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A pilot phase 2 study evaluating dose de-escalation in whole brain radiation therapy with simultaneous integrated boost for patients with brain metastases

Protocol Number:
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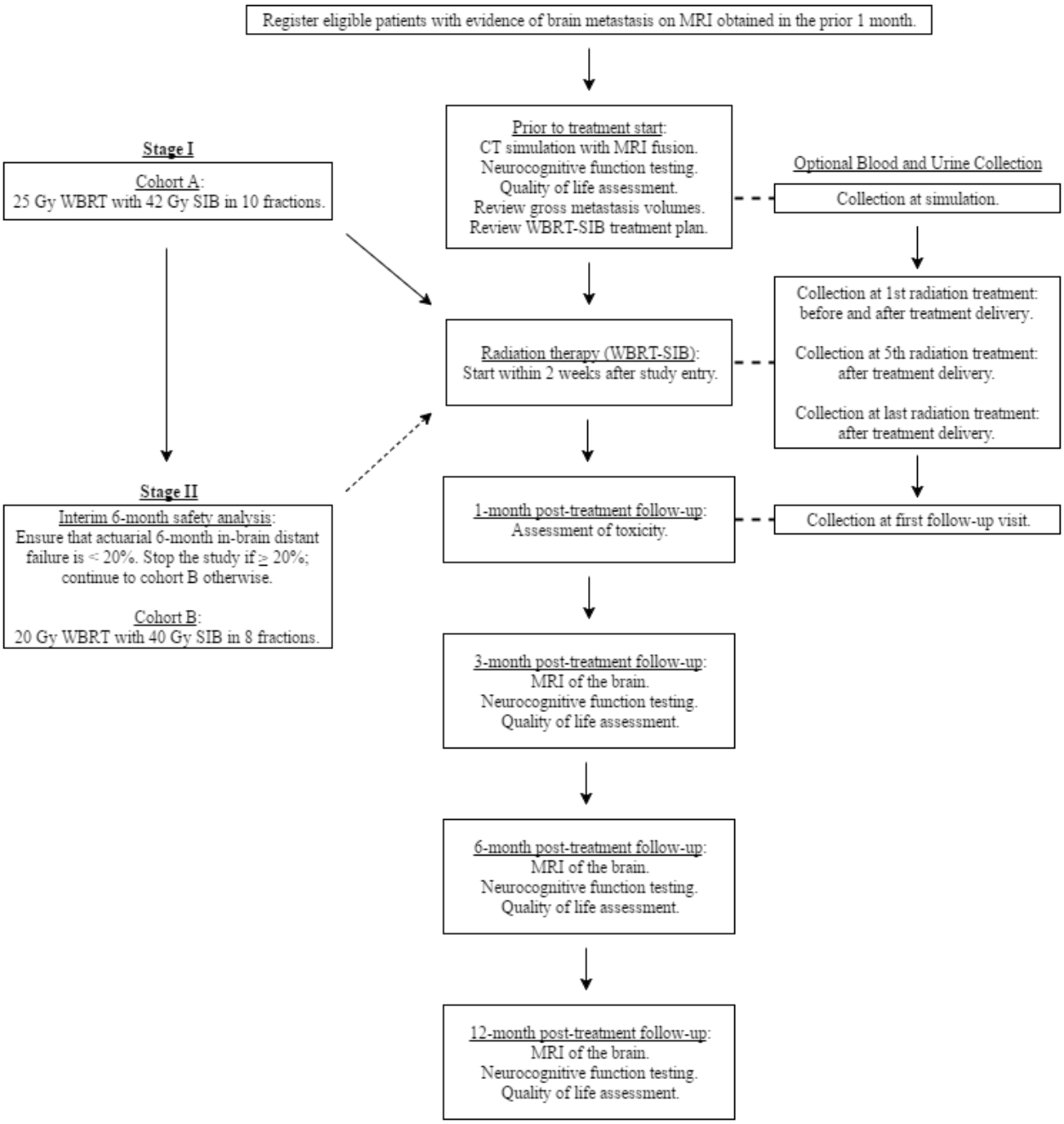
SCHEMA


Register eligible patients with evidence of brain metastasis on MRI obtained in the prior 1 month.
Prior to treatment start:
CT simulation with MRI fusion.
Neurocognitive function testing.
Quality of life assessment.
Review gross metastasis volumes.
Review WBRT-SIB treatment plan.
Optional Blood and Urine Collection
Collection at simulation.
Stage I
Cohort A:
25 Gy WBRT with 42 Gy SIB in 10 fractions.
Radiation therapy (WBRT-SIB):
Start within 2 weeks after study entry.
Collection at 1st radiation treatment:
before and after treatment delivery.
Collection at 5th radiation treatment:
after treatment delivery.
Collection at last radiation treatment:
after treatment delivery.
Stage II
Interim 6-month safety analysis:
Ensure that actuarial 6-month in-brain distant failure is < 20%. Stop the study if ≥ 20%; continue to cohort B otherwise.
Cohort B:
20 Gy WBRT with 40 Gy SIB in 8 fractions.
1-month post-treatment follow-up:
Assessment of toxicity.
Collection at first follow-up visit.
3-month post-treatment follow-up:
MRI of the brain.
Neurocognitive function testing.
Quality of life assessment.
6-month post-treatment follow-up:
MRI of the brain.
Neurocognitive function testing.
Quality of life assessment.
12-month post-treatment follow-up:
MRI of the brain.
Neurocognitive function testing.
Quality of life assessment.

1. BACKGROUND & RATIONALE

1.1. The current role of whole-brain radiation therapy (WBRT).

The treatment of patients with brain metastases comprises a significant proportion of the clinical radiation oncology caseload. An estimated 20 to 40% of all cancer patients will develop brain metastases during the course of their illness. The estimated number of new cases exceeds 250,000 per year, and the burden of brain metastases in terms of both morbidity and mortality is therefore quite significant.

The median survival of a patient with brain metastases is approximately 1 month if untreated and 2 months with steroid treatment alone. Thus, a large proportion of patients, if untreated, will likely die a neurologic death. For patients that are treated with WBRT, additional prognostic information is provided by the Radiation Therapy Oncology Group's (RTOG) recursive partitioning analysis (RPA), which divided patients into three classes based on age, performance status, and systemic disease control. RPA class I patients (under 65 years of age with good performance status and well-controlled systemic disease) have a median survival of approximately 7 months, whereas RPA class III patients (any patient with a Karnofsky performance status of 70 or worse) have a median survival of only 2 months[1, 2]. As most patients unfortunately do not live beyond these expectations, WBRT is very effective at quickly controlling CNS disease and preventing rapid neurologic decline without having time to manifest any long-term neurologic sequelae. Patchell et al. reported a 48% control (crude, not actuarial, rate) of treated lesions at a median overall survival and follow-up of 15 weeks when radiation is used alone[3].

WBRT has also been studied in conjunction with focal treatments—stereotactic radiosurgery (SRS) or surgical resection—and has been found to improve local control in such situations. In particular, Andrews et al. reported on RTOG 95-08, a phase III trial that randomized 333 patients with 1-3 newly diagnosed brain metastases to either WBRT alone vs WBRT followed by an SRS boost. They did not identify a difference between their treatment arms for their primary endpoint of overall survival. However, they did demonstrate a significant difference of 82% 1-year control of treated lesions in patients treated with WBRT + SRS vs 71% in patients treated with WBRT alone[4]. Aoyama et al. conducted a similar phase III randomized controlled trial of 132 patients with 1-4 brain metastases. They randomized patients to receive WBRT + SRS or SRS alone and demonstrated a similar significant difference in 12-month control of treated lesions of 88.7% for WBRT + SRS vs 72.5% for SRS alone[5]. Chang et al. conducted a phase III randomized controlled trial of 58 patients with 1-3 brain metastases to WBRT + SRS or SRS alone. Although this trial's primary endpoint was neurocognitive function, they also reported on 1-year control of treated lesions: 100% for SRS + WBRT vs 67% for SRS alone[6]. In summary, these three randomized trials all demonstrated a significant improvement with combined modality therapy over single modality therapy in terms of treated lesion control, but no difference in overall survival on initial analysis (see below for discussion of secondary analysis).

Once appropriately managed in the manner described above, patients with brain metastases usually die from non-neurologic causes. In a competing risk analysis, the 6-month and 12-month incidence rates of CNS death were 20.6% and 21.6% after WBRT plus salvage radiosurgery as necessary. In that same study, the incidence of non-CNS death was 34.4%

and 35.0%, respectively[7]. Systemic disease is generally considered the main determinant of patient outcome once brain disease is appropriately treated. With more recent advances in cancer therapy in all disciplines, patients are now living longer, even with brain disease. This observation is often represented in a disease-specific graded prognostic assessment (ds-GPA, see Appendix 1), which is divided by histology and dependent on varying combinations of age, performance status, extracranial disease, number of brain metastases, and receptor or gene statuses. Notably, breast cancer patients with good prognostic factors may live as long as a median of 25.3 months even after the development of brain metastases[8-12]. The original ds-GPA data for non-small cell lung cancer (NSCLC) was updated in 2016, which identified EGFR or ALK alterations as prognostic specifically in adenocarcinoma. In addition, survival times for each subcategory was overall improved as well, likely reflecting the impact of better therapies[13].

