Preventive Strategies for Neurocognitive Deficits in the Management of Brain Metastases

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University of Maryland

Disclosures

- **Consultant**: Bristol Meyers Squibb, Cavion, Celldex, Elekta, Novocure, Novartis,
- **Stock Options**: Pharmacyclics
- **Board of Directors**: Pharmacyclics
- **Research Funding**: Novocure, Cellectar
- **Employment**: U Maryland (MPTC)

Current as of October 2015

N0574: Neuro-cognitive injury from WBRT

Early deterioration: N0574 confirms this result

	SRS	SRS+ WBRT	p
Neuro-cognitive progression	64%	92%	.0007
HVLT Total Recall Deterioration	8%	30%	.0043

WBRT clearly and negatively affects neuro-cognition
N0574 among largest trials to date with detailed results

Brown et al, ASCO 2015 (N0574/Alliance)

N0574 Neuro-cognitive injury from WBRT

12 month persistent worsening: N0574 new finding

	SRS	SRS+ WBRT	p
Neuro-cognitive progression	64%	92%	.0007
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Cognitive Test	SRS (n = 15)	SRS +WBRT (n = 19)	p
HVLT Recognition	0.35	-1.43	0.044
COWA	0.34	-0.25	0.071

n et al, ASCO 2015 (N0574/Alliance)

Impact of WBRT on MMSE

	SRS	+ WBRT	p
Median time to 3 point drop	7.6 mo	16.5 mo	.05
1Y freedom from 3 point drop	59 %	76 %	
2Y freedom from 3 point drop	52 %	69 %	

- **Progressive disease is worse than WBRT**

Aoyama H, Int J Radiat Oncol Biol Phys, 68:1388-395, 2007, PMID: 17674975

However, Brain Failure after SRS/S Alone Remains Unacceptably High

Failure	No WBRT	WBRT	Absolute increase
Any brain	70-78%	24-47%	**31-46%**
Local brain	27-69%	0-27%	**27-42%**
Distant brain	42-64%	18-42%	**22-24%**

Composite data from multiple randomized trials

Nieder et al. Radiation Oncology 2014 ***9****:155, PMID: 25016309*

What Other Options Exist?

- Serial surveillance and salvage
- Modulate WBRT negative effects
  - Pharmacologic, e.g. Brown, et al, RTOG 0614, ASTRO 2012 Plenary
  - Dosimetric, e.g. RTOG 0913, HAWBRT (accrual completed Oct 2012)
- Novo-TTF
- BBB-penetrating chemotherapy, e.g. temozolomide, GRN-1005
- BBB-penetrating targeted agents for tumors harboring driver mutations, e.g. lapatinib for her2+ breast cancer, erlotinib for EGFR+ NSCLC, etc.
- Non-BBB approaches such as Ipilimumab for melanoma

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Predictors of Distant Brain Recurrence

- 100 brain met patients treated with GK SRS only, 2003-2005
- **1Y actuarial risk of DBF = 61%**
- Predictors for DBF:
  - **>3 mets (HR = 3.3, p = 0.004)**
  - Extracranial disease (stable or poorly controlled) (HR = 2.16, p = .04)
  - Melanoma (HR = 2.14, p = .02)

Sawrie, Int J Radiat Oncol Biol Phys, 70:181-6, 2008

Is it Disease Progression or Reseeding?

- Low risk: 18/100 patients were non-melanoma, with 3 or fewer mets and controlled systemic disease
- High risk: 82/100, all others

	Low Risk	High Risk
n	18	82
1Y % DBF	17 %	74 %
Median time to DBF	89 weeks	33 weeks

Sawrie, Int J Radiat Oncol Biol Phys, 70:181-6, 2008

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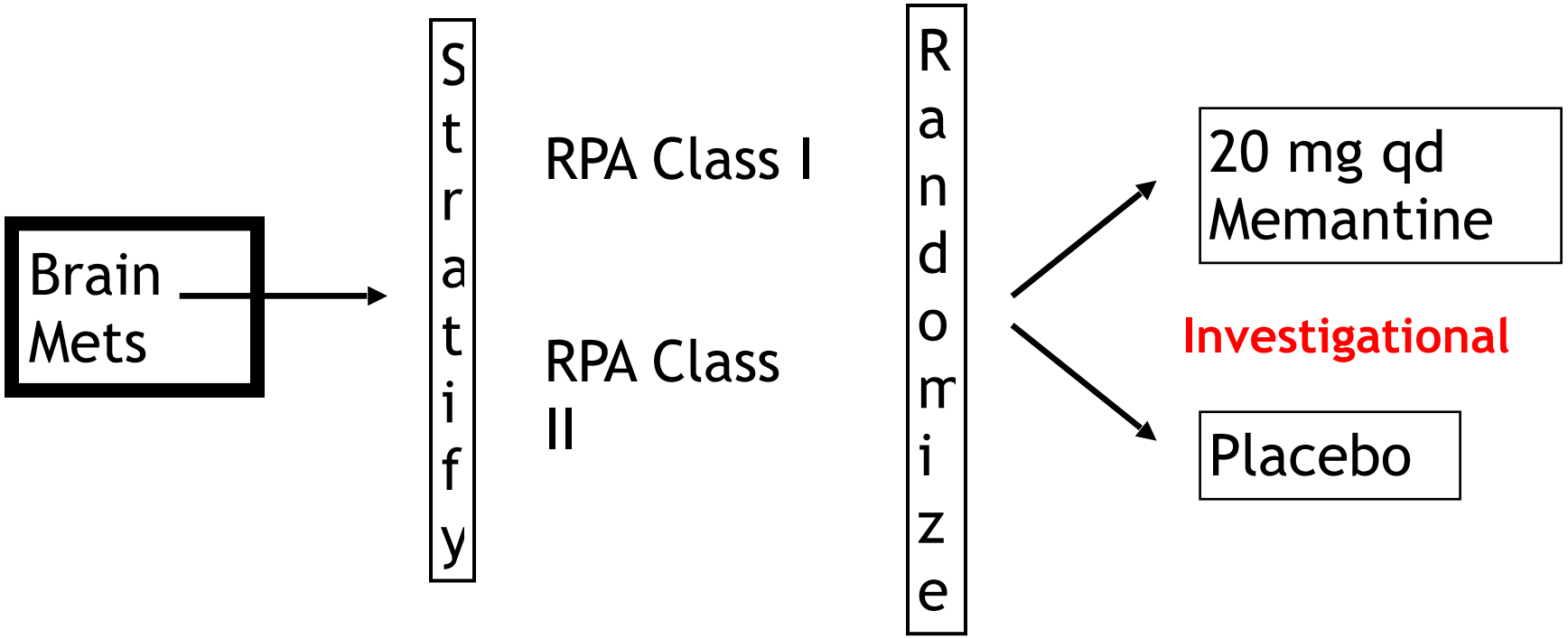
RTOG 0614 Schema



