Multi-disciplinary Panel of Experts

- Dr. Erin Dunbar, facilitator
- Dr. Timothy Cloughesy, neuro-oncology
- Dr. Craig Horbinski, neuropathology
- Dr. Amy Heimberger, neurosurgical-oncology
- Dr. Vinai Gondi, radiation oncology
- Other participants:
  - Therapists (speech, physical, occupational, other)
  - Neurology
  - Medical Oncology
  - Social workers
  - Nursing team
  - Tumor registry
  - Clinical trial coordinators
  - Physical medicine & rehab, physiatry
  - Palliative care
DISCLOSURES & SUPPORT

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

• I have consulting/advisory board agreements with:

• I have pre-clinical laboratory and/or clinical trial support from the following companies:
Three Cases

HOW QUESTIONS WILL BE ADDRESSED:

At the end of each case, we will answer 1-2 questions related to the science and treatment.

At the end of all the cases, we will open the conversation to an “Ask the expert” format.

After the session, you are encouraged to ask a specialist a questions anytime.
Case One

Breast Adenocarcinoma with Brain Metastases
69 y.o. woman with Her-2/neu+ breast adenocarcinoma

- 69 year old woman with Her-2/neu + breast adenocarcinoma has completed her chemotherapy and has been under surveillance for 3 years. Enjoys being outdoors in the sun with her family.
- Develops progressive headaches and a seizure.
- Otherwise, healthy.
- CT head is without bleeding or signs of elevated pressure.
- MRI brain with findings worrisome for metastasis of her breast cancer to the brain (would represent her 1st progression).
• At initial presentation:

• **Dr. Heimberger:** role for surgery
• **Dr. Gondi:** role for focused radiation vs. whole brain radiation
• **Dr. Cloughesy:** role for medicines, ......and if so, is there anything else you want to know before you select the medicine(s)?
- **Molecular/genetic Marker change:**
  - 69 yo brain mets from Her-2/neu breast cancer, s/p multiple prior systemic and CNS treatments
  - Systemic disease controlled
  - Presented with HA, seizure
  - Brain biopsied:
  - **Dr. Heimberger** obtains tissue and gets it to
  - **Dr. Horbinski**, who explains more on next slide

Brastianos, PK et al, *Cancer Discov. Nov. 2015*
Dr. Horbinski:

- Metastatic tissue without Her-2/neu markers anymore
- Caris Life Science Tissue Analysis
- NCI MATCH trial tissue sent
- Proceeded to ALTERNATIVE CNS and systemic treatment

Brastianos, PK et al, Cancer Discov. Nov.2015
Precision Medicine individualizes treatment to the person (Drs. Horbinski and Cloughesy (next slide, too))

Examples of this by using the tumor tissue:
--Caris Lifescience analysis
--Foundation 1
--Institution-specific

<table>
<thead>
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<th>Specimen Information</th>
<th>Ordered by</th>
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<tr>
<td>Name: PATIENT, NAME</td>
<td>Dr. Smith</td>
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<tr>
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<td>Cancer Center Anytown, ST</td>
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<tr>
<td>Sex: Male</td>
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<td>Case Number: TN00000000</td>
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<tr>
<td>Diagnosis: Mucinous adenocarcinoma</td>
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<tr>
<td>Completion of Testing: XX Mon 20XX</td>
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<table>
<thead>
<tr>
<th>High Impact Results</th>
<th>BIOMARKER</th>
<th>METHOD</th>
<th>RESULTS</th>
<th>THERAPY ASSOCIATION</th>
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<tbody>
<tr>
<td>KRAS</td>
<td>NGS</td>
<td>Mutated, Pathogenic Exon 4</td>
<td>A146G</td>
<td>LACK OF BENEFIT cetuximab, panitumumab</td>
</tr>
<tr>
<td>NRAS</td>
<td>NGS</td>
<td>Mutated, Pathogenic Exon 2</td>
<td>A157D</td>
<td>BENEFIT</td>
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<tr>
<td>Microsatellite Instability (MSI)</td>
<td>NGS</td>
<td>MSI High</td>
<td>BENEFIT</td>
<td>nivolumab, pembrolizumab</td>
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<td>Mismatch Repair Status (MPS)</td>
<td>NGS</td>
<td>Deficient</td>
<td>LACK OF BENEFIT</td>
<td>cetuximab, panitumumab</td>
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<td>TP53</td>
<td>NGS</td>
<td>Mutated, Pathogenic Exon 10</td>
<td>R214R</td>
<td>BENEFIT</td>
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<tr>
<td>Tumor Mutational Burden (TMB)</td>
<td>NGS</td>
<td>High</td>
<td>BENEFIT</td>
<td>nivolumab, pembrolizumab</td>
</tr>
</tbody>
</table>


