A Phase III Randomized Study of Ramipril and Memantine Against Radiation-Induced Cognitive Decline

Brandi R. Page, M.D.
Michael D. Chan, M.D.
Ann M. Peiffer, Ph.D.
Edward G. Shaw, M.D., M.A.

Brain Radiotherapy
Why is cytoprotection relevant?

- 200,000 patients/year receive brain radiotherapy
- Increasing # long-term survivors with better cancer treatments
  - Increasing rate of long term cognitive effects
- No successful therapies for cognitive decline once symptoms onset
- Elderly patients at higher risk
  - Vascular comorbidities
- Preclinical data shows promise with ACE-I
  - Suggests cytoprotection is a potential mechanism to ameliorate cognitive decline after brain RT

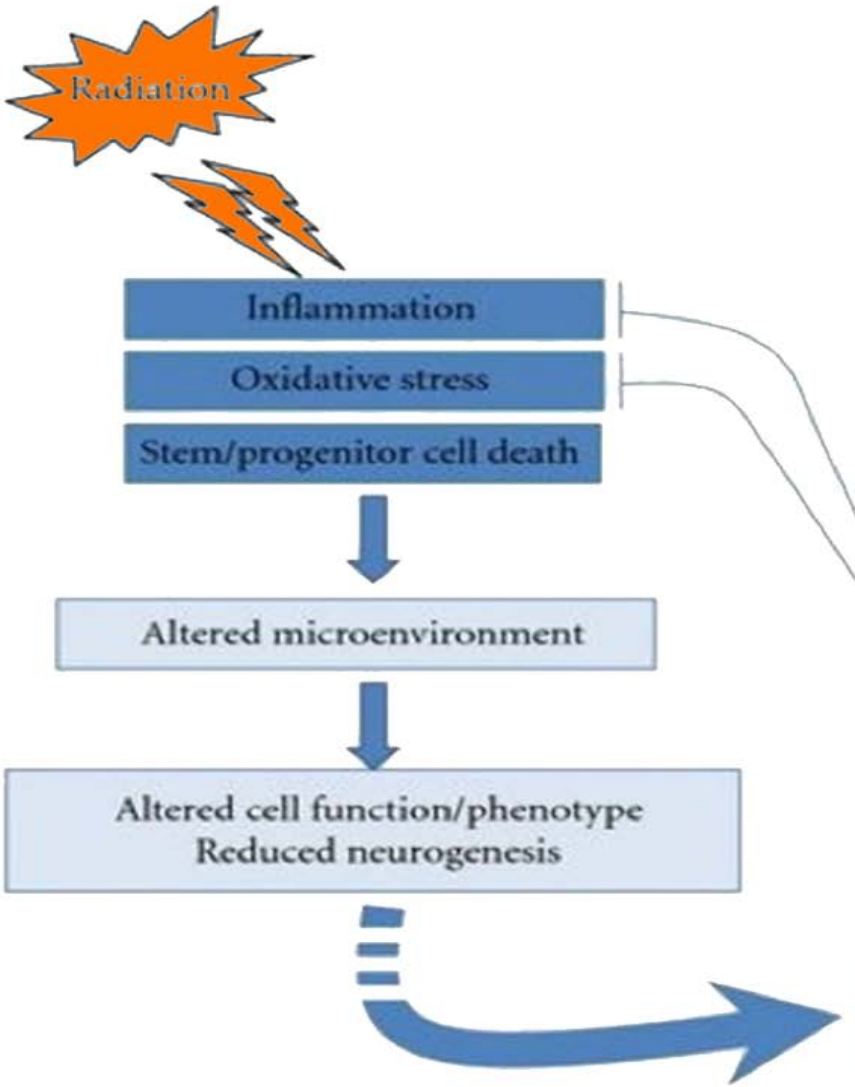
Brain Radiotherapy
Why is cytoprotection relevant?

