

Session II: Key Issues for Clinical Development for Brain Mets

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Identification of Targets for Brain Metastases Clinical Trials

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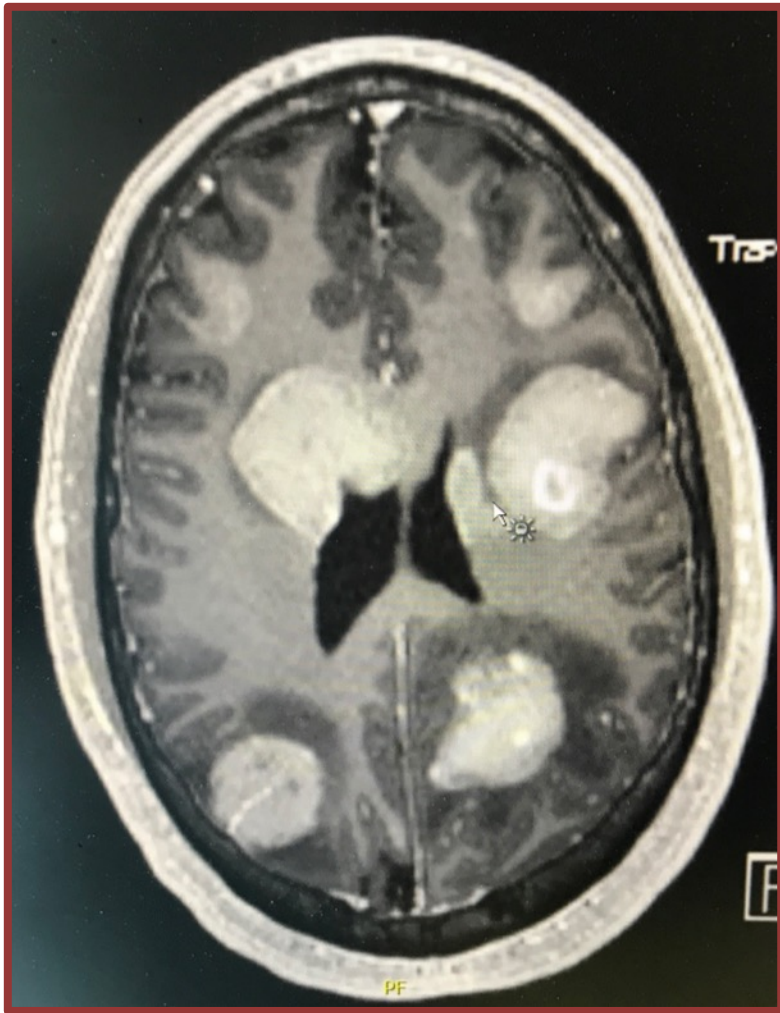
Disclosure Information

- I have the following financial relationships to disclose
 - Consulting: Angiochem, Merck, Genentech-Roche, Lilly
 - Grant/research support: Merck
 - Honoraria: Merck, Genentech-Roche, Lilly

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.

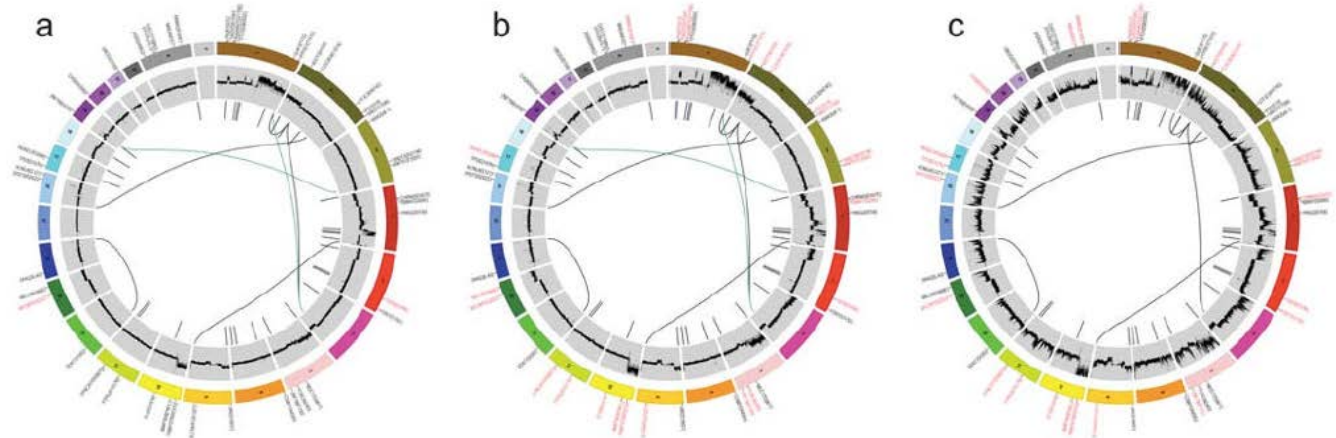
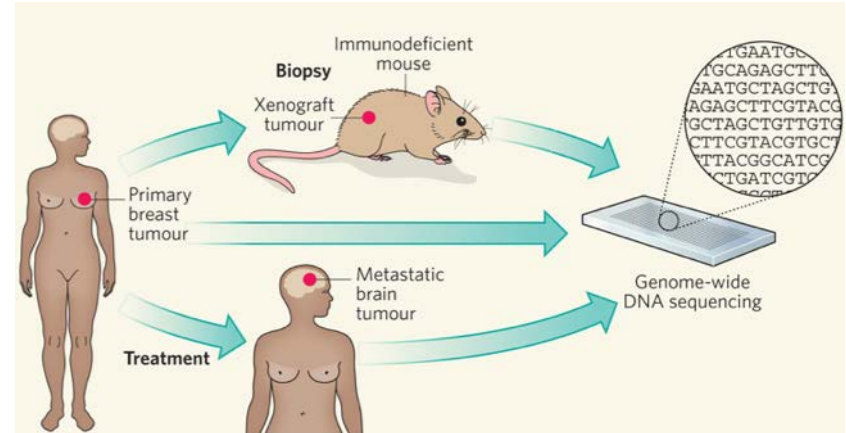
Unanswered clinical questions

