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BRIEFING DOCUMENT FOR NDA# 21-661

Synopsis of Clinical Component

The efficacy database consists of two clinical studies, RT-008 and RT-009. RT-009 was a phase 3, randomized, open-label, comparative study in 538 patients receiving a standard 2-week course of whole brain radiation therapy for brain metastases, 30 Gy fractions per day, with supplemental oxygen, with or without RSR13. There was no statistically significant difference in the primary endpoint of overall survival when analyzed using the log-rank test, median survival time 4.47 months in the control arm vs. 5.26 months in the RSR13 arm, p=0.169. There was also no statistically significant differences in the secondary endpoints of time to radiographic tumor progression in the brain, time to clinical tumor progression in the brain, response rate in the brain, cause of death and quality of life. The sponsor is requesting approval based on the finding of a survival advantage with RSR13 + whole brain radiation therapy/supplemental oxygen vs. WBRT/O₂ alone in a non-prespecified subgroup of breast cancer patients with brain metastases. By subset analysis, the observed median survival time for breast cancer patients in the control arm was 4.57 months compared to 8.67 months for the RSR13 arm (p=0.0061, log-rank). The sponsor also described a response rate in the brain in this non-prespecified breast cancer subgroup, 49.1% in the control arm vs. 71.7% in the RSR13 arm.

RT-008 was a single-arm, multicenter phase 2 study in patients receiving a conventional 2-week course of cranial radiation therapy with RSR13 for brain metastases. Sixty-nine patients participated in this study. The stated objectives included response rate in the brain, median survival, and time to progression. In the setting of a single arm study, it is difficult to interpret time to event endpoints such as survival and time to progression.

The Medical Reviewer has the following concerns regarding the pivotal Phase 3 study:

1. There was no statistically significant difference in survival between the two study arms of RT-009 in the intent to treat population.
2. The sponsor's finding of a survival difference between the two study arms of RT-009 in the breast cancer subgroup represents a non-prespecified subgroup analysis which should be considered exploratory.
3. The marginal findings regarding response rate in the brain in RT-009 cannot be considered reasonably likely to predict clinical benefit since tumor shrinkage could be attributed to radiation therapy given in both treatment arms. Another factor in the uncertainty of this finding is that most deaths were attributed to non-neurological or indistinguishable causes. Other concerns regarding the assessment of response in RT-009 include the following:
 - Confirmatory scans were not required.
 - The designation of CR/PR was given whether or not a new brain parenchymal lesion was documented on a particular evaluation. See briefing document for other concerns.

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See Section IV of this briefing document for the safety analyses, which will be presented in more detail at the Advisory Committee meeting.

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I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Generic Name:	Efaproxiral Sodium
Proposed Trade Name:	Excelar
Established Trade Name:	RSR-13
Chemical Name:	2 – [4-[2-(3,5-dimethylphenyl) amino]-2-oxoethyl]phenoxy]-2-methyl-propanoic acid monosodium salt
Pharmacologic Category:	Radiation-sensitizing agent
Drug Class:	Synthetic allosteric modifier of hemoglobin
Route of Administration:	Intravenous
Dose and Regimen:	75 or 100 mg/kg daily over 30 minutes through a central venous catheter, Monday through Friday, for 2 weeks. Concurrent supplemental oxygen is also administered at a rate of 4 L/min via nasal cannula or facemask beginning 5 minutes prior to initiation of infusion, during infusion and whole brain radiation therapy (WBRT), and for at least 15 minutes after completion of daily WBRT. WBRT must be administered within 30 minutes of the end of the Excelar infusion.
Population Studied:	Patients with brain metastases originating from histologically confirmed solid primary malignancies, excluding small cell carcinoma, lymphoma, and germ cell tumors.
Proposed Indication:	Adjunctive therapy to whole brain radiation therapy for the treatment of brain metastases originating from breast cancer.

B. State of Armamentarium for Indication

Approximately one-third to one half of all adult brain tumors result from hematogenous dissemination of malignant cells from an extracranial source to the central nervous system. The most common sites of origin are the lung, breast, or melanoma skin cancers. The median survival following treatment is only 3 – 6 months when multiple metastatic lesions are present and about 12 months for those with a solitary metastatic deposit.(1) The contrast-enhanced MRI is considered the best imaging study to diagnose brain metastases and will guide the choice of management. There are no FDA approved drugs for the treatment of metastatic tumors to the

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brain. Accepted treatment standards consist of surgical resection followed by post-operative radiation therapy, whole brain radiation therapy (WBRT) alone, stereotactic radiosurgery, interstitial brachytherapy, and anecdotal reports with hormonal therapy in cases of breast cancers responsive to hormones. The use of chemotherapy has been disappointing. Corticosteroids aid in alleviating peritumoral edema. The presence of seizure activity in patients with brain metastases leads to treatment with anticonvulsant therapy. Venous thromboembolic disease also occurs at a higher frequency in patients with brain metastases, often requiring inferior vena caval filters or standard anticoagulation.(2)

Corticosteroids were first used in 1957 in patients with brain metastases originating from the breast, followed by dexamethasone in 1961. Dexamethasone has less mineralocorticoid activity and has been included in the standard treatment ever since. Its main mechanism of action is to reduce the permeability of tumor capillaries.(2)

Primary radiation therapy has been the mainstay of treating metastatic tumor deposits in the brain for 40 years. The median survival of patients with brain metastasis treated with steroids alone or no form of treatment is 1 to 2 months. Conventional whole brain radiation therapy (WBRT) increases the median survival to 3 -6 months. There is no consensus on the optimal irradiation schedule for patients with brain metastasis. Typical irradiation treatment schedules consist of total doses of 30 - 50 Gy in 1.5 – 4 Gy/daily fraction, usually 30 Gy in 10 fractions over 2 weeks. Occasionally, reirradiation is employed at the time of brain recurrence in patients with previously controlled systemic symptoms.(2)

Three randomized prospective studies have evaluated the role of surgery as an adjunct to WBRT for patients with a single brain metastasis. Patchell et al. randomized 48 patients to receive biopsy followed by WBRT (36 Gy in 12 fractions) or surgical resection followed by WBRT.(3) Patients treated with surgery followed by WBRT had fewer local recurrences (20% vs. 52%, $p < 0.02$), improved survival (40 weeks vs. 15 weeks), and had a better quality of life as measured by the Karnofsky Performance Scale. Vecht et al. also randomized patients to WBRT alone or surgical resection followed by WBRT and showed a benefit in the treatment arm consisting of surgery followed by WBRT.(4) However, no biopsy was performed to confirm the presence of metastatic disease to the brain and the radiation used was an unconventional scheme using 40 Gy over 2 weeks. Conversely, Mintz et al. observed no difference in survival or quality of life between patients who underwent surgery plus radiotherapy and those having radiotherapy alone.(5) The results from the 43 patients randomized in that study may not be truly representative given their lower baseline median Karnofsky Performance Status (KPS) and higher proportion of extracranial disease.

Stereotactic radiosurgery is usually reserved for small ($< 3\text{cm}$) lesions. It is performed using high energy roentgenograms produced by the linear accelerator, gamma rays from a gamma knife, or with charged particles produced by a cyclotron. The use of this modality results in a higher concentrated delivery of radiation to the targeted volume and less radiation exposure to normal non-target tissue.(2)

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Interstitial brachytherapy is usually performed at the time of surgical resection with implantation of radioactive nuclides into the wall of the surgical cavity to deliver an additional dose of radiation therapy to the tumor while limiting the irradiation to the surrounding brain. Although interstitial brachytherapy is rarely performed for small lesions suitable for radiosurgery, it may have a limited role for metastases too large for radiosurgery.(2)

There is now evidence that the blood-brain barrier is partially disrupted within a brain tumor. As such, the concept of the inability of chemotherapy to enter the central nervous system has been challenged. Other factors may be contributing to the disappointing results of chemotherapy such as intrinsic resistance to chemotherapy of many tumors that metastasize to the brain.(2)

In patients with hormone-responsive tumors, such as breast cancer, there are anecdotal reports of brain metastases responding to hormonal agents, such as tamoxifen and megestrol acetate.(2)

RSR13 is a synthetic allosteric modifier of hemoglobin (SAM), promoting the release of oxygen to tissue, often referred to as a “right shift” of the hemoglobin-oxygen dissociation curve. The goal of adjunctive RSR13 therapy in cancer patients with brain metastases is to increase tumor oxygen concentrations in an effort to maximize the cytotoxicity of radiation therapy. A Phase 2 study (N = 69) was performed to evaluate median survival time, response rate, and time to tumor progression in patients with brain metastases receiving RSR13. A larger Phase 3 study (N = 538) tested the hypothesis that RSR13 will improve survival. These two efficacy studies are the focus of this review. The sponsor is also conducting randomized phase III studies using RSR13 + WBRT/O₂ vs. WBRT/O₂ in patients with brain metastases originating from breast cancer and NSCLC.

C. Important Milestones in Product Development

Clinical development of RSR13 commenced in July 1995. RSR13 has been studied in 18 different Phase 1 through Phase 3 clinical trials under three different INDs. Twelve clinical trials of RSR13 have been conducted under IND 48,171. During the development of RSR13, studies have been conducted under 2 additional INDs: IND 52,999 (Division of Cardio-Renal Drug Products) for the prevention or treatment of myocardial hypoxia and IND 53,874 (Division of Anesthetic, Critical Care, and Addiction Drug Products) for the prevention of hypoxia associated with surgery.

Regulatory History

June 13, 1995: IND 48,171 was submitted to the FDA.

November 30, 1999: An End of Phase II Meeting was held to discuss Fast Track designation and appropriate endpoints for future Phase II investigations.

October 13, 2000: Fast Track designation was granted.

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February 23, 2001: An End of Phase II meeting was held to discuss increasing the number of patients enrolled in study RT-009 to allow secondary analysis of survival in the subpopulation of patients with brain metastases for non-small cell lung cancer and breast cancer.

November 29, 2001: An End of Phase II Meeting was held to agree on survival as the primary endpoint for a study in patients with newly diagnosed non-small cell lung cancer .

August 30, 2002: Special Protocol Assessment requested for study RT-013: A Phase 3 Randomized, Open-Label, Comparative Study of Induction Chemotherapy Followed by Thoracic Radiation Therapy with Supplemental Oxygen, with or without RSR13 (efaproxiral), in Patients with Locally Advanced, Unresectable (Stage IIIA/IIIB) Non-Small Cell Lung Cancer.

November 12, 2002: A Pre-NDA meeting was held and plans were made to submit the NDA as a rolling submission.

July 16, 2003: Special Protocol Assessment requested for study RT-016: A Phase 3 Randomized, Open-Label, Comparative Study of Standard Whole Brain Radiation Therapy with Supplemental Oxygen, with or without Concurrent RSR13 (efaproxiral), in females with Brain Metastases from Breast Cancer.

July 25, 2003: Pharmacology/Toxicology data was submitted to the FDA as the first component of a rolling NDA.

October 1, 2003: CMC data was submitted to the FDA.

December 4, 2003: Clinical and Statistical data were submitted as the final component of this NDA.

D. Other Relevant Information

RSR13 is not approved in any country.

II. Description of Clinical Data and Sources

A. Overall Data

NDA 21-661 contains the primary data from two efficacy studies, RT-008 and RT-009. RT-009 was conducted in 40 centers in the United States, in addition to 15 in Canada, 4 in Australia, 4 in Hungary, 3 in Belgium, 3 in France, 3 in Germany, 3 in Israel, 3 in the United Kingdom, 2 in Italy, and 2 in Spain. Summary information from 538 patients enrolled into this study from 2-16-00 through 9-24-02 was included in this submission. Rt-008 was conducted in 16 centers in the United States and 1 center in Canada. Summary information from 69 patients enrolled from 2-24-98 through 5-28-99 was included in this submission.

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B. Description of Clinical Trials RT-008 and RT-009

Table 1: Clinical Trials Submitted to NDA 21-661

Study ID	Design	Dose, Route and Regimen	Objective	N	Duration	Tumor of Origin	Primary Endpoint
RSR13 RT-009	Phase 3, randomized, open-label, comparative	<u>RSR13</u> : 100 or 75 mg/kg central IV infusion over 30 minutes daily within 30 minutes of WBRT up to 10 doses (plus supplemental O ₂). <u>CONTROL</u> : WBRT (plus supplemental O ₂) without RSR13.	Efficacy, Safety, and PK	<u>RSR13</u> 271 entered. 271 analyzed for efficacy/266 analyzed for safety. <u>CONTROL</u> : 267 entered. 267 analyzed for efficacy/263 analyzed for safety	2-week treatment phase plus a 1 month follow-up evaluation. Patients were followed for a minimum of 6 months.	Breast, NSCLC, other (melanoma, GU, GI).	Survival.
RSR13 RT-008	Phase 2, nonrandomized, open-label	RSR13: 100 mg/kg with dose reduction to 75 and 50 mg/kg allowed, central IV infusion over 30 minutes daily just prior to WBRT up to 10 doses (plus supplemental O ₂)	Efficacy, Safety, and PK/PD	69 entered 69 analyzed for efficacy/ 69 analyzed for safety	2-week treatment phase plus a 1 month follow-up evaluation. Patients followed until death.	Breast, NSCLC, other (melanoma, GU, GI).	Survival.

Derived from applicant table 2.7.3.2.1 (Summary of Clinical Efficacy)

C. Post-marketing Experience

There is no prior post-marketing experience with this drug.

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D. Literature Review – An extensive literature review, including a review of some of the sources listed below, was performed by the Sponsor.

1. Shaw, Edward G., Bourland, J. D., Marshall, Mark. Cancers of the Central Nervous System. In: Kahn F, Potish R, eds. *Treatment Planning in Radiation Oncology*. Baltimore: Williams and Wilkins, 1998: 491-494.
2. Wen PY, Black PM, Loeffler JS. Treatment of Metastatic Cancer. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practices*. 6th Edition. Philadelphia: Lippincott, Williams and Wilkins, 2001: 2657-2667.
3. Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, Markesbery WR, Macdonald JS, Young B. A Randomized Trial of Surgery in the Treatment of Single Metastases to the Brain. *NEJM*, 1990; 322(8): 494-500.
4. Vecht CJ, Haaxma-Reiche EM, et al. Treatment of Single Brain Metastases: Radiotherapy Alone or in Combination with Neurosurgery? *Annals of Neurology* 1993; 33(6): 583-590.
5. Mintz AP, Kestle J, Rathbone MP, Gaspar L, Hugenholtz H, Fisher B, Duncan G, Skingley P, Foster G, LeVine M. A Randomized Trial to Assess the Efficacy of Surgery in Addition to Radiotherapy in Patients with a Single Cerebral Metastasis. *Cancer* 1996; 78(7): 1470-1476.
6. Akazawa K, Nakamura T, Palesch Y. Power of Logrank Test and Cox Regression Model in Clinical Trials with Heterogeneous Samples. *Statistics in Medicine* 1997;16: 583-597.
7. Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, Wasserman T, McKenna WG, Byhardt R. Recursive Partitioning Analysis (RPA) of Prognostic Factors in Three Radiation Therapy Oncology Group (RTOG) Brain Metastases Trials. *Int. J. Radiation Biol. Phys.*, 1997; 37(4): 745-751.
8. Pors H, Edler von Eyben F, Sorensen OS, Larsen M. Longterm Remission of Multiple Brain Metastases with Tamoxifen. *Journal of Neuro-Oncology*. 1991; 10: 173-177.
9. Gray Robert J. A Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk. *The Annals of Statistics*. 1988; 16(3): 1141-1154.

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III. Efficacy

The efficacy review is based primarily on two multicenter trials of RSR13 entitled:

(1) RT-009: A Phase 3, randomized, Open-Label, Comparative Study of Standard Whole Brain Radiation Therapy with Supplemental Oxygen, With or Without RSR13, in Patients With Brain Metastases

(2) RT-008: A Phase 2 Study To Evaluate the Efficacy and Safety of RSR13 Administered to Patients Receiving Standard Cranial Radiation Therapy for Brain Metastases

Below, the protocols for each of these clinical trials is reviewed independently.

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RT-009:

**A PHASE 3, RANDOMIZED, OPEN-LABEL, COMPARATIVE STUDY OF
STANDARD WHOLE BRAIN RADIATION THERAPY WITH SUPPLEMENTAL
OXYGEN, WITH OR WITHOUT RSR13, IN PATIENTS WITH BRAIN
METASTASES**

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PROTOCOL REVIEW

Table 2. Protocol Milestones (Derived from Sponsor's Table 9.15, Final Study Report)

Milestone	Date	Comments
First patient enrolled	2/16/2000	N/A
Amendment #1	3/2/2000	Stated MRI preferred over CT. PET added as an option for staging. Dosing adjustment Guideline was changed to include the instruction "if SpO ₂ while breathing room air on any RT day < 90%, RSR13 was to be omitted." Physician judgment could be used in determining clinical significance of an AE with respect to omitting or modifying the RSR13 dose.
Amendment #2	6/05/01	Sample size increased to 538 patients. Enrollment completion extended by 6 months. In addition to small cell lung cancer, extrapulmonary small cell carcinomas excluded from enrollment. Calcium channel blockers were added to the list of medicines that could potentiate or possibly interact with RSR13. Expanded warnings about use of concomitant CCBs and ACE inhibitors. A suggestion was added to start RSR13 dosing at 75 mg/kg in patients taking these classes of antihypertensive medications. An additional recommendation for patients who had a previous nephrectomy to start dosing a 75 mg/kg, to advise patients to avoid smoking during the RSR13 resaturation period. The Dosing Adjustment Guideline was expanded to include weight and gender. The scale for evaluation of hypoxemia AEs was initiated. Analysis of the NSCLC/breast population was incorporated.
Amendment #3	10/09/01	Included option to treat brain metastases with Cobalt 60. Clarified the conditions under which concurrent RT could be given to extracranial sites.
Date of Primary Analysis (Data Cutoff Date)	1/31/03	N/A
NDA submitted completed	12/4/03	N/A

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Reviewer comments: The Sponsor stated that it was necessary to enroll 501 patients and observe 402 deaths to claim statistical significance in median survival time and rule out the null hypothesis. Total enrollment was later increased to 538 patients based on the percentage of patients enrolled with primary cancers other than lung and breast (sample size calculation allowed that if 25% of patients enrolled had “other” primary, a total of 501 patients would be enrolled. If “other” primary patients accounted for 30% of patients, then 538 patients would be enrolled).

1.0 Objectives

- To determine the effect of RSR13 on primary and secondary efficacy endpoints in patients with brain metastases receiving daily intravenous doses of RSR13 administered immediately prior to standard WBRT/supplemental oxygen compared to patients receiving standard WBRT/supplemental oxygen.
- To determine the safety of RSR13 in this patient population.
- To assess the pharmacokinetics of RSR13 in the patient cohort receiving the study drug.
- The primary efficacy endpoint in this study was survival in the total population. A secondary analysis of the NSCLC/breast primary tumor subpopulation was also planned with the addition of amendment # 2.
- Secondary efficacy variables were time to radiographic tumor progression, time to clinical tumor progression in the brain, response rate in the brain, cause of death, and quality of life.

1.1 Overall Survival

The primary efficacy endpoint was overall survival using the log-rank statistic unadjusted for covariates. The primary final analyses of this study was undertaken when the planned number of deaths in both the total study population and the NSCLC/breast subpopulation was observed.

Reviewer comment: While overall survival in the intent to treat population was the primary efficacy endpoint in this study, amendment #2 made provisions for a secondary analysis of the NSCLC/breast primary tumor subpopulation as described above. One-hundred-seventy-three patients had been enrolled when amendment 2 was activated (protocol version 3). See statistical review for further comments.

Secondary efficacy endpoints were time to radiographic tumor progression in the brain, time to clinical tumor progression in the brain, response rate in the brain, cause of death, and quality of life.

1.2 Time to Radiographic Tumor Progression in the Brain

Response was determined based upon evaluation of each contrast-enhanced MRI or CT scan performed after completion of the study treatment regimen. Time to radiographic tumor progression in the brain was reported by means of Kaplan-Meier estimates. Gray’s test was used to compare cumulative incidence between treatment arms. Time to first (cranial or extracranial) progression was estimated using Kaplan-Meier. Site of first progression (cranial, extracranial, simultaneous, died without documented progression, or alive without documented progression),

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as well as time to first failure, were summarized by treatment arm and primary site subpopulation.

1.3 Time to Clinical Progression in the Brain

Clinical progression was defined as either neurological progression, as assessed by the Neurological Function (NF) status, or as neurocognitive deterioration as measured by the Mini Mental State Examination (MMSE), or as the use of subsequent therapy for brain metastases such as radiation or surgery. An increase from baseline of 1 or more points in the NF status score indicated neurological disease progression. Neurocognitive deterioration was defined as a decrease from baseline in the MMSE score of 3 or more points. Time to clinical progression was summarized using Kaplan-Meier estimates and compared between treatment arms using cumulative incidence Grays test.

1.4 Response Rate in the Brain

Best response was determined for each patient from evaluation of MRI or CT scans. It was projected at the outset that a differential treatment effect shown by improved response would result in survival benefit. Treatment arms were compared using the Cochran-Mantel-Haenszel test.

1.5 Cause of Death

The frequency of neurologic/non-neurologic/indistinguishable causes of death was tabulated for each treatment arm and compared using the Cochran-Mantel-Haenszel test. Neurologic causes of death included such events as fatal cerebral edema, neurological deterioration, and convulsions. Non-neurologic causes of death included pneumonia, acute renal failure, cachexia, and pulmonary embolus. Patients in the indistinguishable category could not have their causes of death distinguished between neurologic and non-neurologic causes (see section 1.3, FDA Analysis).

1.6 Quality of Life

Quality of life was determined by means of the Spitzer Questionnaire and KPS assessment. The frequency distributions were computed for each treatment by time of follow-up and focused on the 6 and 12-month time-points. The KPS score was categorized analyzed using the Cochran-Mantel-Haenszel test for each time-point.

