HCC 10-027: Phase II study for Curative Intent Treatment for Patients with Oligometastatic Disease at Initial Presentation

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Table of Contents

Summary

Title: Phase II Study for Curative Intent Treatment for Patients Presenting with Oligometastatic Disease at Initial Presentation

Hypothesis: Patients with oligometastatic disease (defined here as 5 or fewer sites of metastatic disease involving 3 or fewer organ systems) are potentially curable with stereotactic radiosurgery (SRS) or stereotactic radiotherapy (SRT) (collectively referred to as stereotactic body radiotherapy or SBRT) to the metastatic disease sites in combination with standard curative therapy to the primary site.

Primary objective: Delivery of SBRT to multiple sites in a safe and effective manner with acceptable toxicity

Primary Endpoints:

- Presence of multiple sites (between 2 and 5 sites)
- Acceptable toxicity: Grade 3 or less

Secondary Objectives/Endpoints:

- Quality of life (as measured by the FACT quality of life surveys, see appendix IV)
- Local control of metastatic sites (with measurable/quantitative assessment): proportion of patients with Complete Response (CR), Partial Response (PR), or Stable Disease (SD)
- Local control of primary site (with measurable/quantitative assessment): proportion of patients with local Complete Response (CR), Partial Response (PR), or Stable Disease (SD)
- Overall survival (OS)
- Two-year Overall Survival
- Analysis of patterns of failure post-SRS/SBRT (subsequent sites of failure and time to failure): proportion of patients with Progressive Disease (PD)

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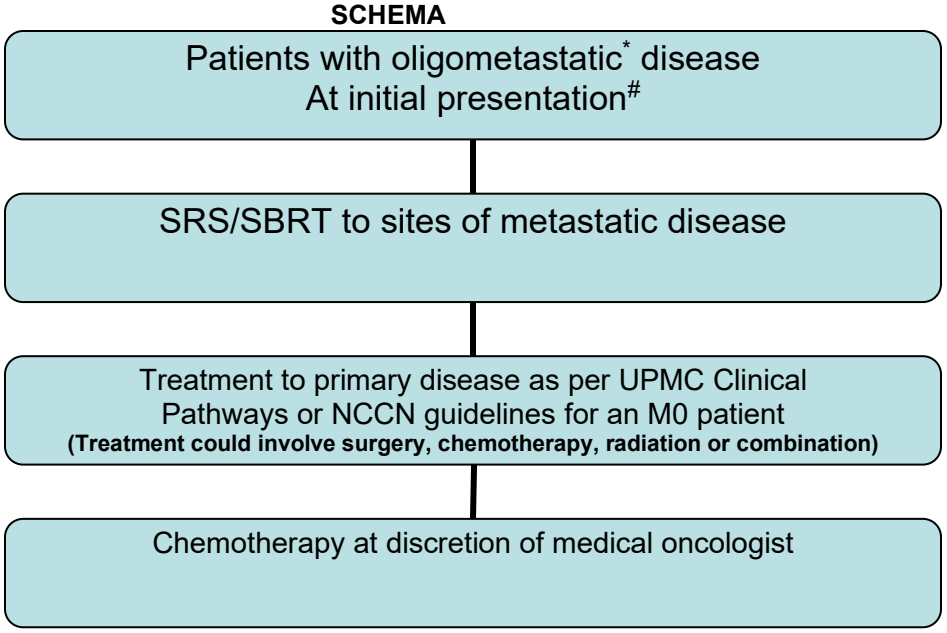

*** oligometastatic disease defined as 5 or fewer sites of metastatic disease involving 3 or fewer organs**
 # Only patients with oligometastatic disease at presentation are eligible. Patients with recurrent disease are not eligible for this study.

Patient Population: (See Section 3.0 for Eligibility)
Patients with stage IV (M1) disease at initial presentation (newly diagnosed) who have 5 or fewer sites of metastatic disease involving 3 or fewer organ systems Patients have not had previous therapy for disease.

REQUIRED SAMPLE SIZE: 44 PATIENTS (SEE SECTION 11.0)

1.0 INTRODUCTION

Death from metastatic cancer is a common cause of death, accounting for 80-90% of cancer deaths (3). The classic thought process is that metastatic disease is incurable and thus treatment, if given, is often palliative. However, it has been reported that a subset of patients with limited volume metastatic disease are in fact curable if given aggressive therapy. This group of patients has become known as “oligometastatic”. The concept of oligometastatic disease was established by Hellman in the mid 90’s (11, 12). The concept states that there is an evolution or progression of malignant cells through acquired mutations or other mechanisms that allow the cancer to have a step-wise pattern of spread. Cancer cells must first acquire the ability to spread beyond the original disease site, then acquire the ability to establish metastatic lesions (often involving vascularization) and then acquire the ability for further spread. Furthermore, tumor cells may require specific conditions at each step in the process, and that different cancers have different host conditions required for successful metastases, this concept is known as the ‘seed and soil’ theory (13-14) which explains a step in the process from localized disease to widespread metastatic disease. The step in the process between localized disease and widespread metastatic disease is referred to as “oligometastatic disease”. Because oligometastatic disease has not yet acquired the ability for widespread tumor cell dissociation, the sites of tumor burden are limited. In theory, if the primary tumor and the sites of oligometastatic disease could be successfully treated, it would be possible to cure such patients.

This theory has been, in retrospective reviews, shown to be potentially true for numerous cancer types. Patients with limited metastatic disease (oligometastatic disease) to the liver from colon cancer who received aggressive therapy to the liver lesions have had survival rates much better than would be predicted for stage IV disease. Five-year survival rates following liver resection for metastatic colon cancer range between 25% and 55% compared with 0% and 5% for non-operated patients (43). This has also been shown to be true for metastatic disease in bone (29), brain (30), pancreas (1) and lung (31).