Furthermore, there is emerging retrospective evidence that certain subgroups of favorable patients may derive an overall survival benefit with WBRT. In particular, Aoyama et al. reported on a secondary analysis of their JROSG 99-1 clinical of SRS with or without WBRT discussed above. Patients with NSCLC were poststratified by the ds-GPA score, and patients with a ds-GPA score of 2.5 to 4.0 were felt to be favorable. Median overall survival in this favorable subgroup was 16.7 months vs 10.6 months in patients receiving WBRT + SRS vs SRS alone, respectively[14]. Similarly, Sperduto et al. performed a secondary analysis of RTOG 95-08 (also discussed previously) evaluating patients with all histologies but breast (insufficient data) poststratified by ds-GPA. This analysis demonstrated that patients with GPA 3.5 to 4.0 had better OS with WBRT + SRS vs WBRT alone, at a median overall survival of 21.0 months vs 10.3 months, respectively. This analysis was upheld regardless of the number of brain metastases, albeit with small total numbers of patients analyzed[12].

The current standard of care in the management of brain metastasis is well-defined by the National Comprehensive Cancer Network (NCCN) guidelines[15]. In patients with 3 or less brain metastases, patients with uncontrolled primary disease are recommended to have WBRT alone or best supportive care. In patients with stable systemic disease or with reasonable treatment options to achieve such, surgical resection is recommended if possible, followed by radiation therapy to the resection cavity (SRS alone, WBRT alone, or a combination). Patients with unresectable disease are recommended to have WBRT and/or SRS. Patients with more than 3 metastases are recommended to have WBRT or SRS. There is also emerging evidence from Yamamoto et al. in a prospective observational study that the volume of brain disease is more representative of disease burden than the number of metastases[16].

1.2. Neurocognitive considerations in the context of WBRT.

As survival times lengthen in patients with brain metastases, the risks of medium- to long-term neurocognitive decline (which is a well-described toxicity of whole brain radiation therapy) must be addressed. Early cognitive decline after WBRT is primarily manifested as a decline in short-term memory within 1 to 4 months. Long-term decline and more permanent adverse effects include cognitive deterioration in other domains (e.g., attention) as well as possible cerebellar dysfunction[17]. Long-term survivors may be at risk of radiation-induced dementia, although this is typically seen primarily with higher dose per fraction regimens (even if the total dose is not high)[18].

Several approaches have been explored to decrease the risk of neurocognitive toxicity secondary to WBRT. Presently, many radiation oncologists favor the use of SRS alone followed by close observation and salvage SRS as needed, with WBRT reserved for salvage treatment of diffuse intracranial recurrence. This approach is supported by the previously described studies of SRS +/- WBRT, which did not identify any overall survival advantage to SRS + WBRT despite the presence of a significant local and distant brain control benefit. Furthermore, these trials suggested that SRS alone was associated with improved neurocognitive outcomes. However, the SRS-alone approach has the disadvantage of higher in-brain distant failure rates at 12 months of 55-63.7% with SRS alone vs 27-41.5% when WBRT + SRS is used[5, 6]. A pooled analysis by Tsao et al. again demonstrated a statistically significant local and in-brain distant control benefit favoring WBRT + SRS over SRS alone, with hazard ratios of 2.61 and 2.15, respectively[19].

Another strategy to decrease the risk of neurocognitive toxicity due to whole brain radiation therapy was studied by RTOG 09-33, a phase II trial investigating the role of hippocampal avoidance in WBRT. The hippocampus is crucial for memory formation and hippocampal radiation is thought to contribute significantly to memory impairment in patients undergoing brain radiation. Thus, Gondi et al. demonstrated that in RTOG 09-33 there was a significant improvement in Hopkins Verbal Learning Test-Revised Delayed Recall at 4 months. While these results were significant and encouraging, criticisms of this study include the fact that only 42 of 113 patients were analyzable (likely due to patient dropout from death), the estimated 5% chance of failure at the hippocampal region, the comparison against historical controls, and the use of only one time point for assessment[20].

Brown et al. reported on RTOG 06-14 in which patients were randomized to WBRT with or without the addition of memantine, a drug thought to be protective against neurocognitive decline. Neurocognitive function was measured by multiple subtests of the Hopkins Verbal Learning Test – Revised (HVLT-R). The trial demonstrated a trend toward improved cognitive function with the addition of memantine that was not statistically significant, possibly due to the fact that only 149 of 508 patients were analyzable at the prespecified analysis point of 24 weeks[21].

Finally, whole brain dose de-escalation is another promising approach and is the strategy we propose to use in the present study. The concept of dose de-escalation in the brain is not novel. In fact, the standard dose for prophylactic intracranial irradiation (PCI) is 25 Gy in 10 fractions, lower than the 30 Gy in 10 fractions for standard WBRT. The goal for PCI is to eliminate microscopic disease, albeit in a relatively radiosensitive tumor histology[22]. Further, RTOG 09-33 as mentioned above essentially dose de-escalated in the hippocampal region alone with good effect. This trial allowed dose to 100% of the hippocampus to be 9 to 10 Gy, and the maximal hippocampal dose to be 16 to 17 Gy[23].

1.3. The concept of simultaneous integrated boost (SIB) with WBRT.

In the context of the current paradigm of SRS alone with close follow-up, reliable patients are ideally identified as early as possible if and when any new lesions should arise. Nonetheless, there is always the risk of patients not returning for follow-up and/or any new lesions causing unsalvageable neurologic deficit[19, 24]. Furthermore, this method is also primarily validated for treating 4 or fewer brain metastases. Patients with more than 4 brain

metastases are most often treated with WBRT with hippocampal avoidance when available, but often insurance denies payment when attempted off trial.

Recently, there have been some data suggesting that WBRT with SIB using intensity-modulated radiation therapy (IMRT) is technically feasible and can potentially approximate WBRT + SRS. Several dosimetric studies have demonstrated that WBRT with simultaneous integrated boosts up to 70.8 Gy is feasible using both reverse and forward planning on both helical tomotherapy and LINAC-based systems[25-28]. In particular, one study discusses that 30 Gy WBRT and 60 Gy SIB provides a similar biologically equivalent dose to the treated lesions as compared to a radiosurgical boost of 18 Gy after 30 Gy WBRT as was studied in RTOG 95-08[29]. Their calculations were based on the concept of the universal survival curve and single fraction equivalent dose[30].

Further, several institutions have reported on retrospective data demonstrating reasonable efficacy in terms of patient outcomes and intracranial disease control across a variety of platforms and dosing regimens. Weber et al. noted a 6 month in-brain progression-free survival of 77.9%[31]. Zhou et al. noted a 1 year local brain failure rate of 13.8% and distant brain failure rate of 19.2%[32]. Kim et al. noted a 1 year intracranial control rate of 67%[33]. Oehlke et al. noted a 1 year in-brain progression-free survival of 45.3%[34]. At a median follow-up of 4 months, Vargo et al. noted local brain control to be 72% and distant brain control to be 92%[35]. Tomita et al. noted a 1 year local control rate of 69%[36]. In addition, the phase I trial by Rodrigues et al. briefly discussed previously was not powered to assess control but did note a crude 75% overall brain control rate. Specifically, it noted that of 32 assessable patients, 4 had local progression, 2 had in-brain distant progression, and 4 had both[29].

The concept of WBRT + SIB has only been explored in a very limited sense as described above. Depending on the modality of SRS utilized (i.e., Gamma Knife vs LINAC-based), the incidental whole brain dose may start to approach therapeutic doses as increasing number of brain metastases and thus increasing number of beams or isocenters generate more low dose scatter throughout the brain. There have been some retrospective studies exploring SRS treatment to more than 4 lesions that attempt to evaluate the dose to normal brain. One study by Takahashi et al. suggests that when patients are treated with LINAC-based radiosurgery to more than 8 targets, 50% of the normal brain received a dose of 8.7 Gy or higher[37]. Studies by Xue et al. and Yamamoto et al. suggests that the normal brain dose is closer to a median of 3-5 Gy with radiosurgery to multiple targets, albeit on the Gamma Knife platform[16, 38]. Although conflicting, these studies do demonstrate a relatively small but potentially significant normal brain dose when treating with radiosurgery.

The theoretical advantage of WBRT + SIB over current, more standard therapeutic options includes maximizing the benefit of combined modality therapy (namely, better treated lesion and distant brain control over single modality treatment) as well as combining two disparate treatment courses into one course, all with little added morbidity or time on the patient's part. The role of WBRT in providing an overall survival benefit in patients with favorable prognosis is also being re-explored given the secondary analyses described in section 1.1.

1.4. The assessment of neurocognitive function.

Neurocognitive function assessment has been an area of investigation in brain radiation for many years, and particularly since the 2000s after the FDA indicated that neurocognitive outcomes were acceptable end points for clinical trials in the late 1990s. Meyers and Brown reviewed this topic in 2006 and identify 6 main characteristics that a neurocognitive test battery should have in order to be useful in the clinical trials setting[39].

1. Brevity – on the order of 30 minutes or less – is important to reduce patient and clinician burden.
2. Repeatability is necessary to account for improvement from pure repetition and learning the test (i.e., practice effects).
3. Psychometric robustness in terms of validity, reliability, and population norming is important to detect true changes in function rather than those related to situational or chance factors.
4. Sensitivity to changes in cognitive function in order to detect fine changes.
5. Standardization and ease of administration.
6. Ease of completion by patients, including those with significant cognitive deficits, which would reduce selection bias for those that will do well.

To assess neurocognitive function, we will use the Hopkins Verbal Learning Test Revised (HVLT-R.) The HVLT-R has been used and validated in multiple trials related to brain metastasis. In particular, RTOG 00-18 was a feasibility study of neurocognitive function testing on a national scale[40]. They demonstrated compliance rate for testing before treatment, at treatment completion, and at 1 month was $\geq$ 95%, $\geq$ 84%, and $\geq$ 70%, respectively. Several tests were assessed, including the HVLT. Meyer et al. reported on a phase III randomized trial investigating the benefit of motexafin gadolinium on the survival and neurologic and neurocognitive outcomes of patients receiving WBRT for brain metastases[41]. Of the several neurocognitive tools used, the HVLT for immediate recall, delayed recall, and recognition were incorporated. This study did not demonstrate any difference in time to neurocognitive function. It did show that compliance with testing was 87-98% at baseline and 77-87% at 6 months.

