Session II:
Key Issues for Clinical Development for Brain Mets

Nancy Lin, MD, Co-Chair, Dana Farber Cancer Institute
Chana Weinstock, MD, Co-Chair, US Food and Drug Administration

Identification of Targets for Brain Metastases Clinical Trials

Priscilla K. Brastianos, MD
Director, Central Nervous System Metastasis Center
Massachusetts General Hospital
Harvard Medical School

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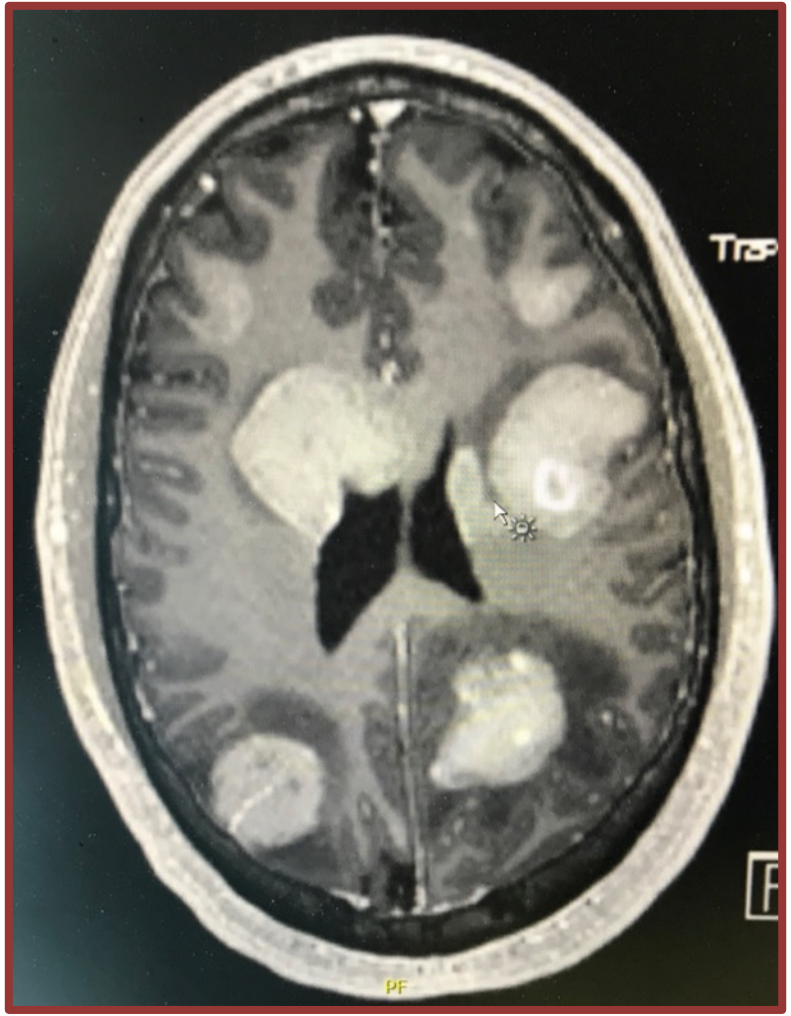
Molecular epidemiology of brain metastases

- Breast cancer:
  - 30-40% of advanced HER2-positive
  - 40-50% of metastatic triple-negative
- Lung cancer:
  - 25-40% of advanced EGFR-positive disease
  - ALK-positive:
    - 27-40% at baseline
    - 35-71% in second-line
- Melanoma
  - 40-50% of advanced BRAF-positive disease

Brastianos et al. JNCCN 2013
Crino et al. JCO 2016
Griesinger et al. Oncotarget 2018
Hsu et al. Lung Cancer 2016
Kim et al. JCO 2016
Lazaro and Brastianos, CNS Oncol 2017
Maxwell et al. Int J Cancer 2016
Peters et al. NEJM. 2018
Shaw et al. NEJM 2013
Wang et al. Clin Neuro and Neurosurg 2017



Patients will often develop **progressive brain metastases** in the setting of stable extracranial disease.