WBRT 37.5 Gy in 15 fractions

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

Brown P, et al, Neuro Oncol, 2013, PMID: 23956241

Time to Cognitive Decline

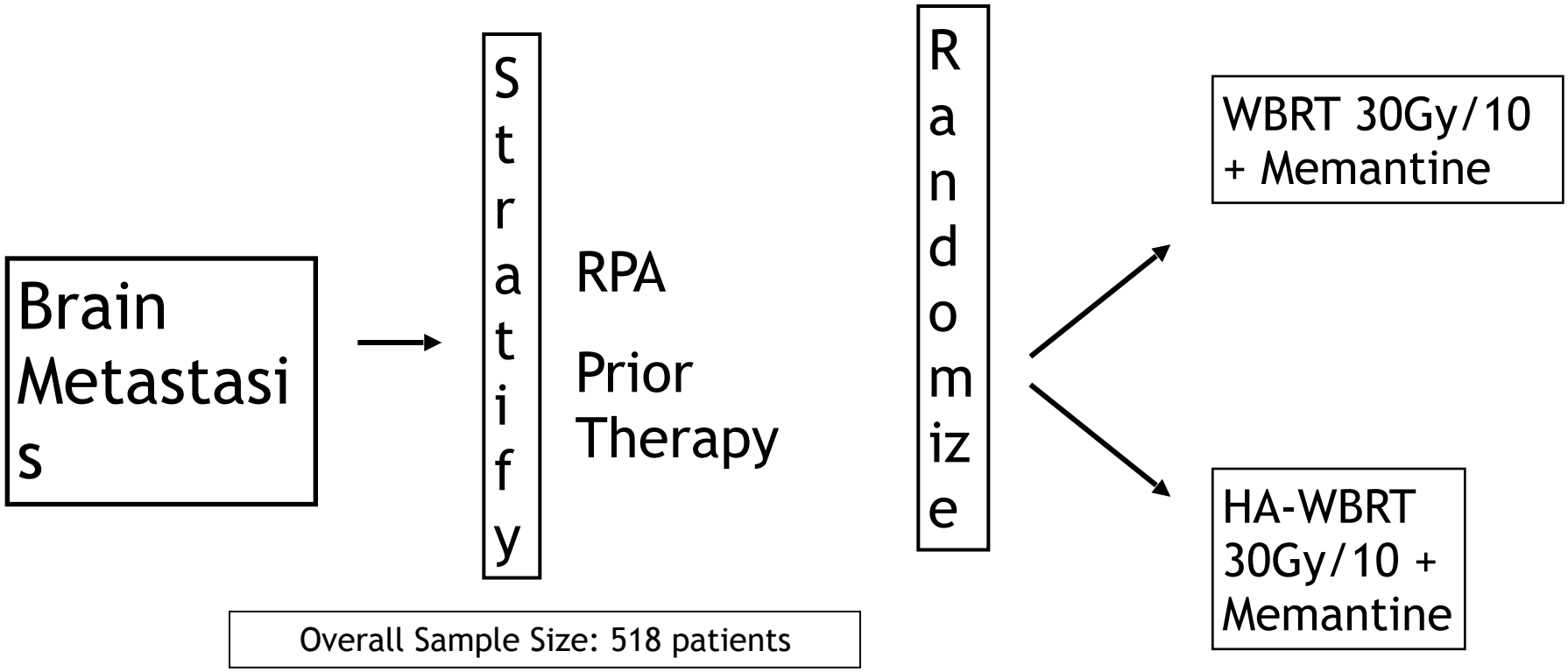
- Time to cognitive decline
  - **Longer for memantine arm (HR 0.78**; 95% CI, 0.62 to 0.99; p=0.02)
- Memantine **improved probability of cognitive preservation** at 24wk
  - 30.6 vs 19.7% for placebo

Investigational

Brown P, et al, Neuro Oncol, 2013, PMID: 23956241

Phase III Trial Memantine and WBRT with or without Hippocampal Avoidance in Patients with Brain Metastases