For the present protocol, we will be using the HVLT-R .The HVLT-R is a 12 noun list with 4 words each from 1 or 3 semantic categories that are learned over the course of three learning trials. After 20-25 minutes, delayed recall and recognition are also assessed. This test is estimated to take 5-10 minutes with a 25 minute delay in the middle to allow for appropriate assessment of delayed recall. The focus of this test is on assessing verbal learning and memory. In situations where in-person visits are discouraged or not allowed (e.g. the COVID-10/SARS-Co-V2 pandemic), we may opt to administer the HVLT-R via a telehealth visit.

A baseline neurocognitive function assessment will be performed at the time of CT simulation. The follow-up time points chosen include 3-, 6-, and 12-months post-treatment. Patients will be seen at 1-month post-treatment as well but will not be assessed for neurocognitive function at that time. Given our inclusion/exclusion criteria of a life expectancy of at least 6 months per ds-GPA (see Appendix 1 for more detail), we anticipate that a large proportion of our patients will be assessed at time points up to 6 months. We acknowledge the possibility that a small but significant proportion of our patients may die before the 12-month assessment but remain interested in attempting to examine long-term

cognitive outcomes. Neurocognitive assessment will be conducted by trained and certified research nurses or associates, these assessments may be conducted either in person or via remote modalities

1.5. The assessment of quality of life.

Quality of life is an important metric, particularly as the goal of therapies move away from curative intent toward palliative intent and life expectancies are limited. We will assess quality of life in our cohort of patients using the Functional Assessment of Cancer Therapy with Brain Subscale (FACT-Br) tool.

FACT-Br is a self-administered questionnaire assessing multiple dimensions of a person's daily life, including physical, social, emotional, and functional well-being, as well as specific questions related to neurocognitive quality of life that might be affected by cancer therapy to the brain. A total of 50 questions arranged on 3 pages are present, all using a 5-point Likert scale. This tool is available free-of-charge to academic institutions with registration of the study at www.facit.org, and with the agreement to provide the organization with a copy of any publications that result from the use of this questionnaire.

Our quality of life assessment will follow the same schedule as noted above for neurocognitive assessment. This may be completed in clinic or electronically or physically mailed to patient and completed survey returned to clinic.

1.6. Summary and specific aim.

Based on the summarized data above, we are interested in exploring the role of WBRT with SIB in the management of brain metastases. The concept is that WBRT with SIB would be expected to maximize both local and in-brain distant control as has already been shown in studies exploring WBRT with SRS boost. However, by itself WBRT with SIB does not address the concern over neurocognitive outcomes. **Therefore, we hypothesize that there is a lower WBRT dose threshold that will maintain acceptable in-brain distant control, particularly in the setting of a SIB to gross lesions to maintain treated lesion control.** In addition, lower overall brain dose (including lower hippocampal dose without specific hippocampal avoidance) may potentially improve neurocognitive function. We are also interested in evaluating treated lesion control, overall survival, neurocognitive sequelae of therapy, quality of life, performance status, and adverse effects of therapy. Biomarker identification for potential correlative circulating tumor DNA and microRNA is an exploratory endpoint to generate data for future prospective evaluation.

Ideally, this method would combine the benefit of combined modality therapy in preventing neurologic decline to due to an uncontrolled gross brain lesion (as demonstrated in SRS + WBRT) with the benefit of lower total brain dose in improving neurocognitive outcomes (as demonstrated by RTOG 09-33 and hippocampal avoidance). More realistically, we would find a balance between neurocognitive deficit from WBRT itself vs neurocognitive deficit from new and/or progressing lesions. We would also be able to treat more than 4 brain metastases as WBRT is already used in the setting of a significant burden of CNS disease. This method could also be an alternative at centers where Gamma Knife or radiosurgery is not available. Further, there is the added time and resource usage benefit of condensing two procedures (WBRT and SRS) into one procedure (WBRT + SIB). There is also a theoretical dosimetric advantage of taking into account both the whole brain aspect

and the boost aspect of the treatment in one planning session. Lastly, some patients are not able to tolerate the head frame placement that is required for Gamma Knife therapy, and WBRT + SIB would provide such patients with an additional treatment option. OBJECTIVES

2.1. Primary Objective

Evaluate two de-escalated whole brain radiation dose levels (in the setting of simultaneous integrated boost to gross lesions) with respect to in-brain distant control for brain metastases, defined as an in-brain failure rate outside of the planning target volume at 6 months of < 20%.

2.2. Secondary Objectives

1. Evaluate treated lesion control at 6 months for brain metastases in the setting of a predetermined total biologically effective SIB dose as determined by radiographic progression within the planning target volume with fusion and overlay of follow-up MRIs.
2. Evaluate overall survival at 6 months for brain metastases in the setting of WBRT with SIB.
3. Evaluate changes in neurocognitive function after WBRT with SIB in the following domains: verbal learning and memory as assessed by the HVLT-R.
4. Evaluate changes in health-related quality of life as assessed by the Functional Assessment of Cancer Therapy with Brain Subscale (FACT-Br) after WBRT-SIB for brain metastases.
5. Evaluate changes in performance status as assessed by the Karnofsky Performance Status tool (see Appendix 2) after WBRT-SIB for brain metastases.
6. Evaluate adverse events after WBRT-SIB for brain metastases according to current CTCAE criteria.

2.3. Exploratory Objective

Identify potential biomarkers that might help us in the future to develop a blood or urine test that can be used to predict response to therapy and radiation therapy side effects for each individual patient. Perform exploratory correlative analyses on blood and urine circulating tumor DNA and microRNA biomarkers with a focus on treated lesion control, in-brain distant control, and overall survival and their correlation to patient and treatment characteristics. To develop this test, we plan to collect blood, urine and tumor tissue (excess tissue that would normally be discarded), medical history, and treatment information. We will then compare the information from the analyses of the samples between patients that had recurrence or developed side effects to radiation therapy with those patients that did not have their cancer come back or have problems with their radiation treatment. The knowledge about these differences can then potentially be used to develop a blood or urine test to identify who will respond well to treatment, is at higher risk for recurrence, detecting it early if it comes back, or developing radiation side effects before radiation treatment is even started.

3. OUTCOME MEASURES

3.1. Primary Outcome Measure

In-brain distant failure, defined as an actuarial 6-month rate of new parenchymal lesions seen outside the planning target volume of any lesion that received SIB on any post-treatment MRI (in all 3 planes) by 6 months. Follow-up MRIs will be fused with the planning scan using our planning software for this assessment.

3.2. Secondary Outcome Measures

1. Treated lesion control, defined as an actuarial 6-month rate of any new, recurrent, or progressing (as defined by RANO criteria, see Appendix 3) tumor within the planning target volume on any post-treatment MRI by 6 months. Follow-up MRIs will be fused with the planning scan for this assessment.
2. Overall survival, defined as an actuarial 6-month rate of patients still alive regardless of disease status at 6 months.
3. Neurocognitive function change, defined as the change from baseline neurocognitive testing scores at a 6-month time point with respect to the HVLT-R.
4. Health-related quality of life change, defined as the change from baseline quality of life assessment at a 6-month time point with respect to the FACT-Br tool.
5. Performance status change, defined as the change from baseline performance status at a 6-month time point with respect to the KPS clinical assessment tool.
6. Incidence of early and late adverse effects as defined by the CTCAE, at any time point during the study follow-up.

3.3. Exploratory Outcome Measure

Generate data for sample size estimates for a future prospective study.

4. ELIGIBILITY CRITERIA

4.1. Inclusion Criteria

1. Age ≥ 18 at time of consent.
2. Ability to provide written informed consent and HIPAA authorization.
3. Pathological diagnosis of any solid tumor histology (from any site in the body).
4. Pathological or clinical/radiographic (i.e., by imaging) diagnosis of brain metastatic tumor lesions.
5. Total volume of lesions ≤ 30 cm^3.
6. Maximum volume of largest lesion ≤ 5 cm^3.
   a. This volume limit would be equivalent to a largest diameter of about 2.1 cm, assuming a perfect sphere.
7. Not a candidate for or eligible for but refused Gamma Knife radiosurgery.

4.2. Exclusion Criteria

1. Previous radiation to the brain, including WBRT or brain radiosurgery.
2. Life expectancy < 6 months (as estimated per the current ds-GPA, see Appendix 1 for details).
3. For histologies not included in the ds-GPA publications or otherwise noted online at *brainmetgpa.com*, the PI will use either published or validated data, or the PI's best clinical judgment to determine the patient's expected survival.
4. Inability to comply with treatment per investigator discretion.
5. Inability to complete neurocognitive assessments per investigator discretion.

Of note, tumor lesion number is not an inclusion or exclusion criteria as we are using volume-based criteria instead.

5. STUDY DESIGN

This trial is a pilot, Phase 2, sequential two-cohort study designed to test two de-escalated WBRT dose levels and assess their ability to maintain acceptable in-brain distant control. The WBRT dose would decrease as we move forward in the study, both in terms of absolute value and EQD2 (i.e., equivalent dose in 2 Gray fractions, as determined by the linear quadratic radiobiological model). The absolute value of the SIB dose will change with each dose level because the number of fractions delivered will depend on the WBRT dose. As such, the SIB dose will be manipulated such that the EQD2 will remain essentially equivalent despite the difference in the number of fractions delivered. This design will ensure that the only variable is the change in WBRT dose.

