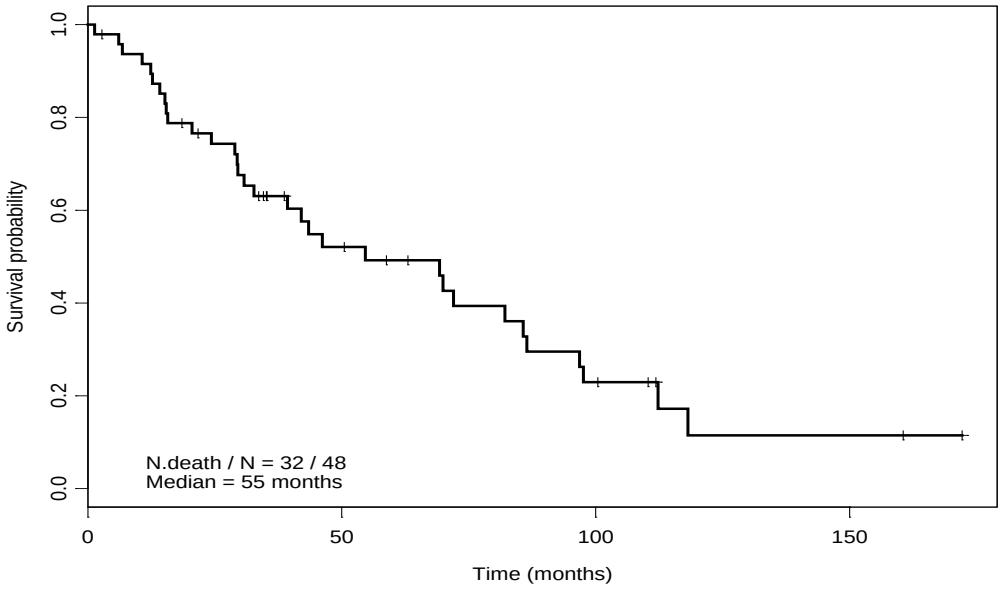


Figure 4. Overall survival from time of treatment: locally recurrent and metastatic HPC/SFT



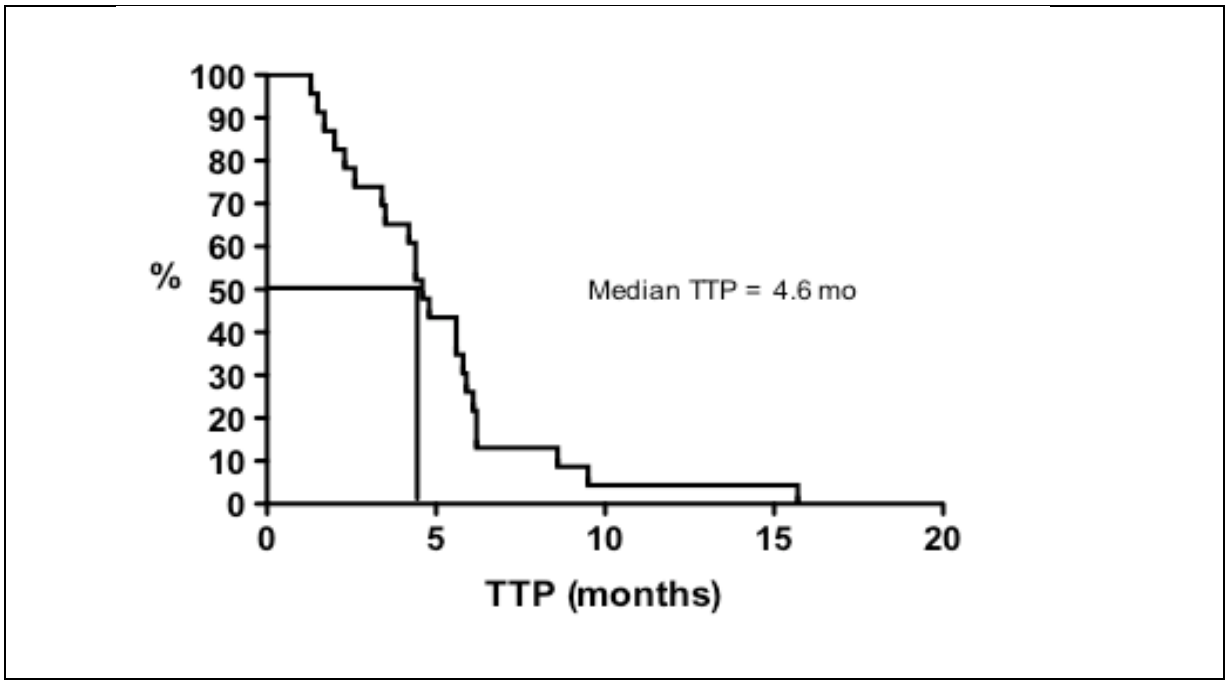
Systemic chemotherapy in primary unresectable, locally recurrent, and/or metastatic HPC/SFT