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

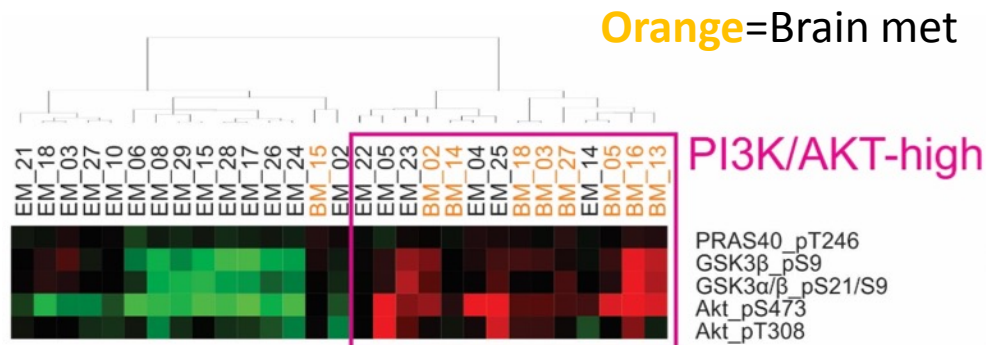
Few *de novo* genetic alterations in brain metastasis ($n = 1$)



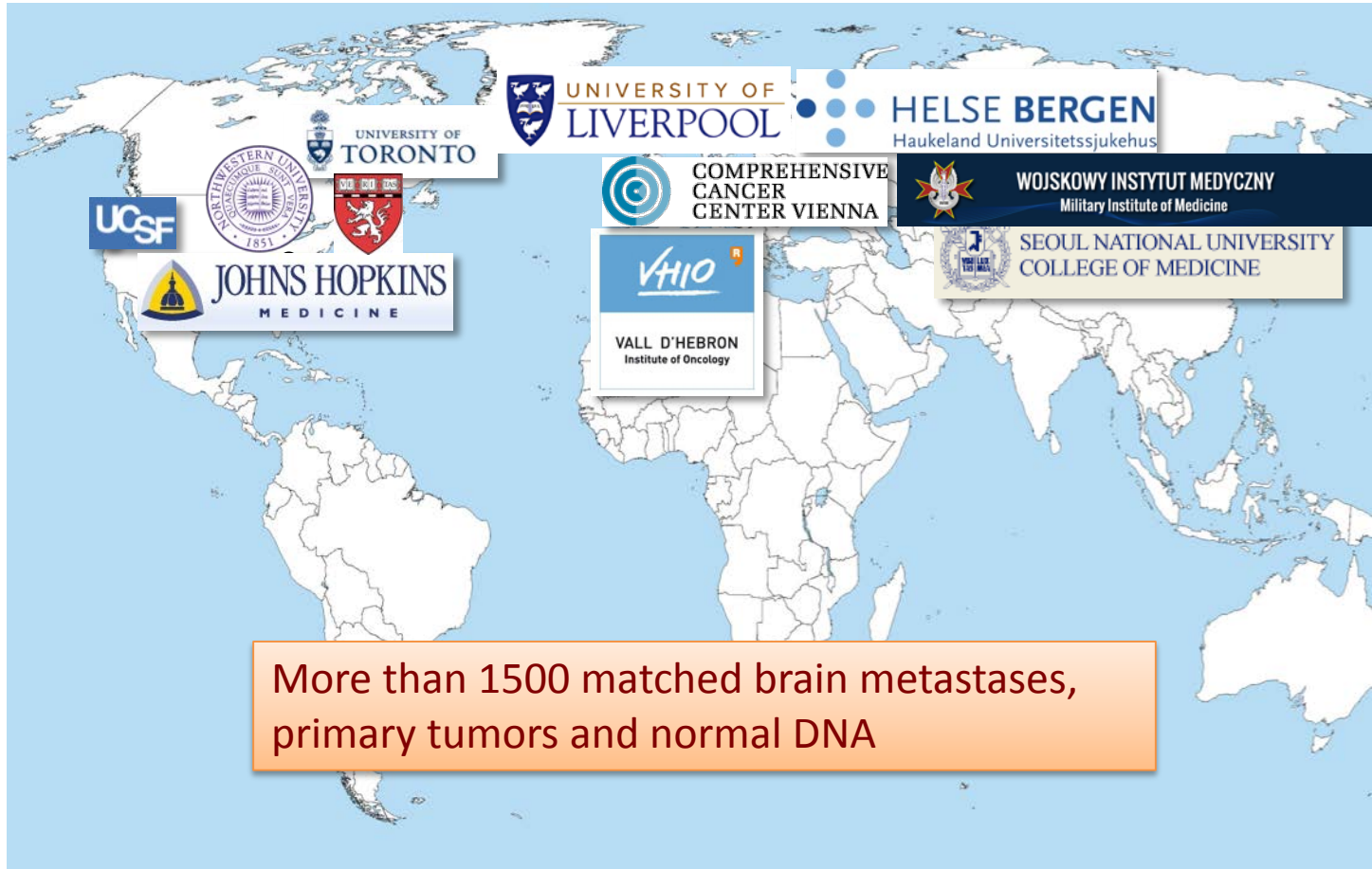
Proteomic analysis of resected brain & extracranial melanoma: **PI3K pathway** activation in CNS mets