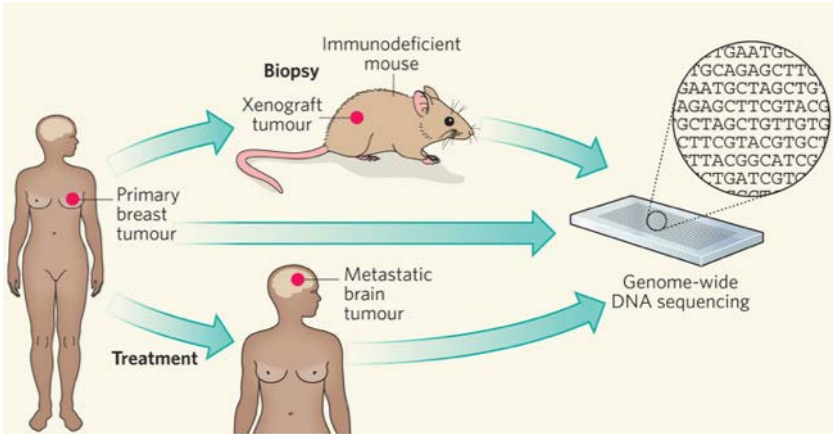
Unanswered clinical questions

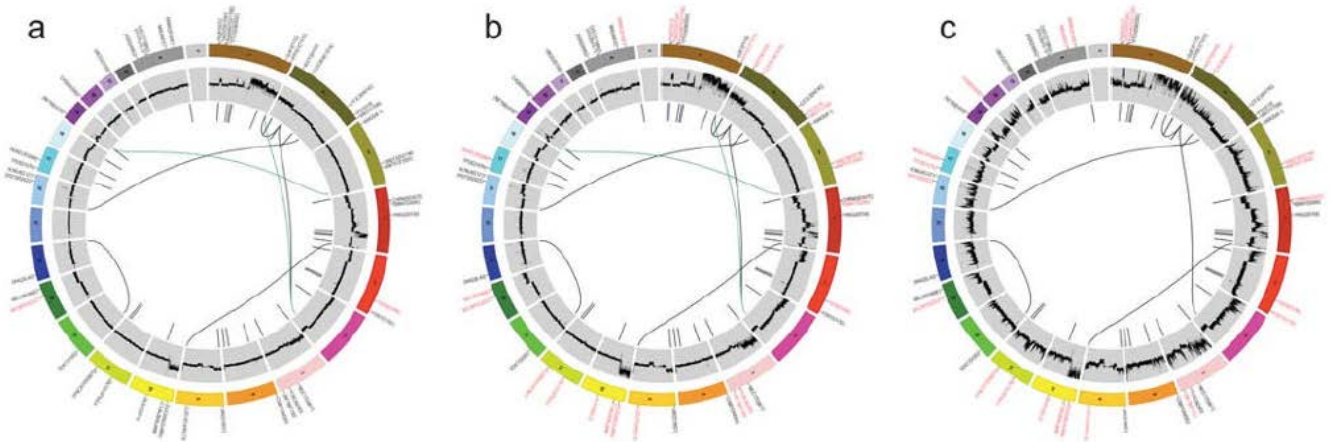
We have a limited understanding of how brain metastases genetically evolve from their primary tumor

- Intracranial progression due to incomplete drug penetration or different genetic drivers?
- What are the targetable mutations in brain metastases?
- Can we rely on a primary biopsy to make decisions for systemic targeted agents in brain metastases?

Massively parallel sequencing of one brain metastasis and matched primary tumor

Few *de novo* genetic alterations in brain metastasis (*n* = 1)



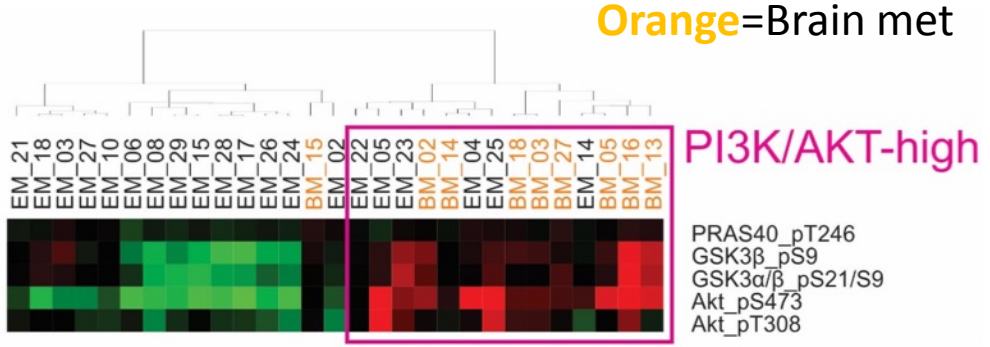


Ding et al, *Nature* 2010

Proteomic analysis of resected brain & extracranial melanoma: **PI3K pathway** activation in CNS mets

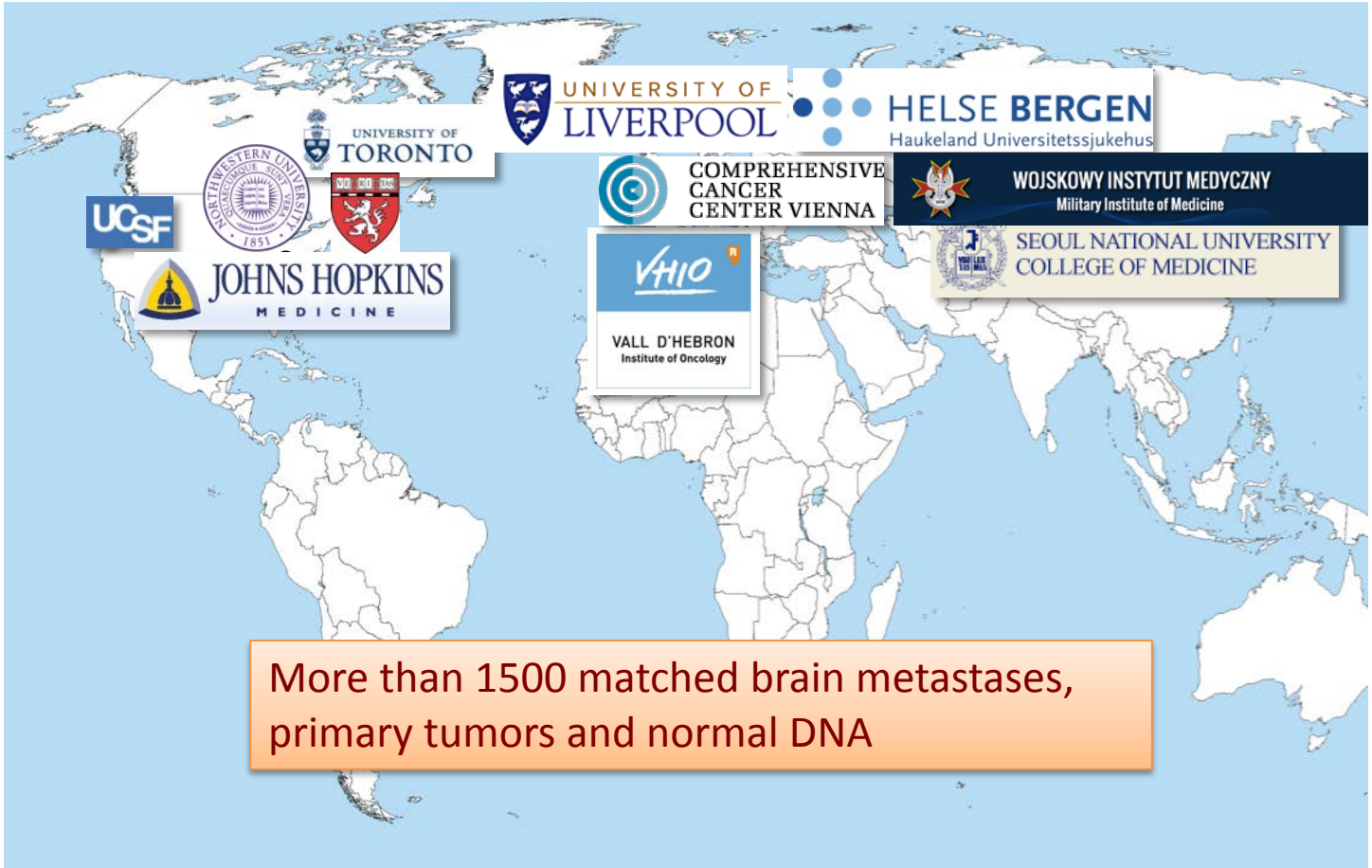
- 7 paired brain & extracranial metastases and 2 un-paired brain and 13 un-paired extracranial metastases

