Results of the Phase III ENRICH (RT-016) Study of Efaproxiral Administered Concurrent with Whole Brain Radiation Therapy (WBRT) in Women with Brain Metastases from Breast Cancer

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Phase III Trial Design
RSR13 RT-009

Study Design	Randomized 1:1, open label
Treatment	WBRT/supplemental O_2 +/- RSR13 3 Gy fractions x 10 days (30 Gy)
Number of Patients Enrolled	538 RPA Class I & II patients at 82 sites in 12 countries
Primary Endpoint	Survival
Secondary Endpoints	Response rate, time to radiographic and clinical tumor progression, cause of death and quality of life
Intent-to-Treat Groups	All tumor types NSCLC/Breast
Stratification	RPA Class I RPA Class II: NSCLC vs Breast vs Other

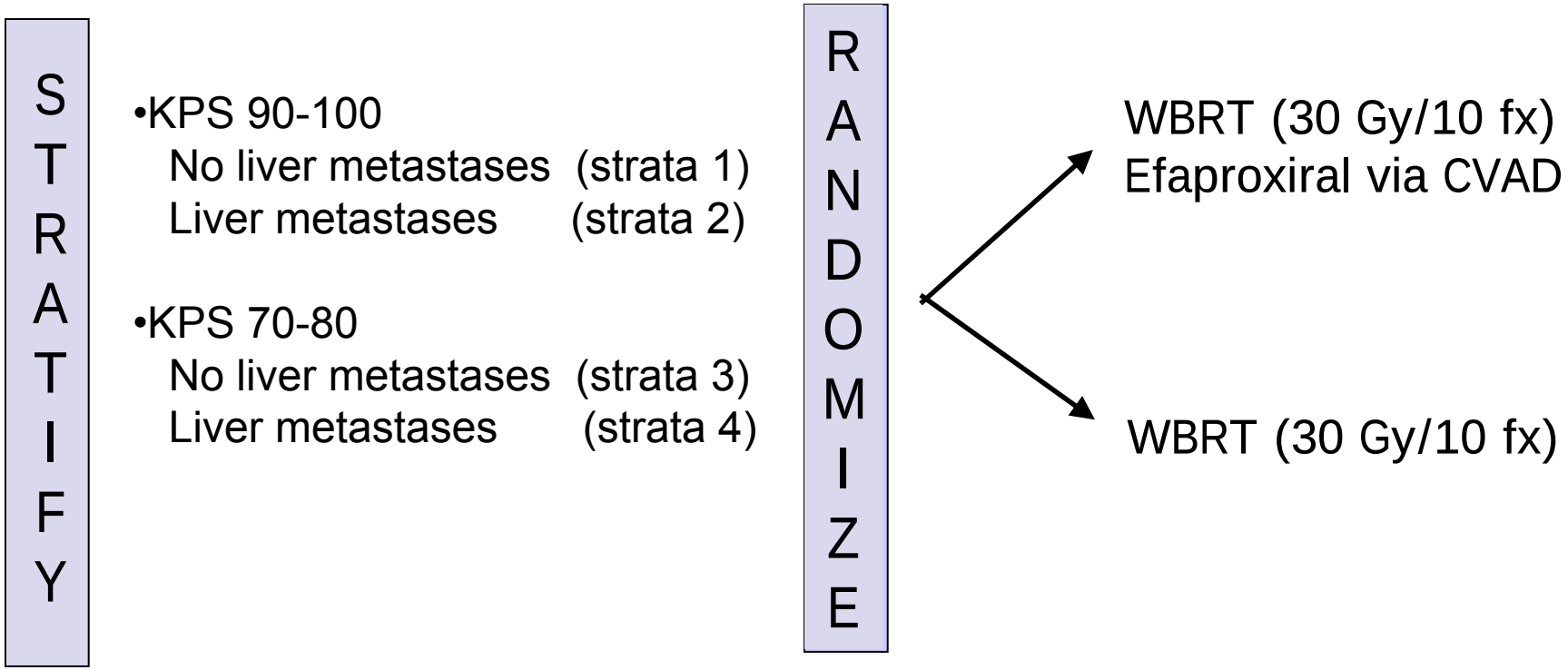
RT-009 phase III trial

Subset Results in Patients with Breast Cancer Primary (N = 115)

Endpoint	Control (N = 55)	RSR13 (N = 60)	p-value
Survival (MST)	4.57 months	8.67 months	---
Unadjusted log-rank test (Cox single regression model)	HR = 0.552		0.0062
Cox multiple regression model	HR = 0 .496		0.0061
Response rate	49.1%	71.7%	0.0155
QOL			
KPS (% stable/improved at 3 m)	18%	35%	0.0013
Spitzer (% stable/improved at 3 m)	24%	37%	0.0014

Phase III Confirmatory Trial (RT-016)

360 eligible women w/ brain metastases from breast cancer



All patients received supplemental oxygen 4L/min

Confirmatory study for breast cancer ENRICH RT-016

- Endpoints:
  - Primary: Survival
  - Secondary:
    - Response rate in the brain at 3 months
    - KPS and neurologic signs and symptoms

Inclusion Criteria

KPS $\geq$ 70

Adequate pulmonary function tests (PFTs) by simple spirometry.

