Management of Brain Metastases

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Epidemiology
Brain Metastases

• Incidence (US):
  – Between 170-300,000 cases of brain metastasis per year
    • >25% of cancer patients overall have brain metastases at autopsy
      – #1 histology = Lung – 34% of patients
      – #2 histology = Breast – 30% of patients
      – #3 histology = Melanoma
        • 10-40% of patients with stage IV melanoma by imaging
        • more than 2/3 in autopsy series\(^1\)
        • Multifocal in 50% of cases\(^3\)
  – Melanoma incidence increasing (2 fold in last 25 years)\(^2\)

Melanoma Brain Metastases

- 10,000 pts with melanoma brain mets per year in US
- Melanoma has the highest propensity of all adult solid tumors to metastasize to the brain
- Risk Factors: males, mucosal, H&N primaries, Breslow depth, ulceration
- Median time to diagnosis from primary: 2.2-3.8 years
Presentation

- Silent: Screening MRI or CT
- Symptoms of increased IC pressure
- Sudden onset symptoms due to hemorrhage ("Tumor TIA")
- Is the initial site of metastases in 15% of new patients with MM
- Pts who respond to aggressive systemic therapy often relapse in the CNS
Management of Brain Metastases in Melanoma: Historical Approach

- Symptomatic
  - Steroids
  - Anticonvulsants
- Definitive
  - Surgery
  - Radiation
  - Chemotherapy
Overview of Management

Categorize patients into 3 groups

- Solitary brain metastasis
- Oligometastatic disease (2-4)
- Multiple brain metastases (>4)

Therapeutic Approach

- Local
- Systemic
Local Therapy
(Surgery, SRS, WBRT)
Solitary Metastasis

• Surgery better than WBRT
  – Improved local control and OS
• Surgery + WBRT better than Surgery alone
  – Improved local control but not OS
• SRS equivalent to WBRT
  – OS same, better QOL for SRS

Patchell et al; Vecht et al; Muacevic et al
Oligometastatic Disease

• WBRT: Increased dose or fraction no better than standard (RTOG)
• Level 1 evidence supports SRS in this subgroup
• Randomized trial of SRS +/- WBRT
  – Improved local control
  – No improvement in survival
• Surgery also an option
  – But no level 1 evidence compared to SRS
Multiple Brain Metastases

- WBRT is standard
- SRS is an option for selected patients
Systemic Therapy

- **Chemotherapy**
  - Temozolomide
  - Fotemustine

- **Immunotherapy**
  - Ipilimumab

- **B-raf Targeted therapy**
  - Vemurafenib/dabrafenib
Temozolomide

- Alkylating agent similar to DTIC
- Spontaneously converted to active metabolite (MTIC); DTIC undergoes hepatic conversion
- Crosses the blood-brain barrier
- 100% orally bioavailable
Study C95-086

A Phase II Study of Temozolomide (SCH 52365) Prior to Radiation Therapy in the Treatment of Patients with Brain Metastases from Malignant Melanoma
### Phase II Study of Temozolomide in Brain Metastases prior to RT

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No Prior Chemotherapy (n = 117)</th>
<th>Prior Chemotherapy (n = 34)</th>
<th>Total (N = 151)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>%</td>
<td>No. of Patients</td>
</tr>
<tr>
<td>Objective Response</td>
<td>8</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Complete</td>
<td>1</td>
<td>1</td>
<td>--</td>
</tr>
<tr>
<td>Partial</td>
<td>7</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Stable disease</td>
<td>34</td>
<td>29</td>
<td>6</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>54</td>
<td>46</td>
<td>19</td>
</tr>
<tr>
<td>Missing*</td>
<td>20</td>
<td>17</td>
<td>9</td>
</tr>
</tbody>
</table>

*Indicates patients who did not have a best objective response recorded by the investigator. Primary reasons were disease progression identified before scheduled scans; investigator decided not to perform scan; patients refused scheduled scans; or patients progressed more quickly than anticipated and died, or not medically stable to undergo scan procedures.

Agarwala SS et al, JCO June 2004
Fig 2. Kaplan-Meier estimate of overall survival for patients who had not received prior chemotherapy (n = 117) and for patients who had received prior chemotherapy (n = 34)

Median OS Arm A 3.5 months, Arm B 2.2 months

Systemic Therapy

• Chemotherapy
  – Temozolomide
  – Fotemustine

• Immunotherapy
  – Ipilimumab
    • Phase II trial (CA184-042)

• B-raf Targeted therapy
  – Vemurafenib/dabrafenib
Ipilimumab: brain metastasis

- Phase II trial on DCR using two different patient subgroups
- Corticosteroids: no (Arm A), yes (Arm B)
- Ipi dose: 10 mg/kg every 3 weeks
- Re-evaluations after 12 weeks

Lawrence et al, J Clin Oncol 28: 7s, 2010
Ipilimumab in Brain Metastases
CA184-042 Study Schema

