Tumor Ablation in Metastatic Sarcoma Stable on Chemotherapy

Washington University School of Medicine
Division of Oncology
660 South Euclid Avenue, Campus Box 8056
St. Louis, MO 63110

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Principal Investigator: Brian A. Van Tine, M.D., Ph.D.
Phone: (314) 362-5817
E-mail: bvantine@wustl.edu

Sub-Investigators	**Modality**
Angela Hirbe, M.D.	Medical Oncology
Jack Jennings, M.D.	Radiology
Ling Chen, Ph.D.	Biostatistics

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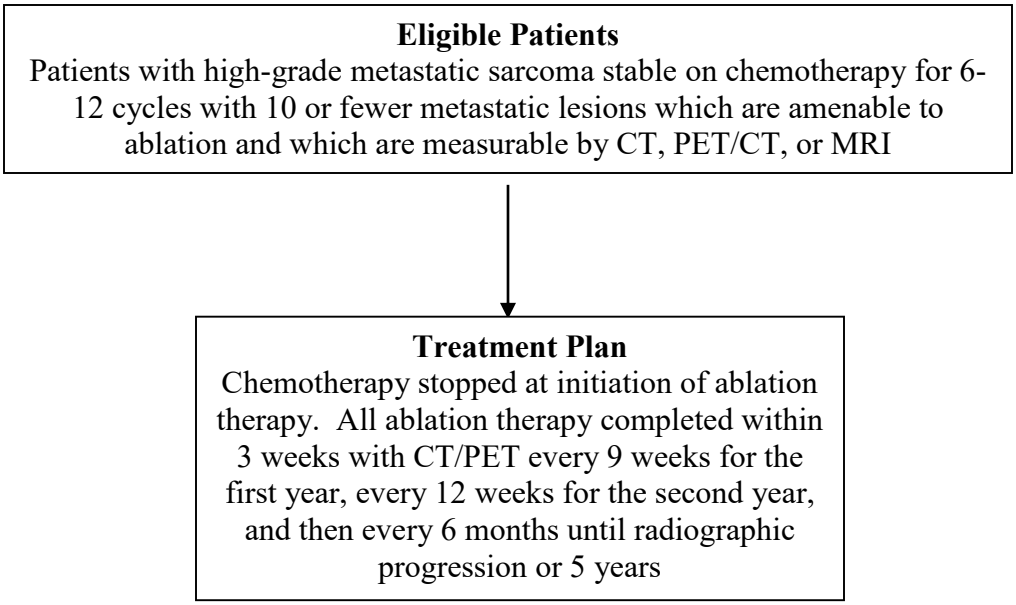
SCHEMA



Glossary of Abbreviations

AE	Adverse event
ALT (SGPT)	Alanine transaminase (serum glutamate pyruvic transaminase)
ANC	Absolute neutrophil count
AST (SGOT)	Aspartate transaminase (serum glutamic oxaloacetic transaminase)
BPI	Brief Pain Inventory
CBC	Complete blood count
CFR	Code of Federal Regulations
CMP	Complete metabolic panel
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
DOB	Date of birth
DSM	Data and Safety Monitoring
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
HRPO	Human Research Protection Office (IRB)
INR	International normalized ratio
IR	Interventional radiology
IRB	Institutional Review Board
IULN	Institutional upper limit of normal
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NIH	National Institutes of Health
OHRP	Office of Human Research Protections
PD	Progressive disease
PET	Positron emission tomography
PFR	Progression-free rate
PFS	Progression-free survival
PI	Principal investigator
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
QASMC	Quality Assurance and Safety Monitoring Committee
QOL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors (Committee)
SAE	Serious adverse event
SCC	Siteman Cancer Center

SD	Stable disease
UPN	Unique patient number
US	Ultrasound
WBC	White blood cell (count)

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1.0 BACKGROUND AND RATIONALE

1.1 Study Disease

Sarcomas encompass a group of an estimated 70 different histologic subtypes with varying biology (1). There are approximately 13,000 new cases of sarcoma per year in the United States, accounting for about 1% of adult malignancies (2). Prognosis is poor for patients with metastatic disease, with only a median survival of 12 months. Given the biological diversity of these tumors, a single drug therapy is not likely to be successful across all subtypes. As such, novel and multidisciplinary approaches will likely be needed to improve survival.