Significant (p<0.05) Matched Brain vs Extracranial Mets	BM/EM (log2)	Paired t-test, *p*
Akt_pS473	1.028	0.022
Rb_pS807_S811	0.863	0.004
mTOR_pS2448	0.414	0.042
Bax	0.337	0.027
eEF2K	0.212	0.005
JNK_pT183_pT185	0.159	0.011
14-3-3_epsilon	-0.178	0.045
Smad1	-0.241	0.034
VASP	-0.252	0.011
Src	-0.264	0.023



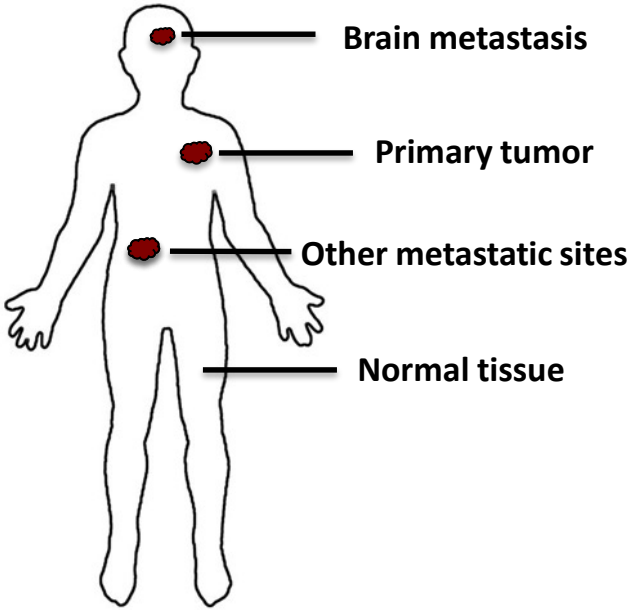
Chen et al. *CCR* 2014

Creation of a large tumor bank of brain metastases and rapid autopsy program

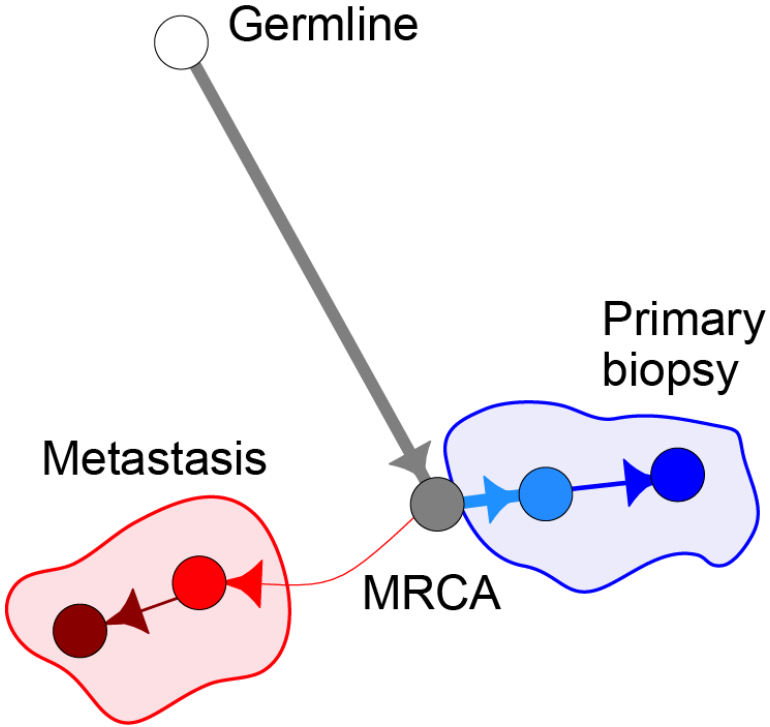


Study design

