Glioma: state of the art approach

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disclosures

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Mutational landscape and clonal architecture of genetic lesions in glioma

Histology: oligoastrocytoma, Molecular: IDHmt, 1p/19q co-deleted: oligodendroglioma

Seizures and multiple lesions on T2 weighted imaging in a 57 year old lady

- Clinically: seizures, progressive weakness left arm and sensory signs on the left
- Multiple abnormalities on T2 weighted imaging
- Dd tumor, inflammatory, mitochondrial, auto-immune disease
- No enhancement, some increase rCBV
- Biopsy: low grade glioma, MIB labeling 2-3%
- Next gen sequencing: IDHwt, EGFR amplification, bi-allelic PTEN inactivation (mutation, loss)
- Diagnosis? OS 23 mo after biopsy, TMZ, RT…
Astrocytoma IDHwt: no single entity and require further molecular diagnostics

- 166 IDHwt cases from a series of 718 WHO II/III patients; OS in H3F3A, TERT or EGFR mutated: median OS 1.23 yrs\(^1\)
  
<table>
<thead>
<tr>
<th>All Tumors (n = 166)</th>
<th>TERTp mut (n = 41)</th>
<th>BRAF-V600E (n = 10)</th>
<th>EGFR amp (n = 20)</th>
<th>H3F3A-K27M (n = 12)</th>
<th>H3F3A-G34R (n = 2)</th>
<th>MYB amp (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>166</td>
<td>41</td>
<td>10</td>
<td>20</td>
<td>12</td>
<td>2</td>
<td>33</td>
</tr>
</tbody>
</table>

- Erasmus MC experience\(^2\)
  - 639 cases, assessed with NGS panel, with assessment CNA 7, 10; and assessment TERT promoter mutations
  - 74 IDHwt: 39 7+/10q- (38 TERTp mt), 14 only TERTp mt
  - Prognosis even worse in TERTp mt only

cIMPACT-NOW update 3

Criteria for **diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma**:

- Histologically grade II, III astrocytoma, IDHwt, with
  - EGFR amplification (high level)
    - or
  - Combined whole chr 7 gain and whole chr 10 loss (+7/-10)
    - or
  - TERT promoter mutation

The histological context is important:

- eg, frequent TERT mutations in PXA, gangliogliomas, anaplastic astrocytoma with piloid features, ependymoma
- MRI consistent? Eg, grade II histology in clearly ring enhancing glioblastoma like lesion: sampling error
A modified WHO 2016 for diffuse glioma

IDH mutated glial precursor

- TP53 mut
- ATRX loss

IDH mutated 1p/19q intact

- low grade astrocytoma
- anaplastic astrocytoma
- grade IV astrocytoma?

IDH mutated 1p/19q codeleted

- low grade oligodendroglioma
- anaplastic oligodendroglioma

7+/10q- glial precursor

- IDH wt glioblastoma

- IDH wt glioblastoma

- diffuse astrocytic glioma, with molecular features of glioblastoma

Grading

- grade 2
- grade 3
- grade 4
## OS in molecularly defined anaplastic glioma as reported in large phase III trials

<table>
<thead>
<tr>
<th>study</th>
<th>histology</th>
<th>Molecular subtype</th>
<th>treatment</th>
<th>n</th>
<th>Median OS</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 9802</td>
<td>Low grade glioma</td>
<td>IDH mutated (all) IDHwt</td>
<td>RT/PCV or RT RT/PCV or RT</td>
<td>71</td>
<td>13.1 yrs</td>
<td>5.1 yrs</td>
</tr>
<tr>
<td>EORTC 26951</td>
<td>Anaplastic oligodendroglioma</td>
<td>1p/19q codeleted IDHmt 1p/19q intact 7+/10q-/TERTpmt</td>
<td>RT/PCV RT/PCV RT or RT/PCV</td>
<td>43</td>
<td>NR (&gt;14 yrs)</td>
<td>8.3 yrs 1.13 yrs</td>
</tr>
<tr>
<td>RTOG 9402</td>
<td>Anaplastic oligodendroglioma</td>
<td>1p/19q IDHmt (all)</td>
<td>RT/PCV</td>
<td>59</td>
<td>14.7 yrs</td>
<td>8.4 yrs</td>
</tr>
<tr>
<td>RTOG 9804</td>
<td>Anaplastic astrocytoma</td>
<td>IDH mt (IHC) IDHwt</td>
<td>RT/chemo</td>
<td>49</td>
<td>7.9 yrs</td>
<td>2.8 yrs</td>
</tr>
<tr>
<td>NOA4</td>
<td>Grade III</td>
<td>1p/19q codeleted IDHmt 1p/19q intact IDHwt</td>
<td>RT or chemo</td>
<td>66</td>
<td>NR</td>
<td>7.0-7.3 yrs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>83</td>
<td></td>
<td>3.1 – 4.7 yrs</td>
</tr>
<tr>
<td>NOA4</td>
<td>Grade III</td>
<td>1p/19q codeleted IDHmt 1p/19q intact IDHwt</td>
<td>RT or chemo</td>
<td>58</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Reported survival after RT/chemo

