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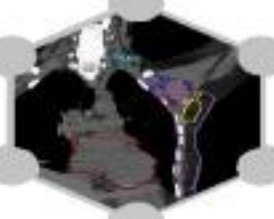

Significant Preservation of Neurocognitive Function and Patient-Reported Symptoms with Hippocampal Avoidance during Whole-Brain Radiotherapy for Brain Metastases: Final Results of NRG Oncology CC001

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*Co-Principal Investigators contributed equally to this work.

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Disclosures for Dr. Gondi

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Background

- Whole-brain radiotherapy is associated with cognitive toxicity
  - 1-4 brain metastases: N0574[1], N107C[2], MD Anderson trial[3]
  - Declining use of WBRT, rising use of radiosurgery

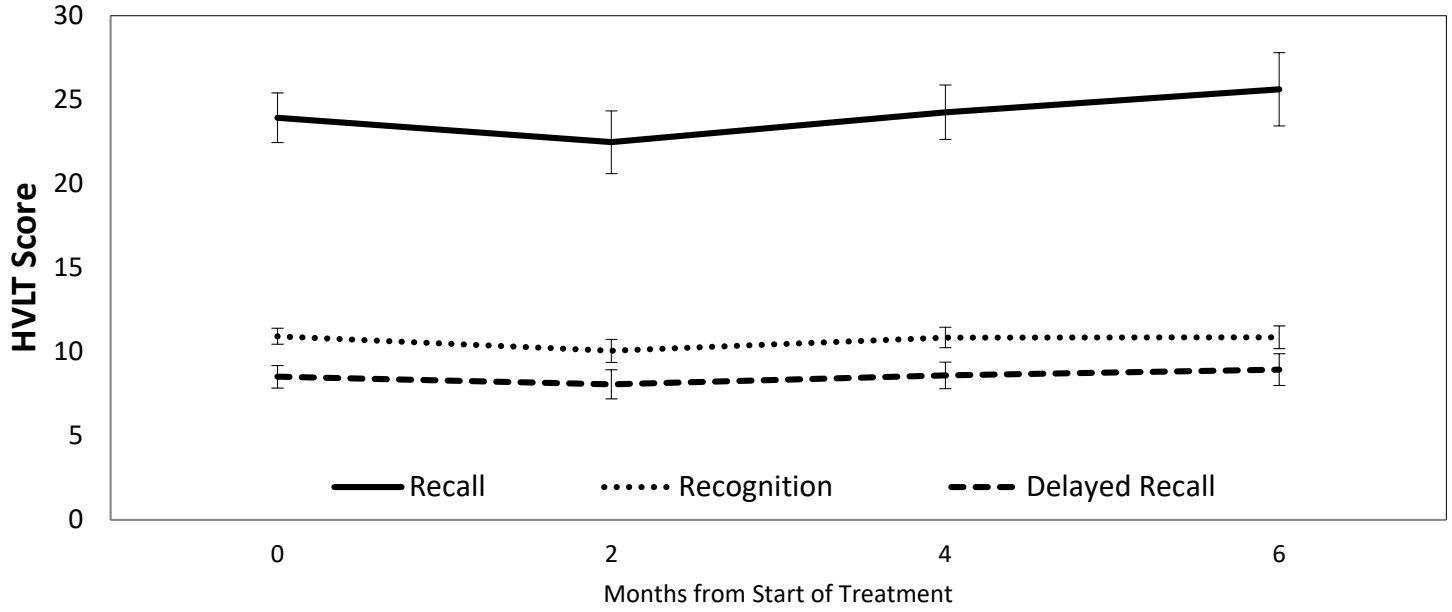
- Neuroregenerative stem cells within the hippocampal dentate gyrus are exquisitely radiosensitive and important to cognition
  - Preclinical/clinical evidence supports the hippocampal dentate gyrus as a memory-specific and radiosensitive structure-at-risk[4]

Hypothesis: Hippocampal avoidance using IMRT prevents cognitive toxicity from WBRT

[1]Brown et al. JAMA 2016
[2]Brown et al. Lancet Oncol 2017
[3]Chang et al. Lancet Oncol 2009
[4]Gondi et al. R&O 2010

RTOG 0933

- Single-arm phase II trial of HA-WBRT (30 Gy in 10 fractions)
  - Credentialing and central review of hippocampal contouring and IMRT planning