Resting SpO_2 $\geq$90% while breathing room air.

Exercise (eg, walking uninterrupted for approximately 50 feet [15m] on level ground) SpO_2 $\geq$90% while breathing room air.

Exclusion Criteria

Planned concurrent systemic (cytotoxic and/or cytostatic) treatment for breast cancer and/or extracranial metastases during WBRT, with the exception of trastuzumab, hormonal, and/or corticosteroid therapy.

Presence of leptomeningeal metastases.

Statistical Considerations for Data Analysis

- Details of pre-specified statistical analyses submitted to FDA based on Statistical Analysis Plan
- Primary endpoint: Overall survival (Stratified log-rank test)
  - Based on study stratification (KPS and Liver metastases)
  - Supportive Cox model also pre-specified
- Secondary endpoints:
  - Response rate in the brain at 3-months (confirmation required)
  - Change in KPS and Neurological Signs and Symptoms from Baseline
- Full analysis set excludes 3 ineligible patients
- Study had 2 interim analyses (O'Brien-Fleming)

Enrollment Summary

- Enrollment duration:
  2/04 – 9/06 (31 months)
- 368 patients enrolled at 78 sites from 15 countries
- Three patients excluded since central review revealed no brain metastases

Region	n randomized (%)
Canada	49 (13)
Europe	124 (34)
South America	110 (30)
USA	85 (23)

Stratum	n randomized (%)
1 (KPS 90-100, - liver mets)	133 (36)
2 (KPS 90-100, +liver mets)	77 (21)
3 (KPS 70-80, - liver mets)	103 (28)
4 (KPS 70-80, + liver mets)	55 (15)

Patient Characteristics

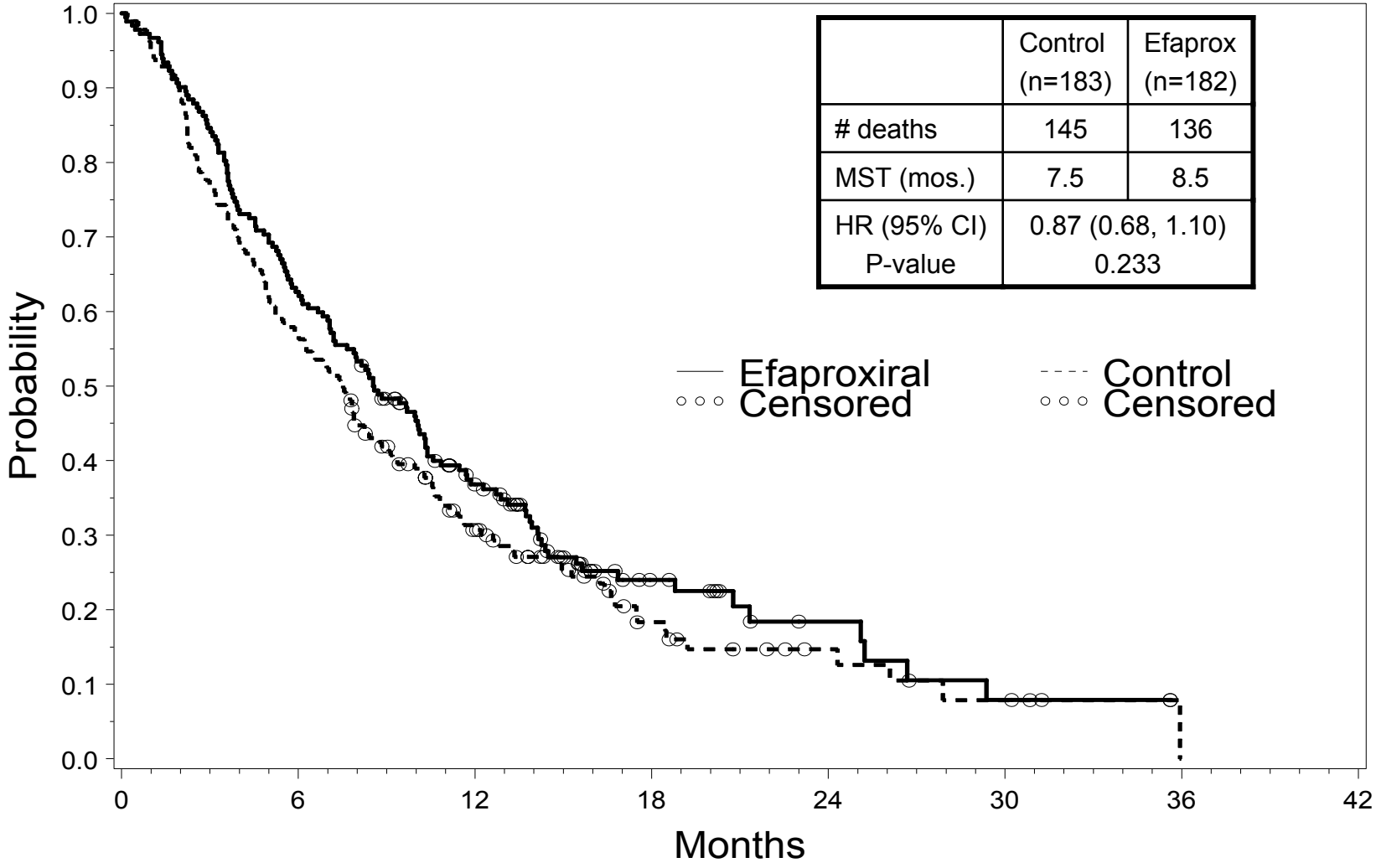
Characteristic	Value	Control (N=183) n (%)	Efaprox (N=182) n (%)
KPS	70	34 (19)	31 (17)
	80	49 (27)	46 (25)
	90	81 (44)	80 (44)
	100	19 (10)	25 (14)
Liver Mets	No	119 (65)	117 (64)
	Yes	64 (35)	65 (36)
Her-2/Neu Status	Negative	78 (43)	73 (40)
	Positive	68 (37)	68 (37)
	Unknown	37 (20)	41 (23)
Extracranial Metastatic Sites	0	39 (21)	38 (21)
	1-2	92 (50)	91 (50)
	>2	52 (28)	53 (29)