- 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 (log ₂)	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



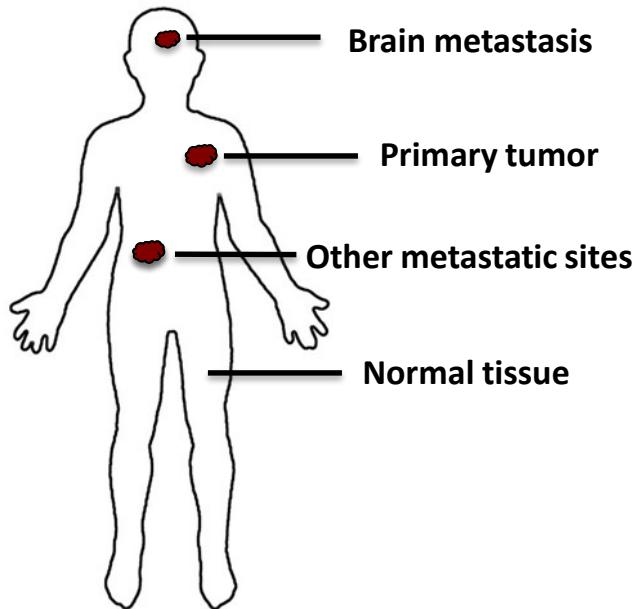
Creation of a large tumor bank of brain metastases and rapid autopsy program



More than 1500 matched brain metastases, primary tumors and normal DNA

Study design

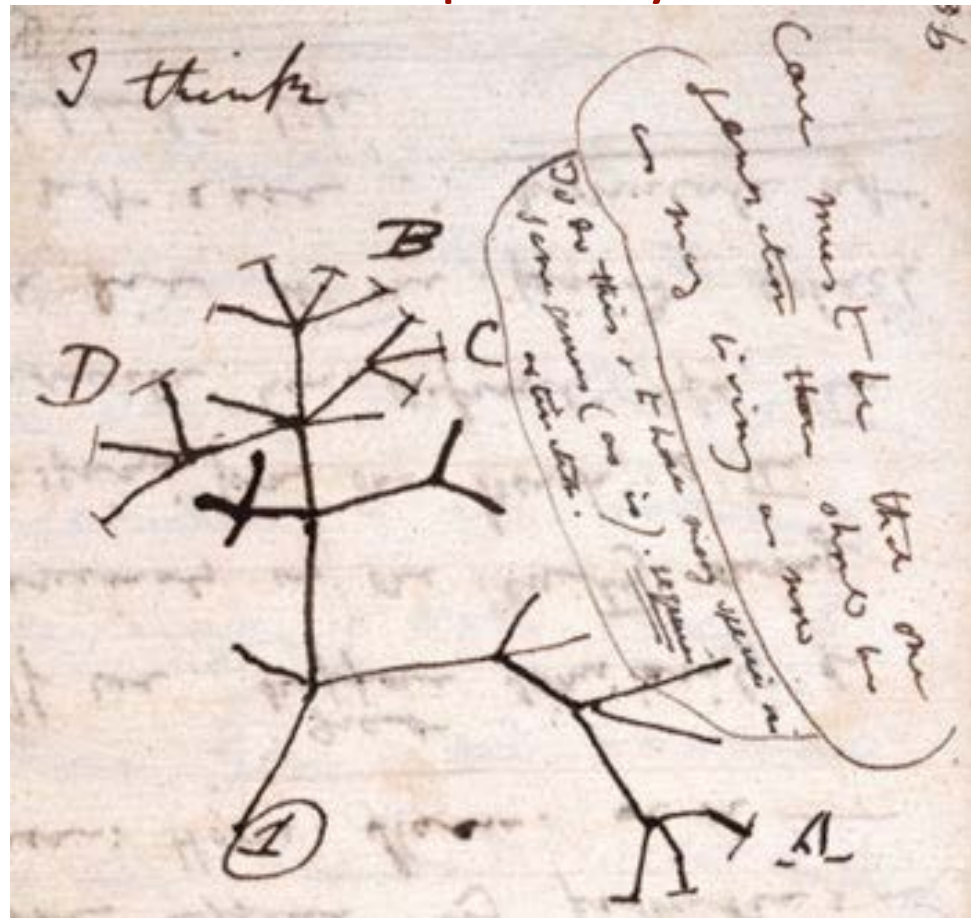
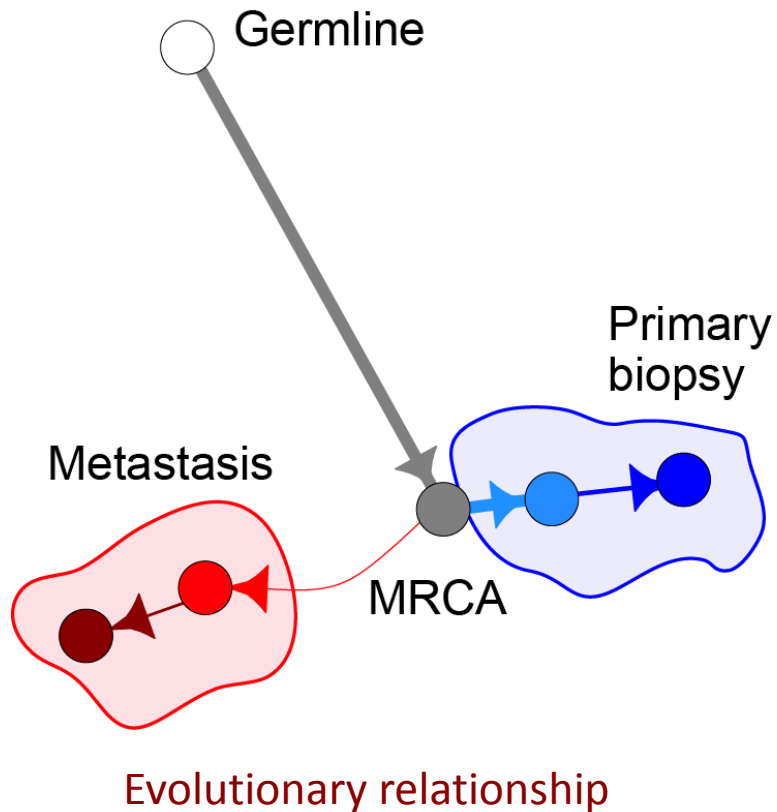
- Whole-exome sequencing of 104 brain metastases matched with primary and normal tissue
- Including 15 with additional extracranial sites or temporally/regionally/anatomically separated brain metastases