The next phase of investigation would depend upon the outcome of this study. If we are able to demonstrate that both treatment levels in this study meet our primary endpoint, it would suggest that we have not yet found the lowest acceptable WBRT dose. As such, we would then consider a similar study in which we lower the WBRT dose further. If we do find the lowest acceptable WBRT dose, we envision that the next step would be an appropriately powered equivalency trial comparing that lowest acceptable WBRT dose with SIB vs standard WBRT alone vs standard radiosurgery alone. Outcomes in this trial would include standard efficacy outcomes, survival outcomes, and neurocognitive outcomes.

6. PATIENT REGISTRATION

Potential patients will be identified and recruited per the recommendation of surgeons, medical oncologists, tumor boards, Department of Radiation Oncology, recommendations from outside physicians, or self-referral. No advertisement will be used to recruit subjects. Patients who appear to be eligible for this trial will undergo the Informed Consent Process and be screened for eligibility utilizing the eligibility criteria. Eligible patients who complete the Informed Consent Process will be registered in the OnCore® database and assigned a patient ID number. Regulatory files will be maintained by the Radiation Oncology Research Office. Applicable regulatory documents must be completed and on file prior to registration of any patients.

STUDY PROCEDURES

7.1. Radiation Therapy

Note: Intensity-modulated radiation therapy (IMRT) with volumetric arc therapy capability (VMAT) is required. Static IMRT is also allowed if VMAT is not available at the treating institution provided that planning goals and critical structure constraints are met. Rapid review by the Principal Investigator is required.

7.1.1. Dose Specifications

1. Prescription dose will be according to the following specifications.
   a. The whole brain planning target volume (PTV-WBRT, which is the whole brain volume minus the PTV tumor volumes without additional margin) will receive the pre-specified dosing schedule based on the study's current dose level (see Table 7-1 below). Treatment will be delivered once daily, 5 fractions per week, with breaks in treatment minimized.

      The gross tumor planning target volume (PTV-tumors) will receive the pre-specified dosing schedule based on the study's current dose level, which again has been determined such that the EQD2 will be essentially identical (see table below). Treatment will be delivered as a simultaneous integrated boost.
   b. The dose is prescribed such that <u>at least</u> 95% of the PTV-WBRT and PTV-tumors are each covered by at least 95% of its prescription dose. As a point of clarity, each individual lesion with "PTV-tumors" should be covered in this fashion.
   c. Maximum dose to 2% of the PTV-WBRT (D2%) is 120% of Rx and minimum dose to 98% of the PTV-WBRT (D98%) is 90% of Rx.
      Maximum dose to 2% of the PTV-tumors (D2%) is 125% of Rx.
   d. Please see section 7.1.6.2 for variations acceptable.

Table 7-1. Study Prescription Dose Table

	WBRT Rx Dose	SIB Rx Dose	# of daily fractions	SIB Dose in EQD2*
Cohort A	25	42	10	49.7 Gy
Cohort B	20	40	8	50.0 Gy
SRS^	20 Gy SRS		1	50.0 Gy

Notes: WBRT = whole brain radiation therapy; Rx = prescription; SIB = simultaneous integrated boost; EQD2 = equivalent dose in 2 Gy fractions; SRS = stereotactic radiosurgery.
*For ease of comparison, the SIB dose is converted to the equivalent dose in 2 Gy fractions using the linear-quadratic model of radiation response and assuming an α/ß ratio of 10 Gy as is seen in most tumor histologies.
^There is no SRS group as a separate study group. This comparison is included to demonstrate that the prescribed SIB doses are similar to a single 20 Gy SRS definitive treatment.

7.1.2. Technical Factors

1. Megavoltage equipment capable of delivering dynamic intensity modulation (using a multileaf collimator or tomotherapy) is required. However, the use of static intensity modulation at centers without dynamic modulation is also acceptable as stated above as long as dose specifications and constraints are satisfied.
2. A megavoltage beam of 6MV or greater must be used, with a minimum source-axis distance of 100 cm.
3. <u>MRI for Radiotherapy</u>

Three-dimensional spoiled gradient (SPGR), magnetization-prepared rapid gradient echo (MPRAGE), or turbo field echo (TFE) axial MRI scan with standard axial and coronal fluid attenuation inversion recovery (FLAIR), axial T2-weighted and gadolinium contrast-enhanced T1-weighted sequence acquisitions will be required to allow for accurate contouring of the hippocampus. To yield acceptable image quality, the MRI scan should use the smallest possible axial slice thickness not exceeding 1.5 mm. The associated coronal and sagittal sequences can be up to 2.5 mm in slice thickness. These imaging sequences should be obtained with the patient in the supine position. The MRI should be obtained within 4 weeks prior to study entry or, if not obtained prior to study entry, within 2 weeks prior to treatment initiation. Immobilization devices used for CT simulation and daily radiation treatments need not be used when obtaining these imaging sequences, but an attempt should be made to image the patient in as close to the same plane as the CT simulation as possible to facilitate fusion of the MRI and CT images.

7.1.3. Localization, Simulation, and Immobilization

1. Patients will be immobilized in the supine position using an immobilization device such as an Aquaplast mask over the head. Patients will be treated in the immobilization device.
2. A non-contrast treatment-planning CT scan of the entire head region using the smallest possible axial slice thickness not exceeding 2.5 mm will be required to define clinical and planning target volumes and hippocampal avoidance regions. The treatment-planning CT scan must be acquired with the patient in the same position and with the same immobilization device as for treatment. This scan should be obtained within 2 weeks prior to initiating treatment.
3. MRI-CT Fusion
   The MRI for radiotherapy planning (see Section 7.1.2) and treatment-planning CT should be fused semi-automatically for contouring of targets and normal structures.

7.1.4. Target Volumes

1. The Gross Tumor Volume is defined for the grossly identified lesions on MRI only (GTV-tumors), and encompasses all visible disease seen on MRI as determined by an appropriately trained physician.
2. The Clinical Target Volumes (CTV) are defined per the following specifications.
   a. For whole brain treatment, CTV-WBRT is defined as the whole brain parenchyma to C1 (if there is no evidence of posterior fossa metastasis) or C2 (if there is MRI evidence of posterior fossa metastasis).
   b. For gross tumor treatment, CTV-tumors is the same as GTV-tumors. In other words, there is no contour expansion difference from GTV to CTV.
3. The Planning Target Volumes (PTV) are defined per the following specifications.
   a. For whole brain treatment, PTV-WBRT is the same as CTV-WBRT. In other words, there is no contour expansion difference between CTV and PTV.
   b. For gross tumor treatment, PTV-tumors is the CTV-tumors contour with a 2 mm uniform expansion in all directions.

7.1.5. Critical Structures

1. The lenses, orbits, optic nerves, optic chiasm, cochlea, pituitary, brainstem, and hippocampi will be contoured as per the experience of the dosimetrist on the case or

the treating physician (in particular, for the hippocampi). Care should be taken to minimize the dose to the lens and orbits. Dose to any point within the optic nerves or optic chiasm cannot exceed 37.5 Gy. Dose to the hippocampi will be noted and recorded but should not change any decisions regarding treatment planning.

2. Please refer to the RTOG hippocampal contouring atlas if needed at https://www.rtog.org/corelab/contouringatlases/hippocampalsparing.aspx.

7.1.6. Radiation Therapy Quality Assurance Review

NOTE: PRIOR TO DELIVERING ANY PROTOCOL TREATMENT, all WBRT-SIB treatment plans must be reviewed and approved by the Principal Investigator. WBRT-SIB treatment cannot be initiated until permission has been granted.

1. The Principal Investigator, Kevin Shiue , MD, will perform an RT Quality Assurance Review for each case from all sites before the start of treatment. Plans should include complete data, including the fused planning MRI-planning CT image set with the associated treatment plan with dose-volume histogram (most often in the DICOM-RT format). Plans must be approved by the Principal Investigator prior to treatment initiation.
2. Acceptable Variations
    a. Plans with up to 5% deviation in the specified dosimetric parameters in sections 7.1.1 and 7.1.7 may be approved by the Principal Investigator at his discretion.
3. Review Process and Unacceptable Deviations
   Treating physicians may be required to modify MRI-CT fusion and repeat the WBRT-SIB planning. Resubmission of the new treatment plan with revised contours does not require review to occur prior to WBRT-SIB initiation UNLESS requested by the Principal Investigator. This determination will be made at the time that unacceptable deviations are communicated to the treating physician.

7.1.7. Critical Structure Constraints

Table 7-2. Critical Structure Constraints

Structure	Dose constraint	
Optic nerves and chiasm	D_{max}	34 Gy
Cochlea	D_{max}	32 Gy
Pituitary	D_{max}	36 Gy
Brainstem	D_{max} < 5 cc	44 Gy > 37.5 Gy

*Assuming α/ß ratio of 2 for CNS normal structures and highest dose per fraction scenario (i.e., 8 fractions).

7.1.8. Use of Neuroprotective Agents

Memantine and other similar neuroprotective agents should not be used with patients on this trial.

7.1.9. Radiation Therapy Interruptions

1. Radiotherapy will be continued without interruption if at all possible.
2. If the sum total of radiotherapy interruptions exceeds 3 normally scheduled treatment days, the treatment will be considered an unacceptable deviation from the protocol**.** This should be reported to the Principal Investigator and the patient will be considered inevaluable on final data analysis.

7.2. Neurocognitive Function Assessment

Neurocognitive function assessment will be performed using the HVLT-R Neurocognitive assessment will be performed on all patients during a clinic visit at baseline (i.e., before first treatment, at the time of simulation if possible) and 3, 6, and 12 months after treatment ends.

7.2.1. HVLT-R

The HVLT-R is a 12 noun list with 4 words each from 1 or 3 semantic categories that are learned over the course of three learning trials. After 20-25 minutes, delayed recall and recognition are also assessed. This test is estimated to take 5-10 minutes with a 25 minute delay in the middle to allow for appropriate assessment of delayed recall. The focus of this test is on assessing verbal learning and memory. Please see Appendix 4 for a sample of one of the forms for the HLVT-R. The forms used for study will need to be purchased. This test may be administered remotely per the discretion of the PI.