1.2 Ablation for Sarcoma

Cytotoxic chemotherapy is the mainstay of therapy for metastatic sarcoma. This alone, however, is very unlikely to result in a durable remission or cure. There is data demonstrating increased survival following surgical removal of pulmonary metastases in the setting of osteosarcoma. The combination of chemotherapy with resection of pulmonary metastases has been shown to increase the 3-year survival in metastatic osteosarcoma from approximately 5% to 65% (3). An alternative procedural approach to treating metastatic cancer includes ablation therapy. We hypothesize that we can use ablation therapy as a form of maintenance therapy in this patient population.

There is retrospective data that radiofrequency ablation is safe in sarcoma patients with lung metastases with a 3-year survival of 65%, similar to what is quoted in surgical studies (4). Given these data, we propose this single arm prospective phase II trial of ablation therapy in metastatic sarcoma patients that have less than 10 lesions that are stable on chemotherapy. These patients must be stable on 6-12 cycles of either cytotoxic or biologic chemotherapy as this is the natural stopping point for Adriamycin-based chemotherapy, which is the standard treatment in soft tissue sarcoma. Ablation therapy will then substitute as a form of maintenance therapy.

Tumor ablation will include radiofrequency ablation, cryoablation, or microwave ablation, and will include vertebral augmentation/cementoplasty of metastases with pathologic fracture or impending risk of fracture in the axial-loading bones including vertebral bodies and pelvis. These techniques are thought to be equivalent and the choice of which type of ablation to use is based on the performing radiologist and the site of metastasis. Others have validated the use of progression-free rate (PFR) as a surrogate for activity in phase II sarcoma studies (5). We hypothesize that there will be at least a 40% 3-month PFR indicating a significant response to ablation therapy.

2.0 OBJECTIVES

2.1 Primary Objectives

To determine the progression-free rate at 3 months in patients with metastatic sarcoma stable on chemotherapy whose lesions have undergone ablation. PFR is defined as the percentage of patients with no progression (local recurrence of an ablated lesion or the appearance of a new lesion) at 3 months after ablation.

2.2 Secondary Objectives

1. To determine the rate of overall survival of patients with metastatic sarcoma stable on chemotherapy whose lesions have undergone ablation. Overall survival is defined as the time from diagnosis of metastatic disease to the time of death.
2. To determine the effects of ablation on quality of life (QOL) as measured with the FACT-G7 validated survey.
3. To determine the effects of ablation on pain as measured by the Brief Pain Inventory (BPI)-Short form, a validated scale for assessment of pain.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

1. Histologically or cytologically confirmed high-grade metastatic sarcoma that has been stable on 6-12 cycles of one chemotherapeutic regimen (cytotoxic or biologic) although a change in chemotherapy is allowed if it is a result of toxicity/tolerability rather than progression. A patient must not have evidence of progression at any time while on chemotherapy in order to be eligible for this trial.

2. Measurable disease defined as lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$10 mm with CT scan, PET CT, or MRI exam.

3. At least 18 years of age.

4. ECOG performance status ≤ 2 (Karnofsky $\geq$60%, see Appendix A)

5. Normal bone marrow and organ function as defined below:
   a. Leukocytes $\geq$ 3,000/mcL
   b. Absolute neutrophil count $\geq$ 1,500/mcl
   c. Platelets $\geq$ 100,000/mcl
   d. Total bilirubin $\leq$ 1.5 x IULN or 3x IULN with normal ALT and AST in patients with Gilbert's disease
   e. AST(SGOT)/ALT(SGPT) $\leq$ 3.0 x IULN

f. Creatinine less than the institutional upper limit of normal
   OR
   Creatinine clearance ≥ 50 mL/min/1.73 m^2
g. INR<1.5 or patient off Coumadin at the time of ablation

6. No more than 10 treatable lesions as evaluated by an experienced interventional oncologic radiologist for eligibility and lesion accessibility as the ablation of more than 10 lesions becomes technically infeasible. These lesions must be treated in a two- to three-week time period from initial interventional radiology evaluation. Lung and liver lesions can range from 1 cm to 7 cm for a single lesion and no greater than 5 cm for multiple lesions. There are no size criteria for the osseous lesions.

7. The lesions will be amenable to a safe, ultrasound/computed tomographic/fluoroscopic guided percutaneous approach. The targeted metastases must be sufficiently separateable from the central nervous system, major peripheral motor nerves, bowel, and bladder. All lesions must be amenable to treatment.

8. If patients have received radiation therapy, there must be a one-month washout period.

9. Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry and for the duration of ablation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately.