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2.0 Eligibility Criteria

- Age = 18 years of age.
- Radiographic studies consistent with brain metastases and a histologically or cytologically confirmed primary malignancy, excluding small cell lung cancer and extrapulmonary small cell carcinomas, germ cell tumors, and lymphomas; or histologically or cytologically confirmed brain metastases consistent with a non-excluded primary malignancy. Patients with leptomeningeal metastases were not eligible.
- Karnofsky Performance Status (KPS) = 70 .
- No prior treatment for brain metastases with WBRT, stereotactic radiosurgery, chemotherapy, hormonal therapy, immunotherapy, or biologic agents. Prior surgical resection was allowed if at least one measurable lesion remained. Prior and current corticosteroid therapy was allowed.
- Adequate hematologic, hepatic, and renal function as defined by: hemoglobin = 10 g/dL, WBC count = 2000 cells/mm³, platelet count = 75,000/mm³, creatinine = 2.0 mg/dL, bilirubin = 2.0 mg/dL, alanine aminotransferase /serum glutamic-pyruvic transaminases and aspartate aminotransferase/serum glutamic-oxaloacetic transaminases = 3.0 times the upper limit of normal.
- Resting and exercise SpO₂ while breathing room air = 90%.
- No other concurrent active malignancy from a second histologic site.
- No use of any investigational drug, biologic, or device within 28 days prior to radiation therapy day 1.
- Adequate pulmonary function tests by simple spirometry were required if the patient had a pulmonary condition that might compromise oxygen loading in the lungs. Adequate PFTs were defined as forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV₁) = 50% of normal for that patient's age, height, and race.
- No chemotherapy for primary tumor or extracranial metastases within 7 days prior to WBRT day 1; no planned chemotherapy during WBRT; no planned additional therapy for brain metastases through the initial follow-up visit (1 month after completion of the RT course).
- No previous exposure to RSR13
- Able to provide written informed consent.
- If female patients who are not post-menopausal (> 12 months since last menses) or surgically sterile, must have a negative serum β-hcg pregnancy test, and must be practicing a medically acceptable contraceptive regimen from the time of consent until the initial follow-up visit. All male patient who are not surgically sterile must be practicing a medically acceptable contraceptive regimen.

Reviewer comment: Inclusion and exclusion criteria were combined under the heading of Eligibility Criteria in Version 4 (final version) of the RT-009 protocol. Amendment #2 specified that in addition to small cell lung cancer, extrapulmonary small cell carcinomas were excluded from enrollment in the study.

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3.0 Treatment Plan

Patients who were randomized to treatment arm A received daily RSR13 within 30 minutes prior to daily WBRT and supplemental oxygen. Patients in treatment arm B received WBRT and supplemental oxygen without placebo. RSR was administered using Dosing Adjustment Guidelines. Patients in treatment arm A received an initial 100 or 75 mg/kg dose of RSR13 at a concentration of 20 mg/mL over 30 minutes through a central venous catheter. All RSR13 infusions were administered using a volumetric pump. The RSR13 was given with supplemental oxygen beginning on Day 1 of radiation initiation and continued every radiation therapy day throughout the 10-day course of WBRT. WBRT was given within 30 minutes of completing the RSR13 infusion. Patients in both treatment arms received supplemental oxygen for at least 35 minutes prior to, during, and for at least 15 minutes after completion of daily WBRT. The flow rate of supplemental oxygen was 4 L/minute as needed to maintain a SpO₂ measurement = 90% during and after RSR13 infusion.

Reviewer comment: According to the treatment protocol, supplemental oxygen was to be administered beginning at least 5 minutes prior to starting the RSR13 infusion. The supplemental oxygen was then continued throughout the duration of the RSR13 infusion and discontinued at least 15 minutes after completion of WBRT. Whole Brain Radiation Therapy was administered within 30 minutes after completion of the RSR13 infusion.

Whole brain radiation therapy was given as 30 Gy at 3 Gy fractions per day, 5 days per week over 10 days. Patients were stratified for enrollment by RPA (recursive partitioning analysis) Classes I and II according to the RTOG RPA of prognostic factors criteria (**Table 3**). RPA Class II patients were further stratified by site of the primary cancer (**Table 4**). The number of patients in each of the 4 strata was not predetermined.

Table 3: Recursive Partitioning Analysis (RPA)

	CLASS I	CLASS II
KPS > 70	Yes	Yes
Primary tumor	controlled	uncontrolled
Age	< 65 years	= 65 years
Metastases	Brain only	Brain and other

Table 4: Stratification at Randomization

Stratification (pre-defined subsets)	Total N	Control	RSR13
RPA Class I patients	57	28	29
RPA Class II NSCLC primary patients	263	131	132
RPA Class II breast primary patients	101	49	52
RPA Class II other primary patients	111	54	57
Totals	532	262	270

Reviewer comment: The protocol stated that 538 patients were analyzed for efficacy (mod 2- vol. 2, p. 14). However, only 532 patients were calculated from the stratification at randomization

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table as shown above. The sponsor was asked to clarify the discrepancy in numbers. They responded by explaining that 6 patients were improperly stratified based on their site of primary disease (patient numbers 2168, 3044, 3089, 4045, 4076, 4100), and were not included in the in-text table. These same 6 patients were included in the post-text table which provides summary information by stratum and site of primary within stratum.

4.0 Treatment Modifications

The selection of the RSR13 doses given in this study was based on the safety and efficacy results obtained in the Phase 2 open-label studies in which over 270 cancer patients (which included 69 patients with brain metastases) received repetitive daily RSR13 infusions prior to RT. In the Phase 2 study RT-008, patients with brain metastases received WBRT with RSR13 at a dose of 100 mg/kg over 30 minutes. Adverse events leading to RSR13 dosing discontinuation were observed at 100 mg/kg in some patients and resulted in the initial development of dosing adjustments for individual patients to limit side effects that could result in early discontinuation of the study drug. Dose reductions to 75 or 50 mg/kg (or the withholding of doses) were allowed if clinical assessments or laboratory criteria indicated that the patient was experiencing exaggerated pharmacological effects or toxicities. Based upon these background data, the starting dose for RT-009 was 75 or 100 mg/kg . See **Table 5**.

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Table 5: Dose Adjustment Guidelines

If the SpO₂ while breathing room air on any WBRT day was <90%, RSR13 was to be omitted.

DETERMINATION OF INITIAL DOSE OF RSR13

1. If SpO₂ while breathing room air at screening (at rest AND during exercise) AND on WBRT Day 1 was = 93%, RSR13 was administered as follows:

a. Males

i. If weight = 95 kg: 100 mg/kg

ii. If weight > 95 kg: 75 mg/kg

b. Females

i. If weight = 70 kg: 100 mg/kg

ii. If weight > 70 kg: 75 mg/kg

2. If SpO₂ while breathing room air at screening (at rest OR during exercise) OR on WBRT day 1 was 90% - 92%: 75 mg/kg.

DOSE ADJUSTMENTS AFTER THE INITIAL DOSE

Down Titration

- Decrease from dose of 100 mg/kg to 75 mg/kg
- Omit RSR13 from dose of 75 mg/kg

DOWN TITRATION IF ANY OF THE FOLLOWING OCCURRED:

a. Duration of supplemental oxygen administration was >3 hours after end-infusion before SpO₂ while breathing room air returned to 90% on the previous dosing day.

b. The patient experienced nausea and/or vomiting (Grade 2 or higher) or clinically significant (investigator judgment) hypotension associated with RSR13 within 12 hours after RSR13 administration on the previous dosing day.

c. The patient developed hypoxemia which required treatment after discharge on the previous dosing day.

d. SpO₂ while breathing room air was 90% - 92% but had been = 93% on the previous dosing day.

UP TITRATION

• Increase from dose of 75 mg/kg to 100 mg/kg

• Resume dosing at 75 mg/kg if RSR13 dose omitted

a. Increase from dose of 75 mg/kg administered on previous dosing day to 100 mg/kg if SpO₂ while breathing room air was 93% and none of the AE listed above a-c had occurred on the previous dosing day.

b. Resume dosing at 75 mg/kg after omitting RSR13 on the previous day:

• If SpO₂ while breathing room air was 90% - 92% and had been 90% - 92% on the dosing day that led to omission of RSR13 dose.

• If SpO₂ while breathing room air was = 93%.

c. Dosing was not to be resumed after omitting RSR13 pm the previous day if SpO₂ while breathing room air was 90% - 92% but had been 93% on the dosing day that led to omitting the RSR13 dose.

(Derived from table 9.6, Final Study Report)

Reviewer comment: Amendment #1 changed the Dosing Adjustment Guideline to omit the use of RSR13 if SpO₂ was < 90% while breathing room air on any day of radiation therapy. This was based on concerns that RSR13 could result in further hypoxemia in patients with compromised SpO₂ levels. The rationale for this amendment was appropriate for patient safety. Adverse events leading to dosing termination were observed in earlier trials of RSR13. This led to the development of these Dosing Adjustment Guidelines that address efficacy and safety issues. These Guidelines were used throughout the duration of whole brain radiation therapy to determine on a daily basis whether a patient should be dosed at 100 mg/kg, 75 mg/kg, or have

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RSR13 held for that day. However, a dose of 50 mg/kg was permitted at the discretion of the investigator.

5.0 Safety Monitoring

All patients were assessed for safety, all adverse events, and all toxicities from randomization until the initial follow-up visit at 1 month after completion of the radiotherapy course. Standard follow-up visits were required 3 months after completion of the radiation therapy and every 3 months thereafter, until both radiographic and clinical progression were demonstrated and documented.

Table 6: Safety Monitoring

Evaluation	Screening Day (D) (D-21 to D0)	Baseline D-5 to D1	D2 to D9	D10	1 month FU (XRT completed)	3 month FU
Spitzer questionnaire		X		X	X	X
Resting SpO ₂	X	X	X	X		
Exercise SpO ₂	X					
PFTs	X					
Physical exam	X	X		X	X	X
KPS	X	X		X	X	X
Neuro exam		X		X	X	X
MRI/CT	X				X	X
EKG	X					
Hematology/chemistry	X	X		X	X	
Serum pregnancy test	X					
Supplemental O ₂		X	X	X		
Mini-MSE		X		X	X	X
AE check		X	X	X	X	X

(Derived from table 9.1, Final Study Report)

If any of the following occurred necessitating the early discontinuation of RSR13 in Treatment Arm A, the patient completed WBRT under Treatment Arm B procedures:

- The development of a significant adverse event/toxicity due to study participation as determined by the Investigator or patient.
- The development of an intercurrent illness, condition, or procedural complication that could interfere with the patient's continuing to receive study drug.
- Voluntary patient withdrawal of consent to continue receiving study drug.
- The Investigator or Sponsor feels that it is medically in the best interest of the patient to discontinue receiving study drug.

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6.0 Response Evaluation

Radiographic progression was defined by radiographic criteria which were evaluated by blinded central review and determined from the date of randomization into the study. Determination of radiographic tumor progression in the brain was based on contrast enhanced MRI or CT scans taken at screening and compared to follow-up scans taken 1 month after the end of WBRT, 3 months after the end of WBRT, and every 3 months thereafter until death. The date of tumor progression was defined as the date of radiographic documentation that any treated lesion had enlarged by more than 25% in the bi-dimensional product. Maximum bi-dimensional measurements were used to compute the bi-dimensional product and for determination of response and radiographic progression (Table 7). **The appearance of new lesions was not considered a sign of progression for the purpose of this study. However, the diagnosis of new lesions was collected.**

The study protocol stated that predefined indicator lesions (the 3 largest well-defined lesions identified before WBRT) would be followed for response to evaluate treatment effect. In patients with 1 to 3 brain metastases, all treated lesions were followed for response. The central reviewer could define *a priori* additional criteria for insuring the most appropriate assessment of response and progression, including definitions of measurable and evaluable lesions.

Table 7: Response Rate and Radiographic Tumor Progression in the Brain

Response (Defined by Central Review)	Bi-dimensional Size of Residual Disease Compared to baseline.
Complete Response (CR)	0% for all indicator lesions, provided no treated lesion meets criteria for progression.
Partial Response (PR)	>0% to = 50% for all indicator lesions, provided no treated lesion meets criteria for progression.
Stable disease (SD)	>50% to = 125% for 1 or more indicator lesions, provided no treated lesion meets criteria for progression.
Progressive disease (PD)	>125% for any treated lesion.

(Derived from table 9.7, Final Study Report)

Reviewer comment: For this study, a partial response was defined as up to a 50% reduction in the bi-dimensional size of residual tumor compared to baseline, provided no treated lesion meets criteria for progression. Stable disease was defined as more than 50% tumor remaining after treatment, and not more than a 25% increase in the bi-dimensional size of residual tumor. Progressive disease represented more than a 25% increase in the bi-dimensional product from baseline. These parameters appear consistent with the WHO criteria of tumor response evaluation. We requested exactly how the response criteria for RT-009 was determined. The Sponsor replied stating that the criteria were established and agreed upon by the investigators, study chairs, Allos clinical and statistical personnel, and the head of the NeuroImaging Core Lab responsible for the central review of scans.

Allos did not require confirmation of response. The designation of CR or PR was based on “Best Response,” which was not defined in the protocol. The FDA sent Allos a query on how Best Response was determined. Allos replied stating that Best Response was determined by selecting the maximal response for a patient, starting at the one month follow-up visit and following over time until progressive disease or subsequent treatment of brain metastases (or

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death) occurred. Furthermore, the designation of CR or PR was made irrespective of the appearance of a new brain lesion or systemic progression.

7.0 Statistical Methods

The primary endpoint, overall survival, was compared between the treatment arms by unadjusted log-rank test. The primary analysis of efficacy endpoints was based on the intent-to-treat population. Enrolled patients could be in RPA Class I or II, which have distinct estimated MST of 7.1 and 4.2 months, respectively. Based on an assumption that there would be a mix in this study of 20% RPA Class I and 80% RPA Class II patients, and based upon the RTOG brain metastases database, the estimated MST for patients treated with WBRT alone was 4.57 months. A total of 402 events (deaths) were required to rule out the null hypothesis with 85% power that the hazard ratio of the 2 treatment arms was 1 versus the alternative hypothesis that the HR of the 2 arms was not equal to 1. Since it was assumed that up to 5% of patients could be ineligible for the analysis, it was necessary to enroll at least 501 patients initially. Total patient enrollment would be 501-538 patients depending on the percentage of patients with primary cancer other than NSCLC or breast. Sample size calculation allowed that if 25% of patients enrolled had other primary, a total of 501 patients would be enrolled. If other primary patients accounted for 30% of patients, then 538 patients would be enrolled.

In the subpopulation of patients with NSCLC and breast primary, a total of 308 deaths from both treatment arms was required to provide 75% statistical power with a two-sided significance level of 0.05 for estimation and hypothesis testing of treatment effect. If patient accrual was longer than the assumed 27 months, fewer patients would be required to observe 402 deaths in the total population and 308 deaths in the NSCLC/breast primary cohort. If accrual was shorter than the assumed 27 months, then either more patients or a longer follow-up period would be required to observe the required number of deaths. The NSCLC/breast primary site subpopulations were determined based on pre-randomization criteria. Allos medical monitors performed a treatment arm blinded review of all patients' primary disease classification prior to the final analysis to assure consistent categorization of primary disease.

The hazard ratio (HR) was compared between treatment arms using the log-rank statistic unadjusted for covariates. A modified Bonferroni adjustment was made for multiple comparisons (co-primary analyses). A p-value < 0.048 was required to reject the null hypothesis that there was no difference in HR in the 2 treatment arms.

Analyses were performed for all randomized eligible patients, the NSCLC/breast subpopulation, and by site of primary. Estimates of survival were calculated based upon the number of RSR13 doses received. Survival was also estimated separately by response category for each treatment arm.

The statistical analysis plan (SAP) specified 18 covariates that were collected prior to or at baseline. Ten of these are categorical variables. Two covariates (number of extracranial metastatic sites, and number of cranial lesions) are ordered and continuous. Five variables are analyzed multiple ways: KPS, age and Hgb are considered as both continuous and categorical, altitude is analyzed as categorical and continuous in both untransformed and log transformed

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scales, and area of cranial lesions is analyzed as ordered and continuous (3 levels), and in log transformed scale. These 5 covariates with multiple definitions, allow for 48 combinations. Cox multiple regression was performed on all 48 combinations using 17 of the 18 covariates that were defined at baseline. Cox single regression, multiple regression including all covariates, and stepwise Cox multiple regression models were performed. In addition to the baseline covariates, the Cox models were also run with subsequent therapy covariates per SAP.

Reviewer comment: The sample size was increased to a maximum of 538 patients with amendment #2 to allow for a statistically powered survival analysis of patients in the non-small cell lung cancer/breast cancer primary subpopulation, in addition to the survival analysis of all patients.

TRIAL RESULTS

*Informed consent

The individual investigator was responsible for preparing the written informed consent document for RT-009. A template for informed consent was provided by the Sponsor. The investigator was allowed to rearrange or reword the contents of the template, and add other elements or language, provided the meaning and content were not changed or deleted. The Sponsor reviewed the informed consent form used before any patient was enrolled. Written informed consent was obtained from all patients who participated in this study prior to enrollment.

*Randomization

Patients were randomized 1:1 to Treatment Arms A or B according to a permuted block design, balancing by institution within strata. The randomization was stratified by RPA Classes I and II and within RPA Class II by site of primary cancer (NSCLC vs. breast vs. other), for a total of 4 strata. Patients were assigned a 4-digit patient identification number with the first digit corresponding to the stratum number followed by the other 3 digits being numbered in the order of randomization sequentially within the stratum. The number served as patient identification for all data collected under the study.

A total of 2271 patients were screened in order to obtain the 538 patients who were randomized into the study: 57 RPA Class I (10.6%) and 481 RPA Class II (89.4%) patients (Figure 10.1). The most frequent reasons for failure to enroll screened patients were “patient unwilling to give consent” and “KPS <70”, both accounting for 312 (17.9%) screen failures. RPA Class I patients represented 10.6% of the total enrollment, thereby meeting the protocol projected mix of 10%-25% RPA Class I patients (Section 9.1). RPA Class II patients were stratified according to the site of the primary cancer (NSCLC vs. breast vs. other) for a total of 4 strata.

Reviewer comment: Twenty-five patients were incorrectly classified at the site of accrual according to their primary tumor diagnosis. This error was captured only after central review of the Case Report Forms at an unspecified time point.

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*Blinding

This study was open-label.

*Central review process

Radiographic data was forwarded to a central location for radiographic review. Radiographic data were forwarded by the investigational sites to Neuroimaging Core Laboratory at the Cleveland Clinic Foundation for centralized radiological review.

Neuroimaging Core Laboratory
Cleveland Clinic Foundation
9500 Euclid Avenue
Section of Neurology/L10
Cleveland, Ohio 44195

Digital data, originals or duplicate originals of films of the magnetic resonance imaging or computed tomography scans obtained at baseline and at follow-up visits were sent for blinded central review for determination of radiographic response and progression in the brain.

Central Laboratory Facilities:

RSR13 Assays in Plasma and Red Blood Cells (RBCs)
Analytical Development Corporation
4405 N Chestnut Street
Colorado Springs, CO 80907

Routine Clinical Laboratory Tests:

Covance Central Laboratory Services SA
Rue Moise-Marcinhes 7
1217 Meyrin, Geneva
Switzerland

Covance Central Laboratory Services
8211 Scicor Drive
Indianapolis, IN 46214-2942

Sonic Clinical Trials
95 Epping Road
North Ryde, NSW 2113
Australia

*Protocol violations

A total of 202 exemptions were granted for protocol violations that occurred during the course of the study. A total of 151 exemptions were granted for failure to comply with protocol-defined time windows. Protocol deviations were defined *a priori* as violations in eligibility, disallowed medications, dosing violations, and patients who should have been withdrawn from the study but were not. Decisions to enroll patients who failed to meet all eligibility criteria were made on a case-by-case basis:

- Five patients in the Control arm were enrolled although they had received chemotherapy or hormonal therapy < 7 days prior to start of WBRT. According to the sponsor, neurological symptoms in these patients indicated immediate need for whole brain radiation treatment. Three patients (2 in the Control arm and 1 in the RSR13 arm) were

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enrolled although their liver function tests were exclusionary. Elevations in ALT in 2 of the 3 patients were the result of metastases extending to the liver. In the third patient, elevated ALT was determined to be a temporary response to a previous biopsy under general anesthesia.

- Two patients (both in the Control arm) were enrolled although they had received another investigational treatment within the previous month. Previous treatment had failed in both patients and neurological symptoms in these patients indicated immediate need for WBRT.
- One patient was enrolled in the Control arm although FEV₁ was 47%. This finding was determined a minor deviation since FVC was 62% and both resting and exercise SpO₂ measurements were 94%.
- One patient was enrolled in the RSR13 arm with a screening Hgb reported at 9.9 g/dL by a local laboratory and as 10.0 g/dL by central laboratory.

Reviewer comments: The five patients not meeting eligibility criteria because of prior chemotherapy or hormonal therapy within 7 days of RT day encompass the administration of 5-fluorouracil 6 days prior to RT day 1 (pt. # 1026), vinorelbine 5 days prior to RT day 1 (pt. # 3021), herceptin (pt. # 3077), letrozole (pt. # 3085), and gemcitabine (pt. # 4041). All five were in the control arm.

The 3 patients not meeting eligibility criteria because of inadequate hepatic function involved patient # 1052 (elevated ALT was attributed to recent biopsy of melanoma under general anesthesia- control arm), patient # 4007 (elevated ALT attributed to widespread metastases to the liver- control arm), and patient# 2016 (ALT value elevated, but value not reported – control arm).

Patient # 2012 and 4058 (both in the control arm) were given other investigational agents within 28 days prior to RT day 1: 2012 had been involved in a phase 2 study prior to entry, and # 4058 had been in a prior phase 3 experimental vaccine therapy for melanoma when this patient developed brain metastases.

Patient # 2006 (control arm) had a screening FEV₁ below 50%, but FVC was 62% and resting and exercise SpO₂ measurements were 94%.

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Table 8: Ineligible Patients Identified by Blinded Central Review of Scans

(Derived from table10.5, Final Study Report)

Reason Ineligible	Primary Site	Control Patient #	RSR13 Patient #
Leptomeningeal mets	NSCLC	2163	2025
		2069	2101
		2190	2263
		2227	
		1043	
	Breast	3065	3016
		3092	3072
		3068	
	Other	4055	4103
		4088	
		4108	
		4040	
No measurable brain lesions (after resection)	NSCLC	2048	
	Breast	1020	
		1025	
Small cell lung cancer	Other	4012	
Dural disease	Breast	3015	

Reviewer comment: The table above identifies the patients found ineligible after central review of scans. Patients were required to have measurable disease for enrollment according to the protocol. Furthermore, patients with leptomeningeal metastases, dural disease or small cell lung cancer were ineligible according to protocol criteria.

*Enrollment

Table 8 lists the regions of accrual to both arms of the study. The top 4 accrual sites were Sheerbrooke, Canada (34), Phoenix, AZ (30), Tucson, AZ (41), and Cleveland, OH (36).

Table 9 lists the number of investigational sites per country.

