What is Personalized Medicine in Brain Tumors?

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Massachusetts General Hospital/Harvard Medical School
DISCLOSURES & SUPPORT

• I have no stocks, patent rights or employment with any company

• I have consulting/advisory board agreements with: Lilly, Angiochem, Tesaro, Genentech-Roche

• I have pre-clinical laboratory and/or clinical trial support from the following companies: Merck, Pfizer, BMS
Personalized therapy has revolutionized the management of cancer
We can now target genetic mutations with drugs.

Leukemia
Lung cancer
Sarcoma
Breast cancer
Melanoma

Mutation discovery

KIT
(Imatinib)

EGFR
(Erlotinib)

HER2
(Trastuzumab)

BRAF
(Vemurafenib)

PIK3CA
(BEZ235)
Example: BRAF is a target in many cancers

- Effective therapy that targets BRAF V600E has dramatically changed the treatment of metastatic melanoma

Bollag et al. Nature 2010
Number of bases that can be sequenced for a given cost has increased one-millionfold since 1990s.

The Human Genome Project in 2001: 13 yrs and $3 Billion.

Sequencing of the Watson Genome in 2007: $2 million.

Whole Genome in 2019: $1,000.
Genomic characterization of craniopharyngiomas

Brastianos et al., *Nature Genet* 2014
Beaty et al., *NEJM* 2014
Overview of craniopharyngiomas

• Craniopharyngiomas are rare suprasellar tumors that occur in children and adults
• Can cause significant impairment through compression of critical structures and morbidity of treatment
• No effective medical treatment
Introduction: classical subtypes

**Adamantinomatous**
- Age Group: Children/Adults
- Histology: 65-70% reported to have mutations in the 3rd exon of β-catenin
- Drivers: β-catenin

**Papillary**
- Age Group: Adults
- Histology: No previously reported drivers
Exome sequencing identifies BRAF mutations in papillary craniopharyngiomas


NATURE GENETICS VOLUME 46 | NUMBER 2 | FEBRUARY 2014
Subtypes are characterized by single driver mutations

**Adamantinomatous**
- 62 of 65 (95%) adamantinomatous tumors with CTNNB1 mutations

**Papillary**
- 37 of 39 (95%) papillary tumors with BRAF V600E mutations

*Driver mutations were mutually exclusive between the subtypes*
Case History: 38 yo with multiple recurrences of craniopharyngioma

Initial resection

7 months after initial resection

Emergent tumor decompression

8.5 months after initial resection

Emergent tumor decompression

9 months after initial resection

Emergent tumor decompression

9.25 months after initial resection

Emergent tumor decompression

10 months after initial resection

BRAF V600E
Rapid response to BRAF targeted therapy in papillary craniopharyngioma harboring BRAF mutation

Dramatic Response of BRAF V600E Mutant Papillary Craniopharyngioma to Targeted Therapy


Brastianos et al. Nature Genetics 2014
Brastianos et al., JNCI 2016
BRAF V600E mutation was detected in patient’s peripheral blood

![Graph showing BRAF V600E levels in different samples](image)
Dramatic responses reported in other cases

Aylwin et al. Pituitary 2016
Rostume et al Acta Neurochirg 2017
Himes et al JNS 2018
Alliance/NCI A071601: Phase II trial of BRAF/MEK inhibitors in papillary craniopharyngiomas

Principal Investigator: Priscilla Brastianos

- Baseline brain MRI (with volumetrics)
- Measurable disease
- Biopsy-papillary craniopharyngioma

Vemurafenib/cobimetinib
4 months of therapy

Brain MRI q8 weeks (with volumetrics)
Surgery or radiation or continuation of BRAF/MEK inhibitors

Cohort A: Newly diagnosed craniopharyngioma
Cohort B: Recurrent craniopharyngioma

Primary endpoint
- CNS response rate after 4 months of therapy

Secondary endpoints
- CNS PFS
- Safety/toxicity profile
• Papillary craniopharyngiomas have **BRAF V600E mutations**.
• BRAF and MEK inhibitors demonstrated a **remarkable response** in a patient with a papillary craniopharyngioma.
• **Circulating BRAF V600E** was detected in the patient’s blood.
• **A clinical trial is underway to further evaluate the role of BRAF/MEK inhibitors in papillary craniopharyngiomas.**
Precision Medicine for Meningiomas
Incidence of primary CNS cancers