7.3. Quality of Life Assessment

7.3.1. FACT-Br

FACT-Br is a self-administered questionnaire assessing multiple dimensions of a person's daily life, including physical, social, emotional, and functional well-being, as well as specific questions related to neurocognitive quality of life that might be affected by cancer therapy to the brain. A total of 50 questions arranged on 3 pages are present, all using a 5-point Likert scale. The FACT-Br is estimated to take 5 minutes to complete.

Participants will be given the FACT-Br to complete either on paper, computer, or tablet either during a clinic visit or completed at home, at baseline (i.e., before first treatment, at simulation if possible) and 3, 6, and 12 months after treatment ends. Please see Appendix 5 for a copy of the FACT-Br.

7.4. Tumor Assessment

Standard diagnostic quality MRIs will be ordered for routine follow-up at 3, 6, and 12 months after treatment ends. Please see Appendix 3 for details regarding the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria. We plan on adhering to the RANO-BM guidelines except in the following situations:

1. RANO-BM specifies that no more than 5 "target lesions" are followed for the study outcome. Further, it cautions on following lesions > 5 mm but < 10 mm in maximal dimension, but does provide guidelines for this situation. We plan on following all (i.e., potentially > 5) lesions that are treated and > 5 mm in maximal dimension for the study outcome using the RANO-BM suggested criteria for lesions < 10 mm in maximal dimension.
2. We also plan on following treated lesions < 5 mm in size for descriptive assessment as per RANO-BM guidelines. In particular, we agree that it is difficult to reliably reproduce small measurements (i.e., measurements for partial response or slight progression) with such small sizes and the limitation of MRI slice thicknesses. However, as these are treated lesions, we would still like to follow them prospectively.

7.5. Correlative Blood and Urine Collection

Blood and urine will be obtained from patients who consent to this optional procedure at the following time points: at baseline (i.e., before first treatment, at simulation if possible), 1st day of radiation treatment (before and after treatment delivery), 5th day of radiation treatment (after treatment delivery), last day of radiation treatment (after treatment delivery), and at the 1-month follow-up visit. One 10 mL tube of blood and approximately one cup of urine (~ 100 mL) will be collected at each time point. Blood and urine will be delivered to the laboratory of Dr. Tim Lautenschlaeger in the IU Department of Radiation Oncology for processing and analysis.

8. STUDY CALENDAR

	Prior to treatment		Treatment	Post WBRT-SIB treatment follow up			
	Within 30 days prior registration	Within 2 weeks prior to treatment start	WBRT-SIB	1 month +/-14 days	3 months +/-30 days	6 months +/-30 days	12 months +/-30 days
REQUIRED ASSESSMENTS							
History and physical	X						
Karnofsky Performance Status evaluation	X			X	X	X	X
GFR/ Cr Cl	X						
Serum pregnancy test (if applicable)		X					
Adverse events		X[2]	X[2]	X	X	X	X
Neurocognitive function assessment		X			X	X	X
Quality of life assessment		X			X	X	X
DISEASE ASSESSMENT							
Contrast-enhanced brain MRI	X						
CT simulation scan		X					
TREATMENT							
WBRT-SIB planning and approval		X					
WBRT-SIB treatment			X				
CORRELATIVE STUDIES							
Optional blood and urine collection[1]		X	X	X			
FOLLOW-UP							
Physical exam and neurologic assessment				X	X	X	X

Footnotes:

1. Time points for correlative blood and urine collection: at time of simulation, 1st day of radiation treatment (before and after treatment delivery), 5th day of radiation treatment (after treatment delivery), last day of radiation treatment (after treatment delivery), and at the 1 month follow-up visit.
2. Adverse events related to blood draw and urine collection only will be documented at these time points.

9. CRITERIA FOR REMOVAL FROM THE STUDY

Every subject should be encouraged to remain in the study. Possible reasons for early withdrawal may include, but are not limited to, the following:

1. Withdrawal of consent – Subject decides to withdraw from the study. This decision must be an "independent decision" that is documented in the source documentation.
2. Principal Investigator and/or treating physician discretion – The Principal Investigator and/or treating physician may choose to withdraw a subject from the study if there are safety (or other) concerns.
3. Subject becomes pregnant.
4. Subject non-compliance.
5. Subject lost to follow-up.
6. Subject death.

10. STATISTICAL METHODS

10.1. General Considerations

Statistical analysis of this study will be the responsibility of the Department of Biostatistics at Indiana University School of Medicine. Parameter estimates and relevant summary statistics will be reported for both efficacy and safety outcomes. Continuous variables will be summarized by means, medians, minima, maxima and standard deviations. Categorical variables will be summarized by frequencies and percentages. Missing data will not be imputed. Additional exploratory analysis will be conducted when appropriate. Changes from the analysis plan will not require an amendment to the protocol unless it changes a significant feature in the protocol. The statistical analysis methods are outline below.

10.2. Study Design

This is a Pilot, Phase 2, sequential two-cohort trial. No randomization or blinding will be done.

10.3. Criteria for Stopping Study

An interim analysis is planned when the final patient in Cohort A finishes their six month assessment. If 20% or more of the evaluable subjects have in-brain distant failure at the 6 month time point, then the study will stop.

Additionally, there will be an early stopping rule in place. Each patient will be evaluated at 6 months for in-brain distant failure. If 4 patients out of the first 10 patients within each cohort have in-brain distant failure at 6 months, then the expected percent of patients would be double of what is expected (40% vs the expected 20%). This finding will prompt a re-assessment of treatment efficacy to determine if the cohort should continue.

10.4. Analysis Datasets

10.4.1. Enrolled Population

The enrolled population comprises all subjects who meet the eligibility criteria and are registered onto the study.

10.4.2. Safety Population

The safety population comprises all subjects who have received at least one dose of radiation. This set will be used for safety analysis.

10.4.3. Efficacy Population

The efficacy population comprises all subjects who have received at least one dose of radiation, and have been evaluated for the primary endpoint (the 6 month scan). This population will be used for efficacy analysis.

10.5. Sample Size

A total sample size of 20 evaluable subjects per cohort was determined to balance the competing goals of assessing the primary objective while not exposing more subjects to an investigational decreased radiation procedure than is required. Historical data has shown that approximately 20% of subjects with standard radiation treatment show in-brain distant failure at 6 months. This trial is looking to see if decreased radiation will provide similar efficacy to the standard of care. There will be an interim analysis after the first cohort completes their 6 month scans. If less than 20% of the subjects have in-brain distant failure, then the second cohort will start.

With 20 evaluable subjects in a cohort, the 90% confidence interval around the proportion of subjects who are expected to have in-brain distant failure at 6 months would extend at most +/- 14.7%. Up to 25 subjects may be enrolled in each cohort. Although subjects who die before 6 months without confirmed in-brain distant failure would be replaced if possible, the following table will show the estimated confidence interval widths assuming the 20% proportion of subjects who may have in-brain distant failure at 6 months:

Number of Patients:	15	20	25
90% Confidence interval width:	17.0%	14.7%	13.2%

As stated in section 7.1.9, patients will not be considered evaluable if the sum total of radiotherapy interruptions exceeds 3 normally scheduled treatment days.

10.6. Patient Characteristics and Significant Protocol Violations

Baseline subject characteristics will be tabulated, such as demographics (age, race, gender), and disease characteristics (KPS score). Significant protocol violations such as with respect to eligibility criteria and cohort will be tabulated.

10.7. Disposition

The reasons for patient treatment and study discontinuation will be summarized by cohort.

10.8. Analysis of Primary Objectives

All analyses will be done by cohort. For the primary objective, the number of patients who have in-brain distant failure in the evaluable patients will be summarized and exact binomial 95% confidence intervals will be determined.

10.9. Analysis of Secondary Objectives

For Local Control and Overall Survival, the median and the corresponding two-sided 95% confidence intervals will be calculated using the Kaplan-Meier method. Estimates and 95% confidence intervals will also be provided for 6 and 12 months.

For quality of life measures and neurocognitive assessments, appropriate subscales will be calculated at each time point, along with change from baseline to 3, 6, and 12 months, and summarized descriptively by cohort. Baseline Karnofsky Performance Status and change from baseline to 1, 3, 6, and 12 months will also be summarized and reported by cohort. Summary descriptive statistics only (i.e. no inferential statistics) will be used for all measures except for HVLT-R. An analysis will be done for HVLT-R to use the change from baseline results and compare them to the results generated from the RTOG 0933 study. Wilcoxon Rank Sum Tests will be used for this comparison.

All safety data will be listed. For the treatment-emergent AEs, namely AEs started or worsened during the on-treatment period, the incidence will be summarized by system organ class and/or preferred term, severity based on CTCAE grades, type of adverse event and the relation to the study drug. Deaths reportable as SAEs and non-fatal serious adverse events will be listed by and tabulated by type of adverse event. This will be done with the safety set.

10.10. Analysis of Exploratory Objective

The biomarkers of circulating tumor DNA and microRNA in blood and urine, both pre-treatment and changes over time, will be correlated with treated lesion control, in-brain distant control, and overall survival using Cox proportional hazards regression. Time dependent ROC curves will be generated to assess predictive ability.

10.11. Interim Analysis

After the first cohort completes the 6 month scans, an interim analysis will be conducted. If less than 20% of the patients have in-brain distant failure, then the next cohort will begin enrollment. If 20% or more of the patients have in-brain distant failure, then the study will stop.