10. Patient (or legally authorized representative if applicable) must be able to understand and willing to sign an IRB approved written informed consent document.

3.2 Exclusion Criteria

1. History of other malignancy ≤ 5 years previous with the exception of basal cell or squamous cell carcinoma of the skin which were treated with local resection only, carcinoma *in situ* of the cervix, or localized prostate cancer.

2. Receiving any other investigational agents simultaneously or within 3 weeks following ablation procedure.

3. Known brain metastases. Patients with known brain metastases must be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

4. Intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

5. Pregnant and/or breastfeeding.

6. Patients whose treatment plans include continuing chemotherapy after ablation as per the treating physician, as ablation therapy is meant to serve as maintenance therapy in lieu of chemotherapy.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center OnCore database
3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility collecting the information listed below:

1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

All patients must be registered through the Siteman Cancer Center OnCore database.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

5.0 TREATMENT PLAN

Eligible patients will have their lesions ablated using any one or more of the procedures described below. The choice of the procedure will be based on the expertise of the interventional oncologic radiologist and the site of metastasis. These techniques are thought to be equivalent.

Pre-and post procedure, patients must fill out a QOL survey and Brief Pain Inventory (BPI)-Short form, which is a validated visual analog scale for assessment of patient pain asking the patient to rate his/her worst pain in 24 hours. These surveys can be done over the phone.

5.1 Cryoablation

Cryoablation is performed under ultrasound, CT and occasional fluoroscopic guidance with CT fluoroscopy available for intermittent use in cyroprobe placement and CT monitoring of ablation. Procedures will be performed on an outpatient basis, but patients can be admitted for observation post-procedure as deemed appropriate by the treating interventional radiologist. Patients are generally under moderate conscious sedation with midazolam and fentanyl with continuous nurse monitoring of pulse oximetry, blood pressure, cardiac rhythm and rate, and respirations. General endotracheal anesthesia is allowed in cases felt clinically appropriate as deemed by the interventional radiologist. One percent lidocaine alone or a 1:1 mixture of 1% lidocaine and 0.25% bupivicaine or 0.5% ropivicaine is used for local and periosteal anesthesia.

Cryoprobes from Endocare Inc. (Irvine CA) or Galil Medical (Arden Hills MN) are either introduced into the lesion co-axially through a bone biopsy needle or directly into the lesions that are amenable to such, i.e., soft tissue, lung, liver, and large lytic lesions with extensive bone destruction. For blastic lesions, a hand drill may be needed for bone access. For larger lesions, additional cryoprobes are placed in parallel arrangement approximately 1.0 cm apart. The Cryocare Surgical System allows the operation of up to twenty-five cryoprobes at a time through 5 controllable channels. The Endocare system allows for the independent operation of up to 16 cryoprobes at a time. Cryoprobe positioning and adequate coverage of bone-tumor interface is confirmed with CT imaging. When necessary thermal protection and temperature monitoring of neural structures is performed and includes placement of thermocouples in the neural foramen and epidural space at the level of the lesion and injection of warm saline or carbon dioxide for thermal insulation. Bowel protection with balloon interposition or with carbon dioxide dissection will be used if necessary.

A single freeze-thaw-freeze cycle is performed for each lesion at 10 minutes, 8 minutes, and 10 minutes, respectively. The freezing portions of the cycle may vary depending on size of the ice-ball and adequacy of coverage and proximity to adjacent critical structures. Non-enhanced computed tomography is performed every 3 to 5 minutes with soft tissue windows (400 HU window, 40 HU level) throughout the freezing cycle to monitor growth of the ice ball. After completion of the final freeze cycle of the cryoablation procedure, the cryoprobes are actively heated with helium until temperature is above 20 degrees Celsius and then the probe is withdrawn.

5.2 Radiofrequency Ablation

Radiofrequency ablation will be predominantly used on metastatic spine lesions and will include use of the Dfine STAR ablation probe. This probe will be placed coaxially through an introducer needle into the spinal metastatic lesion. Time and area of kill is based on temperatures measured at both proximal and distal thermocouples on the probe. The ablation will usually be followed by placement of high viscosity cement for treatment of a fracture or lesions at risk.