Thirty-eight patients with gross, measurable disease received systemic chemotherapy for the management of advanced disease. The majority of the patients had these that were deemed surgically unresectable, while 4 patients had advanced disease that were potentially surgical resectable who received chemotherapy in a neoadjuvant fashion to best reduce the size of tumors prior to surgery. Fifteen patients received Adriamycin-based chemotherapy; 4 patients received gemcitabine-based chemotherapy, while 4 patients received paclitaxel therapy. All received therapy either in the first- or second-line setting. Their responses to therapy, reason for discontinuation of therapy and time to progression (TTP) are summarized in Table 15 and Figure 5. The median PFS for the systemic chemotherapy cohort was 4.6 months (range, 1.3 - 15.7). For the 14 patients who received combination therapy of temozolomide and bevaciuamb, their patient characteristics and clinical outcome are described in detail in Aim 2.

Table 15. Systemic therapy in advanced HPC/SFT

Characteristic	(N=23)	(%)
Chemotherapy		
Adriamycin-based Rx	15	52
Adriamycin + ifosfamide	12	
Adriamycin + DTIC	1	
Adriamycin + cisplatin	1	
Adriamycin	1	
Gemcitabine-based Rx	4	14
Gemcitabine + Docetaxel	1	
Gemcitabine	3	
Paclitaxel	4	14
Stage		
Primary locally advanced	3	13
Locally recurrent	1	4
Metastatic	19	83
Line of Therapy		
First-line	18	78
Second-line	5	22
Number of cycles given		
Median	4	
Range	2-10	
Reason for Stopping Therapy		
Disease Progression	11	48
Toxicities	5	22
Treatment break	3	13
Surgical consolidation	3	13
XRT consolidation	1	4
Best Response (RECIST)		
CR/PR	0	0
SD	19	86
PD	4	14
Time-to-progression		
Median	4.6	
Range	1.3-15.7	

Figure 5. Time-to-progression curve: systemic therapy in advanced HPC/SFT



AIM 2: To describe the activity of TMZ-BEV therapy in advanced HPC/SFT and identify potential clinicopathological factor(s) that correlate with response to therapy and outcome

Patient and Disease Characteristics

Sixteen patients with advanced, recurrent, or metastatic HPC/SFT who received temozolomide-bevacizumab therapy between May 2005 and June 2007 were identified. Two patients for whom radiologic scans were missing were excluded from the analysis. The remaining 14 patients' characteristics are summarized in Table 8. All 14 patients (9 men, 5 women) were white, and the median age was 59 years (range, 44 – 75 years). Ten patients (71%) had HPC and 4 patients (29%) had SFT. The most common site of primary disease was the meninges (n=6). Seven patients had metastatic disease when they began temozolomide-bevacizumab therapy, while the remaining patients had either primary or locally recurrent disease deemed surgically unresectable.

The majority of the patients (86%) had received prior therapy before starting treatment with temozolomide and bevacizumab (Table 8). Five patients had received prior systemic therapy (Table 9). Their best responses to each prior regimen were re-assessed using the Choi criteria. They had often achieved SD and improvement in their symptoms with the previous regimens, but none had achieved Choi PR. The main reasons for starting temozolomide-bevacizumab therapy included symptomatic disease, neoadjuvant treatment to potentially downstage the tumor and enable surgical resection, and disease progression after prior therapy.