Malignant
N = 121,277
30.9%

All Other Malignant
5.5%

Malignant Meningioma
0.5%

Non-Malignant Meningioma
36.7%

Non-Malignant Pituitary Tumors
16.4%

Glioblastoma
14.7%

Non-Malignant Glioma
1.1%

All Other Non-Malignant
6.4%

Non-Malignant Nerve Sheath Tumors
8.5%

Non-Malignant
N = 271,705
69.1%

CBTRUS Report 2018
MENINGIOMAS
THEIR CLASSIFICATION, REGIONAL
BEHAVIOUR, LIFE HISTORY, AND
SURGICAL END RESULTS

By
HARVEY CUSHING, M.D.
Surgical Associate Professor of Surgery, Johns Hopkins University;
Assistant Professor of Surgery, Harvard University, and Surgeon-in-Chief, Peter Bent Brigham Hospital, Boston; Sterling
Professor of Neurology, Yale University

With the Collaboration of
LOUISE EISENHARDT, M.D.
Assistant Professor of Pathology, Yale University School of Medicine; Formerly
Associate in Surgery, Peter Bent Brigham Hospital, Boston

CHARLES C. THOMAS
1938
SPRINGFIELD - ILLINOIS  BALTIMORE - MARYLAND
Management of meningiomas: Surgery

- Recurrence after complete resection:
  - Grade I: 20%
  - Grade II: 40%
  - Grade III: 80%
- 33% are incompletely resected
- Recurrence after subtotal resection: 72–100%
- 5-year overall survival in Grade I–III: 83%, 76%, 32%, respectively

No effective medical therapies to date
Systemic therapy in Grade I meningiomas has demonstrated limited activity thus far.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Author</th>
<th>Year</th>
<th>N</th>
<th>Response Rate</th>
<th>PFS-6</th>
<th>Median OS</th>
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<tbody>
<tr>
<td>Hydroxyurea</td>
<td>Chamberlain</td>
<td>2011</td>
<td>60</td>
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<td>10%</td>
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<td>Temozolomide</td>
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<td>Interferon-α</td>
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<td>54%</td>
<td>8 mo</td>
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<tr>
<td>Mifepristone</td>
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<td>Pasireotide LAR</td>
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<td>Imatinib</td>
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<td>45%</td>
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<td>25%</td>
<td>13 mo</td>
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<td>Agent / Regimen</td>
<td>Author (study type)</td>
<td>Year</td>
<td>WHO Grade</td>
<td>Response Rate</td>
<td>Group</td>
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<td>Hydroxyurea</td>
<td>Chamberlain</td>
<td>2012</td>
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<td>Overall</td>
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<td>Chamberlain</td>
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<td>Pasireotide LAR (SOM230C)</td>
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<td>17</td>
<td>0%</td>
<td>II/III</td>
<td>20%</td>
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<td>Wen</td>
<td>2009</td>
<td>5</td>
<td>0%</td>
<td>II/III</td>
<td>0%</td>
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<td>9</td>
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<td>II/III</td>
<td>29%</td>
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<td>Vatalanib (PTL-787)</td>
<td>Raizer</td>
<td>2011</td>
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<tr>
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<td>Kaley</td>
<td>2010</td>
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<td>II/III</td>
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<tr>
<td>Bevacizumab</td>
<td>Nayak</td>
<td>2012</td>
<td>6</td>
<td>0%</td>
<td>II/III</td>
<td>43.8%</td>
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</tbody>
</table>
Our knowledge of meningioma genetics before 2013

Chr22

~60%  
40–70%
Question: Do meningiomas have clinically actionable mutations?
Genomic characterization of meningiomas
Targetable mutations in gene AKT1

Brastianos et al. *Nature Genet.* 2013
What is **AKT1**?