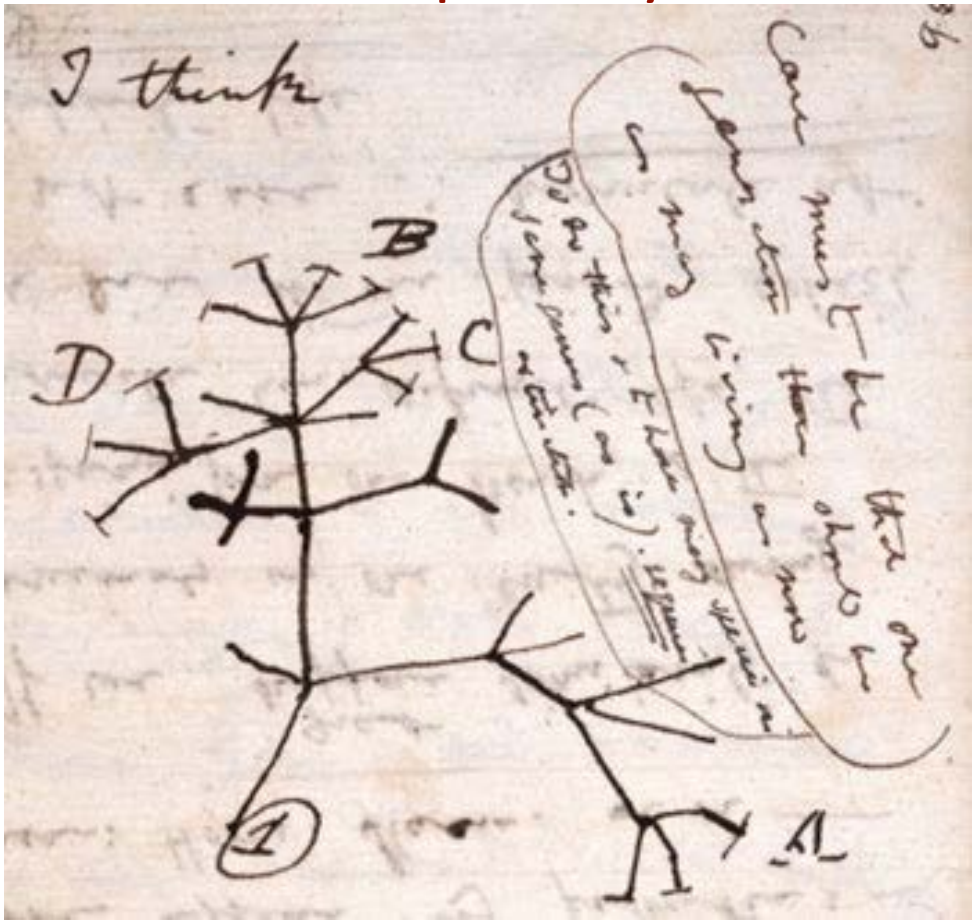
- Whole-exome sequencing of 104 brain metastases matched with primary and normal tissue
- Including 15 with additional extracranial sites or temporally/regionally/ anatomically separated brain metastases



Branched evolution: brain metastasis and primary tumor evolve separately



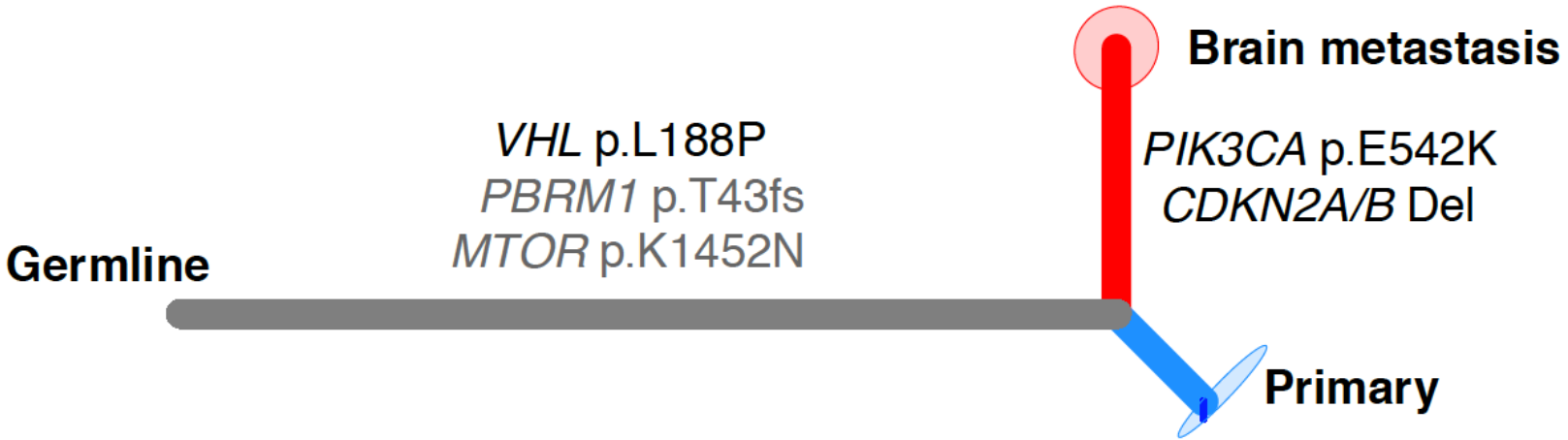
Evolutionary relationship



Charles Darwin 1837

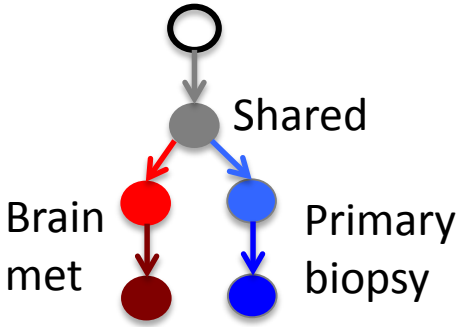
Brain metastases harbor clinically actionable mutations not detected in primary tumors