5.3 Microwave Ablation

Microwave ablation will be predominantly used on metastatic soft tissue lesions and will include use of Covidien's Evident™ MWA System. Microwave ablation is performed under ultrasound, CT, and occasional fluoroscopic guidance with CT fluoroscopy available for intermittent use in probe placement and CT monitoring of ablation. Procedures will be performed on an outpatient basis, but patients can be admitted for observation post-procedure as deemed appropriate by the treating interventional radiologist. Patients are generally under moderate conscious sedation with midazolam and fentanyl with continuous nurse monitoring of pulse oximetry, blood pressure, cardiac rhythm and rate, and respirations. General endotracheal anesthesia is allowed in cases felt clinically appropriate as deemed by the interventional radiologist. One percent lidocaine alone or a 1:1 mixture of 1% lidocaine and 0.25% bupivicaine or 0.5% ropivicaine is used for local and periosteal anesthesia.

Microwave antennae from Covidien (Mansfield, MA) are either introduced into the lesion co-axially through a bone biopsy needle or directly into the lesions that are amenable to such, i.e., soft tissue, lung, liver, and large lytic lesions with extensive bone destruction. For blastic lesions, a hand drill may be needed for bone access. For larger lesions, additional antennae are placed in parallel arrangement approximately 1.0 cm apart. Antenna positioning and adequate coverage of the tumor is confirmed with CT imaging. When necessary, thermal protection and bowel protection with balloon interposition or with carbon dioxide dissection or hydrodissection will be used.

Ablations will be performed according to the manufacturer's recommendations in the package insert. After completion of ablation, tract ablation is performed as the probe is withdrawn.

5.4 Criteria for Ablation

Ablation will be postponed for ANC<1500 or platelets <100,000. Ablation will also be postponed if the creatinine or bilirubin are elevated above baseline until those lab values normalize.

5.5 Evaluation for Severity of Pain and Quality of Life

Patients will be evaluated for severity of pain using the BPI-Short Form (Appendix B) with the assistance of a study coordinator at the following time points:

- Prior to ablation
- 1 day post-ablation
- 1 month post-ablation – from first procedure if more than 1 is done
- Time of disease progression

The patients are asked to answer the questions with respect to the lesion(s) treated. They are not given a copy of the BPI-Short Form and no prior responses are available to review on subsequent visits to minimize bias. Analgesic use following the tumor ablation will be recorded as well.

Patients will be evaluated on quality of life based on the FACT-G7 survey (Appendix C) with the assistance of the study coordinator at the following time points:

- Prior to ablation
- 1 day post-ablation
- 1 month post-ablation – from first procedure if more than 1 done
- Time of disease progression

They are not given a copy of the FACT-G7 form and no prior responses are available to review on subsequent visits to minimize bias.

These surveys may be administered over the phone.

5.6 Evaluability

All patients who undergo ablation are evaluable for toxicity. Patients are evaluated from date of first procedure and for 30 days thereafter.

All patients who undergo ablation are evaluable for disease response provided they have had at least one disease assessment.

5.7 General Concomitant Medication and Supportive Care Guidelines

No restrictions to medications exist with regards to the ablation procedures. However, clopidogrel (anti-platelet medication) should be discontinued for 5-7 days pre-procedure, unless the risk of discontinuation outweighs the risk of bleeding. Blood thinners such as warfarin should be discontinued for 5-7 days prior to the procedure as well.

5.8 Women of Childbearing Potential

Women of childbearing potential (women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes

withdrawal bleeding, and women who have had a tubal ligation) are required to have a negative pregnancy test (serum or urine) within 1 day prior to the ablation procedure.

5.9 Duration of Therapy

Tumor ablation is a one-time procedure. If at any time prior to or during ablation, the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to proceed with ablation, this treatment should be discontinued and the reason(s) for discontinuation documented in the case report forms.

Because the ablation procedures are intended to replace maintenance chemotherapy, chemotherapy should not resume following ablation therapy. If the treating physician feels it is warranted (i.e., the patient develops a lesion that is not amenable to ablation), then the patient will be considered to have progressed and will be taken off trial and replaced.

5.10 Duration of Follow-up

Patients will be followed every 9 weeks for the first year, every 12 weeks for the second year, and then every 6 months for 5 years or until death, progression, consent is withdrawn, or the study is closed, whichever occurs first. Patients will be followed by CT or PET scan and office visits every 9 weeks. CT and PET scans can be performed at outside facilities and mailed to us for review by our radiologists. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. After progression, patients will be followed for survival every 3 months.

6.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outline below.

The Washington University Human Research Protection Office (HRPO) requires that all events meeting the definition of unanticipated problem or serious noncompliance be reported as outlined in Section 6.2.