Patient Characteristics (cont.)

Characteristic	Value	Control (N=183) n (%)	Efaprox (N=182) n (%)
Number of Brain Mets	1	18 (10)	12 (7)
	2-3	36 (20)	44 (24)
	4-10	90 (49)	86 (47)
	>10	35 (19)	37 (20)
	Missing	4 (2)	3 (2)
Age	< 65	148 (81)	161 (88)
	≥ 65	35 (19)	21 (12)
Hemoglobin	< 12 g/dL	33 (18)	43 (24)
	≥ 12 g/dL	150 (82)	132 (73)
	Missing		7 (4)
Albumin	Normal/High	134 (73)	128 (70)
	Low	30 (16)	29 (16)
	Missing	19 (10)	25 (14)

ENRICH Kaplan-Meier Survival Curve

All eligible patients through 281 deaths



	Control (n=183)	Efaprox (n=182)
# deaths	145	136
MST (mos.)	7.5	8.5
HR (95% CI)	0.87 (0.68, 1.10)	
P-value	0.233	

Cox Multiple Regression Model

Characteristic	Value	HR* (95% CI)	P-value
Treatment Group	Control	--	0.542
	Efaproxiral	0.93 (0.72, 1.18)	
KPS	70	--	<0.001
	80	0.86 (0.60, 1.21)	
	90	0.67 (0.48, 0.92)	
	100	0.31 (0.18, 0.51)	
Liver Mets	No	--	0.335
	Yes	0.86 (0.64, 1.17)	
Her-2/Neu Status	Negative	--	0.004
	Positive	0.66 (0.50, 0.87)	
	Unknown	1.04 (0.76, 1.44)	
Extracranial Metastatic Sites	0	--	0.202
	1-2	1.20 (0.87, 1.67)	
	>2	1.44 (0.96, 2.16)	

*HR = Hazard Ratio

Cox Multiple Regression Model (cont.)

Characteristic	Value	HR* (95% CI)	P-value
Number of Brain Mets	1	--	0.092
	2-3	1.15 (0.70, 1.90)	
	4-10	1.08 (0.67, 1.73)	
	>10	1.60 (0.95, 2.69)	
	Missing	0.59 (0.21, 1.71)	
Age	< 65	--	0.078
	≥ 65	1.35 (0.97, 1.89)	
Hemoglobin	< 12 g/dL	--	0.522
	≥ 12 g/dL	1.13 (0.83, 1.54)	
	Missing	1.65 (0.63, 4.31)	
Albumin	Normal/High	--	0.049
	Low	1.50 (1.09, 2.07)	
	Missing	1.20 (0.80, 1.80)	