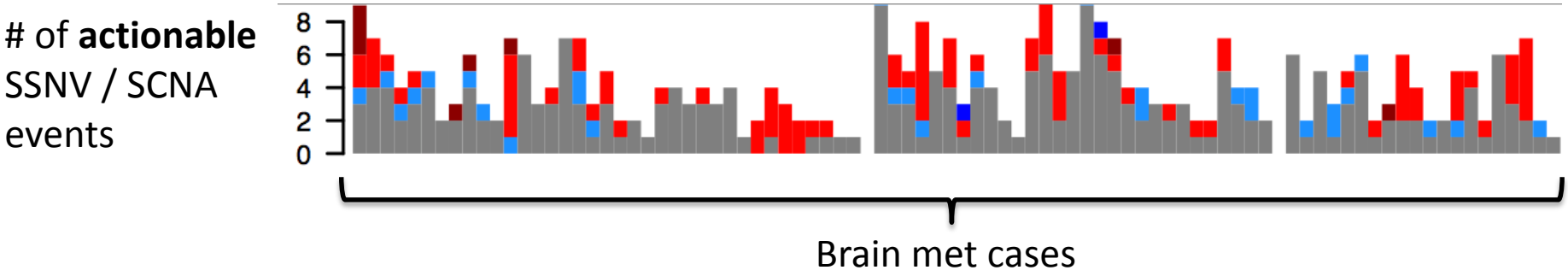
Renal cell carcinoma



Brastianos, Carter et al. *Cancer Discovery 2015*

Clinically actionable alterations occur in all phylogenetic branches



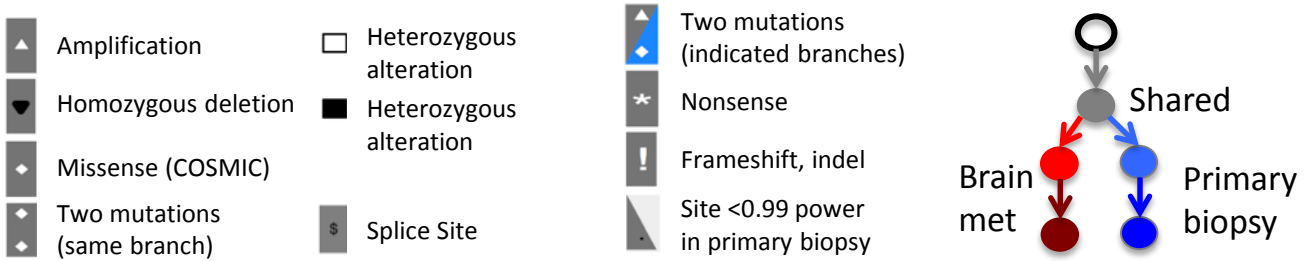


53% of cases have a clinically actionable alteration in the brain metastasis, not detected in the primary biopsy.

Brastianos, Carter et al. ***Cancer Discovery 2015***

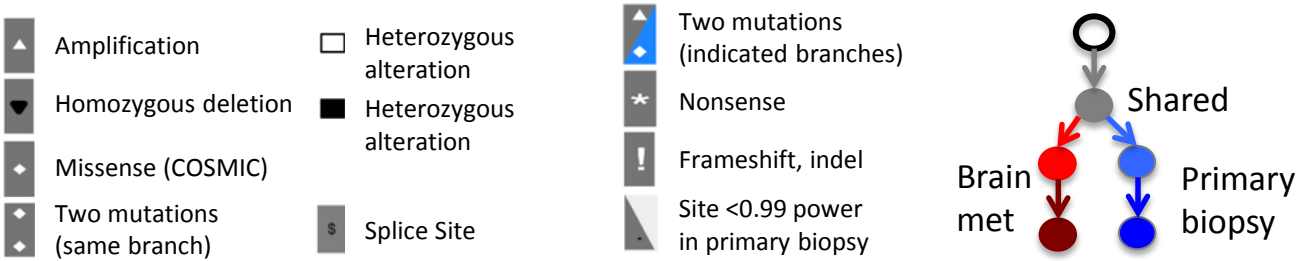
Opportunities to target brain metastases

51% of cases with alterations in the CDK pathway.

