The Potential Role of Immune Checkpoint Inhibitors in Glioblastoma

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I have no conflicts of interest related to this presentation.

Please note that some of the studies reported in this presentation were published as an abstract and/or presented at a conference. These data and conclusions should be considered to be preliminary until published in a peer-reviewed journal.
Overview

1) Background and preclinical data
   • Rationale for immune checkpoint inhibition in GBM

2) Clinical data

3) Challenges and future directions
FDA approvals for immune checkpoint inhibitors

**Pembrolizumab (PD-1)**
- Metastatic/unresectable melanoma
- ≥50% PD-L1 + metastatic NSCLC (1st-line), ≥1% PD-L1+ metastatic NSCLC (2nd-line)
- Recurrent/metastatic HNSCC after progression with platinum (accelerated approval)
- Refractory Classical Hodgkin Lymphoma (accelerated approval)
- Locally advanced/metastatic urothelial carcinoma (2nd line)
- Locally advanced/metastatic urothelial carcinoma (1st line, cisplatin ineligible) (accelerated approval)
- Solid tumors that are MSI-H/dMMR and have progressed on prior treatment (accelerated approval)

**Nivolumab (PD-1)**
- Metastatic/unresectable melanoma
- Metastatic NSCLC (2nd-line)
- Advanced RCC (2nd-line)
- Refractory Classical Hodgkin Lymphoma (accelerated approval)
- Recurrent/metastatic HNSCC after progression with platinum
- Locally advanced/metastatic urothelial carcinoma (2nd-line) (accelerated approval)

**Durvalumab (PD-L1)**
- Locally advanced/metastatic urothelial carcinoma (2nd –line) (accelerated approval)

**Atezolizumab (PD-L1)**
- Locally advanced/metastatic urothelial carcinoma (2nd-line) (accelerated approval)
- Metastatic NSCLC (2nd-line)

**Avelumab (PD-L1)**
- Metastatic Merkel Cell Carcinoma (accelerated approval)
- Locally advanced/metastatic urothelial carcinoma (2nd-line) (accelerated approval)

**Ipilimumab (CTLA-4)**
- Unresectable/metastatic melanoma
- Adjuvant treatment for melanoma
Intracranial activity of immune checkpoint inhibitors

- Phase II trial of patients with untreated brain metastases from lung cancer and melanoma:
  - Treated with single agent pembrolizumab (anti-PD-1)
  - Brain metastasis response was achieved in:
    - 4 (22%) of 18 patients with melanoma
    - 6 (33%) of 18 patients with NSCLC

Goldberg SB et al, Lancet Oncol 2016
Glioblastoma (GBM): a “lukewarm” tumor

• Many studies have demonstrated baseline CD8+ (killer) T cell infiltration in GBM, though the infiltrate is generally weaker than tumors such as melanoma and lung cancer.

CD8+ T cells: GBM
CD8+ T cells: Melanoma

“Lukewarm”
“Hot”

1. Lohr et al, Clin Cancer Res 2011
2. Rutledge WC et al, Clin Cancer Res 2013
5. Kim et al, Clin Cancer Res 2017
PD-L1 expression in GBM: common, but weak

• 60% of GBMs are tumor cell PD-L1+
• However, median % of PD-L1+ tumor cells in GBM by cell surface staining is only 2.8%
  • ~40% have ≥ 5% expression
  • ~20% have ≥ 25% expression
  • ~5% have ≥ 50% expression

Nduom et al, Neuro Oncol 2016
Orthotopic, immunocompetent murine glioblastoma model

**Preclinical glioma models like GL261 may possess higher mutational burden than a typical primary human GBM tissue**
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Phase I data, Recurrent GBM:
Immune checkpoint inhibitors in first recurrence after radiation/temozolomide (bevacizumab-naïve)

<table>
<thead>
<tr>
<th>Pembrolizumab (PD-1)</th>
<th>Nivolumab (PD-1)</th>
<th>Durvalumab (PD-L1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=26</td>
<td>n=10</td>
<td>n=30</td>
</tr>
<tr>
<td>4% ORR (1 patient)</td>
<td>10% ORR (1 patient)</td>
<td>13% ORR (4 patients)</td>
</tr>
<tr>
<td>OS-12 mo = 74%</td>
<td>OS-9 mo = 60%</td>
<td>OS-12 mo = 44%</td>
</tr>
<tr>
<td>15% grade 3/4 AEs</td>
<td>No grade 3/4 AEs</td>
<td>10% grade 3/4 AEs</td>
</tr>
</tbody>
</table>

