Society for Immunotherapy of Cancer (SITC)

Immunotherapy for the Treatment of Brain Metastases

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Advances in Cancer Immunotherapy™ - Nashville
October 2nd, 2015

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Society for Immunotherapy of Cancer

Disclosures: Igor Puzanov, M.D.

I have the following financial relationships to disclose relevant to the content of this presentation:

- Paid Consultant
  - Amgen, Genentech, Roche
- There will be discussion about the use of products for non-FDA approved indications in this presentation.

Overview

- **Challenges of Brain Metastases**
  - ✓ Pathophysiology
  - ✓ BBB-Translating Benefit of Immunotherapy
  - ✓ Imaging Assessment
- **Melanoma as a Model**
  - ✓ Targeted therapy
  - ✓ Immunotherapy
  - ✓ Combos/triplets!

Brain Metastases in Melanoma

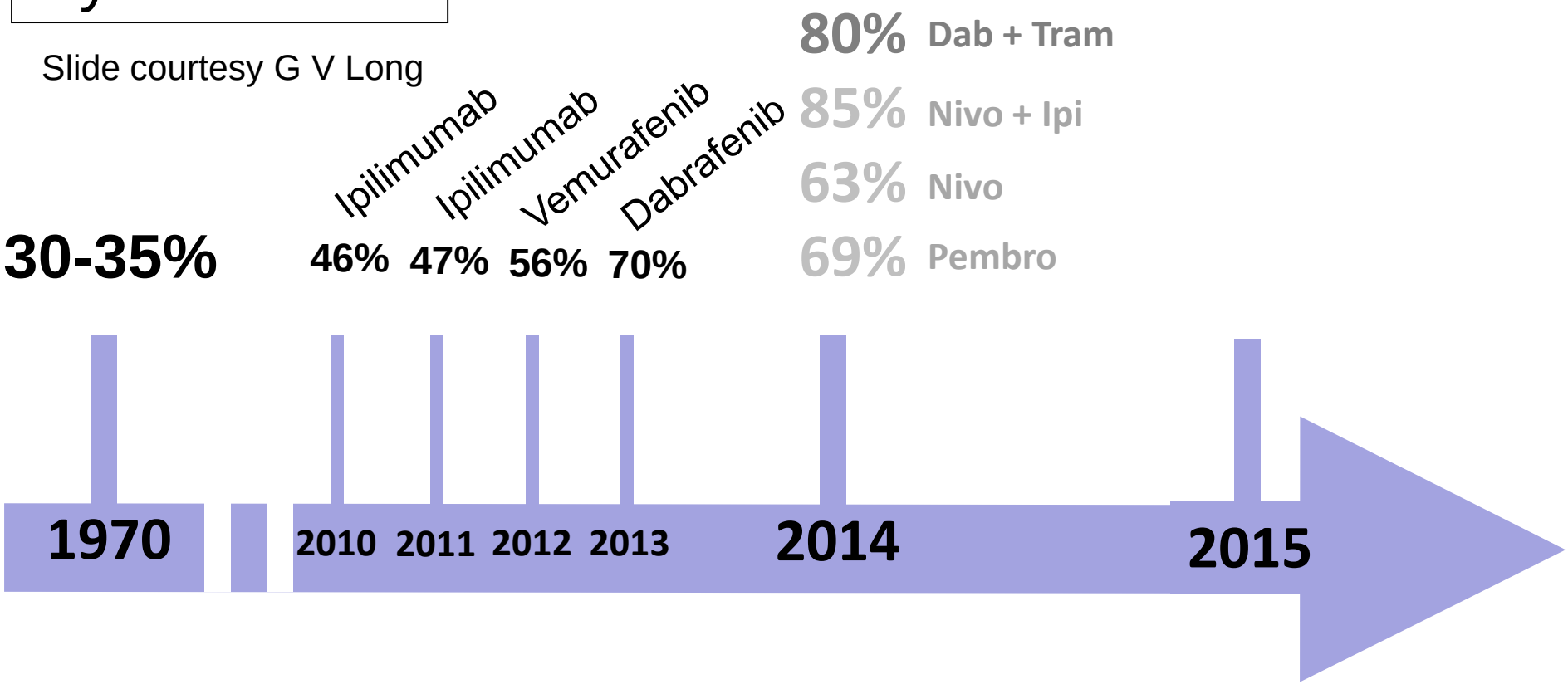
- **Highest propensity for brain mets among solid tumors**
- **Up to 40% of metastatic pts at the time of presentation**
- **Up to 70% at the time of death**
- **Surgery and/or SRS for oligometastatic disease**
- **No benefit from chemotherapy for active brain disease**
- **Excluded from all clinical trials- stability for 8-12 weeks**

Gorantla, Kirkwood, Tawbi- Current Oncology Reports- 2013 Oct;15(5):483-91.

Significantly improved survival in patients

1 year survival

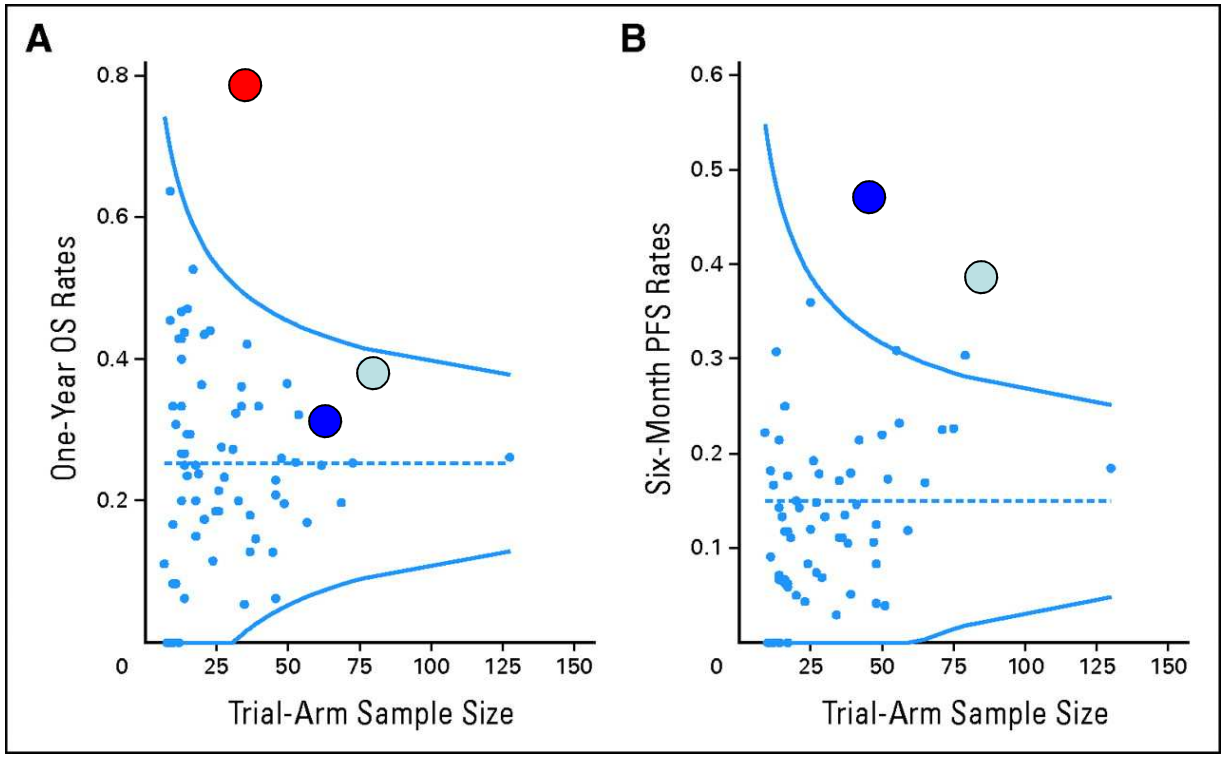
Slide courtesy G V Long



All of these therapies are more effective in patients with a lower disease burden

Korn-Kirkwood Meta-analysis of 70 trial arms (42 Phase II trials 1975-2005, 2100 pts)

- Benchmarks for Phase II trials:
- ✓ Median OS 6.2 m
- Median PFS 1.7 m
- 6-months PFS 15%