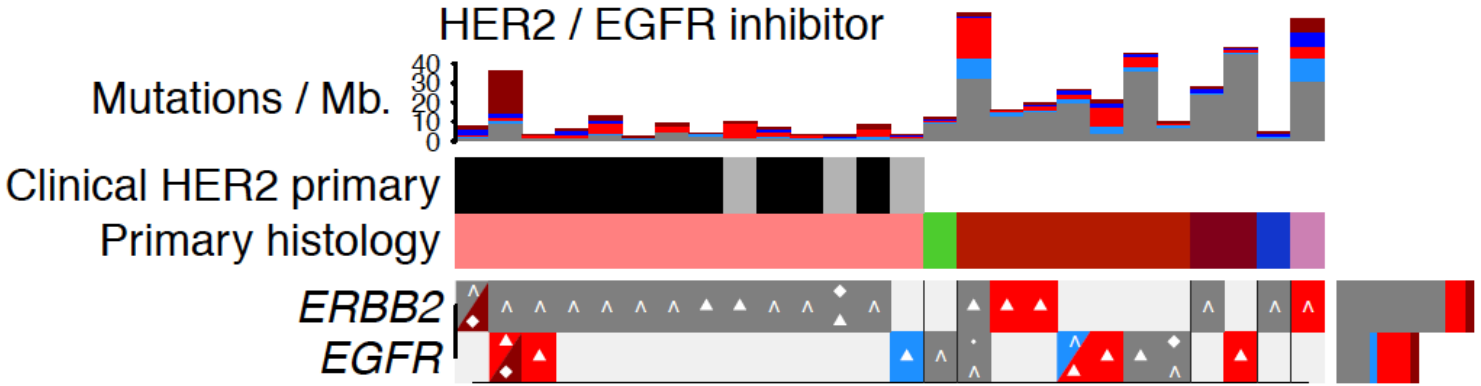


Opportunities to target brain metastases

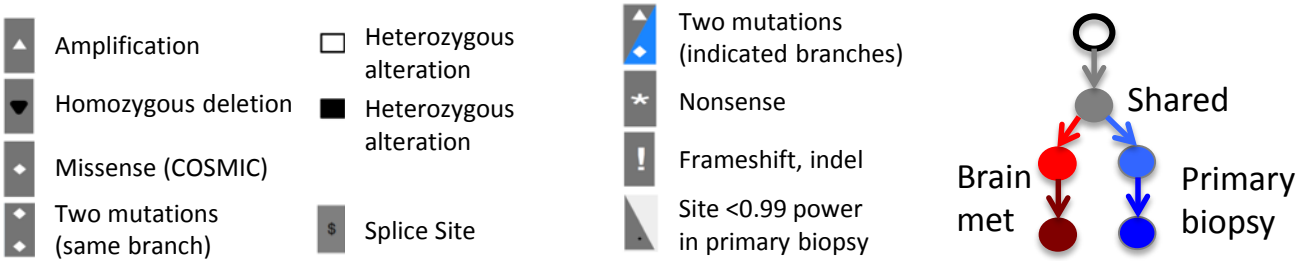
43% of cases with alterations predicting sensitivity to PI3K/AKT/mTOR inhibitor



HER2/EGFR Alterations

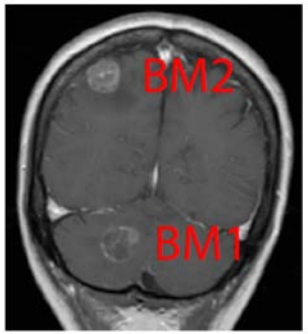


One-third of cases with alterations predicting sensitivity to HER2/EGFR inhibitors

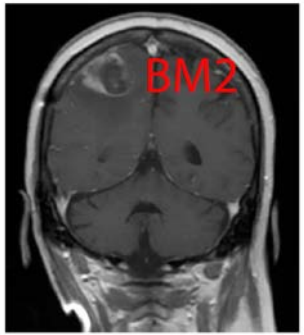


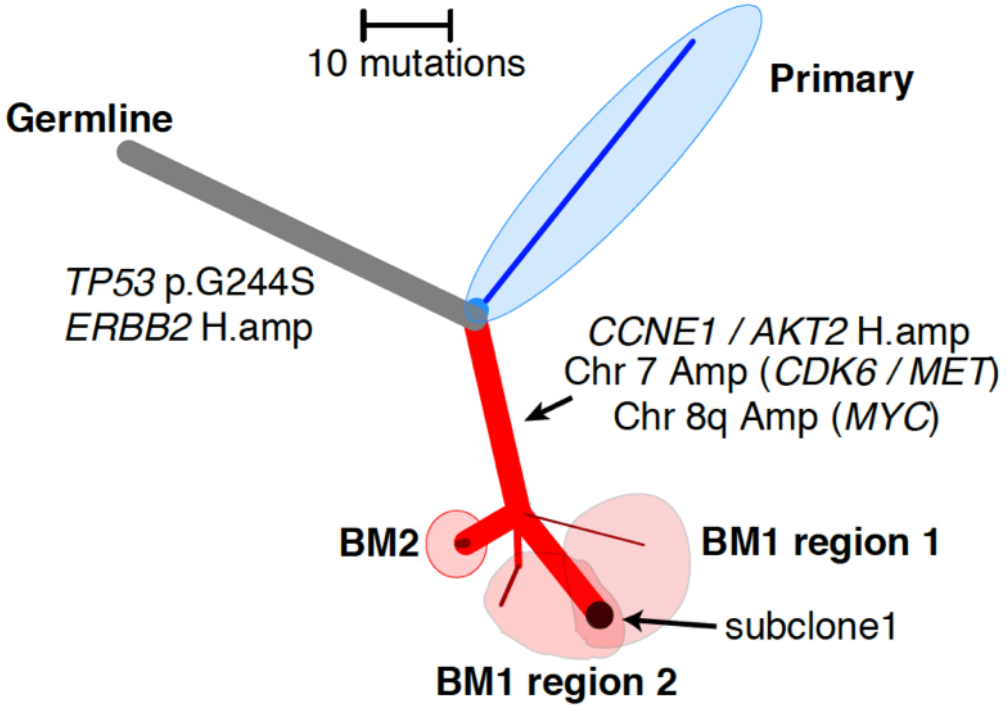
Anatomically distinct brain metastases share all actionable drivers

