NCI Protocol #: N/A

DF/HCC Protocol #: 20-240

TITLE: A double-blind, phase II randomized study of brain-directed stereotactic radiation with or without AGuIX gadolinium-based nanoparticles in the management of brain metastases at higher risk of local recurrence with radiation alone: The Nano-Brain Mets Trial

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Protocol Type / Version # / Version Date: *Original / Version 3 / November 23, 2021*

SCHEMA

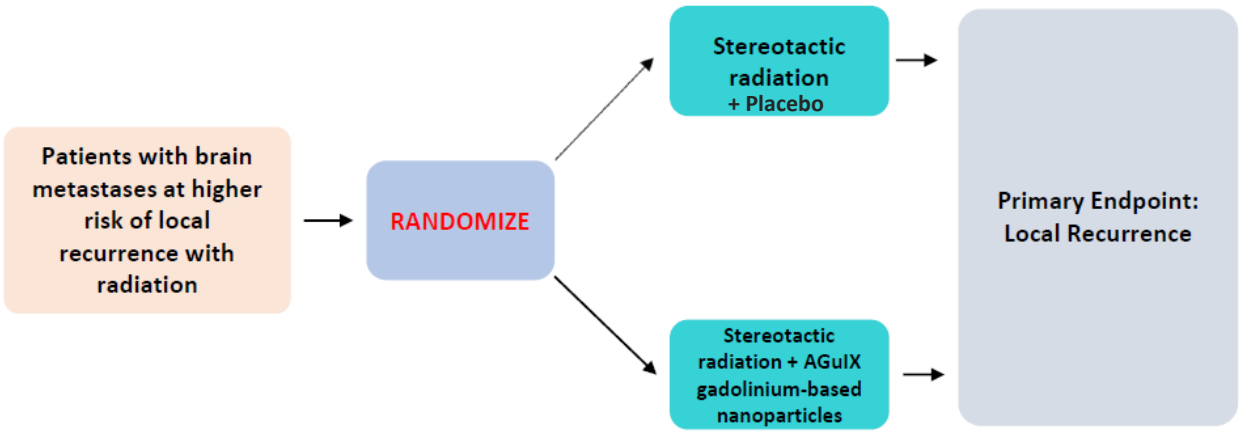

Patients with brain metastases at higher risk of local recurrence with radiation
RANDOMIZE
Stereotactic radiation + Placebo
Stereotactic radiation + AGuIX gadolinium-based nanoparticles
Primary Endpoint: Local Recurrence

TABLE OF CONTENTS

SCHEMA 4

1. OBJECTIVES 7
   - 1.1 Study Design 7
   - 1.2 Primary Objectives 7
   - 1.3 Secondary Objectives 7

2 BACKGROUND 8
   - 2.1 Study Disease(s) 8
   - 2.2 IND Agent 8
   - 2.3 Rationale 9

3 PARTICIPANT SELECTION 11
   - 3.1 Eligibility Criteria 11
   - 3.2 Exclusion Criteria 11
   - 3.3 Inclusion of Women and Minorities 12

4 REGISTRATION And Randomization PROCEDURES 13
   - 4.1 General Guidelines for DF/HCC Institutions 13
   - 4.2 Registration Process for DF/HCC Institutions 13
   - 4.3 General Guidelines for Other Investigative Sites 13
   - 4.4 Registration Process for Other Investigative Sites 13

5. TREATMENT PLAN 14
   - 5.1. Treatment Regimen 14
   - 5.2. Pre-Treatment Criteria 15
   - 5.3. Agent Administration 15
   - 5.4. General Concomitant Medication and Supportive Care Guidelines 15
   - 5.5. Criteria for Taking a Participant Off Protocol Therapy 15
   - 5.6. Duration of Follow Up 16
   - 5.7. Criteria for Taking a Participant Off Study 16
   - 5.8. Radiation Plan 16

6. DOSING DELAYS/DOSE MODIFICATIONS 20

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS 21
   - 7.1. Adverse Event List(s) for AGuIX 21
   - 7.2. Adverse Event Characteristics 26
   - 7.3. Expedited Adverse Event Reporting 27
   - 7.4 Reporting to Hospital Risk Management 27
   - 7.5 Reporting to the Food and Drug Administration (FDA) 27
   - 7.6 Routine Adverse Event Reporting 28

8. PHARMACEUTICAL INFORMATION 29
   - 8.1 IND Agent - AGuIX 29

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES 31

10. STUDY CALENDAR 32

11. MEASUREMENT OF EFFECT 36
11.1. Antitumor Effect – Solid Tumors 36
11.2. Other Response Parameters 39

12. DATA REPORTING / REGULATORY REQUIREMENTS 40
12.1. Data Reporting 40
12.2. Data Safety Monitoring 40
12.3. Multi-Center Guidelines 40
12.4. Collaborative Agreements Language 40

13. STATISTICAL CONSIDERATIONS 41
13.1. Study Design/Endpoints 41
13.2. Sample Size, Accrual Rate and Study Duration 41
13.3. Stratification Factors 42
13.4. Interim Monitoring Plan 42
13.5. Analysis of Primary Endpoints 44
13.6. Analysis of Secondary Endpoints 44
13.7. Reporting and Exclusions 45

14. PUBLICATION PLAN 46

REFERENCES 47

1. OBJECTIVES

1.1 Study Design

A double-blind, randomized phase II clinical trial of brain-directed stereotactic radiation with or without AGuIX gadolinium-based nanoparticles in the management of brain metastases at higher-risk of local recurrence with radiation alone.

1.2 Primary Objectives

To evaluate the hypothesis that, among patients with brain metastases at higher-risk of local recurrence with radiation alone, AGuIX gadolinium-based nanoparticles and brain-directed stereotactic radiation will improve local control, using criteria from the Response Assessment in Neuro-Oncology (RANO) – Brain Metastasis group,[1] relative to brain-directed stereotactic radiation alone.

1.3 Secondary Objectives

To compare the following other endpoints between patients managed with AGuIX gadolinium-based nanoparticles and brain-directed stereotactic radiation versus brain-directed stereotactic radiation alone:

1. Overall survival (i.e. all-cause mortality)
2. Death due to neurologic disease progression (defined as death due to progressive brain metastases on imaging associated with progressive neurologic symptomatology in the setting of systemic disease that has not progressed to a life-threatening nature)
3. Performance status, assessed longitudinally
4. Ability to complete activities of daily living, assessed longitudinally
5. Incidence and time to detection of new brain metastases
6. Incidence and time to development of radiation necrosis
7. Incidence and time to development of leptomeningeal disease
8. Incidence and time to progressive intracranial disease
9. Incidence and time to salvage craniotomy
10. Incidence and time to additional radiotherapeutic treatments after the initial course (stereotactic or whole brain radiation)
11. Progression free survival
12. Incidence and time to the development of seizures
13. Neurocognition, assessed longitudinally
14. Quality of life, assessed longitudinally
15. Steroid use, assessed longitudinally
16. Local recurrence at one year in metastases treated radiotherapeutically using RECIST (response evaluation criteria in solid tumors) criteria

2 BACKGROUND

2.1 Study Disease(s)

Brain metastases are diagnosed in 10-50% of patients with cancer. The number of patients diagnosed with brain metastases in the United States per year is approximately 175,000, and is expected to increase over time.[2] Chemotherapy achieves unreliable and often poor control of brain metastases given limited penetration through the blood-brain barrier.[3] Targeted therapies, such as EGFR inhibitors[4] and ALK inhibitors[5] in non-small cell lung cancer, HER2 targeting agents in breast cancer,[6-8] and BRAF/MEK inhibitors[9] or immunotherapy[10] in melanoma, have shown significant promise in controlling intracranial disease but relatively few patients with brain metastases can be reliably and durably managed with systemic agents. Accordingly, brain-directed radiation represents the mainstay of therapy for most patients with brain metastases.

Increasingly, stereotactic radiation, in which only the visualized metastases are treated, is being used in lieu of whole brain radiation, given the toxicity profile of the latter therapy.[11,12] However, select patients with brain metastases are at especially higher risk of local recurrence with stereotactic radiation alone, including patients with melanoma and progression on immunotherapy,[13] gastrointestinal primaries,[14] HER2 positive breast cancer,[15] cystic brain metastases,[16] larger lesions,[17] and local recurrences after prior stereotactic radiation[18] or whole brain radiation.[19] Local recurrences after stereotactic radiation in these populations can lead to progressive neurologic symptomatology, decline in quality of life and neurocognitive function, and neurologic death.[20] As a result, strategies to promote radiosensitization have significant appeal in such patients.