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Table 9: Number of Patients Enrolled in Each Region by Primary Site Subpopulation and Treatment Arm (ROW = rest of world)

Region	Primary Site	Control (N=267) N(%)	RSR13 (N=271) N(%)
Canada	NSCLC	56(21.0)	52(19.2)
	Breast	11(4.1)	9(3.3)
	Other	16(6.0)	17(6.3)
	Total	83(31.1)	78(28.8)
ROW	NSCLC	30(11.2)	31(11.4)
	Breast	14(5.2)	15(5.5)
	Other	14(5.2)	14(5.2)
	Total	58(21.7)	60(22.1)
USA	NSCLC	65(24.3)	65(24.0)
	Breast	30(11.2)	36(13.3)
	Other	31(11.6)	32(11.8)
	Total	126(47.2)	133(49.1)

(Derived from table 10.1, Final Study Report)

Table 10: Number of Investigational Sites Per Country

COUNTRY	NUMBER OF INVESTIGATIONAL SITES
United States	40
Canada	15
Australia	4
Hungary	4
Belgium	3
Germany	3
Israel	3
France	3
Italy	2
Scotland	2
Spain	2
England	1

(Derived from table 6.1, Final Study report)

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*Baseline Demographics

Table 11: Demographic Variables

	Control				RSR13			
	NSCLC N=151	Breast N=55	Other N=61	All N = 267	NSCLC N=148	Breast N=60	Other N=63	All N = 271
Sex n(%)								
Male	75(50)	1(2)	41(67)	117 (44)	80(54)	0	38(60)	118 (44)
Female	76(50)	54(98)	20(33)	150 (56)	68(46)	60(100)	25(40)	153 (56)
Race n(%)								
Caucasian	136(90)	48(87)	55(90)	239 (90)	134(91)	50(83)	58(92)	242 (89)
Black	7(5)	3(5)	2(3)	12 (4)	7(5)	5(3)	3(5)	15 (6)
Native American	1(1)	0	0	1	0	1(2)	0	1
Asian	1(1)	1(2)	1(2)	3 (1)	1(1)	0	1(2)	2 (1)
Hispanic	3(2)	1(2)	2(3)	6 (2)	3(2)	4(7)	0	7 (3)
Other	1(1)	2(4)	0	6 (2)	2(1)	0	0	2 (1)
Unknown	2(1)	0	1(2)	3(1)	1(1)	0	1(2)	2(1)
Age (years) n(%)								
<65	105(70)	45(82)	47(77)	197 (74)	102(69)	48(80)	46(73)	196 (72)
≥65	46(30)	10(18)	14(23)	70 (26)	46(31)	12(20)	17(27)	75 (28)
Mean	58.2	53.9	56.7	57.0	58.9	52	57.6	57.1
SD	11.0	11.2	10.6	11.0	10.1	11.6	11.4	11.1
Min-Max	26-81	30-78	23-76	23-81	36-80	31-80	30-87	30-87
Weight (kg)								
Mean	71.6	68.2	78.4	72.5	70.2	73.2	72.1	71.3
SD	15.2	17.5	19.7	17.1	15.1	14.7	14.9	15.0
Min-Max	33-122.4	42-124.1	49-140.9	33-140.9	41.1-120.1	46.5-122	39.8-108.6	39.8-122
N Missing	0	2	0	2	0		0	0
Height (cm)								
Mean	167.9	160.7	170.9	167.1	168.5	162.9	169.9	167.6
SD	9.5	6.3	9.4	9.5	9.4	6.1	10.7	9.8
SD	135-186	146-178	155-190.5	135-190.5	155-190.5	150-177.8	145.7-193	141-193
N Missing	2	1	4	7	4	2	1	3

(Derived from table 2.7.3.3.1, Summary of Clinical Efficacy)

Table 12. Reviewer's Description of Tumor Histology

Histology	Control 267 patients N(%)	RSR13 271 patients N(%)
Lung	151(56)	148(55)
Breast	55(20)	60(22)
*Other:	61(23)	63(23)
Melanoma	16(6)	22(8)
Colorectal	10(4)	9(3)
Renal cell	6(2)	10(4)

*Predominant histology of "other" category.

Reviewer comment: The demographic variables and primary tumor histological types for patients enrolled in this study were evenly distributed between the two treatment arms.

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Table 13: Distribution of Controlled and Uncontrolled Primary Tumors Between Treatment Arms

Primary Site	N(%)	Control		RSR13	
		Controlled N(%)	Uncontrolled N(%)	Controlled N(%)	Uncontrolled N(%)
Breast	115(21)	18(27)	37(18)	19(26)	41(21)
NSCLC	299(56)	32(48)	119(60)	30(42)	118(59)
Other	124(23)	17(25)	44(22)	23(32)	40(20)
Total	538	67	200	72	199

Reviewer comment: The distribution of patients with controlled and uncontrolled primary tumors were even except within the “other” histological subgroup in which the RSR13 arm contained more controlled primary tumors than those in the control arm.

Table 14: Distribution of Breast Histology Between Treatment Arms

Primary Site	N(%)	Control N(%)	RSR13 N(%)
Breast:			
Infiltrating ductal:	92(80)	46(84)	46(77)
Infiltrating lobular:	4(3)	1(1)	3(5)
Other:	19(17)	8(15)	11(18)
Total	115	55	60

Reviewer comment: The various breast histological subtypes were evenly distributed between the two treatment arms.

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Table 15: Distribution of KPS Score, Type of Treatment for Primary Malignancy, and Surgical Resection Across Treatment Arms.

Parameter	Control			RSR13		
	NSCLC N=151 %	Breast N=55 %	Other N=61 %	NSCLC N=148 %	Breast N=60 %	Other N=63 %
KPS:						
90 – 100	57	56	43	57	60	59
< 90	43	44	57	43	40	41
Prior Treatment of the Primary Malignancy:						
surgical resection	25	91	54	20	88	68
radiation Therapy	32	64	21	25	50	11
chemotherapy	38	80	36	35	78	43
hormonal Therapy	0	56	2	1	45	2
Surgical Resection of Brain metastases	9	7	20	6	3	16

Reviewer Comment: The NSCLC and Breast subgroups of the control arm had more radiation therapy as prior treatment of the primary malignancy than the corresponding subgroups in the RSR13 arm. This was also noted for hormonal therapy in the breast subgroup.

Table 16: Reviewer’s Table Demonstrating the Distribution of KPS in the Breast Subgroup

KPS	Control (N=55) N(%)	RSR13 (N=60) N(%)
60	0	1(2)
70	9(16)	9(15)
80	15(27)	14(23)
90	24(44)	28(47)
100	7(13)	8(13)

Reviewer comment: The distribution of KPS score was even in both treatment arms. This appears to be the case whether KPS is viewed as two categories or as five categories.

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Table 17: Summary of Prior Treatment by Treatment Arm (Breast Subpopulation)

Location of Malignancy	Treatment	Breast Cancer Subpopulation	
		Control = 55 patients N(%)	RSR13 = 60 patients N(%)
Primary malignancy	Surgical resection	50(91)	54(90)
	Radiation Therapy	39(71)	39(65)
	Chemotherapy	48(87)	57(95)
	Hormonal therapy	34(62)	32(53)
Extracranial metastases	Surgical resection	9(16)	6(10)
	Radiation Therapy	14(25)	17(28)
	Chemotherapy	30(55)	32(53)
	Hormonal Therapy	13(24)	7(12)
Brain metastases	Surgical resection	4(7)	2(3)

Reviewer comment: There were some differences in the distribution of patients exposed to prior treatment of extracranial metastases in the breast cancer subgroup, the most notable of which appear to be in prior hormonal therapy. The number of patients in each subgroup is too small to make a statistical judgment.

Table 18: Number of Brain Lesions According to Baseline Scans (ITT Population)

Number of Brain Lesions	N	Control N(%)	RSR13 N(%)
1	98	53(26)	45(17)
2-3	162	81(31)	81(31)
>3	266	127(49)	139(52)
Total	526	261	265

Reviewer comment: Although the incidence of brain lesions appear evenly distributed between the control and RSR13 arms in the ITT population (Table 18), this did not seem to be the case for the breast subgroup or “other” subgroup (Table 19).

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Table 19: Number of Brain Lesions by Primary Site of Disease in Each Treatment Group

Primary Site	Number of brain mets	Control N(%)	RSR13 N(%)
Breast (N=114)	1	7(13)	13(22)
	2-3	9(16)	14(24)
	>3	40(71)	31(53)
Sub-total		56	58
NSCLC (N=298)	1	35(23)	24(16)
	2-3	51(34)	53(36)
	>3	64(43)	71(48)
Sub-total		150	148
Other (N=114)	1	11(20)	8(14)
	2-3	21(38)	14(24)
	>3	23(42)	37(63)
Sub-total		55	59
Total (526)		261	265

(Derived from primary.xpt and scans.xpt datasets)

Reviewer's comment: The sponsor was queried about the total number of patients in this table adding up to 526, rather than 538. The sponsor explained 12 patients are not included for baseline scans. Nine patients (2126, 2127, 2131, 2232, 3045, 3065, 4012, 4015, and 4113) were categorized as "scans not done", or "scans not evaluable" and considered as patients not evaluable since baseline information was not reliable. The other three patient (3025, 2025, and 4040) had missing values for baseline scan information.

Within the breast subpopulation, the number of patients with =3 brain lesions was higher in the control arm than the RSR13 arm. In addition, the number of patients with only one brain lesion was higher in the treatment arm. This suggests a greater tumor burden in breast cancer patients within the control arm than the RSR13 arm, which could influence outcome. In the "other" subgroup, the control arm appears to have a greater proportion of patients with 2 to 3 brain lesions.

EFFICACY RESULT – SPONSOR'S ASSESSMENT

1.0 Primary Endpoint

1.1 Survival

Overall survival was calculated from the time of randomization into the study until death or 31 Jan 2003, whichever occurred first. All randomized patients in both treatment arms were followed for survival until death or for a minimum of 6 months and patients that were still alive were considered censored. The hazard rate was compared between treatment arms using the log-rank test (unadjusted for covariates).

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Log-rank Test

The observed MST for the Control arm was 4.47 months (n = 267) compared to 5.26 months for the RSR13 treatment arm (n = 271), and no statistically significant difference was detected between the survival distribution functions of the 2 arms using the unadjusted log-rank test (HR = 0.877, p = 0.1688). For all eligible patients (N = 515), the observed MST for the Control arm was 4.37 months compared to 5.39 months for the RSR13 arm, a difference that was not statistically significant by log-rank test (p = 0.1549). There was also no statistically significant difference in survival between the 2 arms for randomized patients in the NSCLC/breast subpopulation (HR = 0.844, p = 0.1217), nor was there a statistically significant difference for patients in Strata 1, 2, or 4 (RPA Class I patients, RPA Class II patients with NSCLC primary, and RPA Class II patients with other primary, respectively).

The sponsor detected a significant difference between survival of the 2 arms for patients in Stratum 3 (RPA Class II patients with breast primary; HR = 0.542, p = 0.0061). There was also a significant difference between the 2 treatment arms in which patients with metachronous brain metastases in the RSR13 arm had a longer MST than metachronous patients in the Control arm (HR = 0.731, p = 0.0069). However, there was no significant difference between the 2 treatment arms for patients with synchronous brain metastases (HR = 1.267, p = 0.1598).

Table 20: Summary of Applicant's Primary Analysis

(Derived from table 14.2.2.1.1, Final Study Report)

Population	Control		RSR13		HR	95% CI	p-value
	N(%)	MST	N(%)	MST			
Patients:							
ITT	267(100)	4.47	271(100)	5.26	0.877	0.727, 1.057	0.1688
Eligible	250(94)	4.37	265(98)	5.39	0.871	0.719, 1.054	0.1549
Breast and Lung	206(77)	4.47	208(77)	5.91	0.844	0.680, 1.047	0.1217
Breast	55(21)	4.57	60(22)	8.67	0.552	0.359, 0.850	0.0061
NSCLC	151(57)	4.37	148(55)	4.94	0.991	0.771, 1.273	0.9426
Other	61(23)	3.75	63(23)	4.01	1.029	0.708, 1.496	0.8812

ITT=intent to treat

MST=median survival time

Reviewer comment: There was no significant difference in overall survival in the intent to treat population using the logrank test. A significant difference in overall survival was noted in the subpopulation of breast cancer patients; however, this subpopulation was a predefined subset of patients identified for stratification purposes only. Any subgroup analysis of breast cancer patients or patients with metachronous disease should be considered exploratory.

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Analyses per SAP

The estimated increase in survival of patients enrolled in arm A (RSR13 arm) was based on the assumption that RSR13 would increase the efficacy of whole brain radiation. In this study, RSR13 was not intended to affect extra-cranial cancers. Given concern that patients may die of progression due to primary or metastatic extra-cranial tumors and that those deaths could decrease overall survival time in both treatment arms, the sponsor analyzed the survival data based on additional subsets of patients. The log-rank test was performed on the subsets of patients with controlled primary cancer and no extra-cranial metastases. It was anticipated that these patients would have a higher probability of death due to neurological progression and therefore are patients where RSR13 may have the greatest impact on survival. Estimates of survival for treatment arm A patients was also provided for each category of number of RSR13 doses received: 0-6 and = 7. One hundred thirty-nine patients were classified as “Primary Disease Controlled”: 67 in the Control arm and 72 in the RSR13 arm. No statistically significant difference in survival was detected between the treatment arms in this subset (HR = 1.006, 95% CI: 0.682-1.484). One hundred eighty patients were classified as having no extracranial metastases: 96 in the Control arm and 84 in the RSR13 arm. No statistically significant difference in survival was detected between the treatment arms (HR = 1.008, 95% CI: 0.718-1.414). Two hundred eighteen (80.4%) of the patients in the RSR13 arm received at least 7 doses of RSR13. Patients in this group had a statistically significant increase in survival as compared to the RSR13 arm receiving fewer than 7 doses (HR = 0.636, p = 0.0060).

Analyses for Patients with NSCLC as the Site of Primary

The observed MST for NSCLC patients in the Control arm (n = 151) was 4.37 months compared to 4.94 months in the RSR13 arm (n = 148), and no statistically significant difference was detected between the survival distribution functions of the 2 arms using the unadjusted log-rank test (HR = 0.991, p = 0.9426).

Reviewer comment: This was not a prespecified analysis. At best, this analysis can only be regarded as exploratory. As outlined in amendment #2, a secondary analysis for the NSCLC/breast primary tumor subpopulation was made at a later date (6/05/01), and did not demonstrate a significant difference in survival.

Analyses for Patients with the Breast as the Site of Primary

The observed MST for breast patients in the Control arm (n = 55) was 4.57 months compared to 8.67 months for the RSR13 arm (n = 60), and the sponsor reported a significant difference between the survival distribution functions of the 2 arms (HR = 0.552, p = 0.0061).

The sponsor also reported significant difference between the survival distribution functions of the 2 arms for patients in Stratum 3 (RPA Class II patients with breast primary; HR = 0.542, p = 0.0061).

Reviewer comment: This was not a prespecified analysis. At best, this analysis can only be regarded as exploratory. As outlined in amendment #2, a secondary analysis for the NSCLC/breast primary tumor subpopulation was made at a later date (6/05/01), and did not demonstrate a significant difference in survival.

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Analyses for Patients with **Other** Primary Site

The observed MST for the patients with other primary in the Control arm (n = 61) was 3.75 months compared to 4.01 months for the RSR13 arm (n = 63), and no statistically significant difference was detected between the survival distribution functions of the 2 arms using the unadjusted log-rank test (HR = 1.029, p = 0.8812).

Reviewer comment: This was not a prespecified analysis.

Cox Regression Models

Of the 538 randomized patients, 10 patients were excluded from the Cox model analysis due to missing values for baseline MRI/CT information (9 patients) and for missing baseline weight (1 patient). A Cox multiple regression model was run for each of the 48 possible models (every variable plus every combination of the five variables with different possible values) for all randomized patients and by site of primary. **Table 21** lists the 17 covariates used by the sponsor.

Table 21: Covariates Included in Cox Multiple Regression Models

Covariate
Site of primary*
KPS*
RPA Class*
Presence of extracranial mets*
Number of metastatic lesions*
Control of primary*
Age*
Presence of liver mets
Timing of diagnosis
Prior cranial met treatment
High enrolling center
Gender
Baseline Hgb
Altitude
Location of center
Dosing algorithm category
BDP total area

*Covariates mentioned in the original protocol as important covariates to test the relative importance of these factors for survival.

Reviewer comment: The sponsor points out that the log-rank test does not adjust for these 17 covariates and that there were imbalances in the prognostic factors between the two treatment arms. After applying Cox multiple regression models to adjust for these imbalances, the sponsor found a statistically significant difference in survival favoring the RSR13 arm. While some of these covariates may influence drug effect (e.g. higher altitude causing more release of oxygen to tissue), a literature review did not find support for the natural history of brain metastases being altered by whether one is from a high enrolling center, center in high altitude center, or any particular center location in general.

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Seven covariates (RPA class, site of primary cancer, primary tumor control, age, presence of extracranial metastases, KPS, and number of metastatic lesions) were alluded to in the original protocol of RT-009. Furthermore, there is overlap of these covariates. For instance, KPS already encompasses age and KPS.

For All Randomized Patients

There was no statistically significant difference for RSR13 effect between the treatment arms for all randomized patients when there were no adjustments for covariates. However, the RSR13 indicator variable was statistically significant in 100% (48/48) of the Cox models where RSR13 treatment effect was adjusted for all other covariates. According to the Cox regression analyses, the most important non-stratification prognostic factors (ie, those that were statistically significant in all 48 Cox models) for predicting survival were: KPS, previous treatment for brain metastases indicator, number of extra-cranial metastases, gender, age, and baseline Hgb. The Control arm had a higher relative frequency of patients with the more favorable level of these covariates for all prognostic factors except KPS. The sponsor feels that this helps to explain why the Cox multiple regression model analyses were able to detect a statistically significant survival advantage for patients in the RSR13 arm compared to patients in the Control arm that the unadjusted log-rank failed to detect.

By Site of Primary

In patients with breast primary, the RSR13 indicator variable was statistically significant in 100% (48/48) of the Cox multiple regression models where RSR13 treatment effect was adjusted for all other covariates as well as the Cox single regression model (HR = 0.552, p = 0.0069). In NSCLC and other primary patients, the RSR13 indicator variable was not statistically significant in any of the Cox multiple regression models nor the Cox single regression model.

Reviewer comment: See statistical review for further discussion of covariate analysis.

2.0 Secondary Endpoints

2.1 Time to Radiographic Tumor Progression in the Brain

Time to radiographic tumor progression (TTRP), as determined by blinded Central Radiology Review, was estimated for all patients using cumulative incidence analysis and Kaplan-Meier methods and tested between treatment arms using Gray's test. Death was recorded as a competing risk when it occurred prior to diagnosed radiographic progression.

All Randomized Patients

There was not a statistically significant difference in the cumulative incidence of radiographic progression between the Control arm and the RSR13 arm ($\chi^2=0.458$, p=0.4986).

By Site of Primary

There was not a statistically significant difference in the cumulative incidence of radiographic progression between the Control arm and the RSR13 arm in the subset of patients with NSCLC ($\chi^2=0.055$, p=0.8142), breast ($\chi^2=0.063$, p=0.8023), or other primary ($\chi^2=0.839$, p=0.3597).

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2.2 Time to Clinical Progression in the Brain

Time to clinical tumor progression (TTCP), was estimated for all patients using cumulative incidence analysis and Kaplan-Meier methods and tested between treatment arms using Gray's, which is used for comparing the cumulative incidence of a particular type of failure among different groups (9). Clinical progression was defined as either neurological progression, as assessed by the Neurological Function (NF) status score, or as neurocognitive deterioration as measured by the Mini Mental State Examination (MMSE) score, or as the use of subsequent therapy for brain metastases such as radiation, surgery, and/or SRS. An increase from baseline of 1 or more points in the NF status score indicated neurological disease progression. Neurocognitive deterioration was defined as a decrease from baseline in the MMSE score of 3 or more points.

Reviewer comment: This is a composite endpoint with subjective measures which can only be considered exploratory in this non-blinded clinical trial. Neurological assessments such as the Neurological Function Status Score and Mini-Mental Status Examination are of limited objectivity, especially in the non-blinded setting. The decision as to the nature and timing of subsequent treatment can be influenced by a number of variables, making interpretation of this composite endpoint even more difficult.

All Randomized Patients

There was not a statistically significant difference in the cumulative incidence of clinical progression between the Control arm and the RSR13 arm ($\chi^2=0.595$, $p=0.4407$).

By Site of Primary

There was not a statistically significant difference in the cumulative incidence of clinical progression between the Control arm and the RSR13 arm in the subset of patients with NSCLC ($\chi^2=1.541$, $p=0.2145$), breast ($\chi^2=0.846$, $p=0.3577$), or other primary ($\chi^2=0.377$, $p=0.5393$).

2.3 Response Rate in the Brain

The distribution of best response in the brain was compared between RSR13 arms using the Cochran-Mantel-Haenszel test.

All Randomized Patients

Four hundred forty-five patients had a scan after the baseline scan from which to assess response; 216 patients in the Control arm and 229 patients in the RSR13 arm. For all randomized patients, there was not a statistically significant difference in the distribution of response between the treatment arms ($\chi^2= 2.3839$, $p = 0.1226$). The point estimates of response rate (complete plus partial response) were 37.5% in the Control arm and 45.4% in the RSR13 arm. The estimated increase in response rate in patients receiving RSR13 was 7.9% with an associated 95% confidence interval of -0.4% to 16.3% ($p = 0.0609$).

Patients with NSCLC as the Site of Primary

For patients with NSCLC primary, there was not a statistically significant difference between the

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arms in distribution of response ($\chi^2 = 1.4216$, $p = 0.2331$). The point estimates of response rate (CR or PR) were 37.7% in the Control arm and 45.3% in the RSR13 arm. The estimated increase in response rate in patients receiving RSR13 was 7.5% with an associated 95% confidence interval of -3.6% to 18.7% ($p = 0.1857$).

Patients with Breast as the Site of Primary

For patients with breast primary, there was a statistically significant difference between the arms in distribution of response ($\chi^2 = 5.8617$, $p = 0.0155$). The point estimates of response rate (CR or PR) were 49.1% in the Control arm and 71.7% in the RSR13 arm. The estimated increase in response rate in patients receiving RSR13 was 22.6% with an associated 95% confidence interval of 5.1% to 40.0% ($p = 0.0112$). There were 2 covariates that were statistically significant for predicting response (CR or PR) when logistic multiple regression was performed for breast primary patients:

RSR13 treatment effect (odds ratio = 2.622 [95% CI: 1.157-5.942], $p = 0.0209$) and patients with a baseline KPS =90 versus <90 (odds ratio = 3.806 [95% CI: 1.680-8.624], $p = 0.0014$).

For patients with breast primary, the number of patients in continuous remission (CR or PR) declined over time of follow-up in the Control arm (21, 11, and 11 patients at 1, 3, and 6 months, respectively) versus the RSR13 arm (22, 26, and 20 patients at 1, 3, and 6 months, respectively).

Patients with Other Sites of Primary

For patients with other sites of primary, there was not a statistically significant difference between the arms in distribution of response ($\chi^2 = 1.1994$, $p = 0.2735$). The point estimates of response rate (complete plus partial response) were 26.2% in the Control arm and 20.6% in the RSR13 arm. The estimated increase in response rate in patients receiving RSR13 was -5.6% with an associated 95% confidence interval of -20.5% to 9.3% ($p = 0.4615$).

Reviewer comment: In assessing response to treatment, the FDA has the following concerns:

- *No predefined criteria for determining Best Response in the protocol*
- *Confirmatory scans were not a protocol requirement*
- *The designation of Complete Response or Partial Response was given regardless of the appearance of a new brain lesion.*

Refer to section 1.2, FDA Analysis.