Pre-XRT, pre-resection cerebellar



Post-XRT, pre-resection of parietal met

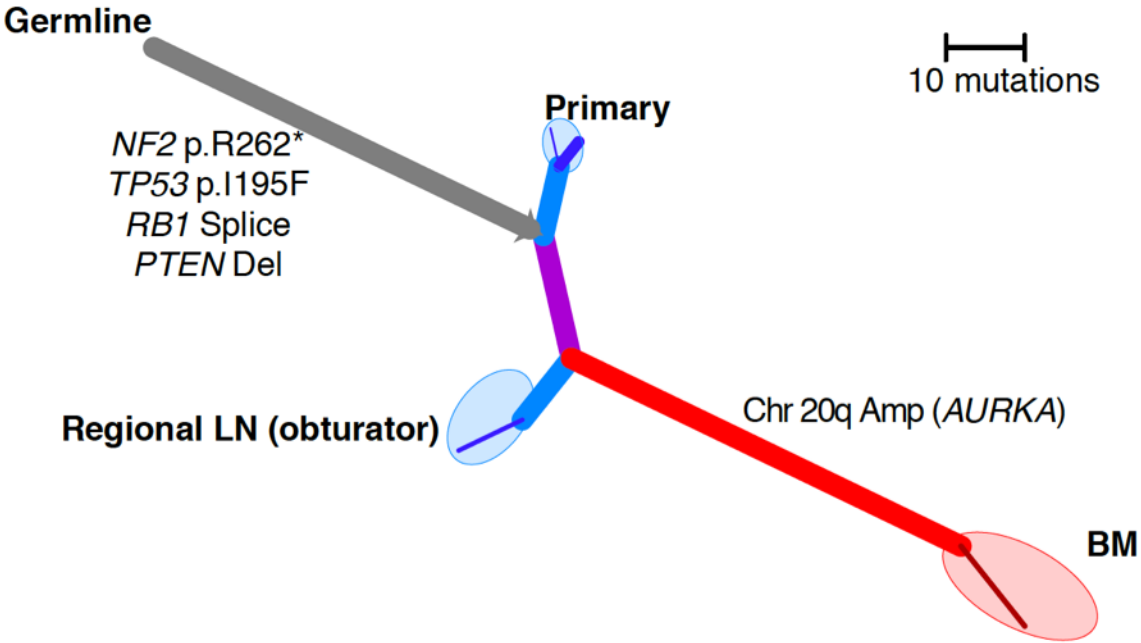




Brastianos, Carter et al. ***Cancer Discovery 2015***

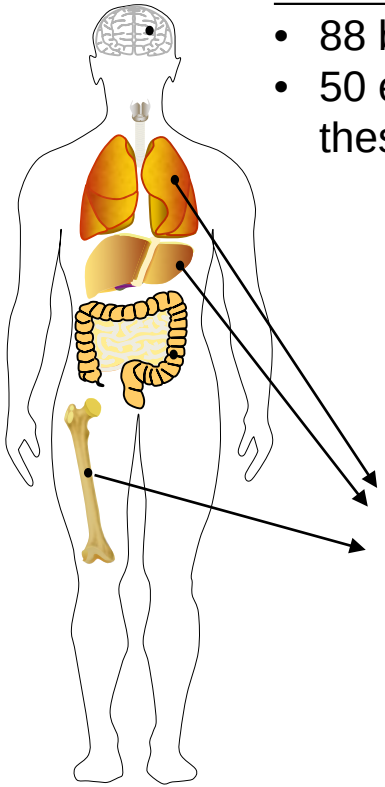
Example: Lymph node not reliable genetic surrogate of brain metastasis

Serous ovarian cancer



Brastianos, Carter et al. *Cancer Discovery 2015*

Oxidative phosphorylation is enriched in melanoma brain metastases compared to patient-matched extracranial metastases

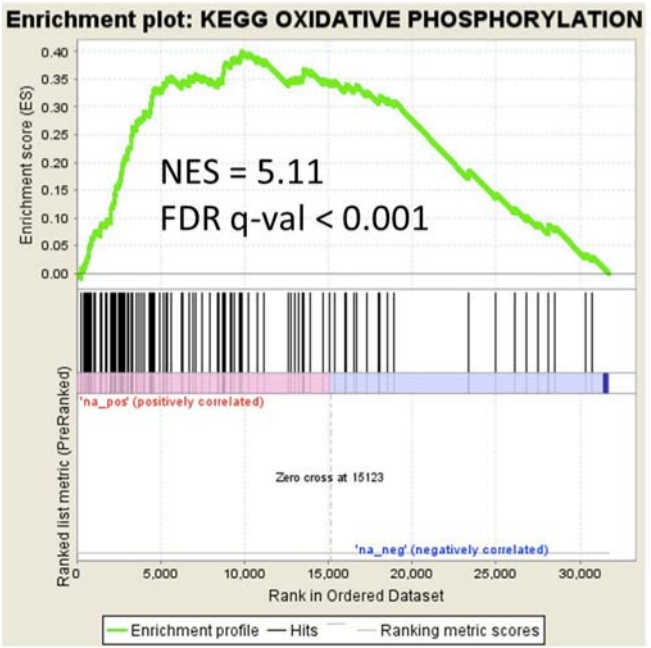


RNA-seq Analysis:

- 88 brain metastases from 76 patients
- 50 extracranial metastases from 34 of these patients