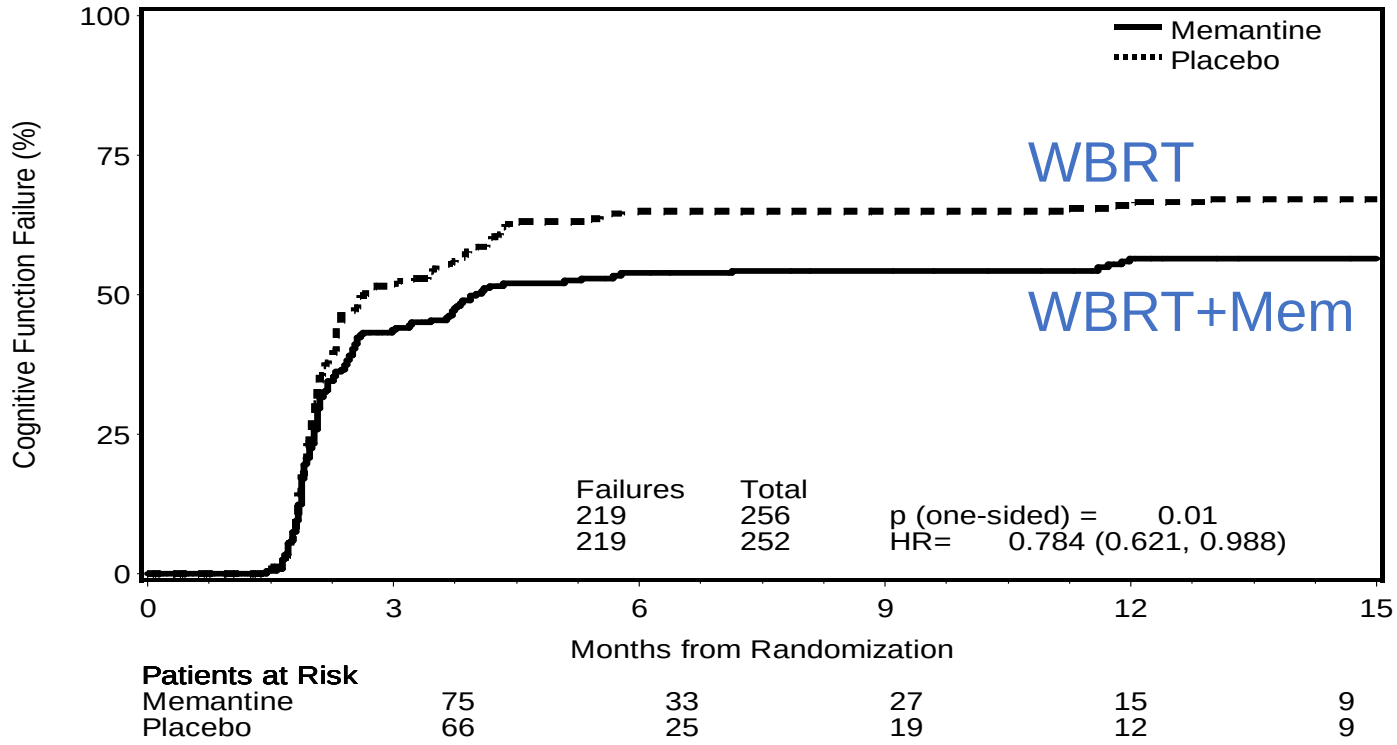
- **Mean decline in HVLT-Delayed Recall from baseline to 4 months:7.0% (95% CI: -4.7-18.7%)**
- Significantly less compared to historical control: 30% (*p*=0.0003)

Need phase III data for level I evidence

Gondi et al. JCO 2014

RTOG 0614

- Phase III trial of WBRT with or without memantine

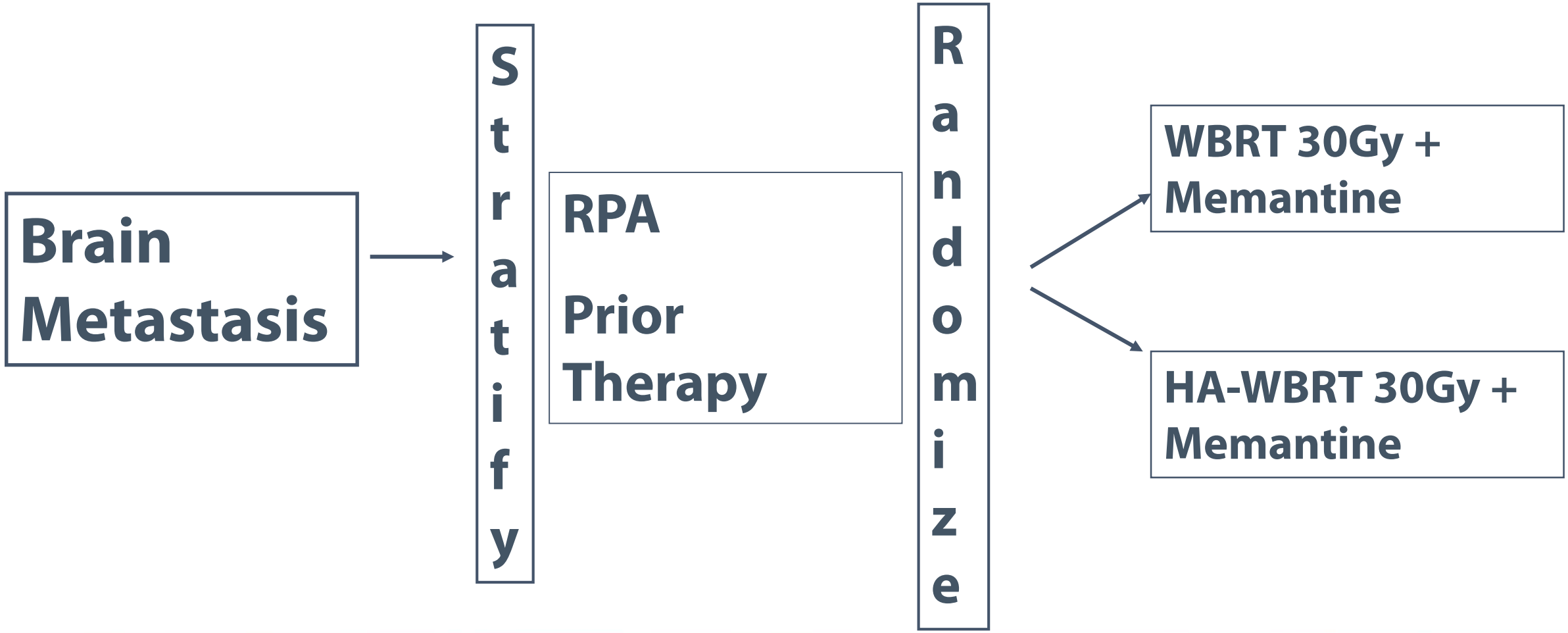


Memantine during WBRT considered standard of care

Brown et al. Neuro-Oncol 2013

NRG-CC001: Phase III Trial Memantine and WBRT with or without Hippocampal Avoidance in Patients with Brain Metastases

Basic Eligibility: Brain metastases 5mm outside hippocampus; KPS≥70; 3D MRI scan; hydrocephalus/ventricular distortion excluded; baseline NCF testing