2.4 Cause of Death

Cause of death was determined by the investigator and attributed to 1 of 3 categories: neurologic, non-neurologic, or indistinguishable. Patients with unknown cause of death were assigned a neurologic cause of death for calculation of all statistical tests.

All Randomized Patients

Four hundred forty-one patients died by the time of data cutoff: 221 in the Control arm and 220 in the RSR13 arm. Three patients withdrew consent and subsequently died, and therefore, have missing values for cause of death. The Cochran-Mantel-Haenszel test did not detect a difference in the distribution of cause of death between the treatment arms ($\chi^2 = 0.4361$,

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$p = 0.5090$). The Cochran-Mantel-Haenszel test did not detect a difference in the distribution of cause of death between the treatment arms in the subset of patients with NSCLC primary ($\chi^2 = 0.0562$, $p = 0.8127$), breast primary ($\chi^2 = 1.4692$, $p = 0.2255$), or other primary ($\chi^2 = 0.0079$, $p = 0.9292$).

2.5 Quality of Life

This was determined with the KPS assessment and the Spitzer Questionnaire that were performed at baseline, WBRT day 10, and all routine follow-up visits. Comparisons of QOL measures between treatment arms focused on the 6-month and 12-month time-points and did not include WBRT day 10. KPS measurements were used to evaluate a patient's condition. A KPS score could range from 100 (normal, no complaints, no evidence of disease) to 0 (death), thus a decrease in score indicated a worsening or deterioration in the patient's condition. Patients must have had a KPS score of at least 70 to be eligible for enrollment. Spitzer Questionnaire (SQ) scores were based on 5 questions each worth 0-2 points for a total of 10 possible points. Patients with at least 3 of the 5 questions answered were given a scaled total score equivalent to the average score per question multiply by 5. The SQ scores at the 6-month and 1-year follow-up visits were compared to baseline for each patient and categorized as one of the following: stable or increasing, decreased by 1-2 points inclusive, or decreased by more than 2 points. The distribution of SQ categories at 6-months and at 1-year was compared between treatment arms using the Cochran-Mantel-Haenzel test.

KPS: All Randomized Patients

For all randomized patients, the distributions of KPS scores were similar at all time-points between the 2 treatment arms, and no statistically significant difference was detected in the distribution of KPS score categories between treatment arms at 6 months or 1 year using the Cochran-Mantel-Haenzel test: $\chi^2 = 2.0318$, $p = 0.1540$ and $\chi^2 = 1.7727$,

KPS: Patients with NSCLC as the Site of Primary

For patients with NSCLC primary, no statistically significant difference was detected in the distribution of KPS score categories between treatment arms at 6 months and 1 year using the Cochran-Mantel-Haenzel test: $\chi^2 = 0.2992$, $p = 0.5844$ and $\chi^2 = 0.1221$, $p = 0.7268$, respectively.

KPS: Patients with Breast as the Site of Primary

For patients with breast primary, a statistically significant difference was detected in the distribution of KPS score categories between treatment arms at 6 months and 1 year using the Cochran-Mantel-Haenzel test: $\chi^2 = 8.0212$, $p = 0.0046$ and $\chi^2 = 7.2717$, $p = 0.0070$, respectively. The percentages of patients with breast primary in the RSR13 arm who had a stable or an increasing KPS score at the 6-month interval (30% [18/60]) was higher than in patients with NSCLC primary (16% [24/148]) and patients with other sites of primary (11% [7/63]). The percentages of Control arm patients with a stable or an increasing KPS score were similar at every time-point across the 3 "Site of Primary" categories but lower than the breast patients in the RSR13 arm.

KPS: Patients with Other Sites of Primary

For patients with other primary, no statistically significant difference was detected in the

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distribution of KPS score categories between treatment arms at 6 months and 1 year using the Cochran-Mantel-Haenzel test: $\chi^2 = 0.9718$, $p = 0.3242$ and $\chi^2 = 0.2715$,

Spitzer Questionnaire: All Randomized Patients

For all randomized patients, the distributions of SQ scores were similar at all time-points between the 2 treatment arms and there was not a statistically significant difference in the distribution of SQ scores between the treatment arms at 6 months or 1 year using the Cochran-Mantel-Haenzel test: $\chi^2 = 1.0232$, $p = 0.3118$ and $\chi^2 = 1.6712$, $p = 0.1961$, respectively. The percentages of patients in the Control arm who had a stable or an increasing SQ score at the 6-month and 1-year intervals (15% [39/267] and 6% [15/267], respectively) were comparable to the RSR13 arm (16% [43/271] and 9% [24/271], respectively).

Spitzer Questionnaire: By Site of Primary

There was not a statistically significant difference in the distribution of SQ scores at the 6-month or 1-year intervals between the Control arm and the RSR13 arm in the subset of patients with NSCLC ($\chi^2 = 1.8099$, $p = 0.1785$ and $\chi^2 = 0.7259$, $p = 0.3942$), or other primary ($\chi^2 = 0.8519$, $p = 0.3560$ and $\chi^2 = 0.2258$, $p = 0.6347$, respectively) and at the 6-month interval in the subset of patients with breast primary ($\chi^2 = 0.2107$, $p = 0.6462$)(chi-square and a p-value were not calculated at 1-year due to missing data).

EFFICACY RESULTS – FDA ASSESSMENT

1.1 Primary Endpoint – Survival

Of the 538 patients randomized at study entry, 23 were subsequently labeled ineligible (refer back to table 8), leaving 515 evaluable patients from the intent to treat population. Amendment #2 provided that the combined results of the NSCLC and breast primary tumor subpopulation would also be analyzed for efficacy. One-hundred-seventy-three patients had been enrolled by the time of this amendment.

The sponsor's proposed indication for the use of RSR13 is as adjunctive therapy to whole brain radiation therapy in the treatment of brain metastases originating from breast cancer. The Sponsor did not find a statistically significant difference in survival between the two treatment arms when analyzed using the log-rank test (median survival time: control=4.47 months vs. RSR13=5.26 months, $p=0.169$). There was also no statistically significant difference in survival between the two arms for randomized patients in the NSCLC/Breast subpopulation (HR=0.877, $p=0.1217$).

The Sponsor retrospectively analyzed the collected data and noted significant p values for overall survival in the non-prespecified breast cancer subpopulation using the log-rank test (control arm=4.57 months vs. 8.67 months, $p=0.0061$).

Primary efficacy analysis per original protocol, comparing overall survival between WBRT and RSR13 + WBRT, in the ITT population using unadjusted log-rank test is presented in **Table 22**.

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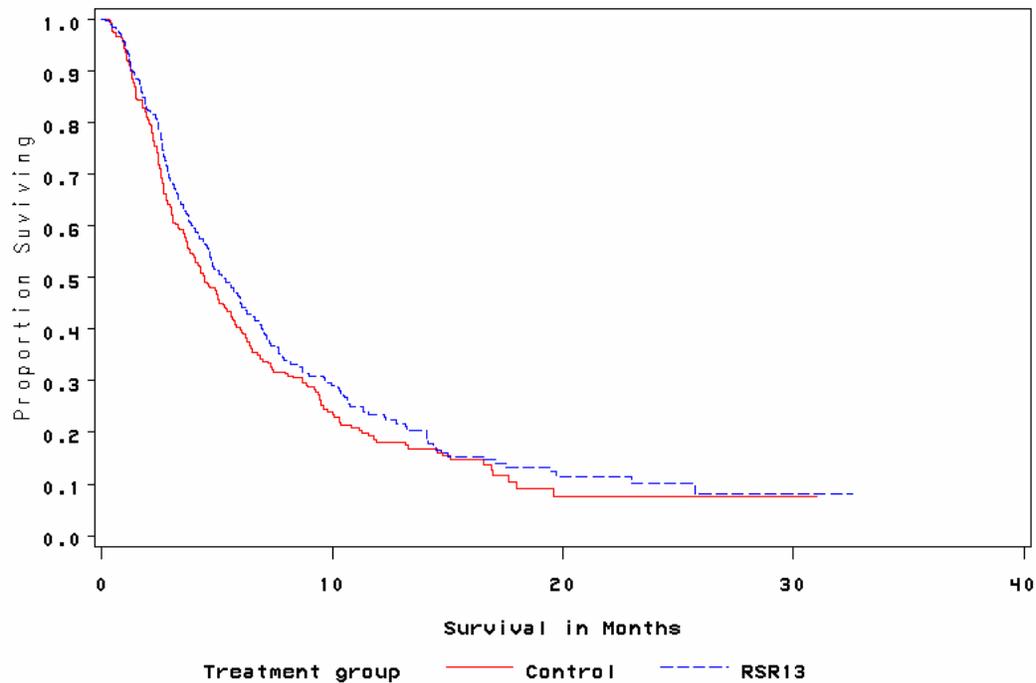
There were a total of 441/538 patients who had events (deaths) at the time of the final analysis. The Kaplan-Meier curves for the ITT population are illustrated in **Figure 1**. The efficacy analysis in the subgroup of NSCLC/Breast primary patients is presented in **Table 23**. The Kaplan-Meier curves for the NSCLC/Breast subgroup is presented in **Figure 2**. There were 331/414 deaths in this subgroup at the time of the final analysis.

Table 22: Primary Efficacy Survival Analysis in ITT Population

Treatment	Number of Deaths	Median Survival in Months ¹ (95% C.I.)	Hazard Ratio ² (95% C.I.)	P-value ³
WBRT	221/267	4.5 (3.7, 5.4)	0.877	0.1688
RSR13 + WBRT	220/271	5.3 (4.5, 6.2)	(0.727, 1.057)	

¹: Kaplan-Meier Estimates; ²: Hazard Ratio of RSR13 + WBRT/ WBRT;
³: unadjusted log-rank test.

Figure 1: Kaplan-Meier Survival Curves in the ITT Population



The FDA analysis confirmed the sponsor’s findings that there was no statistically significant difference in overall survival between the two treatment arms in the intent to treat population.

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Table 23: Co-Primary Efficacy Survival Analysis in NSCLC/Breast Primary Cancer Subgroup*

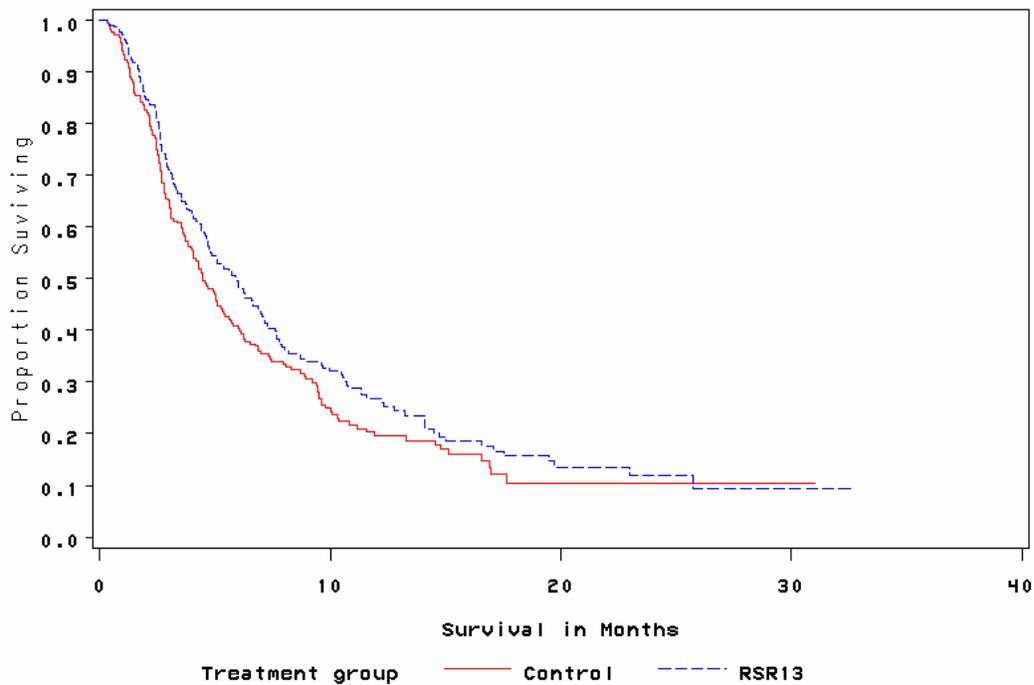
Treatment	Number of Deaths	Median Survival in Months ¹ (95% C.I.)	Hazard Ratio ² (95% C.I.)	P-value ³
WBRT	167/206	4.5 (3.8, 5.4)	0.844 (0.680, 1.048)	0.1217
RSR13 + WBRT	164/208	5.9 (4.7, 7.0)		

*: Corrected for mis-classification (i.e., non-randomized subgroup);

¹: Kaplan-Meier Estimates; ²: Hazard Ratio of RSR13 + WBRT/ WBRT;

³: unadjusted log-rank test.

Figure 2: Kaplan-Meier Survival Curves in the Subgroup of Patients with NSCLC/Breast Primary



The FDA analysis confirmed the sponsor’s findings that there was no statistically significant difference in overall survival between the two treatment arms in the NSCLC/Breast groups combined.

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For enrollment, all patients had to have a KPS score of = 70 (**Table 16**). As for prior (initial) treatment of the primary malignancy, the distribution of surgical resections performed, radiation therapy given, chemotherapy, and hormonal therapy administered was fairly balanced between the two treatment arms, except in the control arm for hormonal therapy (**Table 17**). More patients had received hormonal therapy in the control arm of the breast cancer subpopulation.

Patients were stratified at the time of enrollment by RPA Classes I and II to balance both treatment arms. RPA Class II patients were further stratified by site of the primary cancer (NSCLC vs. breast vs. other). When these results were analyzed using the log-rank test, no statistically significant difference in overall survival was observed between treatment arms. After study completion, a statistically significant difference was observed in the subgroup of breast cancer patients. However, this was a subgroup established for stratification purposes, not as a prespecified endpoint to test survival as a hypothesis in this specific subgroup. The finding in the breast subpopulation can only be considered exploratory at this time. **Table 24** reveals the exploratory survival analysis in the subgroup of patients with primary breast cancer. The International Conference on Harmonisation – Guideline for Industry, section 11.4.2.8 (Examination of Subgroups), states that subgroup analyses “are not intended to ‘salvage’ an otherwise nonsupportive study but may suggest hypotheses worth examining in other studies or be helpful in refining labeling information, patient selection, or dose escalation. When there is a prior hypothesis of a differential effect in a particular subgroup, this hypothesis and its assessment should be part of the planned statistical analyses.” Please see the statistical review for further discussion.

Table 24: Exploratory Survival Analysis in the Subgroup of Patients with Primary Breast Cancer

Treatment	Number of Deaths	Median Survival in Months¹ (95% C.I.)	Hazard Ratio² (95% C.I.)	P-value³
WBRT	47/55	4.6 (3.8, 6.2)	0.552 (0.359, 0.850)	0.0061
RSR13 + WBRT	39/60	8.7 (6.0, 11.3)		

¹: Kaplan-Meier Estimates; ²: Hazard Ratio of RSR13 + WBRT/ WBRT;

³: unadjusted log-rank test and not adjusted for multiple analyses

The sponsor used the Cox multiple regression model to adjust for potential imbalances within the two treatment arms. A reference is given to Akazawa et al. (6), highlighting the regression model’s ability to adjust for the imbalance of prognostic factors between two treatment groups. Such a strategy is not intended to be used as a substitute when the primary analysis has failed according to the log-rank test.

Table 21 listed the seventeen covariates identified by the sponsor as potential imbalances between the control and RSR13 treatment groups. Only seven covariates (site of primary, KPS, RPA class, presence of extracranial metastases, number of metastatic lesions, control of primary malignancy, and age) were mentioned in Version 1 of RT-009. Furthermore, there is overlap of

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these covariates. For instance, KPS already encompasses age and KPS. Again, although covariates such as a high enrolling center and center location may influence the quality of clinical trial conducted, no data is available to support the notion that patients with brain metastases from high enrolling centers have more favorable outcomes than those enrolled from lower enrolling centers. Furthermore, while a high altitude may influence release of drug such as RSR13 to tissue, there is no supportive evidence that patients with brain metastases have more favorable outcomes based on the altitude at which they live.

The FDA has concerns over the existence of imbalances in the number of brain lesions between the two treatment arms in the breast subgroup as presented in **Table 19**. It appears the control arm had a higher percentage of patients with three or more documented brain lesions (71% in the control arm versus 53% in the RSR13 arm). This suggests a greater tumor burden in patients on the control arm within the breast subgroup that were already destined to have a shorter survival when compared to patients with fewer and possibly smaller brain lesions.

As for subsequent treatments - defined as any form of palliative therapy administered after exposure to RSR13, the distribution of surgery, radiation therapy, chemotherapy, hormonal therapy, stereotactic procedures, other research studies, unknown therapies, and no further treatment – several imbalances were noted as outlined under **Tables 25** through **32**. **Tables 25** through **27** focuses on the Intent To Treat population broken down by subsequent treatment of extracranial metastases, primary malignancy, and brain metastases. **Tables 28** through **30** focuses on the Breast subpopulation broken down by subsequent treatment of extracranial metastases, primary malignancy, and brain metastases. **Table 31** and **Table 32** combines subsequent treatment of extracranial metastases and primary malignancy into the category of Systemic Treatment for simplification.

Table 25: Intent to Treat Population- Subsequent Treatment of Extracranial Metastases

Treatment Type	Control (267 patients) N(%)	RSR13 (271 patients) N(%)
Surgical resection	7(3)	4(1)
Radiation therapy	47(18)	51(19)
Chemotherapy	37(14)	39(14)
Hormonal therapy	7(3)	10(4)
Stereotactic radiosurgery	0	0
Other research study	2(1)	0
Other therapy	13(5)	18(7)
Unknown	0	0
No treatment	113(42)	124(46)

The distribution of subsequent treatment types for extracranial metastases was even in both treatment arms in the intent to treat population.

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Table 26: Intent to Treat Population- Subsequent Treatment of Primary Malignancy

Treatment Type	Control (267 patients) N(%)	RSR13 (271 patients) N(%)
Surgical resection	2(<1)	4(1)
Radiation therapy	39(15)	48(18)
Chemotherapy	62(23)	76(28)
Hormonal therapy	7(3)	14(5)
Stereotactic radiosurgery	0	0
Other research study	4(1)	3(1)
Other therapy	8(3)	2(1)
Unknown	0	0
No treatment	161(60)	153(56)

In general, subsequent treatment type (of the primary malignancy) were evenly distributed in the two study arms. Whether the numerically increased percentage of patients receiving chemotherapy in the RSR13 arm (23% vs. 28%) is of significance is difficult to assess.

Table 27: Intent to Treat Population- Subsequent Treatment of Brain Metastases

Treatment Type	Control (267 patients) N(%)	RSR13 (271 patients) N(%)
Surgical resection	9(3)	4(1)
Radiation therapy	8(3)	11(4)
Chemotherapy	7(3)	3(1)
Hormonal therapy	0	0
Stereotactic radiosurgery	13(5)	18(7)
Other research study	0	0
Other therapy	0	0
Unknown	0	1(<1)
No treatment	236(88)	234(86)

The distribution of subsequent treatment types (for brain metastases) was even in both arms.

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Table 28: Breast Subpopulation- Subsequent Treatment of Extracranial Metastases

Treatment Type	Control (55 patients) N(%)	RSR13 (60 patients) N(%)
Surgical resection	3(5)	1(2)
Radiation therapy	11(20)	16(27)
Chemotherapy	16(30)	21(35)
Hormonal therapy	6(11)	9(15)
Stereotactic radiosurgery	0	0
Other research study	0	0
Other therapy	11(20)	12(20)
Unknown	0	0
No treatment	24(44)	21(35)

Subsequent treatment of extracranial metastases in the breast subpopulation with radiation therapy, chemotherapy, or hormonal therapy was numerically greater in the RSR13 arm. It is difficult to assess the significance of this finding given the small number of patients involved.

Table 29: Breast Subpopulation- Subsequent Treatment of Primary Malignancy

Treatment Type	Control (55 patients) N(%)	RSR13 (60 patients) N(%)
Surgical resection	1(2)	1(2)
Radiation therapy	2(4)	2(5)
Chemotherapy	11(20)	12(20)
Hormonal therapy	7(13)	12(20)
Stereotactic radiosurgery	0	0
Other research study	0	0
Other therapy	1(2)	1(2)
Unknown	0	0
No treatment	35(64)	36(60)

Subsequent treatment of the primary malignancy with hormonal therapy was numerically greater in the RSR13 treatment arm compared to control.

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Table 30: Breast Subpopulation- Subsequent Treatment of Brain Metastases

Treatment Type	Control (55 patients) N(%)	RSR13 (60 patients) N(%)
Surgical resection	1(2)	1(2)
Radiation therapy	1(2)	2(3)
Chemotherapy	2(4)	1(2)
Hormonal therapy	0	0
Stereotactic radiosurgery	4(7)	3(5)
Other research study	0	0
Other therapy	0	0
Unknown	0	0
No treatment	49(89)	54(90)

The distribution of subsequent treatment types for brain metastases was even in both arms of the study.

Table 31: Breast Subpopulation: Subsequent Systemic Treatment (Extracranial Metastases and for Primary Malignancy)

Treatment Type	Control (55 patients) N(%)	RSR13 (60 patients) N(%)
Surgical resection	4(7)	2(3)
Radiation therapy	13(24)	18(30)
Chemotherapy	25(45)	32(53)
Hormonal therapy	13(24)	18(30)
Stereotactic radiosurgery	0	0
Other research study	0	0
Other therapy	11(20)	13(22)
Unknown	0	0
No treatment	46(84)	45(75)

Subsequent exposure to radiation therapy, chemotherapy, and hormonal therapy were more frequent in the RSR13 arm. The percentage of patients having no further systemic therapy in the breast subpopulation was lower in the RSR13 treatment arm.

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Table 32: Intent to Treat Population: Subsequent Systemic Treatment (Extracranial Metastases and for Primary Malignancy)

Treatment Type	Control (267 patients) N(%)	RSR13 (271 patients) N(%)
Surgical resection	9(3)	8(3)
Radiation therapy	81(30)	89(33)
Chemotherapy	91(34)	105(39)
Hormonal therapy	14(5)	20(7)
Stereotactic radiosurgery	0	0
Other research study	5(2)	3(1)
Other therapy	20(7)	24(9)
Unknown	0	0
No treatment	207(77)	202(74)

Within the intent to treat population, the distribution of subsequent systemic therapy types was even between both arms of the study.

Cause of death was to be determined by the investigator and documented on the individual CRF according to 1 of 3 categories:

- **Neurologic cause of death:** The patient had stable systemic disease and progressive disease in the brain.
- **Non-neurologic cause of death:** death was not caused by progressive brain disease; the death was further attributed to systemic cancer if extracranial progression occurred (primary or extracranial metastases), or to other causes including unknown.
- **Indistinguishable cause of death:** Death could have been caused by documented progressive disease in the brain and/or by documented extracranial progression.