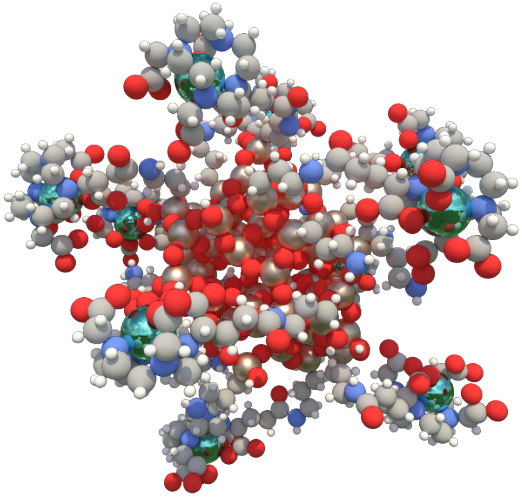
The primary long-term adverse effect associated with stereotactic radiation for brain metastases is radiation necrosis, which manifests as injury to the radiated brain.[21] Radiation necrosis is common and always occurs in the original location of the tumor that was treated. Distinguishing radiation necrosis from tumor recurrence after radiation is difficult.[22] Conventional magnetic resonance imaging (MRI) shows enhancing lesions in both tumor recurrence and radiation necrosis. Other imaging studies, such as perfusion-weighted MRI,[23,24] diffusion-weighted MRI,[25,26] MRI spectroscopy,[27-29] positron emission tomography (PET),[30,31] and single photon emission computed tomography (SPECT)[32,33] have limited sensitivity and specificity for such delineations; none of these tests are routinely used at our institution. Rather, our approach to delineation of radiation necrosis from tumor recurrence has incorporated both radiographic, radiation-based (mapping of radiation dose to imaging scans), and clinical covariates (including response to diagnostic steroids and CNS-active systemic therapy). Such an approach has yielded 90% accuracy in determining the true etiology of growth.[34]

2.2 IND Agent

The radiosensitizing agent evaluated in this study is Activation and Guidance of Irradiation by X-ray (AGuIX), developed by NH TherAguix, a gadolinium-chelated polysiloxane based nanoparticle which is intravenously injectable and visible on magnetic resonance imaging (MRI).[35] AGuIX nanoparticles are comprised of a polysiloxane matrix with gadolinium cyclic

chelates covalently grafted on the inorganic matrix (see Figure 1 below):

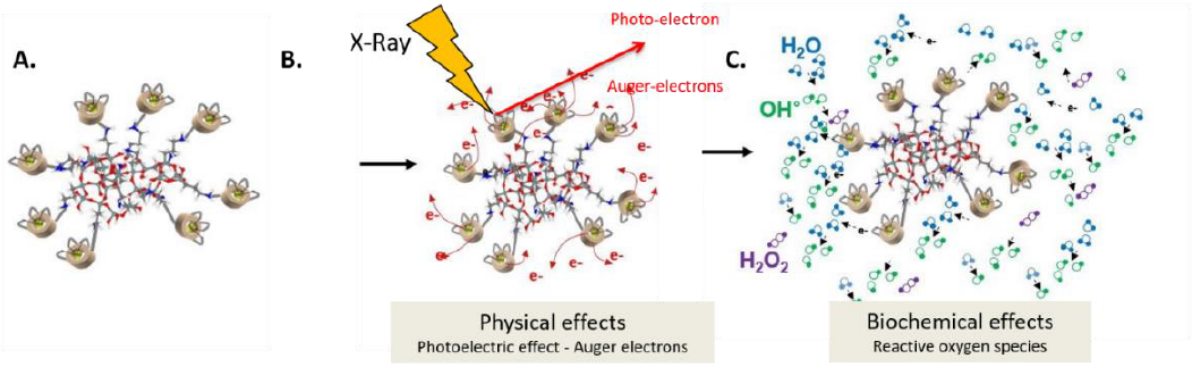
Figure 1: Representative diagram of AGuIX with a polysiloxane matrix and gadolinium chelates (green).



2.3 Rationale

Gadolinium atoms lead to formation of Auger electrons when radiated, inducing reactive oxygen species, thereby potentiating radiation effect,[36] as shown in Figure 2.

Figure 2. Radiosensitization by AGuIX nanoparticles



AGuIX nanoparticles accumulate in brain metastases (sites of blood-brain barrier breakdown) similar to gadolinium-based contrast agents used in diagnostic imaging and are sufficiently small (<5nm) to allow for renal clearance, typically with a blood half-life ranging between 0.8-3.0 hours.[37] However, unlike gadolinium-based contrast agents currently in use for MRI imaging

studies, AGuIX nanoparticles are retained within brain metastases and can be visualized on MRI days after treatment.[38,39] AGuIX nanoparticles have especially high potential for impactful radiosensitization with brain-directed stereotactic radiation, given the uptake of gadolinium in the exact same location as the radiation target, with minimal uptake and radiation deposition to other sites of the brain.

AGuIX nanoparticles were combined with brain-directed radiation in the Nano-Rad clinical trial, in which patients received whole brain radiation in the presence of escalating doses of AGuIX. Evidence of increasing radiosensitization was seen at escalating doses of 15, 30, 50, 75, and 100 mg/kg.[40] No hemodynamic, cardiovascular, renal, hepatic, or other significant acute toxicities were noted. Of the 15 patients evaluated, no "in field" short or long-term grade IV toxicities were noted. One patient developed acute, in field, grade 3 toxicity (intracranial pressure increased); there were two in field late grade 3 toxicities ("confusional state" and "delayed effects of radiation"). In addition, 1 patient had "general physical health deterioration" that was listed as a possibly related SAE. Most SAEs on this study were felt to be related either to brain metastases, extracranial progression or other systemic treatment. Ten patients died during the follow up period of the study. Of these, nine deaths were considered not related to the experimental treatment while one death was felt to be related to disease progression with superimposed radiation related leukoencephalopathy. As a result of safety and early efficacy results, AGuIX based nanoparticles are being evaluated in multiple prospective phase II studies with 100mg/m2 felt to be the optimal dose for brain-directed investigations (NCT03818386, NCT04094077) and are also being evaluated by other trials at BWH/DFCI (DFCI 19-826).

3 PARTICIPANT SELECTION

3.1 Eligibility Criteria

3.1.1. Participants must have a biopsy proven solid malignancy and at least one intracranial measurable lesion spanning ≥5mm in maximal unidimensional size and radiographically consistent with or pathologically proven to be a brain metastasis AND meet one of the following additional criteria regarding the primary site or nature of the intracranial disease:
-Melanoma with intracranial growth consistent with tumor progression despite immunotherapy
-Gastrointestinal primary
-HER2 positive breast cancer (subtype assessed using most representative tissue available in opinion of enrolling clinician and/or study PI)
-Cystic metastases
-Metastases ≥2cm in maximal unidimensional size
-Locally recurrent metastases after prior stereotactic radiation
-Locally recurrent metastases after prior whole brain radiation
**Patients with metastases from melanoma, GI primaries, or HER2+ breast cancer, as well as those with cystic metastases or metastases ≥2cm in maximal unidimensional size, who have local recurrences after prior brain-directed radiation can only be treated in the strata permitting prior radiation (last two strata above)*

3.1.2. Age ≥18 years at diagnosis of brain metastases

3.1.3. Estimated glomerular filtration rate of ≥ 60 mL/min/1.73m2

3.1.4. Karnofsky performance status of at least 70 (i.e. at minimum, "cares for self" but "unable to carry on normal activity or do active work")

3.1.5. Estimated survival based on extracranial disease of at least 3 months in the opinion of the enrolling clinician and/or study PI

3.1.6. Ability to understand and the willingness to sign a written informed consent document

3.1.7. The effects of AGuIX on the developing human fetus are unknown. For this reason, women of child-bearing potential must agree to use adequate contraception prior to study entry and for the duration of the therapeutic component of study participation

3.2 Exclusion Criteria

3.2.1. Participants who cannot undergo a brain MRI

3.2.2. Participants who cannot receive gadolinium

3.2.3. Participants with widespread, definitive leptomeningeal disease

3.2.4. Patients requiring radiation to either >10 targets (if naïve to whole brain radiation) or >20 targets (if whole brain radiation has been given previously) per the discretion of the treating clinician and/or study PI

3.2.5. Pregnant women are excluded from this study because of the potential deleterious effects of gadolinium on the developing fetus. Because there is an unknown but potential risk for adverse events in nursing infants, women who are breastfeeding are

not eligible for this study

3.2.6. In cohorts who have received prior brain-directed radiation, patients are not eligible for this study if they have active (at the time of protocol screening) brain metastases that require radiation that are in or within 1.0cm of the brainstem, eyes, optic nerves, or optic chiasm if the juxtaposed organ at risk (i.e. brainstem, eyes, optic nerves, or optic chiasm) has previously received either >6.0 Gy in a single fraction or, if prior radiation was fractionated, a cumulative dose in 2.0 Gy equivalents, using an alpha/beta ratio of 2, of >40.0 Gy. In addition, all patients who have had prior brain-directed radiation, regardless of technique/dose/fractionation, are not eligible for the study until written approval is provided by the study/site PI.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4 REGISTRATION AND RANDOMIZATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

The eligibility checklist(s) and all pages of the consent form(s) will be faxed to the ODQ at 617-632-2295. The ODQ will (a) review the eligibility checklist, (b) register the participant on the protocol, and (c) randomize the participant.

Randomization can only occur during ODQ business hours (8:30am - 5pm Eastern Time, Monday through Friday excluding holidays).

An email confirmation of the registration and/or randomization will be sent to a secondary clinical research coordinator (secondary CRC, the unblinded coordinator listed below) immediately following the registration and/or randomization. The patient, treating clinician, primary research coordinator, research nurse, study PI, and remainder of the study team will remain blinded to the treatment assignment. The secondary research coordinator will coordinate with the pharmacy to facilitate preparation and distribution of the study agent or placebo and then have no further role in study procedures, as discussed below. The secondary research coordinator will not interact with the patient in any way.

Following registration, participants may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the study PI of the registering site.

4.2 Registration Process for DF/HCC Institutions

Applicable DF/HCC policy (REGIST-101) must be followed.

4.3 General Guidelines for Other Investigative Sites

N/A

4.4 Registration Process for Other Investigative Sites

N/A

5. TREATMENT PLAN

5.1. Treatment Regimen

Blinding

The reason for blinding is that the primary endpoint (local recurrence) will be made by the study PI and a blinded study will reduce bias in this assessment. As noted in section 2 of this protocol, tumor recurrence and radiation necrosis (damage to the underlying brain secondary to radiation) are difficult to delineate. Radiographic assessment alone is insufficient; incorporation of radiation-based and clinical covariates improves the accuracy of this assessment significantly. Therefore, final delineation will be made by the study PI after incorporation of radiation-based and clinical covariates into the assessment; blinding is integral in reducing/eliminating bias. As noted above, the study team has demonstrated an ability to delineate tumor progression from necrosis with 90% accuracy using such an approach.[34] A similar randomized phase II study using whole brain radiation with or without AGuIX gadolinium-based nanoparticles (as opposed to the stereotactic radiation utilized in this study) is also being conducted (NCT03818386).