Basic Eligibility: Brain Mets outside hippocampus; KPS≥70; MRI scan

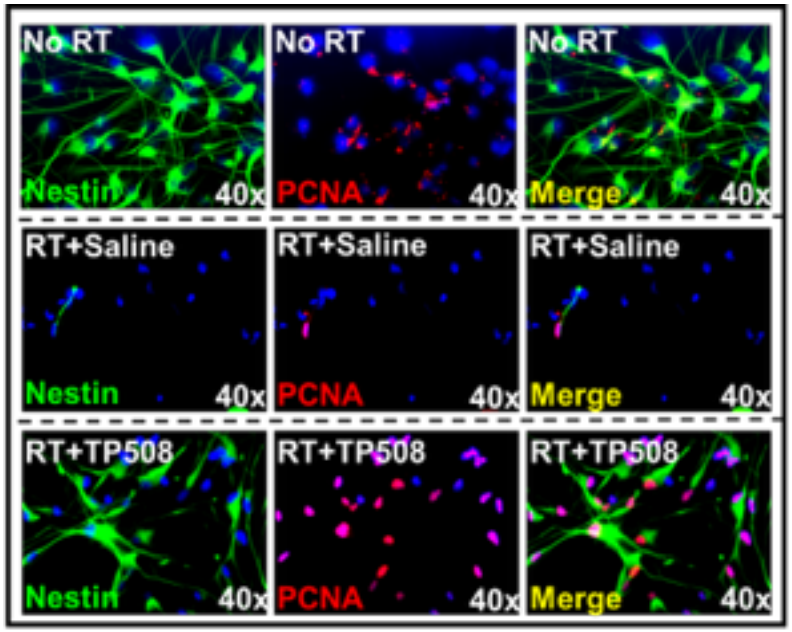


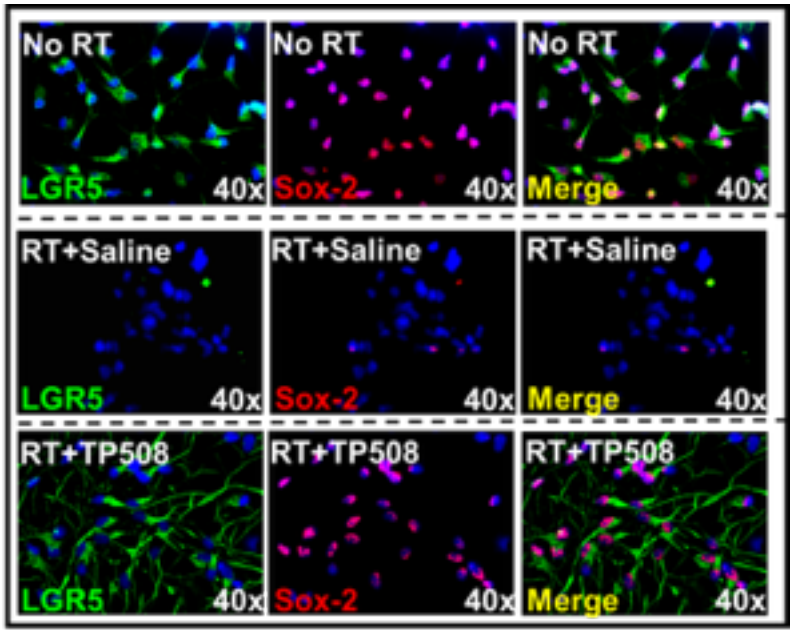
Overall Sample Size: 518 patients

Basic Statistical Design:
Cognitive function failure 53.8% at 6 months with WBRT vs. 42.8% with HA-WBRT. 388 analyzable pts.

NCI Status: Study Approved by Research Strategy, Concept submitted

TP508 Protects Neural Stem Cells Post Radiation





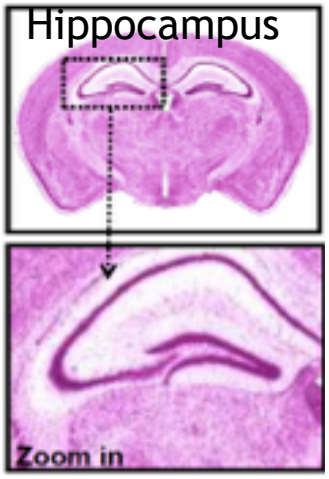
- Human Neural Stem Cells (K048) treated with TP508 1h prior to RT (2Gy)
- IF staining of cells 48h post RT demonstrate that TP508 stimulates proliferation and increases expression of stem cell markers Nestin/LGR5 and pluripotent factor Sox-2

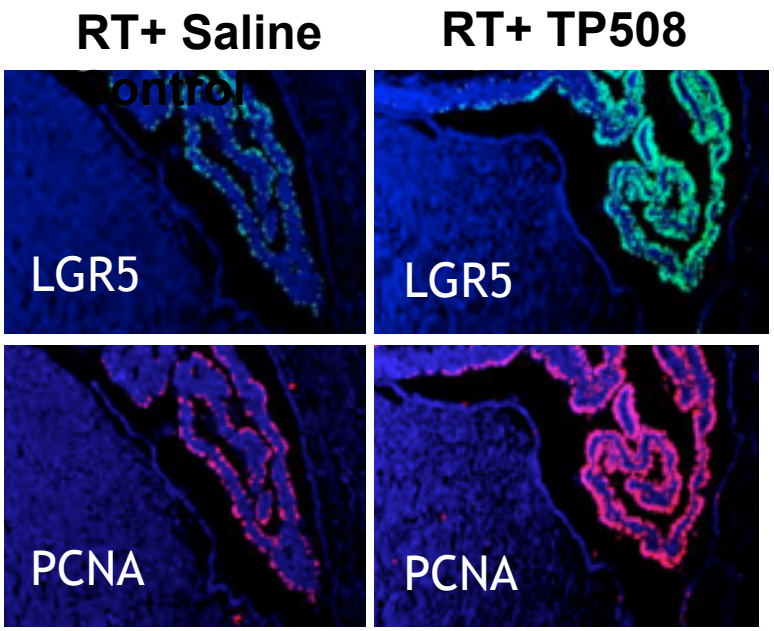
C.Kantara and P.Wu- UTMB

. . . Proof of concept – Neural Stem Cells

TP508 protects/restores proliferation of neural stem cells in vitro and hippocampal region of mice post RT to promote neurogenesis

- RT (7Gy) destroys neural stem cells identified by LGR5 (and other stem cell markers)
- **TP508 treatment 1h prior to RT stimulates neural stem cell proliferation to promote neurogenesis**
- **Single injection mitigates RT effects on neurogenesis**

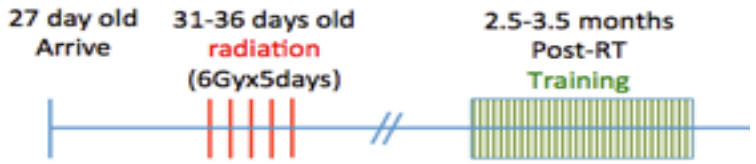




C. Kantara, PhD, UTMB/Chrysalis BioTherapeutics, Inc.

. . . TP508 increases cognitive recovery

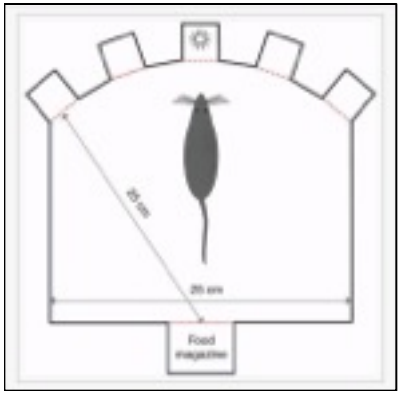
Animal behavioral studies show that TP508 injection on day 1 and 3 of radiation partially mitigates effects of radiotherapy (RT) on hippocampal and frontal lobe activity in juvenile rats measured by 5-choice serial reaction time task (5-CSRTT) 3 months post RT.