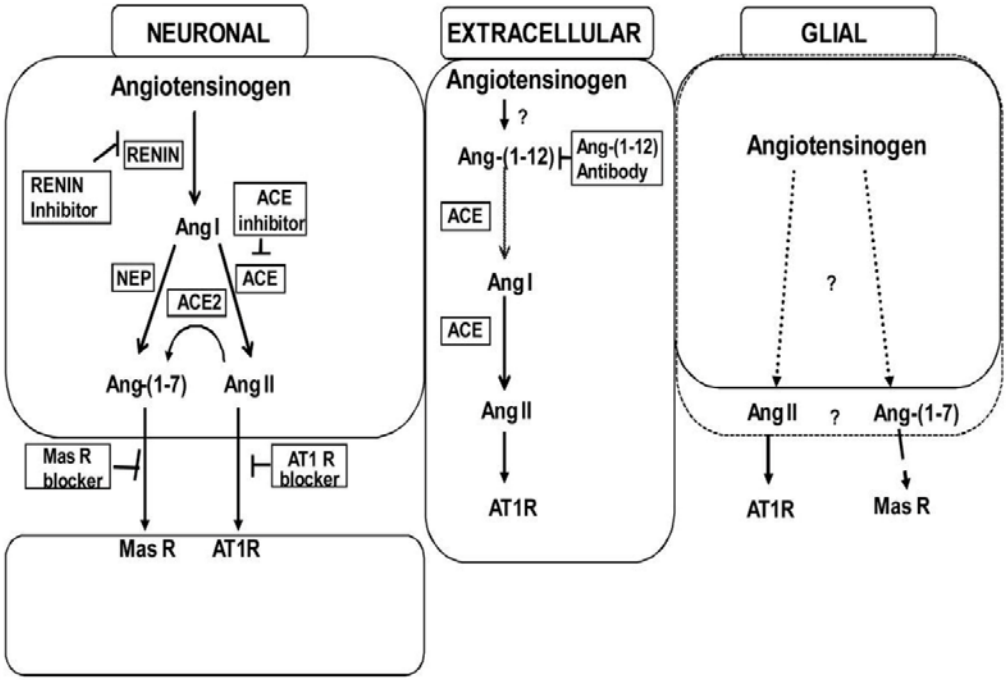
Preclinical Data for Cytoprotection & Amelioration of WBI-induced Cognitive Decline

Author	Agent	Animal Model	Outcome
Jenrow	Ramipril	Rat	Improved neurogenesis
Lee	Ramipril	Rat	Reduced cognitive decline

- Other Common Clinical Indications for Ramipril
  - Stroke prevention (HOPE trial)
  - Hypertension

