N107C

A Phase III Trial of Post-Surgical Stereotactic Radiosurgery (SRS) Compared With Whole Brain Radiotherapy (WBRT) for Resected Metastatic Brain Disease

ClinicalTrial.gov Identifier: NCT01372774

Study Background

Trial Description

RATIONALE: Stereotactic radiosurgery may be able to send x-rays directly to the tumor and cause less damage to normal tissue. Radiation therapy uses high-energy x rays to kill tumor cells. It is not yet known whether stereotactic radiosurgery is more effective than whole-brain radiation therapy in treating patients with brain metastases that have been removed by surgery. PURPOSE: This randomized phase III trial studies how well stereotactic radiosurgery works compared to whole-brain radiation therapy in treating patients with brain metastases that have been removed by surgery.

Arms:

Arm I - WBRT: (Active Comparator): Patients undergo whole brain radiotherapy (WBRT) once a day, 5 days a week, for approximately 3 weeks. Patient observation/follow up occurs at week 12 and months 6, 9, 12, 16 and 24 post registration/randomization. Event monitoring occurs every 6 months until 5 years post registration/randomization.

Arm II - SRS: (Experimental): Patients undergo stereotactic radiosurgery (SRS) using a gamma knife or a linear accelerator procedure. Patient observation/follow up occurs at week 12 and months 6, 9, 12, 16 and 24 post registration/randomization. Event monitoring occurs every 6 months until 5 years post registration/randomization.

Objectives:

- Primary Goals
    1. Overall Survival - To determine in patients with one to four brain metastases whether there is improved overall survival in patients who receive SRS to the surgical bed compared to patients who receive WBRT.
    2. Neurocognitive Progression - To determine in patients with one to four brain metastases whether there is less neurocognitive progression post-randomization in patients who receive SRS to the surgical bed compared to patients who receive WBRT.
- Secondary Goals

1. Quality of Life (QOL) - To determine in patients with resected brain metastases whether there is improved QOL in patients who receive SRS to the surgical bed compared to patients who receive WBRT.
2. Central Nervous System Failure - To determine in patients with one to four brain metastases whether there is equal or longer time to central nervous system (CNS) failure (brain) in patients who receive SRS to the surgical bed compared to patients who receive WBRT.
3. Functional Independence - To determine in patients with one to four brain metastases whether there is longer duration of functional independence in patients who receive SRS to the surgical bed compared to patients who receive WBRT.
4. Long-Term Neurocognitive Status - To determine in patients with one to four brain metastases whether there is better long-term neurocognitive status in patients who receive SRS to the surgical bed compared to patients who receive WBRT.
5. Adverse Events - To tabulate and descriptively compare the post-treatment adverse events associated with the interventions.
6. Local Tumor Bed Recurrence - To evaluate local tumor bed recurrence at 6 months with post-surgical SRS to the surgical bed in comparison to WBRT.
7. Local Recurrence - To evaluate time to local recurrence with post-surgical SRS to the surgical bed in comparison to WBRT.
8. CNS Failure Patterns - To evaluate if there is any difference in CNS failure patterns (local, distant, leptomeningeal) in patients who receive SRS to the surgical bed compared to patients who receive WBRT.

- OUTLINE: This is a multicenter study. Patients are stratified according to age in years (< 60 vs ≥ 60), extracranial disease controlled (≤ 3 months vs > 3 months), number of pre-operative brain metastases (1 vs 2-4), histology (lung vs radioresistant [brain metastases from a sarcoma, melanoma, or renal cell carcinoma histology] vs other), and resection cavity maximal diameter (≤ 3 cm vs > 3 cm). Patient must complete baseline QOL and neurocognitive tests prior to registration/randomization. Patients are randomized to 1 of 2 treatment arms.
  - Arm I: Patients undergo whole-brain radiotherapy (WBRT) once a day, 5 days a week, for approximately 3 weeks.
  - Arm II: Patients undergo stereotactic radiosurgery (SRS) using a gamma knife or a linear accelerator procedure.
- Event monitoring occurs up to 5 years post registration/randomization.

Study Milestones:

Start date: July 2011

Primary Completion Date: August 2016

Publication Information:

Analysis Type: Primary

Pubmed ID: 28687377

Citation: Lancet Oncol. 2017 Aug;18(8):1049-1060. doi: 10.1016/S1470-2045(17)30441-2. Epub 2017 Jul 4.