Note: TP508 increases number of mice achieving Stage 6 from 18% to 46%

Number of Mice Achieving A Given 5--CSRTT Stage (80% Accuracy)

5-CSRTT Stage		No RT	RT-Saline	RT-TP508
Stage 4 and 5	> 2.5 seconds	1 (9%)	9(82%)	7(54%)
Stage 6	< 1.25 seconds	4(36%)	2(18%)	4(31%)
Stage 7 and 8	< 1.0 seconds	3(27%)	0	2(15%)
Stage 9	< 0.8 seconds	3(27%)	0	0



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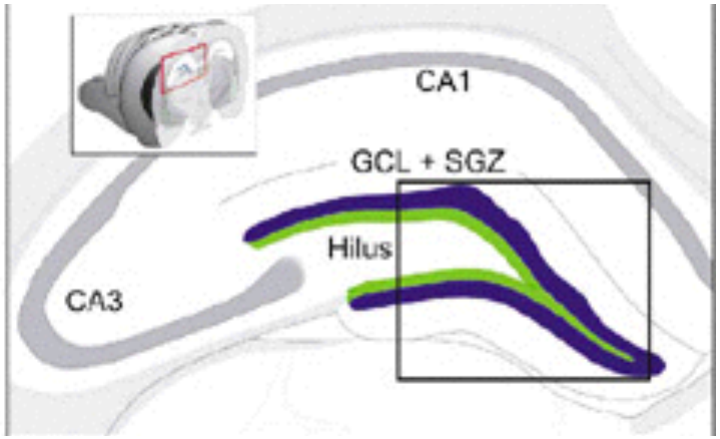
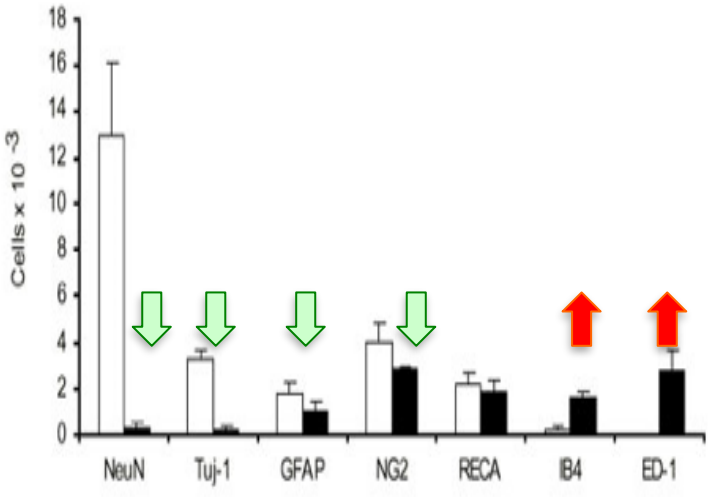
Cranial RT Ablates Hippocampal Neurogenesis



Blue: GCL, Green: SGZ

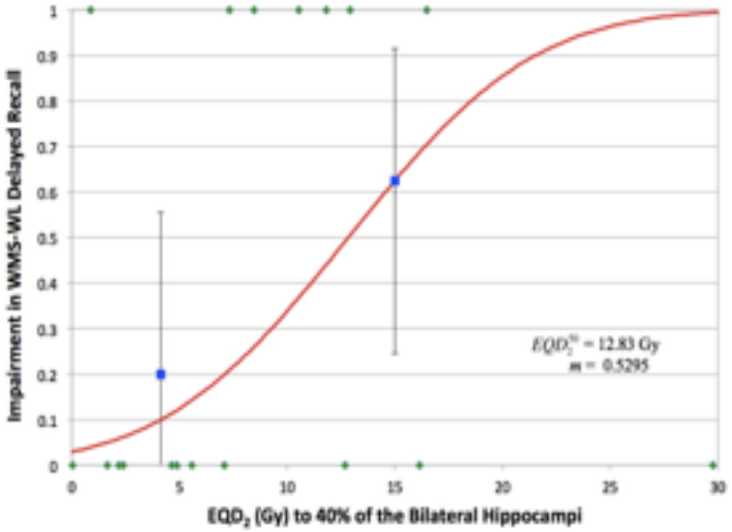


Monje, M et al. Nat Med 2002

- 97% reduction in newborn neurons 2 months after cranial RT
- Increase in microglial differentiation and activation

- NeuN: nuclear antigen for mature neurons; Tuj-1: immature neurons; GFAP: astrocytes; NG2: immature oligodendrocytes; RECA: endothelial cells; IB4: microglial lineage; ED1: activated microglia

Clinical Evidence of Dose Response Relationship



- Dose (in 2-Gy fractions) to 40% of the bilateral hippocampi
  - > 7.3 Gy a/w impairment in list-learning delayed recall at 18 months
    - (Odds ratio 19.3, *p*=0.043)
  - = 12.8 Gy a/w 50% risk of impairment in list-learning delayed recall at 18 mos
    - (95% CI: 11.5-14.1 Gy)

Gondi V, Hermann BP, Mehta MP, and WA Tome. ASTRO 2011

- EQD_2: Equivalent dose in 2-Gy fractions; m=normalized slope of dose-response curve;
- WMS-WL: Wechsler Memory Scale-Word Lists

0933: HVLT Results

HVLT	2 mo	4 mo	6 mo
Total Recall	30.8%	**19.0%**	13.8%
Recognition	35.8%	11.9%	3.6%
Delayed Recall	30.2%	33.3%	17.2%