**Screening**
Patients with melanoma and ≥1 brain mets

**Cohort A**
No steroids

**Cohort B**
Steroids
10 mg/kg Q3W x4

**Induction**

**Maintenance**
10 mg/kg Q12W

**Follow up**

**Ipilimumab dosing:**

<table>
<thead>
<tr>
<th></th>
<th>W1</th>
<th>W4</th>
<th>W7</th>
<th>W10</th>
<th>W24</th>
<th>W36</th>
<th>W48+</th>
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</thead>
<tbody>
<tr>
<td>Screening</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction</td>
<td>10 mg/kg Q3W x4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maintenance</td>
<td>10 mg/kg Q12W</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Tumor assessments**

**Non-CNS lesions:**
B
W6
W12 W16 W24
Q12W → End of treatment

**CNS lesions:**
B
W6
W12 W16 W20
Q12W → End of treatment

Lawrence D et al JCO 28:7s, 2010
### Baseline Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>CA184-042: Cohort A (n=51)</th>
<th>CA184-045 (n=165)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (years)</td>
<td>59</td>
<td>55</td>
</tr>
<tr>
<td>Gender, n (female/male)</td>
<td>18/33</td>
<td>61/104</td>
</tr>
<tr>
<td>ECOG-PS, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>71 (43)</td>
</tr>
<tr>
<td>1</td>
<td>25 (49.0)</td>
<td>71 (43)</td>
</tr>
<tr>
<td>2</td>
<td>26 (51.0)</td>
<td>22 (13.3)</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Any prior systemic therapy, n (%)</td>
<td>40 (78.4)</td>
<td>165 (100)</td>
</tr>
<tr>
<td>Prior radiotherapy to brain, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole brain</td>
<td>20 (39.2)</td>
<td>NA</td>
</tr>
<tr>
<td>Gamma knife/targeted</td>
<td>17 (33.3)</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>4 (7.8)</td>
<td>NA</td>
</tr>
</tbody>
</table>

ECOG-PS = Eastern Cooperative Oncology Group performance status; NA = not available
Ipilimumab: brain metastasis

Arm A (n = 51)

<table>
<thead>
<tr>
<th></th>
<th>global</th>
<th>brain</th>
<th>non-CNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>5</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>SD</td>
<td>4</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>BORR (WHO)</td>
<td>9.8%</td>
<td>15.7%</td>
<td>13.7%</td>
</tr>
<tr>
<td>DCR</td>
<td>17.6%</td>
<td>23.5%</td>
<td>27.5%</td>
</tr>
</tbody>
</table>

Lawrence et al, J Clin Oncol 28: 7s, 2010
Ipilimumab: brain metastasis

Arm B (n = 21)

<table>
<thead>
<tr>
<th></th>
<th>global</th>
<th>brain</th>
<th>non-CNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>SD</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>BORR (WHO)</td>
<td>4.8%</td>
<td>4.8%</td>
<td>4.8%</td>
</tr>
<tr>
<td>DCR</td>
<td>4.8%</td>
<td>9.5%</td>
<td>4.8%</td>
</tr>
</tbody>
</table>

Lawrence et al, J Clin Oncol 28: 7s, 2010
# Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>CA184-042: Cohort A (n=51)</th>
<th>CA184-045&lt;sup&gt;a&lt;/sup&gt; (n=165)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS, median, months (95% CI)</td>
<td>7.0 (4.1, 10.8)</td>
<td>6.0 (3.9, 9.8)</td>
</tr>
<tr>
<td>OS rate at 1 year</td>
<td>31%</td>
<td>20%</td>
</tr>
<tr>
<td>OS rate at 2 years</td>
<td>26%</td>
<td>NA&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>In this study, all patients lost to follow-up were assumed dead
<sup>b</sup>Not available – insufficient data for accurate calculation
Durable Brain Responses in 2 Patients From CA184-042: Cohort A

A: Partial response (PR) in brain and PR in total tumor burden, duration 11+ months

Baseline

Week 16
### Ipilimumab: brain metastasis

<table>
<thead>
<tr>
<th></th>
<th>Arm A (n=51)</th>
<th>Arm B (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>median OS months</td>
<td>7.0 months</td>
<td>5.1 months</td>
</tr>
<tr>
<td>median PFS</td>
<td>2.6</td>
<td>1.3</td>
</tr>
<tr>
<td>median duration of PRs</td>
<td>15.3</td>
<td></td>
</tr>
<tr>
<td>duration of SDs</td>
<td>4.6</td>
<td></td>
</tr>
</tbody>
</table>

no specific CNS toxicity
Summary of Ipilimumab Data in Melanoma Brain Metastases

• Response rates are similar in and out of the brain
• Median survival is about 7 months in phase II trial
• Toxicity is similar in patients with and without brain metastases – no unique CNS toxicity identified
NIBIT trial ipilimumab + fotemustine

- Results
  - 40% overall disease control
  - 50% CNS disease control
- Toxicities 55% gr 3-4
  - Myelosuppression ~25%
  - Hepatotoxicity (transaminase elevations) ~24%
- Phase III of fotemustine + ipilimumab has started

Presented By Kim Allyson Margolin, MD at 2013 ASCO Annual Meeting
Systemic Therapy

