

Innovative Trial Concepts for Brain Metastases

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Not surprisingly, most of them are negative!

In fact, the only positive trials...

- In terms of improved survival have focused on enhanced local control of single brain metastases
 - Patchell et al, surgery + WBRT
 - But not Mintz et al, also surgery + WBRT
 - Andrews et al, SRS + WBRT

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- In terms of improved survival have focused on enhanced local control of single brain metastases
 - Patchell et al, surgery + WBRT
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- Implying that improved intracranial control can translate into improved survival if the systemic burden is low enough to allow the benefit of intracranial control to emerge.

What are the Right Endpoints?

- Overall survival
- Intracranial control/progression
- Neurologic symptom control/survival
- Cognitive/functional outcomes
- Quality of life measures/Symptom burden
- Each calls for a different study design

MGd Trial Neurocognitive Tests Completion

Myth: Brain met patients have low compliance with neurocog testing

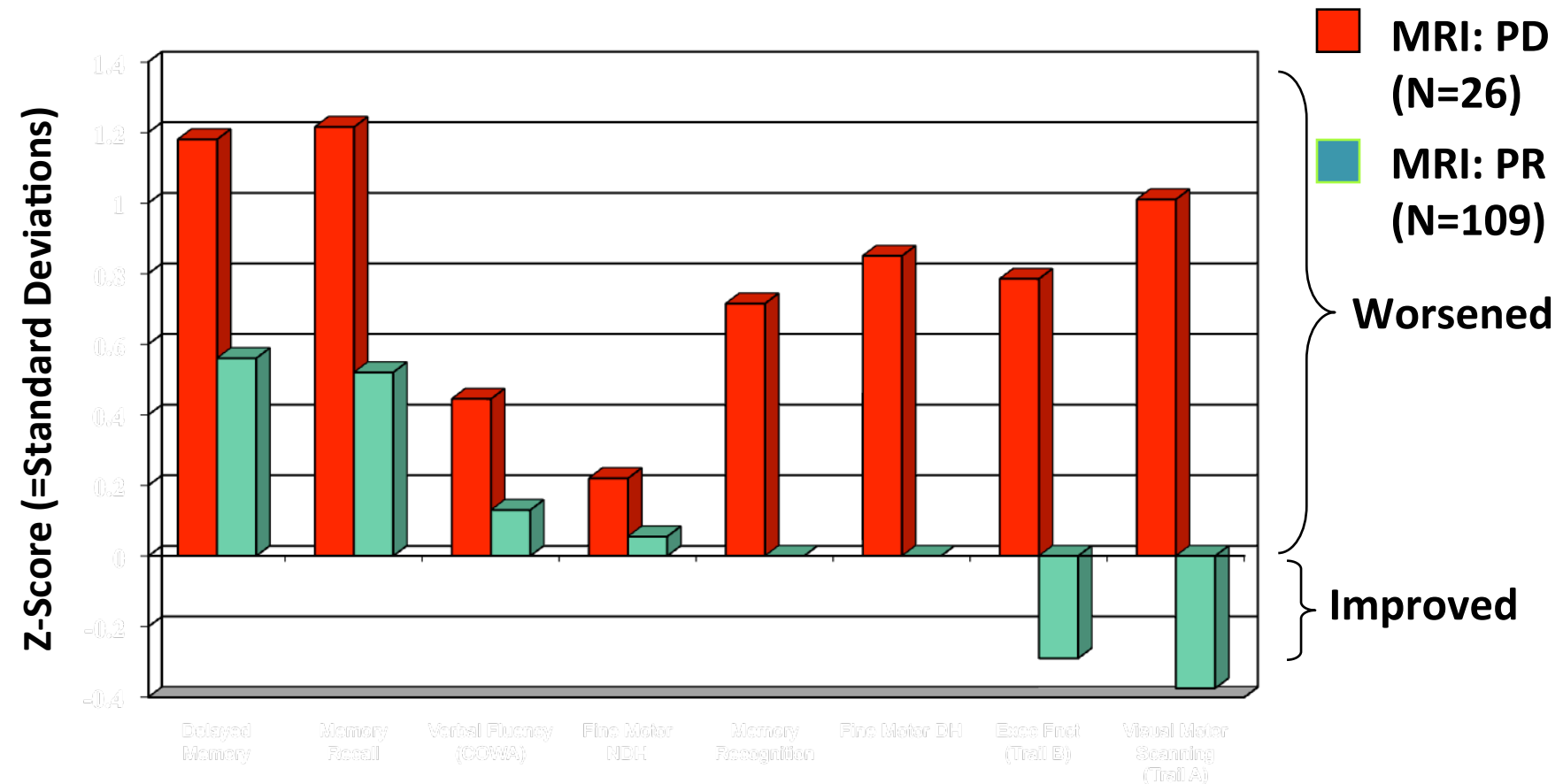
Months After Randomization												Total	Total
Patient Visits	401	327	269	205	178	138	127	66	33	23	13	1783	100
HVLT Recall Completed (%) *	98	90	86	83	84	81	87	89	85	78	62	1577	88
Trail B Completed (%)^	87	82	75	74	74	72	77	86	76	78	62	1409	79

Fact: Brain met patients have high compliance with neurocog testing

* Highest and ^ lowest completion tests

Tumor Growth ~ Neurocognitive Decline

Median Change in Neurocognitive Test Performance (Z-score) at 4 Months in Patients with MRI Data



Alternative Design Options

- Scenario 1: Prophylactic Cranial Irradiation
 - Categorically decreases brain relapse and improves survival in both limited and extensive stage small cell lung cancer