Genomic Characterization of Brain Metastases Reveals Branched Evolution and Potential Therapeutic Targets

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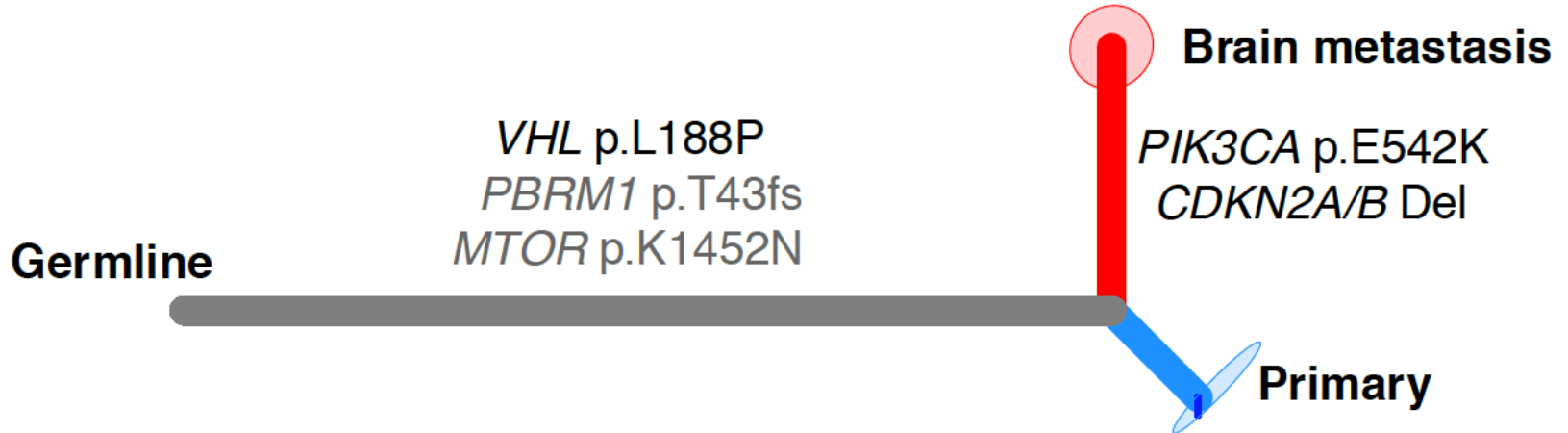
Branched evolution: brain metastasis and primary tumor evolve separately



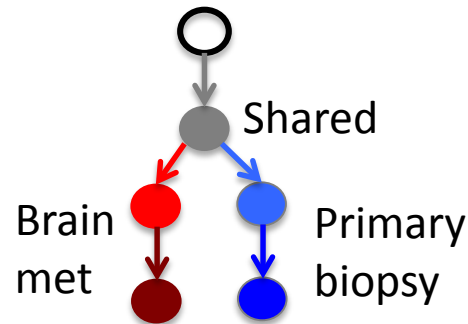
Charles Darwin 1837

Brain metastases harbor clinically actionable mutations not detected in primary tumors