*HR = Hazard Ratio

Overall Survival – Sensitivity Analyses

By subgroup used in stratification

Characteristic	Value	Treatment Group HR (95% CI)*	P-value*
Stratum	1 (KPS 90-100, - liver mets)	0.68 (0.45, 1.04)	0.072
	2 (KPS 90-100, + liver mets)	0.88 (0.52, 1.51)	0.648
	3 (KPS 70-80, - liver mets)	1.23 (0.80, 1.87)	0.345
	4 (KPS 70-80, + liver mets)	0.71 (0.40, 1.25)	0.228
KPS	70	0.98 (0.58, 1.64)	0.937
	80	1.04 (0.67, 1.62)	0.855
	90	0.72 (0.50, 1.03)	0.074
	100	1.46 (0.59, 3.64)	0.411
Liver Mets	No	0.89 (0.66, 1.19)	0.418
	Yes	0.80 (0.54, 1.19)	0.265

*Nominal confidence interval and p-value; not adjusted for multiple testing.

Overall Survival – Sensitivity Analyses

By geographic region

Characteristic	Value	Treatment Group HR (95% CI)*	P-value*
Site location	Canada	0.78 (0.42, 1.45)	0.430
	Europe	0.84 (0.56, 1.28)	0.422
	South America	0.78 (0.51, 1.20)	0.257
	USA	0.97 (0.60, 1.57)	0.890
Selected ex-North America countries (any with >30 pts)	Peru (n=52)	0.88 (0.48, 1.63)	0.688
	France (n=48)	1.03 (0.53, 2.00)	0.933
	Brazil (n=33)	0.58 (0.27, 1.25)	0.159

*Nominal confidence interval and p-value; not adjusted for multiple testing.

Brain Tumor Response at 3-months
Based on Central Radiology Review

	Control (N=183) n (%)	Efaprox (N=182) n (%)	Difference	P-value
CR + PR (confirmed responses only)*	49 (27)	57 (31)	4.5%	0.339
CR + Cru + PR + PRu (confirmed + unconfirmed)	59 (32)	71 (39)	6.8%	0.177

*Pre-specified analysis

KPS and Neurological Signs and Symptoms at 3-months
Percent Stable/Improving from Baseline

	Control (N=183) n (%)	Efaprox (N=182) n (%)	Difference	P-value
KPS*	69 (38)	70 (38)	0.8%	0.882
Headache	103 (56)	112 (59)	5.3%	0.308
Motor	100 (55)	107 (59)	4.1%	0.424
Sensory	108 (59)	110 (60)	1.4%	0.782
Seizure	115 (63)	126 (69)	6.4%	0.198

*Relative to screening

Selected Grade 3/4 Adverse Events

Adverse Event	Control (N=184) n (%)	Efaprox (N=176) n (%)
Overall	53 (29)	65 (37)
Headache	5 (3)	8 (5)
Hypoxia	3 (2)	13 (7)
Fatigue	8 (4)	6 (3)
Vomiting	2 (1)	11 (6)

Conclusions

- The addition of efaproxiral to WBRT did not improve survival for women with brain metastases originating from breast cancer.
- The survival for the control arm was greater than anticipated.
- HER-2 positive patients appeared to survive longer than HER-2 negative patients.
- Additional trials are needed to improve outcomes for these patients.

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Graded Prognostic Assessment (GPA) for brain mets

Evaluated 1960 patients from five randomized RTOG studies

Develop a less subjective, more quantitative, easier to use

	Score		
	0	0.5	1.0
Age	>60	50-59	<50
KPS	<70	70-80	90-100
Number of CNS metastases	>3	2-3	1
Extracranial metastases	Present	-	None

Median survival (months)

3.5-4	11.0
3	6.9
1.5-2.5	3.8
0-1	2.6

Sperduto P Int J Radiat Oncol Biol Phys 70:510, 2008

GPA Score and MST by Arm, ENRICH Study

	Efaprox + WBRT (N=179)		WBRT Alone (N=179)		Total Eligible (N=358*)	
GPA Score	n	MST	n	MST	n	MST
3.5 – 4.0	75	10.8	77	7.9	152	10.0
3	54	7.4	38	7.5	92	7.5
1.5 – 2.5	48	6.0	62	7.1	110	6.8
0 – 1	2	N.E.D.	2	N.E.D.	4	N.E.D

MST = Median survival time in months, N.E.D. = Not enough data

*7 patients did not have measurable intracranial disease so were not assigned a GPA score

Lessons from RT-016

- Survival was better than predicted, ie. RPA was not accurate; hard endpoint to achieve
- Enrollment was slower than expected, ie. US sites did not want to give WBRT
- Confirmed radiographic response w/ WBRT was 30%
- Neurocognitive testing/QOL was not done
- Did not stratify patients based on other factors such as her-2/neu status