Immunotherapy for Malignant Brain Cancer: Overcoming Immune Suppression to Improve the Clinical Experience

Derek Wainwright, PhD
Assistant Professor
Departments of Neurological Surgery, Microbiology-Immunology & Medicine-Division of Hematology/Oncology
Overall survival in advanced melanoma patients treated with PD-1 and/or CTLA-4 antibodies

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nivolumab plus Ipilimumab (N=314)</th>
<th>Nivolumab (N=316)</th>
<th>Ipilimumab (N=315)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best overall response — no. (%)†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>61 (19)</td>
<td>52 (16)</td>
<td>16 (5)</td>
</tr>
<tr>
<td>Partial response</td>
<td>122 (39)</td>
<td>88 (28)</td>
<td>43 (14)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>38 (12)</td>
<td>31 (10)</td>
<td>69 (22)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>74 (24)</td>
<td>121 (38)</td>
<td>159 (50)</td>
</tr>
<tr>
<td>Unable to determine</td>
<td>19 (6)</td>
<td>24 (8)</td>
<td>28 (9)</td>
</tr>
<tr>
<td>Objective response‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients with response</td>
<td>183</td>
<td>140</td>
<td>59</td>
</tr>
<tr>
<td>% of patients (95% CI)</td>
<td>58 (53–64)</td>
<td>44 (39–50)</td>
<td>19 (15–24)</td>
</tr>
<tr>
<td>Estimated odds ratio (95% CI)‡</td>
<td>6.46 (4.45–9.38)</td>
<td>3.57 (2.48–5.15)</td>
<td>—</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>—</td>
</tr>
<tr>
<td>Median duration of response (95% CI) — mo</td>
<td>NR</td>
<td>NR (36.3–NR)</td>
<td>19.3 (8.3–NR)</td>
</tr>
</tbody>
</table>

Wolchok et al., 2017; New England Journal of Medicine
Overall survival in recurrent glioblastoma patients treated with PD-1 or VEGF-A antibodies

Reardon et al., 2017; Neuro-Oncology
Is there an immunological difference between glioblastoma and melanoma?
Melanoma and glioblastoma patients have different associations between survival and T cell infiltration.

**Glioblastoma Pts.**
- Low T cell infiltration (n=97)
- High T cell infiltration (n=26)

**Melanoma Pts.**
- Low T cell infiltration (n=219)
- High T cell infiltration (n=149)

Zhai...Wainwright, 2018; Cell and Molecular Immunology
# Tumor-Induced Immune Exclusion vs. Immunosuppression

<table>
<thead>
<tr>
<th>Immune exclusion</th>
<th>Immunosuppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Predominantly absent for T cells (<strong>cold</strong></td>
<td>- Infiltrated by T cells (<strong>hot</strong>)</td>
</tr>
<tr>
<td>- Vascular barrier</td>
<td>- Increased levels of:</td>
</tr>
<tr>
<td>- Absence of DC</td>
<td>- TGFβ</td>
</tr>
<tr>
<td>- Absence of T cell-recruiting chemokines</td>
<td>- PD-L1</td>
</tr>
<tr>
<td>- High degree of methylation (<strong>ie. mIDH</strong>)</td>
<td>- IDO1</td>
</tr>
<tr>
<td></td>
<td>- IL-10</td>
</tr>
<tr>
<td></td>
<td>- pSTAT3</td>
</tr>
<tr>
<td></td>
<td>- Treg</td>
</tr>
<tr>
<td></td>
<td>- MDSC</td>
</tr>
<tr>
<td></td>
<td>- Loss of antigen</td>
</tr>
<tr>
<td></td>
<td>- Loss of MHC</td>
</tr>
<tr>
<td></td>
<td>- Tolerogenic DC</td>
</tr>
</tbody>
</table>
Immunosuppression

- Infiltrated by T cells
- Increased levels of:
  - TGFβ
  - PD-L1
  - IL-10
  - IFNα/β/γ
  - Treg
  - MDSC
  - Loss of antigen
  - Tolerogenic DC

Leads to:

Leads to:

