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Unique Protocol ID: 16-305

Whole brain radiation versus stereotactic radiation in patients with 5-20 brain metastases: A phase III, randomized clinical trial

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Statistical Analysis Plan

1. Trial Overview

- **Title**: *Stereotactic radiation versus hippocampal avoidance whole brain radiation in 5-20 brain metastases (SHARPER-Brain Met): A phase 3, randomized trial*
- **Design**: Phase 3, multicenter, randomized, open-label, comparative trial
- **Protocol ID**: DFCI 16-305
- **ClinicalTrials.gov Identifier**: NCT03075072
- **Principal Investigator**: Dr. Ayal A. Aizer
- **Participating Institutions**:
    - Brigham and Women's Hospital / Dana-Farber Cancer Institute, Boston, MA
    - Rhode Island Hospital / Brown University Health, Providence, RI
    - Milford Regional Medical Center, Milford, MA
    - South Shore Health, Weymouth, MA
- **Planned Sample Size**: 196 patients (98 per arm)

2. Objectives

- **Primary Objective**: To compare symptom severity and interference in daily function between patients treated with stereotactic radiation (SRS/SRT) versus hippocampal avoidance whole brain radiation (HA-WBRT) using the M.D. Anderson Symptom Inventory – Brain Tumor module (MDASI-BT)
- **Secondary Objectives**:

  -To compare the following per-patient endpoints between treatment arms:

- Overall survival
- Neurologic death
- New brain metastases
- Local recurrence
- Progressive intracranial disease
- Radiation necrosis
- Leptomeningeal disease
- Steroid use
- Seizures
- Salvage SRS/SRT
- Salvage WBRT
- Salvage neurosurgical resection
- Functional independence (Barthel Index)
- Performance status
- Neurocognitive function, including:
    - Hopkins Verbal Learning Test - Revised (HVLT-R) total recall, delayed recall, and recognition
    - Trail Making Test Part A and B (TMT-A/B)
    - Controlled Oral Word Association Test (COWAT)
    - Mini-Mental State Examination (MMSE)
    - Cognitive Functioning Subscale of the Medical Outcomes Study (MOS-COG-R), patient-reported cognitive function

- Motor dexterity: Grooved Pegboard Test

-To compare the following per-metastasis endpoints between treatment arms:

- Local recurrence
- Salvage therapy for local recurrence
- Salvage neurosurgical resection
- Radiographic radiation necrosis
- Symptomatic radiation necrosis

Neurocognitive and functional assessments conducted at baseline, and at 4 and 12 months post-baseline. Brain MRIs obtained every 2 months for 1 year and every 2-4 months thereafter, with adjustment based on clinical need. Performance status assessed at baseline, 3 weeks post-baseline, 2 months post-baseline, and every 2 months thereafter for a total of 1 year, as well as during unscheduled or long-term visits.

3. Study Design

- Randomized phase 3 trial comparing SRS/SRT and HA-WBRT in patients with 5–20 brain metastases. Patients stratified by primary tumor type (breast, non-small cell lung cancer, melanoma, other) and prior neurosurgical resection.

4. Measurement of Effect: Primary Endpoint

- Primary Endpoint: Change in composite MDASI-BT score (symptom severity and interference) from baseline to 6 months post-baseline

- Composite MDASI-BT scores defined as the equally weighted average of mean symptom severity (22 items) and mean symptom interference (6 items)
- Patients assessed at baseline, 3 weeks post-baseline, every 2 months thereafter through 12 months, and during unscheduled or long-term visits. Compliance expected to decline over time primarily due to death. Estimated compliance rates:
    - Baseline: 100%
    - 3 weeks: 85%
    - 4 months: 70%
    - 6 months: 45%
    - 8 months: 20%

The primary analysis focuses on the weighted within-patient average change in MDASI-BT composite scores during the first 6 months (week 3, months 2, 4, and 6) compared to baseline. Based on the number of follow-up assessments, weights applied based on the inverse of the associated standard error:

- 4 assessments: sqrt 4 = 2.00
- 3 assessments: sqrt 3 = 1.73
- 2 assessments: sqrt 2 = 1.41
- 1 assessment: sqrt 1 = 1.00

Assuming a clinically meaningful difference of 0.70 points, a within-patient MDASI-BT standard deviation of 1.38, an individual MDASI-BT standard deviation of 2 points, 80% power, and a two-sided $\alpha = 0.05$, the study requires 83 evaluable patients per arm. Patients without at least one post-baseline assessment would be excluded from the primary analysis; thus, the planned

sample size is inflated by 1/0.85 = 1.18 to account for anticipated dropout. After inflating for dropout, the total sample size is set at 98 per arm (196 total). Secondary analyses include timepoint-specific comparisons and longitudinal modeling of MDASI-BT scores.

5. Sample Size and Power Calculations

- **Power**: 80%
- **Alpha**: 0.05 (two-sided)
- **Clinically meaningful difference in MDASI-BT severity score**: 0.70 points
- **Within-patient standard deviation in MDASI-BT**: 1.38
- **MDASI-BT standard deviation:** 2.0
- **Correlation between baseline and post-baseline assessments:** 0.60
- **Target effect size:** 0.44
- **Required evaluable patients per arm**: 83
- **Planned sample size**: 196 patients (98 per arm), accounting for attrition and expected compliance
- **Analysis population**: Intention-to-treat

6. Randomization

- Randomization performed using permuted blocks, stratified by primary tumor type and prior neurosurgical resection. The trial is open-label.

7. Statistical Methods

- **Primary Endpoint**: MDASI-BT composite change scores compared using weighted t-tests
- **Time-to-event outcomes**:
    - Overall survival: Kaplan-Meier estimates and stratified log-rank test
    - Other time-to-event (*per-patient*, i.e. neurologic death, new brain metastases, local recurrence, progressive intracranial disease, radiation necrosis, leptomeningeal disease, steroid use, seizures, salvage SRS/SRT, salvage WBRT, salvage neurosurgical resection): Cumulative incidence curves; stratified Gray's test
    - Other time-to-event (*per-metastasis*, i.e. local recurrence, salvage therapy for local recurrence, salvage neurosurgical resection, radiographic radiation necrosis, symptomatic radiation necrosis): Fine and Gray competing risks regression, sandwich estimator to account for intrapatient correlations
- **Repeated measures**:
    - Generalized estimating equations (GEE) for longitudinal comparisons of performance status, functional independence (Barthel Index), grooved pegboard, and neurocognitive measures
    - Tests of neurocognitive function, except the MMSE and MOS-COG-R, and grooved pegboard transformed into Z scores with higher scores indicating better function
    - MMSE: 0-30, higher scores indicate better function
    - MOS-COG-R: normative score, higher scores indicate better function

8. Handling of Missing Data

- Every effort will be made to obtain at least one post-baseline MDASI-BT assessment per patient. Multiple imputation will not be employed in order to preserve the integrity of the observed patient-reported data and avoid introducing unverifiable assumptions. Analyses will include all available post-baseline data using weighted or repeated measures models, which allow valid inferences under a missing-at-random assumption.

9. Interim Analyses

- We will monitor adverse events with an early stopping rule on the SRS/SRT arm as follows. If at any time 8 or more of the first 27 patients assigned to SRS/SRT experience neurologic death before 1 year, the study will halt for re-evaluation of the safety of this regimen. In order to ensure adherence to this rule, the cause of death (systemic vs. neurologic) will be recorded for each patient who dies. The study team will alert the statistician whenever a neurologic death is observed within one year of enrollment. Death due to progressive neurologic disease will be defined as marked, progressive radiographic progression in the brain accompanied by corresponding neurologic symptomatology in the absence of systemic disease progression / systemic symptoms of a life- threatening nature. The cause of death (neurologic versus systemic) will be determined from the medical records, available imaging studies, death certificate, and autopsy report.