- MDACC: Probability of HVLT Total Recall deterioration at 4 mos

SRS alone **24%** **SRS+WBRT** **52%**

Gondi, et al, JCO, 2014, PMID: 25349290

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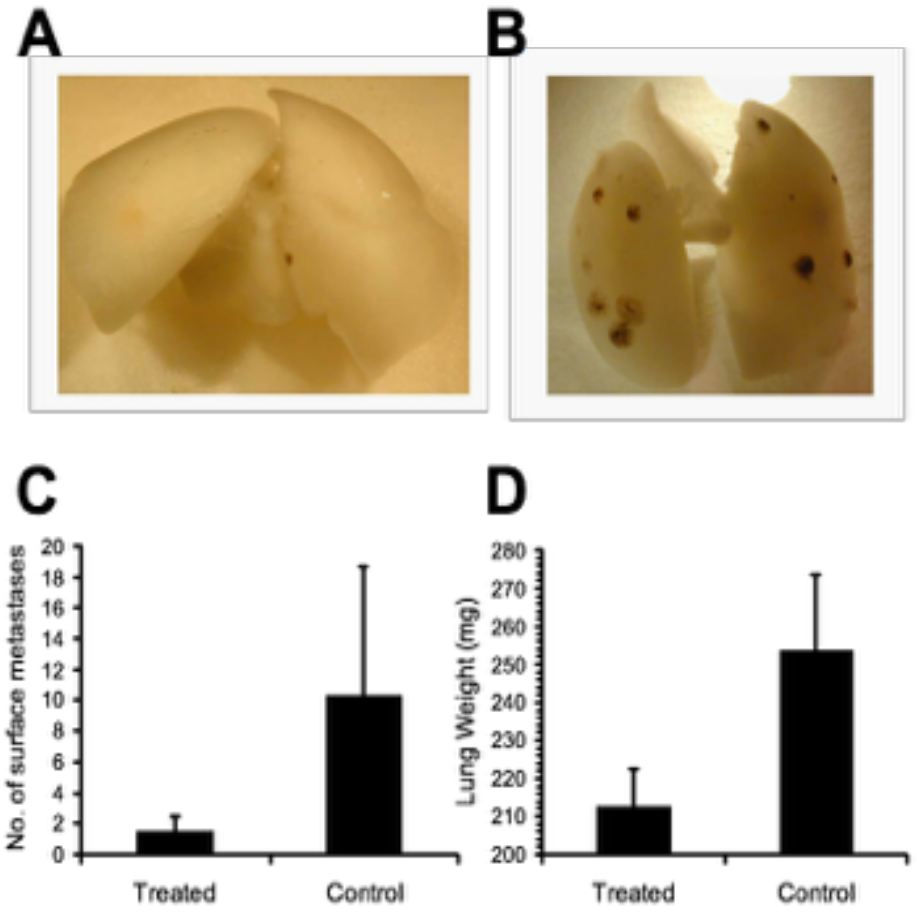
In Vivo TTFields Prevent Metastasis

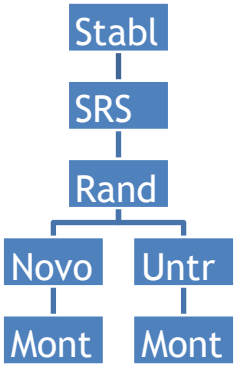
- Mice injected with melanoma cells into tail vein
- TTFields to lungs for 7-14 d
- TTField treated mice had significantly lower metastatic burden in the lungs compared to sham controls



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 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

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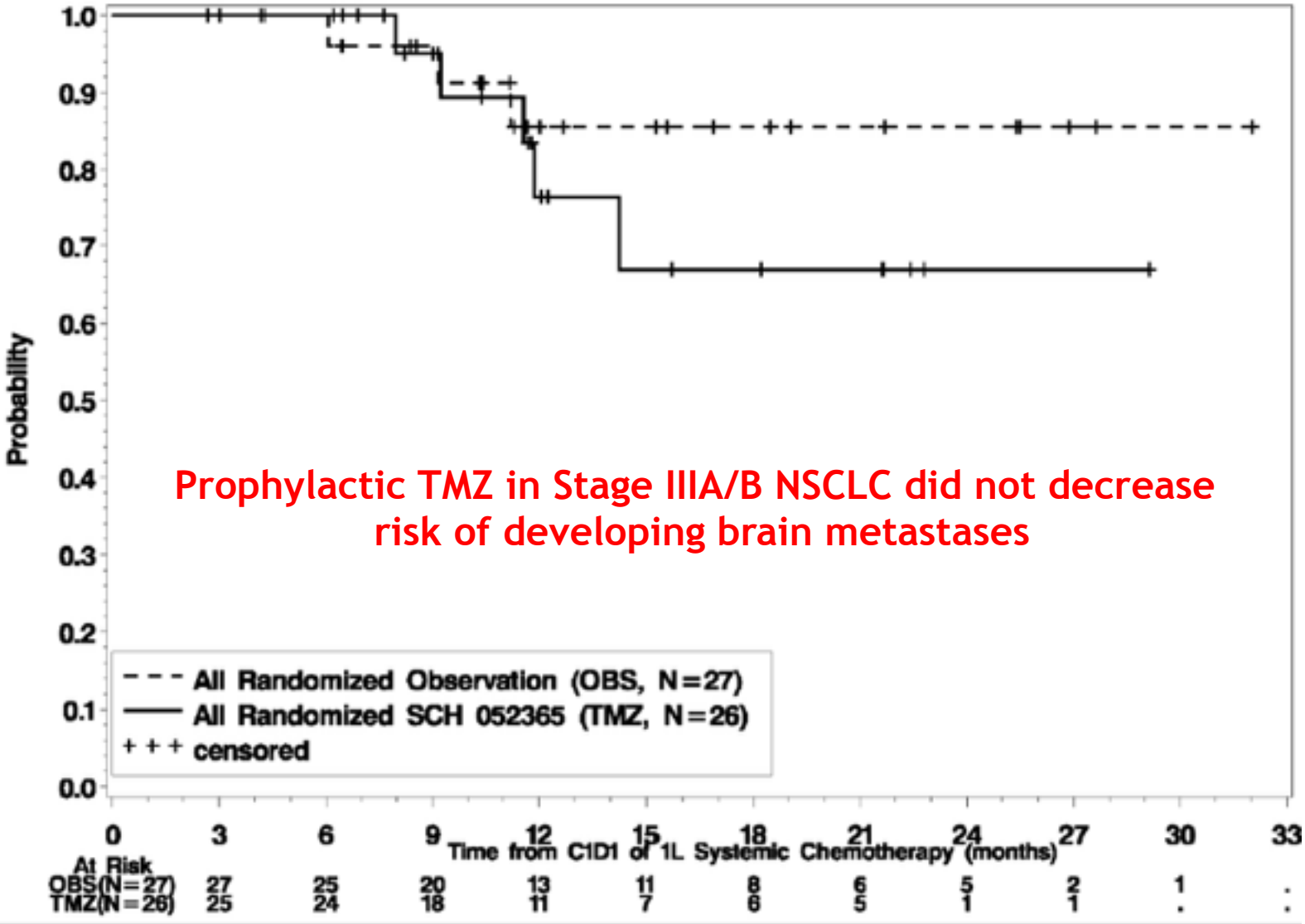
Brain Mets: Temozolomide