<table>
<thead>
<tr>
<th>Anaplastic glioma</th>
<th>Reported survival after RT/chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligodendroglioma, IDHmut &amp; 1p/19q codeleted</td>
<td>&gt; 14 years</td>
</tr>
<tr>
<td>Astrocytoma, IDH mutated</td>
<td>7 - 8 years</td>
</tr>
<tr>
<td>Astrocytoma IDH wt</td>
<td>1 – 4.7 yrs</td>
</tr>
</tbody>
</table>

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Grading of astrocytoma, IDHmt

- Series of AIIIDHmut, AAIIIDHmut, or GBMIDHmut (discovery set 211 pts, with validation in independent datasets 108 and 154 pts)
- Homozygous deletions CDKN2A most relevant for OS ($p = 0.0001$, 38:211 pts)
- Strongest morphological parameters of negative prognostic value:
  - vascular proliferation ($p < 0.0005$)
  - necrosis ($p < 0.00005$)
- Necrosis but no CDKN2A loss: intermediate malignancy
- No necrosis but CDKN2A loss: high malignancy
Global methylation analysis

- The cancer methylome is a combination of both
  - somatically acquired DNA methylation changes
  - characteristics that reflect the cell of origin\(^1\)
- Global methylation assessment also allows copy number assessment
- Works on archival FFPE
- Very well suited for tumor classification based on cell of origin, copy number assessment
- Allows assessment of MGMT promoter methylation status (‘MGMT-\text{STP27}’\(^1\)) based on 2 CpG sites in the promoter region

Heatmap of DNA methylation data. representing 932 TCGA glioma samples grouped according to unsupervised cluster analysis\(^3\)

Predictive significance of MGMT-\text{STP27} assay for benefit of adding PCV to RT in EORTC study 26951

\(^1\)Capper et al, http://www.nature.com/doifinder/10.1038/nature26000
\(^2\)van den Bent et al, Clin Cancer Res; 19(19); 2013:5513–22
\(^3\)Ceccarelli et al, Cell. 2016 January 28; 164(3): 550–563
DNA methylation based classification of CNS tumors. Capper et al

- DNA methylation-based classification of all CNS tumor entities across age groups using Infinium Human Methylation 450K BeadChip arrays
- Reference cohort of 2,801 samples
- Samples analysed by unsupervised clustering both within each entity and across histologically similar tumour entities, to identify
  - distinct DNA methylation classes within one histopathological entity
  - DNA methylation classes comprising tumours displaying a varied histological phenotypes

- Resulted in designation of 82 CNS tumour classes with distinct DNA methylation profiles

Overview of the 82 CNS tumour methylation classes and nine control tissue methylation classes of the reference cohort

Capper et al, http://www.nature.com/doifinder/10.1038/nature26000
Diagnostic power in individual cases

- 1155 diagnostic cases: in 1104 sufficient methylation signal for classification
- Discrepancy between pathological diagnosis (left) and methylation profiling (right) was observed for 139 cases
- Additional external series on 401 diagnostic cases: change of diagnosis in up to 12%

2015: Increasing seizures and a cystic lesion

- Male born 1998
- 2000 surgery for an oligoastrocytoma grade 3, followed by chemotherapy
- 2015 recurrence seizures, and new cystic lesion slowly expanding
- Pathology review 2016: low grade oligoastrocytoma
- Next Generation Sequencing: no mutations
- Illumina Methylation array: consistent with pilocytic astrocytoma
- FISH: positive for BRAF-KIAA fusion gene
Routine NGS diagnostics for glioma: the Erasmus MC experience 2013-2016