Similarly, treatment of the primary lesion in the setting of metastatic disease has been shown to improve survival in breast cancer (33-39), renal cell cancer (40), gastric cancer (41) and melanoma (42).University of Chicago (33) reported 22% long term survival in NSCLC patients presenting with 1-2 metastatic sites treated with aggressive therapy.

While surgical resection has been the first treatment option evaluated in oligometastatic patients, radiation is another viable treatment option. Stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT) involve high radiation doses delivered in a very conformal manner. SRS and SRT (collectively known as stereotactic body radiotherapy or SBRT) involve limited radiation to

surrounding normal tissue yet are capable of curative doses of radiation to the primary target. SBRT is well tolerated and can be performed in patients who are not fit for surgery, the mortality of SBRT is exceedingly low, and the number of treatments for SBRT ranges from 1 to 10 making it less burdensome for patients.

SBRT has been evaluated for treatment of oligometastatic disease in multiple sites. Flickinger (15) reported good outcomes for patients with solitary CNS metastatic lesions treated with gamma knife radiosurgery. Similar good outcomes in this setting have been reported by others (44-46).

Multiple reports are available on SBRT for lung tumors. In several series reporting both primary and metastatic lung tumors treated with SBRT (with 3-5 fractions), local control rates have been impressive, ranging from 70% to 90% (34,42,43). Furthermore, toxicity has been mild, most commonly limited to radiographic lung changes. A phase I dose-escalation trial was performed for patients with lung metastases from various primary sites. SBRT dose was successfully escalated to 60 Gy in three fractions with minimal toxicity reported (21). A case series reported 50 patients with lung metastases who were treated at University of Rochester, most of whom (62%) received 5 Gy/fraction for a total of 50 Gy. Up to five targets were treated per patient. With a mean follow-up of 18.7 months local control of treated lesions was obtained in 42 of 49 evaluable patients (83%). Only 2% had grade 3 toxicity (22). Investigators from Japan reported treating 1–2 pulmonary metastases in 34 patients with various primary tumors using 12 Gy fractions to doses of 48 or 60 Gy, at 2 years, 90% of patients were free of local failure. (18). Little toxicity has been reported when SBRT is used to treat peripheral lung tumors, with pneumonitis rates varying from 0% to 10% (19-20).

The role of SBRT for liver lesions was evaluated in a pilot study of 31 patients with a variety of primary tumors, 17 liver metastases in 14 patients were treated with doses of 7.7–45 Gy in 1–4 fractions. Of 13 lesions treated with greater than 20 Gy, only one lesion progressed with a mean follow-up of almost 10 months (23). A phase I multi-institutional trial sequentially escalated doses up to 60 Gy in three fractions. It was reported that the maximum tolerated dose (MTD) was not reached and a single patient out of 36 patients failed in-field at a median follow-up of 19 months (24).

The outcomes of patients treated with SBRT for multiple organ metastases have also been reported. The University of Rochester reported an analysis on 121 patients with 1–5 metastases treated on two consecutive protocols. Patients on both protocols could have had previous therapy for their disease; only 27 patients had oligometastatic disease at initial presentation. The first protocol treated breast cancer patients with limited metastases, in which no brain lesions were treated. The second protocol included patients with cancer from any primary site and limited metastases including a brain primary. After treatment with ten fractions of 5 Gy over 2 weeks (10 fractions), metastatic lesions were controlled 77% of the time at 2 years (25). Milano (5) reported prospective data on breast cancer patients with oligometastatic disease (less than 5 sites) comparing patients treated with SBRT to those receiving only palliative therapy. Four-year survival was significantly improved in SBRT patients (59% versus 0%). University of Chicago (53) reported on a prospective trial in 29 oligometastatic patients (one to five sites and a life expectancy > 3 months, 81% had prior systemic treatment) who had 56 metastatic lesions treated with SBRT (3 fractions ranging from a total dose of 24 to 36 Gy). The authors found a control rate of 56% for treated sites and only 2 patients had grade 3 or higher toxicity.

From the data available, patients with oligometastatic disease appear to benefit in terms of disease control from SBRT. At this point, no one is able to adequately predict which patients have favorable oligometastatic disease and are good candidates for aggressive and potentially curative therapy and which patients are destined to have development of widespread metastatic disease. Some proposed factors for patients likely to proceed to widespread metastatic disease include size and grade of primary tumor, site of oligometastatic disease, and lymph node status. In order to best treat patients, it is important that careful studies be performed to collect clinical information on patients with oligometastatic disease to analyze patient subsets most likely to benefit from treatment.

While disease outcome is certainly an important endpoint, quality of life (QOL) also is of significant importance, especially in patients with metastatic disease that have traditionally thought to

be incurable. It is important that, until aggressive treatment for oligometastatic disease becomes standard of care, careful attention is paid to the quality of life in treated patients. Multiple validated QOL surveys are available for a variety of cancer sites. Collection of such surveys will help to monitor the impact of treatment on QOL.

To our knowledge, there have not been any prospective trials examining the role of aggressive therapy in the treatment of oligometastatic disease only at initial presentation. None of the previously described reports include only patients at initial presentation; the majority of patients in the prospective and retrospective oligometastatic studies have had previous therapy. In order to better evaluate the role of curative therapy in patients presenting with oligometastatic disease we are proposing a prospective study of this patient cohort. Patients with oligometastatic disease (defined for this study as 5 or fewer sites of disease involving 3 or fewer organ systems) will receive SRS/SBRT to all sites of oligometastatic disease and standard curative therapy to the primary disease. The primary objective for this study will be feasibility with the potential for an eventual phase III study. In addition, clinical and translational information will be collected to better stratify patients with oligometastatic disease for future studies.