Dabrafenib/Vemurafenib

Ipilimumab

Ipi/Nivo for extracranial disease

Korn E L et al. JCO 2008;26:527-534

JOURNAL OF CLINICAL ONCOLOGY

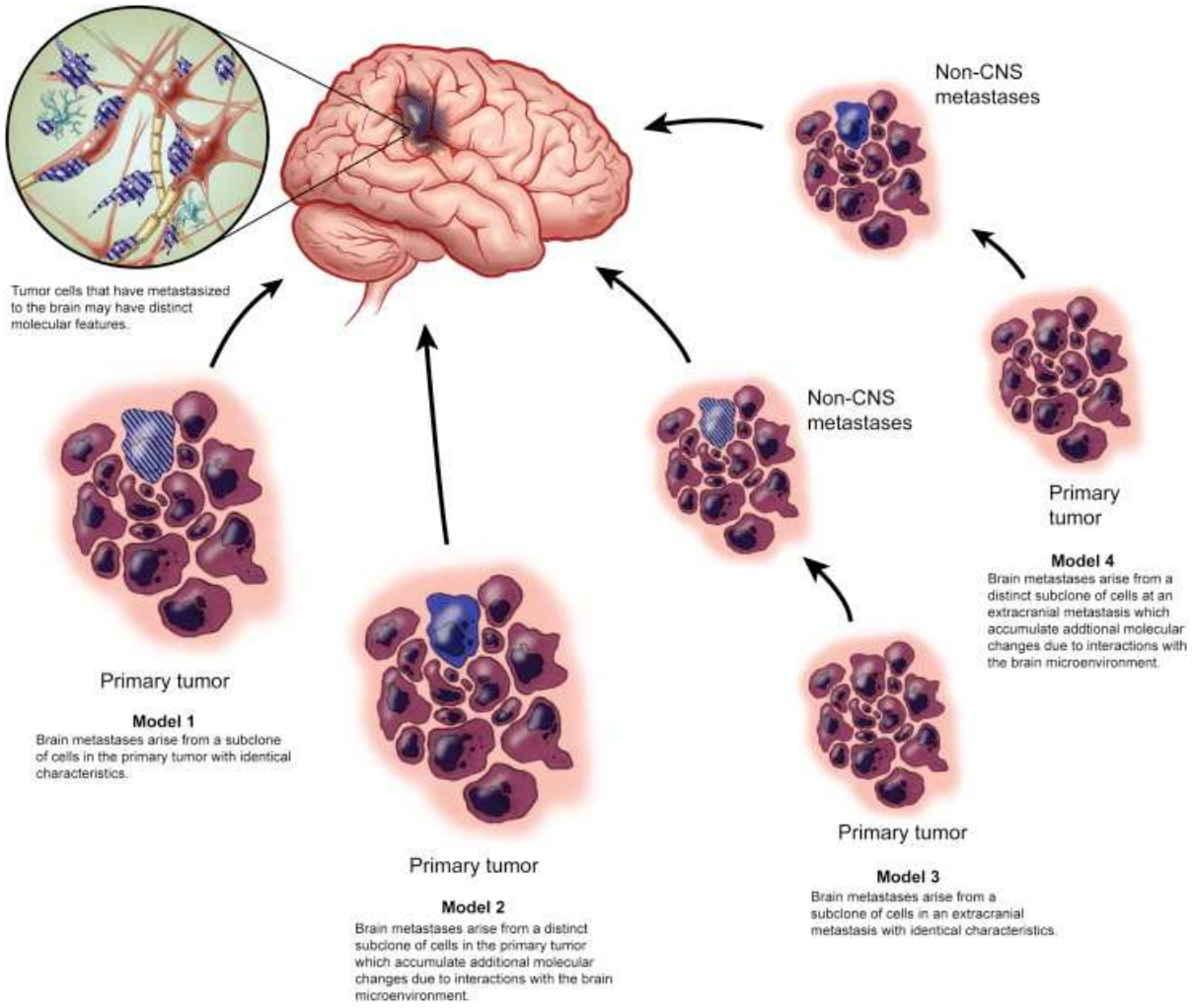
Specific Challenges in MBM

I. **Pathophysiology**
   - ✓ What drives the neurotopism
   - ✓ Immune cell trafficking

II. **Drug Penetration**
   - ✓ BBB- friend or foe?
   - ✓ Translating extracranial benefit

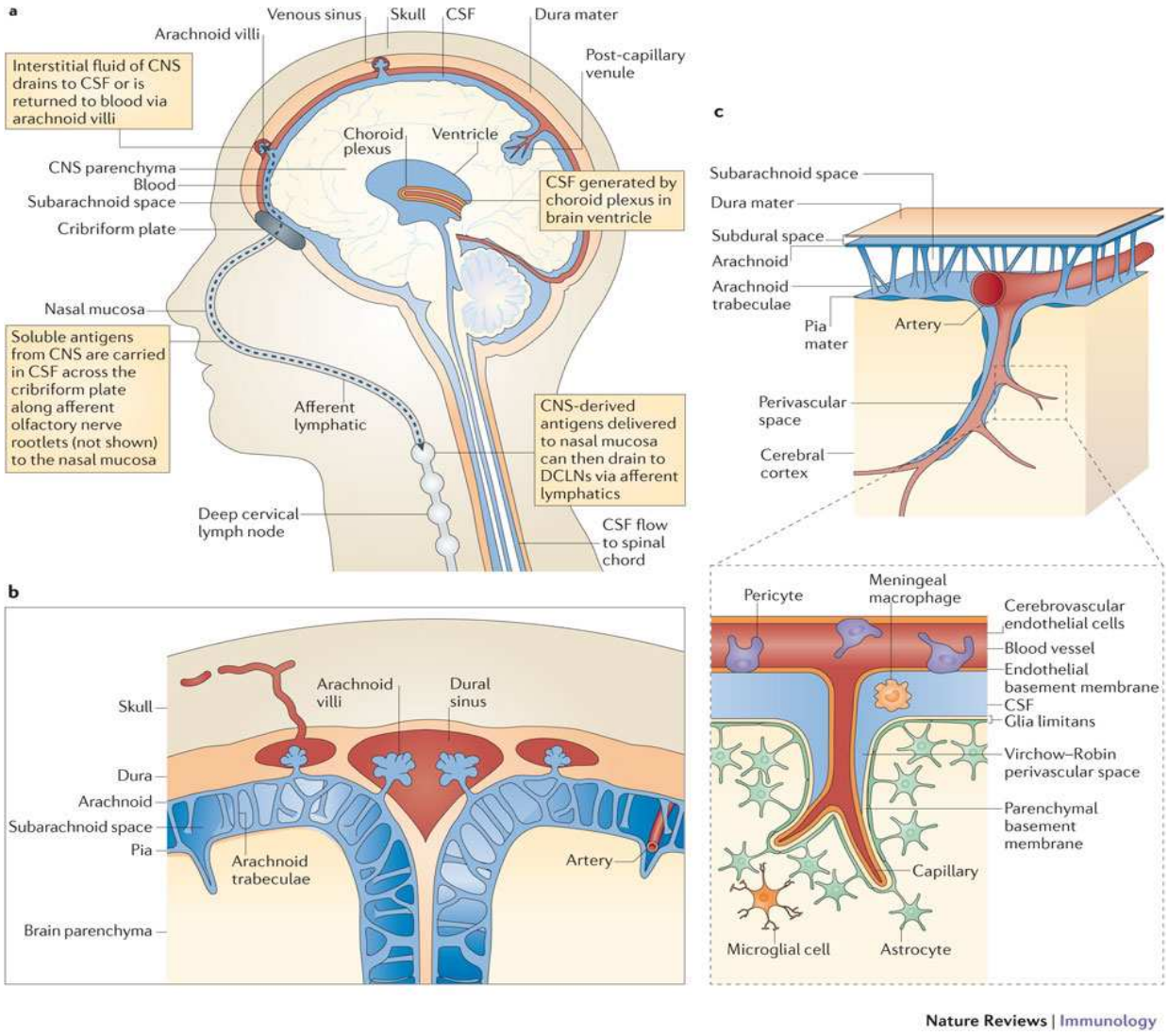
III. **Imaging Assessment**
   - ✓ Conventional 2D-MRI
   - ✓ 3D-MRI and DWI

Challenge I: Pathways into the Brain



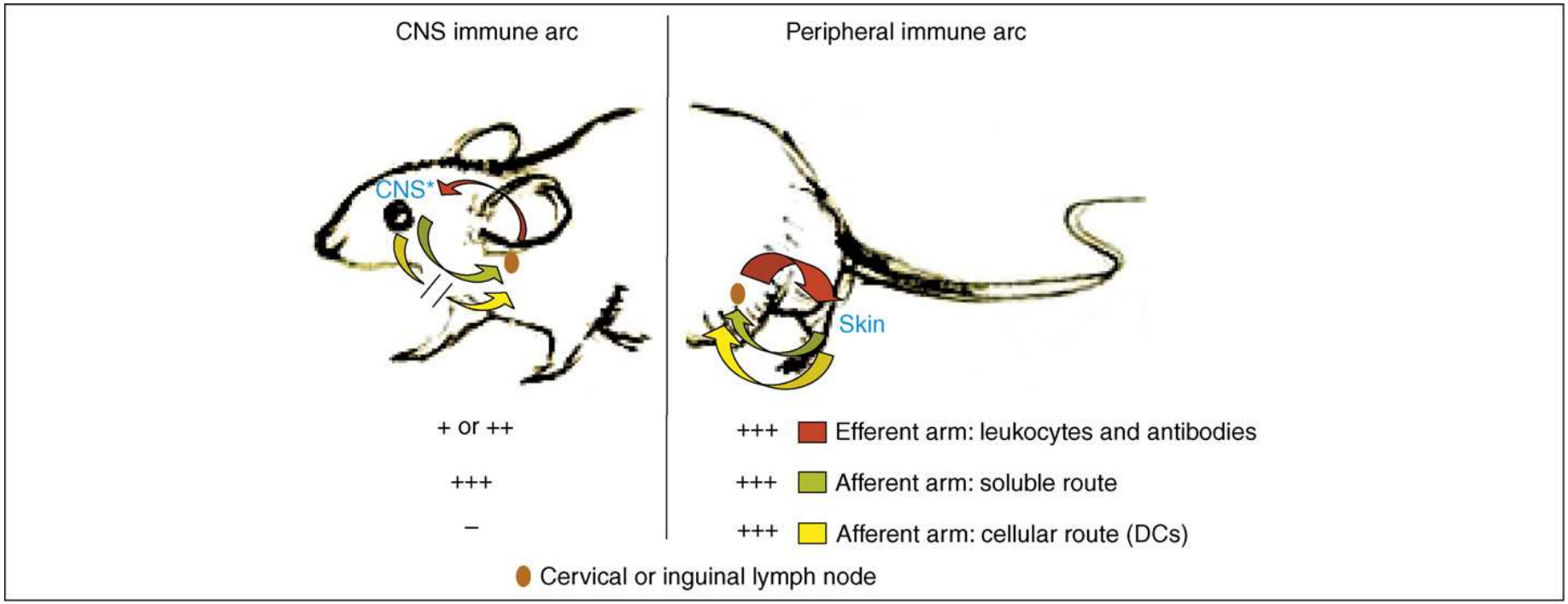
Chen, Davies- Biochemical Pharmacology, 83 (2012):305-314

Challenge I: Pathways out of the Brain



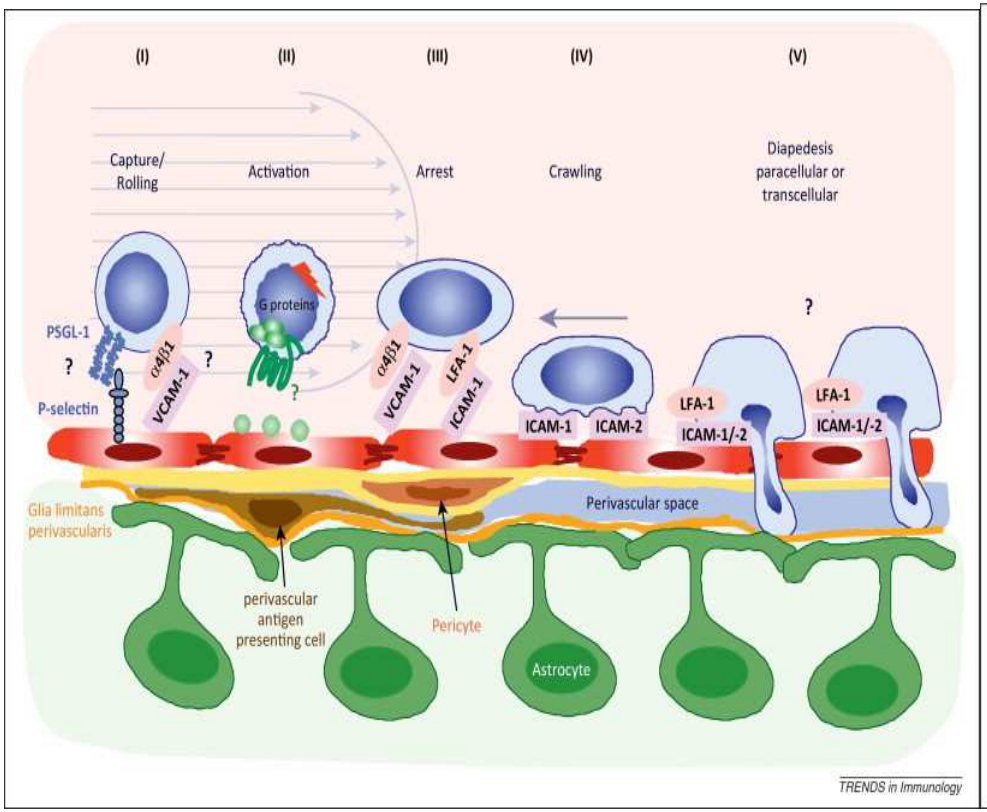
Ransohoff RM, Engelhardt B. Nat Rev Immunol. 2012 Sep;12(9):623-35.