Table 16. TMZ-BEV therapy: patient and disease characteristics

Characteristic	(N=14)	(%)
Age		
median	59 years	
range	44 – 75 years	
Gender		
male	9	64.3
female	5	35.7
Ethnicity		
white	14	100
Diagnosis		
HPC	10	71.4
SFT	4	28.6
Primary tumor site		
meninges	6	42.9
lung/pleura	3	21.4
pelvis	3	21.4
abdominal wall	1	7.1
gluteal region	1	7.1
Tumor classification at diagnosis		
benign	3	21.4
malignant	5	35.7
unknown	6	42.9
Metastatic disease		
no	7	50.0
yes	7	50.0
Prior therapy		
no	2	14.3
yes	12	85.7
Number of prior surgeries		
0	4	28.6
1	3	21.4
2	3	21.4
3	2	14.3
4	1	7.1
6	1	7.1
Prior radiation therapy		
no	7	50.0
yes	7	50.0
Number of prior systemic therapies		
0	9	64.3
1	1	7.1
2	1	7.1
3	1	7.1
4	1	7.1
5	1	7.1

Abbreviations: HPC, hemangiopericytoma; SFT, solitary fibrous tumor.

Table 17. TMZ-BEV therapy: patients' prior systemic therapy history

Tumor	Prior regimen(s)	Duration of therapy (months)	Best response (Choi)	Reason for stopping therapy
SFT	Gemcitabine-docetaxel	2	PD	Disease progression
SFT	Gemcitabine-docetaxel	1	PD	Disease progression
	Doxorubicin-dacarbazine	3	SD	Disease progression
HPC	Imatinib	5	SD	Disease progression
	Imatinib-thalidomide	1	PD	Disease progression
	Imatinib-thalidomide-etoposide	1	SD	Toxicities
				Patient intolerance
	Imatinib-thalidomide-hydrea	7	SD	Disease progression
	Imatinib-hydrea	2.5	SD	Disease progression
HPC	Celecoxib*	14	SD*	Disease recurrence
	Imatinib	2	PD	Disease progression
	Paclitaxel*	6	SD*	Physician decision
	Gemcitabine-docetaxel	3	SD	Disease progression
HPC	Endostatin	7	PD	Disease progression
				Toxicities
	Paclitaxel	8	SD	Disease progression
	Gemcitabine	8	SD	Disease progression

* Received regimen as adjuvant therapy after R0 resection.

Treatment

All patients received temozolomide 150 mg/m^2 orally on days 1-7 and days 15-21, and bevacizumab 5 mg/kg intravenously on day 8 and day 22 on a 28-day cycle. The median number of cycles given was 7.5 (range 2.5-27). Four patients required temozolomide dose modifications or treatment delay because of neutropenia (n=1) or thrombocytopenia (n=3), and one of them received granulocyte colony-stimulating factor support.

Clinical Outcome

The overall response rate was 79% (11 patients, 95% CI 49.2%-95.3%). All 11 patients who responded had Choi PR (Table 10). Two patients (14%) achieved Choi SD, and Choi PD was the best response in 1 patient (7%).