- Activation of *PI3K/Akt* signaling increases cancer cell survival
- **AKT** E17K known targetable mutation in multiple cancers (such as breast cancer)
- Inhibitors in clinical trials
AKT inhibition in solid tumors with AKT mutations

Partial responses in **13/52 (25%) patients** across all solid tumors with AKT1 E17K mutations

Hyman et al. *JCO* 2017
Targetable mutations in SMO

Brastianos et al. *Nature Genet.* 2013
• SMO is a member of the Hedgehog pathway
• Mutations in Hedgehog pathway linked to other cancers:
  • Basal cell carcinoma
  • Medulloblastoma
• FDA approved inhibitors
Vismodegib, SMO inhibitor, demonstrates high response rates in basal cell carcinoma

Sekulic et al., *NEJM* 2012

**Response rate in metastatic basal cell:** 30%

**Response rate in locally advanced basal cell:** 43%
AKT1 and SMO mutated tumors originate in the skull base

Skull base meningiomas are often very surgically challenging tumors.

Clark et al., Science 2013
Alliance A071401: Precision medicine trial in meningiomas

Principal Investigator: Priscilla Brastianos

**Recurrent or progressive meningiomas**

- **SMO mutation**: SMO inhibitor
- **NF2 mutation**: FAK inhibitor
- **NF2, CDK alteration**: CDK inhibitor
- **PIK3CA/ AKT/ PTEN mutation**: AKT inhibitor

**n = 24 (n = 12 Gr1; n = 12 Gr2/3)**

**n = 36 (n = 12 Gr1; n = 24 Gr2/3)**

**n = 24 Gr2/3**

**n = 24 (n = 12 Gr1; n = 12 Gr2/3)**

**Brain MRI every 2 months**

- **Complete response, partial response or stable disease**: Continue on therapy
- **Progressive disease or significant toxicity**: Off study
• Genomics uncovered potential clinically significant alterations.

• A national multicenter Alliance NCI-sponsored trial is underway.

• Targeted therapies will likely play an increasingly important role in the management of meningiomas.
Targeted therapy for high grade gliomas
Preliminary Study of Efficacy and Safety of Dabrafenib + Trametinib in Patients with Recurrent or Refractory BRAF V600E–mutated High-grade Glioma

BRAF mutations in <3% of high grade gliomas
• Open-label, multicenter, phase 2a study (NCT02034110) in patients with BRAF V600E rare cancers with several histologies

Primary endpoint: Investigator-assessed ORR by RANO criteria

Secondary endpoints: DOR, PFS, OS and Safety

Tumor responses were assessed every 8 weeks during the first 48 weeks of the study and then every 12 weeks thereafter.
<table>
<thead>
<tr>
<th>Investigator-assessed Response</th>
<th>HGG Cohort (n = 37)( ^a )</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>ITT-Evaluable WHO Grade III Glioma (n = 9)</td>
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<tr>
<td>Best overall response, n (%)</td>
<td></td>
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<tr>
<td>CR</td>
<td>1 (11)</td>
</tr>
<tr>
<td>PR</td>
<td>1 (11)</td>
</tr>
<tr>
<td>SD</td>
<td>2 (22)</td>
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<tr>
<td>PD</td>
<td>5 (56)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>0</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
</tr>
<tr>
<td>ORR (CR + PR), n (%)</td>
<td>2 (22)</td>
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<tr>
<td>95% CI</td>
<td>2.8-60</td>
</tr>
</tbody>
</table>

Slide courtesy of Patrick Wen, MD
Tumor Regression in a Confirmed PR Response

- Patient aged 37 years with right parietal \( BRAF \) V600E–mutant glioblastoma
  - \( CDKN2A/B \) homozygous deletion, \( IDH1/2 \) wildtype, \( MGMT \) un-methylated
- Treatment was well tolerated
- Patient progressed at 8 months with a new distant lesion
  - Initial target lesion continued to regress
Individualized Screening Trial of Innovative Glioblastoma Therapy (INSIGHT): A Bayesian Adaptive Platform Trial to Develop Precision Medicines for Patients With Glioblastoma