Trial Design

- Primary endpoint: Time to cognitive failure
  - Cognitive battery: Hopkins Verbal Learning Test-Revised, Controlled Oral Word Association, Trail Making Test
  - Cognitive failure: reliable change index defined decline on one or more tests
  - Cumulative incidence to estimate time to cognitive failure
    - Death without cognitive failure treated as competing risk
  - Secondary endpoints: patient-reported symptom burden (MDASI-BT), toxicity, progression-free and overall survival
- Probability of cognitive failure
  - Overall HR = 0.65
  - 382 analyzable patients for 90% power and two-sided α=0.05
  - Sample size increased by 25% for possible non-compliance

Target Accrual: 510 patients

Baseline Characteristics

518 randomized patients

Baseline	WBRT+Mem n=257	HA-WBRT+Mem n=261	*p* value
Age	Median 61	Median 62	0.66
RPA class	Class I: 14.8% Class II: 85.2%	Class I: 12.6% Class II: 87.4%	0.48
Neurologic symptoms	None: 46.3% Minor: 33.5%	None: 43.3% Minor: 35.2%	0.83
Primary tumor	Lung 58.8% Breast 17.5%	Lung 59.8% Breast 19.5%	0.81
KPS	70: 20.6% 80: 29.2% 90-100: 50.2%	70: 18.4% 80: 31.0% 90-100: 50.6%	0.38

No differences in baseline patient characteristics, including cognitive function and patient-reported symptom burden

Toxicity

Toxicity	WBRT+Mem n=257	HA-WBRT+Mem n=261	*p* value
Any relation	Grade 3: 89 (38.4%) Grade 4: 20 (8.6%) Grade 5: 35 (15.1%) **Grade 3+: 144 (62.1%)**	Grade 3: 70 (31.4%) Grade 4: 25 (11.2%) Grade 5: 36 (16.1%) **Grade 3+: 131 (58.7%)**	0.47
Treatment-related toxicity	Grade 3: 36 (15.5%) Grade 4: 7 (3.0%) Grade 5: 3 (1.3%) **Grade 3+: 46 (19.8%)**	Grade 3: 36 (16.1%) Grade 4: 4 (1.8%) Grade 5: 3 (1.3%) **Grade 3+: 43 (19.3%)**	0.88

Treatment-related grade 5 toxicities:

WBRT+mem: Neoplasms benign, malignant and unspecified (n=3)

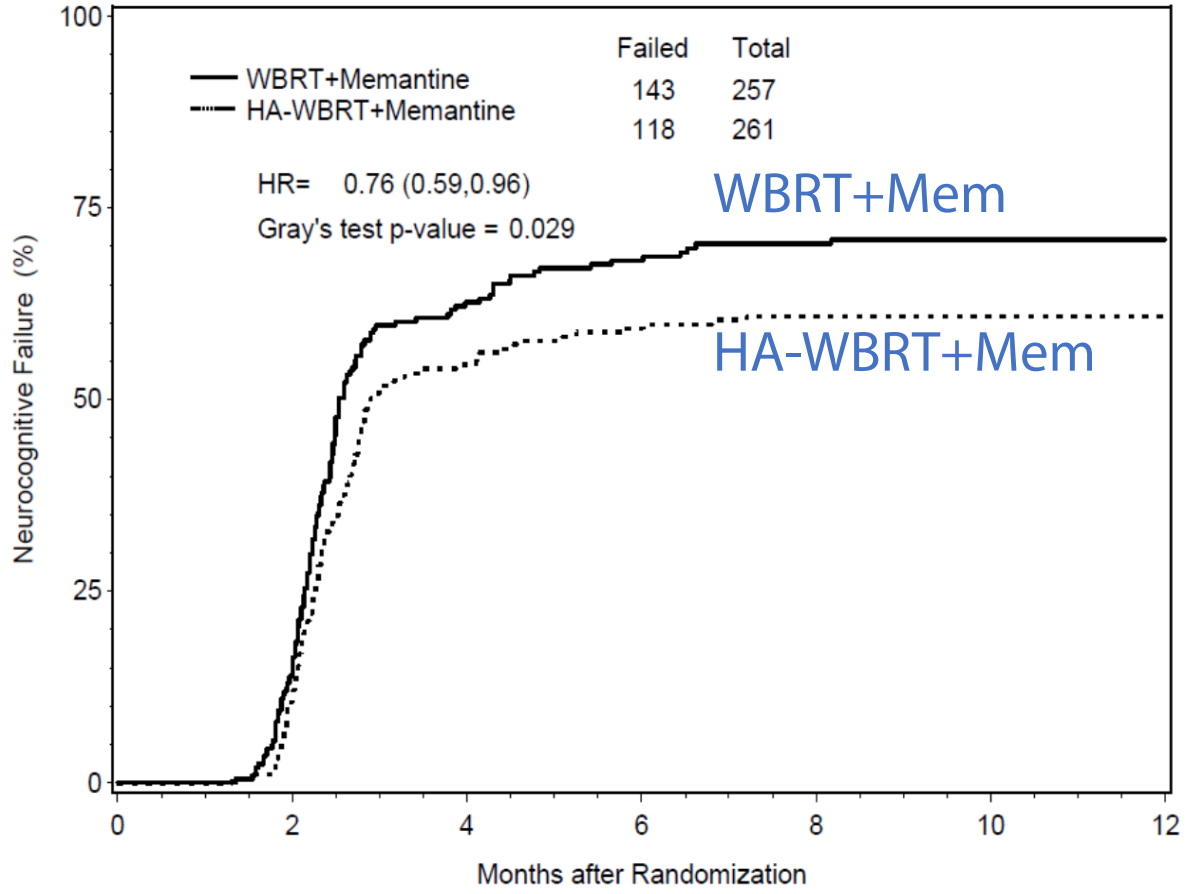
HA-WBRT+mem: Gen d/o's and administration site conditions (n=2, possible)

Somnolence (n=1, possible, 64d after tx start)