6.1 Definitions

6.1.1 Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website: http://www.hhs.gov/ohrp/policy/advevntguid.html

Only AEs that are related to the ablation procedure should be reported for study data.

6.1.2 Serious Adverse Event (SAE)

Definition: any adverse event related to the ablation procedure that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

6.1.3 Unexpected Adverse Experience

Definition: any adverse experience related to the ablation procedure, the specificity or severity of which is not consistent with the current investigator brochure (or risk information, if an IB is not required or available).

6.1.4 Life-Threatening Adverse Experience

Definition: any adverse experience, related to the ablation procedure, that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

6.1.5 Unanticipated Problems

Definition:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

6.1.6 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

6.1.7 Serious Noncompliance

Definition: noncompliance that materially increases risks, that results in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

6.1.8 Protocol Exceptions

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

Pre-approval of all protocol exceptions must be obtained prior to the event.

6.2 Reporting to the Human Research Protection Office (HRPO) at Washington University

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any BJH or SLCH institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification to the PI of the event.

6.3 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI is required to notify the QASMC of any unanticipated problem occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO as reportable. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to a QASMC auditor.

6.4 Timeframe for Reporting Required Events

Reportable adverse events will be tracked for 30 days following ablation. Only AEs that are related to the ablation procedure should be reported for study data.

Deaths	
Any reportable death while on study or within 30 days of study	Immediately, within 24 hours, to PI and the IRB
Any reportable death while off study	Immediately, within 24 hours, to PI and the IRB
Adverse Events/Unanticipated Problems	
Any reportable adverse events as described in Sections 6.1.1 and 6.1.2 (other than death)	Immediately, within 24 hours to PI and within 10 working days to the IRB
All adverse events regardless of grade and attribution should be submitted cumulatively	Include in DSM report
Noncompliance and Serious Noncompliance	
All noncompliance and serious noncompliance as described in Sections 6.1.6 and 6.1.7	Immediately, within 24 hours, to PI and within 10 working days to the IRB

7.0 STUDY CALENDAR

Baseline evaluations are to be conducted within 3 weeks prior to start of protocol therapy. Scans and x-rays must be done no more than 3 weeks prior to the start of ablation.

	Baseline	Ablation	1 day after ablation	1 month after ablation	Follow-up[d]	Progression
Physical exam, incl. medical history, weight, VS, PS	X					
CBC	X					
CMP	X					
PT/PTT and INR	X					
Pregnancy test[a]	X					
IR evaluation[b]	X					
CT or PET scan					X[d]	
FACT-G7	X		X	X		X
BPI short form	X		X	X		X
Adverse events		X[c]				
Survival follow-up						X[e]

a: Women of childbearing potential only

b: Patients must have 10 or fewer treatable lesions when enrolled in the study and will be seen in consultation by an experienced interventional oncologic radiologist with evaluation of available PET, CT, MR, and US images for eligibility and lesion accessibility

c: Tracked for 30 days following ablation

d: The patients will be imaged as per routine care at the following time points: 6 weeks post first-procedure, every 9 weeks for the first year, every 12 weeks for the second year, and every 6 months for 5 years or until death or radiographic progression, whichever comes first.

e. After progression, patients will be followed every 3 months for survival only.

8.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
Registration Form Eligibility Form On-Study Form	Prior to starting treatment
Ablation Form	After treatment
Toxicity Form	30 days following ablation
Tumor Measurement Form Follow Up Form	Baseline 6 weeks after ablation Every 9 weeks during Year 1 Every 12 weeks during Year 2 Every 6 months for all subsequent years for 5 years or until progression or death Every 3 months after progression (survival only)
QOL Form	Baseline 1 day after ablation 1 month after ablation Progression

9.0 MEASUREMENT OF EFFECT

9.1 Antitumor Effect – Solid Tumors

There will be another PET/CT at 42 +/- 3 days following the last procedure (approximately 6 weeks post-procedure) and one every 9 weeks thereafter until progression of disease. All imaging is standard of care.

For the purposes of this study, patients should be re-evaluated for response every 9 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 4 weeks (not less than 4) weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

9.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm by chest x-ray, as >10 mm with CT scan, or >10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

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

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic 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.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

9.3 Methods for Evaluation of Measurable Disease

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response

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

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is

truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

- FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

9.4 Response Criteria

9.4.1 Evaluation of Target Lesions

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

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

Progressive Disease (PD): At least a 20% increase in the sum of the 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 progressions).