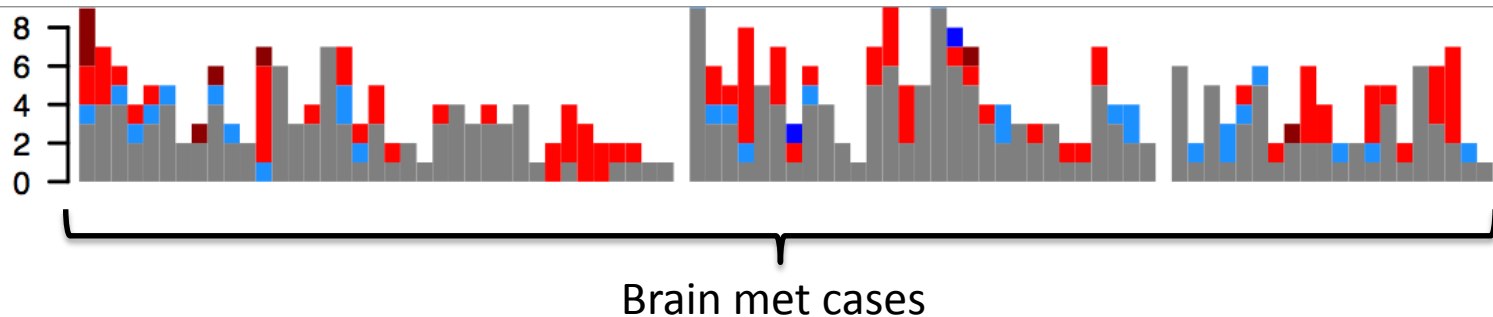
Renal cell carcinoma



Clinically actionable alterations occur in all phylogenetic branches



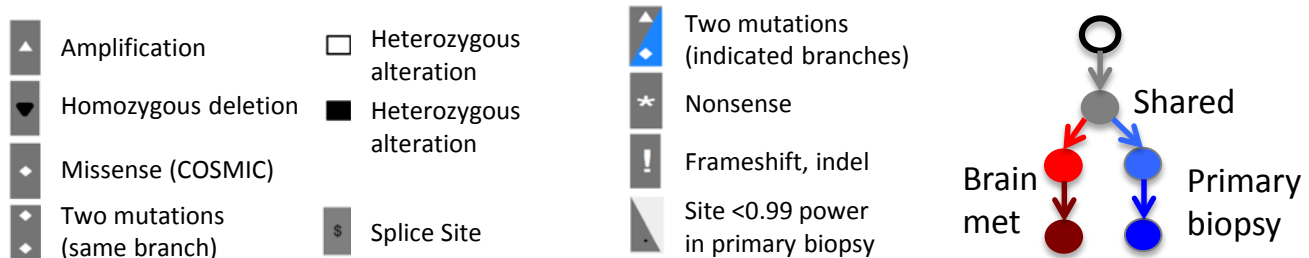
of actionable
SSNV / SCNA
events



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

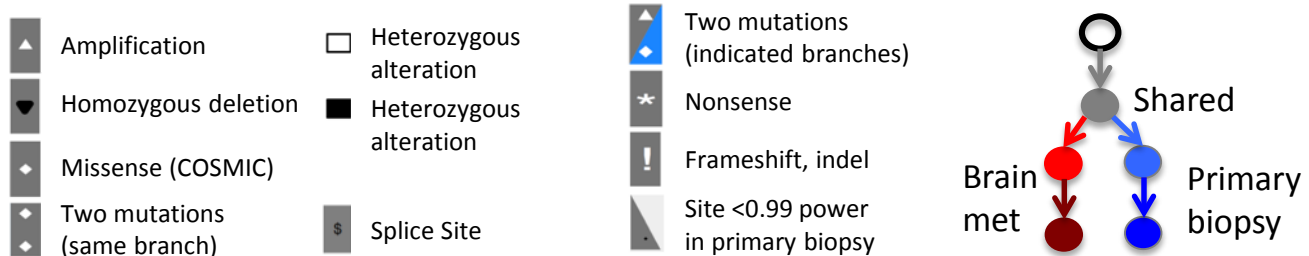
Opportunities to target brain metastases

51% of cases with alterations in the CDK pathway.

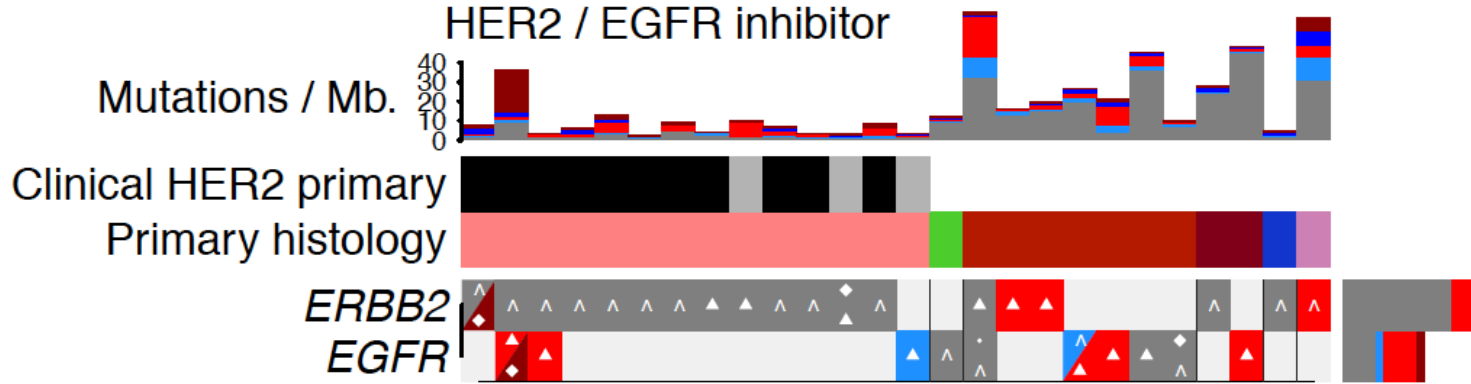


Opportunities to target brain metastases

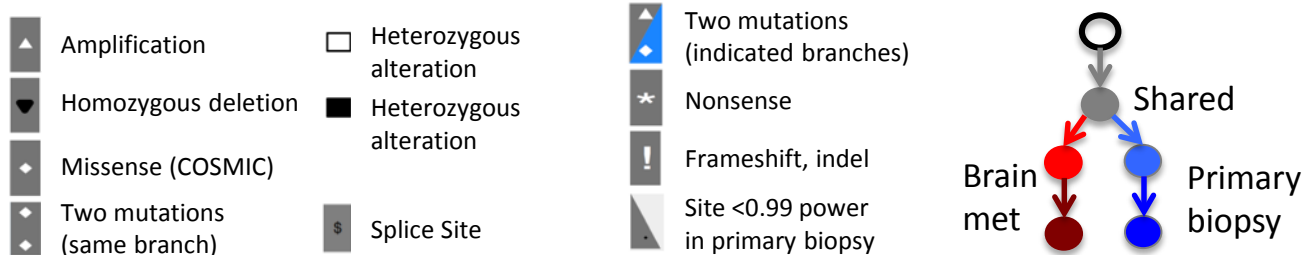
43% of cases with alterations predicting sensitivity to PI3K/AKT/mTOR inhibitor



