Glioblastoma and CNS tumors

PRECEPTORSHIP PROGRAMME
IMMUNO-ONCOLOGY

Amsterdam, 27 May 2017

Patrick Roth
Department of Neurology and Brain Tumor Center
University Hospital Zurich
Challenges in immunooncology

Melanoma

Successful implementation of immunotherapy

Glioblastoma

?
Blood-brain barrier

Tumor-mediated mechanisms:
- VEGF
- Nitric oxide (NO)
- Leukotriens
- Prostaglandins

LETTER

Structural and functional features of central nervous system lymphatic vessels

Antoine Louveau¹,², Igor Smirnov¹,², Timothy J. Keyes¹,², Jacob D. Eccles¹,⁴,⁵, Sherin J. Rouhani³,⁴,⁶, J. David Peske³,⁴,⁶, Noel C. Derecki¹,², David Castle⁷, James W. Mandell⁸, Kevin S. Lee¹,²,⁹, Tajie H. Harris¹,² & Jonathan Kipnis¹,²,³

Received 30 October 2014 | Accepted 20 March 2015 | Published online 01 June 2015

LETTER

Effector T-cell trafficking between the leptomeninges and the cerebrospinal fluid

Christian Schläger¹*, Henrike Körner¹*, Martin Krueger³, Stefano Vidoli⁴, Michael Haber¹, Dorothee Mielke⁵, Elke Brylla³, Thomas Issekutz⁶, Carlos Cabañas⁷, Peter J. Nelson⁸, Tjalf Ziemssen⁹, Veit Rohde⁵, Ingo Bechmann³, Dmitri Lodygin¹, Francesca Odoardi¹* & Alexander Flügel¹,²*

The CNS “macro“environment

- The CNS is not immunologically quiescent, activated lymphocytes can cross the BBB
- Parts of the brain lack a BBB
- The BBB gets partially disrupted in gliomas
- A true lymphatic drainage system exists in the meninges of the dural venous sinuses

→ Potent immune cell infiltration and activity is possible
Increased Immune Gene Expression and Immune Cell Infiltration in High-Grade Astrocytoma Distinguish Long-Term from Short-Term Survivors

Andrew M. Donson, Diane K. Birks, Stephanie A. Schittone, Bette K. Kleinschmidt-DeMasters, Derrick Y. Sun, Molly F. Hemenway, Michael H. Handler, Allen E. Waziri, Michael Wang, and Nicholas K. Foreman

How can we activate the immune system?

J Immunol 2012; 189:1920-1927
Vaccination

• Various approaches: tumor cell lysate, RNA, peptides…

• Best adjuvant remains to be defined

• Focus on peptide vaccines which may activate the immune system very specifically

• Promising data from preclinical models
Review

The EGFRvIII variant in glioblastoma multiforme

Hui K. Gan\textsuperscript{a}, Andrew H. Kaye\textsuperscript{b,c}, Rodney B. Luwor\textsuperscript{b,∗}

\textsuperscript{a} Department of Medical Oncology and Hematology, Princess Margaret Hospital, Toronto, Canada
\textsuperscript{b} Department of Surgery, Level 6, Clinical Sciences Building, University of Melbourne, Royal Melbourne Hospital, Parkville, Victoria 3050, Australia
\textsuperscript{c} Department of Neurosurgery, University of Melbourne, Royal Melbourne Hospital, Parkville, Victoria, Australia

Deletion of AAs 6-273 yields the EGFRvIII.

Extracellular Domain (AAs 1-621)

Insertion of a novel Glycine residue

Trans-membrane Domain (AAs 622-644)

Intracellular Domain (AAs 645-1186)

Wt EGFR  EGFRvIII
Survival Probability

Median (months)

OS at 24 Months

OS at 36 Months

Comparison to Historical Control

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median (months)</th>
<th>OS at 24 Months</th>
<th>OS at 36 Months</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACT III (n=65)</td>
<td>24.6</td>
<td>52%</td>
<td>31%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ACT II (n=22)</td>
<td>24.4</td>
<td>50%</td>
<td>23%</td>
<td>0.0034</td>
</tr>
<tr>
<td>ACTIVATE (n=18)</td>
<td>24.6</td>
<td>50%</td>
<td>33%</td>
<td>0.0003</td>
</tr>
<tr>
<td>Matched historical control (n=17)</td>
<td>15.2</td>
<td>6%</td>
<td>6%</td>
<td></td>
</tr>
</tbody>
</table>

Vaccinations begin approximately 3 months after diagnosis

Median duration of follow-up:
ACT III: 48.7 months
ACT II: 71.8 months
ACTIVATE: 99.3 months
ACT-IV: trial design
Newly diagnosed glioblastoma