Consequently, patients and investigators, including the primary CRC, will be blinded as to whether AGuIX or placebo is being infused. A second, unblinded CRC will confirm the treatment arm with the unblinded pharmacist and work with the pharmacy to mask, with an opaque cover, the preparation made by the unblinded pharmacist prior to dispensing to other study personnel (as the AGuIX solution is colored). Once the infusion is completed, the infusion container will be discarded with the opaque cover in place to ensure continued blinding of all investigators and participants. To ensure completeblinding of the PI, who will be making delineations of local recurrence versus tumor progression, non-brain / non-radiation related symptomatology of minor consequence (grade 1-2 adverse effects) possibly, probably, or definitely relating to the infusion occurring during or after (i.e. within 24 hours) the infusion in patients enrolled by the study PI, will be managed by a nursing / covering physician team that will be separate from the study PI.

Treatment

Radiation will begin within 14 days of the planning MRI (obtained with standard gadolinium). All patients will receive either AGuIX (100mg/kg) or placebo (normal saline, as discussed below) injection 2-5 days before radiation initiation in order to infuse the core of the tumor with AGuIX in those assigned to receive it. A brain MRI will be performed on this date, both pre-infusion and post-infusion. For patients receiving stereotactic radiosurgery (SRS, focused radiation in 1 day) alone the next AGuIX (100mg/kg) or placebo injection will take place 1-5 hours (preferably 2 hours) before the radiation treatment; no further AGuIX / placebo injections will be given. For patients managed with stereotactic radiotherapy (SRT, focused radiation in 5 days) with or without SRS AGuIX (100mg/kg) or placebo injection will be given 1-5 hours (preferably 2 hours) before radiation treatment on day 1 of radiation and 1-5 hours (preferably 2 hours) before radiation on day 3 of radiation. Patients receiving both SRS and SRT can receive treatment over 5 or 6 days, as discussed below. In both cases, SRS should be performed on day 1; SRT would start on day 1 or day 2, respectively.

5.2. Pre-Treatment Criteria

Patients presenting to Brigham and Women's Hospital who meet the eligibility criteria above will be identified by a radiation oncologist, medical oncologist, neuro oncologist, or surgical oncologist and offered participation in the study. All patients must have undergone prior MRI-based imaging of the brain, as is standard of care. Renal function will be assessed if needed (e.g. diagnosis of chronic kidney disease) per standard of care and no other pretreatment evaluations other than current standard of care testing are required.

5.3. Agent Administration

AGuIX is a Gadolinium-chelated polysiloxane based nanoparticle. Its chemical formula is $(GdSi_{3\text{-}8}C_{24\text{-}34}N_{5\text{-}8}O_{15\text{-}30}H_{40\text{-}60}, nH_2O)_x$. Its pharmaceutical form is sterile lyophilized powder (1000 mg of AGuIX/vial). Reconstitution of the solution is utilized with 10.00mL of sterile water for injectable preparation concentration for a final AGuIX concentration of 100 mg/mL. The pH of the final solution is then 7.3 +/- 0.3. AGuIX should be administered as a continuous intravenous infusion using a rate–regulating device per institutional guidelines with associated pre-medications. It should not be administered as an IV push. It should be administered at a dose rate of 2 mL/min. Vials contain no preservative and are suitable for single use only. No intravenous prehydration is required.

5.4. General Concomitant Medication and Supportive Care Guidelines

Women of childbearing potential and men must agree to use adequate contraception (examples include condom, intrauterine device (IUD), oral contraceptive, double-barrier method, etc.), for the duration of study participation.

5.5. Criteria for Taking a Participant Off Protocol Therapy

Treatment will continue until one of the following criteria applies:

- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the infusion regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be

documented in the case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy and/or is off of the study, the participant's status must be updated in OnCore in accordance with REGIST-OP-1.

5.6. Duration of Follow Up

Participants will be followed until death or censoring/withdrawal from the protocol. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.7. Criteria for Taking a Participant Off Study

Participants will be removed from the study when any of the following criteria apply:

- Lost to follow-up despite three attempted contacts from members of the study team
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure the participant's status is updated in OnCore in accordance with REGIST-OP-1.

5.8. Radiation Plan

Radiation therapy will be given per standard of care (i.e. non-investigational) approaches as outlined here:

Physician credentialing

In order to be eligible to treat patients on this study, physicians must be credentialed for contouring and treatment planning for brain-directed stereotactic radiation. All radiation oncologists at an institution participating in the study may enroll patients, but patients cannot be treated until the treating physician is credentialed. The credentialing process will entail a review of the contours and radiation plan for the first enrolled case, prior to treatment, by the study PI. If no significant edits to the contours are indicated and if all planning criteria listed below are met the treating physician will be credentialed and can treat future patients without pre-treatment review. Contours/plans which require significant adjustments by the study PI must be edited prior to treatment initiation; in such cases, the physician seeking credentialing will be provided with feedback and must submit a contour/plan for review prior to treatment of the next patient enrolled.

Timing of radiation

Stereotactic radiation must begin within 21 days after registration and within 14 days of the MRI

used for radiation planning. Patients cannot receive concurrent systemic chemotherapy with radiation. A minimum of five days is required between last administration of chemotherapy and initiation of radiation. A minimum of three days is required between last administration of radiation and initiation of post-radiation chemotherapy. Radiation must be delivered at an enrolling center; stereotactic radiation at outside centers will not be permitted.

Radiation dose

Lesions <2 cm in maximum diameter will be treated with stereotactic radiosurgery (SRS), generally 20 Gy in 1 fraction. Lesions between 2.0 and 2.5-3.0 cm in maximum diameter will generally be treated to 18 Gy in 1 fraction. The volume receiving 12 Gy (V12) should be limited to <10cc; dose reductions are acceptable if the V12 constraint cannot be met via replanning, with a minimum dose of 16 Gy. Lesions >2.5-3 cm will generally be treated with stereotactic radiotherapy (SRT) to 30 Gy in 5 fractions given on consecutive weekdays. Surgical cavities can be treated to 15-20 Gy in one fraction (based on size and V12 criteria above) or, for medium sized cavities (as defined above and below), either 30 Gy in 5 fractions (gross residual/recurrent disease present) or 25 Gy in 5 fractions (no gross residual/recurrent disease present) on consecutive weekdays will be employed. Targets >4-5cm in maximal unidimensional size can be dose reduced to 23-29 Gy in 5 fractions, at the discretion of the treating clinician and/or study PI; in surgically naïve metastases >4-5cm in size, utilization of resection prior to radiation is strongly encouraged. If a metastasis that would be treated normally with SRS is adjacent to a metastasis that must receive SRT (so that a significant degree of scatter dose from the SRT field will include the potential SRS field) it is acceptable for the treating investigator to treat both metastases with SRT. Patients who have received prior radiation which deposited scatter dose to a current intracranial target (e.g. prior head and neck radiation) may have dose / fractionation adjustments at the discretion of the treating clinician and study PI. For patients requiring both SRS and SRT, treatment can be over 5 or 6 days based on whether SRS is administered concurrently or sequentially with SRT (as determined by the treating clinician and/or study PI).

Physical factors

Treatment will be delivered using megavoltage machines with photon beams.

Simulation, immobilization, and localization

The patient will be treated in the supine position. A tightly fitting thermoplastic mask will be employed for immobilization. A CT simulation will be performed, with a maximum slice thickness of 1.5mm.

Treatment planning and patient setup

The GTV will cover the metastasis (or cavity plus any residual tumor in patients who have had neurosurgical resection) as identified by contrast enhanced MRI and CT (contrast optional) obtained within 14 days of the treatment initiation date. The MRI must be obtained with a T1 post contrast sequence with a maximal slice thickness of 1.5 mm (e.g. magnetization prepared rapid gradient echo (MPRAGE), spoiled gradient (SPGR) sequences or equivalent). Contouring

software capable of 3D reformatting is required. No CTV is to be used. The PTV will be 1mm for intact lesions and 2mm for cavities. For patients who have rapidly growing gross disease an extra 0.1-1mm of PTV margin can be added at the discretion of the treating clinician to account for growth between planning and treatment; in such cases the time between planning and treatment should be minimized to the greatest extent possible. Treatments will be delivered through volumetric modulated arc therapy (VMAT) for PTV volumes >1.0 cm in maximum diameter. For PTV volumes with a maximum dimension of 0-1.0 cm in diameter either VMAT, circular collimators, or multiple static fields will be acceptable. More than one isocenter can be used if deemed as indicated by the treating physician and/or study PI. The prescription will generally be normalized to the 60-95% isodose line but alternative normalizations (e.g. using a lower normalization to maximize dose fall off) can be utilized by the treating physician and/or study PI if deemed appropriate. Regarding coverage metrics, 100% of the GTV should be covered by the prescription dose. At least 99% (ideal) / 98% (at minimum) of the PTV should be covered by the prescription isodose line. The entire PTV should be covered by 90% (ideal) / 85% (at minimum) of the prescription dose. Daily set up with cone beam CT or stereoscopic KV imaging and use of a couch capable of making linear and rotational corrections is mandated. Use of real-time motion management with 3-dimensional surface monitoring is optional but encouraged.