Brian M. Alexander, PhD, MPH1,2; Lorenzo Tripodi, PhD1; Sarah Gaffney1; Isabel C. Arrillaga-Romany, MD, PhD2; Eudocia G. Lee, MD2; Mikael L. Rinne, MD, PhD3,4; Manmeet S. Ahluwalia, MD3; Howard Colman, MD, PhD3; Geoffrey Fell, MS1; Evanthia Galanis, MD2; John de Groot, MD3; Jan Drappatz, MD2; Andrew B. Lassman, MD2; David M. Meredith, MD, PhD2,4; L. Burt Nabors, MD1; Sandro Santagata, MD, PhD1,2; David Schiff, MD1,2; Mary R. Welch, MD1,2; Keith L. Ligon, MD, PhD1,2; and Patrick Y. Wen, MD1

2019
Precision Medicine for Brain Metastases
Brain metastases are an unmet clinical need

- Most common cancer of the brain
- Incidence: 200,000/year
- Most are lung, breast and melanoma
- Median survival: 3–23 months
- Clinical trials in US commonly **exclude** patients with brain metastases.
In 20 B.C……

All roads lead to Rome.

• Augustus Ceasar, Millarium Aureum
All roads lead to whole brain radiation therapy
Whole brain radiation therapy has been the mainstay of therapy for brain metastases for > 50 years

Although metastases to the brain are by no means uncommon in patients with various types of cancer, their treatment by irradiation is not widely known, and the palliative results of roentgen-ray therapy in an unselected series of cases have not been evaluated. We are therefore presenting in this report all the cases of brain metastases referred to us in the past four and a half years. No case with

- Palliation of symptoms in 24/38 cases
- Survival 4-8 months
Neurocognitive decline after WBRT

Effective systemic therapies to improve ‘standard of care’ are needed.

Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial
Challenges of precision medicine in brain metastases

- Limited number of prospective trials.
- Many small underpowered studies.
- Most patients with brain metastases have progressed on several therapies.
- *Extent to which brain metastases share genetic profile of primary tumor is unknown.*
Targeted therapies are showing promise in brain metastases.
Brain metastases in melanoma

• ~50% of advanced melanoma patients develop brain metastases.
• BRAF mutations in 50% of melanoma patients.
• BRAF mutations predict sensitivity to BRAF inhibitors
### Prospective studies of systemic agents in melanoma

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<th>Treatment</th>
<th>Number of Patients</th>
<th>Median OS</th>
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<td>New</td>
<td>TMZ</td>
<td>No prior chemo (117) Prior chemo (34)</td>
<td>3.5 mo</td>
<td>7%</td>
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<td>JCO 2004</td>
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<td>Margolin</td>
<td>Both</td>
<td>Ipilimumab</td>
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<td>Both</td>
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<td>Tawbi</td>
<td>Both</td>
<td>Ipi/nivo</td>
<td>75</td>
<td>NR</td>
<td>55%</td>
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<td>NEJM 2018</td>
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<td>Long</td>
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<td>Dabrafenib</td>
<td>No prior treatment (89) Prior treatment (83)</td>
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<tr>
<td>Davies</td>
<td>Both</td>
<td>Dabrafenib/trametinib</td>
<td>125</td>
<td>NR</td>
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<td>Davies ASCO 2017</td>
<td>Both</td>
<td>Dabrafenib/trametinib</td>
<td>125</td>
<td>NR</td>
<td>54%</td>
</tr>
</tbody>
</table>