2.0 OBJECTIVES

Primary objective: Delivery of SBRT to multiple sites in a safe and effective manner with acceptable toxicity

Primary Endpoints:

- Presence of multiple sites (between 2 and 5 sites)
- Acceptable toxicity: Grade 3 or less

Secondary Objectives/Endpoints:

- Quality of life (as measured by the FACT quality of life surveys, see appendix IV)
- Local control of metastatic sites (with measurable/quantitative assessment): proportion of patients with Complete Response (CR), Partial Response (PR), or Stable Disease (SD)
- Local control of primary site (with measurable/quantitative assessment): proportion of patients with local Complete Response (CR), Partial Response (PR), or Stable Disease (SD)
- Overall survival (OS)
- Two-year Overall Survival
- Analysis of patterns of failure post-SRS/SBRT (subsequent sites of failure and time to failure): proportion of patients with Progressive Disease (PD)

3.0 PATIENT SELECTION

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED

3.1 Conditions for Patient Eligibility

3.1.1 Pathologically (histologically or cytologically) proven diagnosis of solid malignancy within 8 weeks of registration

NOTE: FDG-PET/CT scans are required for full staging of metastatic disease. If subject has had an FDG-PET/CT scan within the last 8 weeks, it will not need to be repeated.

NOTE: Pathological confirmation is not required for all disease sites as long as the sites of metastatic disease are radiographically and clinically consistent with metastatic disease from a known (biopsy proven) primary.

NOTE: the primary site does not have to be the site of pathological confirmation. For example, in a patient with a radiographic lung lesion with mediastinal

lymphadenopathy and a liver lesion, a liver biopsy which is constant with lung primary would preclude the necessity for further pathologic diagnosis.

3.1.2 Eligible disease sites include the following newly diagnosed disease types:
1. Breast
2. Prostate
3. GI (including colorectal, anal, esophagus, pancreas, gastric with the exception of colon cancer with resectable liver-only lesions)
4. Head and neck
5. Skin (melanoma and squamous cell carcinoma)
6. Lung (both small cell and non-small cell)
7. Sarcoma (both soft tissue and bone)
8. Gynecologic (endometrial, cervical, ovarian, vaginal, vulvar)

3.1.3 Patients are stage IV (M1) with any combination of T and N with oligometastatic disease as defined by 5 or fewer total sites of metastatic disease involving 3 or fewer organ systems

3.1.3.1 Examples of patients eligible for trial
- T3N2M1 NSCLC with 1 CNS metastatic lesion, 2 liver lesions, and 1 adrenal lesion.
- T4N1M1 colorectal cancer with 1 liver lesion, 4 bone lesions
- T3N0M1 gastric cancer with 1 supraclavicular lymph node, 2 liver lesions, and 2 CNS lesions

3.1.4 Metastatic disease sites must be treatable with SRS (at discretion of treating physician).

3.1.5 Primary disease site must be able to be treated with curative intent

3.1.6 Zubrod Performance Status 0-1

3.1.7 Age ≥ 18

3.1.8 CBC/differential obtained within 4 weeks prior to registration on study, with adequate bone marrow function defined as follows:

3.1.8.1 Absolute neutrophil count (ANC) ≥ 1,800 cells/mm^3;

3.1.8.2 Platelets ≥ 100,000 cells/mm^3;

3.1.8.3 Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable.);

3.1.9 Women of childbearing potential and male participants must practice adequate contraception

3.1.10 Patient must provide study specific informed consent prior to study entry.

3.2 Conditions for Patient Ineligibility

3.2.1 Ineligible disease sites include the following
- Lymphoma
- Leukemia
- Multiple myeloma
- Primary CNS
- Peritoneal carcinomatosis
- Colon cancer with resectable liver-only lesions

3.2.2 Examples of patients ineligible for trial
- T1N1M1 NSCLC with 1 CNS lesion, 1 bone lesion, 1 adrenal lesion and a cervical lymph node (4 sites of metastatic disease)
- T2N1M1 Gastric cancer with 6 liver lesions (more than 5 sites of metastatic disease)

3.2.3 Other
- Lung cancer with pleural effusion (wet IIIB) are not eligible
- Recurrent cancers are not eligible
- Diffuse metastatic spread confined to one organ system is ineligible; examples of this include leptomeningeal spread in the CNS and peritoneal carcinomatosis.

3.2.4 Prior systemic chemotherapy for the study cancer; note that prior chemotherapy for a different cancer is allowable but cannot have any other primary cancer diagnosed or treated within the last 3 years other than cutaneous skin cancers. Patient may have previous chemotherapy as treatment of this previous malignancy as long as the chemotherapy has completed more than 3 years ago.

3.2.5 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields

3.2.6 Severe, active co-morbidity, defined as follows:

- 3.2.6.1 Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months;
- 3.2.6.2 Transmural myocardial infarction within the last 6 months;
- 3.2.6.3 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
- 3.2.6.4 Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for liver function and coagulation parameters are not required for entry into this protocol.

3.2.7 Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

3.2.8 Oligometastatic disease sites not eligible based on concern for toxicity:

*** trachea involvement (direct invasion, tumors close to or abutting trachea are eligible)**

*** heart (direct invasion or involvement, pericardial lymph nodes can be treated)**

3.2.9 Patients unable to have an FDG-PET/CT scan, either through insurance coverage, patient decision or other reason are not eligible for this study.