Critical Structures

Dose constraints for stereotactic radiosurgery to critical structures will be as follows:

Dose constraints for stereotactic radiosurgery*

Organ at Risk	Tolerance	Dose Modification Regimen
Eyes, Optic Nerves, Optic Chiasm	Point dose ≤8 Gy	If point dose >8 Gy, undercover PTV while maintaining 100% GTV coverage. If not achievable, dose reduce GTV to highest dose which meets optic constraint, through 16 Gy. If 100% of GTV cannot be safely covered by 16 Gy, then an acceptable variation will be to convert to stereotactic radiotherapy – see Table below
Brainstem (defined as brainstem volume, inclusive of upper spinal cord, minus GTV)	Dose to 0.035cc ≤12 Gy	If dose to 0.035cc >12 Gy, undercover PTV while maintaining 100% GTV coverage. If not achievable, dose reduce GTV to highest dose which meets brainstem constraint, through 16 Gy. If 100% of GTV cannot be safely covered by 16 Gy, then an acceptable variation will be to convert to stereotactic radiotherapy – see Table below
Volume of normal brain (less the GTV) receiving >12 Gy (per individual lesion, called the V12)	≤10cc	If the V12 is >10cc on a per-metastasis basis, undercover PTV while maintaining 100% GTV coverage. If not achievable, dose reduce GTV to highest dose which meets constraint, through 16 Gy. If 100% of GTV

		cannot be safely covered by 16 Gy, then an acceptable variation will be to convert to stereotactic radiotherapy – see Table below
Normal brain less the GTV (for entire brain)	Mean <5-6 Gy	Administer stereotactic radiation on two or more consecutive weekdays rather than a single day (such cases must be discussed with the study PI)

*inclusive of 20% of stereotactic radiotherapy dose contribution (i.e. 1 of 5 days) if stereotactic radiosurgery and stereotactic radiotherapy are given on the same day; normal tissue constraints pertain only to the radiotherapeutic treatment course delivered on protocol.

Dose constraints for stereotactic radiotherapy to critical structures will be as follows:

Dose constraints for stereotactic radiotherapy (5 fractions)*

Organ at Risk	Tolerance	Dose Modification Regimen
Eyes, Optic Nerves, Optic Chiasm	Point dose of 25	If point dose >25 Gy undercover PTV while maintaining 100% GTV coverage. If not achievable, dose reduce GTV to highest dose which meets constraint, through 23 Gy in 5 fractions. 100% of GTV should always receive at least 23 Gy in such a scenario.
Brainstem (defined as brainstem volume, inclusive of upper spinal cord, minus GTV)	Dose to 0.035cc ≤28 Gy	If dose to 0.035cc >28 Gy, undercover PTV while maintaining 100% GTV coverage. If not achievable, dose reduce GTV to highest dose which meets brainstem constraint, through 23 Gy in 5 fractions. 100% of GTV should always receive at least 23 Gy in such a scenario.

*Inclusive of dose imparted by stereotactic radiosurgery if patient received stereotactic radiosurgery and stereotactic radiotherapy; normal tissue constraints pertain only to the radiotherapeutic treatment course delivered on protocol.

Management of radiation dose to the patient from daily localization

Cone beam CT or stereoscopic KV imaging will be used in this study. The doses used for daily localization images are extremely low. MV imaging (which deposits a markedly greater radiation dose) will not be employed in this study.

Future radiation considerations

For patients with progressive intracranial disease (e.g. local recurrence, distant intracranial failure), stereotactic radiation approaches will be favored over whole brain radiation. In settings of leptomeningeal disease or overwhelming distant intracranial failure with lack of viable systemic therapy, whole brain radiation will be considered/utilized.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 5.0can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Neurologic toxicities per CTCAE v5.0 probably or definitely related to protocol therapy (not applicable to toxicities/symptoms secondary to intracranial tumor burden)	
grade 1 or 2	Continue radiation / AGuIX administrations
grade 3	Hold radiation / AGuIX administrations until ≤ grade 2, then continue both radiation and AGuIX administrations
grade 4	Hold radiation 1 week and until ≤ grade 2, then continue (no further AGuIX will be administered)

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1. Adverse Event List(s) for AGuIX

As AGuIX nanoparticles were injected into few numbers of patients, and given the absence of toxicity reported during the regulatory preclinical studies, the list of potential toxicities has been established by analogy based on the product characteristics summary of gadolinium salts (Gadoteric acid (Dotarem®)), and from the Nano-Rad and NANORAD2 clinical trial safety results, and animal toxicological data of AGuIX (See AGuIX Investigator's Brochure).

Data from Gadoteric acid Summary of Product Characteristics:
System Organ Class (SOC) classification:

Immune system disorders
Uncommon: hypersensitivity
Very rare: anaphylactic reaction, anaphylactoid reaction

Psychiatric disorders
Rare: anxiety
Very rare: agitation

Nervous system disorders
Uncommon: headaches, dysgeusia, vertigo, somnolence, paresthesia
Rare: presyncope
Very rare: coma, seizure, syncope, tremor, parosmia

Eye disorders
Rare: eyelid edema
Very rare: conjunctivitis, ocular hyperemia, blurry vision, lacrimation disorder

Cardiac disorders
Rare: palpitations
Very rare: tachycardia, cardiac arrest, arrhythmia, bradycardia

Vascular disorders
Uncommon: hypotension, hypertension

Very rare: vasodilatation, pallor

Respiratory, thoracic and mediastinal disorders
Rare: sneezing
Very rare: cough, dyspnea, nasal congestion, respiratory arrest, bronchospasm, laryngospasm, pharyngeal edema, dry throat, pulmonary edema

Gastrointestinal disorders
Uncommon: nausea, abdominal pain
Rare: vomiting, diarrhea, salivary hypersecretion

Skin and subcutaneous tissue disorders
Uncommon: rash
Rare: urticaria, pruritus, hyperhidrosis
Very rare: erythema, angioedema, eczema
Undetermined frequency: nephrogenic systemic fibrosis

Musculoskeletal and systemic disorders
Very rare: muscular contractions, muscle weakness, back pain

General disorders and administration site conditions
Uncommon: feeling heat, feeling cold, injection site reactions, asthenia
Rare: chest pain, chills
Very rare: malaise, chest discomfort, fever, facial edema, injection site necrosis, superficial phlebitis

Data from animal toxicological data of AGuIX
Renal and urinary tract disorders
Incidence of renal failure not assessed because data are extrapolated from animal studies with AGuIX. A study in rats (reference Wil Research AB20679) showed the reversibility of the minimal tubular vacuolation phenomenon observed during drug elimination, after a recovery period of 10 weeks, following 2 IV injections at a high dose of 750 mg/kg (HED = 121 mg/kg).

Data from the Nano-Rad phase I clinical trial:

Summary of all serious adverse events (SAE):

Preferred term	Total	Possibly related*
Eye disorders		
Blindness	1	
Gastrointestinal disorders		
Oesophagitis	1	

General disorders and administration site conditions		
Cardiac death	1	
Disease progression	7	
General physical health deterioration	1	1
Infections and infestations		
Device related infection	1	
Sepsis	1	
Injury, poisoning and procedural complications		
Craniocerebral injury	1	
Delayed effects of radiation	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Malignant neoplasm progression	4	
Malignant pleural effusion	2	
Neoplasm progression	1	
Nervous system disorders		
Epilepsy	1	
Intracranial pressure increased	1	
Leukoencephalopathy	1	1
Partial seizures	1	
Psychiatric disorders		
Confusional state	2	1
Respiratory, thoracic and mediastinal disorders		
Pulmonary embolism	2	

*These SAEs were related to radiotherapy and were considered as possibly related to study drug by the Sponsor, as AGuIX acts as a radiosensitizing agent.

Summary of non-serious adverse events:

Preferred Term	Total	Possibly/Probably linked to AGuIX	Low intensity	Moderate intensity
Blood and lymphatic system disorders				
Anaemia	1		1	
Thrombocytopenia	2		2	
Cardiac disorders				
Supraventricular extrasystoles	1			1
Ear and labyrinth disorders				
Hypoacusis	1		1	
Vertigo	1		1	
Endocrine disorders				
Hypothyroidism	1		1	
Gastrointestinal disorders				
Aphthous ulcer	1			1
Constipation	2			2
Diarrhea	1		1	
Nausea	6	1	4	2
Vomiting	2		2	
General disorders and administration site conditions				
Asthenia	4		1	3

Gait disturbation	1			1
Malaise	1			1
Pain	1		1	
Pyrexia	1			1
Infections and infestations				
Sinusitis	1			1
Metabolism and nutrition disorders				
Hypoglycaemia	1			1
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain	1			1
Nervous system disorders				
Aphasia	1			1
Balance disorder	1			1
Cerebellar syndrome	1	1		1
Cognitive disorder	1		1	
Disturbance in attention	1		1	
Dysmetria	1		1	
Headache	6	2	3	3
Hemiplegia	1			1
Intracranial pressure increased	3	1	2	1
Memory impairment	1		1	
Paraesthesia	3		1	2
Parosmia	1			1
Psychomotor skills impaired	1		1	
Psychiatric disorders				
Confusional state	3	1	1	2
Reading disorder	1			1
Skin and subcutaneaous tissue disorders				
Alopecia	1			1
Dermatitis	3	1	2	1
Dry skin	1			1
Livedo reticularis	1		1	

Data from the NANORAD2 phase II clinical trial:

Summary of all serious adverse events (SAE):

Preferred Term	WBRT	AGuIX + WBRT	Total
Infections and infestations			
Pyelonephritis acute	1		1
Sepsis	1		1
Subtotal	*2*		*2*
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)			
Lung adenocarcinoma	1		1
Lung neoplasm malignant	1		1
Lymphangiosis carcinomatosa	1		1
Malignant neoplasm progression	1	1	2
Metastases to meninges	1	1	2
Neoplasm progression	1		
Subtotal	*6*	*2*	*8*
Nervous system disorders			

Preferred Term	WBRT	AGuIX + WBRT	Total
Aphasia	1		1
Cerebral oedema	1		1
Headache		1*	1
Hemiplegia	1		1
Intracranial pressure increased	1		1
Motor dysfunction	1	1	2
Neurological decompensation	1		1
Partial seizures		1	1
Pyramidal tract syndrome	1		1
Seizure	1		1
Subtotal	*8*	*3*	*11*
Respiratory, thoracic and mediastinal disorders			
Bronchial secretion retention		1	1
Dyspnoea		1	1
Pleural effusion		1	1
Pneumonia aspiration	1		1
Pulmonary embolism		1	1
Respiratory arrest		1	1
Respiratory distress	1	1	2
Subtotal	*2*	*6*	*8*
Gastrointestinal disorders			
Nausea	1		1
Rectal haemorrhage	1		1
Vomiting	1		1
Subtotal	*3*		*3*
Musculoskeletal and connective tissue disorders			
Spinal pain	1		1
Subtotal	*1*		*1*
General disorders and administration site conditions			
Asthenia	2		2
Death	1		1
Disease progression	2	3	5
General physical health deterioration	11	4	15
Subtotal	*16*	*7*	*23*
Psychiatric disorders			
Confusional state	1	1	2
Subtotal	*1*	*1*	*2*
Surgical and medical procedures			
Lesion excision		1	1
Subtotal		*1*	*1*
Injury, poisoning and procedural complications			
Fall		1	1
Subtotal		*1*	*1*
Investigations			
SARS-CoV-2 test positive	2		2
Subtotal	*2*		*2*
TOTAL	**41**	**21**	**62**

* This SAE was possibly related to radiotherapy and was considered as possibly related to study drug by the Sponsor, as AGuIX acts as a radiosensitizing agent.