No differences in any or treatment-related toxicity

Primary Endpoint

- Hippocampal avoidance <u>prevents cognitive function failure</u>
  - Hazard ratio = 0.756 p=0.029
  - Separation of the curves starting at 3 months and maintained through the follow-up period



Patients at Risk

WBRT+Memantine	257	133	34	19	11	9	5
HA-WBRT+Memantine	261	124	40	27	22	21	14

Median follow-up for alive patients: **12.1 months**

Primary Endpoint

- Hippocampal avoidance <u>prevents cognitive function failure</u>
  - 26% relative risk reduction
- Multivariate analysis: Treatment arm and age
- No interaction between treatment arm and age
  - Effect of treatment remains significant independent of age

Variable	HR	95% CI	*p* value
Treatment arm (HA-WBRT+Mem vs. WBRT+Mem[RL])	**0.74**	**0.58-0.94**	**0.016**
Age (≤61 vs. >61[RL])	**0.61**	**0.47-0.80**	**0.0003**
RPA Class* (I vs. II[RL])	1.36	0.98-1.87	0.063
Prior radiosurgery* (No vs. Yes[RL])	0.82	0.62-1.08	0.158
Prior surgery* (No vs. Yes[RL])	1.10	0.84-1.44	0.504

*Stratification factor
[RL]: Reference level

Median follow-up for alive patients: **12.1 months**

Cognition Domains at 4 Months

- Hippocampal avoidance reduces deterioration of
  - 4 months: Executive function (Trail Making Test B)

Deterioration at 4 months:

Cognitive Domain	WBRT +Mem n=109	HA-WBRT +Mem n=93	*p*
HVLT-R Total Recall	35.5%	29.0%	0.33
HVLT-R Delayed Recall	33.0%	24.7%	0.19
HVLT-R Recognition	24.8%	14.0%	0.055
Trail Making Test Part A	24.8%	20.4%	0.46
Trail Making Test Part B	**40.4%**	**23.3%**	**0.012**
Controlled Oral Word Association	12.1%	10.5%	0.73

Median follow-up for alive patients: **12.1 months**

Cognition Domains at 6 Months

- Hippocampal avoidance reduces deterioration of
  - 4 months: Executive function (Trail Making Test B)
  - 6 months: Learning and memory (HVLT-R Recognition)

Deterioration at 6 months:

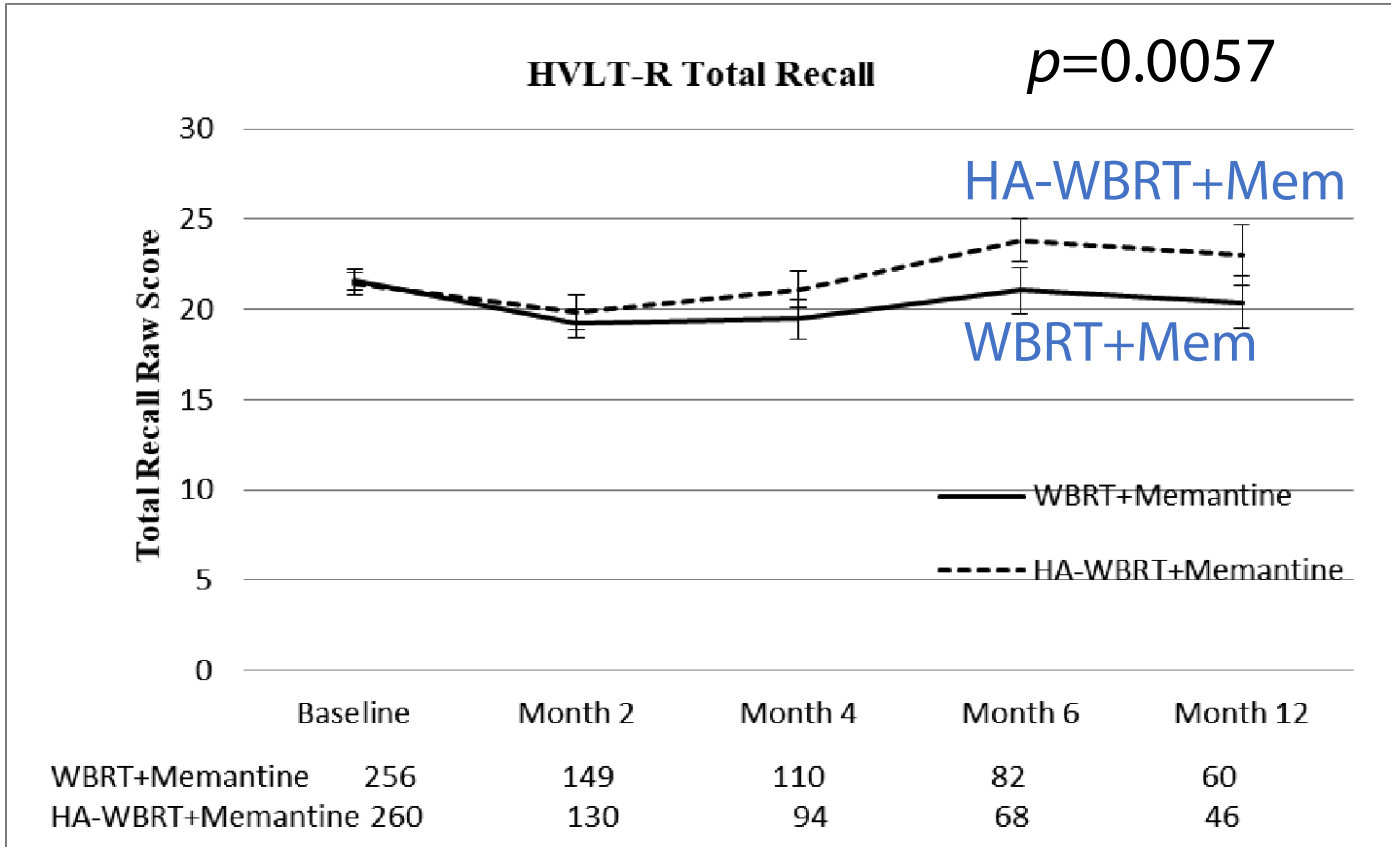
Cognitive Domain	WBRT +Mem n=77	HA-WBRT +Mem n=61	*p*
HVLT-R Total Recall	26.8%	14.7%	0.07
HVLT-R Delayed Recall	30.0%	20.6%	0.19
HVLT-R Recognition	**36.3%**	**17.6%**	**0.011**
Trail Making Test Part A	28.0%	17.6%	0.13
Trail Making Test Part B	35.9%	23.9%	0.12
Controlled Oral Word Association	6.2%	11.8%	0.23