Mechanism of Cytoprotection- ACE I

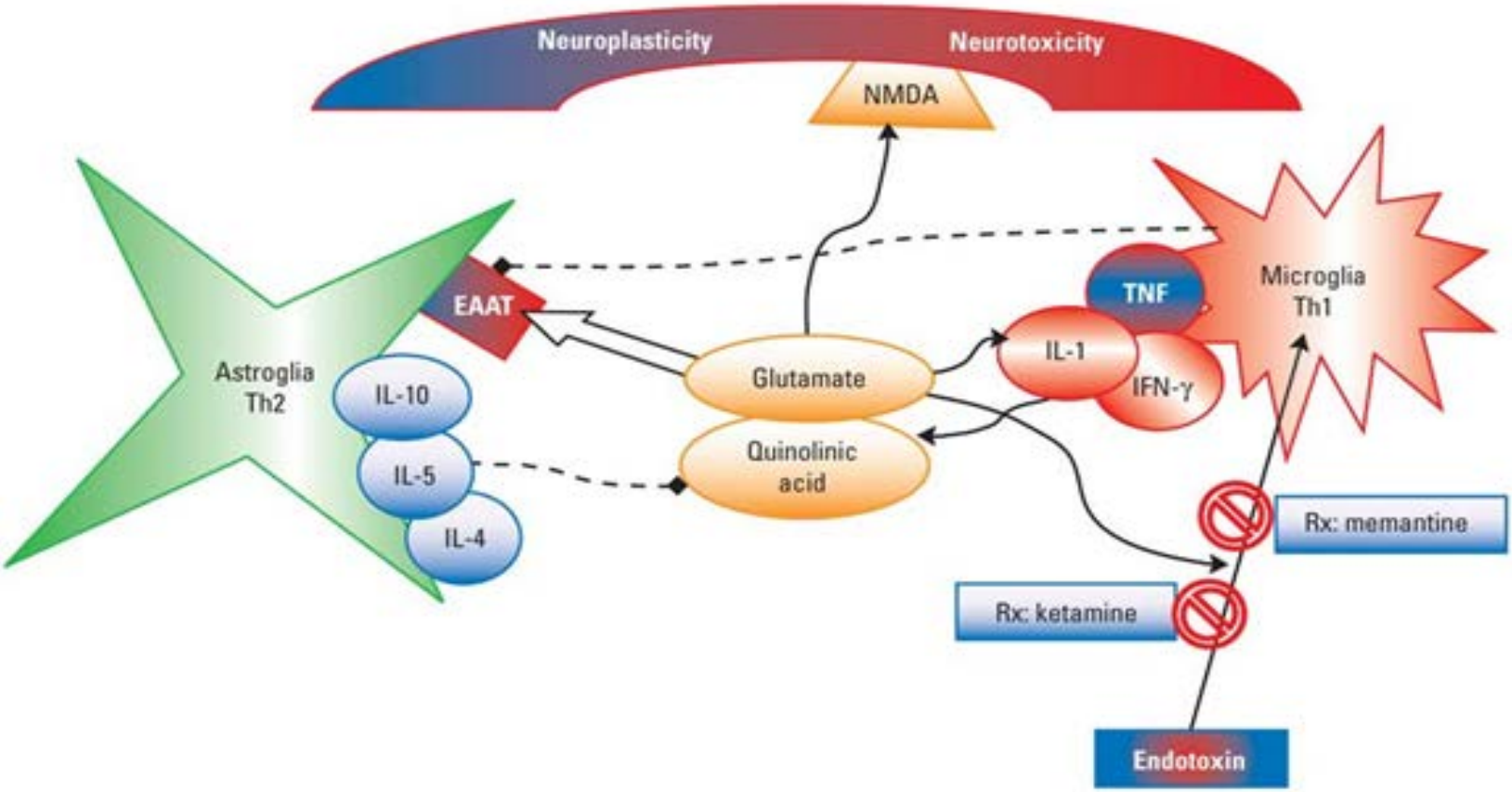




Reactive Oxygenase Species

Mechanism of Memantine

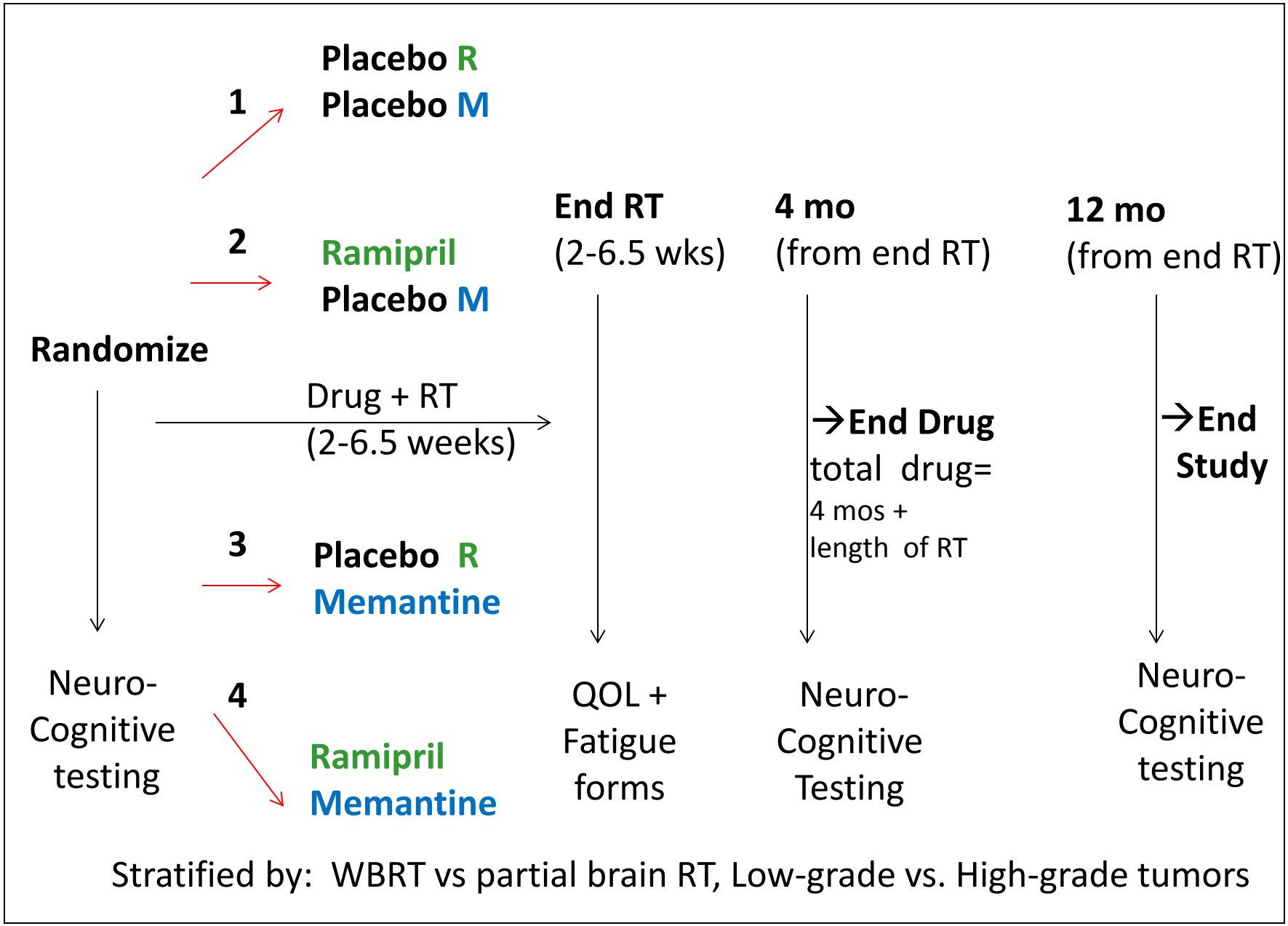
- NMDA Receptor Antagonist
- Targets NMDA receptors, inhibits prolonged influx of Ca++
- Reduces overstimulation and excitotoxicity of neurons
- Used for decrease in clinical deterioration in moderate to severe Alzheimer's disease
- McNally et al *CNS Spectr*. 2008;13(6):501-510