7.1.1. Adverse Event List(s) for brain-directed stereotactic radiation (standard of care):

Immediate Reactions	**Long-Term Reactions**
Common:	**Common:**
• Tiredness • Mild skin reddening & irritation • Temporary regional hair loss	• Permanent hair loss
Uncommon	**Uncommon:**
• Worsening of symptoms • Transient nausea or headache • Skin irritation from tight mask	• Changes to bone, cartilage, or brain tissue. • Swelling of brain tissue
Rare:	**Rare:**
• Tumor hemorrhage • Brain swelling causing neurologic symptoms • Stroke • Loss of speech • Weakness on one side • Numbness or tingling on one side	• Loss of vision • Deafness • Paralysis • Stroke or brain hemorrhage • Radiation injury (necrosis) • Need for neurosurgery to remove damaged tissue or recurrence
Extremely Rare:	**Extremely Rare:**
• Seizures • Death	• Seizures • Total debilitation • Cancers caused by radiation

7.2. Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3. Expedited Adverse Event Reporting

7.3.1. In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the study PI.

7.3.2. Investigators **must** report to the study PI any adverse event (AE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.3.3. DF/HCC Adverse Event Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Attribution	DF/HCC Reportable Adverse Events (AEs)				
	Gr. 2 & 3 AE Expected	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 1 business day of learning of the event.					

The study PI will submit AE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

7.4 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports, sentinel events or unanticipated problems that require reporting per institutional policy.

7.5 Reporting to the Food and Drug Administration (FDA)

The study PI, as study sponsor, will be responsible for all communications with the FDA. The study PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.6 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the study PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or other agents administered in this study can be found in Section 7.1.

8.1 IND Agent - AGuIX

8.1.1 Description

The chemical name of AGuIX is Gadolinium-chelated polysiloxane based nanoparticle and its formula is: $(GdSi_{3\text{-}8}C_{24\text{-}34}N_{5\text{-}8}O_{15\text{-}30}H_{40\text{-}60}, nH_2O)_x$

AGuIX is a nanomedicine under investigation composed of gadolinium macrocyclic chelates covalently linked on a polysiloxane matrix (functionalized silica) created to improve radiotherapy efficacy through its imaging properties and radiosensitization effects.

8.1.2 Form

AGuIX presenting as a sterile lyophilized powder. Its primary packaging is carried out by the French subsidiary of Carbogen AMCIS in a 15 mL sterile glass vial with a bromobutyl rubber stopper containing 1g AGuIX as active ingredient and of $CaCl_2$ and NaCl as inactive ingredients.

8.1.3 Storage and Stability

The investigational product must be stored at [+2°C; +8°C] in a clean and dry area until reconstitution. AGuIX reconstituted solution will be administered minimum 1 hour and maximum 24 hours after reconstitution. The solution can be stored up to half-day at room temperature and up to 24 hours at [+2°C; +8°C] after reconstitution.

8.1.4 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the agent in a self-contained and protective environment.

8.1.5 Availability

The expiry date will be checked by the pharmacist of the Dana-Farber/Brigham and Women's Hospital. The vials should be stored at [+2°C; +8°C] in a clean and dry area, protected from the light until the reconstitution.

AGuIX is provided by investigational supply.

8.1.6 Preparation

The amount of sterile lyophilized AGuIX required will be determined according to the included

patient's data and the desired treatment dose. The corresponding number of vials will be prescribed by the investigator using the prescription provided.

Each 15 mL sterile glass vial containing 1 g of sterile lyophilized powder of AGuIX will be reconstituted with 10.00 mL of sterile water for injection to obtain a solution with a final concentration of 100 mg/mL. The pH of the solution is then at 7.3 ± 0.3.

After reconstitution with water for injection, the reconstituted solutions will be taken into a syringe, before being injected using a syringe pump or Baxter pump.

8.1.7 Administration

The reconstituted solution of AGuIX should be administered as a continuous intravenous infusion using a rate–regulating device per institutional guidelines with associated pre-medications. It should not be administered as an IV push. It should be administered at a dose rate of 2 mL/min.

8.1.8 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.9 Destruction and Return

Empty vials and/or reconstituted but not fully used AGuIX vials will be returned to the hospital pharmacy for accounting and destruction. Out of date and non-used vials will be maintained in quarantine until monitoring by the sponsor and will be returned to NH TherAguix.

8.1.10 Placebo

The placebo will consist of sterile normal saline. The volume of saline will mimic the volume of the AGuIX infusion in patients assigned to the experimental arm. Infusion times will be equivalent in the two cohorts. The process of masking AGuIX and the placebo is described above in section 5.1.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

N/A

10. STUDY CALENDAR

The study calendars below (calendars vary based on the exact type of radiation utilized) present the schedule of treatment and follow up visits. If a participant fails to appear for a visit, the investigator will make every attempt to contact them and determine the reason for the missed visit. Performance status will be assessed via the Karnofsky score. Quality of life will be assessed via the MDASI-BT: M. D. Anderson Symptom Inventory – Brain Tumor survey. General health status will be assessed via the EQ-5D. Quality of life, health status, and performance status will be assessed indefinitely (quality of life and performance status are assessed per usual care, as the MDASI-BT is the instrument used for the BWH initiative to obtain patient-reported outcome measures). Toxicity review will consist of a history at each visit to monitor for relevant toxicity. Neurocognitive assessments (Hopkins Verbal Learning Test - Revised (HVLT-R), Trail Making Test Part A and B (TMT), Controlled Word Association Test (COWAT), Mini Mental Status Examination (MMSE)) will be conducted at baseline and at 3 and 12 months post treatment; this cognitive battery takes 30 minutes to complete. MRIs of the brain will be obtained at 1.5, 3, 5, 7, and 9 months after radiation, and then every three months thereafter. Surveillance MRIs utilized in this study will be performed according to consensus recommendations for standardized brain tumor imaging protocol for clinical trials in brain metastases (BTIP-BM).[41] Representative sequences will generally include but are not limited to 3D T1-weighted sequences with and without contrast in addition to axial T2-weighted sequences, T2 FLAIR, diffuse weighted imaging with ADC, susceptibility-weighted imaging, and dynamic susceptibility contrast (DSC) perfusion (with variations thereof deemed acceptable – e.g. use of fat saturation). If the above sequences cannot be obtained 3D T1-weighted sequences with and without contrast will be prioritized above others. For patients who clinically require more or less frequent MRIs of the brain (e.g. new symptoms warranting evaluation) the MRI and follow up schedule can be adapted if approved by the study PI. Post-radiation the use of whole brain radiation will be minimized, in lieu of stereotactic approaches, unless mandated by development of leptomeningeal disease develop or overwhelming distant intracranial recurrence without systemic agent viability. A participant will be deemed lost to follow-up only after at least 3 attempts to contact him/her have been made over a 3-week period. Participants will be followed until censoring (e.g. patient withdrawal, study completion) or death.

The length of follow up for the neurocognitive secondary endpoint will also be 12 months. The length of follow up for all other endpoints will be until censoring or death. Of note, the usual clinical care for patients with brain metastases involves a radiation oncology visit, history, and an MRI brain every 1.5-3 months until death or other loss to follow up. All secondary endpoints (with the exception of neurocognition and health status) are assessed as part of usual clinical care. Patients can elect to follow-up with a local provider following the completion of radiation if deemed appropriate by the study PI, in which case brain imaging must be retrieved and digitally stored. Providers will call patients whom elect to follow-up with a local provider to discuss imaging results and complete study documentation; in such cases quality of life testing and neurocognition do not need to be pursued.