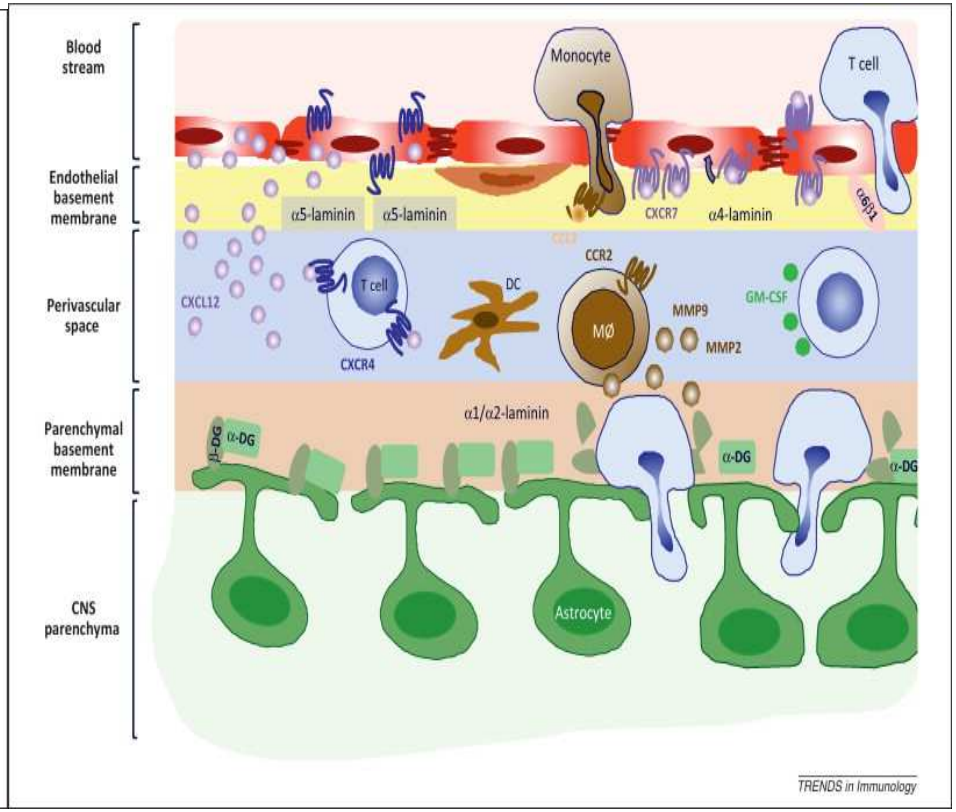
Challenge I: Pathways out of the Brain



Galea I, Bechmann I, Perry VH. Trends Immunol. 2007 Jan;28(1):12-8.

Challenge I: Pathways back to the Brain

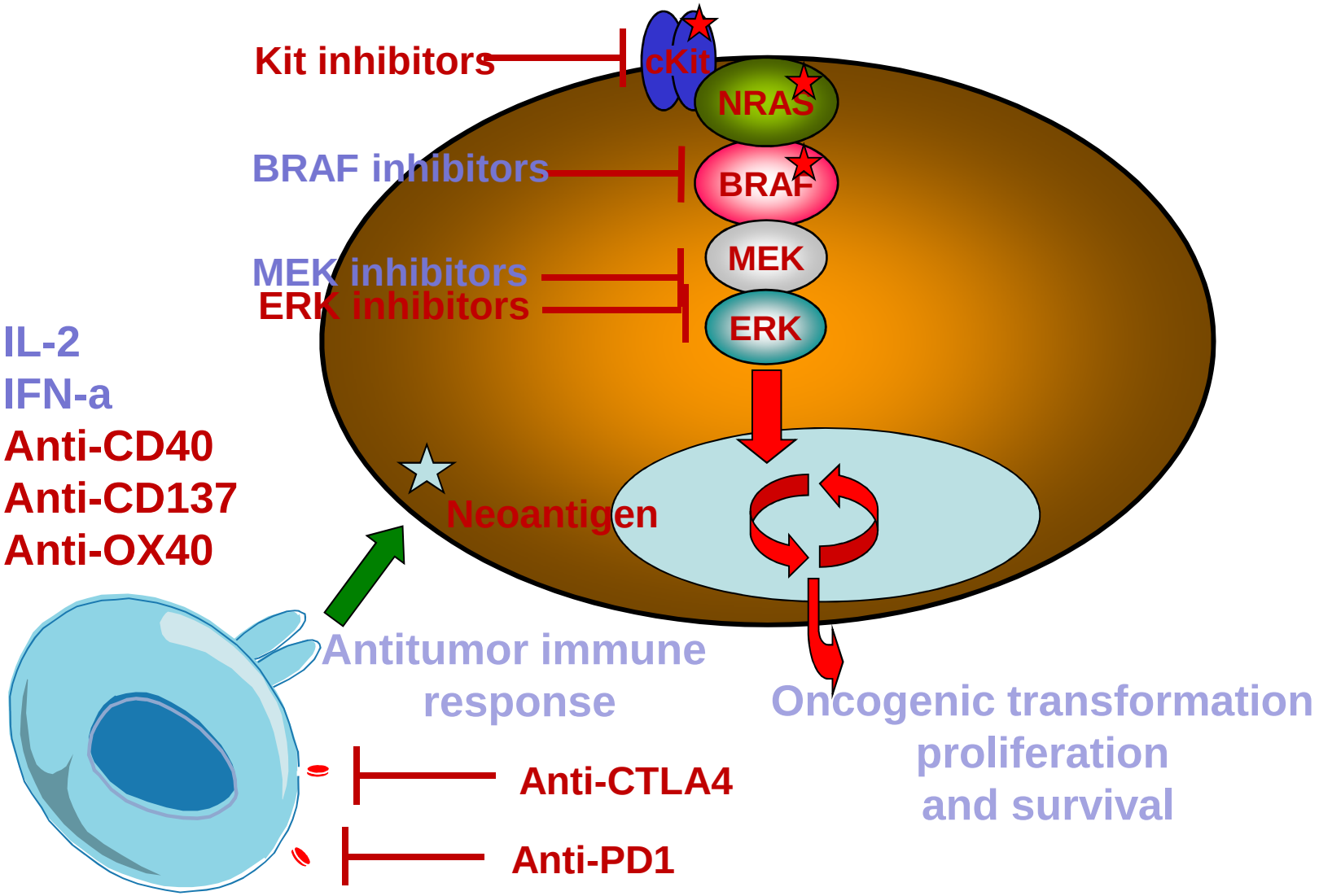




Engelhardt B, Ransohoff RM. Trends Immunol. 2012 Dec;33(12):579-89.