Table 33 illustrates the distribution of neurologic and non-neurologic causes of death in the treatment arms. Neurologic causes of death included cerebral edema, neurological deterioration, and convulsions. The non-neurologic causes of death included pneumonia, acute renal failure, cachexia, and pulmonary embolus. These findings suggest that the majority of breast cancer patients with brain metastases died of non-neurologic causes of death, causes that were not influenced by RSR13. Furthermore, a notable proportion of patients died of causes that were indistinguishable.

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Table 33: Cause of Death - Neurologic vs. Non-neurologic

Cause of Death	Control N(%)	RSR13 N(%)	Total N(%)
Neurologic	34(13)	36(13)	70(13)
Non-neurologic	128(48)	128(47)	256(47)
Indistinguishable	58(22)	53(19)	111(20)
Alive/NA	47(18)	53(19)	100(18)
Unknown	0	1	1
Total	267	271	538

1.2 Secondary Endpoint - Response Rates in the Brain

Table 34: Reported Response Rates in the Brain According to Sponsor (ITT)

Response	Control 267 patients N(%)	RSR13 271 patients N(%)
CR	16(6)	28(10)
PR	84(31)	95(35)
Cr+PR	100(37) CI: 0.32, 0.44	123(45) CI: 0.39, 0.52

Table 34 shows the response rates in the brain within the intent to treat population according to the sponsor's analysis.

As already stated in this review, the FDA has concerns regarding this analysis. First, the method for determining Best Response was not given in the protocol. The sponsor replied to a query dated 2-22-04 that Best Response was determined by selecting the maximal response for a patient, starting at the 1-month follow-up visit and following overtime until progressive disease or subsequent treatment of brain metastases (or death) occurred. This is explained further in **Table 35**.

Table 35: Method of Determining Best Response (Sponsor's Table)

Patient No.	1 month	3 month	6 month	Best
1	SD	PR	CR	CR
2	SD	PR	PD	PR
3	SD	PD	PR	SD
4	PD	SD	SD	PD

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As already stated in this review, the appearance of a new brain parenchymal lesion during or proceeding the treatment was recorded in RT-009, but was not considered a sign of progression. **Table 36** removes four patients (three in the control arm and one in the RSR13 arm) labeled as a CR or PR on the same date as documentation of a new brain lesion. The percentages of actual CR's and PR's do not change.

Table 36: Response Rates in the Brain According to FDA Analysis

Response	Control 267 patients N(%)	RSR13 271 patients N(%)
CR	15(6)	27(10)
PR	82(31)	95(35)
CR+PR	97(36) CI: 0.31, 0.42	122(45) CI: 0.39, 0.51

The sponsor stated in response to our query that confirmatory imaging was not required according to the protocol; however, they provided estimates of confirmed responses as illustrated in **Table 37**. Confirmation of response was assessed by comparing the response of the first scan after the best response to the best response. If the response was the same as best response, response was considered confirmed.

Table 37: Confirmed Best Response in the Brain According to Sponsor*^

RESPONSE	CONTROL 267 PATIENTS N(%)			RSR13 271 PATIENTS N(%)		
	NSCLC	Breast	Other	NSCLC	Breast	Other
Best / Confirmed	151(56)	55(20)	61(23)	148(55)	60(22)	63(23)
CR / CR	8(5)	3(5)	1(2)	12(8)	4(6)	1(1)
CR / PR	1(1)	2(4)	0(0)	5(3)	3(5)	0(0)
PR / PR	22(14)	6(11)	3(5)	19(13)	18(30)	7(11)
Total	31(20)	11(20)	4(6)	36(24)	25(42)	8(12)

(Table provided by sponsor)

*Assessed by comparing the response of the first scan after best response to the best response. If the response was the same as best, response was considered confirmed.

^Median time to confirmation ~ 2.3 months

Because confirmatory imaging studies were not required, it is difficult to interpret the findings shown in **Table 37**. Furthermore, the FDA cannot adequately assess duration of response due to the lack of confirmatory scans. Given that both oxygen and radiation therapy were part of the treatment in both arms and given the issues discussed above, there is uncertainty as to the contribution of RSR13 to tumor response. Therefore, it is not likely that response rate in the brain could be used as a surrogate to predict clinical benefit in this case.

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1.3 Other Secondary Endpoints

There were no statistically significant findings in Time to Radiographic Tumor Progression in the Brain and Time to Clinical Tumor Progression in the Brain.

- Cause of Death
This is discussed under section 1.1.

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**RT-008:
A PHASE 2 STUDY TO EVALUATE THE EFFICACY AND SAFETY OF RSR13
ADMINISTERED TO PATIENTS RECEIVING STANDARD CRANIAL RADIATION
THERAPY FOR BRAIN METASTASES**

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PROTOCOL REVIEW

Table 38: Summary of Protocol Amendments

Amendment Number (Date)	Patient Numbers Affected ^a	Number of Patients Affected	Description of Change
1 (22 Jun 1998)	102-105, 107, 108, 110-114, 219-257	50	<ul style="list-style-type: none"> • Incorporated required Canadian language. • Changed Allos personnel. • Allowed for CT scans. • Revised SAE definitions per new FDA guidelines. • Corrected reference title #9.
2 (28 Jul 1998)	102-105, 107, 108, 110-114, 219-234, 236- 257	49	<ul style="list-style-type: none"> • Changed the preinfusion and discharge arterial oxygen saturation requirements from $\geq 87\%$ to $\geq 90\%$.
3 (12 Oct 1998)	103-105, 107, 108, 110-114, 222, 225-231, 233, 234, 236-257	42	<ul style="list-style-type: none"> • Study eligibility criteria were expanded such that the primary diagnoses for both RPA Class I and II were to include patients with not only breast and NSCLC, but also patients with brain metastases from melanoma, GU, and GI carcinoma. • Allowed for RSR13 dose reductions of 25 to 50 mg/kg (or withholding of doses) if clinical assessments or laboratory criteria indicated that the patient was experiencing exaggerated pharmacological effects or toxicities. • Allowed for RPA Class I patients to receive stereotatic radiosurgery, at the discretion of the investigator, if there was evidence of persistent or progressive disease on the 1-month follow-up scan or later. • Changed the Allos address and telephone numbers.

(Derived from Table 9.4, Final Study Report RT-008)

1.0 Objectives

- Evaluate overall median survival time (MST), response rate (CR and PR in the brain), and time to tumor progression in the brain in patients after receiving daily IV doses of 100 mg/kg RSR13 administered over 30 minutes with standard WBRT for brain metastases.
- Evaluate the safety of daily IV doses of 100 mg/kg RSR13 administered over 30 minutes to patients receiving standard WBRT for brain metastases.
- Determine the PK/PD profile of daily IV doses of 100 mg/kg RSR13 administered over 30 minutes in this patient population.

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1.1 Survival

Survival time was defined as the period from Radiation Therapy (RT) day 1 to death. All patients in this study were followed for survival until death or for a minimum of 24 months.

1.2 Response Rate in the Brain

Response was determined based upon evaluation of each patient's MRI or CT.

1.3 Time to Tumor Progression in the Brain

Time to tumor progression was defined as the time from RT day 1 to documented disease progression.

2.0 Eligibility Criteria

- Patients must have been at least 18 years of age.
- Patients with histologically or cytologically confirmed breast, NSCLC primary carcinoma, melanoma, GU, or GI primary carcinomas. The type of primary carcinoma may have included the following: invasive ductal or invasive lobular adenocarcinoma of the breast; or large cell carcinoma, adenocarcinoma (including bronchoalveolar carcinoma), squamous or epidermoid carcinoma of the lung; or any melanoma, GU, or GI carcinoma.
- Patients must have had either histologically or cytologically confirmed brain metastases or radiographic studies consistent with brain metastases and a histologically or cytologically confirmed malignancy as defined above. If no obvious primary cancer was seen, then a histological diagnosis consistent with a breast, NSCLC, melanoma, GU, or GI primary was sufficient for entry.
- KPS = 70.
- Patients must have met the RTOG criteria for RPA Class I or Class II.
- Patients must have had no prior treatment for brain metastases with RT, surgical resection, chemotherapy, hormonal therapy, immunotherapy, or biologic agents. Corticosteroid therapy was allowed.
- Patients must not have received chemotherapy within 1 week before the start of RT. Patients may not have received chemotherapy during RT and RSR13 administration in the study.
- Patients must have had a baseline resting SpO₂ = 90% on room air.
- Patients must have had adequate hematologic, hepatic, and renal function as defined by:
 - WBC count = 2,000 cells/mm³, hemoglobin = 10 g/dL, platelet count = 100,000 cells/mm³, bilirubin = 2.0 mg/dL, alkaline phosphatase and transaminases = times the upper limit of normal, and creatinine = 2.0 mg/dL.
- Patients must not have used any investigational drug, biologic, or device within 3 weeks before study initiation.
- Patients who had a pulmonary condition that may have compromised oxygen loading in the lungs (eg, significant intrathoracic tumor involvement, COPD, interstitial lung disease, pulmonary embolism) must have met the following requirements: a) adequate pulmonary function tests as defined by forced vital capacity (FVC) and forced expiratory

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volume in 1 second (FEV₁) = 60% of normal for that patient's age, height, and race; and b) an exercise SpO₂ on room air = 90%.

- Patients, if female and not post menopausal (>12 months since last menses) or surgically sterile, must have had a negative serum beta-human chorionic gonadotropin pregnancy test, must not have been breast-feeding, and must have been practicing a medically acceptable contraceptive regimen.

3.0 Treatment Plan

The patient population consisted of patients with brain metastases who were scheduled to receive a standard 2-week course of WBRT.

A total of 69 patients were enrolled into the study: 12 RPA Class I and 57 RPA Class II patients. Patients were enrolled from 17 investigational sites during the period from 24 Feb 1998 to 28 May 1999. The first patient consent was received on 24 Feb 1998, the date the final RSR13 treatment was administered occurred on 16 Jun 1999, and the date of the last initial (1-month) follow-up was 26 July 1999. All patients in this study were followed for survival until death or for a minimum of 24 months. Data were transferred to RTOG as of 23 Jul 2001. This date was used as the censoring date for analysis purposes. As of that date, 3 patients remained alive and each had been followed for a minimum of 24 months. The database for the study was locked as of 23 Apr 2002.

Patients were stratified upon enrollment into RTOG RPA Class I or II because of the very different expected survival between classes (MSTs of 7.1 and 4.2 months for Classes I and II, respectively). Separate sample size calculations were performed by stratum: planned enrollment was 54 RPA Class I and 50 RPA Class II patients to reach 51 and 48 evaluable patients, respectively. Study enrollment was closed shortly after the Class II enrollment target was met; at that time only 12 Class I patients had been enrolled. Enrollment of RPA Class I patients proceeded slowly because of the smaller proportion of Class I patients (20%) compared to Class II patients (65%) in the overall population of brain metastases patients.⁴ In addition, potential Class I participants often received surgery, SRS, or a different RT regimen, all of which would preclude their participation. Of the 69 patients enrolled, 55 patients completed evaluations through the 1-month follow-up visit. Of these 55 patients, there were 4 patients who stopped receiving RSR13 due to AEs. These patients continued their participation in the study by completing the routine follow-up evaluations.

A total of 16 patients terminated their participation in the study. These patients terminated from the study completely as opposed to patients who terminated RSR13 dosing and remained in the study by completing the follow-up visits. There were 10 patients who terminated the study during the RSR13/RT dosing phase: 7 due to AEs, 1 due to death, 1 due to a reason specified as other, and 1 was lost to follow-up. There were 4 patients who terminated the study after completing the RSR13/RT dosing phase but prior to the 1-month follow-up: 3 due to death and 1 due to unsatisfactory response. Two additional patients terminated the study early but following the initial 1-month follow-up: 1 patient for unsatisfactory response and 1 patient for non-compliance.

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RSR13 Injection was supplied by Almedica and was tested and released according to Allos' specifications. RSR13 was formulated as a sterile solution for injection and was supplied in single-use glass bottles as 2 g of RSR13 in 100 mL of 0.225% NaCl at a concentration of 20 mg/mL. The osmolality of 20 mg/mL RSR13 in diluent is approximately equivalent to 0.45% NaCl (half-normal saline). The dose of RSR13 in this study was to be 100 mg/kg (dosing reductions permitted) infused at a concentration of 20 mg/mL through a central venous access device over 30 minutes. The study drug solution for IV administration was prepared by the pharmacist or qualified chemotherapy nurse at the study site. The RSR13 stock solution was removed from the 100 mL glass bottles with a syringe and then passed through a 0.8 or 5.0 micron filter, with adequate capacity, directly into a commercial sterile infusion bag. One filter was to have been used for each 100 mL of RSR13 stock solution. The RSR13 infusion solution was prepared in the sterile infusion bag within 6 hours prior to infusion. RSR13 was administered at a concentration of 20 mg/mL over 30 minutes through a central venous access device at a constant rate using a volumetric pump. If the administration of RSR13 was interrupted or delayed, the infusion was to have been resumed but the total infusion duration was not to have exceeded 45 minutes.

4.0 Treatment Modifications

Early termination from the study by a patient may have been required due to any of the following circumstances:

1. The development of a significant adverse event/toxicity due to study participation as determined by the investigator or the patient.
2. The development of an intercurrent illness, condition, or procedural complication that could have interfered with the patient's continued participation.
3. Voluntary patient withdrawal.
4. The investigator or Allos felt that it was medically in the best interest of the patient to terminate participation in the study.

Procedures listed under 1-month follow-up/early termination in the Schedule of Events were to have been completed in the case of early withdrawal/termination. The reason for early termination was to have been recorded on the termination page of the case report form. Patients who terminated drug dosing, but continued to have routine follow-up visits, were considered to have terminated dosing, but not the study.

All patients were free to withdraw from participation in this study at any time, for any reason, specified or unspecified, and without prejudice.

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5.0 Safety Monitoring

Table 39 : Schedule of procedures for RT-008

RT week	Minus 14 days	Week 1					Week 2					1 month	routine
		1	2	3	4	5	6	7	8	9	10		
RT Day	Screen											FU	FU
RSR13 administration		X	X	X	X	X	X	X	X	X	X		
Oxygen administration		X	X	X	X	X	X	X	X	X	X		
Brain CT/MRI	X												
PFT/exercise SpO2	X												
Pulse oximetry	X	X	X	X	X	X	X	X	X	X	X		
Physical exam	X	X									X	X	X
CXR	X												
Neurological Assessment	X	X									X	X	X
MMSE	X										X	X	X
KPS	X	X									X	X	X
Hematology/coags/chemistry	X	X									X	X	
Urine	X	X									X	X	
PKPD				X					X				

6.0 Response Evaluation

CR was defined as a disappearance of all brain lesions seen on CT scans or MRI for at least 1 month with stable or decreasing steroid dose. PR required at least a 50% decrease in all lesions for at least 1 month with a stable or decreasing steroid dose. A response of Stable Disease was defined as any lesion with shrinkage less than 50% or growth less than 25% (includes all lesions with no change in growth). Disease progression was defined as any lesion in the brain enlarged by more than 25% with a stable or increased steroid dose, any new lesion, or clinical deterioration with a stable scan image. For measurable disease, standard bipерpendicular diameters of the 2-dimensional tumor image at maximum dimension were applied. For patients with more than one lesion in the brain, all lesions must have demonstrated a decrease in size with a stable or decreasing steroid dose to meet the criteria for CR or PR.

7.0 Statistical Methods

The primary objective of this study was to estimate the median survival time (MST) of patients with brain metastases treated with RSR13 and RT. Since MST for patients with brain metastases may be influenced by prognostic factors, sample sizes were calculated for each of the RPA classes addressed in this study. RPA Classes I and II formed the strata for this study.

A two-sample test of significance at 0.10 (one-sided) and a detectable improvement of at least 55% would have had a statistical power of 88% in RPA Class I with 51 evaluable patients compared to the historical control. For RPA Class II patients, the required sample size was 48 evaluable patients for a one-sided significance level of 0.05 and a detectable difference of at least 67%. The target sample sizes of 54 RPA Class I and 50 RPA Class II patients allowed for a 5% rate of unevaluable patients. Patients who received 7 or more doses of RSR13 were

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considered evaluable, however, the criterion was not used in analyses.

No substitutions were made for missing or poor quality samples. No formal interim analyses of study data were performed.

TRIAL RESULTS

*Informed consent

Each patient gave his or her written informed consent to participate in the study prior to or during the screening visit. The consent was witnessed, dated, and retained as part of the study records. A second original of the consent form was given to the patient.

*Randomization

This was an open-label study. There was no placebo control.

*Blinding

This was unblinded.

*Central review process

RSR13 Assays in Plasma and Red Blood Cells
Analytical Development Corporation
4405 N Chestnut Street
Colorado Springs, CO 80907

Pharmacodynamic (PD) Determinations
Allos Pharmacodynamic Laboratory
Virginia Biotech Research Park
800 Leigh Street, Suite 212
Richmond, VA 23219

Routine Clinical Laboratory Tests (Hematology, Chemistry, Coagulation, and Urinalysis Parameters)
Covance Classical Laboratory Services
8211 SciCore Drive
Indianapolis, IN 46214

Study site monitoring was conducted at regular intervals by Allos Clinical Development staff: Carrie VanDuym, Marilyn Craig, Margie Suhs, and Catherine Feutz. Monitoring was also conducted by clinical research associates (CRAs) of Endpoint Research Limited and Health Research Management, Inc. Monitoring was performed in accordance with applicable regulations and Good Clinical Practice guidelines.

Data management and analyses for the final report were provided by Allos. The lead Data Manager was Karen Guisinger. Adam Boyd, John Hackman, and Jim Kennedy performed analyses and produced tables. Allos Clinical Data Management personnel performed a Quality Control (QC) audit of the database for final reporting.

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An analysis comparing results of this study with those of the Radiation Therapy Oncology Group Brain Metastases Database (RTOG BMD) was conducted by Charles Scott, PhD, Associate Director, Quality of Life Research, American College of Radiology; 1101 Market Street, 14th Floor; Philadelphia, PA 19107.

*Protocol violations

Major protocol deviations were defined as violations in eligibility, disallowed medications, dosing violations, and patients who should have been withdrawn from the study but were not. None of the patients with protocol deviations were excluded from analysis.

A total of 12 patients had protocol deviations in 6 different categories of eligibility. For the majority of these deviations, Allos granted an exemption to allow the patient to enter the study. Only 1 patient did not meet more than 1 eligibility criteria (Patient 224). Having prior treatment for brain metastases was the most common violation in eligibility.

Two patients had protocol deviations related to the requirement of having a MRI/CT scan within 2 weeks of the projected start of RT:

- Patient 229 had a CT scan performed 3 weeks before RT.
- Patient 242 had an MRI scan performed 7 weeks before the start of RT. The deviation for Patient 242 was not discovered until after the patient was treated.

Two patients who had serious adverse events (SAEs) also had protocol deviations related to SpO₂ readings. Because these patients experienced SAEs following protocol deviations they are also being noted here:

- Patient 101 (enrolled prior to Amendment 2) was discharged on RT day 2 with an SpO₂ of 87% while breathing supplemental oxygen at 2 L/minute (protocol discharge criteria required SpO₂ = 87% while breathing room air). On RT day 5, the RSR13 infusion was started even though the patient's preinfusion SpO₂ ranged from 85-89% (protocol required preinfusion SpO₂ of = 87% while breathing room air). This patient experienced an SAE on RT day 5 (hospitalization for hypotension, hypoxia, and acute renal failure), and RSR13 dosing was subsequently terminated.
- Patient 215 was discharged on RT days 1, 2, and 3 with SpO₂ values of 88%, 87%, and 74%, respectively, while breathing room air (following IND Safety Letter and Amendment 2, discharge SpO₂ was to be = 90% while breathing room air). On RT day 4 the patient experienced the first of 2 SAEs (hospitalization for nausea, vomiting, increased intracranial pressure, and cerebral edema). The second SAE occurred on RT day 5 (hospitalization for weakness, dizziness, and hyponatremia). In addition, the patient was discharged on RT day 5 with a SpO₂ of 72%.

Minor protocol deviations (eg, not performing scheduled tests, taking blood samples outside scheduled time window, not taking scheduled blood samples) also occurred, but were not deemed to have affected the medical status of the patient and were therefore not quantified. Most exemptions related to dosing adjustments were granted to have RSR13 held on the first day of RT due to procedural/timing difficulties with PICC line placement or completion of laboratory test results. Prior to Amendment 3, exemptions were also granted for dose reductions from 100 to 75 or 50 mg/kg due to results from clinical or laboratory assessments.

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Table 40
(Derived from Table 10.1, Final Study Report)
Protocol Deviations/Exemptions Related to Eligibility Criteria

Eligibility Criteria Not Met	Patient Number and Specific Protocol Deviation	Exemption Granted
Confirmed primary cancer	229 Primary tumor was presumed to be ovarian adenocarcinoma but was not confirmed histologically	Yes
No prior treatment for brain metastases ^a	111 Craniotomy of largest lesion to decrease symptoms	Yes
	239 Craniotomy of cerebellar metastasis	Yes
	247 Resection and SRS of brain metastases	No
	256 Partial resection and craniotomy of brain metastases	No
No chemotherapy within 1 week prior to start of RT	224 Palliative chemotherapy (cyclophosphamide, methotrexate, and 5-Fluorouracil) ^b	Yes
	234 Chemotherapy for breast cancer with metastases to the lung (vinorelbine tartrate)	Yes
Weight ≤120 kg	250 Weight = 129.1 kg	Yes
Adequate hematologic, hepatic, or renal function	224 Screening hemoglobin low (9.8 g/dL)	Yes
	255 Screening platelet count low (88,000 cells/mm ³)	Yes
Adequate pulmonary function: FVC ≥60%, FEV ₁ ≥60%	222 FVC = 58%	Yes
	232 No PFTs	No
	251 FVC = 55%, FEV ₁ = 50%	Yes

^aTwo of these patients, Patients 239 and 256, had prolonged survival times of 18.27 and 26.48 months, respectively.

^bThe exemption was only granted for methotrexate and 5-Fluorouracil. The patient was later found to have received Cytosan (cyclophosphamide) on RT Day 1 in violation of the protocol.

*Enrollment

A total of 69 patients were enrolled from 16 study centers in the United States and one center in Canada.

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*Baseline Demographics

Table 41: Demographic Variables

Parameter	RSR13 Total N=69 patients N(%)
Sex	
Male	31(45)
Female	38(55)
Race	
Caucasian	62(90)
Black	5(7)
Native American	0
Asian	0
Hispanic	2(3)
Other	0
Age	
<65	51(74)
=65	18(26)
mean	55.8
Weight (kg)	
Mean	73.0
SD	14.5
KPS Score	
Median	90
RPA Classification	
RPS Class I	12(17)
RPA Class II- NSCL primary	33(48)
RPA Class II- Breast primary	18(26)
RPA Class II- Other	6(9)

(Derived from Table 2.7.3.3.1, Summary of Clinical Efficacy)

Reviewer comment: Sex, age, race, and weight were comparable to those participating with RT-009 on either treatment arm. Refer to Table 11.