Adjuvant TMZ/Placebo ➤ P maintenance

- RT/TMZ completed
- EGFRvIII mutation

Adjuvant TMZ/Rindopepimut ➤ R maintenance

- Blinded study vaccine (rindopepimut/GM-CSF or KLH as control)
- **Priming**: 2 injections, 2 weeks after RT/TMZ
- During adjuvant TMZ: 1 injection on day 22 of every cycle
- Maintenance: 1 injection per month
ACT-IV outcome

Overall survival

- **Rindopepimut**
  - Median (Mo) (95% CI): 17.4 (16.1, 19.4)
  - HR (95% CI): 0.89 (0.75, 1.07)
  - Logrank p: 0.22

- **Control**
  - Median (Mo) (95% CI): 17.4 (16.2, 18.8)

Number at Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
<th>42</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rindopepimut</td>
<td>371</td>
<td>345</td>
<td>261</td>
<td>159</td>
<td>72</td>
<td>32</td>
<td>12</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Control</td>
<td>374</td>
<td>347</td>
<td>268</td>
<td>149</td>
<td>73</td>
<td>25</td>
<td>8</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

Weller et al., SNO meeting 2016
ACT-IV outcome

Humoral immune response

Anti-EGFRvIII Humoral Response

ACT IV: MRD Population
- Rindopepimut
- Control

ACT IV: “Bulky Disease”
- Rindopepimut
- Control

ACT III Study*
- Rindopepimut

ReACT Study**
- Rindopepimut
- Control

Weller et al., SNO meeting 2016
**ICT-107:**
autologous six-antigen DC vaccine

Matured, activated, peptide-loaded DC

Six 9-10 amino acid antigen epitopes
- MAGE-1 (HLA - A1)
- AIM-2 (A1)
- gp100 (HLA - A2)
- IL-13Rα2 (A2)
- HER2/neu (A2)
- TRP-2 (A2)

- Targeting multiple antigens may minimize tumor immune escape
- Promising data in a randomized phase II trial
- Phase III trial ongoing: ICT-107 or placebo in addition to temozolomide-based radiochemotherapy in patients with newly diagnosed glioblastoma
Targeting the microenvironment
Multiple immunosuppressive mechanisms

- Glioma cells
- Microglial cells
- T cells
- NK cells

TGF-β

- Proliferation ↓
- Cytotoxicity ↓

Antigen presentation ↓
GLIOBLASTOMA CELLS RELEASE INTERLEUKIN 1 AND FACTORS INHIBITING INTERLEUKIN 2-MEDIATED EFFECTS

ADRIANO FONTANA, HANS HENGARTNER, NICOLAS de TRIBOLET, and ELISABETH WEBER

From the *Section of Clinical Immunology, the Neurosurgical Department, and the Institute for Pathology, University Hospital, Zürich; and from the Neurosurgical Department, University Hospital, CHUV, Lausanne, Switzerland
**TGF-β**

Master immunosuppressive cytokine

![Graph showing the survival rates of different treatments](image)

- **Survivors [%]**
  - 0
  - 20
  - 40
  - 60
  - 80
  - 100

- **Time [days]**
  - 0
  - 10
  - 20
  - 30
  - 40

- **Vehicle SD-208**

- **HE**
- **CD8**
- **CD11b**

**Uhl et al., Cancer Res 2004**
Conclusions:
Galunisertib alone or galunisertib + lomustine failed to demonstrate improved OS relative to lomustine alone. → Efficacy outcomes were similar in all 3 arms.
Glioma immunobiology
Multiple immunosuppressive mechanisms

Glioma cells
- HLA-E/G
- FasL
- IDO/TDO
- STAT3
- GDF-15
- IL-10
- Prg-E
- Galectin-1
- PD-L1
- PD-1
- CTLA-4

Microglial cells

NK cells

T cells
- proliferation
- cytotoxicity

Antigen presentation

T cells
- TGF-β
- LLT-1
- PD-L1

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Immune checkpoint inhibitors

• Immune checkpoint inhibitors may exert strong anti-tumor activity:

  => Melanoma: anti-CTLA-4 alone vs. anti-PD-1 alone vs. combined treatment

  => Pembrolizumab and nivolumab have been approved for advanced melanoma and other tumor entities

• May these drugs also mount anti-tumor immune responses against neoplasms in the CNS?
Checkpoint inhibitors are active against brain metastases

Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial


Lancet Oncol 2016; 17: 976–83

Efficacy of anti-PD-1 therapy in patients with melanoma brain metastases

Sagun Parakh1,2,3,11, John J Park4,5,11, Shehara Mendis6, Rajat Rai5,7, Wen Xu8, Serigne Lo5,7, Martin Drummond5,7, Catherine Rowe8, Annie Wong8, Grant McArthur8, Andrew Haydon6, Miles C Andrews1,2, Jonathan Cebon1,2, Alex Guminski5,7,9, Richard F Kefford4,7,10, Georgina V Long5,7,9, Alexander M Menzies5,7,9, Oliver Klein1,2,12, and Matteo S Carli1,4,5,7,12
Expression of PD-1 and PD-L1 in glioblastoma tissue