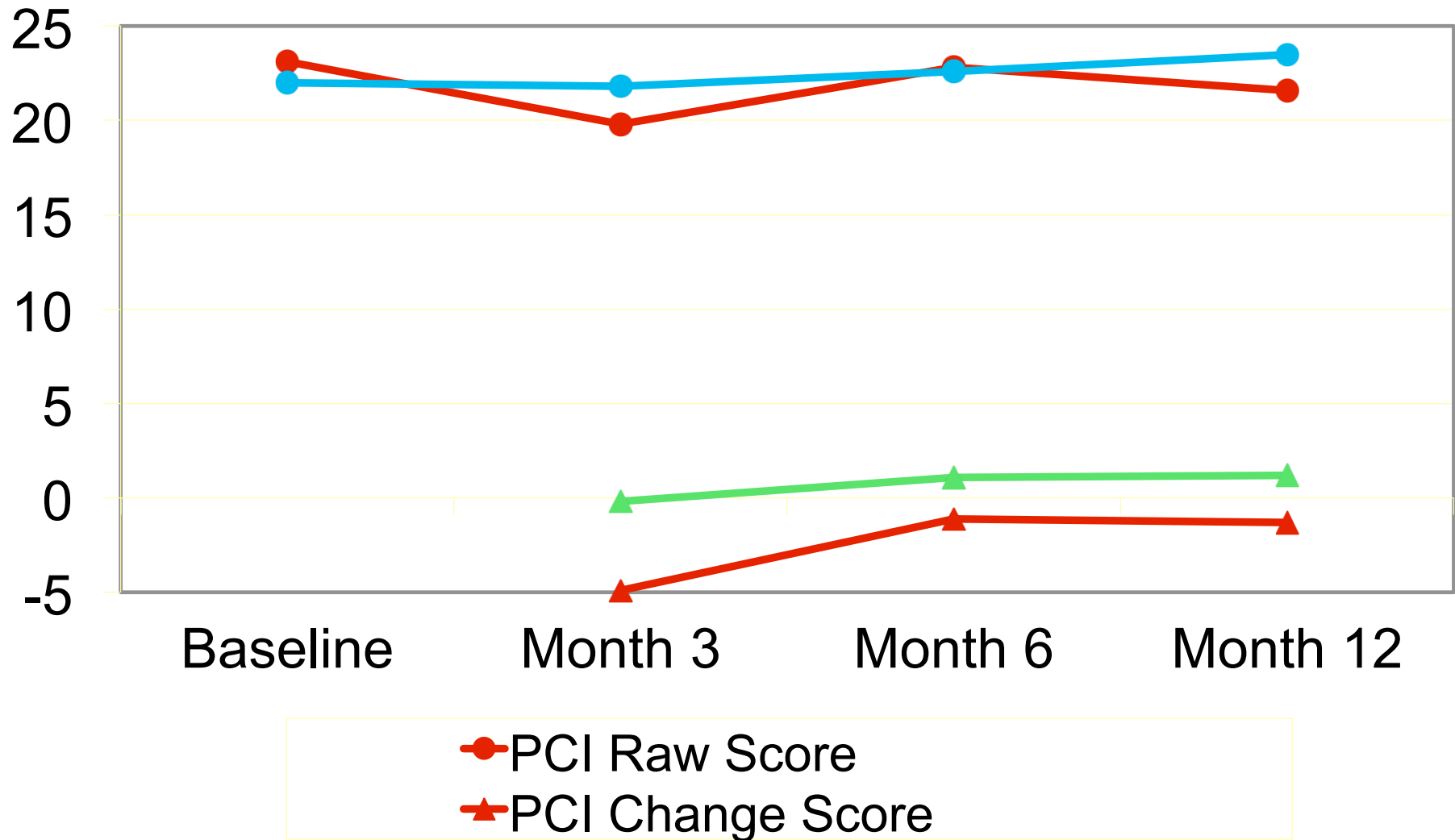
Alternative Design Options

- Scenario 1: Prophylactic Cranial Irradiation
 - Categorically decreases brain relapse and improves survival in both limited and extensive stage small cell lung cancer
 - Categorically decreases brain relapse in multiple non-small cell stage lung cancer trials
 - Without improving overall survival
 - And with associated cognitive decline

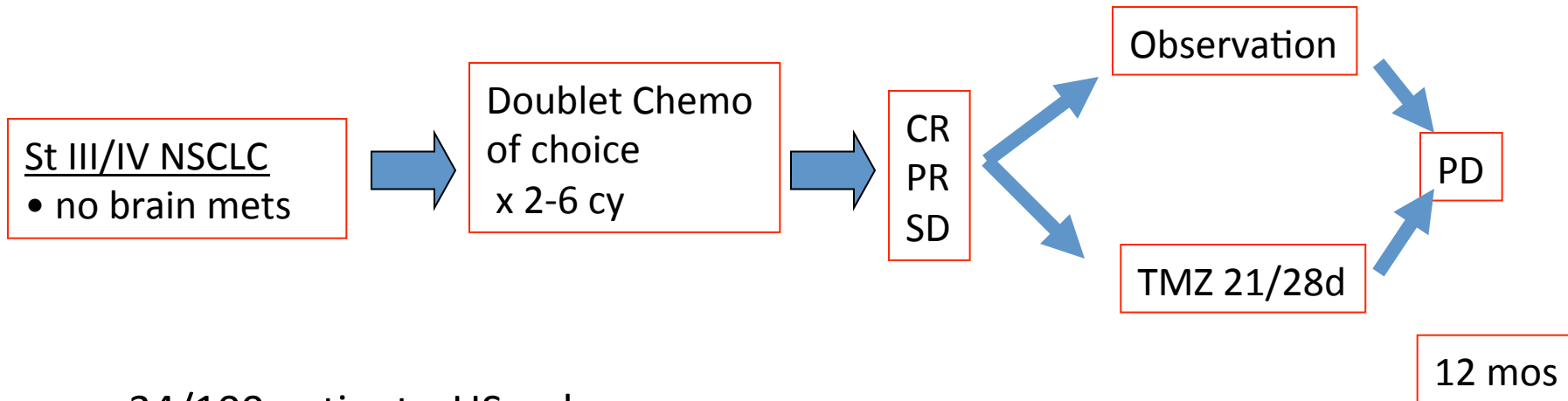
All PCI NSCLC Trials Show Benefit

Study	N	CNS Failures		p value
		No PCI	PCI	
VALG, JAMA 1981	281	13%	6%	0.04
MDACC, J Neuro-Onc 1984	97	27%	4%	0.002
RTOG 8403, IJROBP 1991	187	19%	9%	0.1
Pottgen et.al, JCO 2007	112	24%	9%	0.02
RTOG 0214, ASTRO 2009	340	18%	8%	0.004
Cumulative Experience	1017	13-27%	4-9%	

HVLT-R Decline: The Price of WBRT



Phase IIR Study of TMZ vs Observation in Stable or Responding Stage III/IV NSCLC PO5146



n=34/100 patients, US only
25/26 sites

Stratifications: Avastin, Yes or no; SD vs PR/CR; Stage III vs Stage IV

Endpoints:

Primary: incidence of brain mets at 12 mo post initiation of CTX

Secondary: Survival, toxicity, TT Brain mets, TTP, QOL

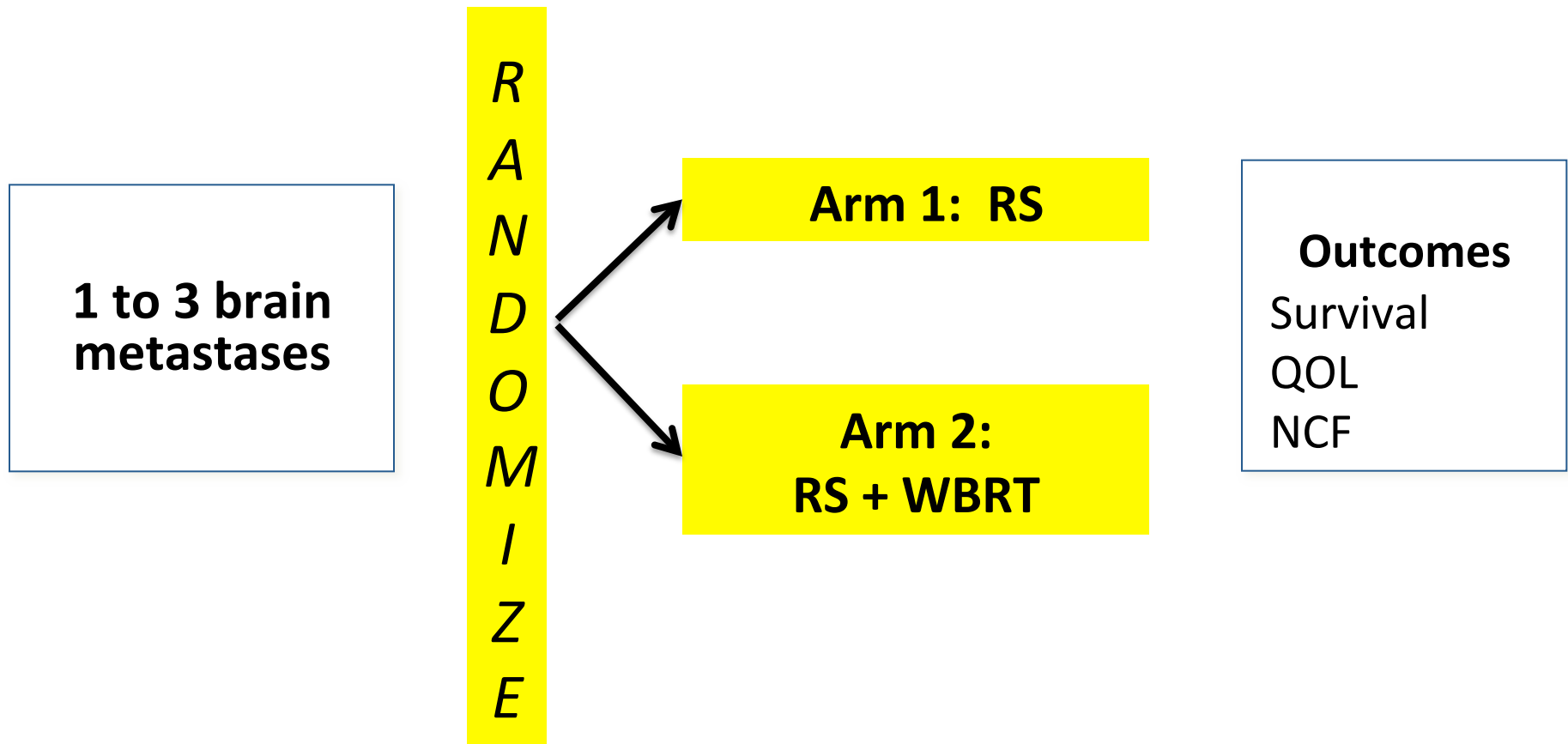
Negative Trial

Alternative Design Options

- Scenario 2: Diminish the Cognitive Sequale
 - Withhold WBRT
 - Completed Intergroup Trial
 - Use BBB penetrating agents
 - LANDSCAPE Trial
 - Pharmacologic
 - NMDA Receptor Agonists, e.g. Memantine
 - Dosimetric
 - Hippocampal Avoidance
 - Technological
 - Alternating electric field therapy

Can we withhold WBRT?

Recently Completed Intergroup Trial



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LANDSCAPE and UMD 1345

- The LANDSCAPE trial (lapatinib and capecitabine; 45 pts) for HER2+ patients who developed new brain metastasis reported a response rate of **66%** (all PRs), which compares favorably to historical data for WBRT.