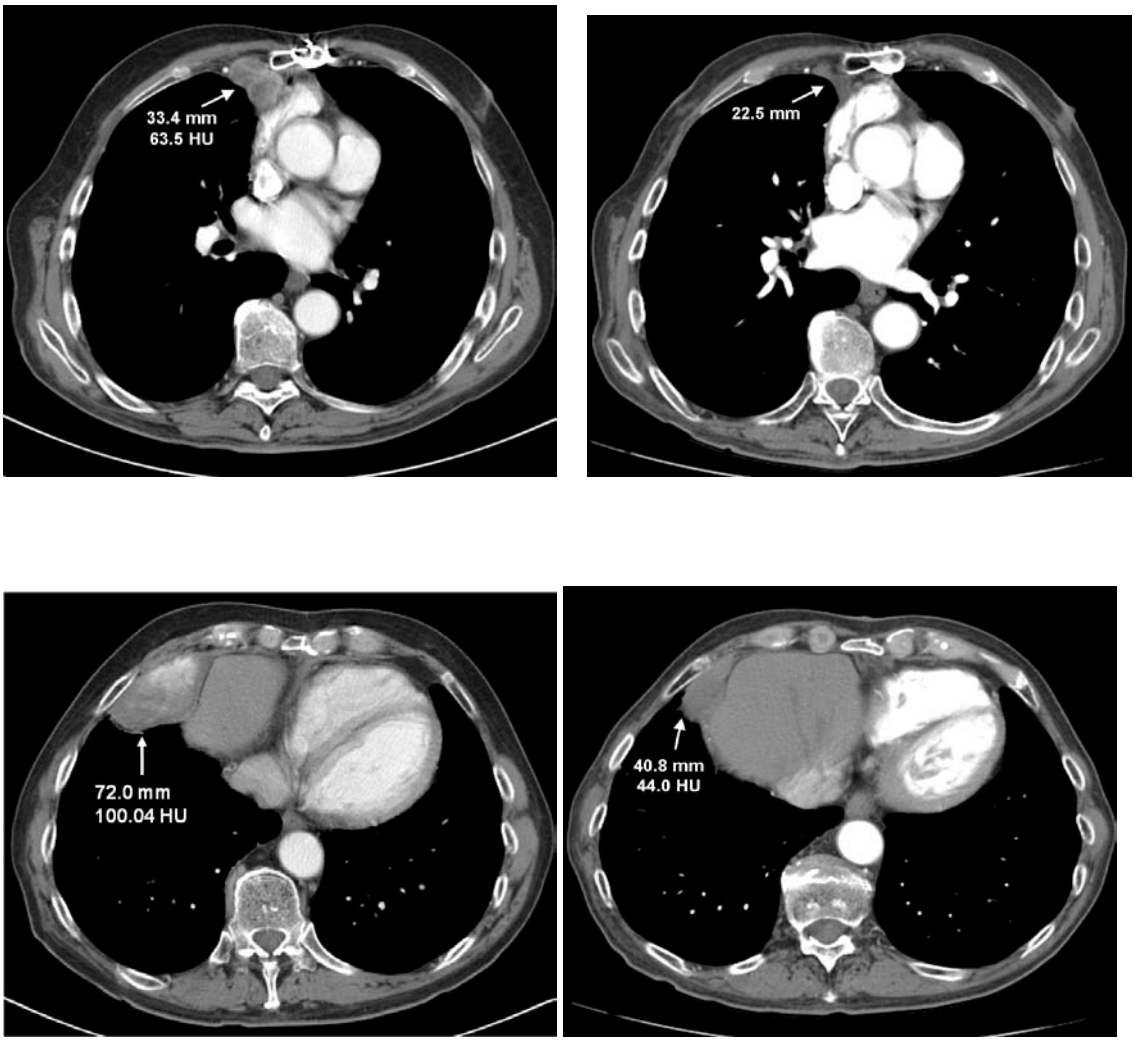
Response was observed as a decrease in size (n=1), in density (n=3), or in both (n=7). (Figure 1) Ten patients (71%) demonstrated some degree of tumor shrinkage; their median tumor size change was -10.1% (range -56.2%-15.5%). Ten patients (71%) demonstrated at least a 15% reduction in tumor density, and the median percent change in density was -26.2% (range -67.6%-5.4%). For the patients who demonstrated a Choi PR, response was seen early during treatment, with all patients achieving PR after 2 to 4 cycles; the median time to response was 2.5 months (range 1.6-4.7 months). For the seven patients who had symptomatic disease at the time of starting therapy, six achieved Choi PRs, which were seen with improvements in their symptoms.

Table 18. Overall response to TMZ and BEV

Patient	Tumor	Maximum change in tumor size (%)	Maximum change in density (%)	Best response (Choi)			Best response (RECIST)
1	HPC	-56.2	-41.3	PR	↓Size	↓HU	PR
2	SFT	-42.1	-67.6	PR	↓Size	↓HU	PR
3	SFT	-26.7	-16.2	PR	↓Size	↓HU	SD
4	HPC	-19.5	-19.1	PR	↓Size	↓HU	SD
5	HPC	-18.5	-39.4	PR	↓Size	↓HU	SD
6	SFT	-13.7	-83.1	PR	↓Size	↓HU	SD
7	SFT	-6.5	-23.7	PR	↓Size	↓HU	SD
8	HPC	-26.9	N/A*	PR	↓Size		SD
9	HPC	-6.1	-28.7	PR		↓HU	SD
10	HPC	-3.4	-60.5	PR		↓HU	SD
11	HPC	4.9	-15.5	PR		↓HU	SD
12	HPC	0	N/A*	SD			SD
13	HPC	4.6	4.4	SD			SD
14	HPC	15.5	5.4	PD			SD
Median		-10.1	-26.2				

Abbreviations: HPC, hemangiopericytoma; SFT, solitary fibrous tumor; PR, partial response; SD, stable disease; PD, progressive disease; HU, Hounsfield units.
* Response assessment done with MRI; unable to measure density changes.

Figure 6. CT images demonstrating a Choi PR to TMZ and BEV in a patient with recurrent, unresectable SFT of pleura. Left, images show baseline disease at the start of therapy. Right, images show the decrease in size and density of disease after 27 cycles of treatment.