Previous Clinical Data: Memantine vs. Placebo (RTOG 0614)

- Memantine vs. Placebo for patients receiving WBRT
- 20 mg Memantine initiated <3 days of starting RT
- 1° Outcome: Memory (HVLT)
  - No improvement with memantine
- 2° Outcome: Cognition (Trail Making tests A and B, COWA, Medical Outcomes Cognitive Scale, MMSE)
  - Memantine arm had improved cognitive function at 24 weeks, longer time to cognitive decline, and superior executive function.
- Conclusion:
  - Treatment with memantine should be considered to maintain cognitive function

Schema: Memantine vs. Ramipril



Inclusion Criteria

- Patients with ≥12 month prognosis for survival
- ≥16 y/o, KPS ≥60
- Must receive ≥30 Gy partial brain or Whole Brain RT
- Can receive chemotherapy

Low Grade Histologies	High Grade Histologies
■Low grade glioma ■Meningioma ■Pituitary adenoma ■Craniopharyngioma ■Chordoma ■Chondrosarcoma	■Germ cell tumors ■PNET/medulloblastoma ■Anaplastic Astrocytoma or Oligodendroglioma ■Ependymoma ■RPA Class III/IV GBM ■RPA III: Age < 50, KPS ≥ 90 ■RPA IV: Age < 50, KPS < 90 OR Age < 50, KPS < 90 ■Brain Metastases ■NSCLC, SCLC, Melanoma, Renal Cell, GI Cancer: GPA Score ≥3.5 ■Breast Cancer: GPA Score ≥3

Exclusion Criteria

- Prior allergic reaction to ACE inhibitor or memantine
- Hypotension (CTCAE Grade $\geq$3)
- Renal insufficiency
  - Creatinine clearance (<40 ml/min)
  - History of solitary kidney or renal arterial stenosis
- Pregnant
- Currently on ACE inhibitor/ARB
- Current use of centrally acting medications for dementia
  - Cholinesterase inhibitors: Donepezil , Galantamine, Rivastigmine
  - Antipsychotics : Clozapine, Risperdone, Aripiprazole, Olanzapine, Quetiapine, Ziprasidone
- KPS<60
- Unstable comorbid medical conditions requiring hospitalization
  - (COPD, MI, CHF, unstable angina)

Enrollment

- Phase III Clinical Trial
  - 267 patients
    - Includes estimated 25-30% attrition based on prior CCOP trials
    - 90% power to detect an absolute difference of 2 units on the HVLT
  - Goal 8 patients accrual per month =2.7 years
    - 2 x 2 design

	HVLT-DR Score (Placebo)	HVLT-DR score (20 mg Memantine)
Placebo		
10 mg Ramipril		

Endpoints

- Primary:
  - Hopkins Verbal Learning Test –Delayed Recall at 4 months
- Secondary:
  - Neurocognitive Function and Quality of Life at Baseline, 4, and 12 months from end of RT.
  - QOL at end of RT.
  - Imaging (done as per clinician judgment)