**1 to 10 her2+
brain mets
(size limit)**

SRS
<10cc: 22Gy
>10 cc: 18Gy

**Brain
penetrating
antiHer2 Rx**
**LapCap or
TDM1**

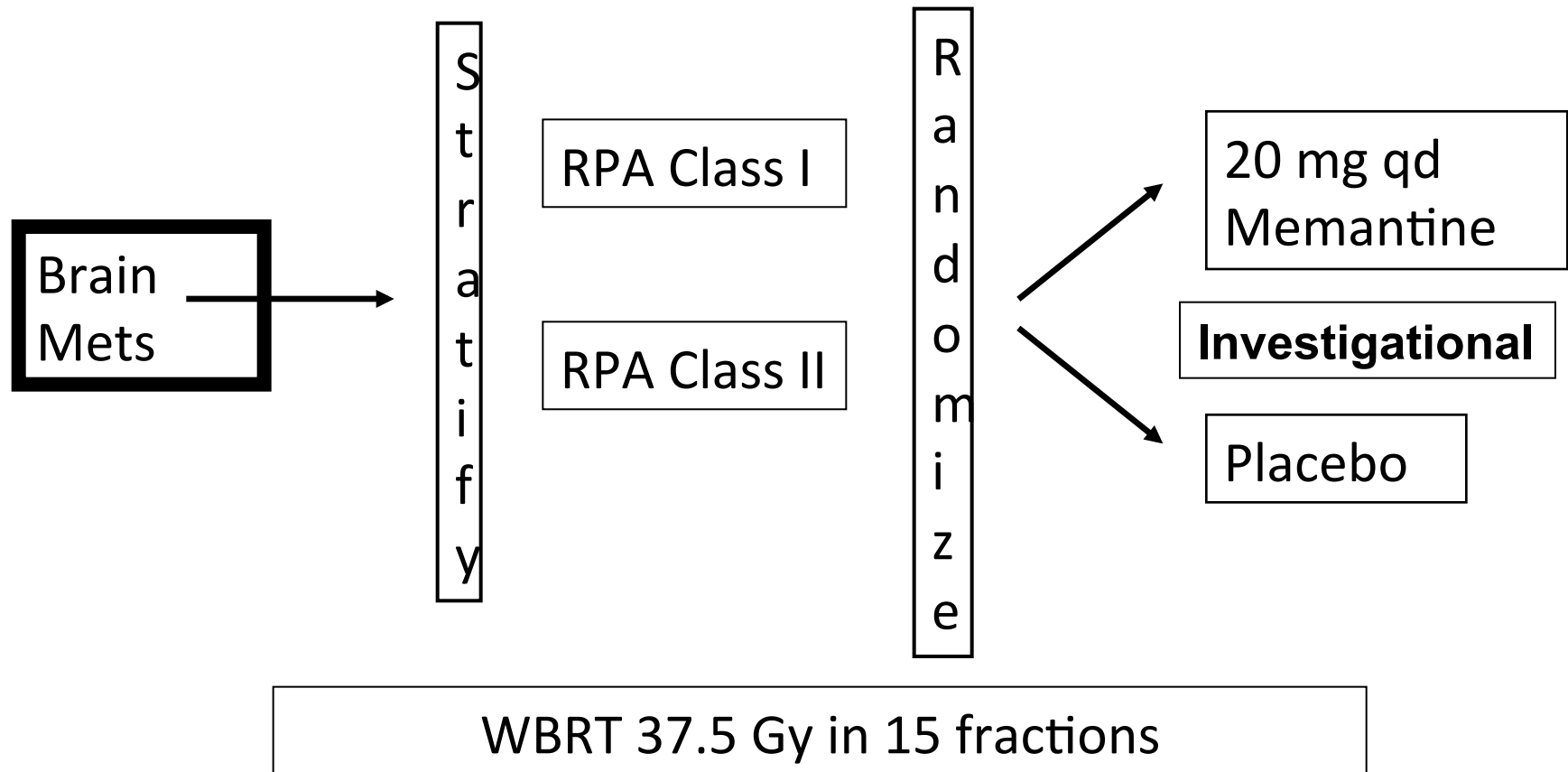
**Brain MRI
and
neurocog
q3 mo**

1° end pt: 6 month distant brain relapse rate

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RTOG 0614 Schema



554 patients enrolled from March 2008 to July 2010; 70% NSCLC

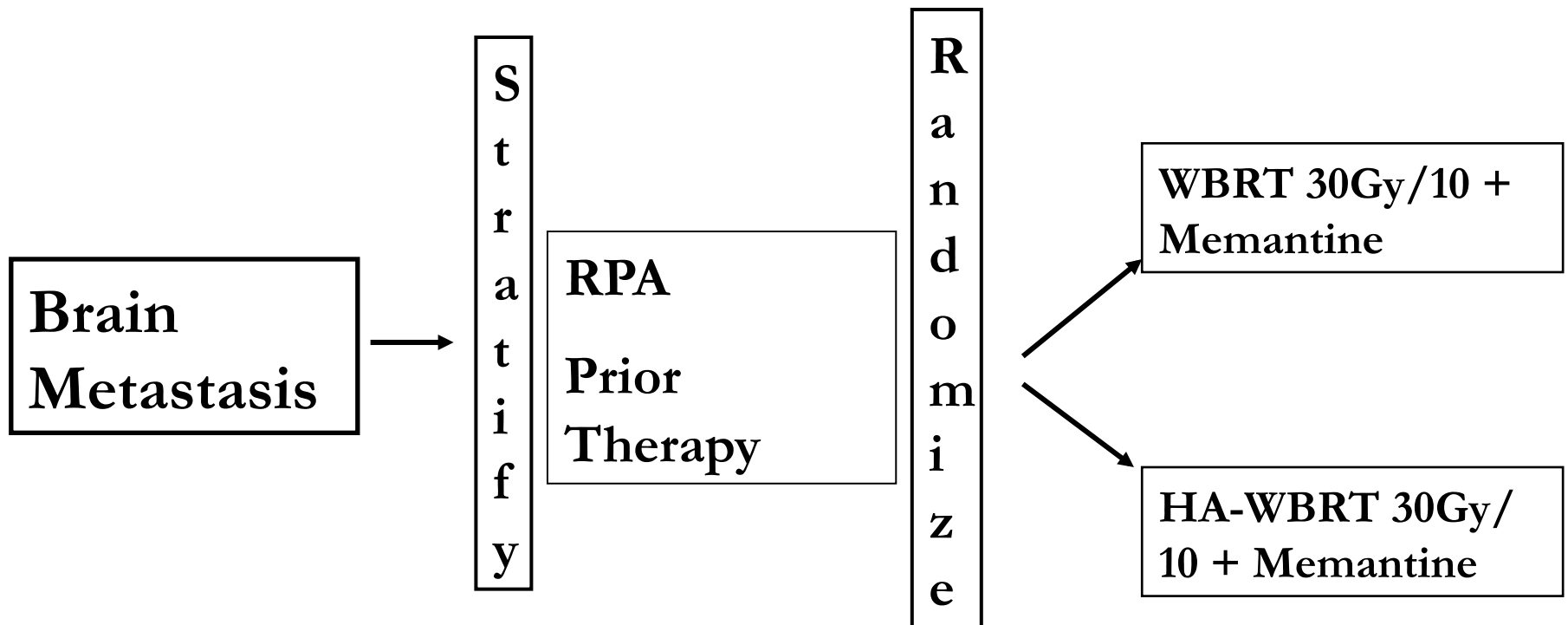
0614: Time to Cognitive Decline

- Time to cognitive decline
 - **Longer for memantine arm (HR 0.78; 95% CI, 0.62 to 0.99; $p=0.02$)**
- **Memantine improved probability of cognitive preservation at 24wk**
 - 30.6 vs 19.7% for placebo

NRG CC001

Phase III Trial

Basic Eligibility: Brain Mets >5mm outside hippocampus;
KPS \geq 70; Thin-slice volumetric MRI; English-speaking



518 patients

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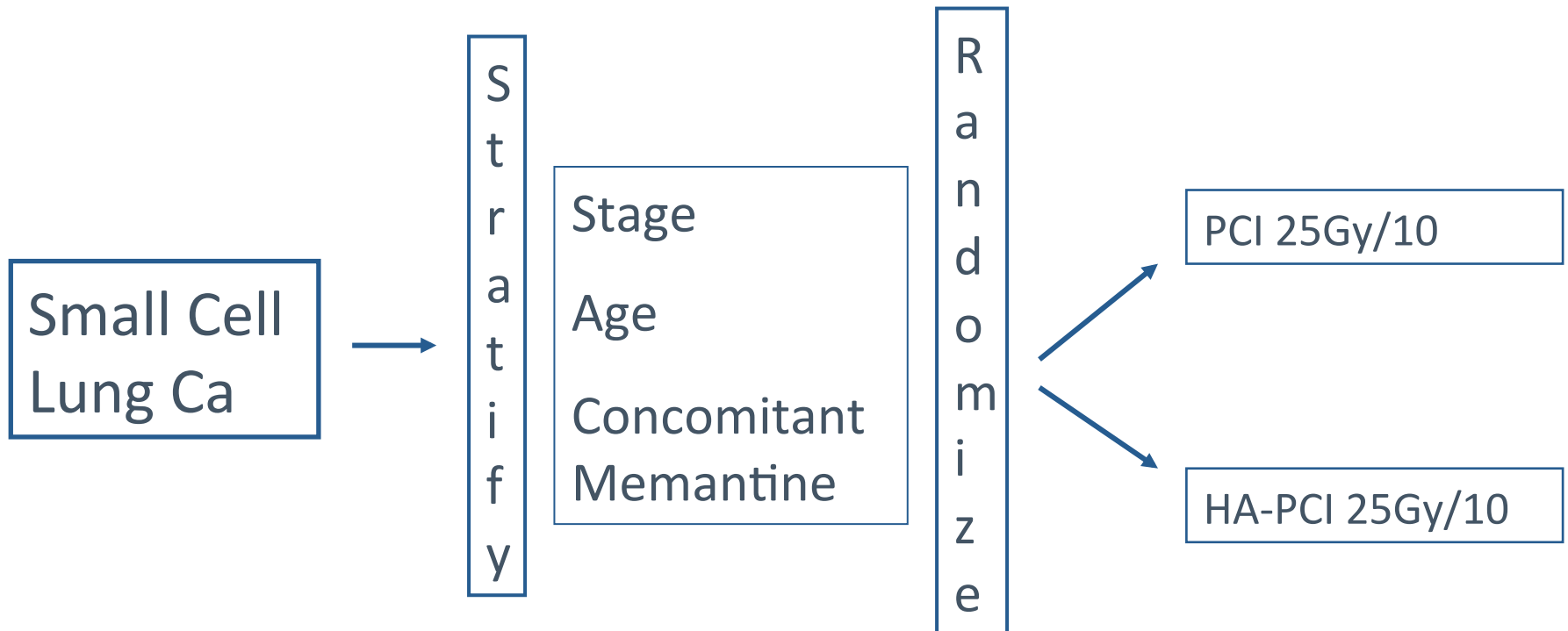
RTOG 0933