**Immunotherapy**
Targeting the immune system
## Targeted therapy

### Prospective studies of systemic agents in melanoma

<table>
<thead>
<tr>
<th>Study</th>
<th>New or Recurrent</th>
<th>Treatment</th>
<th>Number of Patients</th>
<th>Median OS</th>
<th>Cerebral RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agarwala JCO 2004</td>
<td>New</td>
<td>TMZ</td>
<td>No prior chemo (117) Prior chemo (34)</td>
<td>3.5 mo</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.2 mo</td>
<td></td>
</tr>
<tr>
<td>Hofmann J Neuroonc 2006</td>
<td>Both</td>
<td>TMZ/XRT</td>
<td>TMZ (13) Prior chemo (12)</td>
<td>5 mo</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TMZ + SRS (12)</td>
<td>9 mo</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TMZ + WBRT (10)</td>
<td>7 mo</td>
<td>10%</td>
</tr>
<tr>
<td>Margolin Lancet Oncol 2012</td>
<td>Both</td>
<td>Ipilimumab</td>
<td>Asymptomatic (51) Symptomatic (21)</td>
<td>7.0 mo</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.7 mo</td>
<td>5%</td>
</tr>
<tr>
<td>Goldberg Lancet Oncol 2016</td>
<td>Both</td>
<td>Pembrolizumab</td>
<td>18</td>
<td>NR</td>
<td>22%</td>
</tr>
<tr>
<td>Tawbi NEJM 2018</td>
<td>Both</td>
<td>Ipi/nivo</td>
<td>75</td>
<td>NR</td>
<td>55%</td>
</tr>
<tr>
<td>Long Lancet Oncol 2012</td>
<td>Both</td>
<td>Dabrafenib</td>
<td>No prior treatment (89) Prior treatment (83)</td>
<td>33.1 wks</td>
<td>39.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>31.4 wks</td>
<td>30.8%</td>
</tr>
<tr>
<td>Davies ASCO 2017</td>
<td>Both</td>
<td>Dabrafenib/trametinib</td>
<td>125</td>
<td>NR</td>
<td>54%</td>
</tr>
</tbody>
</table>
Brain metastases in nonsmall cell lung cancer (NSCLC)

- 40% of advanced NSCLC patients will develop brain metastases.

- Targeted therapies with promising activity in brain metastases:
  - **EGFR inhibitors:** erlotinib, gefitinib, afatinib, osimertinib
  - **ALK inhibitors:** crizotinib, ceritinib, alectinib

Brastianos et al., JNCCN 2013
Targeted therapies are promising in lung cancer brain metastases

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>N</th>
<th>Median overall survival</th>
<th>Response rate in brain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu (Lung Cancer 2007)</td>
<td>Gefinitib</td>
<td>40</td>
<td>15.0 mo</td>
<td>38%</td>
</tr>
<tr>
<td>Kim (Lung Cancer 2009)</td>
<td>Gefinitib or erlotinib</td>
<td>23</td>
<td>18.8 mo</td>
<td>73.9%</td>
</tr>
<tr>
<td>Chiu (Lung Cancer 2004)</td>
<td>Gefitinib</td>
<td>76</td>
<td>9.9 mo</td>
<td>50%</td>
</tr>
<tr>
<td>Gadgeel (Lancol Oncol 2014)</td>
<td>Alectinib</td>
<td>21</td>
<td>NR</td>
<td>52%</td>
</tr>
<tr>
<td>Mok (ASCO 2017)</td>
<td>Osimertinib</td>
<td>46</td>
<td>NR</td>
<td>70%</td>
</tr>
</tbody>
</table>

Brastianos et al., *JNCCN* 2013
Brain metastases from breast cancer

• Brain metastases are common in breast cancer:
  • 30-40% of advanced HER2-positive breast cancer

• Targeted therapies with activity in the brain (anti-HER2):
  • Lapatinib:
    • Response rate (single agent): 6%
    • Response rate (with chemotherapy): 20-65%
  • TDM1: response rate: 40%
  • Neratinib + chemotherapy: 65%

Brastianos et al., JNCCN 2013
Better therapies are *urgently* needed for brain metastases patients.

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

• What are the targetable mutations in brain metastases?
• Patients often progress only in the brain. Can this be due to genetic changes that are different in the brain metastases?
• Can we rely on a primary tumor biopsy to make decisions for targeted agents in brain metastases? (current standard of care)
Genomic characterization of brain metastases
International team of collaborators

**Challenges**
- Brain metastases not routinely banked
- Normal tissue not routinely collected historically
- Old, low-quality primary tumor blocks
- Consent requirements
Study funded by ABTA

- Comprehensive genomic characterization of 104 brain metastases matched with primary and normal tissue
- Including 15 with additional metastatic sites.
Branched evolution: brain metastasis and primary tumor evolve separately
Charles Darwin, 1837
Question: Do brain metastases harbor targetable mutations absent in their primary tumors?
Example: targetable mutations in brain metastasis, not in primary tumors

HER2+ breast carcinoma

Brastianos, Carter et al., Cancer Discovery 2015
Were their commonalities across the entire cohort, so we can start thinking about clinical trials in brain metastases? Indeed, we found targetable mutations that were common across the entire cohort. The most common alterations were those predicting sensitivity to therapies called CDK inhibitors – 51% of cases had alterations predicting sensitivity to CDK inhibitors, and this was a recurrent theme. There are currently several CDK inhibitors in clinical trials, and one is FDA approved for breast cancer. So this is a potential drug target for brain metastases from many different types of cancer.