- Since 2013 next-generation sequencing (NGS) targeting CNA and mutations relevant for diffuse gliomas (glioma dedicated NGS panel)
  - mutations in *ATRX*, *CIC*, *EGFR*, *FUBP1*, *NOTCH1*, *PTEN*, *H3F3A*, *IDH1/2*, *PIK3CA*, and *BRAF*, amplifications in *EGFR* or *MDM2* and copy number alterations (CNA) of chromosome 1p, 7, 10 and 19q
  - Updated version also assesses *TERT* promoter mutations

- 2013 – 2016: assessment of 433 samples, histology:
  - 176 cases grade 2 or 3 glioma (40.6%), 201 cases glioblastoma (46.4%), of the remaining 56 patients: 22 inconclusive histology.

- In 378 cases (87.1%) a diagnosis solely based on glioma-targeted NGS could be established, different from histopathology in ~ 1/4 of the cases.

- In 17 : 22 cases without a conclusive histological diagnosis NGS resulted in a molecular diagnosis

Extent of resection in IDHmt Astrocytoma

- Series on low grades, anaplastic IDHmt astrocytoma\(^1,\)\(^2\)
- Both show early and significant effect from less than total resection on OS
- 2nd look surgery in case of less than complete resection?
- Bias remains: smaller tumors more likely to get extensively resected

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\(^1\)Wijnenga et al Neurooncol 2017 doi:10.1093/neuonc/nox176
\(^2\)Kawaguchi et al, J Neurooncol 2016;129:505-14
And chemo for all grade II and III!

Low grade glioma: RTOG 9802

10 year survival
PCV+RT: 60%
RT alone: 40%

1p/19q codeleted anaplastic oligodendroglioma: EORTC 26951

Median Survival
PCV+RT: >14 yrs
RT alone: 11 years

1p/19q intact anaplastic astrocytoma: the EORTC CATNON trial

5 year survival
RT / adj TMZ: 56 %
RT no adj TMZ: 44%
EORTC TAVAREC trial: bevacizumab and temozolomide in recurrent 1p/19q intact grade II / III glioma

NON 1p/19q-codeleted Grade II / III glioma (local diagnosis)

FIRST treatment with RT and/or TMZ/PCV

FIRST relapse with enhancing lesion

Temozolomide Monotherapy

Temozolomide Bevacizumab

Overall survival

PP population

TMZ alone N=73

TMZ + BEV N=70

Primary endpoint

Patients alive at 12m* 44:72st (61%) 39:70 (56%)

Overall Survival

P=0.66* Hazard Ratio= 1.09, 95% CI (0.75,1.59)

Progression Free Survival

P=0.95* Hazard Ratio= 0.99, 95% CI (0.70-1.40)

van den Bent et al, Lancet Oncol 2018 doi: 10.1016/S1470-2045(18)30362-0

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CETEG Trail: NOA-09 temozolomide vs lomustine in newly diagnosed methylated glioblastoma

- Lomustine vs temozolomide + lomustine
- Eligible: glioblastoma, MGMT methylated only
  - Age 18-70
  - KPS 70% or higher
  - Resection or biopsy
- N = 2 x 64

Herrlinger et al, Lancet, in press
The CeTeG trial anticipated potential imbalances of prognostic factors

To minimize their influence by using a test stratified for center and RPA class

In an unstratified analysis the difference is less clear

Reflecting the drawback of a smaller study with a limited sample size

Overall survival: Kaplan-Meier graph for overall survival including all 129 patients of the mITT population corresponding to an unstratified logrank analysis (p=0.65).