Study calendars are presented here:

Patients managed with SRS

	Baseline[a]	Radiation Planning	2-5 Days Before Radiation Initiation	Radiation Day 1[b]	Follow Up[c]	eDC Timepoints
Informed consent	X					
Medical history	X				X	Baseline
Karnofsky performance status	X				X	Baseline, Follow-up
CT simulation		X				Pre-Radiation
MRI brain			X[d]		X	Pre-Radiation, Follow-up
SRS				X		Radiation
AGuIX or placebo administration			X	X		Pre-Radiation, Radiation
Quality of life assessment	X				X	Baseline, Follow-up
Health status assessment	X				X	Baseline, Follow-up
Neurocognitive Assessment	X				X[e]	Baseline, Follow-up
Volumetric imaging	X				X	Baseline, Follow-up
AE assessment[f]	X		X[g]	X[g]	X	Baseline, Pre-Radiation, Radiation, Follow-up

Abbreviations: AE=Adverse Event; AGuIX=Activation and Guidance of Irradiation by X-ray; CT=Computed Tomography; MRI=Magnetic Resonance Imaging; SRS=Stereotactic Radiosurgery; SRT=Stereotactic Radiotherapy

a. Within 21 days

b. Within 14 days of radiation planning MRI

c. Follow up visits occur post radiation at approximately 1.5/3/5/7/9 months, and every 3 months thereafter (+/- 4 weeks except 1.5 month visit which is +/- 1 week)

d. To be performed before and after administration of AGuIX vs placebo

e. Neurocognitive assessments occur in the follow up period at 3 months and 12 months

f. For the purpose of this protocol, acute adverse events collected and documented on CRFs are only acute non-hematologic grade 3 or higher toxicities that did not predate radiation and are possibly, probably or definitely related to radiation/AGuIX

g. Adverse effects on days that AGuIX is administered will be assessed prior to administration of AGuIX

Patients managed with SRT (including those managed with SRS and SRT over 5 days)

	Baseline[a]	Radiation Planning	2-5 Days Before Radiation Initiation	Radiation Day 1[b]	Radiation Day 2	Radiation Day 3	Radiation Day 4	Radiation Day 5	Follow Up[c]	eDC Timpoints
Informed consent	X									
Medical history	X									Baseline
Karnofsky performance status	X								X	Baseline, Follow-up
MRI brain			X[d]						X	Pre-Radiation, Follow-up
CT simulation		X								Baseline, Follow-up
SRS				X[e]						Radiation
SRT				X	X	X	X	X		Radiation
AGuIX or placebo administration			X	X		X				Pre-Radiation, Radiation
Quality of life assessment	X								X	Baseline, Follow-up
Health status assessment	X								X	Baseline, Follow-up
Neurocognitive Assessment	X								X[f]	Baseline, Follow-up
Volumetric imaging	X								X	Baseline, Follow-up
AE assessment[g]	X		X[h]	X[h]					X	Baseline, Pre-Radiation, Radiation, Follow-up

Abbreviations: AE=Adverse Event; AGuIX=Activation and Guidance of Irradiation by X-ray; CT=Computed Tomography; MRI=Magnetic Resonance Imaging; SRS=Stereotactic Radiosurgery; SRT=Stereotactic Radiotherapy

a. Within 21 days

b. Within 14 days of radiation planning MRI

c. Follow up visits occur post radiation at approximately 1.5/3/5/7/9 months, and every 3 months thereafter (+/- 4 weeks except 1.5 month visit which is +/- 1 week) d. To be performed before and after administration of AGuIX vs placebo

e. If indicated

f. Neurocognitive assessments occur in the follow up period at 3 months and 12 months

g. For the purpose of this protocol, acute adverse events collected and documented on CRFs are only acute non-hematologic grade 3 or higher toxicities that did not predate radiation and are possibly, probably or definitely related to radiation/AGuIX

h. Adverse effects on days that AGuIX is administered will be assessed prior to administration of AGuIX

Patients managed with SRS and SRT over 6 days:

	Baseline[a]	Radiation Planning	2-5 Days Before Radiation Initiation	Radiation Day 1[b]	Radiation Day 2	Radiation Day 3	Radiation Day 4-6	Follow Up	eDC Timepoints
Informed consent	X								
Medical history	X								Baseline
Karnofsky performance status	X							X	Baseline, Follow-up
MRI brain			X[d]					X	Pre-Radiation, Follow-up
CT simulation		X							Baseline
SRS				X					Radiation
SRT					X	X	X		Radiation
AGuIX or placebo administration			X	X		X			Pre-Radiation, Radiation
Quality of life assessment	X							X	Baseline, Follow-up
Health status assessment	X							X	Baseline, Follow-up
Neurocognitive Assessment	X							X[e]	Baseline, Follow-up
Volumetric imaging	X							X	Baseline, Follow-up
AE assessment[f]	X		X[g]	X[g]				X	Baseline, Pre-Radiation, Radiation, Follow-up

Abbreviations: AE=Adverse Event; AGuIX=Activation and Guidance of Irradiation by X-ray; CT=Computed Tomography; MRI=Magnetic Resonance Imaging; SRS=Stereotactic Radiosurgery; SRT=Stereotactic Radiotherapy

a. Within 21 days

b. Within 14 days of radiation planning MRI

c. Follow up visits occur post radiation at approximately 1.5/3/5/7/9 months, and every 3 months thereafter (+/- 4 weeks except 1.5 month visit which is +/- 1 week) d. To be performed following before and after administration of AGuIX vs placebo

d. To be performed following before and after administration of AGuIX vs placebo

e. Neurocognitive assessments occur in the follow up period at 3 months and 12 months

f. For the purpose of this protocol, acute adverse events collected and documented on CRFs are only acute non-hematologic grade 3 or higher toxicities that did not predate radiation and are possibly, probably or definitely related to radiation/AGuIX

g. Adverse effects on days that AGuIX is administered will be assessed prior to administration of AGuIX

11. MEASUREMENT OF EFFECT

11.1. Antitumor Effect – Solid Tumors

For the purposes of this study, participants will be re-evaluated for local control at 1.5, 3, 5, 7, and 9 months, and every 3 months thereafter (+/- 4 weeks except 1.5 month visit which is +/- 1 week). Unless noted otherwise, response and progression in this study will be derived from the Response Assessment in Neuro-Oncology (RANO) – Brain Metastasis group.[1] Only radiated lesions will be assessed for response and local control.

11.1.1. Definitions

Evaluable for Target Disease response. Participants will have their response classified according to the definitions stated below.

Evaluable Non-Target Disease Response. Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

It is mandated all MRIs include a T1 post sequence with a maximal slice thickness of 1.5mm (e.g. MPRAGE, SPGR, or equivalent) and be amenable to 3D reformatting (standard of care at Brigham and Women's Hospital / Dana-Farber Cancer Institute).

11.1.2. Disease Parameters

Measurable/assessable disease. Measurable lesions are defined as those that can be accurately measured at ≥ 5 mm on at least two dimensions on an MRI.[1] Lesions must be visible on two or more axial slices no more than 1.5mm apart. Gross disease abutting a resected metastasis (cavity) is measurable if the above criteria are met (the surgical cavity itself will not be measured). Dural lesions are measurable if not secondary to disease in underlying bone (i.e. primary dural metastases are measurable). Cystic metastases are measurable if enhancement is present.[16] All tumor measurements must be recorded in millimeters.

Non-measurable/non-assessable disease. All other lesions (or sites of disease), including small lesions (one of longest two diameters <5 mm), are considered non-measurable disease. Bone lesions and leptomeningeal disease are not measurable and are not relevant to this study.

Target lesions. For patients with multiple measurable lesions targeted with radiation on study, between 2-5 measurable lesions in total will be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (e.g. lesions with the longest diameter) and be representative of the radiated disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself

to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. Bidimensional measurements will be obtained.

Non-target lesions. All other radiated lesions including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline.

11.1.3. Methods for Evaluation of Disease

Metastases will be measured on T1 post MPRAGE or SPGR sequences, or equivalent. MRIs acquired over the course of the study for a given patient must be fused / registered to ensure consistency of evaluation and remove imprecision related to head position / slicing during scan acquisition. Measurements will made digitally and saved electronically for future reference. All baseline evaluations should be performed as closely as possible to the beginning of treatment as possible.

11.1.4. Response Criteria

11.1.4.1. Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest size on study (this includes the baseline size 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 of the target lesions. Enlargement due to necrosis in the opinion of the study PI does not count as PD.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest diameters while on study.

11.1.4.2. Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s)

Progressive Disease (PD): U*nequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status.

Enlargement due to necrosis in the opinion of the study PI does not count as PD.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician and/or study PI should prevail in such circumstances, and the progression status should be confirmed at a later time by the study PI.

11.1.4.3. Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent changes other than tumor).

11.1.4.4. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Participants with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	Overall Response
CR	CR	CR
CR	Non-CR/Non-PD	PR
PR	Non-CR/Non-PD	PR
SD	Non-CR/Non-PD	SD
PD	Any	PD
Any	PD	PD

11.1.5. Local recurrence at the individual metastasis level

Definition of local recurrence: Local recurrence (PD in a radiated metastasis) at the individual metastasis level represents the primary endpoint of the study and will be measured from the date of enrollment to the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). For lesions ≥10mm in largest unidimensional size at post-radiation nadir, a 20% increase in diameter will constitute a local recurrence. Lesions <10mm in maximal unidimensional size prior to PD must display 2-3mm of definitive progression to be considered to have displayed a local recurrence. Metastases that enlarge by <20% but which are treated with definitive local

therapy (for example, a metastasis that increases from 21mm to 25mm, at which point a craniotomy is performed) will be right-censored. Enlargement due to radiation necrosis as determined by the Study PI will not count as progression. The study PI (blinded to treatment assignment per the above procedures) will make the delineation of local recurrence versus not.

As a sensitivity analysis, metastases considered to have displayed a local recurrence prompting salvage therapy but not meeting criteria for radiographic PD (for example, a metastasis that increases from 21mm to 25mm, at which point a craniotomy is performed) will be treated as a local recurrence on the date that salvage therapy is initiated.

11.1.6. Other outcomes

Overall Survival: Overall Survival (OS) is defined as the time from enrollment to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from enrollment to the earlier of progression of radiated lesions or death due to any cause. Participants alive without disease progression in radiated lesions are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from enrollment to progression of radiated lesions, or censoring at date of last disease evaluation for those without progression reported.

11.1.7. Response/Recurrence Review

The study PI will make all final determinations of response, progression, and recurrence. For patients requiring whole brain radiation as salvage therapy, irradiated lesions will be censored for all response and recurrence-based outcomes at the point of the preceding imaging assessment.

11.2. Other Response Parameters

N/A

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1. Data Reporting

12.1.1. Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2. Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the Office of Data Quality (ODQ) in accordance with DF/HCC policies.

12.2. Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Board (DSMB) will review and monitor study progress, toxicity, safety and other data from this study. The Board is chaired by a medical oncologist from outside of DF/HCC and its membership composed of internal and external institutional representation. Information that raises any questions about participant safety or protocol performance will be addressed by the Sponsor-Investigator, statistician and study team. Should any major concerns arise, the DSMB will offer recommendations regarding whether or not to suspend the study.