Median follow-up for alive patients: **12.1 months**

Cognition Domains Over Time

- Hippocampal avoidance reduces deterioration of
  - 4 months: Executive function (Trail Making Test B)
  - 6 months: Learning and memory (HVLT-R Recognition)
- Hippocampal avoidance preserves all learning and memory domains over time
  - HVLT-R total recall, delayed recall and recognition

Mixed effects models using multiple imputation:



Higher score indicates better performance

Median follow-up for alive patients: **12.1 months**

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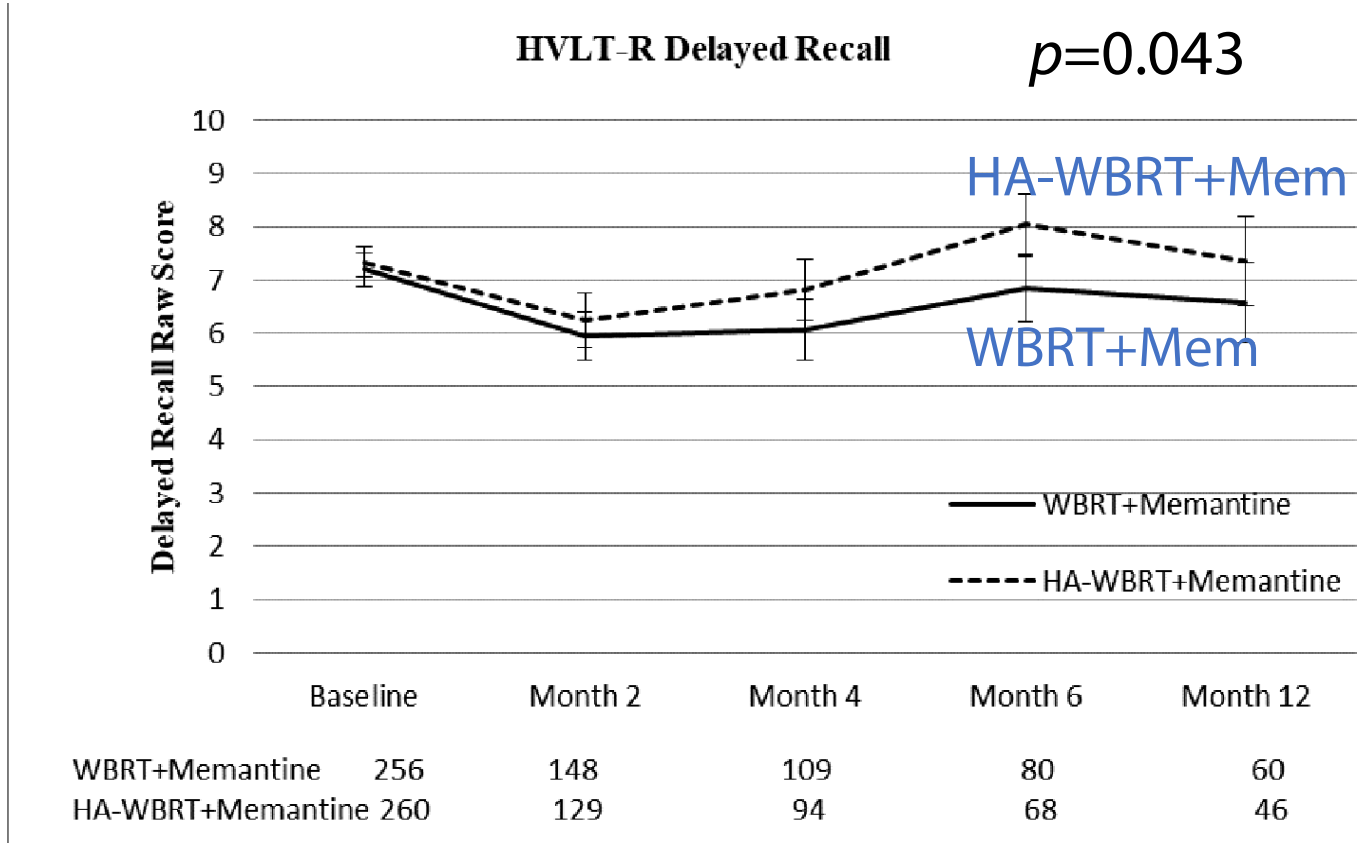