The overall response rate was also calculated using the RECIST criteria. Two patients (14%) achieved a RECIST PR (95% CI 1.8%-42.8%). The remaining 12 patients all achieved RECIST SD, with 11 patients (79%) demonstrating RECIST

SD for more than 4 months (95% CI 49.2%-95.3%). No statistically significant associations were found between response and any patient or tumor characteristics, including primary tumor location (meningeal vs. non-meningeal) and primary tumor histologic classification (benign vs. malignant vs. unknown).

At the time of analysis, the median follow-up was 34 months. The median Choi PFS was 9.67 months (95% CI 7.31 months-not estimable), and the proportion of patients who were progression-free at 6 months was 78.6% (Figure 7). The median RECIST PFS was 10.8 months (95% CI 8.13 months-not estimable) (Figure 8), and the 6-month PFS was 92.9%. To date, 5 patients are alive and 4 (28.6%) of them remain progression-free. Ten (71.4%) patients had ultimately had PD or had died. The median OS was estimated at 24.3 months.

Figure 7. Kaplan-Meier estimates for progression-free survival (PFS) (Choi criteria).

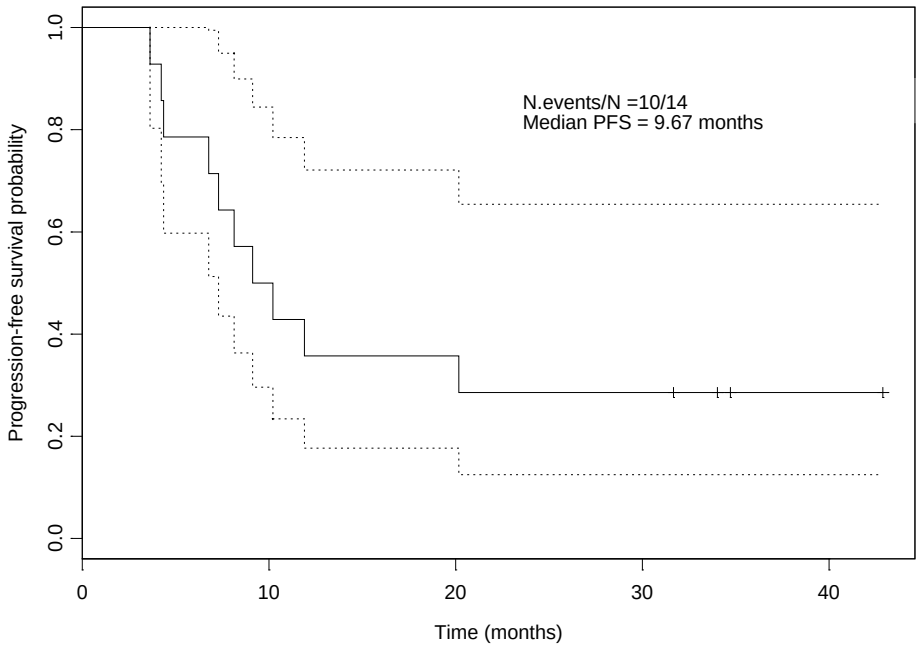
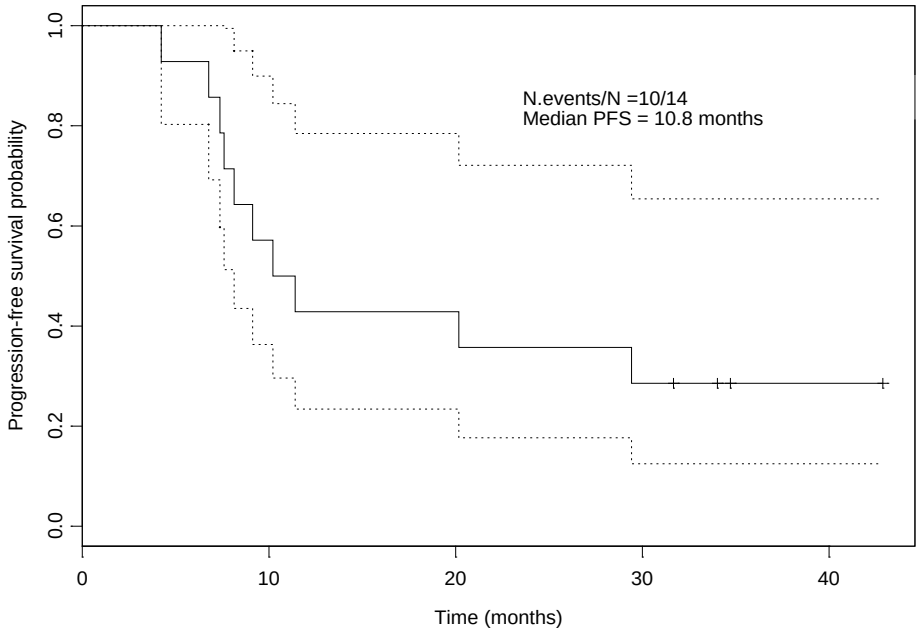