Prophylactic TMZ in Stage IIIA/B NSCLC did not decrease risk of developing brain metastases

PMID 25069747. Boggs DH, et al:, Clin Lung Ca, 15(6):433-40, November 2014.

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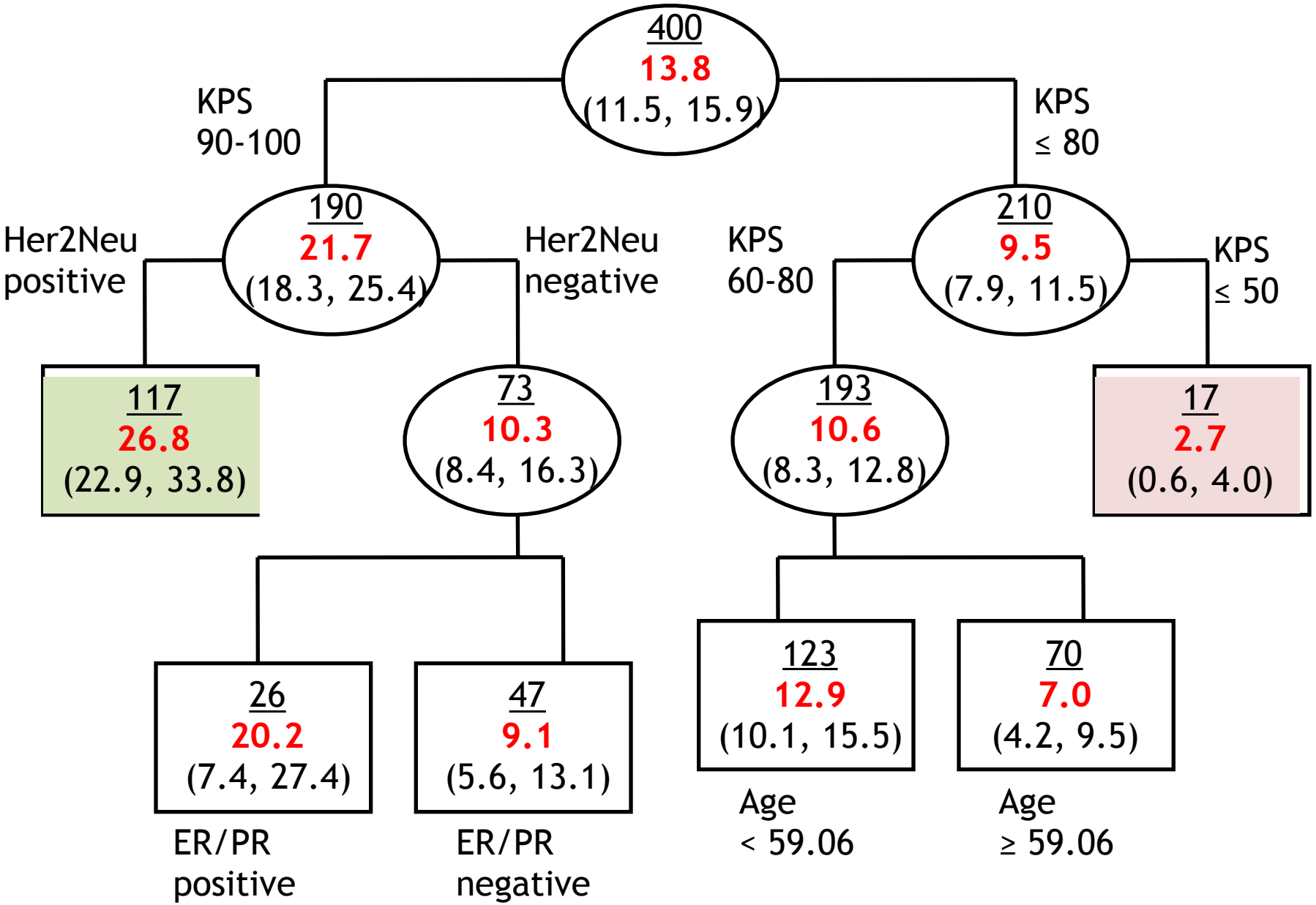
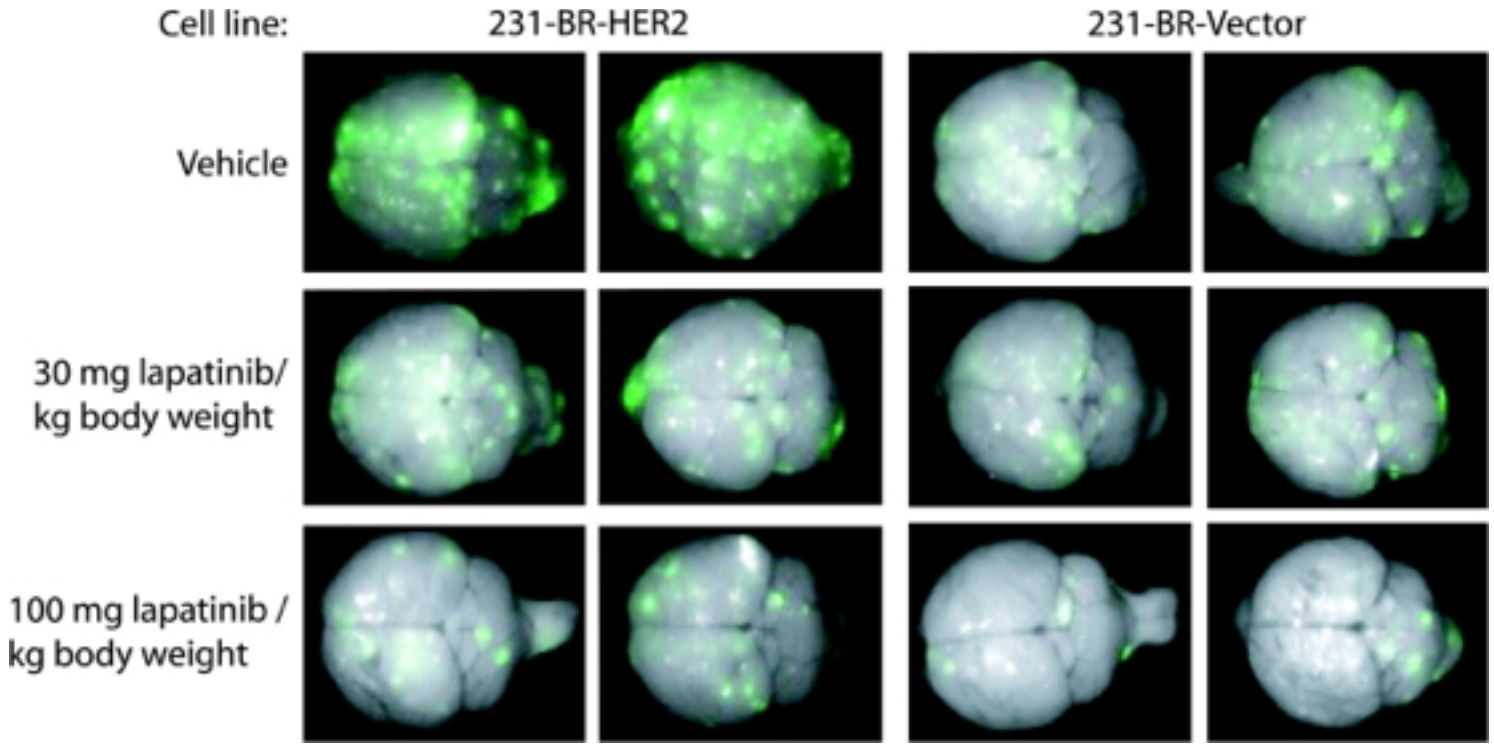
Recursive Partitioning Analysis