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.

9.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

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

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

9.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	>4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	>4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once >4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

9.4.4 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 progressive 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, including the baseline measurements.

9.4.5 Other Definitions

Progression-free rate: PFR is defined as the percentage of patients with no progression (local recurrence of an ablated lesion or the appearance of a new lesion) at 3 months after ablation.

Overall survival: OS is defined as the time from diagnosis of metastatic disease to the time of death.

9.4.6 Response Review

For trials where the response rate is the primary endpoint, all responses will be reviewed by an expert independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

10.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least five patients have been enrolled) or one year after accrual has opened (if fewer than five patients have been enrolled at the six-month mark).

The Principal Investigator will review all patient data at least every six months, and provide a semi-annual report to the QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

11.0 STATISTICAL CONSIDERATIONS

11.1 Power

Our power analysis is based on the following hypotheses. The null hypothesis assumes that the 3-month progression-free survival (PFS) for treatment with ablation therapy is

overall 20% for patients with metastatic sarcoma. We hypothesize in the alternative hypothesis that the 3-month PFS will be at least 40% with ablation therapy. This is based on data from a clinical trials database used to provide reference values for conducting phase II studies in sarcoma with PFR as the principal endpoint (5). An enrollment of 36 patients can achieve at least 80% power to conclude that the alternative hypothesis is true based on a two-sided test of one-sample proportion at a significance level of 0.05.

11.2 Data Analysis

Possible covariates in the analysis include sex, age, number of lesions and total diameter of all ablated lesions. Descriptive statistics (mean, median, range and standard deviation) will be provided for continuous variables and frequencies will be tabulated for categorical variables for the patients. Kaplan-Meier survival estimates will be obtained for 3-month PFS for patients with ablation therapy. For categorical covariates such as sex, number of lesions (<5 vs. >=5) and total diameter of all ablated lesions (10cm vs. >=10cm), if there are sufficient number of patients in each stratum, Kaplan-Meier survival curves will be plotted for each stratum and log-rank test will be performed to test if 3-month PFS is significantly different across strata. Overall survival will be analyzed with the same strategy as for 3-month PFS.

To determine whether or not there is an improvement in quality of life (QOL), since the variables related to QOL are in ordinal scale and will be measured at baseline, one day post ablation, one month post ablation and at time of disease progression, the GEE analysis implemented in SAS PROC GENMOD will be used to take into account the correlation of repeated measures from the same subject. Contrast statements will be used to compare mean QOL scores between any two times. The same analysis strategy will be performed to determine if BPI changes over time.

All analyses will be two-sided at a significance level of 0.05 and will be performed with statistical software SAS 9.3.

12.0 REFERENCES

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2. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ**.** Cancer statistics, 2009. CA Cancer J Clin. 2009;59(4):225-49.
3. Carter SR, Grimer RJ, Sneath RS, Matthews HR**.** Results of thoracotomy in osteogenic sarcoma with pulmonary metastases. Thorax. 1991;46(10):727-31.
4. Palussiere J, Italiano A, Descat E, Ferron S, Cornelis F, Avril A, et al. Sarcoma lung metastases treated with percutaneous radiofrequency ablation: results from 29 patients. Ann Surg Oncol;18(13):3771-7.
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APPENDIX A: ECOG Performance Status Scale

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: Brief Pain Inventory

STUDY ID# _____ HOSPITAL # _____

DO NOT WRITE ABOVE THIS LINE

Brief Pain Inventory (Short Form)

Date: ____/____/____ Time: ____

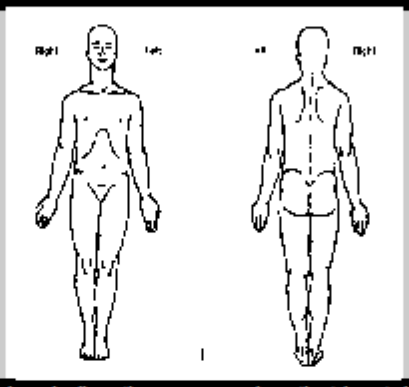
Name: _____ _____ _____

Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

4. Please rate your pain by circling the one nuimber that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

APPENDIX C: FACT-G7

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy.....	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4
GF5	I am sleeping well.....	0	1	2	3	4
GF3	I am able to enjoy life.....	0	1	2	3	4
GF7	I am content with the quality of my life right now.....	0	1	2	3	4