3.2.10 Patients unable to have SRS/SBRT through insurance coverage or ability to pay for SRS/SBRT

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

NOTE: This section lists baseline evaluations needed before the initiation of protocol treatment that do not affect eligibility.

4.1 The following are to be completed prior to treatment

- Complete history and physical
- Staging workup to determine oligometastatic disease, note that FDG-PET/CT scan is mandatory. Minimum metastatic workup is per NCCN guidelines for specific cancer type. If subject has had an FDG-PET/CT scan within the last 8 weeks, it will not need to be repeated.
- Measurements of metastatic disease sites (number of lesions and size of lesions, preferably volumetric data is available for better estimate of lesions).

4.2 The following will be ascertained at Study Registration:

- Name of institutional person registering this case

- Patient eligibility status
- Date the study-specific Consent Form was signed (must be signed prior to study entry)
- Patient's Initials (First Middle Last)
- Verifying Physician
- Patient's ID Number
- Date of Birth
- Race
- Ethnic Category (Hispanic or Latino; Not Hispanic or Latino; Unknown)
- Gender
- Treatment Start Date

5.0 TREATMENT OVERVIEW

- Treatment of metastatic disease: all sites of metastatic disease will be treated with SRS or SBRT (see section 6.0)

- Treatment of primary disease: primary disease will be treated using surgery, chemotherapy, radiation, or a combination of all three (see section 6.0, 7.0, 8.0). Treatment of the primary disease will be as per the UPMC pathway guidelines or NCCN guidelines individualized for the patient's stage and disease site with the exception that the patient will be considered M0 instead of M1. (For example, T3N3M1 NSCLC would be considered T3N3M0 and treated with definitive chemoradiotherapy).

- Sequence of therapy: SRS/SBRT will be used for all sites of metastatic disease in close approximation to initiation of treatment for the primary disease site (within 6 weeks). Ideally, SRS/SBRT would occur first followed by treatment to primary site. However, in some circumstances surgical resection of the primary site could precede SRS/SBRT, especially if surgical resection is required for pathological confirmation of disease. After completion of SRS/SBRT to the oligometastatic sites and treatment to the primary site, systemic chemotherapy can be given at the discretion of the medical oncologists (see Section 7.0).

6.0 RADIATION THERAPY

6.1 Non-radiosurgery radiation

External beam radiation (when indicated) would be initiated after completion of stereotactic radiosurgery. Details of radiation (IMRT or 3D, radiation energies, field sizes, doses, etc) is at the discretion of the treating radiation oncologist, encouragement will be given towards adherence to the UPMC Clinical Pathways specific to disease and patient characteristics. In some disease sites no radiation will be used after the completion of SRS/SBRT (for example, T2N0M1 lung cancer treated with SRS/SBRT to oligometastatic site then receiving surgical resection). Patients will be treated as if they are M0.

6.2 Stereotactic Radiosurgery (SRS) and Stereotactic Body Radiation Therapy (SBRT)

See Appendix IV for site-specific SRS/SBRT details. The following are general guidelines.

6.2.1 SRS/SBRT Timing: All SRS/SBRT treatments will be completed within 3 weeks (preferably 2 weeks).

6.2.2 Technical factors
SRS/SBRT has been formally defined and described in a published guideline from the American College of Radiology and American Society for Therapeutic Radiology and Oncology (47). This protocol will respect those guidelines. The term stereotactic for the purposes of this protocol implies the targeting, planning, and directing of therapy using beams of radiation along any trajectory in 3-D space toward a target of known 3-D coordinates. The coordinate system is defined by reliable “fiducial” markers. This differs from conventional radiation therapy, in which therapy is directed toward less-than-reliable skin marks or bony landmarks that are indirectly referenced to the tumor (surrogates). This protocol will require treatments to be conducted with the use of a fixed 3-D coordinate system defined by fiducials. The coordinate system defined by the fiducials should be directly related to the radiation-producing device (e.g., couch and gantry) in a reproducible and secure fashion. Capability should exist to define the position of targets within the patient according to this same 3-D coordinate system. As such, the patient is set up for each treatment with the intention of directing the radiation toward an isocenter or target according to the known 3-D coordinates as determined in the process of treatment planning. The nature of the fiducials themselves may include radiopaque markers or rods placed at known locations in a frame or fixed structure adjacent to the patient as well as use of the tumor itself as a fiducial (e.g., acquiring tomographic views of the tumor simultaneously with the treatment). Metallic “seeds” placed within the tumor will be allowed to constitute a fiducial so long as the methods are validated and a plan is in place to identify seed migration (e.g., redundant seeds placed). To allow fiducial stabilization and resolution of swelling, planning studies will be imaged 5-10 days after fiducial placement.

6.2.3 Patient Positioning
Patients will be positioned in a stable position capable of allowing accurate reproducibility of the target position from treatment to treatment. Positions uncomfortable for the patient should be avoided so as to prevent uncontrolled movement during treatments. A variety of immobilization systems may be used, including stereotactic frames that surround the patient on three sides and large rigid pillows (conforming to patients’ external contours) with reference to the stereotactic coordinate system (see Section 6.1). Patient immobilization must be reliable enough to ensure that the gross tumor volume (GTV) does not deviate beyond the confines of the planning treatment volume (PTV) as defined in Section 6.2.4 with any significant probability (i.e., < 5%).

6.2.4 Localization
Isocenter or reference point port localization images (anterior/posterior and lateral) should be obtained at each treatment on the treatment unit or patients should undergo a tomographic imaging study immediately before treatment to ensure proper alignment of the geometric center (i.e., isocenter) of the simulated fields.

6.2.5 Treatment Planning/Target
Gross target volume (GTV) will be the tumor lesion defined by CT scan, FDG-PET scan and clinical information. Planning treatment volume (PTV) will be GTV with margin appropriate for set-up error and movement. There will be no elective nodal coverage.