Figure 8. Kaplan-Meier estimates for progression-free survival (PFS) (RECIST).



Toxicity

Treatment was generally well tolerated, but because it was not administered in a clinical trial setting, toxicity data were not recorded systematically. The most notable toxic effect was myelosuppression, with neutropenia and thrombocytopenia requiring treatment modifications and/or delays in 4 patients. Fever, chills, fatigue, nausea, and headache were also noted.

One patient developed a pulmonary infiltrate after 20.5 cycles of temozolomide-bevacizumab therapy, at which point therapy was withheld. A follow-up chest CT study 6 weeks later showed a persistent lung nodule. A biopsy of the lesion showed inflammation and the cultures were positive for Cryptococcus. The

patient was successfully treated with oral fluconazole, and the infection subsequently resolved.

One patient died during treatment. The 48-year-old woman with a recurrent HPC tumor adjacent to the cervical spine had undergone 3 prior surgeries and radiation therapy. On day 11 of cycle 4 of temozolomide-bevacizumab therapy, she was admitted to the hospital with *Staphylococcus aureus* bacteremia secondary to infected hardware in her cervical spine. She was treated with intravenous antibiotics and the bacteremia resolved. She received 2 additional cycles of treatment but was admitted again on day 7 of cycle 6 with renal failure, altered mental status, and hypotension. She died the following day.

AIM 3: To design a prospective phase II trial to determine the efficacy of TMZ-BEV regimen in locally advanced, recurrent, and metastatic HPC/SFT.

The concept of this protocol was submitted to Sarcoma Alliance for Research and Collaboration (SARC) consortium as a potential multi-institutional trial. The concept has been accepted for submission for a full protocol proposal. The final version of the protocol (the most recent version appears on the Appendix B) will be submitted to SARC. Funding is being sought through Schering and/or Genentech.

Chapter 4

DISCUSSION

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Currently, the combination of doxorubicin and ifosfamide is the standard systemic chemotherapy regimen for many subtypes of soft tissue sarcoma. Gemcitabine combined with docetaxel has also emerged as a good therapeutic choice for these patients. Although cases of HPC/SFT responding to these chemotherapeutic agents have been sporadically reported,(10, 16-18, 41, 42) no systematic review or clinical trial to date has identified an effective systemic regimen for unresectable HPC/SFT.

To better understand the impact of temozolomide and bevacizumab in HPC/SFT, we decided to expand our examination of the historical HPC/SFT cohort of patients who had received standard-of-care systemic chemotherapy. Thus in this largest retrospective study of advanced HPC/SFT patients to date, we show that for patients who are not candidates for surgical resection, systemic chemotherapy is only minimally effective for the majority of the patients. Most patients did not achieve objective radiologic response to chemotherapy, and many progressed early on during treatment, as evidenced by the modest median PFS of 4.6 months. The type of chemotherapy administered did not appear to make a difference in response or PFS, although the small number of patients examined limits us from drawing any more definitive conclusions.

In addition, the review of our temozolomide and bevacizumab HPC/SFT patients' prior systemic chemotherapy regimens showed that doxorubicin,

gemcitabine-docetaxel, and paclitaxel did not produce a radiologic response in any of the 5 patients. Since their responses had been initially determined by RECIST, we retrospectively re-assessed their responses using the Choi criteria, and concluded that none of the patients had achieved a Choi PR to prior therapy, but all 5 had a PR to temozolomide and bevacizumab.