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Table 42: Distribution of RPA Class by Primary Tumor Site

RPA Class	Primary Tumor Histology	Total N=69
I	NSCLC	6
	Breast	3
	Other	3
	Total	12
II	NSCLC	33
	Breast	18
	Other	6
	Total	57
All		69

Reviewer comment: The distribution of primary tumor histology by RPA Class was comparable to RT-009.

Table 43: Distribution of Tumor Types in RT-008

Primary Site	69 Total Patients N(%)	Controlled Primary Tumor (31 Patients)	Uncontrolled Primary Tumor (38 Patients)
Breast	21(30)	13(42)	8(21)
GI	1(1)	1(3)	0(0)
GU	3(4)	1(3)	2(5)
Lung	39(56)	13(42)	26(68)
Melanoma	5(7)	3(9)	2(5)

Reviewer comment: Like RT-009, non-small cell lung cancer made up the majority of primary tumor type, with breast being the next most common. The distribution of tumor types was comparable to RT-009.

Table 44: Distribution of Breast Histology in RT-008

Histology	N=69 N(%)
Infiltrating ductal	16(23)
Infiltrating lobular	1(1)
Other	4(6)

Reviewer comment: As is the case for RT-009, most patients had infiltrating ductal carcinoma.

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Table 45: Distribution of KPS Score in RT-008

KPS Score	All Patients (N=69)	Breast Subpopulation (N=21)
70	15	5
80	15	5
90	30	9
100	9	2

Reviewer comment: The distribution of KPS scores was comparable to RT-009.

EFFICACY RESULT – SPONSOR’S ASSESSMENT

Survival time was defined as the period from RT day 1 to death. All patients in this study were followed for survival until death or for a minimum of 24 months. The survival results from RT-008 were compared to a separate study performed by the RTOG BMD (Brain Metastases Database). Survival data from the RPA Class II patients in RT-008 were compared to all patients in the RTOG BMD.

According to the sponsor, the observed median survival time (MST) for the overall population (N = 69) was 6.4 months. The MST for the RPA Class I (N = 12) and RPA Class II (N = 57) groups was also 6.4 months for each group. For RTOG BMD RPA Class II patients, median survival time was 4.1 months (6.4 months vs. 4.1 months, p=0.0174). In RT-008, the largest differences in MST observed in the overall population were for the categories of best maximal response, age, baseline KPS, and number of RSR13 doses. Patients with a best response of CR had a longer MST than patients with a response of Stable Disease (12.2 vs 4.9 months); patients younger than 65 years of age had a longer MST than patients 65 years or older (7.1 vs 3.2 months); patients with a baseline KPS score of 90-100 had a longer MST than patients with a score of 70- 80 (8.5 vs 4.9 months); patients receiving 7 or more RSR13 doses had a longer MST than patients who received less than 7 doses (6.6 vs 2.3 months). MST appeared slightly longer when patients had a controlled disease status, or when patients had a non-neurologic (defined as no progressive disease in the brain) cause of death. According to the Sponsor, MST was less affected by the covariates of gender, site of primary disease, presence of extracranial metastases, mental status, or timing of diagnoses.

For RPA Class II patients, 2 of 7 patients (29%) who received 0-6 doses of RSR13 exceeded the expected MST of 4.2 months. However, 34 of 50 patients (68%) who received 7-10 doses of RSR13 exceeded the expected MST. The differences in MST within each category were generally as expected for the overall population and the Class II group. The sponsor states that comparisons between the Class I and Class II groups and conclusions regarding Class I patients are difficult to make due to the small sample size of Class I patients.

Best maximal response was categorized as either CR, PR, Stable Disease, or Other. The “other” category included data from patients with progressive disease, patients without a follow-up MRI

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or CT scan, or patients that terminated the study prior to follow-up. The sponsor feels the results of this study demonstrates that patients with a more favorable response (CR or PR) tended to survive longer and were more likely to remain progression-free for a longer time than patients with a less favorable response (Stable Disease or Other).

Reviewer comment: Although the sponsor does not directly mention response rate in this study, 7/7 patients with CR and 8/13 patients with PR were alive in these response categories after six months of follow-up.

Median time to progression in the brain was measured from the start date of radiation therapy. The date of progressive disease is defined as the date on which any lesion in the brain is enlarged by more than 25% with a stable or increased steroid dose. For patients with more than one lesion in the brain, all lesions needed to demonstrate a decrease in size with a stable or decreasing steroid dose to meet the standard oncology criteria of complete or partial response. Complete response was defined as disappearance of all brain lesions seen on CT or MRI for at least one month with a stable or decreasing steroid dose. Partial response was defined as at least a 50% decrease in all lesion(s) with a stable or decreasing steroid dose for at least one month. Stable disease was defined as any lesion with shrinkage less than 50% or increase less than 25%. Mixed responses were described as any other combination of responses not defined above.

Standard oncology criteria for complete and partial responses, along with stable and progressive disease was based on both measurable and evaluable disease within the cranium. For measurable disease, standard biperpendicular diameters of the two-dimensional tumor image at maximum dimension was applied. This was compared to the indicator image on repeat CT or MRI one month apart. For evaluable disease, the reference neuro-radiologist used his/her radiographic judgment in applying the response criteria.

Reviewer comment: In the setting of a single arm study, it is difficult to interpret time to event endpoints such as survival or time to progression. Unlike RT-009, the protocol for RT-008 required confirmation of response.

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D. Efficacy Conclusions

Given that RT-008 was a single-arm trial, time to event endpoints such as survival or time to progression are uninterpretable.

IV. Review of Safety

A. Introduction

RSR13 has been studied in 18 Phase 1 to Phase 3 studies. The submitted NDA contains safety data through December 31, 2002. The data collected from the Phase 3 study RT-009 and the Phase 2 study RT-008 provide the safety information of RSR13 use in the target population (intent to treat population and NSCLC/breast combined). Six-hundred-ninety-one patients have received at least 1 dose of RSR13. A total of 535 patients received one or more doses of RSR13 as sole adjunct to radiation therapy. Of these, 332 received WBRT for brain metastases.

B. Description of Patient Exposure

This section will include exposure analyses for both RT-008 and RT-009 performed by the sponsor and by the FDA.

Table 46: Clinical Studies of RSR13 as Sole Adjunct to Radiation Therapy

Phase	Study	Target Population
Phase 1	RT-002	Any solid tumor
	RT-006	Glioblastoma multiforme
Phase 2	RT-007	Glioblastoma multiforme
	RT-008	Brain metastases
	RT-010	NSCLC
Phase 3	RT-009	Brain metastases

Investigators graded adverse events outside the radiation portal using the NCI Common Toxicity Criteria (CTC). The European Organization for Research and Treatment of Cancer/Radiation Therapy Oncology Group (EORTC/RTOG) acute morbidity criteria were used to score/grade toxicity(ies) from RT. The criteria are relevant from day 1, the commencement of therapy, through day 90. Thereafter, the EORTC/RTOG Criteria of Late Effects were utilized. In clinical study reports, NCI Common Toxicity Criteria were incorporated into the overall WHOART adverse event profile using the following algorithm to code severity: Grade 1 = mild, Grade 2 = moderate, Grade 3= severe, and Grade 4 = very severe or life threatening.

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RSR13 decreases hemoglobin oxygen-binding affinity and reduces oxygen loading in the lungs at ambient oxygen pressure. This pharmacodynamic effect is manifested by a transient reduction in arterial oxygen saturation (SaO₂). Patients receiving RSR13 have predictable, dose-related, transient reductions in SpO₂ that have been managed through titration of the supplemental oxygen. Additionally, supplemental oxygen administration was employed to ensure a maximal pharmacologic effect by fully saturating the hemoglobin binding sites.

In the early Phase 1 and Phase 2 studies of RSR13, the grading of the severity of treatment-emergent hypoxemia was arbitrary by individual investigators and based on the observed variances in the flow and duration of supplemental oxygen until maintenance of a protocol-defined SpO₂ value on room air. The presence of signs and symptoms contemporaneously associated with hypoxemia were not consistently included in the grading of adverse events by the investigators. In addition, according to the existing definition and grading of hypoxia/hypoxemia (hypoxemia) in the NCI CTC scale, the use of supplemental oxygen attributes the severity of the event as Grade 4. Since all subjects received supplemental oxygen per protocol, an Allos-defined grading scale for hypoxemia as an adverse event was introduced in late Phase 2 and Phase 3 studies.

Table 47: Criteria for Hypoxemia Grading in RT-009

Grades				
0	1	2	3	4
Normal*	Supplemental oxygen required >3 hours but < 4 hours post-end RSR13 infusion.	SpO ₂ < 90% while breathing supplemental oxygen @ 4 L/min. Supplemental oxygen required = 4hours post-end RSR13 infusion. Increase in supplemental oxygen > 4 L/min during the RSR13 infusion and/or during the 4-hours recovery period.	Symptomatic hypoxemia defined as decreased SpO ₂ with headache, dizziness, dyspnea or hypotension. Pre-infusion SpO ₂ <90% attributed to RSR13. Decreased SpO ₂ requiring hospitalization.	Decreased SpO ₂ requiring continuous positive pressure and/or mechanical ventilation.

*-supplemental oxygen administered = 3 hours.

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Two-hundred-seventy-one patients received RSR13 as an adjunct to WBRT (30 Gy, 10 fractions over 2 weeks) and supplemental oxygen at 4 L/min. Within each of the 4 strata, subjects were randomized 1:1 to the 2 treatment arms comprised of a 10-day course of WBRT with supplemental oxygen \pm RSR13. Subjects received RSR13 100 mg/kg IV (with dose modifications to 75 mg/kg or 50 mg/kg) over 30 minutes daily. Safety and tolerability were determined by assessment of the incidence, nature, and severity of treatment-emergent adverse events; clinical assessments of laboratory test results (hematology and serum chemistry); vital signs (including SpO₂); and physical examination findings.

Reviewer comment: The Dose Adjustment Guidelines provided in Table 5 of this review do not provide justification for a RSR13 dose of 50 mg/kg. If a dose of 100 mg/kg was given and required downward titration, the next lower dose level was given as 75 mg/kg. The guidelines indicate that any further downward titrations from 75 mg/kg should lead to omission of RSR13 for that day. A dose reduction to 50 mg/kg was allowed by the investigator if clinical assessments or laboratory criteria indicated that the patient was experiencing exaggerated pharmacological effects or toxicities.

In study RT-009, a total of 538 subjects were enrolled in the study and the majority received 10 doses of WBRT (251/267 [94%] in the Control arm and 252/271 [93%] in the RSR13 arm). According to the sponsor, 263/271 (97%) patients in the RSR13 arm received at least 1 dose of RSR13. The mean number of RSR13 doses administered was 8.4 (SD 2.6; range 1-10 doses). The mean daily RSR13 dose was 84.5 mg/kg (SD 13.4; range 14.6-106.7 mg/kg). The mean number of WBRT doses was 9.8 (SD 1.2; range 0-10 doses) and the mean total WBRT dose given was 29.2 Gy (SD 3.7; range 3-30 Gy). RSR13 dosing was discontinued in 47/271 (17%) subjects. The principle reason for study drug discontinuation was adverse event(s).

RT-008 was a non-randomized, open-label study in subjects receiving RSR13 as an adjunct to WBRT. Subjects received RSR13 100 mg/kg IV (with dose modifications to 75 mg/kg or 50 mg/kg) over 30 minutes daily with WBRT (30 Gy, 10 fractions over 2 weeks). Safety and tolerability were determined by assessment of the incidence, nature, and severity of treatment-emergent adverse events; clinical assessments of laboratory test results (hematology, coagulation, serum chemistry, and urinalysis); vital signs (including SpO₂); physical examination findings; and concomitant medications.

Reviewer comment: RT-008, unlike RT-009, allowed downward titrations to occur by 25-50% if needed.

In study RT-008, a total of 69 subjects were enrolled in the study and the majority received 10 doses of WBRT (3 subjects received 6, 7, and 8 RT doses, respectively). According to the sponsor, the mean number of RSR13 doses administered was 8.9 (SD 2.1; range 1-11 doses). The mean daily RSR13 dose was 92.8 mg/kg (SD 10.6; range 61.8-100.6 mg/kg). The mean number of WBRT doses was 9.9 (SD 0.6; range 6-10 doses) and the mean total WBRT dose given was 29.6 Gy (SD 2.0; range 17-30 Gy). Overall, 40/69 subjects (58%) received the

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complete treatment per protocol. RSR13 dosing was discontinued in 12/69 (17%) subjects. The principle reason for study drug discontinuation was adverse event(s).

**Table 48: Extent of RSR13 Exposure in Patients Participating in RT-009
(Sponsor's Analysis)**

Exposure Variable	Statistic	Total Patients Receiving RSR13 N=271	Breast Subgroup N=60	NSCLC Subgroup N=148
Number of RSR13 Doses	N	263	59	144
	Mean	8.4	8.0	8.3
	SD	2.6	3.0	2.6
	Min/Max	1/10	1/10	1/10
RSR13 Dose (mg/kg)	N	263	59	144
	Mean	84.5	84.7	84.6
	SD	13.4	12.9	13.8
	Min/Max	14.6/106.7	50/101.3	14.6/101.2
RSR13 Duration (min)	N	262	59	143
	Mean	31.2	31.4	31.3
	SD	4.6	3.5	5.8
	Min/Max	3.0/83.0	27.6/47.9	3/83

(Derived from Table 2.7.4.1.8, Summary of Clinical Safety)

N=number of patients receiving at least 1 dose of RSR13

Mean=arithmetic mean

SD=standard deviation

Min/Max=minimum-maximum amount

Reviewer comment: According to the sponsor, the mean number of RSR13 doses given, dose received (mg/kg), and the duration of administration were comparable between the overall patients and breast subgroup receiving RSR13.

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**Table 49: Extent of Radiation Exposure in Patients Participating in RT-009
(Sponsor's Analysis)**

	Statistic	Control (N=267)	RSR13 (N=271)
Number of RT Doses	N	267	271
	Mean	9.7	9.6
	SD	1.5	1.8
	Min/Max	0/14	0/10
Total RT Dose (Gy) Over 2 Week Treatment Period	N	263	266
	Mean	29.6	29.2
	SD	2.5	3.7
	Min/Max	9.0/35.0	3.0/30.0

(Derived from Table 2.7.4.1.11, Summary of Clinical Safety)

n=number of patients receiving at least 1 dose of WBRT

Mean=arithmetic mean

SD=standard deviation

Min/Max=minimum-maximum amount

Reviewer comment: According to the sponsor, total radiation doses given over a two week treatment period were comparable in both arms of the study.

Below are the FDA analyses of RSR13 exposure, radiation exposure and oxygen exposure.

Table 50: Exposure of RSR13 in RT-009 (FDA Analysis)

Exposure Variable	Statistic	RSR13 Arm (271 patients)	Breast Subgroup (60 patients)	NSCLC Subgroup (148 patients)
Number of RSR13 Doses	N	263	59 ¹	144 ²
	Mean	8.4	8.0	8.3
	SD	2.6	3.0	2.6
	Min/Max	1/10	1/10	1/10
RSR13 Dose delivered (mg/kg)	N	263	59	144
	Mean	85.0	83.5	85.6
	SD	15.1	15.0	15.0
	Min/Max	13.5/166.7	13.5/101.4	14.6/101.5
RSR13 Duration (hrs)	N	262 ³	59	143 ²
	Mean	0.52	0.53	0.52
	SD	0.08	0.08	0.08
	Min/Max	0.05/2.08	0.10/1.28	0.05/2.08

1- one patient never received RSR13 infusion. 263 patients received at least 1 dose of RSR13

2- missing data for patients accounts for number discrepancies

3- no information on one patients from original 263

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Reviewer comment: The FDA analysis for drug exposure was similar to the Sponsor's analysis. RSR13 exposure duration is reported in minutes in the Sponsor's analysis and in hours in the FDA analysis.

Table 51: Radiation Therapy Exposure for the Intent To Treat Population of RT-009 (FDA Analysis)

Exposure Variable	Statistic	Control Arm (N=267)	RSR13 Arm (N=271)
Number of RT Doses	N	267	271
	Mean	9.7	9.6
	SD	1.4	1.6
	Min/Max	1/14	1/11
Total RT Dose Delivered (Gy) Per Day	N	267	271
	Mean	3.0	2.9
	SD	0.08	0.04
	Min/Max	1/3.0	1.5/3.0

Reviewer comment: The FDA analysis for radiation exposure was similar to the Sponsor's analysis. Total RT dose delivered is reported over the two week treatment period in the Sponsor's analysis and per day in the FDA analysis.

Table 52: Radiation Therapy Exposure for the Breast and NSCLC Subgroups in RT-009 (FDA Analysis)

Exposure Variable	Statistic	Breast N=115		NSCLC N=299	
		Control N=55	RSR13 N=60	Control N=151	RSR13 N=148
Number of RT Doses	N	55	60	151	148
	Mean	9.8	9.7	9.8	9.7
	SD	1.6	1.3	1.0	1.6
	Min/Max	1/14	2/10	1/12	1/11
Total RT Dose Delivered (Gy)	N	55	60	151	148
	Mean	3.0	3.0	3.0	3.0
	SD	0.1	0.1	0.1	0.03
	Min/Max	2.0/3.0	1.5/3.0	1.0/3.0	2.5/3.0

Reviewer comment: The number of RT doses and total RT doses delivered seem to be comparable between the control arm and treatment arm of both the breast and NSCLC subgroups.

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**Table 53: Oxygen Exposure for the Breast and NSCLC Subgroups in RT-009
(FDA Analysis)**

Exposure Variable	Statistic	Breast N=115		NSCLC N=299	
		Control N=55	RSR13 N=60	Control N=151	RSR13 N=148
Total Duration of O₂ Delivered (4 L/min) Reported in Hours	N	55	60	151	148
	Mean	1.1	2.0	1.2	2.3
	SD	0.3	2.7	0.2	7.2
	Min/Max	0.6/5.3	0.3/52.5	0.5/3.1	0.4/200.5

Reviewer comment: Patients with breast or NSCLC receiving RSR13 appear to have received a longer duration of oxygen therapy than counterparts on the control arm. This finding brings into question whether this could influence outcome of the treatment regimen.

Table 54: Extent of RSR13 Exposure in Patients Participating in RT-008

Exposure Variable	Statistic	Total Patients Receiving RSR13 N=69	Breast Subgroup N=21	NSCLC Subgroup N=39
Number of RSR13 Doses	n	69	21	39
	Mean	8.9	8.0	9.1
	SD	2.1	2.4	2.1
	Min/Max	1/11	2/10	1/11
RSR13 Dose (mg/kg)	n	69	21	39
	Mean	92.8	93.1	93.3
	SD	10.6	12.1	9.5
	Min/Max	61.8/100.6	61.8/100.3	72.5/100.6
RSR13 Duration (min)	n	69	21	39
	Mean	31.7	30.3	32.7
	SD	4.3	0.8	5.5
	Min/Max	28.6/57.3	29.7/32.8	28.6/57.3

(Derived from Table 2.7.4.1.8, Summary of Clinical Safety)

n=number of patients receiving at least 1 dose of RSR13

Mean=arithmetic mean

SD=standard deviation

Min/Max=minimum-maximum amount

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**Table 55: RSR13 Exposure in Patients Participating in RT-008
(FDA Analysis)**

Exposure Variable	Statistic	Total Patients Receiving RSR13 N=69	Breast Subgroup N=21	NSCLC Subgroup N=39
Number of RSR13 Doses	N	69	21	39
	Mean	10.0	9.9	10.1
	SD	0.4	0.2	0.5
	Min/Max	8/12	9/10	8/12
RSR13 Dose (mg/kg)	N	69	21	39
	Mean	92.6	93.4	93.1
	SD	12.1	13.5	11.3
	Min/Max	47.8/105.0	47.8/102.7	50.1/105.0
RSR13 Duration (hrs)	N	69	21	39
	Mean	0.5	0.5	0.5
	SD	0.1	0.04	0.1
	Min/Max	0.3/1.0	0.3/0.8	0.42/1.0

*Reviewer comment: Patients in RT-008 were more likely to complete 10 days of therapy than those in RT-009, where the mean number of doses given was 8. Patients also received a higher dose of RSR13 in RT-008 than RT-009 (92.6 mg/kg vs. 85 mg/kg). Refer to **Table 50**.*

Table 56: Extent of Radiation Exposure in Patients Participating in RT-008

Exposure Variable	Statistic	N=69
Number of RT Doses	N	69
	Mean	9.9
	SD	0.6
	Min/Max	6/10
Total RT Dose (Gy)	n	69
	Mean	29.6
	SD	2.0
	Min/Max	17.0/30.0

(Derived from Table 2.7.4.1.11, Summary of Clinical Safety)

n=number of patients receiving at least 1 dose of

Mean=arithmetic mean

SD=standard deviation

Min/Max=minimum-maximum amount

*Reviewer comment: The exposure to radiation therapy was comparable in RT-008 to that in RT-009. Refer to **Table 51**.*

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Table 57: Radiation Therapy Exposure for the Breast and NSCLC Subgroups in RT-008 (FDA Analysis)

Exposure Variable	Statistic	N=69 Patients	Breast Subgroup (N=21)	NSCLC Subgroup (N=39)
Total RT Dose Delivered (Gy)	N	69	21	39
	Mean	3.0	3.0	1.6
	SD	0.03	0.05	0.9
	Min/Max	2.5/3.0	2.5/3.0	0.8/9.2

Reviewer comment: Radiation exposure was comparable in the Breast subgroup in RT-009 (control arm and RSR13 arm) and RT-008. There was greater radiation exposure in the NSCLC subgroup in RT-009 when compared to the NSCLC patients participating in RT-008.

Table 58: Oxygen Exposure for the RT008 (FDA Analysis)

Exposure Variable	Statistic	N=69	Breast Subgroup (N=21)	NSCLC Subgroup (N=39)
Total Duration of O₂ Delivered (4 L/min)	N	69	21	39
	Mean	1.6	1.8	1.6
	SD	1.1	1.6	0.9
	Min/Max	0.7/18.9	0.7/18.9	0.8/9.2

*Reviewer comment: There was more oxygen exposure in the RSR13 treatment arm of RT-009 than in NSCLC patients participating in RT-008. Refer to **Table 53**.*

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C. Adverse Events

Treatment-emergent Adverse Events: Sponsor and FDA Analysis/Critique.

Table 59 represents the sponsor's assessment of treatment – emergent adverse events in RT-008 and RT-009. Given the lack of a comparison arm in RT-008, the emphasis here is on RT-009.