HER2/EGFR Alterations

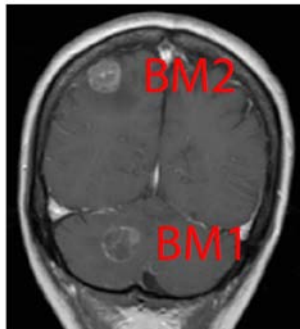


One-third of cases with alterations predicting sensitivity to HER2/EGFR inhibitors

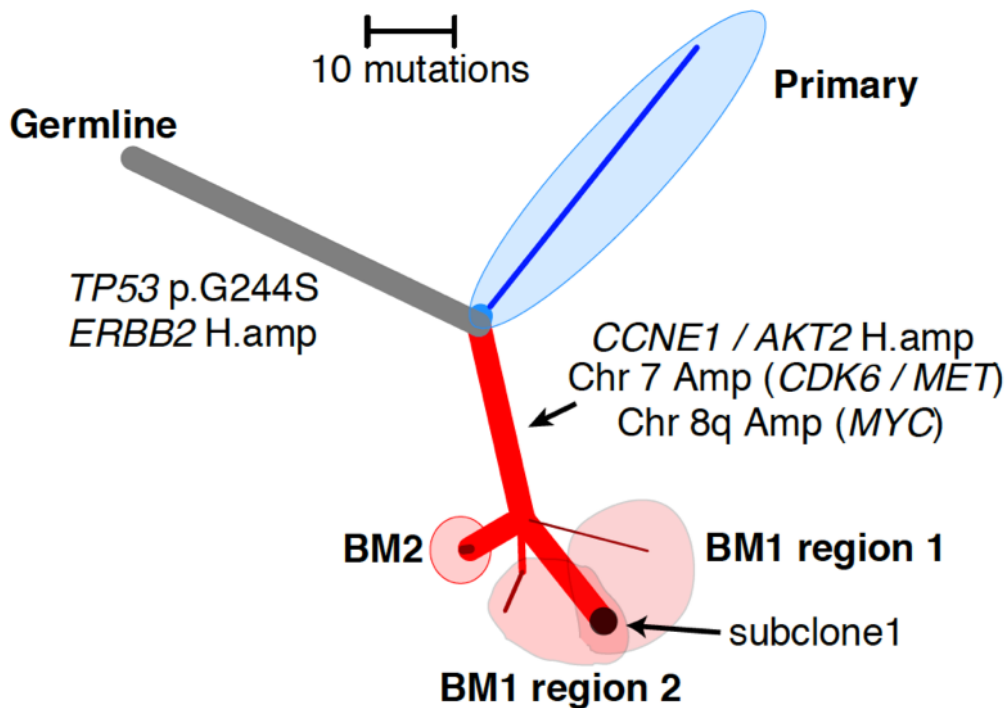
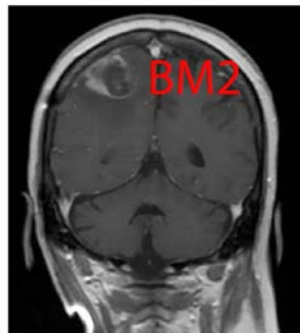