**Additional Results**

<table>
<thead>
<tr>
<th>BIOMARKER</th>
<th>METHOD</th>
<th>RESULTS</th>
<th>OTHER FINDINGS (see page 2 for additional results)</th>
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<tbody>
<tr>
<td>BRAF</td>
<td>NGS</td>
<td>No mutation detected</td>
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<tr>
<td>MLH1</td>
<td>IHCl</td>
<td>Positive</td>
<td>1+, 80%</td>
</tr>
<tr>
<td>MSH2</td>
<td>IHCl</td>
<td>Positive</td>
<td>1+, 80%</td>
</tr>
<tr>
<td>MSI</td>
<td>IHCl</td>
<td>Positive</td>
<td>1+, 80%</td>
</tr>
<tr>
<td>PMS2</td>
<td>IHCl</td>
<td>Positive</td>
<td>1+, 80%</td>
</tr>
<tr>
<td>PD-L1</td>
<td>IHCl</td>
<td>Positive</td>
<td>1+, 80%</td>
</tr>
</tbody>
</table>

**Important Note**

A pathogenic mutation was detected in BRCAl and may be of germline origin. Germline mutations in BRCAl are causal for hereditary breast and ovarian cancer. Counseling with patient’s personal and familial cancer history is recommended.

Clinical Trials Connector: 225 Chemotherapy Trials | 210 Targeted Therapy Trials. See page 8.

Doctors and researchers are excited about new therapies derived from the study of the human genome that hold the promise of curing multiple forms of cancer using the patients’ own DNA to undo cancer cells. Mary Lee, USA TODAY
Precision Medicine, via Re-investigating Tumor Tissue, Helps with:
(Drs. Horbinski and Cloughesy)

- Tumor \textit{(alive and growing)} vs. Treatment-effect \textit{(dead = necrosis)}
- Tumor vs. other (infection, etc.)
- Current grade and molecular/genetic aberrations
- Tissue for FDA approved drug
- Tissue for a specific clinical trial
- Tissue for drug-to-tissue-target match
At initial presentation:

Initial very good Partial Response, then Stable Disease for >12 months.
• She later developed symptoms worrisome for elevated intracranial pressure
• Presented with HA, hypersomnolence, n/v, gait, visual changes
• Endoscopic Third Ventriclestomy performed
• **Dr. Heimberger**, discuss the role of intervening when there is elevated intracranial pressure. Anything else you can do (e.g., sample tissue, etc.)?
Case 2

Malignant Glioma
55 y.o. man with a Malignant Glioma

- Left occipital mass
- R homonymous hemianopsia
- Dr. Heimberger: the role of biopsy vs. “maximal safe resection”. Briefly describe techniques used in the OR.
- Visual field cut stable post-operatively
Mitotic activity

**Anaplastic Astrocytoma, WHO Grade III**

- **Mitotic activity** high: 9 mitoses per HPF
- **Ki-67** elevated at 40%

**Molecular/genetic markers:**
- IDH-1/2-wild type
- MGMT promoter methylated
- Etc.

**Dr. Horbinski, briefly describe:**

<table>
<thead>
<tr>
<th>IDH status</th>
<th>Histology</th>
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<tbody>
<tr>
<td>IDH-mutant</td>
<td>Diffuse astrocytic and oligodendroglial gliomas WHO grade II or grade III</td>
</tr>
<tr>
<td>IDH-wild-type</td>
<td>Diffuse astrocytic gliomas/glioblastomas WHO grade IV</td>
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</table>