11. DATA FORMS AND SUBMISSION SCHEDULE

This study will utilize electronic Case Report Form completion in the OnCore® database for all measures. A calendar of events and required forms are available in OnCore®. The OnCore® database is a comprehensive, web-based, Clinical Trial Management System (CTMS) which utilizes an Oracle database. OnCore® was developed by Forte Research Systems, Inc. and is used by the IUSCCC Clinical Trials Office (CTO) and supported by the Indiana Clinical and Translational Sciences Institute (CTSI). OnCore® properly used is compliant with Title 21 CFR Part 11.

OnCore® provides users secure access with unique IDs/passwords and restricts access by assigned roles, from any location, to record, manage, and report on data associated with the operation and conduct of clinical trials.

All source documents are to remain in the patient's clinic file. All documents should be kept according to applicable federal guidelines. Clinical trial data in OnCore® are periodically monitored by the IU Simon Comprehensive Cancer Center Data Safety Monitoring Committee.

12. PATIENT CONSENT AND PEER JUDGMENT

The protocol and informed consent form for this study must be approved in writing by the appropriate Institutional Review Board (IRB) prior to any patient being registered on this study.

Changes to the protocol, as well as a change of principal investigator, must also be approved by the Board. Records of the Institutional Review Board review and approval of all documents pertaining to this study must be kept on file by the investigator (housed in the Radiation Oncology Clinical Trials Office) and are subject to inspection at any time during the study. Periodic status reports must be submitted to the Institutional Review Board at least yearly, as well as notification of completion of the study and a final report within 3 months of study completion or termination.

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

13. DATA AND SAFETY MONITORING PLAN

Investigators will conduct continuous review of data and patient safety. **Monthly review meetings** for **moderate risk trials** are required and will include the principal investigator, clinical research specialist and/or research nurse (other members per principal investigator's discretion). **Monthly** meeting summaries should include review of data, the number of patients, significant toxicities as described in the protocol, and responses observed. Summaries will be submitted and reviewed monthly by the DSMC. Submit to DSMC@iupui.edu.

13.1. Study Auditing and Monitoring

All trials conducted at the IUSCCCare subject to auditing and/or monitoring. Reports will be reviewed by the full DSMC at the time of study review (Reference Risk Table in full DSMC Charter).

13.2. Early Study Closure

At any time during the conduct of the trial, if it is the opinion of the investigators that the risks (or benefits) to the patient warrant early closure of the study, this recommendation should be made in writing to the Data Safety Monitoring Committee. Alternatively, the DSMC may initiate suspension or early closure of the study based on its review of the investigator reports.

13.3. Reporting Guidelines

The DSMC has streamlined the reporting process by utilizing reports from OnCore®. This has allowed direct view of reports within the Clinical Trials Management System (CTMS); thus discontinuing paper reports. SAE reports are entered into OnCore® monthly and reviewed by the DSMC chair and/or coordinator monthly. Findings will be reported to the full DSMC at the time of study review.

13.4. Study Accrual Oversight

Accrual data will be entered into the IU Simon Comprehensive Cancer Center OnCore® system. The Protocol Progress Committee (PPC) reviews study accrual twice per year while the PPC coordinator reviews accrual quarterly.

13.5. Protocol Deviations

Protocol deviations are entered into OnCore® and reviewed by the DSMC chair and/or coordinator monthly. Findings will be reported to the full DSMC at the time of study review.

14. REPORTING ADVERSE EVENTS

14.1. Definitions of Adverse Events

14.1.1. Adverse Event (AE)

An **adverse event** is defined as untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention related. An adverse event can be **ANY** unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporarily associated with the use of an intervention, whether or not considered related to the intervention (attribution of 'unrelated', 'unlikely', 'possible', 'probable', or 'definite'). Adverse events will be graded according to current CTCAE criteria.

14.1.2. Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence resulting in one or more of the following:

- Results in death or ANY death occurring within 30 days of a biopsy procedure (even if it is not felt to be related).
- Is life-threatening (defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization ≥ 24 hours or prolongation of existing hospitalization

  NOTE: Hospitalizations that are not considered SAEs are:
  - Hospitalization planned prior to biopsy procedure
  - Hospitalization < 24 hours in duration
  - Hospitalization for elective treatment of a pre-existing condition unrelated to biopsy procedure.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the patient or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.

14.1.3. Unanticipated Problems

Investigators are required to submit unanticipated problems to the Indiana University Simon Comprehensive Cancer Center (IUSCCC) Data Safety Monitoring Committee (DSMC) (see Section 11.2 below) concurrent with their submission of them to the IRB. Prompt reporting of unanticipated problems to the IRB is defined as within 5 days for on-site studies.

Unanticipated problems that will be reported promptly to the IRB include:

- Major protocol deviation/violation

- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject (e.g. purposeful and for subject safety)
- Complaint of a subject that indicates unexpected risks, or complaint that cannot be resolved by the research team
- Publication in the literature, safety monitoring report, interim result or other finding that indicates an unexpected change to the risks or potential benefits of the research, in terms of severity or frequency
- Investigator- or sponsor-initiated suspension or hold
- Serious or continuing non-compliance
- Adverse events (see Section 14.2 below)

14.1.4. Determining Attribution to the Intervention(s)

Attribution is an assessment of the relationship between the AE and the medical intervention. CTCAE v5.0 attribution categories will be used. CTCAE does not define an AE as necessarily *"caused by a therapeutic intervention"*. After naming and grading the event, the clinical investigator must assign an attribution to the AE using the attribution categories in Table 14-1 below.

Table 14-1. CTCAE Attribution Categories

Relationship	Attribution	Description
Unrelated to investigational intervention	Unrelated	The AE is clearly **NO**T related
	Unlikely	The AE is **doubtfully related**
Related to investigational intervention	Possible	The AE **may be related**
	Probable	The AE **is likely related**
	Definite	The AE **is clearly related**

14.2. Adverse Event (AE) and Serious Adverse Event (SAE) Reporting

Adverse events (AEs) will be recorded from the time of registration through 12 months after treatment (i.e., WBRT-SIB) regardless of whether or not the event(s) are considered related to the study procedure. All AEs considered related to study procedures will be followed until resolution, return to baseline, or deemed clinically insignificant, even if this occurs post-trial. Any death occurring within 30 days after the last study procedure must be reported as an SAE regardless of attribution.

14.2.1. Reporting to the IRB

Unanticipated problems involving risks to subjects or others will be reported **promptly** to the IRB if they:

- are unexpected;
- are related or possibly related to participation in the research; and
- suggest that the research places subjects or others at a greater risk of harm than was previously known or recognized.

If the serious adverse event does not meet all three (3) criteria listed above, the event does not have to be promptly reported to the Indiana University IRB. However, it should be reported at the time of continuing review.

Prompt reporting of unanticipated problems to the IRB is defined as within 5 days from becoming aware of the event.

14.2.2. Reporting to the IUSCCC Data Safety Monitoring Committee

Regardless of study sponsorship, the study team must enter all initial and follow-up SAE, expedited, and noncompliance reports into OnCore® for review by the DSMC chair and/or coordinator. Expedited reports may include IRB Prompt Report Forms and additional SAE forms as required by the sponsor. When follow-up information is received, a follow-up report should also be created in OnCore®. This DSMC reporting requirement is **in addition to any other** regulatory bodies to be notified (i.e. IRB, FDA, pharmaceutical company, etc.). The DSMC chair and/or coordinator will review all SAE, expedited, and noncompliance reports monthly and findings will be reported to the full DSMC quarterly.

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16. APPENDICES

16.1. Appendix 1. Disease-Specific Graded Prognostic Assessment for Brain Metastases (ds-GPA)

Table 16-1. Disease Specific Graded Prognostic Assessment Criteria for Brain Metastases[8-11, 13]

Variable	Points						
	0	0.5	1	1.5	2	3	4
NSCLC							
Age, y	≥ 70	< 70	-	-	-	-	-
KPS	< 70	80	90 - 100	-	-	-	-
# of cranial metastases	> 4	1 - 4	-	-	-	-	-
Extracranial metastases	Present	-	Absent	-	-	-	-
Gene status (adenocarcinoma only)	EGFR neg/unk and ALK neg/unk	-	EGFR pos or ALK pos	-	-	-	-
SCLC							
Age, y	> 60	50 - 60	< 50	-	-	-	-
KPS	< 70	70 - 80	90 - 100	-	-	-	-
# of cranial metastases	> 3	2 - 3	1	-	-	-	-
Extracranial metastases	Present	-	Absent	-	-	-	-
Breast							
KPS	≤ 50	60	70-80	90 – 100	-	-	-
Histologic subtype	Basal	-	LumA	Her2	LumB	-	-
Age	≥ 60	< 60	-	-	-	-	-
Renal | Melanoma							
KPS	< 70	-	70 - 80	-	90 - 100	-	-
# of cranial metastases	> 3	-	2 - 3	-	1	-	-
GI							
KPS	< 70	-	70	-	80	90	100

Notes: neg = negative; unk = unknown; pos = positive; basal = triple-negative; LumA = luminal A = ER/PR+ her2-; Her2 = ER/PR- her2+; LumB = luminal B = triple-positive.

Table 16-2. Median Overall Survival (months) per ds-GPA Score[10, 13]

GPA Score	NSCLC		SCLC	Melanoma	Renal cell	Breast	GI
	Adenocarcinoma	Nonadenocarcinoma					
0.0 - 1.0	6.9	5.3	3.0	3.4	3.3	3.4	3.1
1.5 - 2.0	13.7	9.8	5.5	4.7	7.3	7.7	4.4
2.5 - 3.0	26.5	12.8	9.4	8.8	11.3	15.1	6.9
3.5 - 4.0	46.8	-	14.8	13.2	14.8	25.3	13.5
Overall	15.2	9.2	4.9	6.7	9.6	13.8	5.4

Please refer to http://www.brainmetgpa.com/ for the most up-to-date web-based version of this data that streamlines the scoring and assessment process for each patient. The table reproduced above was current at protocol inception, but the most up-to-date web-based version at time of registration should be used for each patient.