- Phase II study of HA-WBRT
- Primary endpoint: HVLT-delayed recall at 4 months
- Historical control: WBRT without hippocampal avoidance on a prior published phase III trial
 - 30% mean relative decline in HVLT-delayed recall from baseline to 4 months after WBRT
- **51 analyzable patients to detect mean relative HVLT-delayed recall decline $\leq 15\%$ (50% relative improvement): Observed rate was 7%**
 - Power = 80%, one-sided alpha = 0.05
- Target sample size = 102; 113 accrued (100 eligible)

RTOG 1330 Protocol design

Phase IIR/III Trial

Basic Eligibility: Small cell lung cancer; PR or CR to chemo; ECOG PS≤70; MRI scan English-speaking



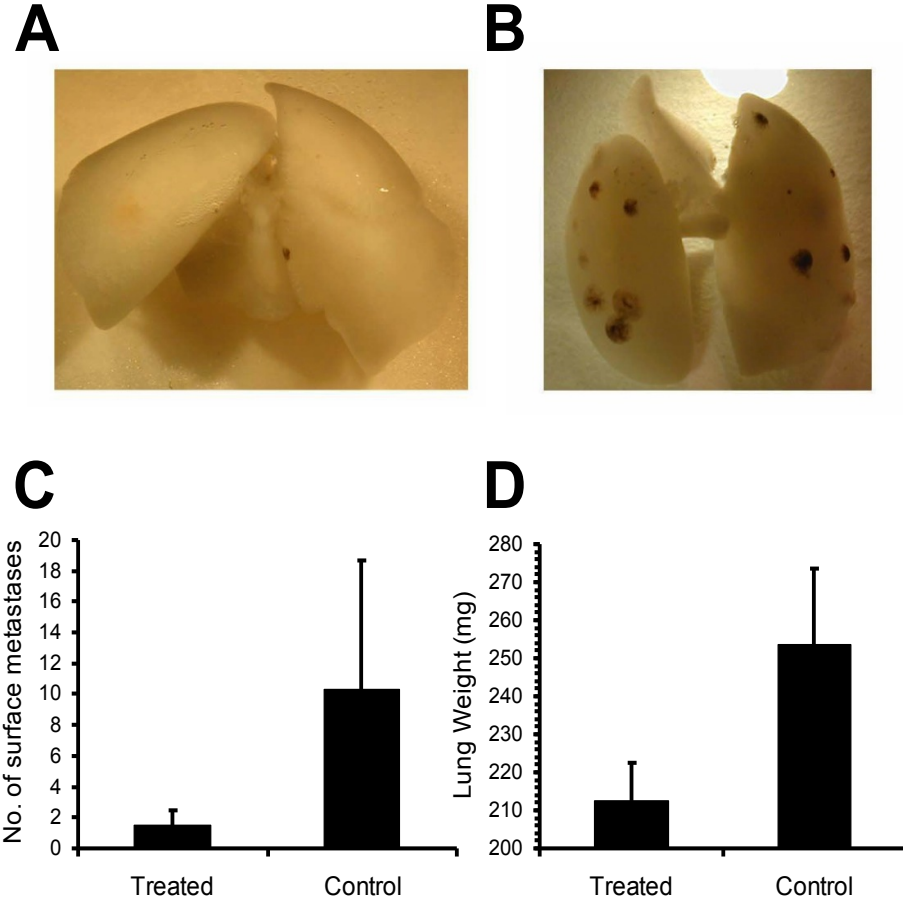
Sample Size: 304 patients

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In Vivo TTFields Prevent Metastasis

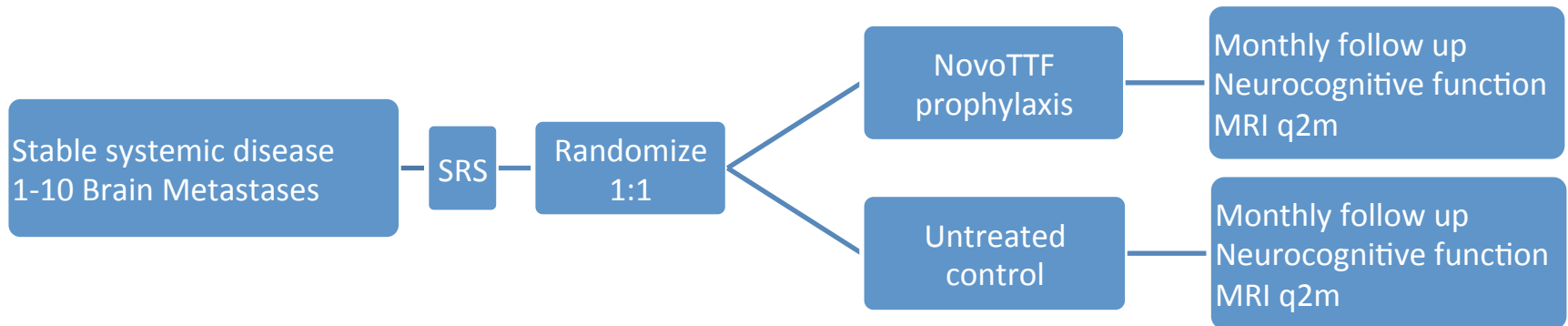
- Mice injected with melanoma cells into tail vein
- TTFields to lungs for 7-14 d
- TTField treated mice had significantly lower metastatic burden in the lungs compared to sham controls



Kirson et al., *Clin Exp Metastasis* 2009

TTField therapy is not approved for melanoma. The safety and effectiveness of the device for melanoma has not been established.