Associated Datasets: NCT01372774-D1-Dataset.csv (baseline), NCT01372774-D2-Dataset.csv (barthel), NCT01372774-D3-Dataset.csv (cogdata), NCT01372774-D4-Dataset.csv (qoldata), NCT01372774-D5-Dataset.csv (aedata)

Dataset Information:

Dataset Name: NCT01372774-D1-Dataset.csv (baseline)

Description: Dataset NCT01372774-D1-Dataset.csv (baseline) is one of 5 datasets associated with PubMed ID 28687377. This dataset contains one record per patient. It contains information that that is presented in the baseline characteristics table and time to event analyses.

Notes:

- This dataset contains information presented in Table 1 and Figures 2 and 3 in the publication and Supplemental Table S3.
- Data can be used to approximate published study findings, but exact reproduction of previous manuscripts may not be possible in some cases (e.g., when data must be modified for de-identification purposes or have undergone further data cleaning).

NCT01372774-D1-Dataset.csv (baseline) Data Dictionary:

LABEL	NAME	ELEMENTS	COMMENTS
Patient Reference	PATREF		
Data Center Assigned Protocol Number	STUDY_ID	N107C	
Arm	ARM	A = WBRT, B = SRS	SRS = Stereotactic Radiosurgery WBRT = Whole Brain Radiotherapy
Long-Term Survivor	ltsurv	N=No, Y=Yes	Patients who had a cognitive evaluation 12 months or later from time of randomization
Age Group	AGEGRPC	<60, >=60	Years
Extra cranial disease controlled	DZCNTLC	<=3, >3	Period of systemic disease control prior to study entry (in months)
Number Brain Mets	N_BRMETC	1, 2 to 4	
Histology	HISTO_C	Lung, Other, Radioresistant	

Resection Cavity Diameter (cm)	CAVDIAMC	<=3 cm, >3 cm	
Started protocol therapy	STARTTX	Y = patient started protocol treatment N = patient withdrew prior to beginning protocol treatment	
Gender	SEX	m, f	
Age at study entry	AGE		Years
Race	RACEW	0 = Non-White 1 = White	Category “Non-White” includes: • Black or African American • Asian • American Indian or Alaska Native • Unknown/Not reported
ECOG Performance Score	PS	0 = Normal activity. 1 = Symptoms, but ambulatory. 2 = In bed < 50% of the time.	
Extent Resection	EXT_SURG	2 = Subtotal Resection 3 = Total (gross) Resection	
Surgical approach	SURGTYPE	1 = En bloc 2 = Piecemeal Missing = data not available	
Cranial Nerves	CRANIAL	Normal, Abnormal, Missing= data not available	
Sensation	SENSATN	Normal, Abnormal, Missing= data not available	
Motor	MOTOR	Normal, Abnormal, Missing= data not available	

Cerebellar	CEREBELR	Normal, Abnormal, Missing= data not available	
Surgical Bed Progression	sbedpg	1 = censor 2 = event	
Time to Surgical Bed Progression	sbedpgtm		Days from randomization to date of surgical bed progression or, if no surgical bed progression: last assessment
Local Brain Progression	localpg	1 = censor 2 = event	
Time to Local Brain Progression	localpgtm		Days from randomization to date of local brain progression or, if no local brain progression: last assessment
Distant Brain Progression	distpg	1 = censor 2 = event	
Time to Distant Brain Progression	distpgtm		Days from randomization to date of distant brain progression or, if no distant brain progression: last assessment
Leptomeningeal Disease	leptodz	1 = censor 2 = event Missing = data not available (i.e., assessment not reported)	
Time to Leptomeningeal Disease Diagnosis	leptotm	Missing = data not available (i.e., assessment not reported)	Days from randomization to date of leptomeningeal disease diagnosis
Systemic Disease Progression	sysdzpg	1 = censor 2 = event Missing = data not available (assessment not reported)	Refers to primary cancer
Time to Systemic Disease Progression	sysdzpgtm	Missing = data not available (i.e., assessment not reported)	Days from randomization to date of primary cancer progression or, if no