Therapeutic Targets in Melanoma

Host **Tumor**

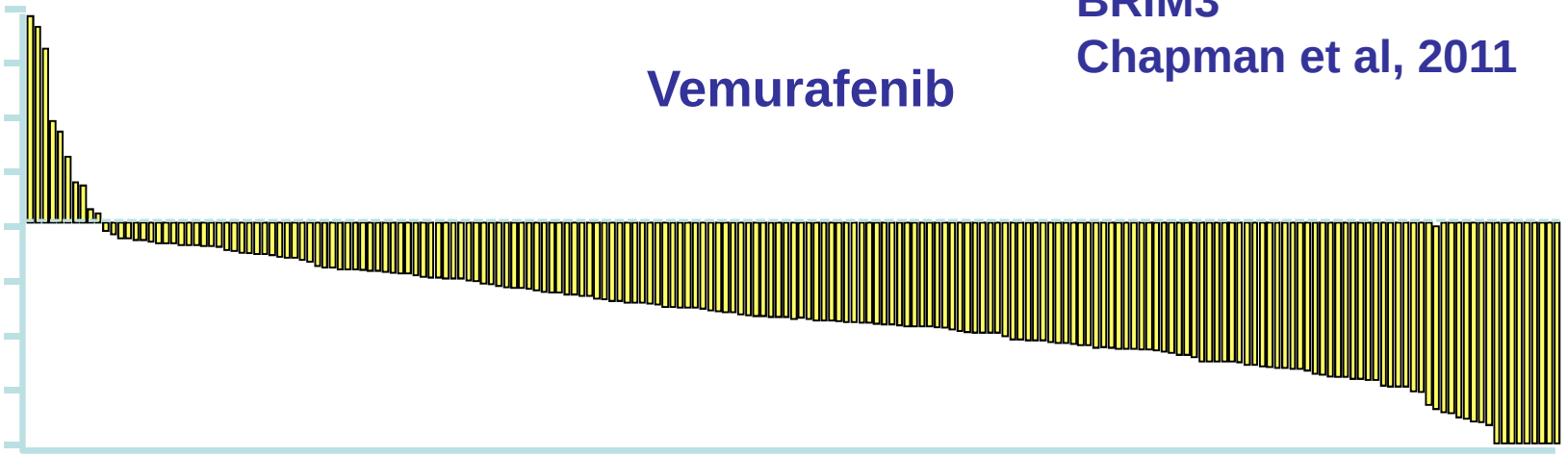


Fecher et al, 2007; Xing,2010

Comparison of Maximum Response With Vemurafenib and Dabrafenib

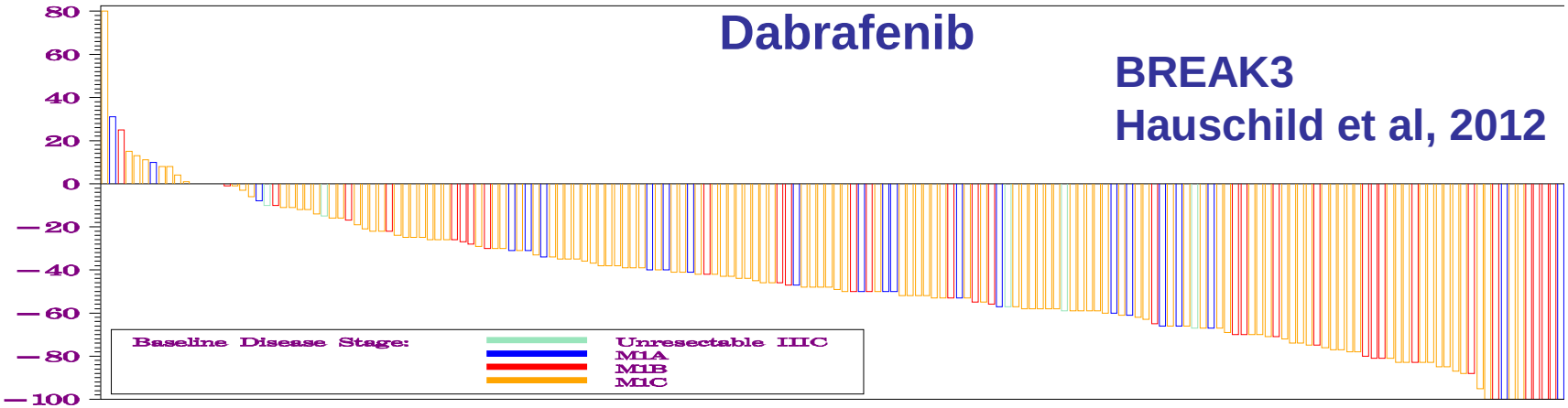
Vemurafenib

BRIM3
Chapman et al, 2011



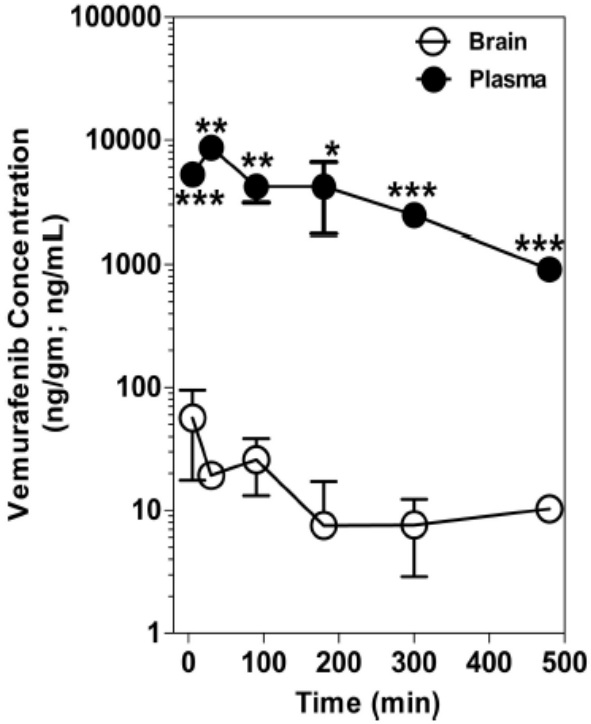
Dabrafenib

BREAK3
Hauschild et al, 2012



Challenge II: Drug Penetration through BBB

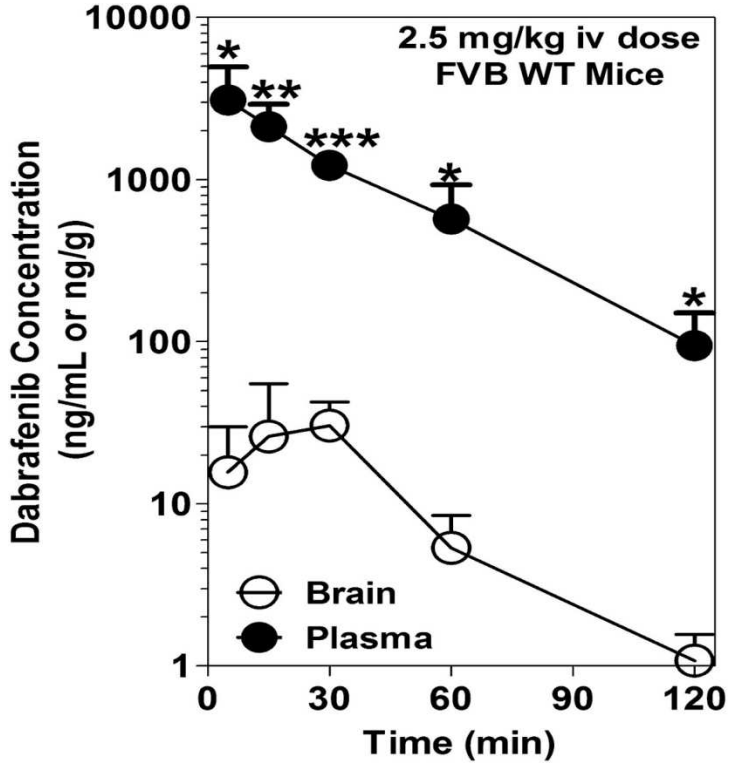
Vemurafenib



- IV infusion in mice- 3 log difference
- After steady state: 80-fold lower
- PgP (MDR-1) and BRCP1 dependent

Mittaplli, et al., J Pharmacol Exp Ther 2012 Jul;342(1):33-40

Dabrafenib



- IV infusion in mice- Ratio 0.023
- PgP (MDR-1) and BRCP1 dependent
- Dabrafenib has 10-fold better than vemurafenib

Mittapalli, et al., J Pharmacol Exp Ther 344:655–664, March 2013

Challenge II: Translation of Clinical Benefit

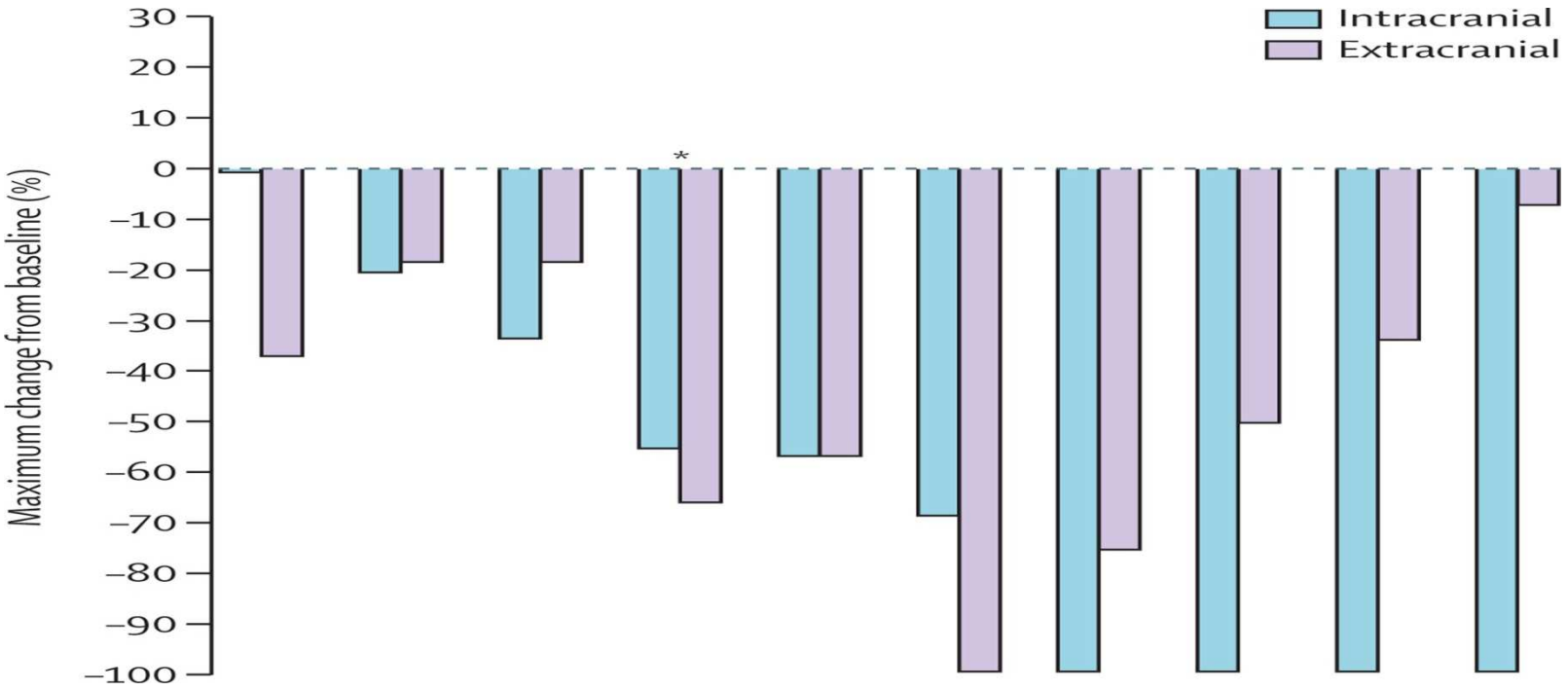
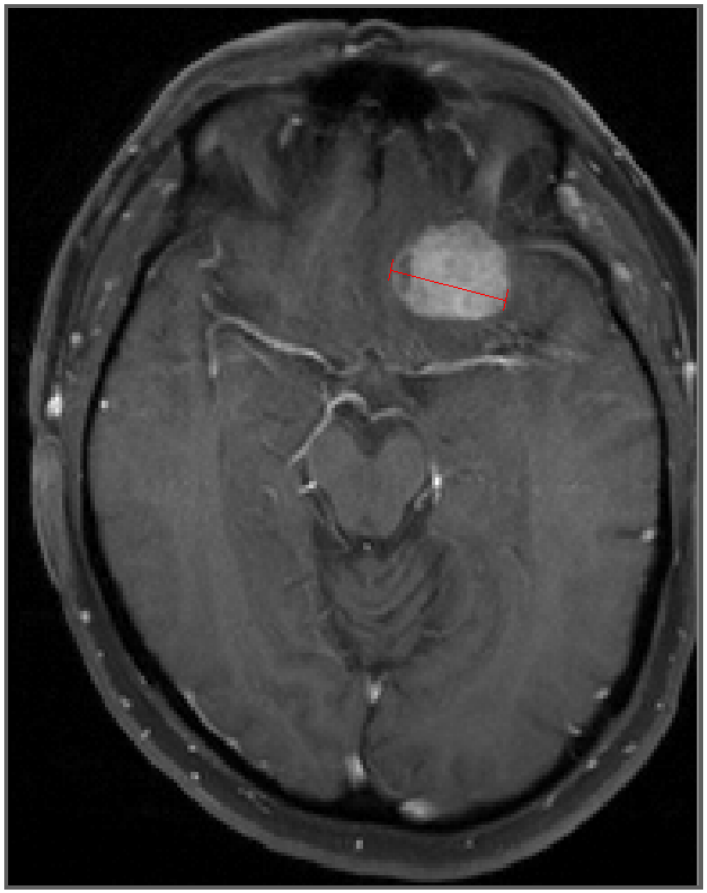