Anatomically distinct brain metastases share all actionable drivers

Pre-XRT, pre-resection cerebellar



Post-XRT, pre-resection of parietal met



Example: Lymph node not reliable genetic surrogate of brain metastasis

Serous ovarian cancer

Germline

NF2 p.R262*
TP53 p.I195F
RB1 Splice
PTEN Del

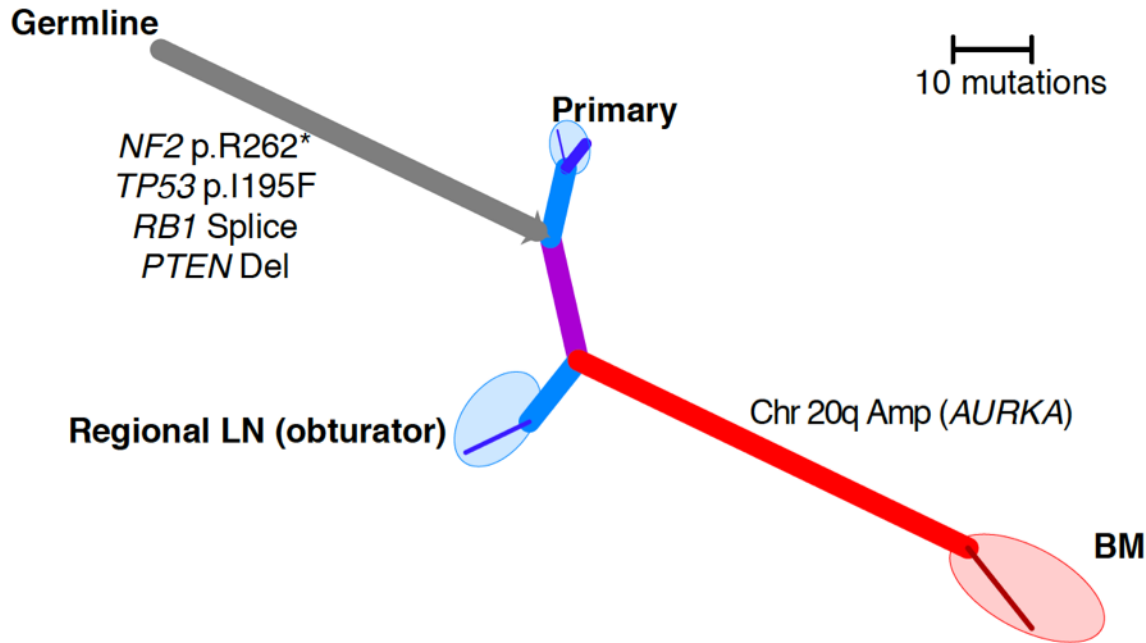
Primary

10 mutations

Regional LN (obturator)

Chr 20q Amp (*AURKA*)

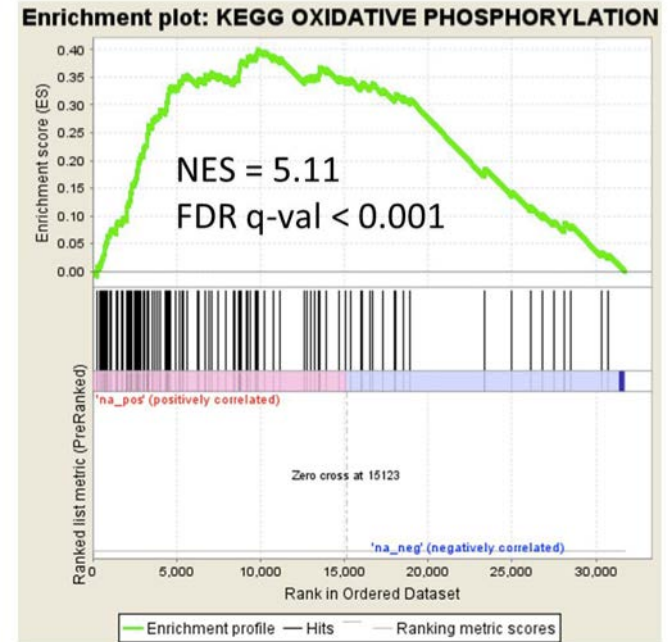
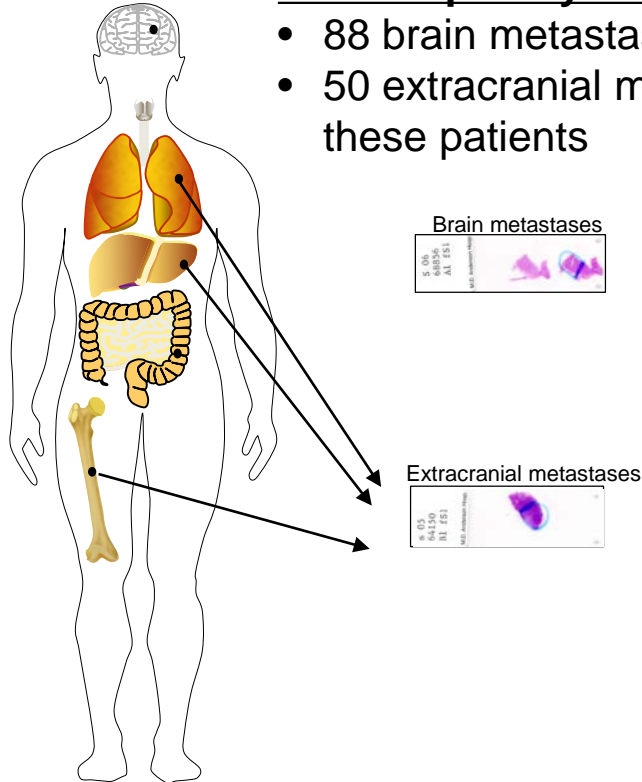
BM



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

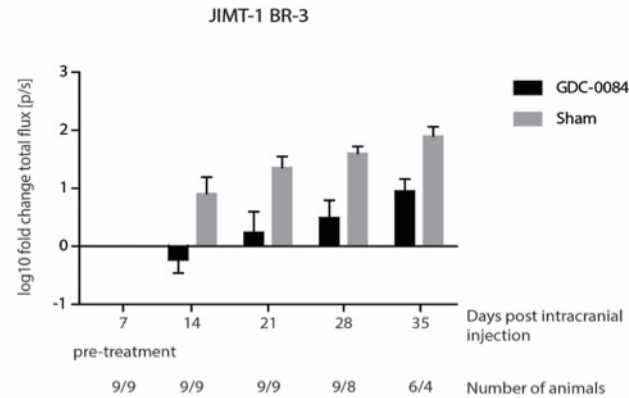


Efficacy of PI3K inhibitor in patient derived xenograft model of breast cancer brain metastases

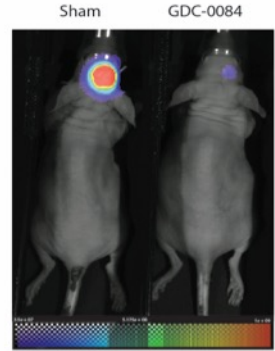
GDC-0084 inhibits tumor growth in vivo in a *PIK3CA*-mutant cell line and not in a *PIK3CA*-wt cell line