			primary cancer progression: last assessment of primary disease reported
Follow-up Status	FU_STAT	Dead, Alive	
Study entry to Last Known Alive/Death	fu_time		Days from study entry to date last known alive or death date. fu_time is equal to 0 for one patient who refused/withdrew prior to beginning protocol therapy and did not provide any follow-up data. Note: follow-up data is available for 8 patients who did not start protocol treatment.
Subsequent Treatment	subtx	"Chemo", "Chemo, SRS", "Chemo, SRS, WBRT, Surgical Res", "Chemo, WBRT", "SRS", "SRS, Surgical Res", "Surgical Res", "WBRT", "Other" Missing = No subsequent treatment reported	Treatment received after protocol therapy ended.
Evaluable for AE	ae_eval	N = Not evaluable for adverse events Y = At least one adverse events evaluation	Consort diagram: included in safety population – where ae_eval=Y
Necrosis Grade	necrosis_grd	0, 1, 2, 3 Missing values indicate data was not collected or unavailable (patient is not evaluable for adverse events).	Maximum reported grade. Graded per CTCAE v4.0
Safety and Toxicity	ae3plus	Y = Yes N = No	Patient experienced at least one grade 3 or higher adverse event.

		Missing values indicate patient was not evaluable for adverse events.	
Baseline Cognitive Evaluation Completed	ptflow1	Y = Yes N = No	
3-month Cognitive Evaluation Completed	ptflow2b	Y = Yes N = No	Missing values indicate data was not collected or unavailable.
Vital Status at 3 months	ptflow2	A = Alive D = Died L = Lost to follow-up	If a patient had a 3-month evaluation and died, for example, on day 90, this indicator variable is set to "A" (alive). Missing values indicate data were not collected or unavailable.
6-months Cognitive Evaluation Completed	ptflow3b	Y = Yes N = No	Missing values indicate data was not collected or unavailable.
Vital Status at 6 months	ptflow3	A = Alive D = Died L = Lost to follow-up	Missing values indicate data was not collected or unavailable. If a patient had a 6-month evaluation and died, for example, on day 181, this indicator variable is set to "A" (alive).
Cognitive deterioration–free survival: Time	cpg_time		Days from study entry to event or, days to last known alive if no event.
Cognitive deterioration–free survival: Status	cpg_stat	0 = censor (alive and no cognitive deterioration) 1 = event	Events for this endpoint are: - confirmed cognitive deterioration - presumed cognitive deterioration - death

Cognitive deterioration–free survival: Event Category	cpg_event	C = confirmed cognitive deterioration P = presumed cognitive deterioration D= died blank = censor (alive and no cognitive deterioration at last evaluation/contact)	
Grade 5 Adverse Event Term	grd5ae	blank = no grade 5 adverse event reported	Common Terminology Criteria for Adverse Events (CTCAE) - version 4.0
Grade 5 Adverse Event Attribution (per treating site)	grd5attr	Unrelate dUnlikely Possible Definite blank = attribution was not reported by treating site	Note: Only applicable for patients with grade 5 AEs (gr5ae ≠ blank) This variable contains grade 5 AE attribution as originally reported by treating sites. Variable *related* in dataset NCT01372774-D5 contains updated and corrected grade 5 AE attribution after further review. Thus, the grade 5 attribution in this variable does not match with *related* in dataset D5.
Cause of Death	codth		blank = patient alive at last follow-up
Timepoint at which last follow-up or death occurred	futimepoint	0 = Baseline 1 = 3-month 2 = 6-month 3 = 9-month 4 = 12-month 5 = 16-month 6 = 24-month	Note: This variable contains follow-up timepoint information as presented in table S4c
Memantine/ Namenda use at study entry	memantine0	No	blank = data not available
Memantine/ Namenda use at 12 weeks from study entry	memant12wk	Yes	blank = no Memantine / Namenda use at 12 weeks from study entry was reported

WBRT Dose	wbrtdose	2.5 Gy = 2.5 Gy in 15 fractions 3.0 Gy = 3.0 Gy in 10 fractions	blank = patient did not receive WBRT during protocol intervention
Duration of functional independence: Status	fi_stat	1 = censor 2 = event	Event was defined as a drop to below baseline score blank = data unavailable
Duration of functional independence: Time	fi_mnth		Time (in months from study entry) to event or last assessment without prior decline below baseline
Time to WBRT Salvage Treatment	ttosalv_wbrt		Days from study entry to start of WBRT salvage therapy blank = no WBRT salvage therapy was reported