Hopkins Verbal Learning Test-DR **Trailmaking A/B** **COWA** **Digit Span Test**	**FACT- COG** **Brief Fatigue Inventory (BFI)** **PH-Q9**

*Power the study to detect change in HVLT-DR (memory) as primary outcome measure

Thank You

If there are questions…

Drug Administration

Starts the day before RT

Ramipril	Daily AM Dose	Daily PM Dose
Week 1	2.5 mg	None
Week 2	5 mg	None
Week 3 until “end drug”	10 mg	None

Memantine	Daily AM Dose	Daily PM Dose
Week 1	5 mg	None
Week 2	5 mg	5 mg
Week 3	10 mg	5 mg
Week 4 until “end drug”	10 mg	10 mg

- INCLUSION CRITERIA:
  - Determining Eligibility for patients with Brain metastases
- Include NSCLC, SCLC, Melanoma, Renal Cell, GI cancer Patients with GPA score of ≥3.5, or Breast Cancer patients with score ≥3.0

Graded Prognostic Assessment for patients with Brain Metastases

Sperduto et al. "Diagnostic-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi-institutional analysis of 4,259 patients." Int J. Radiation Biol Phys Vol 77, Number 3, 2010

Table 4. Median survival stratified by diagnosis and diagnosis-specific GPA score for patients with newly diagnosed BMs

		DS-GPA			
Diagnosis	Overall	0–1.0	1.5–2.5	3.0	3.5–4.0
NSCLC	7.00 (6.53–7.50)	3.02 (2.63–3.84)	6.53 (5.90–7.10)	11.33 (9.43–13.10)	14.78 (11.79–18.80)
SCLC	4.90 (4.30–6.20)	2.79 (2.04–3.12)	5.30 (4.63–6.83)	9.63 (7.50–14.95)	17.05 (6.10–27.43)
Melanoma	6.74 (5.90–7.57)	3.38 (2.73–4.27)	4.70 (4.17–5.42)	8.77 (6.83–10.77)	13.23 (9.40–15.64)
RCC	9.63 (7.66–10.91)	3.27 (2.17–5.10)	7.29 (3.73–10.91)	11.27 (8.83–14.80)	14.77 (9.72–19.79)
Breast cancer	11.93 (9.69–12.85)	6.11 (3.88–8.28)	9.37 (7.92–11.24)	16.89 (13.96–19.90)	18.74 (11.31–29.37)
GI cancer	5.36 (4.30–6.30)	3.13 (2.40–4.57)	4.40 (3.37–6.53)	6.87 (5.03–11.63)	13.54 (9.92–27.12)
Other	6.37 (5.22–7.49)	—	—	—	—
Total	7.23 (6.90–7.60)	3.43† (3.02–3.84)	6.40† (5.78–6.90)	11.56† (10.47–12.78)	14.77† (12.85–17.05)

Abbreviations: DS-GPA = diagnosis-specific graded prognostic assessment; other abbreviations as in Table 1.
Data in parentheses are 95% confidence intervals.

Patient Inclusion: Brain Mets

- Sum of Four factors by Histology gives overall Score
- Age, KPS, Extracranial metastases, Number of Brain metastases
- Histology: NSCLC/SCLC, Melanoma/Renal Cell Carcinoma, Breast/GI cancer
- Score patients with brain metastases based on the table below

Table 3. Definition of diagnosis-specific graded prognostic assessment indexes for patients with newly diagnosed brain metastases

GPA of newly diagnosed BMs	Significant prognostic factors	GPA scoring criteria				
NSCLC/SCLC		0	0.5	1	—	—
	Age	>60	50–60	<50	—	—
	KPS	<70	70–80	90–100	—	—
	ECM	Present	—	Absent	—	—
	No. of BMs	>3	2–3	1	—	—
Melanoma/ renal cell cancer		0	1	2	—	—
	KPS	<70	70–80	90–100	—	—
	No. of BMs	>3	2–3	1	—	—
Breast/GI cancer		0	1	2	3	4
	KPS	<70	70	80	90	100

Abbreviations: GPA = graded prognostic assessment; other abbreviations as in Table 1.

For all diagnoses, GPA of 4.0 indicates best prognosis and 0.0 indicates worst.

- 3-4% of patients on previous TRAIT study (patients getting brain radiotherapy at WFUBMC) are concurrently on an ACE-I or ARB