Brain Mets –Proposed Phase II Trial



Inclusion Criteria:

NSCLC, Stable systemic disease, may continue with systemic therapy

Two cohorts: 1-4 brain mets amenable to SRS; 5-10 brain mets

Primary endpoint: Time to recurrence in the brain (superiority)

Secondary endpoint: Neurocognitive function

N = 240

Scenario 3: Improve Intracranial Control - The RT+ Brain Met Trial Design

Basic Assumptions for WBRT+ Trials

- This trial design is specifically for the RT+ concepts
- The expectation is that patients with multiple brain mets, routinely treated with WBRT would be enrolled
- The basic design would be a multi-arm Phase II randomized trial, with early discontinuation of arms that do not meet a defined outcome threshold

Basic Assumptions for WBRT+ Trials

- Ph I dosing, of drug plus RT, if not already available, would be conducted separately
- Primary endpoint: either response rate in the brain, or lack of intracranial progression at a pre-defined early time point
- WBRT alone control arm would be included
- NSCLC and Breast Ca constitute the 2 main entities of interest and can either be folded in separate arms in a single trial, or be segregated into 2 separate trials

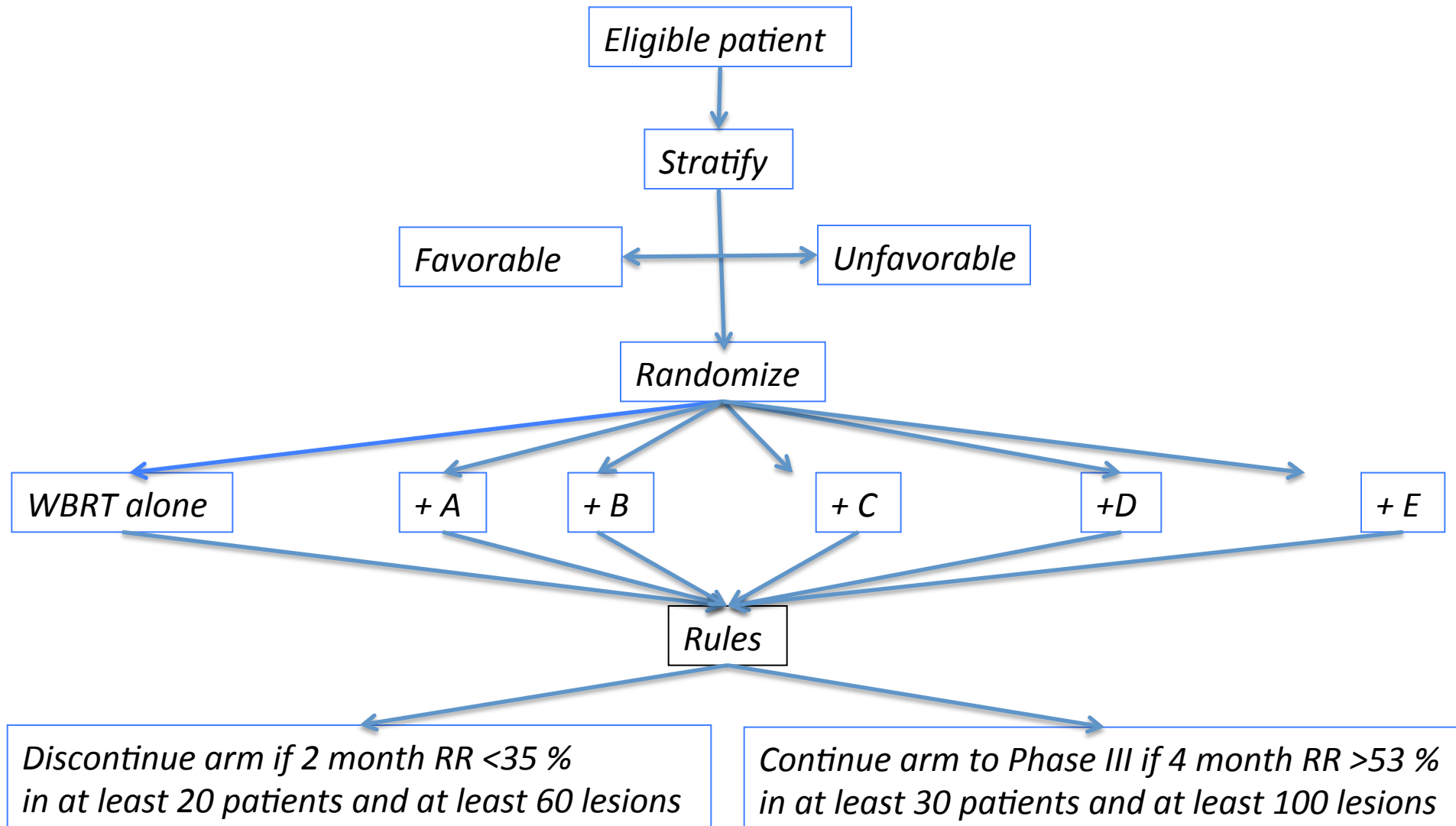
Rules for “Drug of Interest”

- CR+PR rates of approximately 30-40% at 2 and 4 months would constitute the benchmark with WBRT alone.
- A drug would be considered “of interest to progress to Phase III” if it improved upon the historic response rate by at least 33%, i.e. yield a 4-month response rate of 53%.

Combining the Targeted Drug with WBRT

- Use a 3 week WBRT schedule to maximize the potential for synergy (37.5 Gy in 15 fractions)
- Consider using the drug for a 3 to 6 week period of time, including, as feasible, pre-, during, and post-RT
- Provide a mechanism to either continue the drug beyond the 6 week period based on investigator preference, or discontinuing it
- This is necessary to permit appropriate systemic regimens to be folded in

A Possible Complex 6-arm Trial



RTOG 1119 : Phase IIR Study of WBRT+Lapatinib in Her2+ Breast Ca Brain mets: RTOG/KROG