Table 59
(Derived from Sponsor's Table 2.7.4.2.9)

Treatment-emergent Adverse Events Reported in ≥5% of RSR13-treated Subjects in Studies of RSR13 as Adjunct to WBRT, RSR13-treated Subjects Versus Control Subjects

WHOART BODY SYSTEM TOTAL PREFERRED TERM	RT-009 Control (N=263)		RT-009 RSR13 (N=266)		RT-008 RSR13 (N=69)		All RSR13 (N=335)	
	n	(%)	n	(%)	n	(%)	n	(%)
Treatment-emergent Adverse Events Reported in ≥5% of RSR13-treated Subjects in the Study of RSR13 as Adjunct to WBRT, RSR13 Versus Control								
ALL	262	(100)	261	(98)	69	(100)	330	(99)
CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS	171	(65)	195	(73)	57	(83)	252	(75)
Headache	86	(33)	126	(47)	34	(49)	160	(48)
Dizziness	40	(15)	58	(22)	22	(32)	80	(24)
Convulsions	9	(3)	20	(8)	9	(13)	29	(9)
Confusion	18	(7)	23	(9)	4	(6)	27	(8)
Paresthesia	8	(3)	18	(7)	5	(7)	23	(7)
Hypoesthesia	7	(3)	8	(3)	11	(16)	19	(6)
GASTROINTESTINAL SYSTEM DISORDERS	174	(66)	200	(75)	52	(75)	252	(75)
Nausea	80	(30)	124	(47)	31	(45)	155	(46)
Vomiting	45	(17)	102	(38)	26	(38)	128	(38)
Constipation	41	(16)	58	(22)	12	(17)	70	(21)
Anorexia	44	(17)	43	(16)	7	(10)	50	(15)
Dyspepsia	33	(13)	23	(9)	3	(4)	26	(8)
Abdominal Pain	22	(8)	19	(7)	5	(7)	24	(7)
Diarrhea	9	(3)	20	(8)	4	(6)	24	(7)
BODY AS A WHOLE-- GENERAL DISORDERS	194	(74)	194	(73)	53	(77)	247	(74)
Fatigue	114	(43)	131	(49)	29	(42)	160	(48)
Edema Peripheral	29	(11)	37	(14)	8	(12)	45	(13)
Fever	17	(7)	23	(9)	14	(20)	37	(11)
Chest Pain	13	(5)	26	(10)	8	(12)	34	(10)
Back Pain	19	(7)	20	(8)	9	(13)	29	(9)
Pain	26	(10)	24	(9)	4	(6)	28	(8)
Asthenia	38	(14)	11	(4)	7	(10)	18	(5)
Weight Decrease	20	(8)	15	(6)	3	(4)	18	(5)
SKIN AND APPENDAGES DISORDERS	166	(63)	178	(67)	37	(54)	215	(64)
Alopecia	129	(49)	136	(51)	19	(28)	155	(46)
Radiation Dermatitis	66	(25)	69	(26)	15	(22)	84	(25)
Rash	10	(4)	22	(8)	7	(10)	29	(9)
RESPIRATORY SYSTEM DISORDERS	94	(36)	159	(60)	47	(68)	206	(62)
Hypoxemia	10	(4)	109	(41)	28	(41)	137	(41)
Coughing	30	(11)	34	(13)	8	(12)	42	(13)
Dyspnea	37	(14)	30	(11)	9	(13)	39	(12)
Rhinitis	11	(4)	26	(10)	6	(9)	32	(10)
Pneumonia	8	(3)	18	(7)	3	(4)	21	(6)
PSYCHIATRIC DISORDERS	89	(34)	92	(35)	33	(48)	125	(37)
Insomnia	46	(18)	38	(14)	15	(22)	53	(16)
Anxiety	16	(6)	23	(9)	5	(7)	28	(8)
Somnolence	19	(7)	23	(9)	5	(7)	28	(8)
Amnesia	11	(4)	12	(5)	6	(9)	18	(5)

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Table 59 (continued)

WHOART BODY SYSTEM TOTAL PREFERRED TERM	RT-009 Control (N=263)	RT-009 RSR13 (N=266)	RT-008 RSR13 (N=69)	All RSR13 (N=335)
	n (%)	n (%)	n (%)	n (%)
Treatment-emergent Adverse Events Reported in ≥5% of RSR13-treated Subjects in the Study of RSR13 as Adjunct to WBRT, RSR13 Versus Control				
MUSCULOSKELETAL SYSTEM DISORDERS	79 (30)	86 (32)	24 (35)	110 (33)
Muscle Weakness	39 (15)	36 (14)	13 (19)	49 (15)
Arthralgia	18 (7)	22 (8)	2 (3)	24 (7)
Myalgia	11 (4)	16 (6)	3 (4)	19 (6)
Skeletal Pain	16 (6)	14 (5)	4 (6)	18 (5)
INFUSION SYMPTOMS	0	71 (27)	19 (28)	90 (27)
Perioral	0	56 (21)	13 (19)	69 (21)
Eyes (during infusion)	0	18 (7)	6 (9)	24 (7)
Skin (during infusion)	0	16 (6)	4 (6)	20 (6)
RESISTANCE MECHANISM DISORDERS	70 (27)	59 (22)	13 (19)	72 (22)
Moniliasis	52 (20)	42 (16)	9 (13)	51 (15)
APPLICATION SITE DISORDERS	4 (2)	54 (20)	15 (22)	69 (21)
URINARY SYSTEM DISORDERS	19 (7)	49 (18)	13 (19)	62 (19)
Urinary tract infection	6 (2)	10 (4)	7 (10)	17 (5)
CARDIOVASCULAR DISORDERS, GENERAL	16 (6)	47 (18)	14 (20)	61 (18)
Hypotension	3 (1)	36 (14)	10 (15)	46 (14)
METABOLIC & NUTRITIONAL DISORDERS	50 (19)	47 (18)	13 (19)	60 (18)
Dehydration	16 (6)	16 (6)	5 (7)	21 (6)
NEOPLASM	67 (26)	46 (17)	13 (19)	59 (18)
Disease Progression	67 (26)	45 (17)	0	45 (13)
VASCULAR (EXTRACARDIAC) DISORDERS	29 (11)	36 (14)	9 (13)	45 (13)
RED BLOOD CELL DISORDERS	15 (6)	33 (12)	11 (16)	44 (13)
Anemia	14 (5)	33 (12)	11 (16)	44 (13)
HEART RATE AND RHYTHM DISORDERS	19 (7)	27 (10)	11 (16)	38 (11)
Tachycardia	10 (4)	19 (7)	5 (7)	24 (7)
SPECIAL SENSES OTHER, DISORDERS	15 (6)	32 (12)	4 (6)	36 (11)
Taste Perversion	11 (4)	28 (11)	2 (3)	30 (9)
ENDOCRINE DISORDERS	11 (4)	18 (7)	3 (4)	21 (6)
Glucocorticoids Increased	7 (3)	18 (7)	3 (4)	21 (6)

RT-008, RT-009: Brain metastases (2 wks WBRT with concurrent RSR13 QD)

RT-009 Control Group: Brain metastases (2 wks WBRT)

N: total number of subjects analyzed for safety (ie, received at least 1 protocol-defined treatment RSR13 and/or RT)

n(%): number (percentage) of subjects with a given adverse event

The sponsor's results were verified by FDA analysis. The most commonly occurring treatment-emergent adverse events in the intent to treat population were alopecia, radiation dermatitis, headache, nausea, vomiting, fatigue, hypoxemia, hypotension, anemia, and taste perversion. The following treatment-emergent adverse events were encountered more commonly in the RSR13 treatment arm: headache, nausea, vomiting, hypoxemia, hypotension, anemia, and taste perversion.

Table 60 reproduces the majority of treatment-emergent adverse events reported in RT-009. Nine patients were not evaluable for safety because they never received according to the sponsor.

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**Table 60: FDA Analysis Treatment-emergent Adverse Events Reported by Subgroup in
=5% of RSR13-treated Patients in RT-009**

WHOART Body System Total Preferred Term	Control			RSR13		
	NSCLC N(%)	Breast N(%)	Other N(%)	NSCLC N(%)	Breast N(%)	Other N(%)
N	150	54	59	145	60	63
Fatigue	64(43)	24(44)	26(44)	73(50)	32(53)	26(41)
Edema peripheral	20(13)	3(6)	6(10)	27(19)	2(3)	8(13)
pain	20(13)	5(9)	1(2)	11(7)	6(10)	7(11)
asthenia	19(13)	7(13)	12(20)	8(5)	1(2)	2(3)
Fever	14(9)	3(6)	0	12(8)	6(10)	5(8)
Back pain	10(7)	6(11)	3(5)	11(7)	4(5)	5(8)
Chest pain	12(8)	0	1(2)	18(12)	6(10)	2(3)
Weight decrease	10(7)	3(6)	7(12)	10(7)	2(3)	3(5)
Leg pain	8(5)	2(4)	1(2)	3(1)	1(2)	4(6)
Weight increase	2(1)	3(6)	3(6)	9(6)	1(2)	2(3)
Rigors	5(3)	1(2)	1(2)	9(6)	1(2)	2(3)
Nausea	46(31)	14(26)	20(34)	58(4)	39(65)	27(43)
Vomiting	27(18)	7(13)	11(19)	47(32)	31(52)	24(38)
Anorexia	35(23)	3(6)	6(10)	32(22)	4(7)	7(11)
Dyspepsia	24(16)	3(6)	6(10)	14(10)	4(7)	5(8)
Mouth dry	3(2)	4(7)	3(5)	6(4)	2(3)	4(6)
Abdominal pain	9(6)	4(7)	9(15)	11(7)	5(8)	5(8)
Diarrhea	4(3)	2(4)	3(5)	10(7)	7(12)	3(5)
Headache	47(31)	15(28)	24(41)	57(39)	35(58)	34(54)
Dizziness	27(18)	6(11)	7(12)	30(21)	14(23)	14(22)
Confusion	11(7)	2(4)	5(9)	12(8)	4(7)	7(11)
Convulsions	4(3)	1(2)	4(7)	8(5)	4(7)	8(13)
Paresthesia	7(5)	0	0	10(7)	5(8)	3(5)
Gait abnormal	5(3)	1(2)	1(2)	8(5)	1(2)	1(1)
Ataxia	11(7)	1(2)	1(2)	3(1)	1(2)	4(6)
Speech disorder	4(3)	1(2)	1(2)	1(1)	2(3)	4(6)
Tremor	8(5)	2(4)	5(8)	8(5)	1(2)	0
Alopecia	78(52)	25(46)	26(41)	80(55)	30(50)	26(41)
Radiation dermatitis	34(23)	13(24)	19(32)	35(24)	12(20)	22(35)
Rash	5(3)	1(2)	4(7)	14(10)	6(10)	2(3)
Pruritus	1(1)	1(2)	1(2)	3(1)	3(5)	2(3)
Hypoxia	8(5)	2(4)	0	62(43)	23(38)	24(38)
Dyspnea	30(20)	4(7)	3(5)	22(15)	4(7)	4(6)
Coughing	18(12)	6(11)	6(10)	23(16)	5(8)	6(9)
Pneumonia	10(7)	0	2(3)	12(8)	2(3)	6(9)
Somnolence	9(6)	4(7)	6(10)	13(3)	2(3)	8(13)
Depression	7(5)	1(2)	3(5)	3(1)	1(2)	7(11)
Anxiety	11(7)	1(2)	4(7)	14(10)	5(8)	4(6)
Muscle weakness	22(15)	8(15)	9(15)	18(12)	7(12)	11(17)
Arthralgia	9(6)	5(9)	4(7)	12(8)	5(8)	5(8)
Dehydration	11(7)	3(6)	2(3)	14(10)	0	2(3)

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Acute renal failure	0	0	1(2)	4(3)	0	4(6)
Creatinine blood increased	0	0	0	5(3)	4(7)	2(3)
Vision abnormality	15(10)	4(7)	3(5)	11(7)	7(12)	5(8)
Hypotension	3(2)	0	0	23(16)	7(12)	6(9)
Hypertension	4(3)	3(6)	3(6)	2(1)	3(5)	1(1)
Anemia	9(6)	2(4)	3(5)	17(12)	5(8)	11(17)
Tachycardia	8(5)	1(2)	1(2)	11(7)	6(10)	3(5)
Thrombocytopenia	3(2)	0	0	5(3)	2(3)	3(5)
Taste perversion	4(3)	4(7)	3(5)	17(12)	7(12)	4(6)
Glucocorticoids increased	3(2)	2(4)	2(4)	10(7)	5(8)	3(5)

Few discrepancies were encountered. For example, 10 cases of pneumonia were reported in the NSCLC subgroup in the control arm according to FDA analysis, while 7 cases of pneumonia were reported in this same subgroup according to the sponsor's analysis. Pneumonia was recorded in two body systems in the sponsor's analysis (Respiratory and Resistance Mechanism Disorders). The FDA reported preferred term irrespective of body system. Furthermore, three patients of the nine that were not evaluable for safety had records included in some of the datasets, but not others. This may account for some of the slight differences in the numeric value for a given adverse event.

The following treatment-emergent adverse events varied by one or two patients between the FDA analysis and Sponsor's analysis in the control arm of RT-009: abdominal pain, facial edema, weight increase, rigors, speech disorder, tremor, paresthesia, disease progression, urinary tract infection, and hypertension

Grade 3 and 4 Adverse Events Encountered in RT-009 and RT-008 are reviewed below. **Tables 61 through 65** represent the sponsor's analysis of these events. The FDA analysis was very similar. Any difference in outcome are discussed below.

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Table 61
(Derived from Sponsor's Table 2.7.4.2.13)
Grade 3 Adverse Events Reported in ≥1% RSR13-treated Subjects in Studies of RSR13 as Adjunct to WBRT,
RSR13-treated Subjects Versus Control Subjects

WHOART BODY SYSTEM TOTAL PREFERRED TERM	RT-009		RT-008
	Control (N=263)	RSR13 (N=266)	RSR13 (N=69)
	n (%)	n (%)	n (%)
Treatment-emergent Grade 3 Adverse Events in the Study of RSR13 as Adjunct to WBRT			
ALL	80 (30)	79 (30)	31 (45)
CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS			
Headache	8 (3)	18 (7)	8 (12)
Convulsions	1 (0)	6 (2)	4 (6)
Confusion	1 (0)	5 (2)	0
Gait abnormal	2 (1)	2 (1)	1 (1)
Edema cerebral	1 (0)	3 (1)	1 (1)
Hemiparesis	4 (2)	5 (2)	0
GASTROINTESTINAL SYSTEM DISORDERS	31 (12)	31 (12)	4 (6)
Nausea	7 (3)	12 (5)	2 (3)
Vomiting	8 (3)	12 (5)	1 (1)
Constipation	10 (4)	9 (3)	0
Anorexia	2 (1)	3 (1)	1 (1)
Abdominal Pain	7 (3)	5 (2)	1 (1)
BODY AS A WHOLE—GENERAL DISORDERS	25 (10)	23 (9)	8 (12)
Fatigue	9 (3)	11 (4)	3 (4)
Back pain	3 (1)	4 (2)	1 (1)
Pain	4 (2)	2 (1)	3 (4)
Asthenia	7 (3)	2 (1)	1 (1)
SKIN AND APPENDAGES DISORDERS	5 (2)	8 (3)	1 (1)
Alopecia	3 (1)	2 (1)	1 (1)
RESPIRATORY SYSTEM DISORDERS	24 (9)	36 (14)	11 (16)
Hypoxemia	6 (2)	30 (11)	7 (10)
Dyspnea	15 (6)	4 (2)	1 (1)
Pleural effusion	1 (0)	3 (1)	2 (3)
PSYCHIATRIC DISORDERS	6 (2)	16 (6)	3 (12)
Insomnia	2 (1)	1 (0)	0
Somnolence	3 (1)	6 (2)	2 (3)
Amnesia	1 (0)	2 (1)	0
Depression	0	4 (2)	1 (1)
MUSCULOSKELETAL SYSTEM DISORDERS	27 (10)	11 (4)	4 (6)
Muscle Weakness	14 (5)	5 (2)	2 (3)
Skeletal Pain	7 (3)	3 (1)	1 (1)
Fracture pathological	1 (0)	2 (1)	1 (1)
INFUSION SYMPTOMS	0	2 (1)	1 (1)
Perioral	0	2 (1)	1 (1)
APPLICATION SITE DISORDERS	0	8 (3)	1 (1)
Thrombosis venous arm	0	3 (1)	0
URINARY SYSTEM DISORDERS	4 (2)	8 (3)	2 (3)
Urinary incontinence	2 (1)	3 (1)	1 (1)

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Table 61 (continued)

WHOART BODY SYSTEM TOTAL PREFERRED TERM	RT-009		RT-008
	Control (N=263) n (%)	RSR13 (N=266) n (%)	RSR13 (N=69) n (%)
Treatment-emergent Grade 3 Adverse Events in the Study of RSR13 as Adjunct to WBRT			
CARDIOVASCULAR DISORDERS, GENERAL	3 (1)	6 (2)	4 (6)
Hypotension	1 (0)	3 (1)	1 (1)
Hypertension	2 (1)	3 (1)	2 (3)
METABOLIC & NUTRITIONAL DISORDERS	16 (6)	12 (5)	5 (7)
Dehydration	5 (2)	6 (2)	2 (3)
Hypokalemia	0	3 (1)	0
Hyponatremia	3 (1)	3 (1)	0
NEOPLASM	19 (7)	10 (4)	4 (6)
Disease Progression	19 (7)	10 (4)	0
Neoplasm growth accelerated	0	0	3 (4)
VASCULAR (EXTRACARDIAC) DISORDERS	9 (3)	8 (3)	0
Thrombosis venous leg deep	4 (2)	2 (1)	0
Thrombophlebitis deep	3 (1)	0	0
RED BLOOD CELL DISORDERS	3 (1)	4 (2)	3 (4)
Anemia	2 (1)	4 (2)	3 (4)
HEART RATE AND RHYTHM DISORDERS	9 (3)	4 (2)	0
Tachycardia	3 (1)	3 (1)	0
Fibrillation atrial	3 (1)	2 (1)	0
Tachycardia supraventricular	3 (1)	0	0
WHITE CELL & RETICULOENDOTHELIAL DISORDERS^a	3 (1)	3 (1)	0
LIVER & BILIARY SYSTEM DISORDERS	1 (0)	3 (1)	0
Hepatomegaly	0	3 (1)	0

Table includes only adverse reported in ≥1% of subjects in either treatment arm

Control: subjects treated with WBRT + supplemental oxygen

RSR13: subjects treated with WBRT + RSR13 + supplemental oxygen

N: total number of subjects analyzed for safety (ie, received at least 1 protocol-defined treatment RSR13 and/or RT)

n(%): number (percentage) of subjects with a given adverse event

^aComprised of adverse events reported in <1% of subjects in either treatment arm (events included febrile neutropenia, granulocytopenia, leukocytosis, pancytopenia)

The most common Grade 3 adverse events encountered in RT-009 were headache, nausea, vomiting, dyspnea, hypoxemia, and muscle weakness. Hypoxemia and headache occurred most frequently in the RSR13 treatment arm.

The following Grade 3 adverse events differed by only one to two patients between the FDA analysis and Sponsor analysis: headache, convulsions, anorexia, dyspnea, hypertension, dehydration, hypokalemia, and hyponatremia. These differences were noted in the control arm. Two cases of acute renal failure occurred in the RSR13 treatment arm (Grade 3).

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Table 62
(Derived from Sponsor's Table 2.7.4.2.15)

Grade 3 Adverse Events According to Primary Site Subpopulation in the Study of RSR13 as Sole Adjunct to WBRT, RSR13-treated Subjects Versus Control Subjects

WHOART BODY SYSTEM TOTAL PREFERRED TERM	CONTROL			RSR13		
	NSCLC (N=150)	Breast (N=54)	Other ^a (N=59)	NSCLC (N=144)	Breast (N=60)	Other ^a (N=71)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Grade 3 Adverse Events Reported in 2 or More Subjects in Any Primary Cancer Cohort in Study RT-009						
ALL	50 (33)	17 (32)	13 (22)	45 (31)	19 (32)	15 (21)
BODY AS A WHOLE - GENERAL DISORDERS	16 (11)	2 (4)	7 (12)	16 (11)	2 (3)	5 (7)
Fatigue	6 (4)	1 (2)	2 (3)	7 (5)	2 (3)	2 (3)
Edema Peripheral	2 (1)	0	0	0	0	0
Chest Pain	4 (3)	0	0	3 (2)	0	0
Asthenia	2 (1)	1 (2)	4 (7)	1 (0.7)	1 (2)	0
Back Pain	1 (0.7)	1 (2)	1 (2)	2 (1)	1 (2)	1 (1)
Syncope	0	0	0	3 (2)	0	1 (1)
Pain	4 (3)	0	0	1 (0.7)	0	1 (1)
GASTROINTESTINAL SYSTEM DISORDERS	18 (12)	3 (6)	10 (17)	12 (8)	12 (20)	7 (10)
Nausea	5 (3)	0	2 (3)	3 (2)	5 (8)	4 (6)
Vomiting	6 (4)	1 (2)	1 (2)	4 (3)	5 (8)	3 (4)
Constipation	6 (4)	0	4 (7)	6 (4)	3 (5)	0
Anorexia	0	1 (2)	1 (2)	2 (1)	0	1 (1)
Abdominal Pain	1 (0.7)	1 (2)	5 (9)	3 (2)	1 (2)	1 (1)
CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS	14 (9)	6 (11)	3 (5)	19 (13)	6 (10)	11 (15)
Headache	4 (3)	2 (4)	2 (3)	8 (6)	3 (5)	7 (10)
Confusion	1 (0.7)	0	0	3 (2)	1 (2)	1 (1)
Convulsions	1 (0.7)	0	0	2 (1)	2 (3)	2 (3)
Gait Abnormal	2 (1)	0	0	2 (1)	0	0
Hemiparesis	3 (2)	0	1 (2)	3 (2)	0	2 (3)
Neuropathy peripheral	0	0	1 (2)	2 (1)	1 (2)	0
Ataxia	4 (3)	0	0	1 (0.7)	0	0
Edema cerebral	1 (0.7)	0	0	2 (1)	0	1 (1)
RESPIRATORY SYSTEM DISORDERS	19 (7)	3 (6)	2 (3)	23 (16)	8 (13)	5 (7)
Hypoxia	5 (3)	1 (2)	0	20 (14)	4 (7)	6 (8)
Dyspnea	13 (9)	1 (2)	1 (2)	3 (2)	1 (2)	0
Pneumonia	4 (3)	0	1 (2)	8 (6)	1 (2)	0
Bronchospasm	1 (0.7)	0	0	2 (1)	1 (2)	0
Pleural Effusion	1 (0.7)	0	0	3 (2)	0	0
Upper Resp Tract Infection	2 (1)	0	0	0	0	0

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Table 62 (continued)