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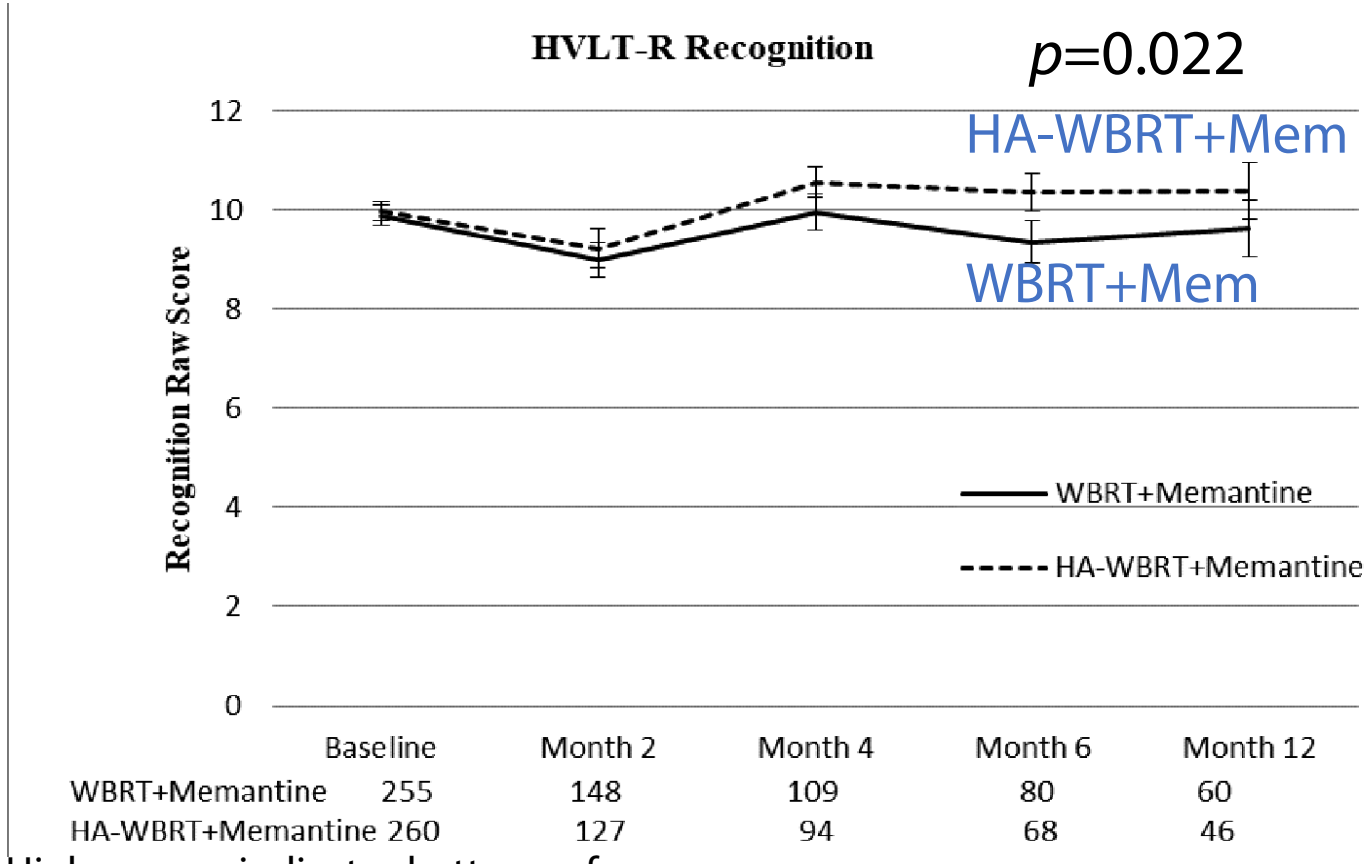


Higher score indicates better performance

Median follow-up for alive patients: **12.1 months**

Patient-Reported Symptom Burden

- Hippocampal avoidance preserves patient-reported symptoms at 6 months:
  - Neurologic symptom burden
  - Interference of neurologic symptoms in daily activities

Change from Baseline to 6 months:

Variable	Estimate	p value	Estimate	p value
	Complete Data		Imputed Data	
Symptom	-0.26	0.083	**-1.37**	**<0.001***
Interference	**-5.07**	**0.003***	**-1.93**	**0.0016***
Cognitive factor	-0.05	0.77	-0.17	0.35
Neurologic factor	0.213	0.32	-0.13	0.56

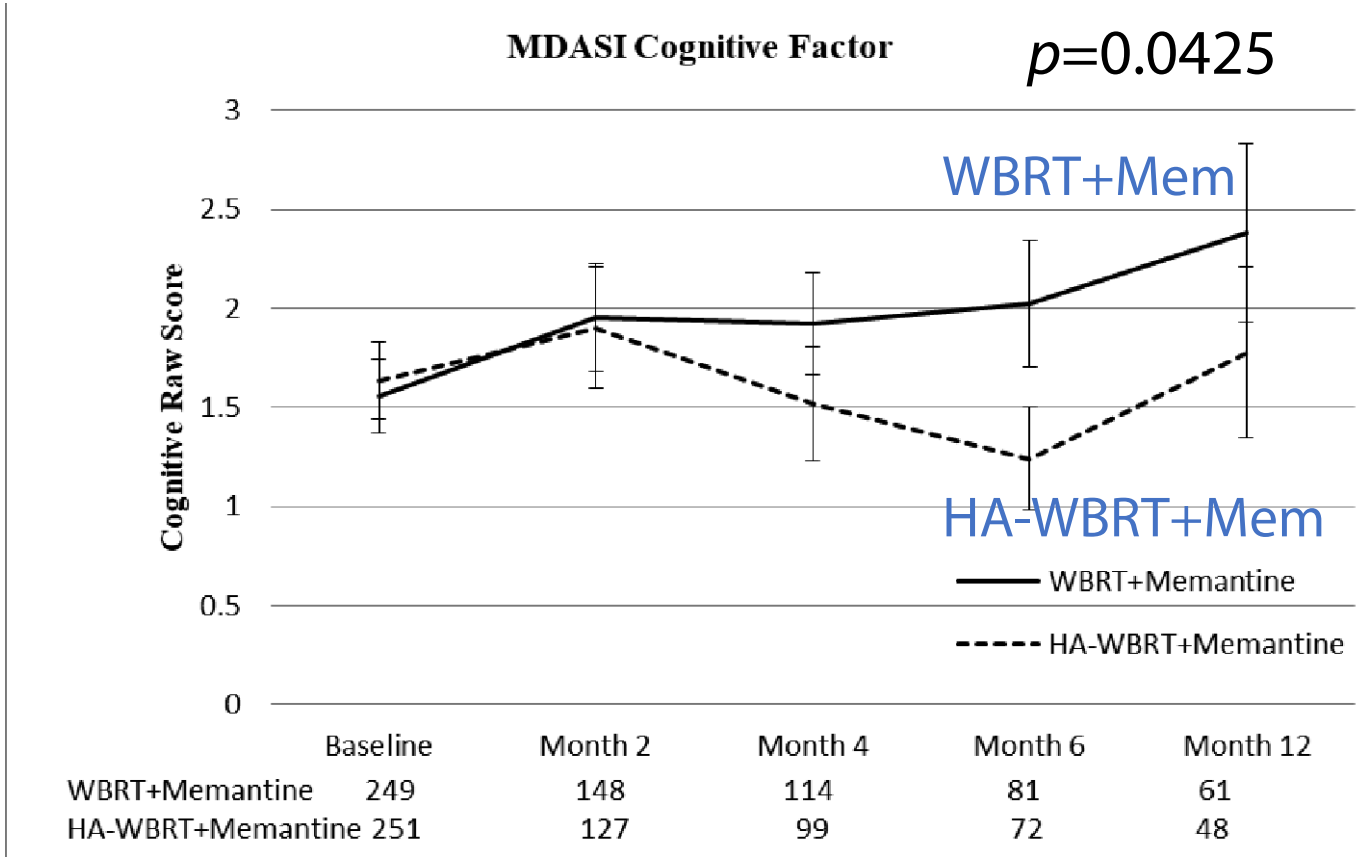
*Significant using Hochburg's multiplicity adjustment