<table>
<thead>
<tr>
<th>ATRX status</th>
<th>IDH-mutant</th>
<th>IDH-wild-type</th>
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</thead>
<tbody>
<tr>
<td>Nuclear ATRX retained</td>
<td>IDH-mutant</td>
<td>IDH-wild-type</td>
</tr>
<tr>
<td>Nuclear ATRX lost</td>
<td>IDH-wild-type</td>
<td>IDH-mutant</td>
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<table>
<thead>
<tr>
<th>1p/19q status</th>
<th>IDH-mutant</th>
<th>IDH-wild-type</th>
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</thead>
<tbody>
<tr>
<td>1p/19q-codleted</td>
<td>IDH-mutant</td>
<td>IDH-wild-type</td>
</tr>
<tr>
<td>1p/19q-non-codeled</td>
<td>IDH-wild-type</td>
<td>IDH-mutant</td>
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</table>

<table>
<thead>
<tr>
<th>H3-K27M status</th>
<th>IDH-mutant</th>
<th>IDH-wild-type</th>
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<tbody>
<tr>
<td>Oligodendroglioma, IDH-mutant and 1p/19q-codleted, WHO grade II or III</td>
<td>IDH-mutant, WHO grade II or III</td>
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<tr>
<td>Astrocytoma, IDH-mutant, WHO grade II or III</td>
<td>IDH-mutant, WHO grade II or III</td>
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<tr>
<td>Astrocytoma, IDH-wild-type, WHO grade IV</td>
<td>IDH-mutant, WHO grade IV</td>
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<tr>
<td>Astrocytoma, IDH-wild-type, WHO grade IV</td>
<td>IDH-mutant, WHO grade IV</td>
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</tr>
<tr>
<td>Diffuse midline glioma, H3-K27M-mutant</td>
<td>H3-K27M-mutant</td>
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</tbody>
</table>

**Integrated diagnosis**
- Oligodendroglioma, IDH-mutant and 1p/19q-codleted, WHO grade II or III
- Astrocytoma, IDH-mutant, WHO grade II or III
- Astrocytoma, IDH-wild-type, WHO grade IV
- Diffuse astrocytic gliomas/glioblastomas WHO grade IV
Anaplastic Astrocytoma

- Drs. Gondi and Cloughesy, briefly describe the scientific rationale and practical aspects of:
- Concurrent radiation (RT) + oral temozolomide, followed by plans for 6 months of maintenance oral temozolomide cycles ("Stupp protocol")
Restaging

• 1\textsuperscript{st} post-RT study ( \sim 1 month after ending RT)
• Clinically stable
• working full time
• no steroids
Subsequent Restaging

Reminder of initial restaging:

- Clinically stable
- Yet worsening imaging....

Worsening Imaging:
Dr. Gondi:

Treatment Course Impacts Imaging and Symptoms

Radio-graphic & Often Clinical “worsening” for ~ 2-6+ mo. before improvement
Treatment Decisions

Drs. Gondi and Heimberger, next steps:

- Continue surveillance, with close restaging, vs. intervention
- Intervention would be both diagnostic and therapeutic

TOOLS:
- CNS Tumor Conference
- RANO Guidelines
- MRI and other imaging
- Biopsy for tissue interrogation +/- debulking
- Combination
Restaging with MRI with perfusion and FDG-PET

- Drs. Gondi and Cloughesy:
- 8 months later, he is clinically stable, working and on steroids: 0-2mg daily
Next Step in Management (All)

- He remained clinically and radiographically stable for numerous more months.....
- Possible future scenarios:
  - I. Discern if tumor vs. treatment effect
  - Restage using RANO guidelines
  - Biopsy (and/or debulk)
- II. Treat symptoms
  - Steroids or avastin
  - Debulking with tissue interrogation
- III. Treat progressive tumor
  - Debulking
  - Routine medicines
  - Clinical trial
  - Optune TTF device
  - Repeat radiation

Multidisciplinary CNS Tumor Conferences:
- In-depth review
- Consensus recommendations
Case 3

Meningioma
Meningioma

- 33 y.o., 6 month history of painless vision loss
- MRI: Diffuse multifocal abnormalities involving the base of skull, frontal and temporal dura with invasion into the cavernous sinus bilaterally
- Left optic nerve atrophy, Left optic neuropathy, and global Left visual field defect
New Diagnosis