The DSMB will meet twice a year to review accrual, toxicity, response and reporting information. Information to be provided to the DSMB may include: participant accrual; treatment regimen information; all adverse events and serious adverse events reported across all sites by category; summary of any deaths on study; audit results; and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3. Multi-Center Guidelines

N/A

12.4. Collaborative Agreements Language

N/A

13. STATISTICAL CONSIDERATIONS

13.1. Study Design/Endpoints

The primary endpoint of this study is local control on a per metastasis level. This study seeks to evaluate, in a signal-finding randomized phase II study, whether brain-directed stereotactic radiation in the presence of AGuIX nanoparticles demonstrates a signal towards improved local control relative to brain-directed stereotactic radiation alone. The study will have one phase. We will capitalize on the fact that many patients will harbor more than one intracranial tumor. Accordingly, even after accounting for intra-patient correlations, we can conduct a randomized trial with a smaller sample size than would typically be required. The study seeks to accrue 474 brain metastases from approximately 134 patients over a period of approximately 2.8 years. We plan to accrue approximately 47-48 patients per year. All patients will be followed for at least 12 months; however, the primary analysis point will be mature 6 months post the end of recruitment (in order to maintain statistical power).

We hypothesize that brain metastases will display a signal toward improved local control when managed with brain-directed stereotactic radiation and concurrent AGuIX nanoparticles as opposed to stereotactic radiation alone. In total 474 brain metastases from 134 patients would provide 90% power to detect a HR of 0.60 with radiation and AGuIX nanoparticles using a baseline local recurrence rate of 27.5% at one year (among historical controls managed with radiation alone at Brigham and Women's Hospital/Dana-Farber Cancer Institute), a one-sided type I error of 0.10, an accrual period of 2.8 years, a minimum follow up period of 6 months and 20% inflation for the competing risk of systemic death, and 33% inflation for intra-patient correlation among metastases. A stratified, correlated log rank test will be the primary method of analysis. Given this design, a final one-sided p value <0.10 in this hypothesis-generating study will suggest that a phase III randomized trial comparing brain-directed stereotactic radiation with or without AGuIX nanoparticles for patients with brain metastases is warranted.

One interim analysis for efficacy using a stratified, clustered log rank test will be conducted at 50% information time for the primary endpoint of local recurrence projected to occur roughly 6 months prior to the end of full accrual (study time 2.3 years). An O'Brien-Fleming boundary function will be used at that time to control type I error. If this rule is met, further study accrual will halt but patients already enrolled will be followed.

The randomization will be stratified as outlined below. If 2 or more potential strata could apply to a given patient, the enrolling clinician can select the stratum that is most appropriate.

13.2. Sample Size, Accrual Rate and Study Duration

As noted above, the study will enroll 474 brain metastases from approximately 134 patients. It is expected that approximately 67 patients will be randomized to each arm. The study will conclude after all protocol-specified time points have elapsed and follow up data are sufficiently mature for analysis. We estimate the study will accrue over 2.8 years.

Accrual Targets

Ethnic Category	**Sex/Gender**					
	Females		**Males**		**Total**	
Hispanic or Latino	3	+	3	=	6	
Not Hispanic or Latino	64	+	64	=	128	
Ethnic Category: Total of all subjects	67 (A1)	+	67 (B1)	=	134 (C1)	
Racial Category						
American Indian or Alaskan Native	1	+	1	=	2	
Asian	5	+	5	=	10	
Black or African American	8	+	8	=	16	
Native Hawaiian or other Pacific Islander	1	+	1	=	2	
White	52	+	52	=	104	
Racial Category: Total of all subjects	67 (A2)	+	67 (B2)	=	134 (C2)	
	(A1 = A2)		(B1 = B2)		(C1 = C2)	

13.3. Stratification Factors

As noted above patients will be stratified into the following strata:

-Melanoma with intracranial growth consistent with tumor progression despite immunotherapy
-Gastrointestinal primary
-HER2 positive breast cancer
-Cystic metastases
-Metastases ≥2cm in maximal unidimensional size
-Locally recurrent metastases after prior stereotactic radiation
-Locally recurrent metastases after prior whole brain radiation

Patients with metastases from melanoma, GI primaries, or HER2+ breast cancer, as well as those with cystic metastases or metastases ≥2cm in maximal unidimensional size, who have local recurrences after prior brain-directed radiation can only be treated in the strata permitting prior radiation (last two strata above).

We will mandate that each stratum contain at least 12 patients by the end of the study in order to ensure a reasonable number of patients per stratum, with the exception of the locally recurrent metastases after prior stereotactic radiation stratum, which may be closed early if at least 12 patients have been accrued to the other strata. The treatment naïve metastases ≥2cm in maximal unidimensional size stratum will target 44 patients as this stratum represents an important and prevalent brain metastasis population. No other stratum will be permitted to accrue more than 22 patients. Accrual to individual strata will be monitored as the study progresses.

13.4. Interim Monitoring Plan

Neurologic death in patients with brain metastases often is secondary to local progression of disease that has often been radiated in excess of one time. Consequently strata involving prior radiation potentially represent patients who may benefit the most from radiosensitization. However, symptomatic radiation necrosis may be more common in such cohorts given the prior treatment. Accordingly, an early stopping rule will be employed to monitor for excess toxicity in this subset of patients. If two or more of the first six patients randomized to receive AGuIX in either strata involving prior radiation (for the purposes of the early stopping rule these strata will be combined) display symptomatic radiation necrosis requiring resection within three months of treatment these strata of the study will be closed to further enrollment. Symptomatic radiation necrosis will be defined as radiographic changes consistent with necrosis in combination with predominant necrotic change seen on pathology at resection. If the true rate of symptomatic radiation necrosis requiring resection is 33%, then there is a 65% chance that at least two of the first six patients would experience such toxicity. If this early stopping rule is met, then any plans to re-open the study with a modified treatment plan will need to be formally reviewed and approved by the sponsor and by the DF/HCC SRC/IRB prior to activation. If there are less than two instances of symptomatic radiation necrosis requiring resection within the first three patients enrolled, these strata will proceed to full accrual. Case report forms in strata involving prior radiation will be monitored monthly by the unblinded CRC until either the early stopping rule is met or it is determined that the early stopping rule cannot be met.

In addition, we utilize a second early stopping rule applicable to the entire cohort. If two or more of the first six patients randomized to receive AGuIX display an acute, grade 3-5 non-hematologic toxicity within 1.5 months of the end of protocol-based treatment that is possibly, probably, or definitely related to AGuIX administration the study will be closed to further enrollment. If the true rate of such toxicity is 33%, then there is a 65% chance that at least two of the first six patients would experience it. If this early stopping rule is met, then any plans to re-open the study with a modified treatment plan will need to be formally reviewed and approved by the sponsor and by the DF/HCC SRC/IRB prior to activation. If there are less than two instances of acute, grade 3-5, non-hematologic toxicity within 1.5 months of the end of protocol-based treatment that are possibly, probably, or definitely related to AGuIX administration among the first six patients, the study will proceed to full accrual. Of note the first post-treatment assessment will occur at 1.5 months. Case report forms for such patients will be monitored weekly by the unblinded CRC until either the early stopping rule is met or it is determined that the early stopping rule cannot be met.

The study will incorporate an early stopping rule for futility. After 50% of the total patient accrual (that is, 67 of the 134 patients) have been observed through 9 months, we will evaluate the best intracranial response rate (iRR) achieved over 9 months for the pre-specified futility analysis. It is expected that the control iRR rate is on the order of 70% and the experimental iRR rate will be improved to at least 86%. Under this scenario, the overall study has 83% power for this comparison at full information (98 intracranial responses) using a one-sided 0.10 level test of proportions. For 50% information time on iRR (49 intracranial responses), it is projected that this will be reached roughly at study month 26, given an expected accrual of 47-48 patients per year, 17 months of accrual and 9 months follow-up for the first 67 patients. The Wieand rule will be used to assess futility. If the iRR is higher the experimental arm the study will proceed to full accrual. If the iRR is high in the non-experimental/placebo arm we will examine local control on

a per metastasis level before abandoning the study. If local control on a per metastasis level is also better in the non-experimental/placebo arm then the study will be abandoned. If local control is better in the experimental arm the study will proceed to full accrual. The interim analysis for efficacy based on local control is described above in section 13.1.

13.5. Analysis of Primary Endpoints

Time to local failure on a per metastasis basis will be performed using the Kaplan-Meier curves, the log-rank test, and Cox regression for clustered data. Intrapatient correlations will be accounted for using a sandwich estimator.

13.6. Analysis of Secondary Endpoints

Secondary endpoint will be analyzed as follows

1. Overall survival (i.e. all cause mortality) Kaplan-Meier curves, log-rank test, Cox regression)
2. Death due to neurologic disease progression (defined as death due to progressive brain metastases on imaging associated with progressive neurologic symptomatology in the setting of systemic disease that has not progressed to a life-threatening nature; cumulative incidence curves, Gray's test, Fine and Gray's regression)
3. Performance status, assessed longitudinally (longitudinal regression)
4. Ability to complete activities of daily living, assessed longitudinally (longitudinal regression)
5. Incidence and time to detection of new brain metastases (Kaplan-Meier curves, log-rank test, Cox regression)
6. Incidence and time to development of radiation necrosis (Kaplan-Meier curves, log-rank test, Cox regression)
7. Incidence and time to development of leptomeningeal disease (Kaplan-Meier curves, log-rank test, Cox regression)
8. Incidence and time to progressive intracranial disease (Kaplan-Meier curves, log-rank test, Cox regression)
9. Incidence and time to salvage craniotomy (Kaplan-Meier curves, log-rank test, Cox regression)
10. Incidence and time to additional radiotherapeutic treatments after the initial course (stereotactic or whole brain radiation) (Kaplan-Meier curves, log-rank test, Cox regression)
11. Progression free survival (Kaplan-Meier curves, log-rank test, Cox regression)
12. Incidence and time to the development of seizures (Kaplan-Meier curves, log-rank test, Cox regression)
13. Neurocognition, assessed longitudinally (longitudinal regression)
14. Quality of life, assessed longitudinally (longitudinal regression)
15. Steroid use, assessed longitudinally (longitudinal regression)
16. Local recurrence at one year in metastases treated radiotherapeutically using RECIST (response evaluation criteria in solid tumors) criteria (Kaplan-Meier curves, log-rank test, Cox regression)

13.7. Reporting and Exclusions

13.7.1. Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first treatment.