Median follow-up for alive patients: **12.1 months**

Patient-Reported Outcomes

- Hippocampal avoidance preserves patient-reported symptoms at 6 months:
  - Neurologic symptom burden
  - Interference of neurologic symptoms in daily activities
- Hippocampal avoidance preserves patient-reported cognitive factor over time:
  - Hippocampal avoidance associated with less problems remembering things at 6 months (p=0.016)

Mixed effects models using multiple imputation:



Higher score indicates more symptoms

Median follow-up for alive patients: **12.1 months**

Survival

Toxicity	WBRT+Mem n=257	HA-WBRT+Mem n=261	*p* value
Intracranial Progression-Free Survival	Median: 5.3 months 95% CI: 4.7-6.0	Median: 5.0 months 95% CI: 4.4-6.2	**0.076**
	HR = 1.20 95% CI: 0.98-1.47		
Overall Survival	Median: 7.6 months 95% CI: 5.8-10.1	Median: 6.3 months 95% CI: 4.0-7.7	**0.242**
	HR = 1.14 95% CI: 0.91-1.43		

No significant differences in intracranial PFS or overall survival

HA region relapses:

HA-WBRT+Mem 11 WBRT+Mem 17

Median follow-up for alive patients: **12.1 months**

Conclusions

- Hippocampal avoidance during WBRT plus memantine preserves cognitive function and patient-reported symptoms in brain metastasis patients
  - Improvements in patient-reported cognition over time and 6-month change in neurologic symptom burden, interference of neurologic symptoms with daily activities, and problems remembering things
  - Benefits in executive functioning at 4 mos, recognition at 4 and 6 mos, and all domains of learning and memory over time
  - Similar toxicity, intracranial PFS and overall survival outcomes

For brain metastasis patients eligible to receive WBRT and whose survival is expected to be 4 months or longer, hippocampal avoidance using IMRT should be considered standard of care.

Conclusions

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2019
Central Nervous System Cancers

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Discussion

PRINCIPLES OF RADIATION THERAPY FOR BRAIN AND SPINAL CORD

Brain Metastases

- WBRT: Doses vary between 20 and 40 Gy delivered in 5–20 fractions.
  - The standard regimens include 30 Gy in 10 fractions or 37.5 Gy in 15 fractions.
  - Nevertheless, 20 Gy in 5 fractions is a good option for patients with poor predicted prognosis.[19]
  - For patients with a better prognosis, consider memantine during and after WBRT for a total of 6 months.[20]
  - For patients with a better prognosis (4 months or greater), consider hippocampal-sparing WBRT.[21-22]

For brain metastasis patients eligible to receive WBRT and whose survival is expected to be 4 months or longer, hippocampal avoidance using IMRT should be considered standard of care.