- **Chemotherapy**
  - Temozolomide
  - Fotemustine

- **Immunotherapy**
  - Ipilimumab

- **B-raf Targeted therapy**
  - Vemurafenib/dabrafenib
Phase II two-cohort study in melanoma brain metastasis

Cohort A (n = 89) (No prior brain treatment)
Cohort B (n = 83) (Prior brain treatment)

Dabrafenib 150 mg BID

Screened (N = 325)
Enrolled (n = 172)

✓ Metastatic melanoma
✓ Centrally confirmed BRAF$^{V600E/K}$ mutation
✓ Asymptomatic brain metastases
✓ No prior treatment with MEK or BRAF inhibitors

• Primary endpoint: intracranial response (investigator assessed, OIRR) for BRAF$^{V600E}$ mutation-positive patients
• Secondary endpoints: OIRR for BRAF$^{V600K}$ mutation-positive patients; ORR, DoR (intracranial and overall), PFS and OS for BRAF$^{V600E/K}$ mutation-positive patients

DoR, duration of response; OIRR, overall intracranial response rate; ORR, overall response rate; PFS, progression-free survival

Long et al, Lancet Oncology 2012
No prior brain treatment: Cohort A
BRAFV600E mutation-positive patients maximal intracranial target lesion reduction

OIRR: 39%
ORR: 38%
Intracranial disease control rate: 81%
Overall disease control rate: 80%

Long et al, Lancet Oncology 2012
Prior brain treatment: Cohort B
BRAFV600E mutation-positive patients maximal intracranial target lesion reduction

OIRR: 31%
ORR: 31%
Intracranial disease control rate: 89%
Overall disease control rate: 83%

Long et al, Lancet Oncology 2012
BREAK-MB: OS in $BRAF^{V600E}$ Mutation–Positive Patients

No prior brain treatment
Median OS: 33.1 weeks (95% CI, 25.6 weeks-NR)

Prior brain treatment
Median OS: 31.4 weeks (95% CI, 25.7 weeks-NR)

Cohort A, V600E 74 73 71 69 62 43 29 17 10 2 1
Cohort B, V600E 65 65 65 60 51 39 29 20 7 1 0

## BREAK-MB: Summary of Efficacy Endpoints for BRAF<sup>V600E</sup> Mutation-positive Patients

<table>
<thead>
<tr>
<th></th>
<th>No prior brain treatment</th>
<th>Prior brain treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>OIRR, %</td>
<td>39</td>
<td>31</td>
</tr>
<tr>
<td>Intracranial disease control, %</td>
<td>81</td>
<td>89</td>
</tr>
<tr>
<td>ORR, %</td>
<td>38</td>
<td>31</td>
</tr>
<tr>
<td>Median PFS, weeks</td>
<td>16.1</td>
<td>16.6</td>
</tr>
<tr>
<td>Median OS, weeks</td>
<td>33.1</td>
<td>31.4</td>
</tr>
</tbody>
</table>
Pilot Study of Vemurafenib in Patients With mM With Brain Metastases

• Study aims: Safety and tolerability; Efficacy (BORR)*

Screened (n=35)

Enrolled (n=24)
ITT population

Safety Population (n=24)

Total Screening Failures (n=11, 31.4%)
• BRAF mutation test negative (n=4)
• Failed eligibility criteria (n=1)
• Other (n=6)

Deaths (n=19)
• Disease progression (n=18, 75.0%)
• Adverse event (n=1, 4.2%)

Treatment Discontinuations (n=24, 100%)
• Disease progression (n=22, 91.7%)
• Withdrawal of consent (n=1, 4.2%)
• Adverse event (n=1, 4.2%; Ileus, Grade 3)

*Based on RECIST V1.1
Vemurafenib in Patients With Brain Metastases: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of Patients (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>13 (54.2)</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>47 (24-70)</td>
</tr>
<tr>
<td>Median baseline number of brain mets, n (range)</td>
<td>4.0 (1-20)</td>
</tr>
<tr>
<td>Previous treatment for brain mets, n (%)</td>
<td></td>
</tr>
<tr>
<td>WBRT</td>
<td>14 (58.3)</td>
</tr>
<tr>
<td>Precision RT</td>
<td>6 (25.0)</td>
</tr>
<tr>
<td>Surgery</td>
<td>4 (16.7)</td>
</tr>
<tr>
<td>Systemic therapy</td>
<td>20 (83.3)</td>
</tr>
</tbody>
</table>

\(^a\)RECIST v1.1.

Vemurafenib in Patients With Brain Metastases: Maximum Tumor Shrinkage

Vemurafenib in brain and liver mets
(from Reinhard Dummer, Zurich)
Melanoma Brain Metastases: Summary

- Local control and therapy is still the backbone of management
  - RPA helps treatment decisions
  - SRS and surgery with or without WBRT
- New systemic therapeutic options are changing the treatment paradigm
  - High response rates, DCR and OS with targeted therapies
  - Promising survival, safe with ipilimumab
Change in Treatment Paradigm

Patient Selection: Check mutational status

Treatment Selection
- Ipilimumab
- B-raf/MEK-/c-kit-inhibitors
- Chemotherapy
- Clinical trials
and/or conventional surgery, radiotherapy