Immune exclusion
- Predominantly absent for T cells
- Vascular barrier
- Absence of DC
- Absence of Th1 chemokines
- High degree of methylation (i.e. mIDH)

Ladomersky et al., 2015; Oncommunology
Immune exclusion
- Predominantly absent for T cells
- Vascular barrier
- Absence of DC
- Absence of Th1 chemokines
- High degree of methylation (i.e., mIDH)

Immunosuppression
- Infiltrated by T cells
- Increased levels of:
  - TGFβ
  - PD-L1
  - IL-10
  - IFNα/β/γ
  - Treg
  - MDSC
  - Loss of antigen
  - Tolerogenic DC

Leads to:

Ladomersky et al., 2015; Oncommunology
Rindopepimut with temozolomide for patients with newly diagnosed, EGFRvIII-expressing glioblastoma (ACT IV): a randomised, double-blind, international phase 3 trial

Michael Weller, Nicholas Butowski, David D Tran, Lawrence D Recht, Michael Lim, Hal Hirte, Lynn Ashby, Laszlo Mechtler, Samuel A Goldlust, Fabio Iwamoto, Jan Drappatz, Donald M O’Rourke, Mark Wong, Mark G Hamilton, Gaetano Finocchiaro, James Perry, Wolfgang Wick, Jennifer Green, Yi He, Christopher D Turner, Michael J Yellin, Tibor Keler, Thomas A Davis, Roger Stupp, and John H Sampson, for the ACT IV trial investigators

Findings Between April 12, 2012, and Dec 15, 2014, 745 patients were enrolled (405 with MRD, 338 with significant residual disease [SRD], and two unevaluable) and randomly assigned to rindopepimut and temozolomide (n=371) or control and temozolomide (n=374). The study was terminated for futility after a preplanned interim analysis. At final analysis, there was no significant difference in overall survival for patients with MRD: median overall survival was 20.1 months (95% CI 18.5–22.1) in the rindopepimut group versus 20.0 months (18.1–21.9) in the control group (HR 1.01, 95% CI 0.79–1.30; p=0.93). The most common grade 3–4 adverse events for all 369 treated patients in the rindopepimut group versus 372 treated patients in the control group were: thrombocytopenia (32 [9%] vs 23 [6%]), fatigue (six [2%] vs 19 [5%]), brain oedema (eight [2%] vs 11 [3%]), seizure (nine [2%] vs eight [2%]), and headache (six [2%] vs ten [3%]). Serious adverse events included seizure (18 [5%] vs 22 [6%]) and brain oedema (seven [2%] vs 12 [3%]). 16 deaths in the study were caused by adverse events (nine [4%] in the rindopepimut group and seven [3%] in the control group), of which one—a pulmonary embolism in a 64-year-old male patient after 11 months of treatment—was assessed as potentially related to rindopepimut.

Weller et al., 2017; Lancet Oncology
Antigen escape is one immunosuppressive mechanism that may have contributed to Rintega failure.

Sampson et al., 2010; Journal of Clinical Oncology
Treg accumulation is another immunosuppressive mechanism why Rindopepimut therapy may have failed

Sampson et al., 2012; PLoS One     Mitchell et al., 2012; Blood
CAR T cells targeting EGFRvIII enhance immunosuppression in patient glioblastoma post-infusion

O’Rourke et al., 2017; Science Translational Medicine
CAR T cells targeting EGFRvIII enhance immunosuppression in patient glioblastoma post-infusion

O’Rourke et al., 2017; Science Translational Medicine
Tumor cell IDO1 decreases overall survival in an immunocompetent GBM model

Wainwright et al., 2012; Clinical Cancer Research
High IDO1 expression is associated with decreased glioblastoma patient survival

Zhai...Wainwright et al., 2017; Clinical Cancer Research
Infiltrating T cells specifically increase IDO1 expression in human glioblastoma
Infiltrating T cells specifically increase IDO1 expression in human glioblastoma. Can we inhibit IDO1 and achieve a survival benefit?
Monotherapy with an IDO1 enzyme inhibitor does not increase survival against mouse glioblastoma

