4.0 STUDY POPULATION

This is an international multi-centre, open-label, randomized phase III trial comparing stereotactic radiosurgery (SRS) to hippocampal-avoidant whole brain radiotherapy (HA-WBRT) plus memantine in patients with 5 or more brain metastases.

A two step registration/randomization process will be used for this trial.

4.1 Eligibility Criteria

There will be NO EXCEPTIONS to eligibility requirements at the time of registration or randomization. Questions about eligibility criteria should be addressed prior to enrolment.

The eligibility criteria for this study have been carefully considered. Eligibility criteria are standards used to ensure that patients who enter this study are medically appropriate candidates for this therapy. For the safety of the patients, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar diseases, it is important that no exceptions be made to these criteria for admission to the study.

Patients must fulfil all of the following criteria to be eligible for admission to the study:

4.1.1 Patients must have 5 or more brain metastases as counted on a T1 contrast enhanced MRI obtained ≤ 30 days from randomization.

4.1.2 Patients must have a pathological diagnosis (cytological or histological) of a non-hematopoietic malignancy.

4.1.3 The largest brain metastasis must measure <2.5 cm in maximal diameter.

The total tumour volume must be 30 cm^3 or less. Lesion volume will be approximated by measuring the lesion's three perpendicular diameters on contrast-enhanced, T1-weighted MRI and the product of those diameters will be divided by 2 to estimate the lesion volume (e.g. xyz/2). Alternatively, direct volumetric measurements via slice by slice contouring on a treatment planning software package can be used to calculate the total tumour volume.

4.1.4 Centre must either have the ability to treat patients with either a Gamma Knife, Cyberknife, or a linear accelerator-based radiosurgery system, or access to a centre at which the trial is open which can treat with using one of these systems.

4.1.5 Patient must be≥ 18 years of age.

4.1.6 Patient is able (i.e. sufficiently fluent) and willing to complete the quality of life questionnaires in either English or French either alone or with assistance. The baseline assessment must be completed within required timelines, prior to randomization.

Patient must also be able and willing to complete the neurocognitive testing without assistance from family and companions. Because this is one of the primary goals of this study, patients must be fluent in English or French, and fully testable in one of those languages.

A patient that is able but unwilling to complete the questionnaires will be considered ineligible.

4.1.7 ECOG performance status 0, 1, or 2.

4.1.8 Creatinine clearance must be ≥ 30 ml/min within 28 days prior to registration.

4.1.9 The Neurocognitive Testing examiner must have credentialing confirming completion of the neurocognitive testing training.

4.1.10 The enrolling facility is credentialed by IROC to perform SRS and HA-WBRT - or have access to a centre where these treatments are credentialed and the study is open. The treating centre must have completed stereotactic radiosurgery credentialing of the specific system(s) to be used in study patients. The treating centre must have completed IMRT credentialing of the specific IMRT system(s) to be used in study patients for the purposes of HA-WBRT.

4.1.11 Patient consent must be appropriately obtained in accordance with applicable local and regulatory requirements. Each patient must sign a consent form prior to enrolment in the trial to document their willingness to participate.

A similar process must be followed for sites outside of Canada as per their respective cooperative group's procedures.

4.1.12 Patients must be accessible for treatment and follow-up. Investigators must assure themselves the patients randomized on this trial will be available for complete documentation of the treatment, adverse events, and follow-up.

4.1.13 In accordance with CCTG policy, protocol treatment is to begin within 14 days of patient enrolment.

4.1.14 Women/men of childbearing potential must have agreed to use a highly effective contraceptive method. A woman is considered to be of "childbearing potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation, or vasectomy/vasectomized partner. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

Women of childbearing potential will have a pregnancy test to determine eligibility as part of the Pre-Study Evaluation (see Section 5.0); this may include an ultrasound to rule-out pregnancy if a false-positive is suspected. For example, when beta-human chorionic gonadotropin is high and partner is vasectomized, it may be associated with tumour production of hCG, as seen with some cancers. Patient will be considered eligible if an ultrasound is negative for pregnancy.

4.2 Ineligibility Criteria

Patients who fulfill any of the following criteria are not eligible for admission to the study:

4.2.1 Pregnant or nursing women.

4.2.2 Men or women of childbearing potential who are unwilling to employ adequate contraception.

4.2.3 Inability to complete a brain MRI.

4.2.4 Known allergy to gadolinium.

4.2.5 Prior cranial radiation therapy.

4.2.6 Planned cytotoxic chemotherapy within 48 hours prior or after the SRS or HA-WBRT.

4.2.7 Primary germ cell tumour, small cell carcinoma, or lymphoma.

4.2.8 Widespread definitive leptomeningeal metastasis. This includes cranial nerve palsy, leptomeningeal carcinomatosis, ependymal involvement, cranial nerve involvement on imaging, suspicious linear meningeal enhancement, or cerebrospinal fluid (CSF) positive for tumour cells.

4.2.9 A brain metastasis that is located ≤ 5 mm of the optic chiasm or either optic nerve.

4.2.10 Surgical resection of a brain metastasis (stereotactic biopsies will be allowed).

4.2.11 Prior allergic reaction to memantine, or hypersensitivity to any excipients of memantine.

4.2.12 Current alcohol or drug abuse.

4.2.13 Current use of NMDA antagonists, such as amantadine, ketamine, or dextromethorphan.

4.2.14 Diagnosis of chronic liver disease/cirrhosis of the liver (e.g. Child-Pugh class B or C).

4.2.15 Clinically significant untreated or uncontrolled cardiovascular conditions, and/or symptomatic cardiac dysfunction (i.e. unstable angina, congestive heart failure, myocardial infarction within the previous year, cardiac ventricular arrhythmias requiring medication, history of 2nd or 3rd degree atrioventricular conduction defects, uncontrolled hypertension).