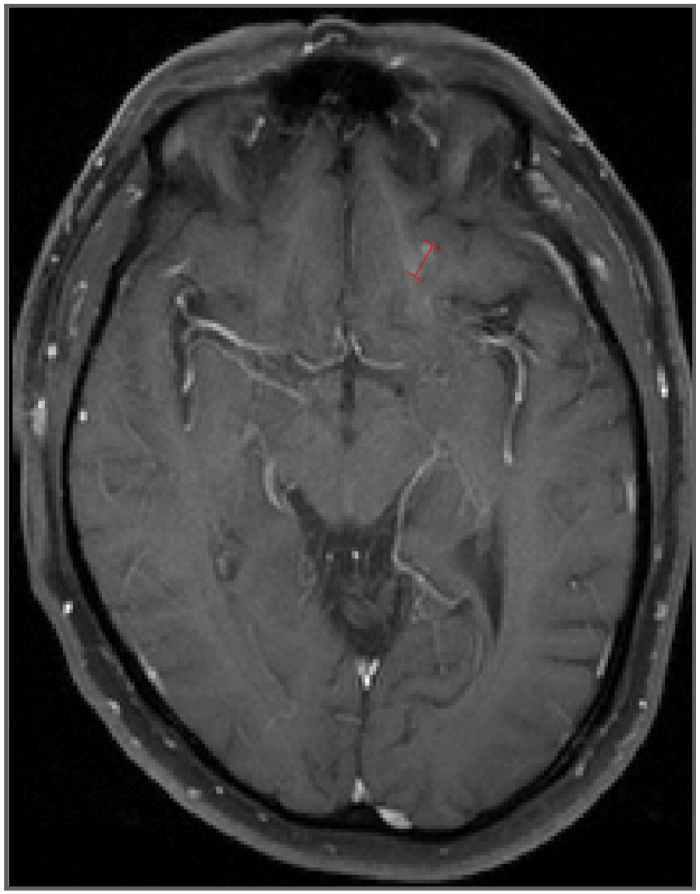
Figure 5 Change in intracranial and extracranial tumour size in the ten patients with Val600 BRAF-mutant melanoma and untreated brain metastases given the recommended phase 2 dose *Patient with Val600Lys mutation.

Falchook et al., Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumours: a phase 1 dose-escalation trial, The Lancet, Volume 379, Issue 9829, 2012, 1893 - 1901

BREAK-MB
Phase II two-cohort open-label study

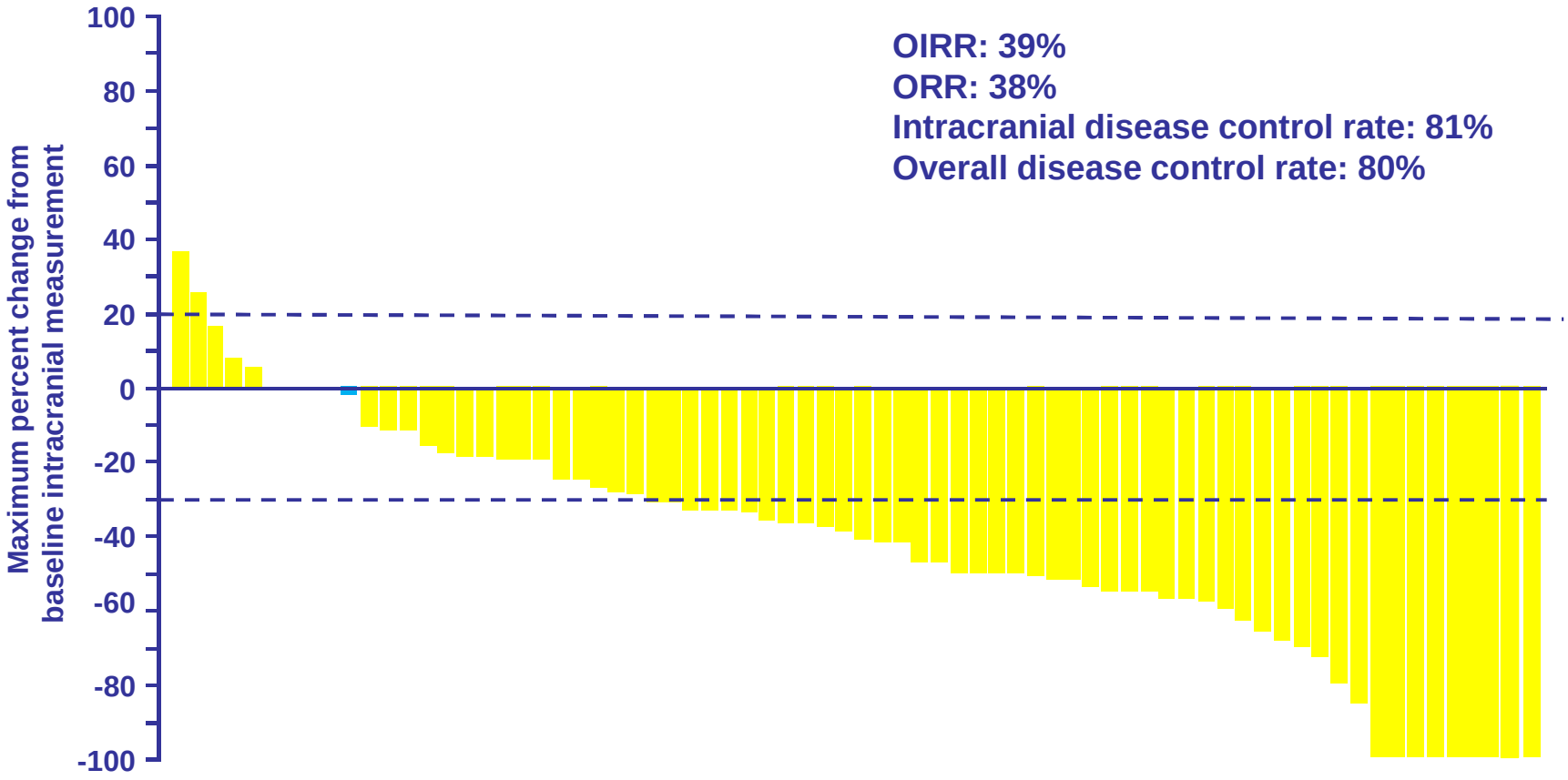


Baseline

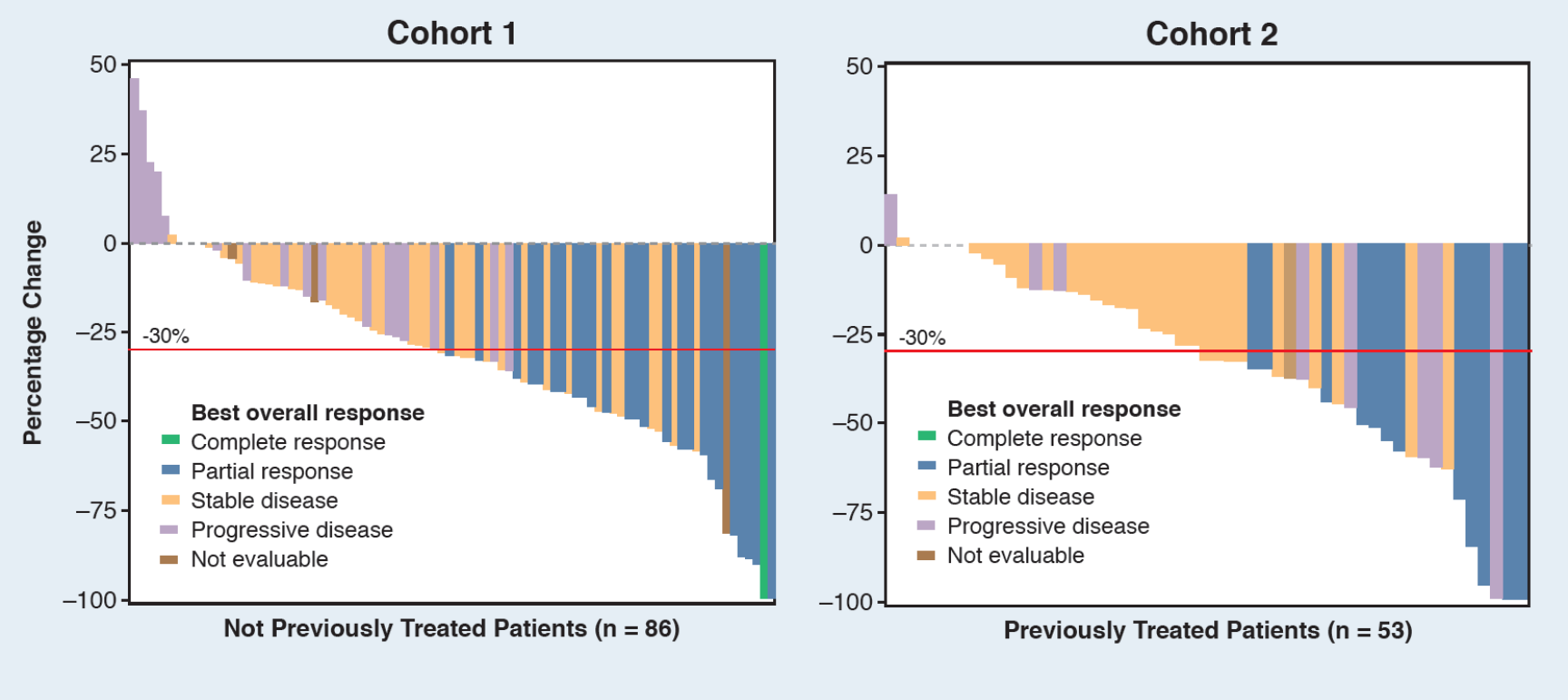


Week 32

No prior brain treatment: Cohort A $BRAF^{V600E}$ mutation-positive patients maximal intracranial target lesion reduction