Lapatinib: Her2/Neu-Pos Breast Ca



Lapatinib effective at preventing the emergence of brain metastases

Gril, JNCI, 100:1092-1103, 2008

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

Bachelot, T., et al., The Lancet Oncology, 2013.

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

SCHEMA

S
T Sx or Steroids Y/N
R
A bRAF pos/neg
T
I GPA0-1.0
F 1.5-2.0
Y 2.5-3.0
3.5-4.0

R
A
N Arm 1: ICI
D induction then maint. until CNS
O progression, then SRS to all BM
M
I Arm 2: ICI + SRS
Z induction then maint. with SRS
E betwn 1st & 2nd dose of induction

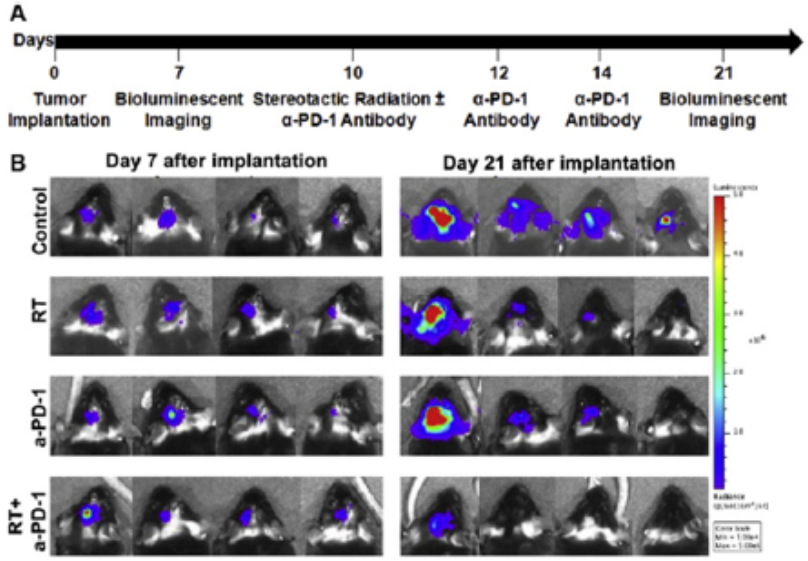
Preclinical Testing of Anti-PD-1 (with XRT) in Intracranial Glioblastoma

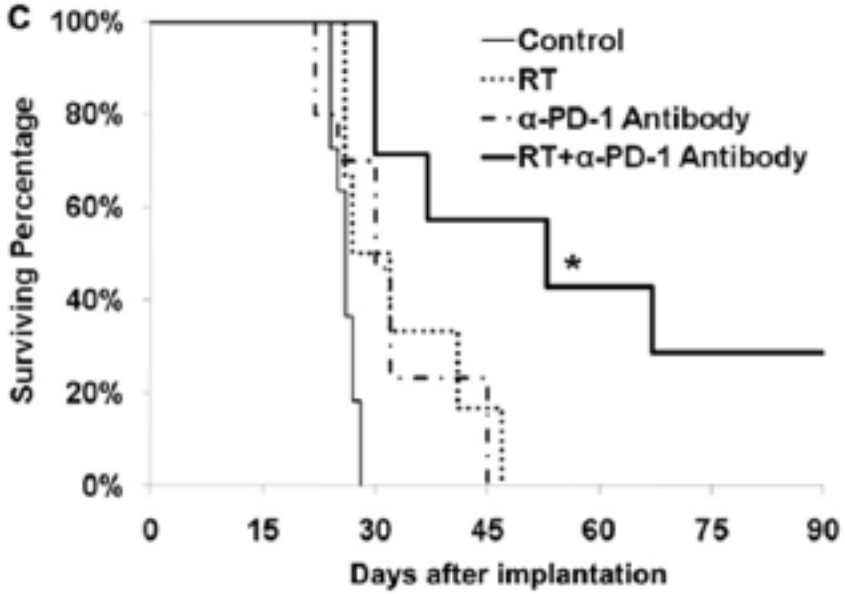
International Journal of Radiation Oncology biology ➔ physics
www.redjournal.org