*All studies had small tails to the Kaplan-Meier curves present:
  - Durvalumab: 5 patients remained free of progression at 1 year
  - Pembrolizumab: 1 patient had ongoing stable disease at 86 weeks

* No grade 4/5 cerebral edema reported in any of the studies

**Bottom line:** Safe and well-tolerated, with encouraging signs of efficacy in highly selected populations

Reardon DA et al, Society for Neuro-Oncology Annual Meeting 2016
Lim M et al, ASCO Annual Meeting 2016
Randomized Phase 3 Study: Nivolumab vs Bevacizumab in Patients With Recurrent Glioblastoma (CheckMate 143)

- \( N=369 \) patients with no prior VEGF therapy
- Randomized 1:1: nivolumab 3 mg/kg every 2 weeks or bevacizumab 10 mg/kg every 2 weeks
  - At baseline in both arms, \( \sim 80\% \) of patients had measurable disease and \( \sim 40\% \) of patients required corticosteroids
- Grade 3–4 treatment-related adverse events:
  - 18% (nivolumab)
  - 15% (bevacizumab)
- Primary endpoint was overall survival (OS) – no difference in median OS or OS rate at 12 months
  - Also no difference in multiple subgroup analyses (e.g. PD-L1 expression at cut-off of 1%)
Among patients who received nivolumab:

- Response rate 8%
- Median duration of response 11.1 months
- 2 complete responses
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Mutational load and benefit from immune checkpoint inhibition

**Melanoma**

![Graphs showing mutational load and benefit from immune checkpoint inhibition in Melanoma.](image)

*Johnson et al, Cancer Immunol Res 2016*

**NSCLC**

![Graphs showing mutational load and benefit from immune checkpoint inhibition in NSCLC.](image)

*Rizvi et al, Science 2015*
Mutational load is generally low in GBM

Use of radiotherapy to enhance tumor neoantigen presentation

World Federation of Neuro-Oncology Societies 2017

Synergistic effect of reirradiation and PD-1 inhibitors in recurrent high-grade gliomas

- 20 patients with recurrent high grade glioma were treated with the combination of reirradiation and PD-1 inhibitors.
  - 55% had received prior bevacizumab
  - Median reirradiation dose was 35 Gy
  - 7 partial responses (35% ORR)
  - Median duration of response was 5 months (2.2 to 10+ months).
  - No cases of cerebral edema related to treatment

Zeng et al, IRJOBP 2013

Kim et al, Clin Can Res 2017
Other strategies for enhancing the anti-tumor immune response in GBM

• Immune checkpoint inhibitors in combination with:
  
  • Dendritic cell therapies
  
  • Vaccines
  
  • CAR T cell therapies
    • EGFRvIII?
  
• Other monoclonal antibodies
  
  • Immune checkpoint inhibitors, immune co-stimulatory receptor agonists
    • ABTC-1501 currently open at Penn: Anti-LAG-3 or Urelumab (Anti-CD137) Alone and in Combination with Nivolumab in Treating Patients with Recurrent Glioblastoma
Immune checkpoint inhibitors in glioblastoma: Conclusions

The Challenges:
- Nivolumab does not improve survival over bevacizumab in recurrent GBM
  - Low mutational burden = no immune recognition
- Unclear which patients with GBM stand to benefit from checkpoint inhibitors
  - Limit to patients with minimal residual disease?
  - Should patients be off steroids?
  - Do patients need to have a high degree of PD-L1 expression? Other molecular markers?
- How to integrate with other therapies?
  - Role of radiation?
  - Combine with targeted therapies?
  - Chemotherapy? Other immunotherapies?

The Promise:
- Tumor-infiltrating CD8+ T cells and PD-1/PD-L1 expression are present in GBM
- Checkpoint inhibitors have demonstrated intracranial activity in other tumor types
- PD-1 inhibitors are safe and well-tolerated in GBM
- Single agent checkpoint inhibitor therapy has led to durable responses in GBM, including complete responses, in a small minority of patients
Thank you

Questions?

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