The activity of temozolomide and bevacizumab in advanced HPC/SFT observed in this retrospective review, therefore, seems to be much more favorable than that with standard chemotherapy regimens. In patients with locally advanced, recurrent, or metastatic HPC/SFT who were treated with temozolomide and bevacizumab, reductions in tumor size and/or density consistent with PRs as assessed by the Choi criteria were evident in most patients. Several patients also demonstrated long periods of freedom from disease progression, with 5 patients having a time-to-progression period of ≥20 months. Our study has the typical limitations of a retrospective analysis, including the possibilities of patient selection bias and observer bias, a small sample size, and the lack of a systematic, comprehensive recording of toxicities. Nevertheless, the degree of radiologic responses and the long duration of PFS observed in out patients appear superior to those observed in historical studies with chemotherapy regimens, as well as our own cohort of patients as described in Aim 1.

Several studies have demonstrated that RECIST may be insensitive for evaluating response in gastrointestinal stromal tumor (GIST) patients treated with imatinib and the Choi criteria have recently emerged as a more sensitive tool for assessing the degree of tumor necrosis in response to therapy in that setting.(39,

43) Other soft tissue sarcomas, treated with cytotoxic or biologic therapies, display similar patterns of response as GIST treated with imatinib, with patients exhibiting long time-to-progression periods despite a lack of significant reduction in their tumor size.(44, 45) Therefore, we chose to use the Choi criteria to assess the activity of temozolomide and bevacizumab in HPC/SFT, because we believed that a Choi response is more reliable for predicting potential therapeutic benefit than a RECIST response is. Using the Choi criteria, one can detect response – or lack of response – early in the course of treatment and thereby quickly identify potential non-responders who may benefit from switching to another therapy. In addition, because the Choi criteria for PD are more stringent than RECIST (≥10% increase in tumor size), failure of therapy may also be detected earlier. This earlier detection explains the shorter median PFS we found when using the Choi criteria than when using RECIST.

Due to the limitations of the radiologic study archival techniques for our historical chemotherapy cohort, we were not able to obtain Choi response rates for the majority of the patients. Although it is theoretically possible that some of the patients who had RECIST SD could have achieved Choi PR, the difference in PFS (RECIST) – 4.6 months vs 9.3 months -- suggests that chemotherapy may indeed be inferior to temozolomide and bevacizumab. The strength of our assertions are limited by the small sample size, which does not allow us to show statistical significance between these two groups.

Although toxicity data were not systematically gathered for the temozolomide-bevacizumab cohort, all available clinic notes and laboratory values

were thoroughly reviewed to capture as many side effects as possible. The majority of the patients did not exhibit significant complications while receiving treatment as scheduled. We did not note any serious side effects (e.g. thromboembolic events, cardiac toxicity, or gastrointestinal bleeding) associated with bevacizumab,. Although one patient died during treatment, we found no definitive evidence that temozolomide and/or bevacizumab directly contributed to the immediate factors that resulted in her death. Rather, the patient's treating physician believed that her overall poor performance status most likely led to her death.

Our patients on temozolomide-bevacizumab received a wide range of number of doses of therapy. Most patients received treatment until PD or intolerable side effects developed, but a few patients were empirically given treatment breaks because of patient or physician preferences. It is difficult to conclude, based on the sample size, how long temozolomide-bevacizumab therapy should be continued or whether it could be interrupted and resumed without significantly reducing the therapeutic benefit. Also unclear is the potential additional benefit of radiation therapy. Three patients with isolated sites of disease had received radiation therapy within 4 months before or after temozolomide and bevacizumab. All had achieved Choi PR after with their first treatment modality. Two patients were still responding when they initiated their second treatment modality, while one was exhibiting tumor re-growth. Despite having discontinued their last treatment 18-23 months prior to the time of our analysis, all three continue to show a long, durable maintenance of their responses, with PFS of 34-43 months to date. Further information regarding

the potential synergistic effect of temozolomide-bevacizumab therapy and radiation is needed to confirm this encouraging finding.

The exact mechanisms by which temozolomide and bevacizumab exert their effect on HPC/SFT remain to be determined. Further studies will be needed to better elucidate the key therapeutic targets in HPC/SFT. Analysis of our patients' available tumor specimens for potential molecular correlative factors is currently under development.

Chapter 5

Potential Pitfalls, Summary and Future Directions

Potential Pitfalls

As discussed previously, our study contains all the typical limitations of a retrospective review, including the possibilities of patient selection bias and observer bias, a relatively small sample size, and the lack of a systematic, comprehensive recording of toxicities. In our retrospective review of our institution's experience of all HPC/SFT patients, despite representing the largest published series in the current literature, we are still limited in our abilities to draw firm statistically significant conclusions in several clinical variables. This illustrates the fact that HPC/SFT is a frustratingly heterogeneous clinical entity and remains a challenge to those who wish to inconclusively define its natural history, prognosis, and optimal treatment.