6.2.6 Radiation doses and fractionation:
Dose and fractionation will be dependent on the lesion location and lesion size, the exact fractionation and dose is at the discretion of the treating physician. However, encouragement is made to adhere to the guidelines outlined in Appendix III. A minimum of 48 hours must be used in between SRS/SBRT treatments at each site. Note that patients can have SRS/SBRT everyday or multiple SRS/SBRT sessions in one day as long as the minimum time for each treatment site is met.

For example, if two lung lesions, adrenal, and liver sites were being treated, both lung sites could be treated Monday, Wednesday, and Friday, the liver on Tuesday, Thursday and the following Tuesday, and the adrenal on Monday, Wednesday, Friday of the second week.

EXAMPLE:

	Mon	Tues	Weds	Thurs	Fri
Wk 1	Lung #1 Lung #2	Liver	Lung #1 Lung #2	Liver	Lung #1 Lung #2
Wk 2	Adrenal	Liver	Adrenal		Adrenal

7.0 DRUG THERAPY

Chemotherapy

7.1 Chemotherapy guidelines for primary disease

Chemotherapy (when indicated) would be initiated after completion of stereotactic radiosurgery. Chemotherapy choice of agents is at the discretion of the treating medical oncologist, encouragement will be given towards adherence to the UPMC Clinical Pathways specific to disease and patient characteristics. In some disease sites no chemotherapy will be used.

7.2 Chemotherapy guidelines after treatment for metastatic disease

At the discretion of the medical oncologist, chemotherapy may be initiated after treatment of the primary disease site has been completed in accordance with UPMC Clinical Pathways or NCCN guidelines for treatment of M1 disease for the patient's primary disease site.

For example; T1N0M1 NSCLC with solitary adrenal lesion is treated with SBRT to the adrenal lesion followed by lobectomy (treatment option for T1N0M0 NSCLC). After surgical resection, medical oncologists could choose to place patient on systemic chemotherapy that would be indicated for patient with M1 NSCLC).

8.0 SURGERY

8.1 Surgery guidelines

Surgery (when indicated) would be initiated after completion of stereotactic radiosurgery. Type of surgical operation is at the discretion of the treating surgeon, encouragement will be given towards adherence to the UPMC pathways specific to disease and patient characteristics. In some disease sites no surgery will be used.

9.0 OTHER THERAPY

9.1 Permitted Supportive Therapy

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication. [Include the following sections as appropriate]

9.1.1 Anticonvulsants
9.1.2 Antiemetics
9.1.3 Anticoagulants
9.1.4 Antidiarrheals
9.1.5 Analgesics

9.1.6 Hematopoietic Growth Factors
9.1.7 Herbal products
9.1.8 Nutritional supplementation

10.0 PATIENT ASSESSMENTS

10.1 Study Parameters: See Appendix I.

10.2 Evaluation during Study

10.2.1 If clinically indicated, blood counts and other labs should be obtained during therapy.

10.2.2 Toxicity will be evaluated during the study using Common Cancer Toxicity Criteria V 4.0

10.3 Evaluation after study

10.3.1 Patients will be seen in follow-up with study physicians 6 weeks after completion of SRS/SBRT and then at 3 month intervals for 3 years and 6 months thereafter.

10.3.2 QOL survey to be performed prior to therapy, after SRS/SBRT and at subsequent follow-up visits using the FACT-G survey. See Appendix IV.

10.3.3 Toxicity will be evaluated after the study using Common Cancer Toxicity Criteria V 4.0

10.3.4 Follow-up imaging should be performed at least every 3 months for the first two years from completion of therapy and every 6 months afterwards until five years from the completion of therapy. FDG-PET/CT scan for follow-up is recommended but not required.

10.3.5 Measurement of Response for CT scans
Response will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [JNCI 92(3): 205-216, 2000] See http://ctep.info.nih.gov/guidelines/recist.html for further details.

1. Measurable disease **-** the presence of at least one measurable lesion; if the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
2. Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥ 20 mm using conventional techniques or ≥ 10 mm with spiral CT scan.
3. Non-measurable lesions - all other lesions, including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques

Response Criteria: Evaluation of target lesions

*Complete Response (CR):	Disappearance of all target lesions
*Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
*Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions

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

10.3.6 Measurement of Response for FDG-PET scans

Since it is extremely difficult to quantify the size of a lesion(s) by FDG-PET scan, the conventional RECIST criteria will not be used for the qualitative, non-SUV-based FDG-PET scan interpretation after chemoradiotherapy. Instead, the qualitative visual criteria from MacManus et al will be utilized, as follows:

Response Criteria: Evaluation of target lesions

*Complete Response (CR): CR will be defined as no tumor FDG uptake in the tumor bed, or activity in the tumor bed similar to that in the adjacent normal tissue;

Partial Response (PR): appreciable reduction in intensity of tumor FDG uptake or tumor volume apparent to the nuclear medicine physician when pre-, during-, and post-treatment PET scans are displayed side by side;

Progressive Disease (PD): appreciable increase in the intensity of tumor FDG uptake or volume of the tumor apparent to the nuclear medicine physician when pre-, during, and post-treatment PET scans are displayed side by side.

Stable Disease (SD): no appreciable change in intensity of tumor FDG uptake or tumor volume between scans and no new sites of disease apparent to the nuclear medicine physician when pre-, during-, and post-treatment PET scans are displayed side by side;

* *For these determinations, the pre-, during-, and post-treatment FDG-PET scans must be analyzed using the same display techniques to provide a consistent intensity of background soft-tissue activity.*

10.4 Criteria for Discontinuation of Protocol Treatment

- Progression of disease as measured by RECIST criteria outlined above, PET scan RECIST criteria will be used for patients with follow-up PET scans, CT scan RECIST criteria will be used for patients with follow CT scan only.