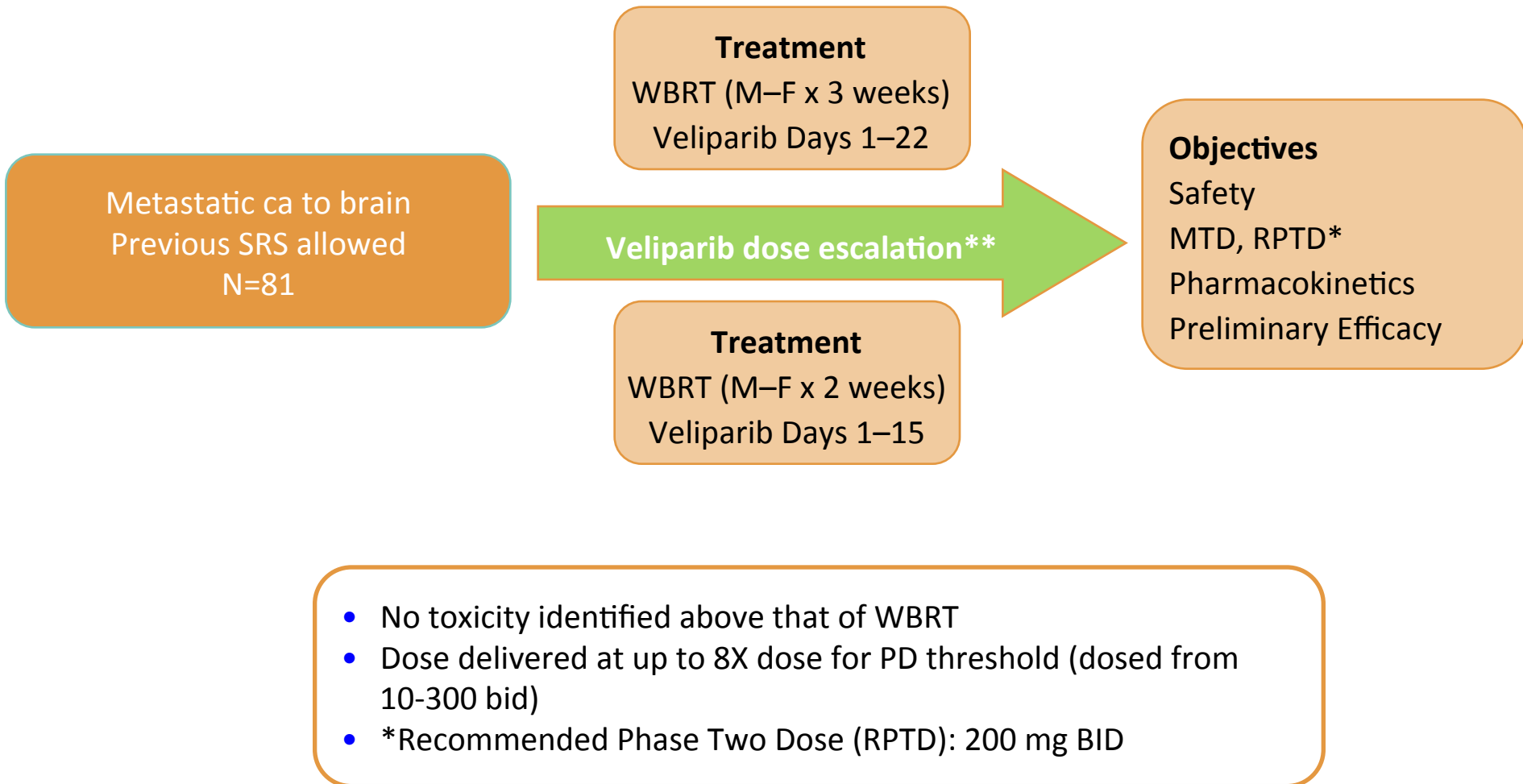
PI: In Ah Kim

Schema

S T R A T I F Y	<i>Graded Prognostic Assessment : 1.5-2 vs. 2.5-3 vs. 3.5-4</i>	R A N D O M I Z E	<u>Arm A</u>
	<i>Concurrent Use of Non-CNS–Penetrating HER2 Blockade at Study Entry: Yes vs. No: trastuzumab± pertuzumab</i>		<i>WBRT: 37.5 Gy in 15 fx for 3 weeks</i>
	<i>Previous Stereotactic Radiosurgery or Surgical Resection : Yes vs. No</i>		<i>vs.</i>
			<u>Arm B</u>
			<i>WBRT: 37.5 Gy in 15 fx for 3 wks</i>
			<i>Plus</i>
			<i>Lapatinib : 1000mg once daily starting up to 1 day before the first day of WBRT and continuing until 21 days after the final day of WBRT</i>