Brain metastases

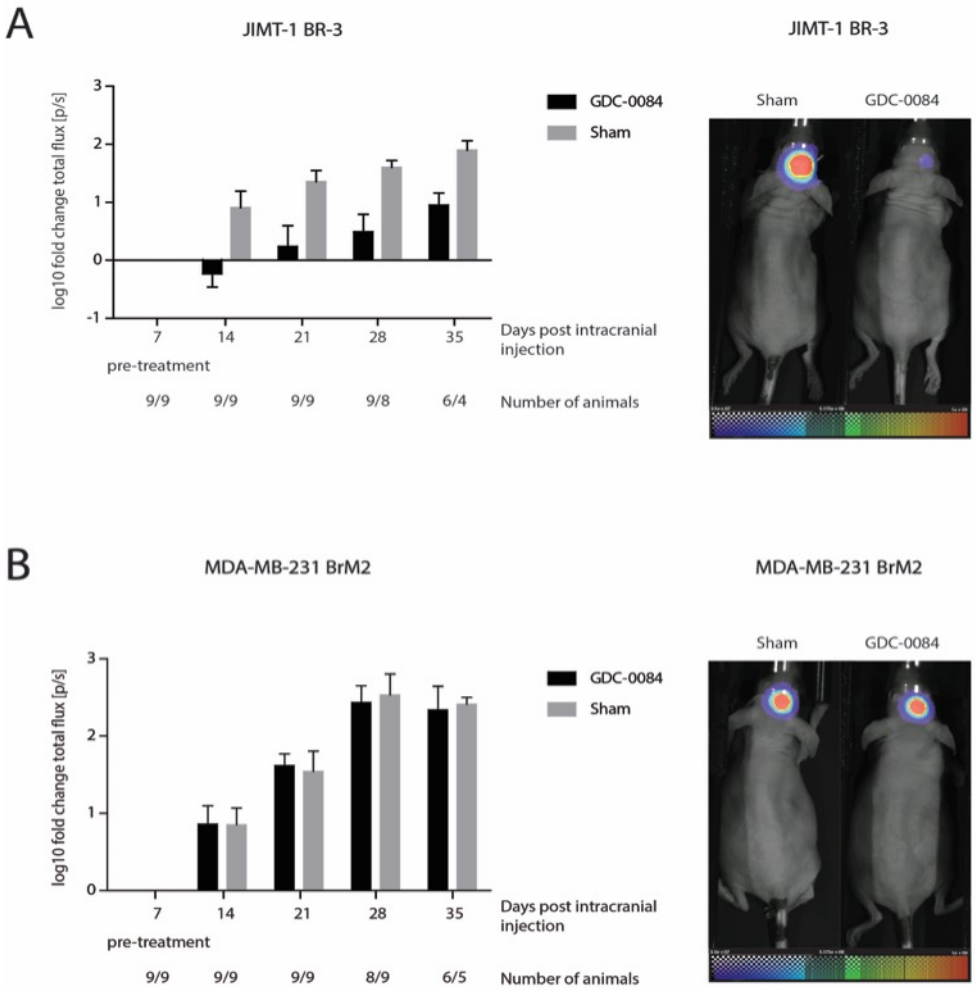
Extracranial metastases



Fischer…Davies. Cancer Discovery, *In Press*

Efficacy of PI3K inhibitor in patient derived xenograft model of breast cancer brain metastases

GDC-0084 inhibits tumor growth in vivo in a *PIK3CA*-mutant cell line and not in a PIK3CA-wt cell line

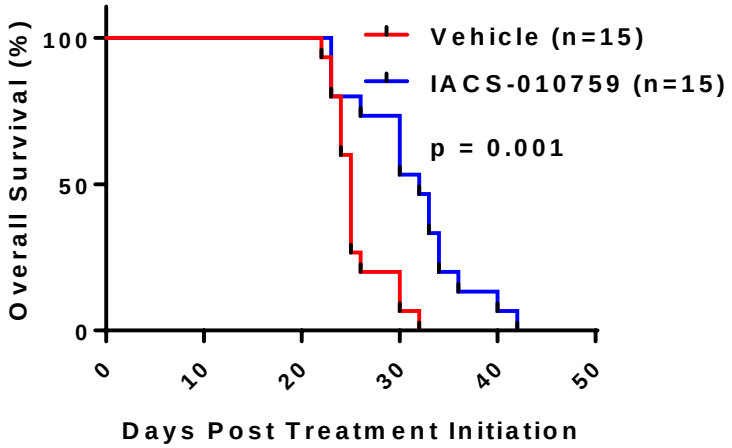


Ippen...Brastianos. Clinical Cancer Research 2019

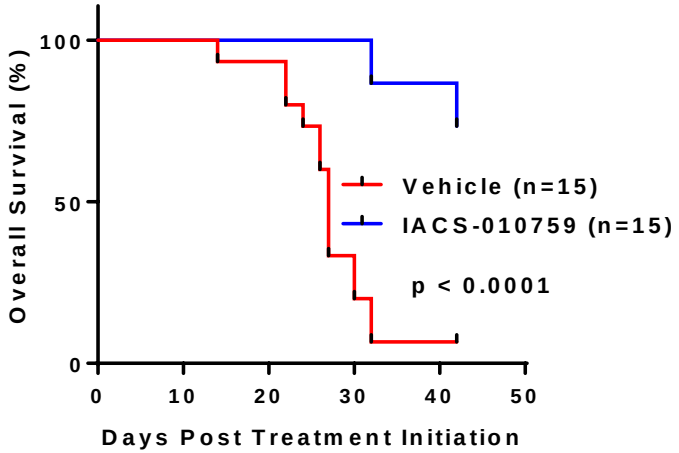
Efficacy of Oxphos inhibitor in murine model of melanoma brain metastases

- Treated nude mice with human xenografts with vehicle or IACS-010759
- Mice treated with IACS-010759 lived significantly longer

A375-R1 (Acquired MAPKi-Resistant) MBMs



SKMEL5 (*De Novo* MAPKi-Resistant) MBMs



Fischer…Davies, *In press*

National biomarker driven trial in brain metastases

Study Chairs: Priscilla Brastianos, Eva Galanis
Correlative PI: Scott Carter

- Progressive brain metastases
- Histologically confirmed solid malignancy
- Measurable CNS disease
- Any brain metastasis tissue and extracranial site for sequencing

- Brain MRI and systemic staging
- Circulating biomarkers

- Brain MRI and systemic staging q8wks
- Circulating biomarkers q4wks

Actionable alteration in CDK pathway	• Lung (n=21) • Breast (n=21) • Other (n=21)	CDK inhibitor		CNS or systemic progression
Actionable mutation in PI3K/AKT/mTOR pathway	• Lung (n=21) • Breast (n=21) • Other (n=21)	PI3K inhibitor		CNS or systemic progression
ALK/NTRK/ROS1 translocation	• Lung (n=10)	ALK/NTRK/ROS inhibitor		CNS or systemic progression

Primary endpoint
- CNS response rate

Secondary endpoints
- OS
- CNS, systemic PFS
- Systemic response
- Safety

Exploratory endpoints
- Correlation of response with biomarkers
- Duration of response
- First site of progression

Conclusions

- Brain metastases harbored **distinct** clinically actionable genetic alterations, compared to their primary tumors.
- Different brain metastasis regions are relatively **homogeneous**.
- Extracranial metastases are **not a reliable surrogate** for brain metastases.
- Alterations in the **CDK** and **PI3K pathways** are frequent in brain metastases.
- A national genomically guided trial is planned.

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