PD-L1 and PD-1 Expression in Melanoma Brain Metastasis with Survival Stratification across Treatments

Poster: 42630

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**Background**

- Metastatic melanoma is a devastating disease that disproportionately affects young adults. Despite treatment, patients with metastatic melanoma often develop brain metastasis, which usually leads to death within months to a year.

- Immune checkpoint inhibitors are an emerging class of therapeutics which targets the interaction between programmed death receptor one on T-cells (PD-1) and programmed death ligand one (PD-L1) on tumor cells.

- A significant proportion of primary and metastatic melanomas express the PD-L1 ligand and many melanoma patients have had impressive responses to this therapy. Currently these therapies are in clinical trials to assess their effectiveness in melanoma patients with brain metastasis.

- Another ligand-receptor combination that is expressed in many melanomas that modulates the immune response is VEGF-A and its receptor VEGFR1, which is more consistently expressed in melanomas.

- The PD-L1 ligand and VEGFR1 receptor have been demonstrated in some brain metastases; it is unclear if this is consistent across all brain metastases or if expression patterns change after treatments such as chemotherapy, radiation, immunotherapy, and surgery.

**Aims of project:**

- To verify PD-L1, PD-1, and VEGFR1 expression along with T-cell infiltrates in brain metastasis samples from metastatic melanoma patients.

- To evaluate expression of PD-L1, PD-1, and VEGFR1 with survival across treatment strategies.
• Retrospective data review of all patients with metastatic melanoma and brain metastasis using neuropathology database
  - Project approved by IUSM IRB
  - Ten years of consecutive data from IU Neuropathology (2007-2017) revealed 68 specimens of metastatic melanoma to the brain from 59 patients who had metastatic melanoma who had at least one symptomatic brain metastasis that was resected
  - Of these patients, only four had their primary melanoma resected at an IU affiliated hospital and had primary tissue available for examination

• Data collected
  - Demographic information
    - Age at presentation of primary melanoma
    - Time to development of symptomatic brain metastasis after primary diagnosis
    - Survival from primary diagnosis
    - Survival after brain metastasis resection
  - Clinical characteristics
    - Brain metastasis location(s)
    - Number of resections for metastatic brain melanoma
  - Treatment information
    - Immunotherapy use
    - Chemotherapy use
    - Radiotherapy (WBXRT and SRS)
  - Immunohistochemistry and immunofluorescence
    - IF for CD4, CD8, FoxP3, PD-1, VEGFR1
    - IHC for PD-L1, VEGFR1
<table>
<thead>
<tr>
<th>Demographics &amp; Clinical Information</th>
<th>Patient</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at melanoma diagnosis (years)</td>
<td>53</td>
<td>35</td>
<td>51</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Time after primary diagnosis to development of symptomatic brain metastasis (years/months)</td>
<td>6y 11m</td>
<td>8y 10m</td>
<td>2y 6m</td>
<td>2m</td>
<td></td>
</tr>
<tr>
<td>Survival after melanoma diagnosis (months)</td>
<td>90</td>
<td>126</td>
<td>102 (still alive)</td>
<td>56 (still alive)</td>
<td></td>
</tr>
<tr>
<td>Survival after brain metastasis resection (months)</td>
<td>7</td>
<td>20</td>
<td>72</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Survival after initiation of immunotherapy (months)</td>
<td>--</td>
<td>24</td>
<td>60</td>
<td>14</td>
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</tr>
<tr>
<td>Brain metastasis location(s)</td>
<td>R frontal (multiple), L frontal, R caudate, R temporal, L cerebellum (multiple)</td>
<td>R occipital, L frontal</td>
<td>R parietal, L lateral ventricle</td>
<td>L temporal</td>
<td></td>
</tr>
<tr>
<td>Number of resections for brain metastasis</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Information</th>
<th>Immunotherapy use</th>
<th>Immunotherapy timing</th>
<th>Chemotherapy use</th>
<th>Radiotherapy use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>--</td>
<td>temozolomide</td>
<td>WBXRT (post-resection)</td>
</tr>
<tr>
<td></td>
<td>Yes (IL-2, 2 courses)</td>
<td>Between resections</td>
<td>Vemurafinib (BRAF V600E inhibitor) MEK inhibitor (trial)</td>
<td>WBXRT (after first resection) SRS (pre-op to L frontal lesion)</td>
</tr>
<tr>
<td></td>
<td>Yes (ipilimumab)</td>
<td>After resection</td>
<td>temozolomide</td>
<td>Hypofractionated XRT to cavity (post-op) SRS x2 (post-op)</td>
</tr>
<tr>
<td></td>
<td>Yes (pembrolizumab)</td>
<td>After resection</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>
### Results (cont)

**IHC and IF**

<table>
<thead>
<tr>
<th>Expression</th>
<th>PD-L1</th>
<th>VEGFR1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary &amp; Brain Metastasis Matched</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Primary &gt; Brain Metastasis</td>
<td>C</td>
<td>C</td>
</tr>
<tr>
<td>Brain Metastasis &gt; Primary</td>
<td>A, B, D</td>
<td>A, B, D</td>
</tr>
</tbody>
</table>
Results (cont)

PD-L1

Primary

Metastasis
VEGFR1

Primary

Metastasis

Results (cont)
Of the four patients with primary and brain metastasis tissue available

- All lived > 6 months from their metastasis diagnosis
- Those receiving immunotherapy (CTLA-4 and PD-1 inhibitors) did live longer
- Both PD-L1 and VEGFR1 expression was downregulated in metastatic tissue in one patient (C – the only one with high staining in primary lesion) whereas in the other three expression was slightly increased in metastatic tissue
- Different brain metastases (excised at different times and from different brain locations) demonstrated differing expression of PD-L1 and VEGFR1 by comparison to their original primary

Tissue staining for PD-L1 and VEGFR1 in metastatic melanoma to the brain may provide more targeted therapeutic options for patients as expression of these molecules in primary tissue does not necessarily predict expression/treatment response in brain metastasis.