WHOART BODY SYSTEM TOTAL PREFERRED TERM	CONTROL			RSR13		
	NSCLC (N=150)	Breast (N=54)	Other ^a (N=59)	NSCLC (N=144)	Breast (N=60)	Other ^a (N=71)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Grade 3 Adverse Events Reported in 2 or More Subjects in Any Primary Cancer Cohort in Study RT-009						
SKIN & APPENDAGES						
DISORDERS	4 (3)	1 (2)	0	3 (2)	3 (5)	2 (3)
Alopecia	2 (1)	1 (2)	0	1 (0.7)	1 (2)	0
Rash	0	0	0	2 (1)	1 (2)	0
PSYCHIATRIC DISORDERS	4 (3)	0	2 (3)	8 (6)	2 (3)	6 (8)
Insomnia	2 (1)	0	0	1 (0.7)	0	0
Somnolence	2 (1)	0	1 (2)	3 (2)	0	3 (4)
Amnesia	0	0	1 (2)	2 (1)	0	0
Depression	0	0	0	1 (0.7)	1 (2)	2 (3)
MUSCULOSKELETAL SYSTEM DISORDERS	14 (9)	7 (13)	6 (10)	3 (2)	1 (2)	7 (10)
Muscle Weakness	6 (4)	4 (7)	4 (7)	1 (0.7)	0	4 (6)
Skeletal Pain	5 (3)	1 (2)	1 (2)	2 (1)	1 (2)	0
Arthralgia	1 (0.7)	2 (4)	0	0	0	2 (3)
APPLICATION SITE DISORDERS	0	0	0	6 (4)	1 (2)	1 (1)
Thrombophlebitis Arm	0	0	0	2 (1)	0	0
RESISTANCE MECHANISM DISORDERS	10 (7)	1 (2)	3 (5)	1 (0.7)	0	1 (1)
Moniliasis	4 (3)	0	0	0	0	0
Abscess	4 (3)	0	0	0	0	0
Infection	0	0	3 (5)	0	0	0
METABOLIC & NUTRITIONAL DISORDERS	7 (5)	4 (7)	5 (9)	6 (6)	2 (3)	2 (3)
Dehydration	4 (3)	0	1 (2)	5 (3)	0	1 (1)
Hyperglycemia	2 (1)	3 (6)	2 (3)	0	0	0
Hypokalemia	0	0	0	2 (1)	1 (2)	0
Hyponatremia	3 (2)	0	0	1 (0.7)	1 (2)	1 (1)
INFUSION SYMPTOMS	0	0	0	0	2 (3)	0
Perioral	0	0	0	0	2 (3)	0
CARDIOVASCULAR DISORDERS, GENERAL	1 (0.7)	2 (4)	0	4 (3)	1 (2)	1 (1)
Hypotension	1 (0.7)	0	0	3 (2)	0	0
Hypertension	0	2 (4)	0	1 (0.7)	1 (2)	1 (1)
URINARY SYSTEM DISORDERS	3 (2)	0	1 (2)	5 (3)	0	3 (4)
Urinary Incontinence	2 (1)	0	0	2 (1)	0	1 (1)
Urinary Tract Infection	0	0	2 (3)	0	0	0
NEOPLASM	11 (7)	4 (7)	4 (7)	5 (3)	1 (2)	4 (6)
Disease Progression	11 (7)	4 (7)	4 (7)	5 (3)	1 (2)	4 (6)
VASCULAR (EXTRACARDIAC) DISORDERS	8 (5)	1 (2)	1 (2)	2 (1)	1 (2)	5 (7)
Thrombophlebitis Leg	0	0	0	2 (1)	0	0
Thrombosis Venous Leg						
Deep	3 (2)	1 (2)	0	0	0	2 (3)
Thrombophlebitis Deep	3 (2)	0	0	0	0	0
RED BLOOD CELL DISORDERS	1 (0.7)	2 (4)	0	3 (2)	0	1 (1)
Anemia	1 (0.7)	1 (2)	0	3 (2)	0	1 (1)
HEART RATE & RHYTHM DISORDERS	7 (5)	0	2 (3)	2 (1)	0	2 (3)
Tachycardia	3 (2)	0	0	2 (1)	0	1 (1)
Tachycardia Supraventric.	3 (2)	0	0	0	0	0
Fibrillation Atrial	1 (0.7)	0	2 (3)	1 (0.7)	0	1 (1)
HEARING & VESTIBULAR DISORDERS	2 (1)	0	0	1 (0.7)	0	0
Tinnitus	2 (1)	0	0	1 (0.7)	0	0

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Table 62 (continued)

WHOART BODY SYSTEM TOTAL PREFERRED TERM	CONTROL			RSR13		
	NSCLC (N=150)	Breast (N=54)	Other ^b (N=59)	NSCLC (N=144)	Breast (N=60)	Other ^b (N=71)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Grade 3 Adverse Events Reported in 2 or More Subjects in Any Primary Cancer Cohort in Study RT-009						
PLATELET, BLEEDING & CLOTTING DISORDERS	4 (3)	1 (2)	0	1 (0.7)	1 (2)	0
Thrombocytopenia	2 (1)	0	0	1 (0.7)	1 (2)	0
LIVER & BILIARY SYSTEM DISORDERS	0	1 (2)	1 (2)	2 (1)	1 (2)	1 (1)
Hepatomegaly	0	0	0	2 (1)	0	1 (1)
WHITE CELL & RETICULOENDOTHELIAL SYSTEM DISORDERS ^a	1 (0.7)	2 (4)	0	1 (0.7)	2 (3)	0

Control: Patients treated with WBRT + supplemental oxygen

RSR13: Patients treated with WBRT + RSR13 + supplemental oxygen

N: total number of subjects analyzed for safety (ie, received at least 1 protocol-defined treatment RSR13 and/or RT)

n(%): number (percentage) of subjects with a given adverse event

^aComprised of various primary cancers including malignant melanoma, colorectal cancer, renal cell carcinoma, cancers of the ovary, lung (other than NSCLC), esophagus, cervix, uterus, pancreas, bladder, tonsil, nasopharynx

^bComprised of adverse events reported in only 1 subject in any cohort

The most frequently observed Grade 3 adverse event by subgroup were fatigue, nausea, vomiting, constipation, abdominal pain, headache, hypoxia, dyspnea, pneumonia, muscle weakness, hyperglycemia, and disease progression.

Nausea, vomiting, headache, and hypoxia were more common in the RSR13 treatment arm. Constipation, abdominal pain, dyspnea, muscle weakness, hyperglycemia, and disease progression were more common in the control arm.

Again, the differences noted between the FDA analysis and Sponsor's analysis were only by one or two patients. These included anorexia, headache, convulsions, cerebral edema, dyspnea, pneumonia, dehydration, hypokalemia, and hypertension.

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Table 63
(Derived from Sponsor's Table 2.7.3.2.14)

All Grade 4 Adverse Events in Studies of RSRL3 as Adjunct to WBRT, RSRL3-treated Subjects Versus Control Subjects

WHOART BODY SYSTEM TOTAL PREFERRED TERM	RT-009		RT-008
	Control (N=263) n (%)	RSRL3 (N=266) n (%)	RSRL3 (N=69) n (%)
Treatment-emergent Grade 4 Adverse Events in the Study of RSRL3 as Adjunct to WBRT			
ALL	58 (22)	60 (23)	5 (7)
CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS	12 (5)	8 (3)	1 (1)
Headache	3 (1)	0	0
Convulsions	3 (1)	2 (1)	0
Aphasia	1 (0.4)	1 (0.4)	0
Agitation	0	1 (0.4)	0
Edema Cerebral	0	1 (0.4)	0
Neuropathy Peripheral	1 (0.4)	0	0
Stupor	0	1 (0.4)	1 (1)
Neurologic Deterioration	1 (0.4)	0	0
Hypertension Intracranial	0	0	1 (1)
Sensory Disturbance	1 (0.4)	0	0
Coma	2 (1)	1 (0.4)	1 (1)
Hemiplegia	1 (0.4)	1 (0.4)	0
Neuralgia	1 (0.4)	0	0
Paralysis	1 (0.4)	0	0
Cerebral spinal fluid leak	1 (0.4)	0	0
GASTROINTESTINAL SYSTEM DISORDERS	1 (0.4)	10 (4)	0
Vomiting	0	2 (1)	0
Abdomen Enlarged	0	1 (0.4)	0
Anorexia	1 (0.4)	1 (0.4)	0
Radiation dysphagia	0	1 (0.4)	0
Gastrointestinal disorder NOS	0	1 (0.4)	0
Intestinal perforation	0	1 (0.4)	0
Melena	0	1 (0.4)	0
Colitis	0	1 (0.4)	0
Diverticulitis	0	1 (0.4)	0
Intestinal obstruction	0	1 (0.4)	0
BODY AS A WHOLE-- GENERAL DISORDERS	6 (2)	4 (2)	0
Fatigue	3 (1)	0	0
Pain	1 (0.4)	2 (1)	0
Condition aggravated	2 (1)	1 (0.4)	0
Asthenia	1 (0.4)	0	0
Edema Generalized	0	1 (0.4)	0
Condition Aggravated	2 (0.8)	1 (0.4)	0
RESPIRATORY SYSTEM DISORDERS	5 (2)	12 (5)	1 (1)
Dyspnea	4 (2)	4 (2)	0
Pneumonia	0	5 (2)	1 (1)
Respiratory insufficiency	1 (0.4)	3 (1)	0
Pulmonary Edema	1 (0.4)	0	0
Adult Respiratory Distress Syndrome	1 (0.4)	0	0
MUSCULOSKELETAL SYSTEM DISORDERS	1 (0.4)	2 (1)	0
Muscle Weakness	1 (0.4)	1 (0.4)	0
Fracture Accidental	0	1 (0.4)	0
RESISTANCE MECHANISM DISORDERS	2 (1)	2 (1)	0
Infection	0	1 (0.4)	0
Sepsis	1 (0.4)	0	0
Meningitis	1 (0.4)	1 (0.4)	0

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Table 63 (continued)

WHOART BODY SYSTEM TOTAL PREFERRED TERM	RT-009		RT-008
	Control (N=263) n (%)	RSR13 (N=266) n (%)	RSR13 (N=69) n (%)
Treatment-emergent Grade 4 Adverse Events in the Study of RSR13 as Adjunct to WBRT			
URINARY SYSTEM DISORDERS	1 (0.4)	5 (2)	0
Creatinine Blood Increased	0	1 (0.4)	0
Oliguria	0	1 (0.4)	0
Renal Failure Acute	1 (0.4)	5 (2)	0
CARDIOVASCULAR DISORDERS, GENERAL	2 (1)	4 (2)	0
Hypotension	0	2 (1)	0
Hypertension	1 (0.4)	0	0
Cardiac Failure	0	1 (0.4)	0
Circulatory Failure	0	1 (0.4)	0
Left Ventricular Dysfunction	1 (0.4)	0	0
METABOLIC & NUTRITIONAL DISORDERS	6 (2)	5 (2)	1 (1)
Dehydration	1 (0.4)	1 (0.4)	0
Hyperglycemia	2 (1)	0	0
Hypokalemia	2 (1)	0	0
Hyponatremia	0	1 (0.4)	0
Hyperkalemia	0	1 (0.4)	0
Diabetes Mellitus Aggravated	1 (0.4)	1 (0.4)	0
Diabetes Mellitus	0	0	1 (1)
Ketosis	0	1 (0.4)	0
Hypercalcemia	1 (0.4)	0	0
NEOPLASM	33 (13)	29 (11)	3 (4)
Disease Progression	33 (13)	29 (11)	0
Neoplasm Growth Accelerated	0	0	3 (4)
VASCULAR (EXTRACARDIAC) DISORDERS	8 (3)	6 (2)	0
Embolism Pulmonary	3 (1)	4 (2)	0
Thrombosis	0	1 (0.4)	0
Thrombosis Venous Leg Deep	1 (0.4)	1 (0.4)	0
Cerebrovascular Disorder	1 (0.4)	1 (0.4)	0
Cerebral Hemorrhage	1 (0.4)	0	0
Hemorrhage Intracranial	2 (0.8)	0	0
Thromboembolism	1 (0.4)	0	0
Thrombophlebitis Deep	1 (0.4)	0	0
Thrombosis Venous Arm	1 (0.4)	0	0
HEART RATE AND RHYTHM DISORDERS	2 (1)	2 (1)	0
Tachycardia	0	1 (0.4)	0
Cardiac Arrest	1 (0.4)	1 (0.4)	0
Arrhythmia Atrial	1 (0.4)	0	0
PSYCHIATRIC DISORDERS	1 (0.4)	1 (0.4)	0
Somnolence	1 (0.4)	1 (0.4)	0
SKIN & APPENDAGES DISORDERS	1 (0.4)	0	0
Stevens Johnson Syndrome	1 (0.4)	0	0
APPLICATION SITE DISORDERS	1 (0.4)	0	0
Sepsis	1 (0.4)	0	0
HEARING & VESTIBULAR DISORDERS	0	1 (0.4)	0
Deafness	0	1 (0.4)	0
SECONDARY TERMS	0	2 (1)	1 (1.4)
Medication Error	0	2 (1)	0
Spinal Cord Compression	0	0	1 (1.4)

Grade 4 events were few, but included dyspnea, pneumonia, and acute renal failure. Five patients in the RSR13 treatment arm had acute renal failure compared with one patient in the control arm.

There were no discrepancies in the number of patients with Grade 4 adverse events between the FDA analysis and the Sponsor's analysis.

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Table 64
(Derived from Sponsor's Table 2.7.4.2.16)
Grade 4 Adverse Events in the Study of RSR13 as Adjunct to WBRT, Subjects Stratified According to Primary Cancer (RT-009)

WHOART BODY SYSTEM TOTAL PREFERRED TERM	CONTROL			RSR13		
	NSCLC (N=150)	Breast (N=54)	Other ^a (N=59)	NSCLC (N=144)	Breast (N=60)	Other ^a (N=71)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
All Grade 4 Adverse Events According to Primary Site Cohort in Study RT-009						
ALL	29 (19)	10 (19)	19 (32)	29 (20)	11 (18)	20 (28)
BODY AS A WHOLE - GENERAL DISORDERS	3 (2)	3 (6)	0	1 (0.7)	2 (3)	1 (1)
Fatigue	2 (1)	1 (2)	0	0	0	0
Pain	1 (0.7)	0	0	1 (0.7)	0	1 (1)
Asthemia	1 (0.7)	0	0	0	0	0
Edema Generalized	0	0	0	0	1 (2)	0
Condition Aggravated	0	2 (4)	0	0	1 (2)	0
GASTROINTESTINAL SYSTEM DISORDERS	1 (0.7)	0	0	7 (5)	0	3 (4)
Vomiting	0	0	0	2 (1)	0	0
Anorexia	1 (0.7)	0	0	1 (0.7)	0	0
Radiation Dysphagia	0	0	0	1 (0.7)	0	0
Intestinal Perforation	0	0	0	1 (0.7)	0	0
Colitis	0	0	0	1 (0.7)	0	0
Diverticulitis	0	0	0	1 (0.7)	0	0
Gastrointestinal Disorder NOS	0	0	0	1 (0.7)	0	0
Abdomen Enlarged	0	0	0	0	0	1 (1)
Intestinal Obstruction	0	0	0	0	0	1 (1)
Melena	0	0	0	0	0	1 (1)
CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS	6 (4)	1 (2)	5 (8)	4 (3)	3 (5)	1 (1)
Headache	2 (1)	1 (2)	0	0	0	0
Convulsions	1 (0.7)	0	2 (3)	0	1 (2)	1 (1)
Coma	1 (0.7)	0	1 (2)	1 (0.7)	0	0
Aphasia	0	0	1 (2)	1 (0.7)	0	0
Stupor	0	0	0	1 (0.7)	0	0
Hemiplegia	0	0	1 (2)	1 (0.7)	0	0
Neuralgia	1 (0.7)	0	0	0	0	0
Paralysis	1 (0.7)	0	0	0	0	0
Neuropathy Peripheral	0	0	1 (2)	0	0	0
Cerebral Spinal Fluid Leak	0	0	1 (2)	0	0	0
Neurologic Deterioration	0	0	1 (2)	0	0	0
Sensory Disturbance	0	0	1 (2)	0	0	0
Edema Cerebral	0	0	0	0	1 (2)	0
Agitation	0	0	0	0	1 (2)	0
RESPIRATORY SYSTEM DISORDERS	3 (2)	0	2	7 (5)	1 (2)	4 (6)
Dyspnea	3 (2)	0	1 (2)	4 (3)	0	0
Pneumonia	0	0	0	2 (1)	0	3 (4)
Respiratory Insufficiency	0	0	1 (2)	1 (0.7)	1 (2)	1 (1)
Pulmonary Edema	0	0	1 (2)	0	0	0
Adult Respiratory Distress Syndrome	1 (0.7)	0	0	0	0	0
SKIN & APPENDAGES DISORDERS	0	0	1 (2)	0	0	0
Stevens Johnson Syndrome	0	0	1 (2)	0	0	0
PSYCHIATRIC DISORDERS	0	1 (2)	0	0	1 (2)	0
Somnolence	0	1 (2)	0	0	1 (2)	0

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Table 64 (continued)

WHOART BODY SYSTEM TOTAL PREFERRED TERM	CONTROL			RSR13		
	NSCLC (N=150)	Breast (N=54)	Other ^a (N=59)	NSCLC (N=144)	Breast (N=60)	Other ^a (N=71)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
All Grade 4 Adverse Events According to Primary Site Cohort in Study RT-009						
MUSCULOSKELETAL SYSTEM DISORDERS	1 (0.7)	0	0	0	2 (3)	0
Muscle Weakness	1 (0.7)	0	0	0	1 (2)	0
Fracture Accidental	0	0	0	0	1 (2)	0
RESISTANCE MECHANISM DISORDERS	1 (0.7)	1 (2)	0	1 (0.7)	1 (2)	0
Meningitis	1 (0.7)	0	0	0	1 (2)	0
Infection	0	0	0	1 (0.7)	0	0
Sepsis	0	1 (2)	0	0	0	0
METABOLIC & NUTRITIONAL DISORDERS	5 (3)	1 (2)	0	2 (1)	2 (3)	1 (1)
Dehydration	1 (0.7)	0	0	1 (0.7)	0	0
Hyperglycemia	2 (1)	0	0	0	0	0
Hypokalemia	1 (0.7)	1 (2)	0	0	0	0
Hyperkalemia	0	0	0	1 (0.7)	0	0
Diabetes Mellitus Aggravated	1 (0.7)	0	0	0	1 (2)	0
Hypercalcemia	1 (0.7)	0	0	0	0	0
Ketosis	0	0	0	0	1 (2)	0
Hyponatremia	0	0	0	0	0	1 (1)
CARDIOVASCULAR DISORDERS, GENERAL	2 (1)	0	0	1 (0.7)	1 (2)	2 (3)
Hypotension	0	0	0	1 (0.7)	0	1 (1)
Hypertension	1 (0.7)	0	0	0	0	0
LV Dysfunction	1 (0.7)	0	0	0	0	0
Cardiac Failure	0	0	0	0	0	1 (1)
Circulatory Failure	0	0	0	0	1 (2)	0
URINARY SYSTEM DISORDERS	0	0	1 (2)	1 (0.7)	0	4 (6)
Renal Failure Acute	0	0	1 (2)	1 (0.7)	0	4 (6)
Creatinine Blood Increased	0	0	0	0	0	1 (1)
Oliguria	0	0	0	0	0	1 (1)
NEOPLASM	18 (12)	6 (11)	9 (15)	12 (8)	4 (7)	13 (18)
Disease Progression	18 (12)	6 (11)	9 (15)	12 (8)	4 (7)	13 (18)
VASCULAR (EXTRACARDIAC) DISORDERS	3 (2)	1 (2)	4 (7)	5 (4)	0	1 (1)
Embolism Pulmonary	1 (0.7)	1 (2)	1 (2)	4 (3)	0	0
Thrombosis Venous Leg Deep	1 (0.7)	0	0	1 (0.7)	0	0
Thrombosis	0	0	0	1 (0.7)	0	0
Cerebrovascular Disorder	1 (0.7)	0	0	0	0	1 (1)
Thromboembolism	1 (0.7)	0	0	0	0	0
Thrombophlebitis Deep	1 (0.7)	0	0	0	0	0
Thrombosis Venous Arm	1 (0.7)	0	0	0	0	0
Cerebral Hemorrhage	0	0	1 (2)	0	0	0
Hemorrhage Intracranial	0	0	2 (3)	0	0	0
HEART RATE & RHYTHM DISORDERS	1 (0.7)	0	1 (2)	1 (0.7)	0	1 (1)
Cardiac Arrest	0	0	1 (2)	1 (0.7)	0	0
Arrhythmia Atrial	1 (0.7)	0	0	0	0	0
Tachycardia	0	0	0	0	0	1 (1)
HEARING & VESTIBULAR DISORDERS	0	0	0	1 (0.7)	0	0
Deafness	0	0	0	1 (0.7)	0	0

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Table 64 (continued)

WHOART BODY SYSTEM TOTAL PREFERRED TERM	CONTROL			RSR13		
	NSCLC (N=150)	Breast (N=54)	Other ^a (N=59)	NSCLC (N=144)	Breast (N=60)	Other ^a (N=71)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
All Grade 4 Adverse Events According to Primary Site Cohort in Study RT-009						
LIVER & BILIARY SYSTEM DISORDERS	0	0	1 (2)	0	1 (2)	0
SGOT Increased	0	0	0	0	1 (2)	0
Jaundice	0	0	1 (2)	0	1 (2)	0
MYO ENDO PERICARDIAL & VALVE DISORDERS	2 (1)	0	1 (2)	0	0	0
Pericardial Effusion	2 (1)	0	0	0	0	0
Cardiac Tamponade	1 (0.7)	0	0	0	0	0
Myocardial Infarction	1 (0.7)	0	1 (2)	0	0	0
APPLICATION SITE	0	0	1 (2)	0	0	0
Sepsis	0	0	1 (2)	0	0	0
SECONDARY TERMS	0	0	0	0	0	2 (3)
Medication Error	0	0	0	0	0	2 (3)

Control: Patients treated with WBRT + supplemental oxygen

RSR13: Patients treated with WBRT + RSR13 + supplemental oxygen

N: total number of subjects analyzed for safety (ie, received at least 1 protocol-defined treatment RSR13 and/or RT)

n(%): number (percentage) of subjects with a given adverse event

^aComprised of various primary cancers including malignant melanoma, colorectal cancer, renal cell carcinoma, cancers of the ovary, lung (other than NSCLC), esophagus, cervix, uterus, pancreas, bladder, tonsil, nasopharynx

In the RSR13 treatment group, four patients in the “other” subgroup and one patient with NSCLC had acute renal failure. In the control arm, one patient in the “other” subgroup developed acute renal failure. The majority of Grade 4 events recorded in all subgroups included convulsions, coma, aphasia, stupor, hemiplegia, neuralgia, paralysis, peripheral neuropathy, dyspnea, pneumonia, pulmonary edema, respiratory insufficiency, dehydration, hypokalemia, diabetes mellitus, and ketosis.

Only headache and muscle weakness differed between the FDA analysis and Sponsor’s analysis, again by only one patient for each adverse event.