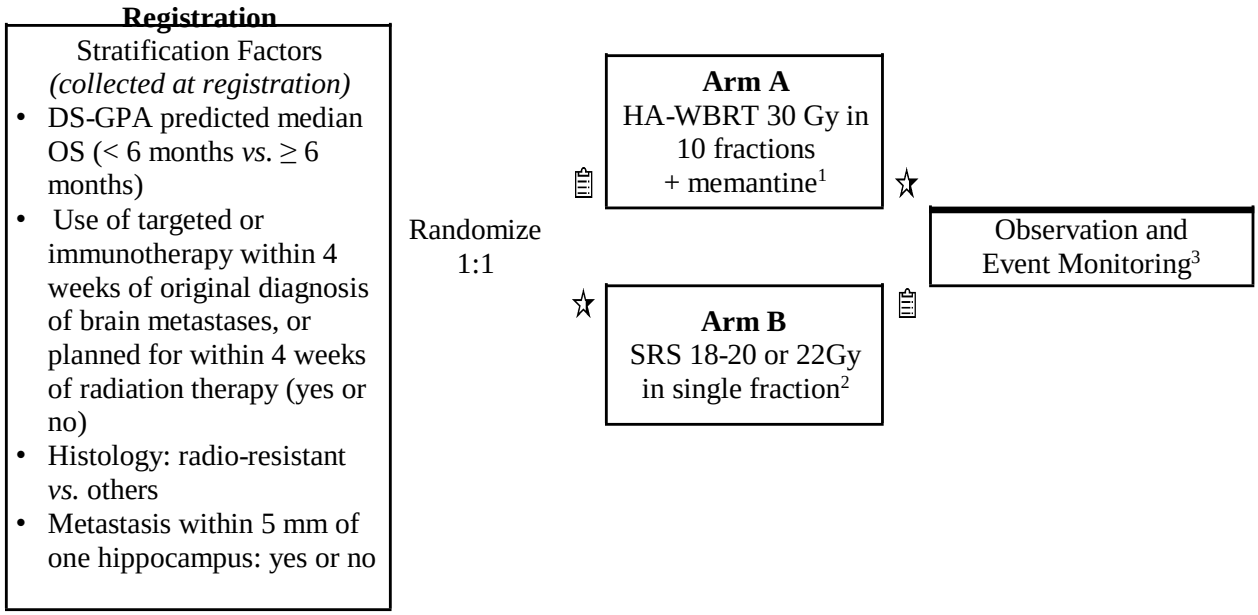
CCTG CE.7 TREATMENT SCHEMA

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 to 15 brain metastases.

Stratification

- DS-GPA predicted median overall survival *[Sperduto 2012; Sperduto 2017]* (< 6 months vs. ≥ 6 months)
- Use of targeted or immunotherapy within 4 weeks of original diagnosis of brain metastases, or planned for within 4 weeks of radiation therapy (yes or no)
- Histology (radio-resistant* vs. other)
- Metastasis within 5 mm of one hippocampus (yes or no)

* Radio-resistant is defined as brain metastases from a sarcoma, melanoma, or renal cell carcinoma histology.



1. Memantine will start the same day as HA-WBRT and must start no later than before the fourth HA-WBRT treatment. The target dose for memantine is 20 mg (10 mg divided twice daily). Dose will be escalated by 5 mg per week.
2. Lesions < 4 cc in volume will receive 22Gy while lesions 4-10 cc in volume will receive 18-20; details as outlined in the treatment section.
3. In the event of progressive brain metastases or systemic progression the patient remains under observation

N = 206

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 to 15 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 (maximum 15 brain metastases).

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 $\leq$ 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 More than 15 brain metastases on a volumetric T1 contrast MRI (voxels of $1mm^3$ or smaller) performed within the past 14 days, or more than 10 metastases in the case of a non-volumetric MRI.

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

4.2.13 Current alcohol or drug abuse.

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

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

4.2.16 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).

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

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

4.2.19 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.

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