4.2.16 Current active or uncontrolled urinary tract infections (UTI).

4.2.17 History of epilepsy or seizures, and not currently taking anti-epileptic medication.

4.2.18 Any other serious intercurrent illness or medical condition judged by the local investigator to compromise the patients safety, preclude safe administration of the planned protocol treatment, or would not permit the patient to be managed according to the protocol guidelines.

4.2.19 Patients with architectural distortion of lateral ventricular systems which, in the opinion of the local investigator, makes hippocampal delineation challenging.

5.0 PATIENT EVALUATION FLOWSHEET: PRE-TREATMENT, ON STUDY, AND AFTER TREATMENT

All patients entered on study must be evaluated according to the schedule outlined below with documentation submitted according to the schedule in Appendix III.

Required Investigations	Pre-study (within 14 days prior to randomization)	End of Protocol Treatment	After Protocol Treatment						
			Week 8	Month 4	Month 6	Month 9	Month 12	Month 16	Month 24 *****
History and Physical Exam									
Including: Height, Weight, Performance Status, Handedness	X	X	X	X	X	X	X	X	X
Disease History, Prior Therapy	X								
Concurrent Illness and Concomitant Medications	X	X	X	X	X	X	X	X	X
Clinical tumour measurements (if applicable)	X		X	X	X	X	X	X	X
Ophthalmology Exam	As clinically indicated								
Biochemistry* (within 28 days of randomization)									
Creatinine, Creatinine Clearance, BUN	X	X	X	X	X				
Radiology†									
MRI of the Brain	X (within 30 days prior to randomization)		X	X	X	X	X	X	X
Other Investigations**									
Neurocognitive Assessment	X		X	X	X	X	X	X	X
Pregnancy Test (if applicable)	X	As clinically indicated							
Correlative Studies***									
Whole Blood for cfDNA quantification and extraction	X	X	X	X	X		X		
Whole Blood, Plasma, Serum for circulating biomarkers	X	X	X	X	X		X		
Whole blood, Plasma, Serum for banking (optional)	X	X	X	X	X		X		
Urine	X	X	X	X	X		X		
Adverse Events									
Adverse Event Assessment	X	X	X	X	X	X	X	X	X
Quality of Life****									
EORTC QLQ-C30 + BN20	X		X	X	X	X	X	X	X
Health Economics									
Health Utilities Index (EQ-5D-5L)	X		X	X	X	X	X	X	X
Resource Utilization Assessment (CNS directed utilization only)			X	X	X	X	X	X	X

footnotes on next page …

*	Bloodwork Timing: Pre-treatment blood draws may be done the day prior to treatment if necessary, and when treatment is to begin on a Monday, may be done on the previous Friday (maximum 72 hours prior to treatment). In order to ensure that nadir counts are not missed, every effort should be made to do interim blood draws within 24 hours of the day specified in the protocol.
**	Pregnancy test (in women of childbearing potential), as part of Pre-Study Evaluation, may include an ultrasound to rule out pregnancy. See Appendix VII for details of neurocognitive assessments.
***	Correlative blood samples to be collected at baseline, immediately after RT, and at 8 weeks, 4, 6 and 12 months after RT.
****	Required prior to randomization (baseline), and thereafter as outlined in the table above. Also required at the time of disease progression. The average time to complete these questionnaires is approximately 10-15 minutes. See Appendix V for QLQ-C30+BN20 details and Appendix VI for Health Utilities Index (EQ-5D-5L) details.
*****	After Month 24, follow up may continue on an annual basis for survival status, new cancer treatments, and assessment of related adverse events. A short follow-up report form may be used for this purpose.
†	Note that complete MRI imaging data sets must also be uploaded using TRIAD (see section 11.1 of protocol), in addition to submission of the MRI reports and tumour measurement worksheets using the Central Monitoring portal. MRI must be contrast enhanced while on study

5.1 Follow-up for Ineligible Patients

The follow-up requirements for ineligible patients who have received no protocol therapy include submission of the Baseline Report plus an annual short follow up form. Data submission for ineligible participants who have received at least one dose of protocol therapy should be followed according to the protocol to allow for treatment and adverse event assessment.

5.2 Follow-up After Progression in the Brain or Progression of Systemic Disease

In the event of progressive disease (PD) in the brain or progression of systemic disease, a Relapse/Progression Folder should be completed. Patients will continue to be followed as per the test schedule in Section 5 for survival status, new cancer treatments, correlative studies, adverse events, and health economic evaluations.

Quality of life and neurocognitive assessment information should be reported at the time of progression, but follow-up should also continue post progression as per Section 5 of the protocol.

Radiological investigation is no longer required after objective progression has been documented, and will be at the discretion of the investigator.

For patients who transfer to palliative care post progression and are no longer able to attend clinic for protocol specified visits or complete the protocol specified investigations, short follow up reports may be used for follow-up reporting. These short follow up reports should be completed at the same schedule as outlined in Section 5 of the protocol for regular follow up reporting.