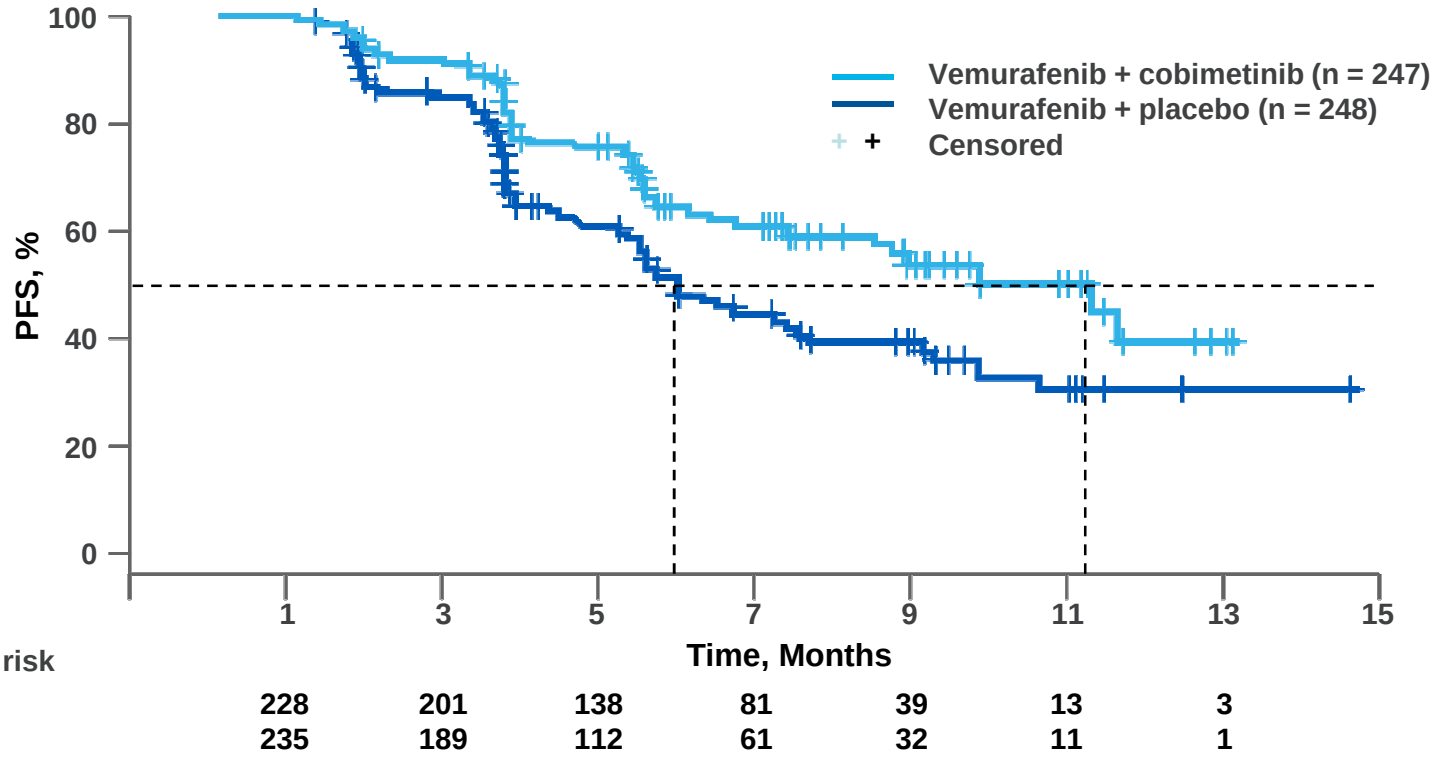


Vemurafenib in Metastatic Melanoma Patients With Brain Metastases: An Open-Label, Single-Arm, Phase 2, Multicenter Study



Kefford, et al. Psented at the 10th International Meeting of the Society for Melanoma Research; November 17-20, 2013; Philadelphia, Pennsylvania, USA

coBRIM* (GO28141) Phase 3 Study of Cobimetinib in Combination With Vemurafenib vs Vemurafenib Alone in *BRAF*^{V600}-Mutated Metastatic Melanoma: **IRF-Assessed PFS in the ITT Population†**



No. of patients at risk							
Vem + cobi	228	201	138	81	39	13	3
Vem + placebo	235	189	112	61	32	11	1

	Vem + Placebo	Vem + Cobi
Patients with events, n	117	82
Median PFS, months (95% CI)	6.0 (5.6-7.5)	11.3 (8.5-NE)
Hazard ratio (95% CI) *P* value	0.60 (0.45-0.79) 0.0003	

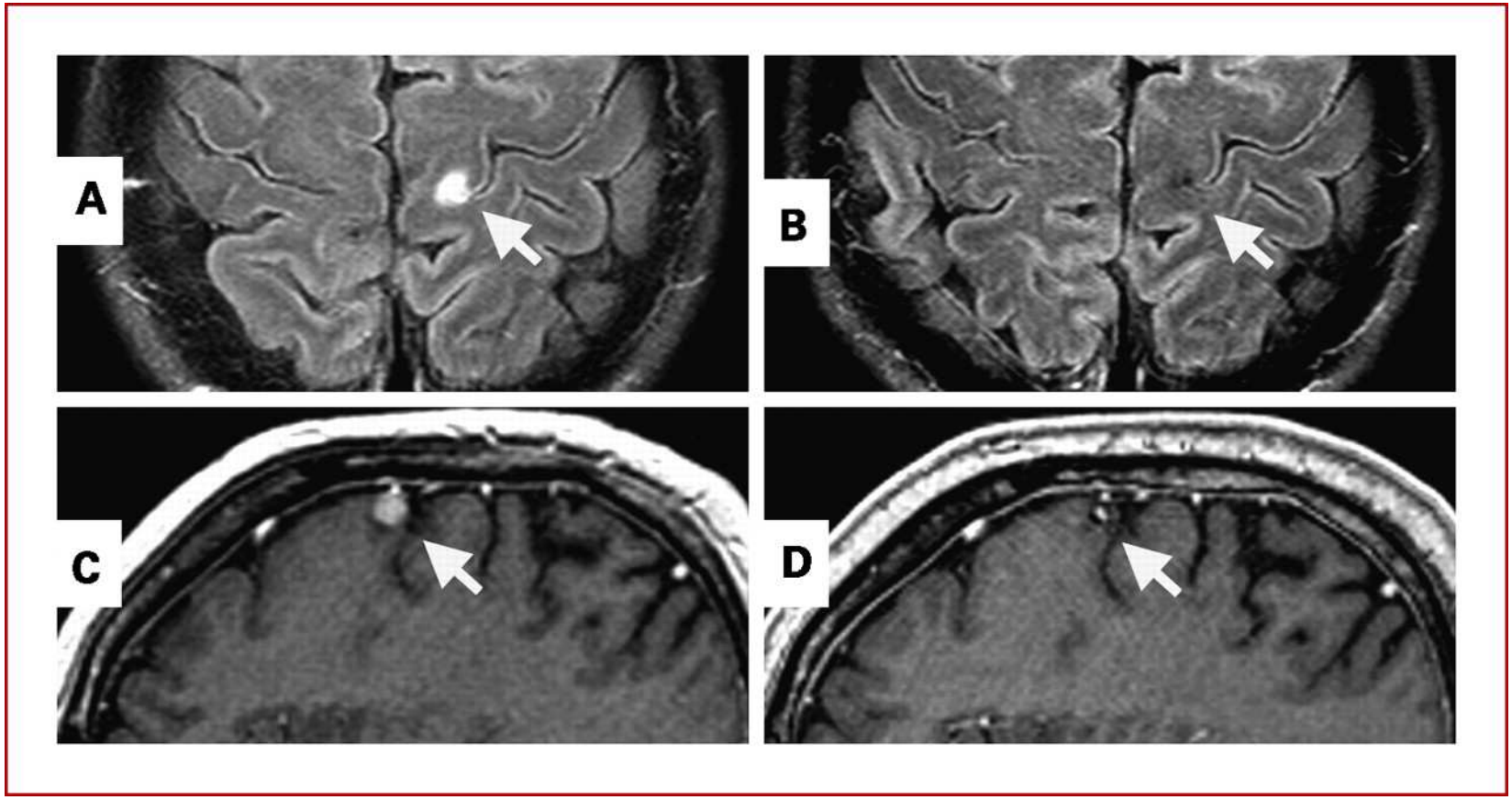
Larkin J, et al. [Online supplementary appendix.] N Engl J Med. 2014:doi:10.1056/NEJMoa1408868.