11.0 STATISTICAL CONSIDERATIONS

Primary objective: Delivery of SBRT to multiple sites in a safe and effective manner with acceptable toxicity

Primary Endpoint(s):

- Presence of multiple sites (between 2 and 5 sites)
- Acceptable toxicity: Grade 3 or less

Secondary objectives/Endpoints:

- Quality of life (as measured by the FACT quality of life surveys, see appendix IV)
- Local control of metastatic sites
- Local control of primary site
- Overall survival (OS), Two-year Overall Survival
- Analysis of patterns of failure post-SRS/SBRT (subsequent sites of failure and time to failure)

11.1 Objectives of the proposed study

The primary objective of the proposed phase II study is to evaluate the feasibility of this curative intent treatment approach (SRS/SBRT to the metastatic disease sites in combination with standard curative therapy to the primary site) to patients presenting with oligometastatic disease.

11.2 Sample size

Phase II studies are usually small trials, recruiting participants up to about 20, although often a lot less. However, we plan to analyze the data stratified by different primary cancer such as breast, prostate, and etc., since we are trying to detect which patient subsets are most likely to benefit from the proposed treatment. The sample size can be set at approximately 10 for each patient subset in order to have a reasonable estimate of overall survival, local control, and quality of life for each subset. We estimate that most of the patients will have breast, lung, and prostate primaries and that there will be smaller numbers with other primary types. Based on these assumptions, we estimate a sample size of 40 patients and expect a 10% drop-out rate and thus have set an estimated sample size of 44 patients.

11.3 Data analysis

Two-year survival rate will be calculated for all the patients and each patient subset respectively by using Kaplan-Meier survival analyses, with survival and event times defined from the day of enrollment until either an event or last follow-up. We can compare these two year survival rates with those from the patients using traditional therapy. Median overall survival will also be estimated.

Univariate survival analysis will be performed to identify the statistically significant variables, using Log-Rank test or univariate Cox proportional hazard regression based on the data type of predictor variables. Significant (P <.05) variables on univariate analyses will then be tested with multivariate analyses by using Cox proportional hazard regression model (Milano MT, et al., 2007).

Quality of life outcomes will be analyzed by using univariate and multivariate logistic regression successively and the quality of life will be coded as “improved” or “non-improved”.

We will also report the entire patient characteristics at initial presentation of oligometastatic disease and characteristics of Long-term (>=2 years) survivors by using descriptive statistics.

12.0 DATA SAFETY AND RECORDING

12.1 Data and Safety Monitoring Plan

Investigators/Sub-investigators, regulatory, CRS management, clinical research coordinators, research coordinators, clinical research associates, data managers, and clinic staff meet regularly in disease center Data Safety Monitoring Boards (DSMB) to review and discuss study data to include, but not limited to, the following:

- **serious adverse events**
- **subject safety issues**
- **recruitment issues**
- **accrual**
- **protocol deviations**
- **unanticipated problems**
- **breaches of confidentiality**

Minutes from the disease center DSMB meetings are available to those who are unable to participate during the scheduled meeting time.

All toxicities encountered during the study will be evaluated on an ongoing basis

according to the NCI Common Toxicity Criteria Version 4.0. All study treatment associated adverse events that are serious, at least possibly related and unexpected will be reported to the IRB. Any modifications necessary to ensure subject safety and decisions to continue, or close the trial to accrual are also discussed during these meetings. If any literature becomes available which changes the risk/benefit ratio or suggests that conducting the trial is no longer ethical, the IRB will be notified in the form of an Unanticipated Problem submission and the study may be terminated.
All study data reviewed and discussed during these meetings will be kept confidential. Any breach in subject confidentiality will be reported to the IRB in the form of an Unanticipated Problem submission. The summaries of these meetings are forwarded to the UPMC Hillman Cancer Center DSMC which also meets regularly following a designated format.
For all research protocols, there will be a commitment to comply with the IRB's policies for reporting unanticipated problems involving risk to subjects or others (including adverse events). DSMC progress reports, to include a summary of all serious adverse events and modifications, and approval will be submitted to the IRB at the time of renewal.
Protocols with subjects in long-term (survival) follow-up or protocols in data analysis only, will be reviewed bi-annually.
Both the UPMC Hillman Cancer Center DSMC as well as the individual disease center DSMB have the authority to suspend accrual or further investigate treatment on any trial based on information discussed at these meetings.
All records related to this research study will be stored in a locked environment. Only the researchers affiliated with the research study and their staff will have access to the research records.

12.2 Adverse Event Reporting

12.2.1 Definitions

The following definitions of terms apply to this section:

Adverse event: **Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.**

Life-threatening adverse event or life-threatening suspected adverse reaction: **An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.**

Serious adverse event or serious suspected adverse reaction: An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Events not to be considered as AEs/SAEs:

- Medical conditions present at the initial trial visit that do not worsen in severity or frequency during the treatment plan are defined as baseline medical conditions and NOT to be considered AEs/SAEs
- Visits to the emergency room or other hospital department < 24 hours, that do not result in admission (unless considered an important medical or life-threatening event)
- Elective surgery, planned prior to signing consent, and admissions for a planned medical/surgical procedure
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)
- Admission for administration of anticancer therapy in the absence of any other SAEs.

Suspected adverse reaction: **Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.**

Adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

Unexpected adverse event or unexpected suspected adverse reaction: An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

12.2.2 Eliciting AE Information

Research subjects will be routinely questioned about AEs at study visits.