Wild-type mice ic. unmodified GL261

Control (n=7)  IDO1 inhibitor (BGB-5777; n=8)

Percent Survival

Days Post-Intracranial Injection

Ladomersky…Wainwright, 2017; Clinical Cancer Research
Can we combine IDO1 inhibition with a standard of care treatment to achieve a survival benefit?
Dual radiotherapy (RT) with IDO1 enzyme inhibitor fails to increase long-term survival in a glioma model.
Reading to my daughter got me thinking
Reading to my daughter got me thinking
Reading to my daughter got me thinking

Zoey Wainwright
Reading to my daughter got me thinking
PD-1 blockade fails to increase recurrent glioblastoma patient survival as a monotherapy

Reardon et al., 2017; Neuro-Oncology
PD-1 blockade fails to increase recurrent glioblastoma patient survival as a monotherapy.

Will the triple combination of IDO1 inhibitor, radiation and PD-1 antibody synergize to achieve a long-term survival benefit?

Reardon et al., 2017; Neuro-Oncology
Simultaneous treatment with IDO1 inhibitor, radiotherapy and PD-1 blockade, durably increases survival against glioma

Wild-type mice ic. mouse GBM cells

- IgG Control (n=7)
- RT (n=8)
- PD1 mAb (n=8)
- IDO1 inhibitor (n=8)
- IDO1 inhibitor + PD1 mAb (n=9)
- IDO1 inhibitor + RT + PD1 mAb (n=9)

**Percent Survival**

**Days Post-Intracranial Injection**

Ladomersky….Wainwright, 2018; Clinical Cancer Research
Simultaneous treatment with IDO1 inhibitor, radiotherapy and PD-1 blockade, durably increases survival against glioma.

**Cancer Therapy: Preclinical**

**Clinical Cancer Research**

**IDO1 Inhibition Synergizes with Radiation and PD-1 Blockade to Durably Increase Survival Against Advanced Glioblastoma**

Erik Ladomersky, Lijie Zhai, Alicia Lenzen, Kristen L. Lauing, Jun Qian, Denise M. Scholtens, Galina Gritsina, Xuebing Sun, Ye Liu, Fenglong Yu, Wenfeng Gong, Yong Liu, Beibei Jiang, Tristin Tang, Ricky Patel, Leonidas C. Platanias, C. David James, Roger Stupp, Rimas V. Lukas, David C. Binder, and Derek A. Wainwright.
Combination of checkpoint inhibition and IDO1 inhibition together with standard radiotherapy or chemoradiotherapy in newly diagnosed glioblastoma. A phase 1/2a clinical and translational trial.

Principal Investigator: Rimas Lukas, MD (Northwestern U.)

1° Objective: Explore the feasibility and toxicity of simultaneous standard radiotherapy, PD-1 mAb and IDO1 inhibitor treatment in newly-diagnosed adult patients with glioblastoma.
Already, we are asking questions to improve future clinical efficacy in newly-diagnosed adult patients with glioblastoma.
TMZ does not improve the OS benefit of trimodal immunotherapy in a GBM model

Wild-type mice ic. mouse GBM cells

A

GL261

TMZ

PD-1 mAb

2Gy Rad.

IDO1 inhibitor

B

14dp-ic.

C

IDO1 i + RT + PD1 mAb (n=10)

IDO1 i + RT + PD1 mAb + TMZ (n=10)

Percent Survival

Days Post-Intracranial Injection

P=0.06

Ladomersky….Wainwright, 2018; Clinical Cancer Research
Trimodal immunotherapy is less effective for treating glioma in old age

Ladomersky….Wainwright, 2018; Clinical Cancer Research
Summary/Future Considerations

- Exhaustively search for weaknesses in the trimodal immunotherapeutic approach, to improve the efficacy of future derivative clinical trials for GBM patients.
ACKNOWLEDGEMENTS

Rimas Lukas, MD
Erik Ladomersky, PhD
Kristen Lauing, PhD
Lijie Zhai, PhD
Alecia Lenzen, MD
Roger Stupp, MD
C. David James, PhD
James Chandler, MD
Matt Lesniak, MD
Craig Horbinski, MD/PhD