Biology Contribution

Anti-PD-1 Blockade and Stereotactic Radiation Produce Long-Term Survival in Mice With Intracranial Gliomas

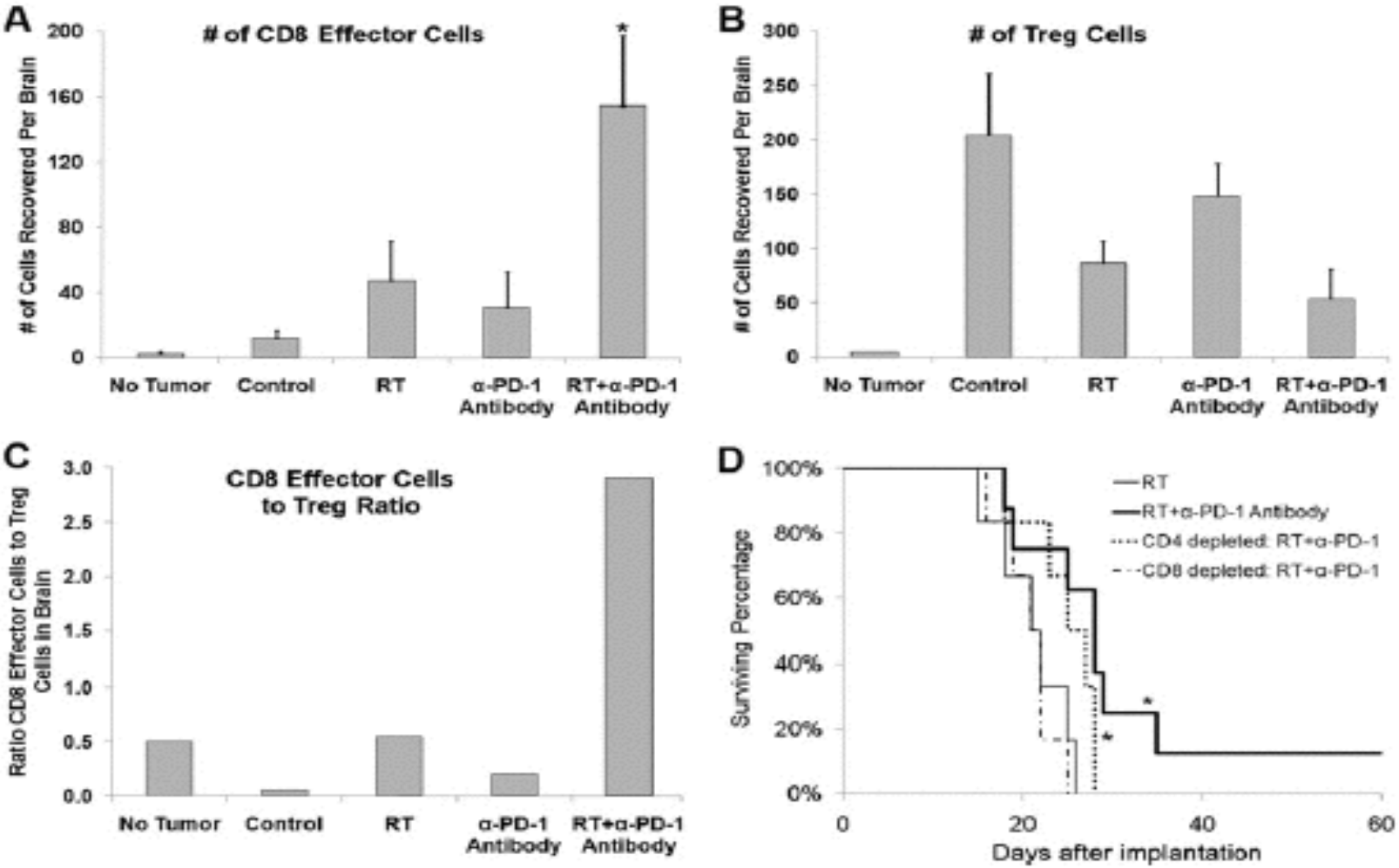
Jing Zeng, MD,* Alfred P. See, BS,† Jillian Phallen, BS,† Christopher M. Jackson, BA,† Zineb Belcaid, MS,† Jacob Ruzevick, BS,† Nicholas Durham, BS,‡ Christian Meyer, MD, PhD,§ Timothy J. Harris, MD, PhD,* Emilia Albesiano, PhD,† Gustavo Pradilla, MD,† Eric Ford, PhD,* John Wong, PhD,* Hans-Joerg Hammers, MD, PhD,‡ Dimitris Mathios, MD,† Betty Tyler, BS,† Henry Brem, MD,† Phuoc T. Tran, MD, PhD,* Drew Pardoll, MD, PhD,‡ Charles G. Drake, MD, PhD,‡ and Michael Lim, MD†





Int J Radiation Oncol Biol Phys, Vol. 86, No. 2, pp. 343–349, 2013

Preclinical Testing of Anti-PD-1 (with XRT) in Intracranial Glioblastoma



Int J Radiation Oncol Biol Phys, Vol. 86, No. 2, pp. 343–349, 2013

Ipilimumab Prolongs Survival After SRS

- Chart review to assess 77 (35% received ipilimumab) melanoma brain met patients treated with SRS alone.
- **MS: 21.3 vs.4.9 months in favor of Ipi. 2-year survival 47.2% vs. 19.7% in favor of Ipi.**
- Survival of pts with melanoma brain mets managed with ipilimumab and SRS can exceed the commonly anticipated 4-6 months.

Knisley, J Neurosurg, 201

Conclusions

- Brain mets: a common problem
- Avoidance of WBRT or toxicities associated with it is reasonable for some patients
  - Several new approaches reduce NC decline
    - Dosimetric
    - Pharmacologic
    - Substituting WBRT with
      - Temozolomide
      - Novo-TTF
      - Targeted agents
      - Immune check point inhibitors