Ippen...Brastianos. Clinical Cancer Research 2019

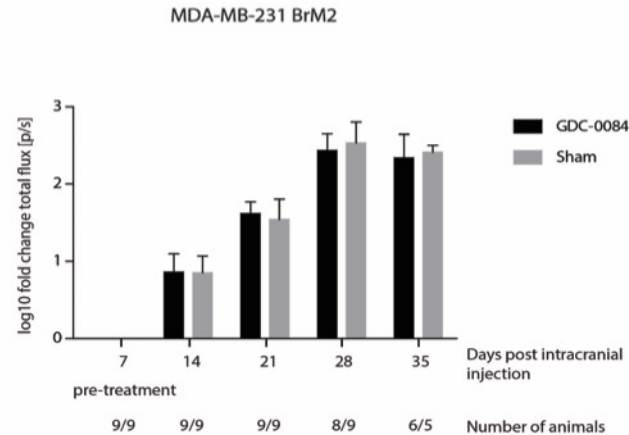
A



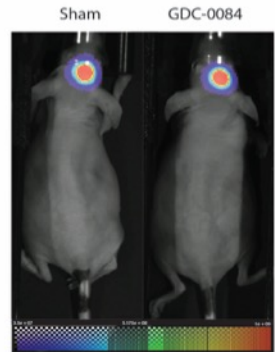
JIMT-1 BR-3



B



MDA-MB-231 BrM2

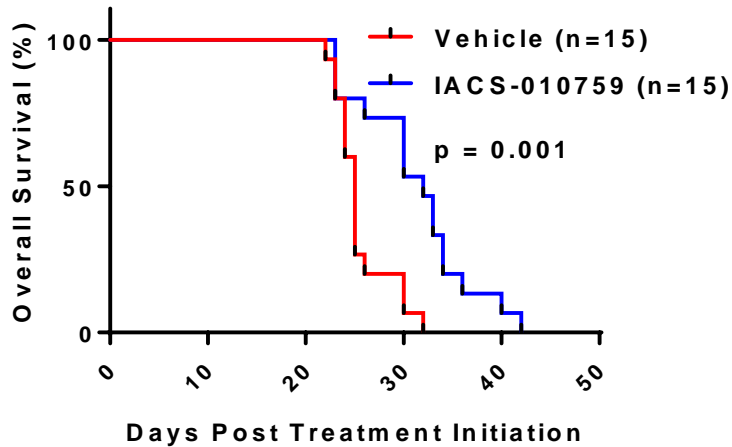


Efficacy of Oxphos inhibitor in murine model of melanoma brain metastases

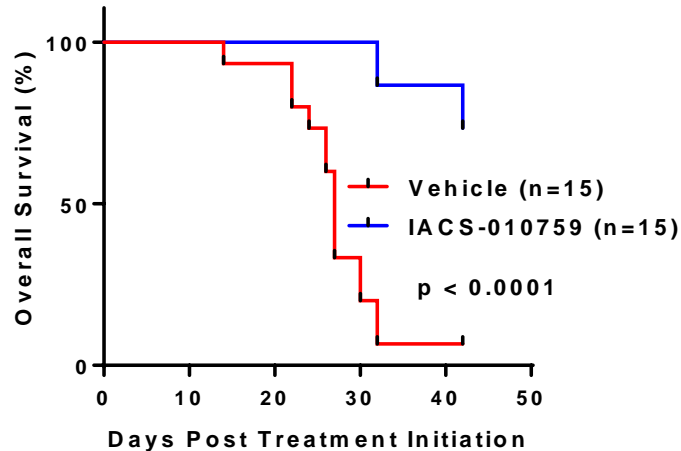


- Treated nude mice with human xenografts with vehicle or IACS-010759
- Mice treated with IACS-010759 lived significantly longer

A375-R1 (Acquired MAPKi-Resistant) MBMs



SKMEL5 (De Novo MAPKi-Resistant) MBMs



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

Actionable alteration in CDK pathway

Actionable mutation in PI3K/AKT/mTOR pathway

ALK/NTRK/ROS1 translocation

- Brain MRI and systemic staging
- Circulating biomarkers

- Lung (n=21)
- Breast (n=21)
- Other (n=21)

- Lung (n=21)
- Breast (n=21)
- Other (n=21)

- Lung (n=10)

CDK inhibitor

PI3K inhibitor

ALK/NTRK/ROS inhibitor

- Brain MRI and systemic staging q8wks
- Circulating biomarkers q4wks

CNS or systemic progression

CNS or systemic progression

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.

Acknowledgements

Brastianos Lab:

Christopher Alvarez-Breckenridge
Ugo Chukwueke
Taylor Conroy
Nate Goss
Franziska Ippen
Ben Kuter
Matt Lastrapes
Mohini Singh
Joana Mora
Naema Nayyar
Brian Shaw
Jackson Stocking
Matt Strickland
Megha Subramanian
Michael White

Carter Lab

Scott Carter
Matt Lastrapes
David Shih

MGH:

Daniel Cahill
Tracy Batchelor
David Louis

Broad Institute:

Eric Lander
Gad Getz
Alex Shalek
Amaro Taylor-Weiner

Comprehensive Cancer Center

Vienna

Anna Berghoff
Matthias Preusser

Vall D'Hebron University

Josep Tabernero
Joan Seoane
Elena Martinez-Saez

DFCI

Toni Choueiri
Nancy U. Lin
Bruce Johnson
Eric Winer

Seoul National University College of Medicine

Sun Ha Paek
Sung-Hye Park

Santagata Lab:

Sandro Santagata
Parker Merrill

Medical University of Gdansk

Jacek Jassem

Military Institute of Medicine Poland

Renata Duchnowska

Funding