12.2.3 Recording Requirements

All observed or volunteered adverse events (serious or non-serious) and abnormal test findings, regardless of study group or suspected causal relationship to the study drug(s) will be recorded in the subjects' case histories. For all adverse events, sufficient information will be pursued and/or obtained so as to permit 1) an adequate determination of the outcome of the event (i.e., whether the event should be classified as a *serious adverse event*) and; 2) an assessment of the casual relationship between the adverse event and the study drug(s).

Adverse events will be followed until resolution while the patient remains on-study. Once the patient is removed from study, events thought to be related to the study medication will be followed until resolution or stabilization of the adverse event, or until the patient starts a new treatment regimen, or death, whichever comes first. Subjects will be followed for AEs/SAEs for 30 days after their last dose of study drug(s).

AEs or abnormal test findings felt to be associated with the investigational drug or

study treatment(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the Sponsor-Investigator.

12.3 CAUSALITY

The investigator must determine the relationship between the administration of radiation and study drug(s) and the occurrence of an AE/SAE as defined below:

- Definitely Related – The AE is clearly related to radiation and/or study drug(s). There is a reasonable causal relationship between study treatment and the AE. The event responds to withdrawal of study treatment (dechallenge) and recurs with rechallenge when clinically feasible.
- Probably Related – The AE is likely related to to radiation and/or study drug(s). There is a reasonable causal relationship between study treatment and the AE. The event responds to dechallenge.
- Possibly Related – The AE may be related to radiation and/or study drug(s). There is a reasonable possibility that study treatment caused the adverse event. The investigator can provide a rationale or evidence to suggest a causal relationship between study treatment and the AE other than just a temporal relationship.
- Unlikely Related– The AE is doubtfully related to radiation and/or study drug(s). There is only a temporal relationship to study treatment, but not a reasonable causal relationship between study treatment and the AE.
- Unrelated – The AE is clearly NOT related to radiation and/or study drug(s). There is no temporal relationship to study treatment. There is a reasonable causal relationship to another drug product, concurrent disease, or circumstance.

12.2.2.2 Abnormal Test Findings

An abnormal test finding will be classified as an *adverse event* if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms.
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy.

  Note: simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an AE.
- The test finding leads to a change in study dosing or discontinuation of subject participation in the clinical study.
- The test finding is considered an AE by the Sponsor-Investigator of the IND application.

REPORTING OF SERIOUS ADVERSE EVENTS

All events meeting the definition of a serious adverse event, which occur after the date of first dose of study treatment and within 30 days of the last dose of study treatment, should be reported according to the departmental SAE checklist and SAE form. The initial SAE form should be sent to the following within 24 business hours / 1 business day of the Principal Investigator becoming aware:

1. Investigator: burtons@upmc.edu
2. CRSSafetySubmissions@upmc.edu
3. Local Institutional Review Board when reporting requirements are met.

In addition to completing appropriate patient demographic and suspect medication information, the report should include as applicable the following information that is available at the time of report within the Sections B and C of the departmental SAE form:

- CTCAE term(s) and grade(s)
- current status of study drug
- all interventions to address the AE (testing and result, treatment and response)

- hospitalization and/or discharge dates
- event relationship to study drug

Follow-up reports:

Additional information may be added to a previously submitted report by adding to the original departmental SAE form and submitting it as follow-up or creating supplemental summary information and submitting it as follow-up with the original departmental SAE form.

12.2.3 Reporting adverse events to the responsible IRB

In accordance with applicable policies of the University of Pittsburgh Institutional Review Board (IRB), the Investigator will report, to the IRB, any observed or volunteered adverse event that is determined to be 1) associated with the investigational drug or study treatment(s); 2) serious; and 3) unexpected. Adverse event reports will be submitted to the IRB in accordance with the respective IRB procedures.

Applicable adverse events will be reported to the IRB as soon as possible and, in no event, later than 10 calendar days following the investigator's receipt of the respective information. Adverse events which are 1) associated with the investigational drug or study treatment(s); 2) fatal or life-threatening; and 3) unexpected will be reported to the IRB within 24 hours of the Sponsor-Investigator's receipt of the respective information. Follow-up information to a reported adverse event will be submitted to the IRB as soon as the relevant information is available. If the results of the Investigator's follow-up investigation show that an adverse event that was initially determined to not require reporting to the IRB does, in fact, meet the requirements for reporting; the Investigator will report the adverse event to the IRB as soon as possible, but in no event later than 10 calendar days, after the determination was made.

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APPENDIX I - Schedule of events

	Pre-Treatment	During Treatment	Follow-Up
Histo/cyto eval	X		
History/physical	X		X
Imaging of sites of disease (FDG-PET/CT)	X*		X
Performance status	X	X	X
CBC w/ diff & ANC	X		
Serum pregnancy test (if applicable)	X		
Informed consent	X		
Tumor response eval			X
Adverse event eval		X	X
QOL surveys	X		X

* If one was done within the past 8 weeks, then do not repeat.