*Genentech-Roche Sponsored Study

Immunotherapy in Active Brain Mets
High-Dose IL-2

- Active brain mets generally exclusion
- Selected case reports or series of 3-5 pts
- Mostly focused on safety and minor responses- e.g., CR in a 2 mm lesion
- NCI- Surgery Branch series- 37 pts with 5.6% response compared to up to 19% in ECM
- UPCI Series- 271 pts treated with IL-2, presence of CNS mets poor prognostic factor (Davar, Kirkwood, Tawbi)

Immunotherapy in Active Brain Mets
Adoptive T Cell Therapy



- 26 pts treated- 1 hemorrhage associated with thrombocytopenia
- 22-41% intracranial response reported

Jenny J. Hong et al. Clin Cancer Res 2010;16:4892-4898

Immunotherapy in Active Brain Mets Ipilimumab

- Parallel cohorts- non-randomized Phase II
- 2 independent cohorts each with a 2-stage design
- Asymptomatic: 51 pts- ORR 10%
- Symptomatic on steroids: 21 pts, ORR 5%
- Anti-CTLA4 active and safe but only in patients with asymptomatic disease off-steroids
- Ipi + fotemustine- 50% response in 20 Italian pts

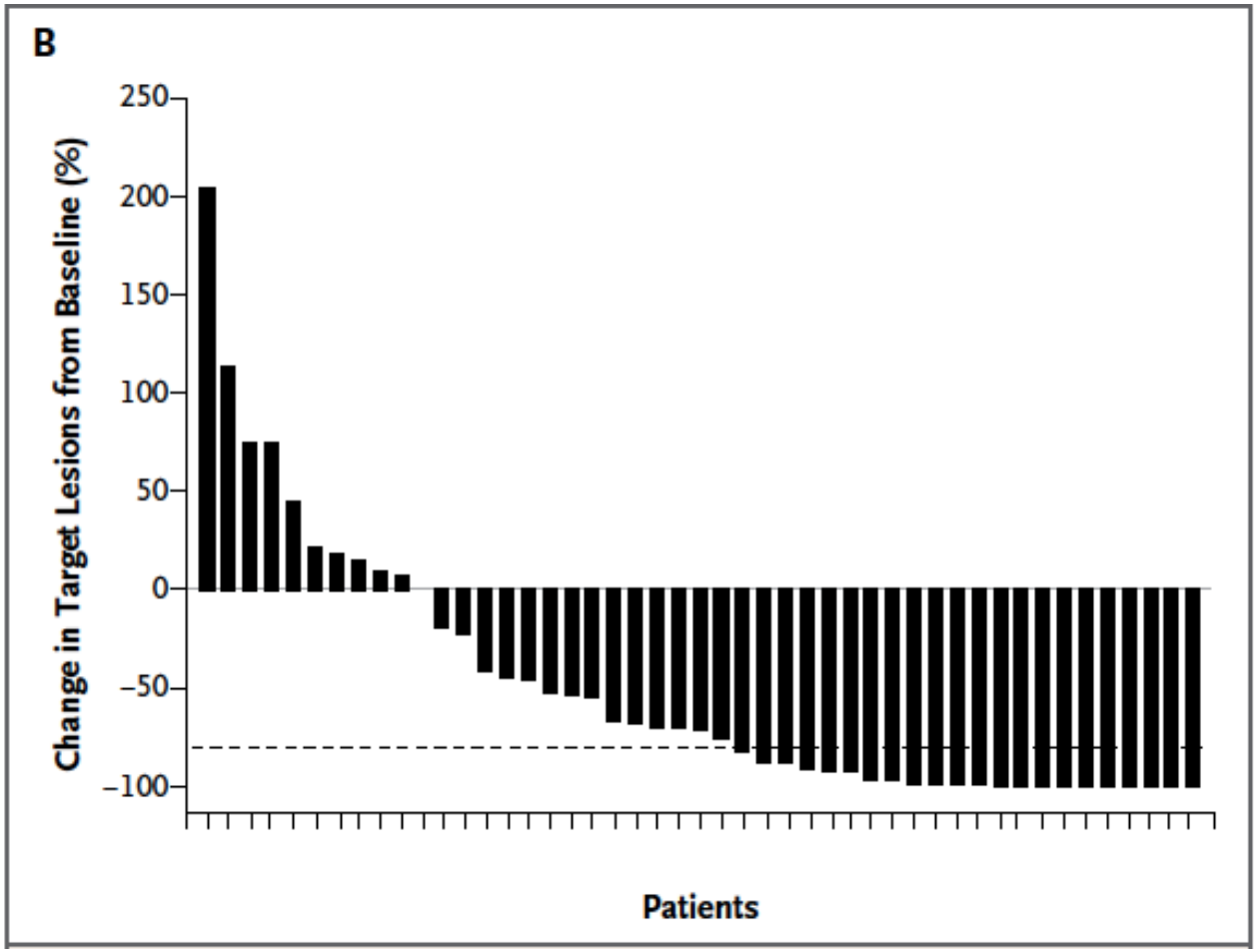
Margolin, et al. Lancet Oncology 2011

Immunotherapy in Active Brain Mets
Single Agent Pembro

- 18 melanoma pts reported at ASCO 2015
- Intracranial responses observed
- 22% OIRR by modified RECIST
- Parallels extracranial activity
- Steroids utilized to manage brain edema

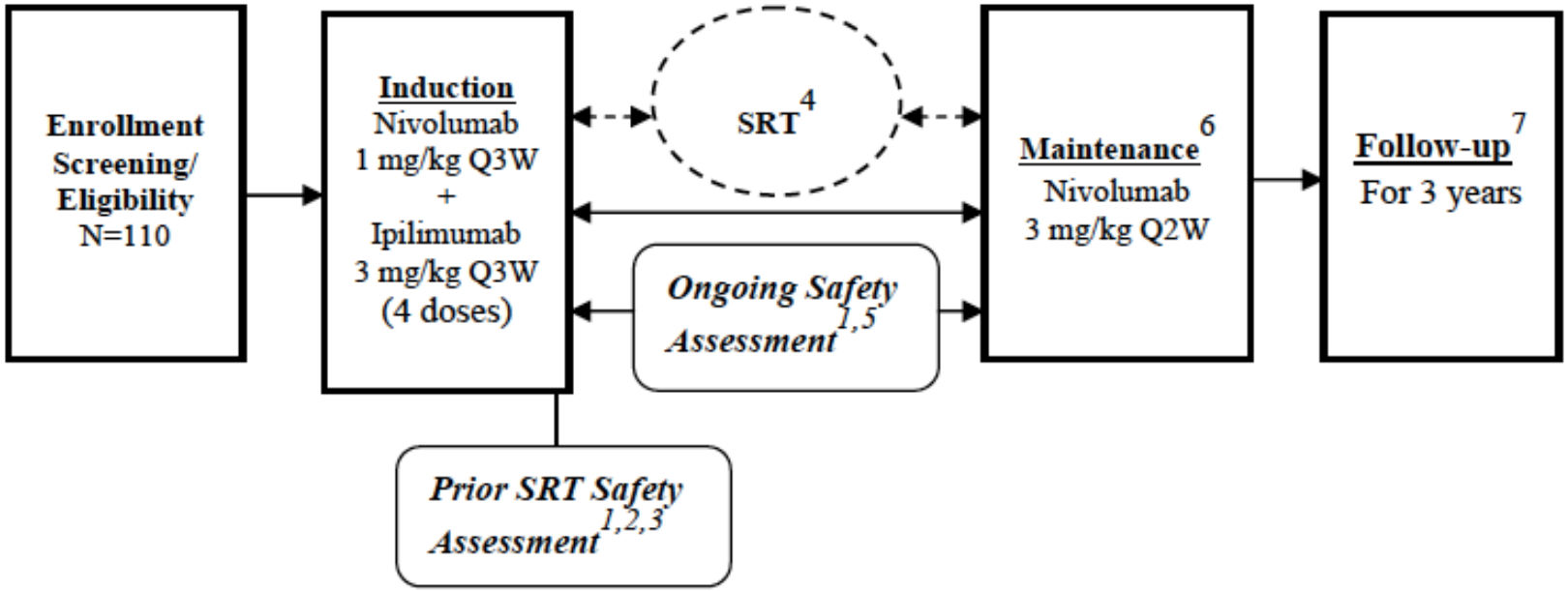
Kluger, et al. Abstract #8035, ASCO 2015

Ipilimumab + Nivolumab!!..



Wolchock, NEJM, 2013

CHECKMate 204: Cytokine Working Group Phase 2 of ipilimumab + nivolumab in MBM

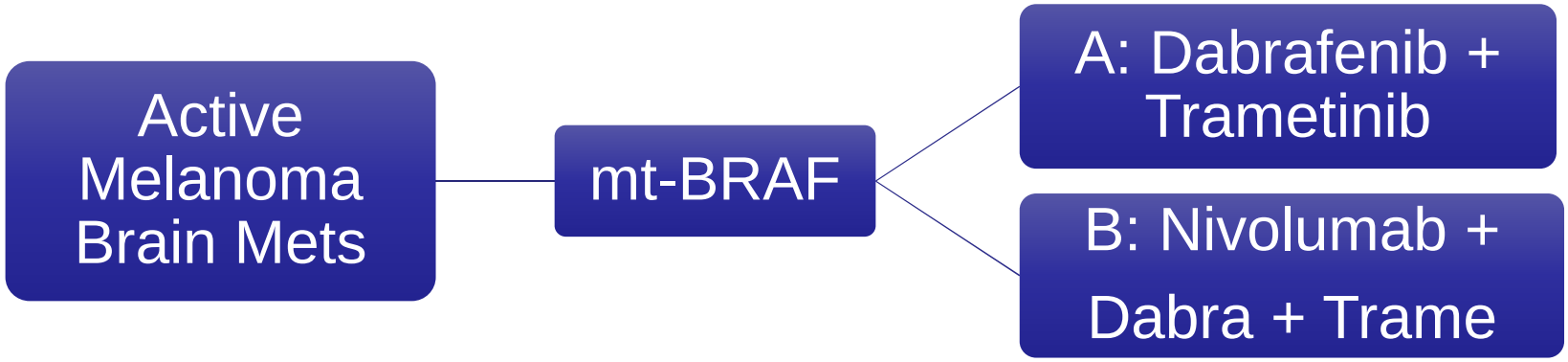


- BMS and Cytokine Working Group- PI Tawbi
- Modified RECIST as primary endpoint- 110 pts planned

Targeted + Immunotherapy Combinations

- **Ipilimumab + vemurafenib (Ribas, et al. NEJM April 2013)**
  - ✓ **Closed for liver toxicity- G3 transaminase elevatioN**
  - ✓ **Schedule and dose may have been an issue**
- **Phase I for Ipi + dabrafenib +/- trametinib**
  - ✓ **Ipi+dabrafenib appears tolerable- expansion and Phase II finished**
  - ✓ **Triple combination resulted in bowel perforations (Minor et al, PCMI 2015)**

EA6145- Proposed Study Re-Design



Sample Size

- Primary endpoint:
  - Objective Intracranial Response (OIRR) by 3D-MRI

- Randomized phase II comparing ORR in A vs. B
  - A- Trametinib + Dabrafenib OIRR 50%
  - B- Nivolumab + Trametinib + Dabrafenib OIRR 70%

- one-sided type I error of 0.1 and 80% power
- sample size for each arm will be about 65/arm
- Stratification by Prior SRS, Steroids, and V600E vs K