• **PD-1 expression on tumor-infiltrating lymphocytes (TIL)**
  – 34/117 (29.1%) specimens with scattered PD1+ TIL infiltration

• **Different PD-L1 staining patterns**
  – Diffuse/fibrillary PD-L1 expression throughout the tumor tissue
  – Distinct membranous PD-L1 expression in tumor cell aggregates
CheckMate 143
Randomized phase III trial

Screening/Randomization Phase
- Patients (N = 369)
  - First recurrence of GBM
  - Prior 1L treatment with at least RT and TMZ
- Randomized 1:1
  - Stratified by measurable disease at baseline (yes/no)

Treatment Phase
- Nivolumab 3 mg/kg Q2W
  - n = 184
- Bevacizumab 10 mg/kg Q2W
  - n = 185

Follow-up Phase
- Treatment until:
  - Confirmed progression
  - Unacceptable toxicity
  - Discontinuation due to other reason
- Follow-up:
  - Safety for ≥ 100 days
  - Progression
  - Survival every 3 months
• The most common AEs leading to discontinuation (> 2 patients in either arm [nivolumab; bevacizumab]) were cerebrovascular accident (0%; 2%) and pulmonary embolism (< 1%; 2%)

• No patient in either arm died due to study drug toxicity

Reardon et al., WFNOS meeting 2017

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab n = 182&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Bevacizumab n = 165&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td>18 (9.9)</td>
<td>15 (8.2)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>84 (46.2)</td>
<td>52 (28.6)</td>
</tr>
<tr>
<td>Neurological AEs</td>
<td>135 (74.2)</td>
<td>41 (22.5)</td>
</tr>
<tr>
<td>Deaths, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease</td>
<td>152 (83.5)</td>
<td>146 (80.2)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (2.2)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (1.1)</td>
<td></td>
</tr>
</tbody>
</table>
CheckMate 143
Progression-free and overall survival

### Progression-Free Survival

**HR = 1.97 [95%CI: 1.57, 2.48]**

*P < 0.0001*

<table>
<thead>
<tr>
<th>Events, n</th>
<th>Median PFS [95% CI], months</th>
<th>12-Month PFS Rate [95% CI], months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>171</td>
<td>1.5 [1.5, 1.6]</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>146</td>
<td>3.5 [2.9, 4.6]</td>
</tr>
</tbody>
</table>

### Overall Survival

**HR = 1.04 [95%CI: 0.83, 1.30]**

*P = 0.76*

<table>
<thead>
<tr>
<th>Events, n</th>
<th>Median OS [95% CI], months</th>
<th>12-Month OS Rate [95% CI], months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>154</td>
<td>9.8 [8.2, 11.8]</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>147</td>
<td>10.0 [9.0, 11.8]</td>
</tr>
</tbody>
</table>

Reardon et al., WFNOS meeting 2017
**PD-1 inhibition**

**Ongoing trials**

**CheckMate 498:** Nivolumab or TMZ in combination with RT in newly diagnosed patients with *MGMT*-unmethylated GBM

- **Patients**
  - Newly diagnosed GBM
  - *MGMT* unmethylated status

- **Randomized**

  - **Nivolumab + RT**
    - Nivolumab + RT
    - Nivolumab

  - **RT + TMZ**
    - RT + TMZ
    - TMZ

  - **Treatment until progression / unacceptable toxicity**

**CheckMate 548:** Nivolumab or placebo in combination with RT + TMZ in newly diagnosed patients with *MGMT*-methylated or indeterminate GBM

- **Patients**
  - Newly diagnosed GBM
  - *MGMT* methylated or indeterminate status

- **Randomized**

  - **Nivolumab + RT + TMZ**
    - Nivolumab + RT and TMZ
    - Nivolumab + TMZ

  - Placebo + RT + TMZ
    - Placebo + RT and TMZ
    - Placebo + TMZ

  - **Treatment until progression / unacceptable toxicity**
MMR-deficient tumors may respond better to PD-1 inhibition
Challenges associated with the use of immune checkpoint inhibitors

Pseudoprogression vs. (true) progression
61 yo man, recurrent glioblastoma

Roth et al., Neuro Oncol 2017
Novel approaches to CAR T cells

Regr

Before Infusion

After Infusion

Day 108

Day 295

T4

T4

T7

T7

T5

T5

Day 108

Day 295

Chimeric therapy

Starr, M.S.,

Injo, B.A.,

Patrick, M.S.N.,

Jenni, Ph.D.,

D’Apuzzo, M.D.,

Barish, Ph.D.,

Fermon, M.D.,

9, 2016
Glioblastoma and CNS tumors
Take home messages

• The particular immunological situation in the CNS does not preclude anti-tumor immune responses

• 2 negative phase III trials with rindopepimut and nivolumab in glioblastoma patients

• Advanced vaccines, checkpoint inhibitors in combination with conventional treatment modalities and CAR T cells are currently being explored in clinical trials