13.7.2. Evaluation of the Primary Efficacy Endpoint

All analyses will be intent-to-treat.

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then the initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

REFERENCES

1. Lin NU, Lee EQ, Aoyama H, et al. Response assessment criteria for brain metastases: proposal from the RANO group. Lancet Oncol 2015;16:e270-8.
2. Barnholtz-Sloan JS, Sloan AE, Davis FG, Vigneau FD, Lai P, Sawaya RE. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. J Clin Oncol 2004;22:2865-72.
3. Stewart DJ. A critique of the role of the blood-brain barrier in the chemotherapy of human brain tumors. J Neurooncol 1994;20:121-39.
4. Wu YL, Zhou C, Cheng Y, et al. Erlotinib as second-line treatment in patients with advanced non-small-cell lung cancer and asymptomatic brain metastases: a phase II study (CTONG-0803). Ann Oncol 2013;24:993-9.
5. Li S, Qi X, Huang Y, Liu D, Zhou F, Zhou C. Ceritinib (LDK378): a potent alternative to crizotinib for ALK-rearranged non-small-cell lung cancer. Clin Lung Cancer 2015;16:86-91.
6. Lin NU, Dieras V, Paul D, et al. Multicenter phase II study of lapatinib in patients with brain metastases from HER2-positive breast cancer. Clin Cancer Res 2009;15:1452-9.
7. Lin NU, Carey LA, Liu MC, et al. Phase II trial of lapatinib for brain metastases in patients with human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol 2008;26:1993-9.
8. Jacot W, Pons E, Frenel JS, et al. Efficacy and safety of trastuzumab emtansine (T-DM1) in patients with HER2-positive breast cancer with brain metastases. Breast Cancer Res Treat 2016;157:307-18.
9. Falchook GS, Long GV, Kurzrock R, et al. Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumours: a phase 1 dose-escalation trial. Lancet 2012;379:1893-901.
10. Tazi K, Hathaway A, Chiuzan C, Shirai K. Survival of melanoma patients with brain metastases treated with ipilimumab and stereotactic radiosurgery. Cancer Med 2015;4:1-6.
11. Brown PD, Jaeckle K, Ballman KV, et al. Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases: A Randomized Clinical Trial. JAMA 2016;316:401-9.
12. Kocher M, Soffietti R, Abacioglu U, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. J Clin Oncol 2011;29:134-41.
13. Lesueur P, Lequesne J, Barraux V, et al. Radiosurgery or hypofractionated stereotactic radiotherapy for brain metastases from radioresistant primaries (melanoma and renal cancer). Radiat Oncol 2018;13:138.
14. Sanghvi SM, Lischalk JW, Cai L, et al. Clinical outcomes of gastrointestinal brain metastases treated with radiotherapy. Radiat Oncol 2017;12:43.
15. Cagney DN, Lamba N, Montoya S, et al. Breast cancer subtype and intracranial recurrence patterns after brain-directed radiation for brain metastases. Breast Cancer Res Treat 2019;176:171-9.
16. Brigell RH, Cagney DN, Martin AM, et al. Local control after brain-directed radiation in patients with cystic versus solid brain metastases. J Neurooncol 2019;142:355-63.
17. Angelov L, Mohammadi AM, Bennett EE, et al. Impact of 2-staged stereotactic radiosurgery for treatment of brain metastases >/= 2 cm. J Neurosurg 2018;129:366-82.

18. Balermpas P, Stera S, Muller von der Grun J, et al. Repeated in-field radiosurgery for locally recurrent brain metastases: Feasibility, results and survival in a heavily treated patient cohort. PLoS One 2018;13:e0198692.
19. Yomo S, Hayashi M. The efficacy and limitations of stereotactic radiosurgery as a salvage treatment after failed whole brain radiotherapy for brain metastases. J Neurooncol 2013;113:459-65.
20. McTyre ER, Johnson AG, Ruiz J, et al. Predictors of neurologic and nonneurologic death in patients with brain metastasis initially treated with upfront stereotactic radiosurgery without whole-brain radiation therapy. Neuro Oncol 2017;19:558-66.
21. Blonigen BJ, Steinmetz RD, Levin L, Lamba MA, Warnick RE, Breneman JC. Irradiated volume as a predictor of brain radionecrosis after linear accelerator stereotactic radiosurgery. Int J Radiat Oncol Biol Phys 2010;77:996-1001.
22. Minniti G, Clarke E, Lanzetta G, et al. Stereotactic radiosurgery for brain metastases: analysis of outcome and risk of brain radionecrosis. Radiat Oncol 2011;6:48.
23. Sugahara T, Korogi Y, Tomiguchi S, et al. Posttherapeutic intraaxial brain tumor: the value of perfusion-sensitive contrast-enhanced MR imaging for differentiating tumor recurrence from nonneoplastic contrast-enhancing tissue. AJNR Am J Neuroradiol 2000;21:901-9.
24. Mitsuya K, Nakasu Y, Horiguchi S, et al. Perfusion weighted magnetic resonance imaging to distinguish the recurrence of metastatic brain tumors from radiation necrosis after stereotactic radiosurgery. J Neurooncol 2010;99:81-8.
25. Asao C, Korogi Y, Kitajima M, et al. Diffusion-weighted imaging of radiation-induced brain injury for differentiation from tumor recurrence. AJNR Am J Neuroradiol 2005;26:1455-60.
26. Rock JP, Scarpace L, Hearshen D, et al. Associations among magnetic resonance spectroscopy, apparent diffusion coefficients, and image-guided histopathology with special attention to radiation necrosis. Neurosurgery 2004;54:1111-7; discussion 7-9.
27. Kimura T, Sako K, Tanaka K, et al. Evaluation of the response of metastatic brain tumors to stereotactic radiosurgery by proton magnetic resonance spectroscopy, 201TlCl single-photon emission computerized tomography, and gadolinium-enhanced magnetic resonance imaging. J Neurosurg 2004;100:835-41.
28. Henry RG, Vigneron DB, Fischbein NJ, et al. Comparison of relative cerebral blood volume and proton spectroscopy in patients with treated gliomas. AJNR Am J Neuroradiol 2000;21:357-66.
29. Davidson A, Tait DM, Payne GS, et al. Magnetic resonance spectroscopy in the evaluation of neurotoxicity following cranial irradiation for childhood cancer. Br J Radiol 2000;73:421-4.
30. Horky LL, Hsiao EM, Weiss SE, Drappatz J, Gerbaudo VH. Dual phase FDG-PET imaging of brain metastases provides superior assessment of recurrence versus post-treatment necrosis. J Neurooncol 2011;103:137-46.
31. Doyle WK, Budinger TF, Valk PE, Levin VA, Gutin PH. Differentiation of cerebral radiation necrosis from tumor recurrence by [18F]FDG and 82Rb positron emission tomography. J Comput Assist Tomogr 1987;11:563-70.
32. Buchpiguel CA, Alavi JB, Alavi A, Kenyon LC. PET versus SPECT in distinguishing radiation necrosis from tumor recurrence in the brain. J Nucl Med 1995;36:159-64.
33. Lai G, Mahadevan A, Hackney D, et al. Diagnostic Accuracy of PET, SPECT, and Arterial Spin-Labeling in Differentiating Tumor Recurrence from Necrosis in Cerebral

Metastasis after Stereotactic Radiosurgery. AJNR Am J Neuroradiol 2015;36:2250-5.
34. Cagney DN, Martin AM, Catalano PJ, et al. Impact of pemetrexed on intracranial disease control and radiation necrosis in patients with brain metastases from non-small cell lung cancer receiving stereotactic radiation. Radiother Oncol 2018.
35. Lux F, Tran VL, Thomas E, et al. AGuIX((R)) from bench to bedside-Transfer of an ultrasmall theranostic gadolinium-based nanoparticle to clinical medicine. Br J Radiol 2018:20180365.
36. Sancey L, Lux F, Kotb S, et al. The use of theranostic gadolinium-based nanoprobes to improve radiotherapy efficacy. Br J Radiol 2014;87:20140134.
37. Sancey L, Kotb S, Truillet C, et al. Long-term in vivo clearance of gadolinium-based AGuIX nanoparticles and their biocompatibility after systemic injection. ACS Nano 2015;9:2477-88.
38. Kotb S, Detappe A, Lux F, et al. Gadolinium-Based Nanoparticles and Radiation Therapy for Multiple Brain Melanoma Metastases: Proof of Concept before Phase I Trial. Theranostics 2016;6:418-27.
39. Verry C, Dufort S, Lemasson B, et al. Targeting brain metastases with ultrasmall theranostic nanoparticles, a first-in-human trial from an MRI perspective. Sci Adv 2020;6:eaay5279.
40. Verry C, Sancey L, Dufort S, et al. Treatment of multiple brain metastases using gadolinium nanoparticles and radiotherapy: NANO-RAD, a phase I study protocol. BMJ Open 2019;9:e023591.
41. Kaufmann TJ, Smits M, Boxerman J, et al. Consensus recommendations for a standardized brain tumor imaging protocol for clinical trials in brain metastases (BTIP-BM). Neuro Oncol 2020.