16.2. Appendix 2. Performance Status Scales

ECOG or Zubrod		Karnofsky		Lansky	
Score	Activity	Score	Activity	Score	Activity
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	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.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

16.3. Appendix 3. Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM)

16.3.1. Definitions Associated with RANO-BM[46]

1. **Measurable disease** is defined as a contrast-enhancing lesion that can be accurately measured in at least one dimension, with a minimum size of 10 mm, and is visible on two or more axial slices that are preferably 5 mm or less apart with 0 mm skip (and ideally ≤ 1.5 mm apart with 0 mm skip).
   a. Additionally, although the longest diameter in the plane of measurement is to be recorded, the diameter perpendicular to the longest diameter in the plane of measurement should be at least 5 mm for the lesion to be considered measurable.
   b. If the MRI is performed with thicker slices, the size of the measurable lesion at baseline should be at least double the slice thickness. Interslice gaps, if present, should also be considered in the determination of the minimum size of measurable lesions at baseline.

2. **Non-measurable disease**
   Non-measurable disease includes all other lesions, including lesions with longest dimension less than 10 mm, lesions with borders that cannot be reproducibly measured, dural metastases, bony skull metastases, cystic-only lesions, and leptomeningeal disease.

3. **Special considerations regarding lesion measurability**
   a. For investigators who choose to lower the minimum size limit of **measurable disease** to 5 mm, the RANO-BM working group strongly recommends MRI imaging with 1.5 mm slice thickness or less.

      Complete response and unequivocal progressive disease can probably be interpreted even with lesions as small as 5 mm. However, measurement of small changes, such as the minimum 20% increase in the longest diameter to determine progressive disease or the minimum 30% decrease in longest diameter to determine partial response, might not be robust or reproducible. With the intrinsic uncertainty of measurements of small lesions, any lesion less than 10 mm in longest diameter should be regarded as unchanged from baseline unless there is a minimum 3 mm change in the measured longest diameter.

      For studies in which CNS objective response is the primary endpoint, the RANO-BM working group generally recommends a cutoff of 10 mm to limit the study to measurable disease.
   b. **Cystic or surgical cavities** should be considered non-measurable as noted above unless there is a nodular component that measures 10 mm or more in longest diameter and 5 mm or more in the perpendicular plane. The non-nodular component (i.e., the cyst or surgical cavity) should not be included in the measurement for determination of a response.
   c. The decision to include patients with multiple lesions with a sum diameter of 10 mm or more but of which the largest lesion measures less than 10 mm should be taken with caution if objective response is the primary endpoint. If such patients are included, response should be assessed using the sum of the longest diameters of the lesions, and the response criteria should be clearly delineated in the protocol. Thin-section MRI imaging with 1.5 mm or thinner slice thickness would be necessary in this setting.

4. **Methods of measurement**
   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. Consistent use of imaging techniques across all imaging time points is important to ensure that the assessment of interval appearance, disappearance of lesions, or change in size is not affected by scan parameters such as slice thickness. Use of thin section imaging is particularly important for the assessment of lesions less than 10 mm in longest diameter or small changes in lesion size, or both.

   Gadolinium-enhanced MRI is the most sensitive and reproducible method available to measure CNS lesions selected for response assessment. MRI is strongly encouraged as the default standard imaging technique, although CT with and without contrast could be considered in specific circumstances (e.g., countries with limited medical resources or contraindication for MRI).

5. **Tumor response assessment**
   Only patients with measurable CNS disease at baseline should be included in protocols where objective CNS tumor response is the primary endpoint. For studies in which objective response is not the primary endpoint, the protocol must specify prospectively whether entry is restricted to those with measurable disease or if patients with non-measurable disease are also eligible.
   a. Assignment of CNS response is independent of systemic disease response. CNS lesions are to be assessed according to RANO-BM criteria, whereas non-CNS lesions would most typically be assessed according to RECIST 1.1 criteria.
   b. Generally, CNS lesions should initially be re-assessed by MRI at protocol-specified intervals 6–12 weeks apart, although there might be specific circumstances in which longer (or shorter) intervals are desirable. For patients who remain stable for extended periods of time, a longer interval between scans might be appropriate. All baseline assessments should be done as close as possible to the treatment start and no more than 4 weeks before the beginning of treatment.
   c. For previously treated lesions, we recommend documentation of how each lesion was previously treated (e.g., stereotactic radiosurgery, whole brain radiotherapy, surgical resection).
   d. When more than one measurable lesion in the CNS is present at baseline, all lesions up to a maximum of five CNS lesions should be identified as target lesions and will be recorded and measured at baseline. All measurements should be recorded in metric notation. Target lesions should be selected on the basis of their size (longest diameter) and as those that can be measured reproducibly. For patients with recurrent disease who have multiple lesions, of which only one or two are increasing in size, the enlarging lesions should be prioritized as target lesions for the response assessment.
   e. Lesions with prior local treatment (i.e., stereotactic radiosurgery or surgical resection) can be considered measurable if progression has occurred since the time of local treatment. However, careful consideration should be given to lesions previously treated with stereotactic radiosurgery, in view of the possibility of treatment effect, which is discussed below. Whether such lesions can be considered measurable should be

specified prospectively in the clinical protocol. If lesions not previously treated with local therapies are present, these are preferred for selection as target lesions.

f. A sum of the diameters for all target lesions will be calculated and reported as the baseline sum of longest diameters. All other CNS lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be classified as present, absent, or unequivocal progression, and followed up.

16.3.2. Response assessment of target and non-target lesions[46]

Please see Table 16-3 and Table 16-4 for a partial summary of this section.

1. While on study, all CNS target lesions should have their actual measurement recorded, even if very small (e.g., 2 mm). If the lesion disappears, the value should be recorded as 0 mm. However, if the lesion is sufficiently small (but still present) to be assigned an exact measurement, a default value of 5 mm should be recorded on the case report form.
2. Lesions might coalesce during treatment. As lesions coalesce, a plane between them may be maintained that would aid in obtaining maximum longest diameter of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.
3. New lesions can appear during treatment. The finding of a new CNS lesion should be unequivocal and not due to technical or slice variation. A new lesion is one that was not present on prior scans.
   a. If the MRI is obtained with slice thickness of 1.5 mm or less, the new lesion should also be visible in axial, coronal, and sagittal reconstructions of 1.5 mm or thinner projections.
   b. If a new lesion is equivocal, for example because of its small size (i.e., $\leq$ 5 mm), continued therapy can be considered, and a follow-up assessment will clarify if it really is new disease. If repeated scans confirm a new lesion, progression should be declared using the date of the initial scan showing the new lesion.
   c. In the case of immunotherapy, however, new lesions alone cannot constitute progressive disease (see below).
4. Unequivocal progression of non-target lesions can merit discontinuation of therapy.
   a. When a patient also has measurable disease, to be deemed as having unequivocal progression on the basis of non-target disease alone there must also be an overall substantial worsening in non-target disease such that, even in the presence of stable disease or partial response in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.
   b. When the patient has only non-measurable disease, there must be an overall level of substantial worsening to merit discontinuation of therapy.
5. The RANO-BM group acknowledges the case of patients who have been treated with stereotactic radiosurgery or immunotherapy-based approaches, for whom there has been radiographical evidence of enlargement of target and non-target lesions, which do not necessarily represent tumor progression. If radiographical evidence of progression exists, but clinical evidence indicates that the radiological changes are due to treatment effect (and not to progression of cancer), additional evidence is needed to distinguish between true progression and treatment effect, in which case standard MRI alone is insufficient. The methods used to distinguish between true progression and treatment effect should be

specified prospectively in the clinical protocol. Patients can be continued on protocol therapy pending further investigation with one or more of the following options.

The scan can be repeated at the next protocol-scheduled assessment or sooner, and generally within about 6 weeks. An investigator can choose a shorter time interval if progressive symptoms or other clinical concerns arise. Continued tumor growth might be consistent with radiographical progression, in which case the patient should leave the study. Stabilization and shrinkage of a lesion can be consistent with treatment effect, in which case the patient can stay in the study. For patients with equivocal results even on the next restaging scan, the scan can be repeated again at a subsequent protocol-scheduled assessment or sooner, although surgery or use of an advanced imaging modality (in the case of stereotactic radiosurgery), or both, are strongly encouraged. Surgical pathology can be obtained via biopsy or resection.

a. For lesions treated by stereotactic radiosurgery, additional evidence of tumor progression or treatment effect (radionecrosis) can be acquired with an advanced imaging modality, such as perfusion MRI, magnetic resonance spectroscopy, or ^{18}FLT or ^{18}FDG PET. Current recommendations suggest involving a multidisciplinary team to decide on the appropriate next step. Irrespective of the additional testing obtained, if subsequent testing shows that progression has occurred, the date of progression should be recorded as the date of the scan this issue was first raised.

   Patients can also have an equivocal finding on a scan (e.g., a small lesion that is not clearly new). Continued treatment is permissible until the next protocol-scheduled assessment. If the subsequent assessment shows that progression has indeed occurred, the date of progression should be recorded as the date of the initial scan where progression was suspected.

b. In patients receiving immunotherapy-based treatment, an initial increase in the number and size of metastases can be followed by radiographical stabilization or regression. This pattern might be related to the mechanism of action of immunotherapy, including immune infiltrates, and the time to mount an effective immune response. Thus, progressive disease should not be solely defined by the appearance of new lesions but rather as a minimum 20% increase in the sum longest diameter of CNS target and new lesions, as unequivocal progression of existing enhancing non-target CNS lesions, as unequivocal progression of existing non-enhancing (T2/FLAIR) CNS lesions, or as clinical decline related to the tumor. If immune response-related radiographical changes are suspected, we advise to not change treatment until a short interval scan is obtained. If the subsequent assessment confirms that progression has indeed occurred, the date of progression should be recorded as the date of the initial scan where progression was suspected.