Example: targetable mutations in brain metastasis, not in primary tumors
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There are currently several CDK inhibitors in clinical trials, and one is FDA approved for breast cancer. So this is a potential drug target for brain metastases from many different types of cancer.

53% of cases have a targetable 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 predicting sensitivity to drugs called **CDK inhibitors**

43% of cases with alterations predicting sensitivity to drugs called **PI3K inhibitors**
Were their commonalities across the entire cohort, so we can start thinking about clinical trials in brain metastases?

Indeed, we found targetable mutations that were common across the entire cohort. The most common alterations were those predicting sensitivity to therapies called CDK inhibitors – 51% of cases had alterations predicting sensitivity to CDK inhibitors, and this was a recurrent theme. There are currently several CDK inhibitors in clinical trials, and one is FDA approved for breast cancer. So this is a potential drug target for brain metastases from many different types of cancer.

<table>
<thead>
<tr>
<th>Genomic/molecular profiling</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIT (Imatinib)</td>
</tr>
<tr>
<td>EGFR (Erlotinib)</td>
</tr>
<tr>
<td>HER2 (Trastuzumab)</td>
</tr>
<tr>
<td>BRAF (PLX4032)</td>
</tr>
<tr>
<td>PIK3CA (BEZ235)</td>
</tr>
</tbody>
</table>

53% of cases had at least one targetable genetic alteration in the brain metastasis, not detected in the primary tumor.
Were there commonalities across the entire cohort, so we can start thinking about clinical trials in brain metastases?

Indeed, we found targetable mutations that were common across the entire cohort. The most common alterations were those predicting sensitivity to therapies called CDK inhibitors – 51% of cases had alterations predicting sensitivity to CDK inhibitors, and this was a recurrent theme. There are currently several CDK inhibitors in clinical trials, and one is FDA approved for breast cancer. So this is a potential drug target for brain metastases from many different types of cancer.

**Biomarker driven trial in brain metastases**

**Alliance A071701**
**PI: Priscilla Brastianos**

- Progressive brain metastases
- Histologically confirmed solid malignancy
- Any brain metastasis tissue for sequencing

- Brain MRI and systemic staging
- Brain MRI and systemic staging q6wks

- Actionable alteration in CDK pathway
  - CDK inhibitor
  - CNS or systemic progression

- Actionable alteration in PI3K/AKT/mTOR pathway
  - PI3K inhibitor
  - CNS or systemic progression

- ALK/NTRK/ROS1 translocation
  - ALK/NTRK/ROS inhibitor
  - CNS or systemic progression
Conclusions

- Mapping the genetic profiles of primary and metastatic brain tumors is critical for uncovering therapeutic targets.

- Precision medicine is a promising approach for primary and metastatic brain tumors.
Indeed, we found targetable mutations that were common across the entire cohort. The most common alterations were those predicting sensitivity to therapies called CDK inhibitors – 51% of cases had alterations predicting sensitivity to CDK inhibitors, and this was a recurrent theme. There are currently several CDK inhibitors in clinical trials, and one is FDA approved for breast cancer. So this is a potential drug target for brain metastases from many different types of cancer.

Acknowledgments

Massachusetts General Hospital
Daniel Cahill
Tracy Batchelor
David Louis
Gad Getz
Fred Barker
Julie Miller
Ganesh Shankar
Anat Stemmer-Rachamimov
Dora Dias-Santagata
Mario Suva

Brastianos Lab:
Christopher Alvarez-Breckenridge
Ugo Chukwueke
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

DFCI
Patrick Wen

Genentech
Fred de Sauvage

University of Pennsylvania
Adam C Resnick
Phillip B Storm

Lab funding

Thanks to ABTA for support, and to patients and families for graciously participating in research efforts.

Egypt
Hala Taha

Alliance
Eva Galanis (Mayo Clinic)
Carey Anders
Peter Kaufman

Ignytta
Pratik Multani
Edna Chow Maneval
Maria Brastianos (1957–2014)
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