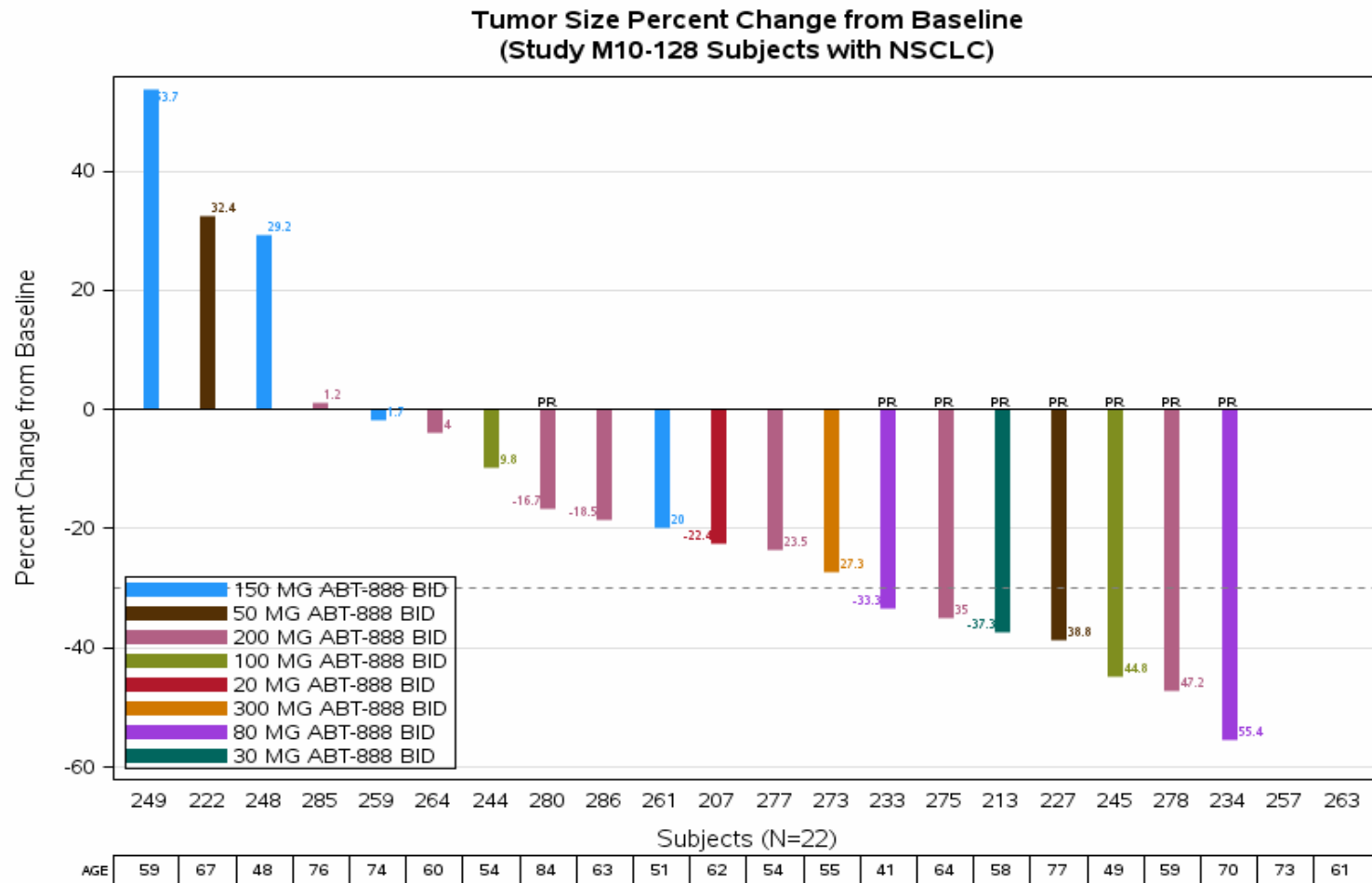
Veliparib + radiotherapy gateway

Supporting Phase 1 study



Phase 1 (M10-128) Data

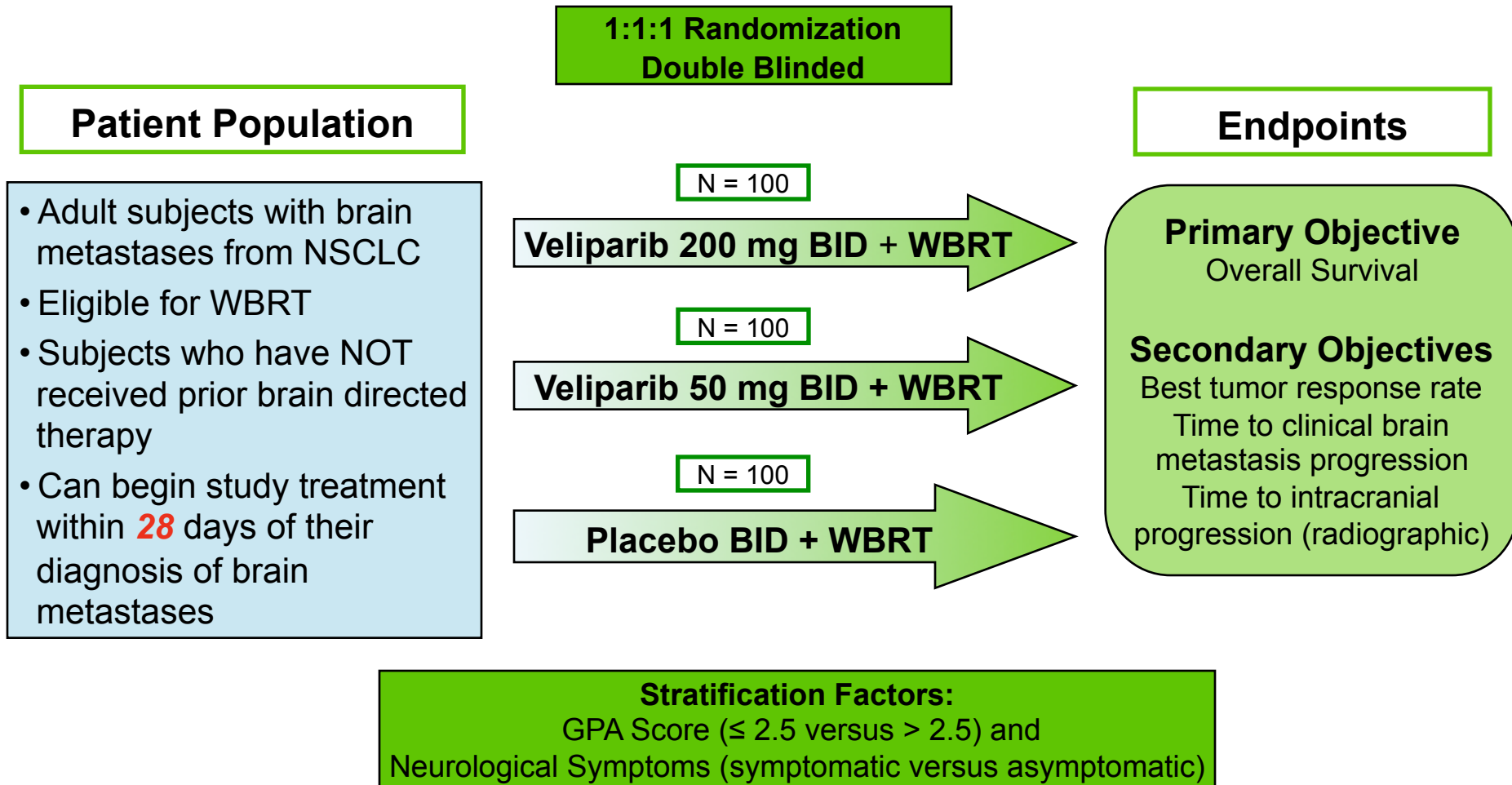
Tumor Size Percent Change from Baseline for Patients with NSCLC



NOTE: INCLUDE SUBJECTS WITH MEASURABLE DISEASE AT BASELINE, AND HAD AT LEAST ONE POSTBASELINE ASSESSMENT.

NOTE: SUBJECTS NOT 80% COMPLIANCE WITH VELIPARIB OR NOT FINISHED WHOLE COURSE OF WBRT WERE EXCLUDED.

M10-897 Overall Study Design



Scenario 4: Radiation as a Vaccine

**NRG Developing Concept:
A Phase II Randomized Trial of Immune
Checkpoint Inhibitor (ICI) with or without
Stereotactic Radiosurgery (SRS) in
Melanoma Patients with \leq 10 Brain
Metastases & Extracranial Metastases: A
Study of ICI Activity, Radiation-Induced
Immune Enhancement and Toxicity**

SCHEMA

S		R	
T	Sx or Steroids Y/N	A	
R		N	Arm 1: ICI
A	bRAF pos/neg	D	induction then maint. until CNS
T		O	progression, then SRS to all BM
I	GPA0-1.0	M	
F	1.5-2.0	I	Arm 2: ICI + SRS
Y	2.5-3.0	Z	induction then maint. with SRS
	3.5-4.0	E	betwn 1 st & 2 nd dose of induction

Thank You