   Note that the advanced imaging modalities discussed for treatment effect above have not been extensively studied with regards to immunotherapy-based approaches and therefore cannot be recommended to distinguish between tumor progression and immune-related changes at present.

6. In the absence of clinical deterioration related to the tumor, an increase in corticosteroid dose alone should not be used as a sole determinant of progression. Patients with stable imaging results and whose corticosteroid dose has increased for reasons other than clinical deterioration related to the tumor do not qualify as having stable disease or progression.

These patients should be observed closely, and if their corticosteroid dose can be reduced back to baseline, they will be considered as having stable disease, but if further clinical deterioration related to the tumor becomes apparent, they will be considered as having progression.

The definition of clinical deterioration is left to the discretion of the treating physician, but it is recommended that patients who have a decrease in score on the Karnofsky performances scale from 100 or 90 to 70 points or less, a decrease of minimum 20 points from 80 or less, or a decrease from any baseline to 50 points or less, for at least 7 days, be considered as having neurological deterioration, unless this functional impairment is attributable to comorbid events, treatment-related toxicity, or changes in corticosteroid dose.

Table 16-3. Response assessment of target and non-target lesions[46]
Target lesions
Complete response
Disappearance of all CNS target lesions sustained for at least 4 weeks; with no new lesions, no use of corticosteroids, and patient is stable or improved clinically.
Partial response
At least a 30% decrease in the sum longest diameter of CNS target lesions, taking as reference the baseline sum longest diameter sustained for at least 4 weeks; no new lesions; stable to decreased corticosteroid dose; stable or improved clinically.
Progressive disease
At least a 20% increase in the sum longest diameter of CNS 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%, at least one lesion must increase by an absolute value of 5 mm or more to be considered progression.
Stable disease
Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter while on study.
Non-target lesions
Non-target lesions should be assessed qualitatively at each of the time points specified in the protocol.
Complete response
Requires all of the following: disappearance of all enhancing CNS non-target lesions, no new CNS lesions.
Non-complete response or non-progressive disease
Persistence of one or more non-target CNS lesion or lesions.
Progressive disease
Any of the following: unequivocal progression of existing enhancing non-target CNS lesions, new lesion(s) (except while on immunotherapy-based treatment), or unequivocal progression of existing tumor-related non-enhancing (T2/FLAIR) CNS lesions. In the case of immunotherapy-based treatment, new lesions alone may not constitute progressive disease.

16.3.3. Other considerations[46]

1. Volumetric criteria are currently experimental and the existing data is not strong enough to support the universal requirement of volumetric response criteria in clinical trials. Nevertheless, the RANO-BM working group believes that assessment and reporting of

volumetric data and response will further research in this future and encourage its inclusion as a secondary endpoint when feasible. For investigators choosing to report volumetric response data, please note the following recommendations.

a. Partial volumetric response should be defined as 65% or greater decrease in the sum volume of CNS target lesions, in addition to the corticosteroid and clinical status criteria outlined previously.
b. Volumetric response should be reported as a waterfall plot to provide a global sense of potential efficacy.

2. Response of non-CNS (extracranial) disease should be assessed separately from CNS (intracranial) disease. Typically RANO-BM would be used for CNS disease and RECIST 1.1 for non-CNS disease. As this trial does not involve the assessment of non-CNS disease, RECIST 1.1 is excluded from this protocol.
3. Please refer to Table 16-5 for RANO-BM recommendations for bi-compartmental assessment of response, i.e. when considering local control and distant brain failure separately.

Table 16-4. Summary of the response criteria for CNS metastases proposed by RANO-BM[46]

	Complete response	Partial response	Stable disease	Progressive disease
Target lesions	None	≥ 30% decrease in sum longest distance relative to baseline	< 30% decrease relative to baseline but < 20% increase in sum longest distance relative to baseline	≥ 20% increase in sum longest distance relative to nadir*
Non-target lesions	None	Stable or improved	Stable or improved	Unequivocal progressive disease
New lesion(s)^	None	None	None	Present*
Corticosteroids	None	Stable or decreased	Stable or decreased	Not applicable#
Clinical status	Stable or improved	Stable or improved	Stable or improved	Worse*
Requirement for response	All	All	All	Any#

*Progression occurs when this criterion is met.

^A new lesion is one that is not present on prior scans and is visible in a minimum of two projections. If a new lesion is equivocal, for example because of its small size, continued therapy can be considered, and follow-up assessment will clarify if the new lesion is new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan showing the new lesion. For immunotherapy-based approaches, new lesions alone do not define progression.

#Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

Table 16-5. Sites of inclusion for assessment of bi-compartmental CNS outcomes.[46]

	Local CNS lesions	Distant CNS lesions	Non-CNS lesions*
Bi-compartmental progression-free survival*	x	x	x
CNS progression-free survival	x	x	
Non-CNS progression-free survival*			x
CNS_{local} progression-free survival	x		

*Non-CNS disease is not assessed in the current protocol.

16.4. Appendix 4. Hopkins Verbal Learning Test - Revised (HVLT-R)

Patient ID_____ Date of Evaluation_____

Patient Initials _____ Name of person administering tests _____

HOPKINS VERBAL LEARNING TEST (HVLT) - FORM 1

Instructions: Read the list of 12 words in Part A (at a rate of 1 word every 2 seconds), then have the patient repeat as many of the words as s/he can recall. Do this for 3 trials. After completing Trial 3, continue to Part B. Read each word and ask the patient to respond with "Yes" if the word was on the list or "No" if it was not.

After ALL Neurocognitive tests have been administered to the patient for this visit, ask the patient to recall the words you read to them at the beginning of the test. Mark the box next to each word the patient accurately recalls for each trial.

FREE RECALL & RECOGNITION: *Semantic Categories: Four-Legged Animals, Precious Stones, Human Dwellings*

1. PART A - FREE RECALL: For each trial, mark the box next to each word word the patient accurately recalls for each trial.

3. PART C - DELAYED RECALL

	Trial 1	Trial 2	Trial 3	Delayed Recall
LION	☐	☐	☐	☐
EMERALD	☐	☐	☐	☐
HORSE	☐	☐	☐	☐
TENT	☐	☐	☐	☐
SAPPHIRE	☐	☐	☐	☐
HOTEL	☐	☐	☐	☐
CAVE	☐	☐	☐	☐
OPAL	☐	☐	☐	☐
TIGER	☐	☐	☐	☐
PEARL	☐	☐	☐	☐
COW	☐	☐	☐	☐
HUT	☐	☐	☐	☐

2. PART B - RECOGNITION: "x" Yes or No beside each word to indicate the patient's response.

	Y	N		Y	N		Y	N		Y	N		Y	N		Y	N
HORSE	☐	☐	ruby*	☐	☐	CAVE	☐	☐	balloon	☐	☐	coffee	☐	☐	LION	☐	☐
house*	☐	☐	OPAL	☐	☐	TIGER	☐	☐	boat	☐	☐	scarf	☐	☐	PEARL	☐	☐
HUT	☐	☐	EMERALD	☐	☐	SAPPHIRE	☐	☐	dog*	☐	☐	apartment*	☐	☐	penny	☐	☐
TENT	☐	☐	mountain	☐	☐	cat*	☐	☐	HOTEL	☐	☐	COW	☐	☐	diamond*	☐	☐

4. Discontinued: Testing discontinued? ☐ Yes *(Complete the Neurocognitive Tests Discontinued/Not Done CRF)*

☐ No

RETAIN DATA SHEETS IN PATIENT STUDY FILE

16.5. Appendix 5. Functional Assessment of Cancer Therapy with Brain Subscale (FACT-Br)

Patient ID_____

FACT-Br (Version 4)

Patient Initials_____ Date of Evaluation_____

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>.**

	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-Br (Version 4)

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

	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

FACT-Br (Version 4)

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

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
Br1	I am able to concentrate	0	1	2	3	4
Br2	I have had seizures (convulsions)	0	1	2	3	4
Br3	I can remember new things	0	1	2	3	4
Br4	I get frustrated that I cannot do things I used to	0	1	2	3	4
Br5	I am afraid of having a seizure (convulsion)	0	1	2	3	4
Br6	I have trouble with my eyesight	0	1	2	3	4
Br7	I feel independent	0	1	2	3	4
NTX6	I have trouble hearing	0	1	2	3	4
Br8	I am able to find the right word(s) to say what I mean	0	1	2	3	4
Br9	I have difficulty expressing my thoughts	0	1	2	3	4
Br10	I am bothered by the change in my personality	0	1	2	3	4
Br11	I am able to make decisions and take responsibility	0	1	2	3	4
Br12	I am bothered by the drop in my contribution to the family	0	1	2	3	4
Br13	I am able to put my thoughts together	0	1	2	3	4
Br14	I need help in caring for myself (bathing, dressing, eating, etc.)	0	1	2	3	4
Br15	I am able to put my thoughts into action	0	1	2	3	4
Br16	I am able to read like I used to	0	1	2	3	4
Br17	I am able to write like I used to	0	1	2	3	4
Br18	I am able to drive a vehicle (my car, truck, etc.)	0	1	2	3	4
Br19	I have trouble feeling sensations in my arms, hands, or legs	0	1	2	3	4
Br20	I have weakness in my arms or legs	0	1	2	3	4
Br21	I have trouble with coordination	0	1	2	3	4
An10	I get headaches	0	1	2	3	4