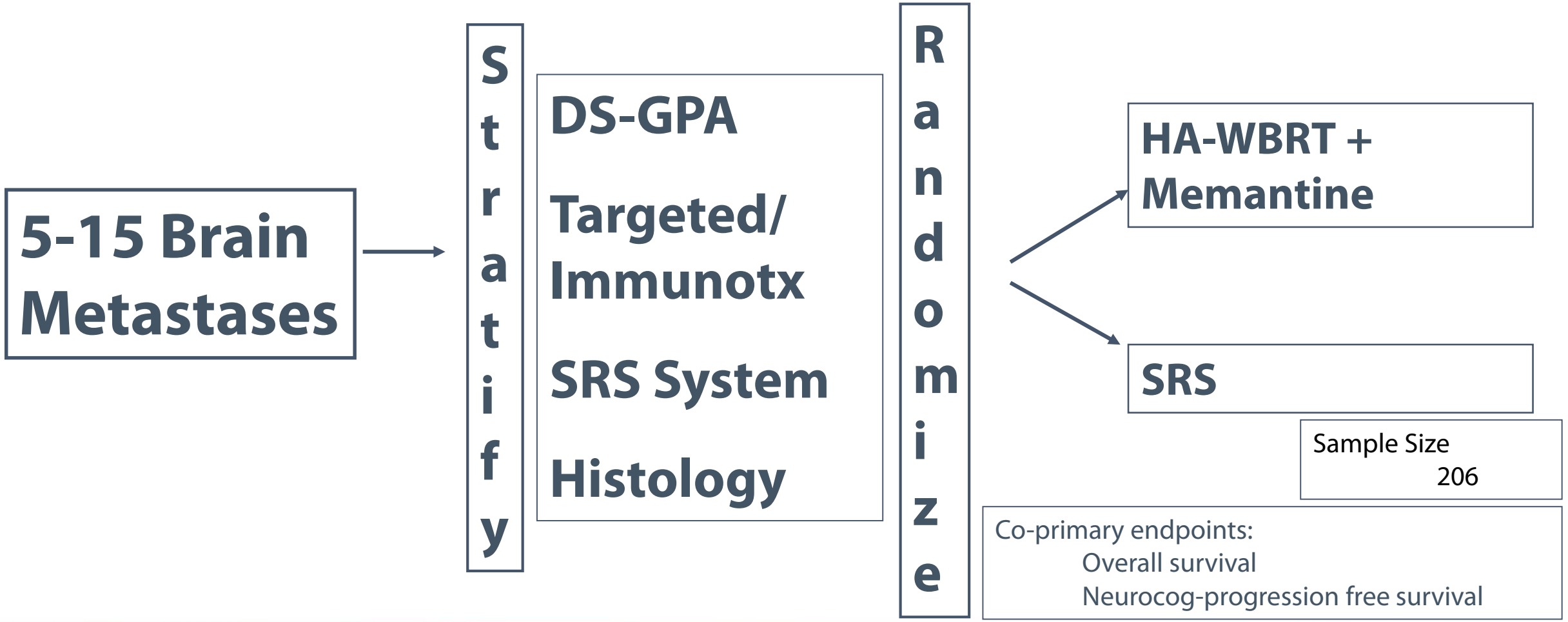
Conclusions

- Contributes to debate over SRS vs. WBRT for brain metastases
  - RTOG 0614: HR=0.78 with addition of memantine to WBRT
  - NRG CC001: HR=0.74 with addition of HA to WBRT+memantine
  - Combined HR with memantine+HA = 0.78 x 0.74 = 0.58

Comparable to phase III trials favoring SRS in lieu of WBRT

CCTG CE.7: Phase III Trial Stereotactic Radiosurgery versus Hippocampal Avoidant WBRT+memantine for 5-15 Brain Metastases

Basic Eligibility: 5-15 brain mets; largest met <2.5cm; total brain met vol ≤30cc



Conclusions

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  - RTOG 0614: HR=0.78 with addition of memantine to WBRT
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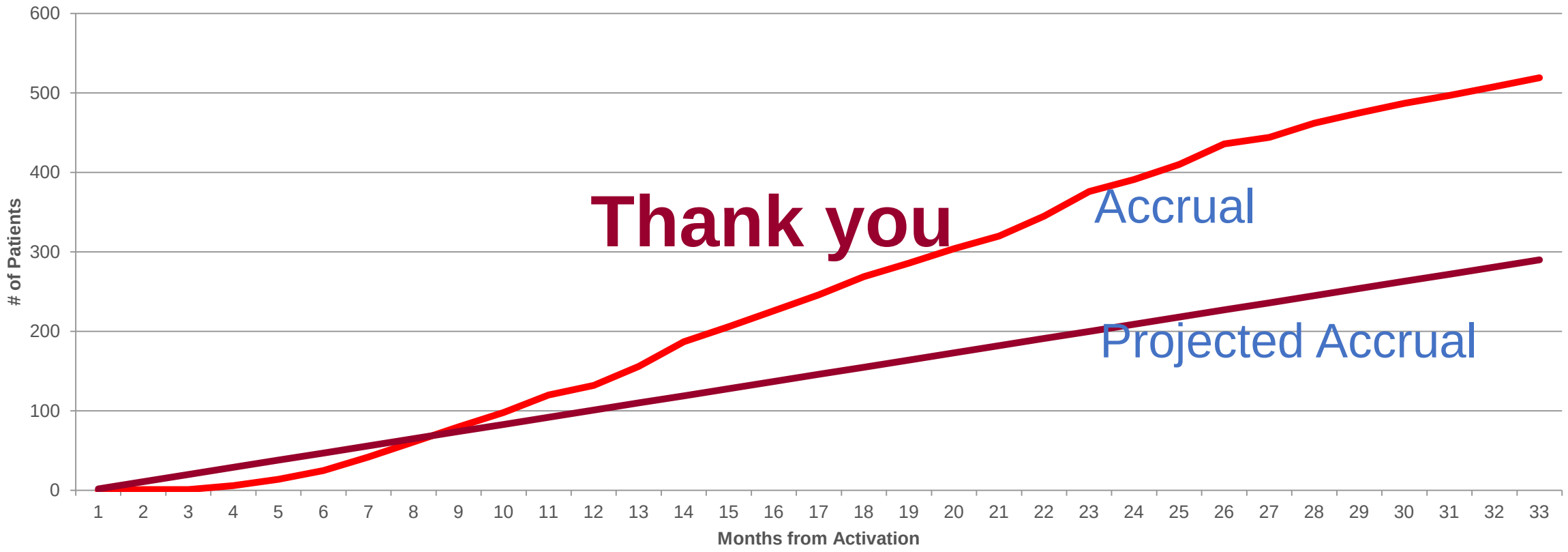
  - Combined HR with memantine+HA = 0.78 x 0.74 = 0.58

Comparable to phase III trials favoring SRS in lieu of WBRT

- Evidence strongly supports hippocampal radiosensitivity
  - Radiosensitivity of regenerative stem cell niche in the hippocampal dentate gyrus is central to cognitive effects of brain irradiation
  - Builds upon decades of preclinical/clinical research on the pathophysiology of hippocampal radiosenstivity

Supports the hippocampus as a cognition-specific organ at risk for all forms of brain irradiation

NRG CC001 Accrual



Accrual 16 pts/month Completed 2 years earlier than projected

Community's interest in developing safer approaches to deliver WBRT