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
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

References:
- 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
- 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

• 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?

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

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

Orange = Brain met

Chen et al. *CCR* 2014
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
**Branched evolution**: brain metastasis and primary tumor evolve separately

- **Germline**
- **Primary biopsy**
- **Metastasis**

**Evolutionary relationship**

*Charles Darwin 1837*
Brain metastases harbor clinically actionable mutations not detected in primary tumors

Renal cell carcinoma

Germline

- VHL p.L188P
- PB1M p.T43fs
- MTOR p.K1452N

Brain metastasis

- PIK3CA p.E542K
- CDKN2A/B Del

Primary

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

Opportunities to target brain metastases
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

Brastianos, Carter et al. *Cancer Discovery* 2015

Serous ovarian cancer
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

**Enrichment Plot: KEGG OXIDATIVE PHOSPHORYLATION**
- NES = 5.11
- FDR q-val < 0.001

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 \textit{PIK3CA}-mutant cell line and not in a \textit{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

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

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

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/ROS1 inhibitor → CNS or systemic progression

Brain MRI and systemic staging
- Circulating biomarkers

Brain MRI and systemic staging q8wks
- Circulating biomarkers q4wks

Brain MRI and systemic staging
- Circulating biomarkers

Brain MRI and systemic staging q8wks
- Circulating biomarkers q4wks

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

CNS or systemic progression

CNS or systemic progression

Brain MRI and systemic staging
- Circulating biomarkers

Brain MRI and systemic staging q8wks
- Circulating biomarkers q4wks

CNS or systemic progression

Brain MRI and systemic staging
- Circulating biomarkers

Brain MRI and systemic staging q8wks
- Circulating biomarkers q4wks

CNS or systemic 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 Taberner o
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**

[Logos and links to funding sources]