APPENDIX II - Performance status scoring

ZUBROD PERFORMANCE SCALE

0	**Fully active, able to carry on all predisease activities without restriction**
1	**Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature. For example, light housework, office work**
2	**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	**Capable of only limited self-care, confined to bed or chair 50% or more of waking hours**
4	**Completely disabled. Cannot carry on self-care. Totally confined to bed**
5	**Death**

KARNOFSKY PERFORMANCE SCALE

100	**Normal; no complaints; no evidence of disease**
90	**Able to carry on normal activity; minor signs or symptoms of disease**
80	**Normal activity with effort; some sign or symptoms of disease**
70	**Cares for self; unable to carry on normal activity or do active work**
60	**Requires occasional assistance, but is able to care for most personal needs**
50	**Requires considerable assistance and frequent medical care**
40	**Disabled; requires special care and assistance**
30	**Severely disabled; hospitalization is indicated, although death not imminent**
20	**Very sick; hospitalization necessary; active support treatment is necessary**
10	**Moribund; fatal processes progressing rapidly**
0	**Dead**

APPENDIX III - Guidelines for SRS/SBRT dosing and fractionation

Guidelines for SRS (see also section 6.2)

CNS
Treatment will be performed with single fraction SRS/SBRT. Patient will be positioned in supine position with appropriate fixation device, frameless SRS/SBRT can be performed if set-up uncertainty is minimal. SRS/SBRT doses are dependent on lesion size as follows:

Lesion Diameter (cm)	SRS/SBRT dose (Gy)
< 2	24/ 1 fx
2-3	18/ 1 fx
> 3	15 / 1 fx
> 4	30 / 3 fx

For larger lesions, fractionated SRS/SBRT may be used (3 fractions of 10 Gray per fraction) instead of a single fraction of 15 Gy.

LUNG
SBRT to lung lesions will consist of 3-5 treatments depending on location of tumor. Patient will be positioned in supine position with gated treatments or tumor tracking with fiducial markers. For central tumors (defined as within 2 cm of carina, right and left main bronchi, right and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus, and left lower lobe bronchus) SRS dose will be 48 Gy in 4 fractions. For non-central lesions, SBRT dose will be 60 Gy in 3 fractions.

Dose constraints for 48 Gy in 4 fractions:

Organ	Volume	Volume Max	Max Point Dose
Spinal Cord	<0.25 cc	22.5 Gy (4.5 Gy/fx)	30 Gy (6 Gy/fx)
Skin	<10 cc	30 Gy (6 Gy/fx)	32 Gy (6.4 Gy/fx)
Lung (both right and left lung volumes)	1500 cc	12.5 Gy (2.5 Gy/fx)	
Skin	< 10 cc	33.2 Gy (8.3 Gy/fx)	36 Gy (9 Gy/fx)
Chest wall	Any point	32 Gy (8 Gy/fx)	40 Gy (10 Gy/fx)

Dose constraints for 60 Gy in 3 fractions:

Organ	Volume	Max Point Dose
Spinal Cord	Any point	18 Gy (6 Gy per fx)
Esophagus	Any point	27 Gy (9 Gy per fx)
Heart/Pericardium	Any point	30 Gy (10 Gy per fx)
Bronchus	Any point	30 Gy (10 Gy per fx)
Skin	Any point	24 Gy (8 Gy per fx)
Chest wall	Any point	24 Gy (8 Gy per fx)

ADDRENAL
SBRT dose will be 50 Gy in 5 fractions. Patient will be positioned in supine position with gated treatments or tumor tracking with fiducial markers.

Dose constraints

	Normal Tissue Constraints
Organ	**Maximum Dose in 5 Fractions**
Contralateral Kidney (2/3 volume)	5 Gy
35% of Total (left & right) Kidney Volume	25 Gy
Spinal Cord	20 Gy
Stomach	35 Gy

BONE
Dose and fractionation dependent on size and location. For lesions in vertebral bodies near the spinal cord, single fraction with doses 18-25 Gy. If fractionation is necessary (as deemed by the treating physician, 24 Gy in 3 fractions may be used (8 Gy/fraction). Bone metastatic lesions will not have received previous radiotherapy (see 3.0 for eligibility criteria)

LIVER
Liver lesions less than 6 cm in diameter will be treated to 60 Gy in 3 fractions or 60 Gy in 4 fractions at the discretion of treating physicians. Preference should be giving for 60 Gy in 4 fractions, but the shorter course radiotherapy be used to allow for all SBRT treatments to occur within the 3 week time frame. . Patient will be positioned in supine position with gated treatments and/or near real-time tumor tracking with fiducial markers.

Dose constraints for liver lesions:
typical estimate of normal liver size is 2000 cm^3. At least one-third of the liver should be spared from receiving a dose likely to cause notable hepatic dysfunction, meaning that 700 cm^3 should receive a total SBRT dose of less than 15 Gy over 3 fractions and 25 Gy over 5 fractions.
Two-thirds of the right kidney cannot receive a dose of more than 15 Gy in 3 fractions or 25 Gy in 5 fractions.
The percent of total kidney volume receiving a dose of 15 Gy in 3 fractions or 25 Gy in 5 fractions must be less than 35% of the total kidney volume
The maximum dose to any point within the spinal cord can not exceed 18 Gy total in 3 fractions or 20 Gy total in 5 fractions.
The maximum point dose to the stomach can not exceed 30 Gy in 3 fractions or 35 Gy in 5 fractions.

	Normal Tissue Constraints	
Organ	**Maximum Dose in 3 Fractions**	**Maximum Dose in 4 Fractions**
Liver (700 cm^3)	15 Gy	25 Gy
Right Kidney (2/3 volume)	15 Gy	25 Gy
35% of Total (left & right) Kidney Volume	15 Gy	25 Gy
Spinal Cord	18 Gy	20 Gy
Stomach	30 Gy	35 Gy

LYMPH NODES
Lymph nodes that are considered M1 for primary tumor site will be treated based on size and location. SBRT can range from single fraction 18-24 Gy or 3 fractions to 60 Gy, or 5 fractions to 50 Gy.

Appendix IV - Sample of QOL form (FACT-G)

FACT-G (Version 4)

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 past 7 days.**

	PHYSICAL WELL-BEING	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
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-G (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4