• **Dr. Gondi and others:** Differential diagnosis of her imaging:

• **Dr. Heimberger:** Next step in her evaluation & management

• Role of resection (one or more lesions)

• Role of RT

• Role of “medicines”

• Role of clinical trial
Initial Evaluation

- **Dr. Cloughesy**: Next steps in her management:
- Lumbar puncture: No evidence of inflammatory, demyelinating or malignant disease
- Blood: No evidence of nutritional deficiencies, or inflammatory, demyelinating or malignant diseases
- Spine MRI - normal
- Neuro-ophthalmology exam: Left optic neuropathy, left optic atrophy, global left visual field defect
- Tumor conference consensus decision for Biopsy
Meningioma, WHO Grade I
Dr. Horbinski:

- Meningioma, WHO Grade I
- Atypical Meningioma, WHO Grade II
  - Mitoses >4/10 hpf, chordoid or clear cell histology, or 3/5 atypical histologic features
  - Brain invasion
- Anaplastic Meningioma, WHO Grade III
  - Mitoses >20/10 hpf, rhabdoid or papillary histology, or sarcomatoid/carcinomatoid areas
- Emerging molecular/genetics
  - H3K27 trimethylation by immunohistochemistry
  - Mitotic Index Using the Mitosis Marker Anti–Phosphohistone H3
- others
  - Sporadic vs. Neurofibromatosis (NF)

REFERENCE: WHO 2016 Meningioma Classification/Grading
**Biopsy**

- **Dr. Heimberger: Surgical grade of resection**
- Briefly discuss general trends in risk/timing of progression compared to:
  - Simpson grade
  - Subsequent treatment, e.g., RT

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition of Corresponding Resection</th>
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<tbody>
<tr>
<td>I</td>
<td>macroscopically complete resection w/ excision of dural attachment &amp; abnormal bone</td>
</tr>
<tr>
<td>II</td>
<td>macroscopically complete resection w/ coagulation of dural attachment</td>
</tr>
<tr>
<td>III</td>
<td>macroscopically complete resection w/o resection or coagulation of its attachment</td>
</tr>
<tr>
<td>IV</td>
<td>subtotal resection</td>
</tr>
<tr>
<td>V</td>
<td>simple decompression of the tumor</td>
</tr>
</tbody>
</table>

Source: Neurosurg Focus © 2003 American Association of Neurological Surgeons

Rogers L, Mehta M, Neurosurgery, 2007; EORTC/NRG definitions; various refs
Post-biopsy

- Post-op imaging – stable
- Drs. Gondi and Cloughesy:
  - Next step in her management
- Observation
- Radiation
- Medicines
- Clinical Trial
- Combination

Meningioma

NF2 | Non-NF2
---|---
NF2 Mut | KLF4 Mut
SMO Mut | AKT1 Mut
NF2 loss | 22q loss

TRAF7 mutations
BRAFv600E mutations
PI3K-Akt mutations
Evaluation and management

- Imaging - stable
- Vision - stable

**Dr. Gondi:** Next step in her management

- Radiation – 54.4 gray, 28 fxns
  - Dr. Gondi to discuss goal and approach

**Dr. Coughesy:**

- Importance of her Family History: sister with breast cancer in her 30’s.
  - Referral to genetic counselor.
  - Later, they were identified to have a heritable syndrome of familial meningioma syndrome associated with early onset breast cancer.
  - She and her other sisters are now in an accelerated screening program.
Dr. Cloughesy: Next steps in management at a possible future progression ~ 8 years later?

- Re-biopsy for interrogation and tissue collection
  - E.g., sporadic vs. NF2 or other
  - Molecular/genetic aberrations

- Clinical Trial

- “Off-label” use of medicine

- Re-RT

Medical Treatments are Increasingly Influenced by Molecular/Genetics

TRAF7 mutations
BRAFv600E mutations
PI3K-Akt mutations
Questions for the Specialists………
Thank you!

• Neuro-pathology – Dr. Horbinski
• Neuro-oncology – Dr. Cloughesy
• Neurosurgical-oncology – Dr. Heimberger
• Radiation-Oncology – Dr. Gondi
• Facilitator – Dr. Dunbar

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www.piedmont.org/cancer/brain/brain-tumor-home