Our patient population had a higher proportion of patients who either presented with or developed advanced disease, reflecting the referral bias to our highly specialized cancer center. Patients who could not follow up after their initial evaluation were also excluded, thus potentially creating another patient selection bias. For the patients treated with temozolomide and bevacizumab, our findings are limited by a relatively small sample size. Although the TMZ-BEV patient cohort represent the consecutive series of patients with advanced HPC/SFT encountered at MD Anderson, potential patient selection bias certainly exist.

The lack of toxicities attributed to bevacizumab observed in this group may be because of the small sample size. The true toxicity profile of this regimen may in fact be greater than described here. Our phase II trial design, therefore, will specifically address this issue by making safety an independent primary endpoint.

Summary and Future Directions

To our knowledge, our report nevertheless represents the largest published series of patients with advanced HPC/SFT treated with systemic chemotherapy to date. We found that the combination of temozolomide and bevacizumab had a remarkably high rate of overall response and a favorable duration of disease control. For these rare sarcoma subtypes that lack a well-established systemic therapeutic option, temozolomide-bevacizumab is a promising therapeutic regimen that warrants further investigation.

The precise mechanisms by which temozolomide and bevacizumab exert their effect on HPC/SFT are not clear. Bevacizumab has been previously combined with chemotherapeutic agents to increase vascular permeability, leading to subsequent synergistic cytotoxicity. Temozolomide's activity on soft tissue sarcomas as a single agent, although not specifically evaluated in HPC/SFT, has not been robust. (27) Bevacizumab may enhance temozlomide's cytotoxic activity or may play an anti-angiogenic role by modulating the VEGF signaling pathway. There is evidence, however, that temozolomide may possess intrinsic antiangiogenic properties. Bevacizumab, when combined with temozolomide, may also play a synergistic role in its antiangiogenic effect. (46) The VEGF-VEGFR

pathway, which plays a key mediator role in angiogenesis, has recently emerged as the key therapeutic target in HPC/SFT. The anti-VEGF receptor tyrosine kinase inhibitors sorafenib and sunitinib were recently reported to produce Choi responses and disease stabilization for up to 22 months in HPC/SFT patients. (23, 24, 47) These examples also provide additional evidence that antiangiogenic approaches to targeting HPC/SFT is a rational one. For future studies, correlative studies consisting of deep sequencing analysis, tissue microarrays examining patterns of alterations in key antiangiogenic pathways, as well as serum angiogenic and cytokine profiles may determine the effects by which this regimen may exert its effects on HPC/SFT.

Our encouraging results should be validated in a prospective trial, which would also allow additional insight into the efficacy, safety, and biologic mechanisms of temozolomide and bevacizumab in HPC/SFT. We have therefore designed a single-arm phase II study which will prospectively address the true role of temozolomide and bevacizumab. It will also be the first study dedicated solely to this rare subtype, which will also allow us to gather information specific to the biology of HPC/SFT. We hope that this study will not only provide a potential new therapy for HPC/SFT, but also provide invaluable insight regarding the biological drivers of this disease entity and additional potential therapeutic targets.

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Min S. Park, MD was born in Seoul, South Korea on February 8, 1976. After completing high school at Council Rock High School in Newtown, PA in 1995, she entered Harvard and Radcliffe Colleges in Cambridge, MA. She graduated in 1999 with a Bachelor of Arts degree with magna cum laude honors in Cognitive Neuroscience, a Joint degree in Psychology and Biology. She attended the University of Pennsylvania School of Medicine in Philadelphia, PA, and received her medical doctorate degree in 2003. Dr. Park completed her internal medicine residency at the Hospital of the University of Pennsylvania in Philadelphia, PA from 2003 to 2006. She then spent a year at the University of Pennsylvania School of Medicine under the mentorship of Marcia S. Brose, MD, PhD as a postdoctoral research fellow in the Department of Otorhinolaryngology from 2006 to 2007. She then completed her medical oncology fellowship at the University of Texas MD Anderson Cancer Center in Houston, Texas from 2007 to 2010. In 2008, she entered the University of Texas Health Science Center at the Houston Graduate School of Biomedical Sciences.