Challenge III:
Imaging assessment of intracranial response

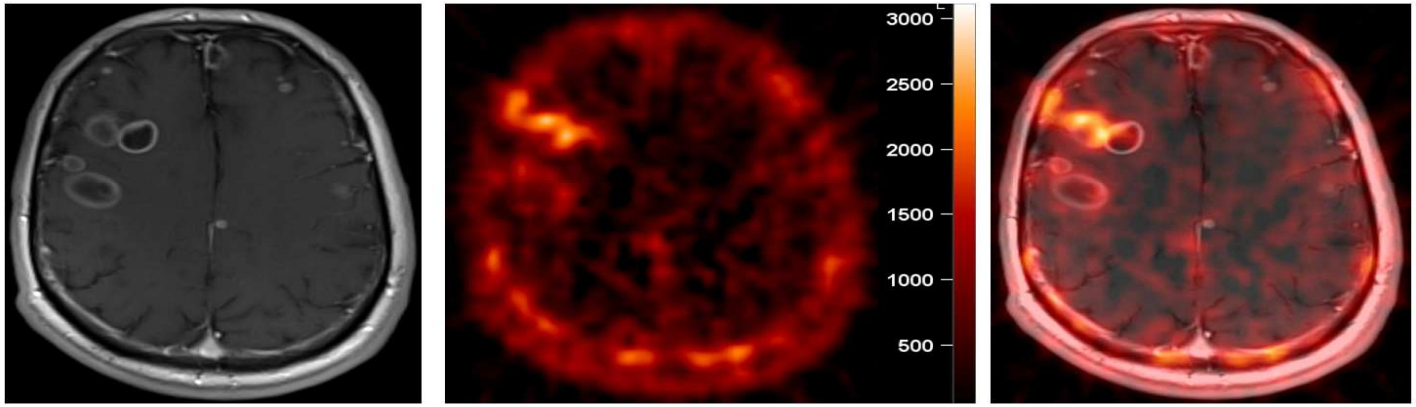
- BREAK-MB- OIRR as assessed by the investigator
- Modified RECIST
- significant discordance between investigator assessment and an independent review committee in 42% of the cases.
- Independent adjudication committee upheld the investigator assessment 68% of the time.
- Intrinsic T1 hyperintensity/hemorrhagic disease
- RANO-BM (Response Assessment Criteria in Neuro-Oncology- Brain Metastases) Lin et al., Lancet Oncology June 2015

EA6145 Primary Endpoint- 3D-MRI as an Integral Biomarker

- 3D techniques are more promising than conventional imaging assessments in predicting survival outcome
  - Reduce the effect of intrinsic T1 hyperintensity
  - Reduce inter-observer variability
- Not more than 3-5 added minutes on SOC MRI
- important implications for imaging trials of other intracranial neoplastic disease.
- 2 independent readers + adjudicator
- Central read provided to participating center within 7 d- ACRIN 6677/RTOG 0625

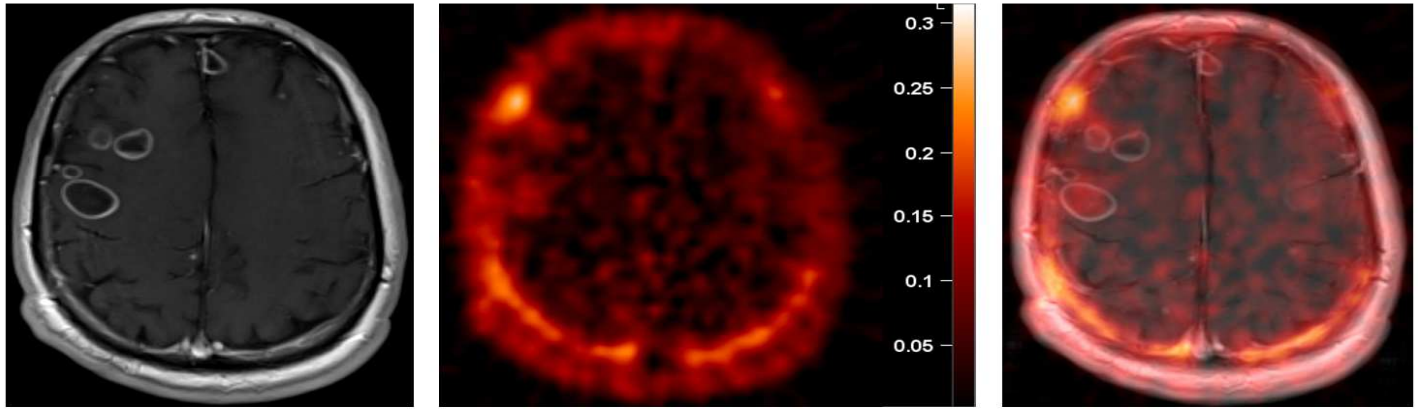
Challenge III: Novel Imaging- PET-MRI

Baseline Scan Date
12/18/2013



Contrast Enhanced MRI | FLT PET | FLT PET fused to Contrast MRI

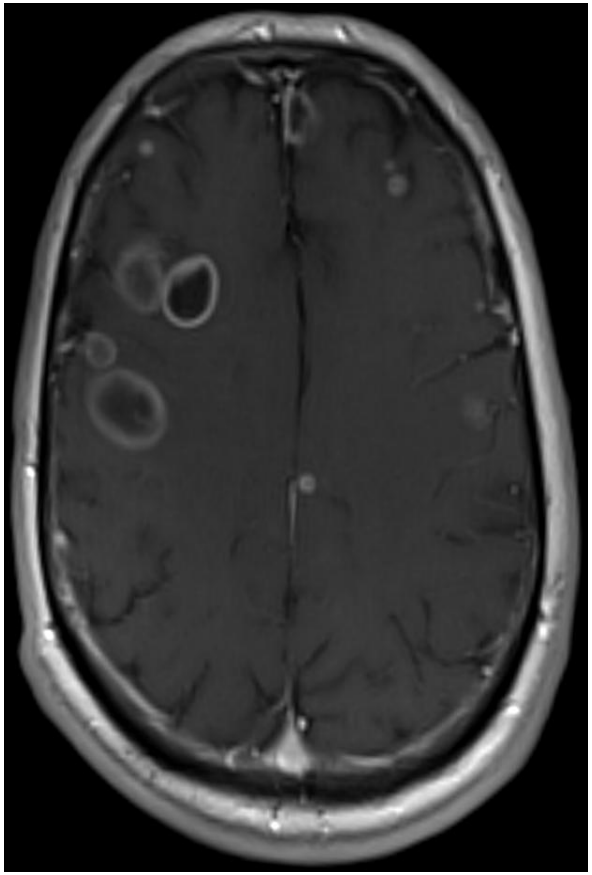
Follow-up Scan Date
1/8/2014



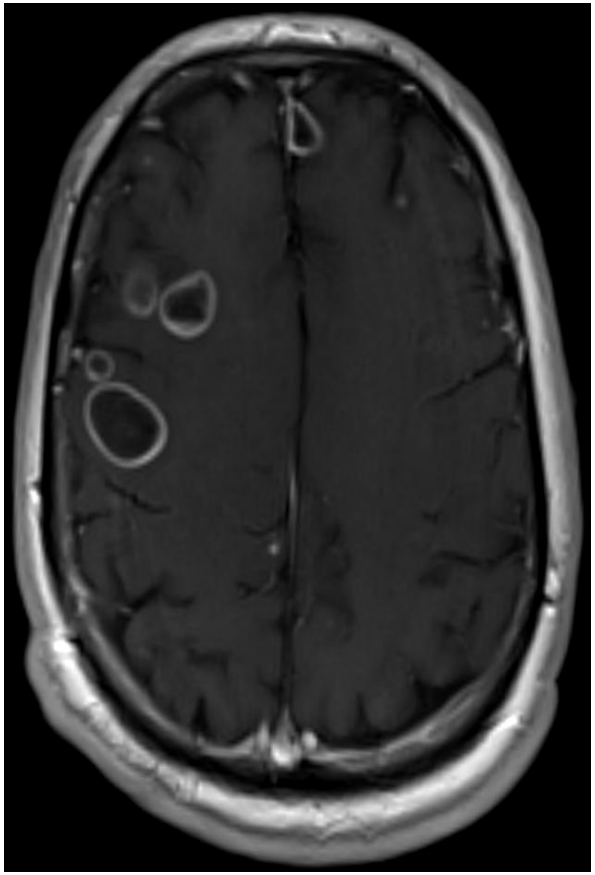
Contrast Enhanced MRI | FLT PET | FLT PET fused to Contrast MRI

Conventional 2D-MRI

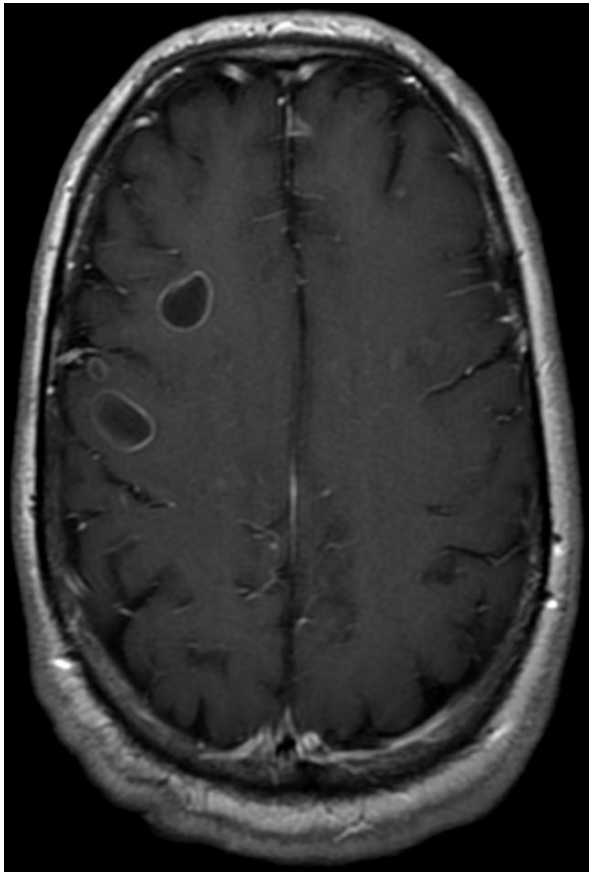
Baseline
12/18/2013



Follow-up
1/8/2014



Post-Therapy
Clinical 2/18/2014



TAKE HOME MESSAGES

- **Progress in immunotherapy is accelerating**
- **Combinations are in doublets and potentially triplets with targeted therapy**
- **Translation of the benefit to the MBM population remains slow and requires a comprehensive translational approach:**
  - ✓ **Tissue-driven- pathobiology**
  - ✓ **Innovative combo trial designs - EA6145**
  - ✓ **Novel imaging assessments**