Herrlinger et al, Lancet, in press
### Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>TMZ</th>
<th>CCNU/TMZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (mo, 95% CI)</td>
<td>30.4 (27-44.9)</td>
<td>46.9 (31-NA)</td>
</tr>
<tr>
<td>1y OS (% , 95% CI)</td>
<td>84.4 (80.5-97)</td>
<td>88.8 (81.5-96.7)</td>
</tr>
<tr>
<td>2y OS (% , 95% CI)</td>
<td>65.4 (57.3-81.6)</td>
<td>71.4 (61.2-83.4)</td>
</tr>
<tr>
<td>3y OS (% , 95% CI)</td>
<td>42.3 (31.1-57.5)</td>
<td>57.4 (46.3-71.1)</td>
</tr>
<tr>
<td>4y OS (% , 95% CI)</td>
<td>31.4 (20.8-47.5)</td>
<td>48.8 (37.5-63.5)</td>
</tr>
<tr>
<td>5y OS (% , 95% CI)</td>
<td>27.7 (17.3-44.5)</td>
<td>34 (22.9-50.5)</td>
</tr>
</tbody>
</table>

- Analysis using **Inverse Probability Weights** (Cole et al., 2004) acknowledging an imbalance of RPA group distribution in 3 large centers (no RPA V patients in the control arm)

- **CCNU/TMZ**: mOS prolonged by 16.5 Mo, almost 50% 4 year survival

- **Analysis without Inverse Probability Weights**: mOS was prolonged from 31.4 to 37.9 mo
Is this the new standard of care in methylated glioblastoma patients?

- A 2nd trial is unlikely to happen
- It shows the possible value of an old class of agents
- Ongoing discussion about the role of PCV vs TMZ in anaplastic oligodendroglioma
  - Subgroup and retrospective analysis suggesting superior outcome of PCV compared to TMZ
# Trials on EGFR inhibition in recurrent glioblastoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>n</th>
<th>6 mo PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raizer et al 1</td>
<td>erlotinib</td>
<td>44</td>
<td>3%</td>
<td>6 mo</td>
</tr>
<tr>
<td>van den Bent et al 2</td>
<td>erlotinib BCNU, TMZ</td>
<td>54</td>
<td>11%</td>
<td>7.7 mo</td>
</tr>
<tr>
<td>Rich et al 3</td>
<td>gefitinib</td>
<td>53</td>
<td>13%</td>
<td>9 mo</td>
</tr>
<tr>
<td>Neyns 4</td>
<td>cetuximab</td>
<td>55</td>
<td>7.3%</td>
<td>5 mo</td>
</tr>
<tr>
<td>Eisenstat 5</td>
<td>afatinib afatinib + TMZ</td>
<td>41</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TMZ</td>
<td>39</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>39</td>
<td>22%</td>
<td></td>
</tr>
</tbody>
</table>

No indication of improved outcome in patients with EGFR amplification or EGFRvIII mutation

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Depatux-M (ABT414) is a monoclonal Antibody Drug Conjugate (ADC) directed against EGFR

Presence of ligand promotes conditions where receptor untethering allows exposure of a unique epitope for ABT-414 binding.
OS with 24+ months follow-up: depatux-m with TMZ and depatux-m monotherapy

**Histological confirmed recurrent de novo (primary) GBM**
- Centrally confirmed *EGFR* amplification
- ≤ 1 line of chemotherapy
- WHO score 0-2
- No prior EGFR- or EGFRvIII-directed therapy

<table>
<thead>
<tr>
<th>Arm</th>
<th>Description</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 1</td>
<td>depatux-m + TMZ</td>
<td>80</td>
</tr>
<tr>
<td>Arm 2</td>
<td>depatux-m</td>
<td>80</td>
</tr>
<tr>
<td>Arm 3</td>
<td>lomustine or TMZ</td>
<td>80</td>
</tr>
</tbody>
</table>

**Primary Objective:**
- Overall survival (OS)

**Secondary Objectives:**
- PFS (per RANO, IRC)
- Objective response rate (IRC)
- OS (*EGFRvIII* subgroup)

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**Graph 1:**
- **Objective:** Overall survival (OS)
- **Details:**
  - Hazard Ratio: 0.66, 95% CI (0.47 – 0.93)
  - p = 0.016*

**Graph 2:**
- **Objective:** PFS (per RANO, IRC)
- **Details:**
  - Hazard Ratio: 0.96, 95% CI (0.69-1.33)
  - p = 0.80*
Dabrafinib, trametinib in BRAF V600E glioma

- High grade glioma cohort, BRAF V600E evaluable population
- N = 28
- Independant review: 29% CR and PR
- 5 responses ongoing for ≥ 12 months

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BRAF mutations: an actionable target

- BRAF mutations: frequent in (anaplastic) PXA (43-66%), ganglioglioma (18-43%), epitheloid glioblastoma and pilocytic astrocytoma (especially non-fossa posterior: 33%)
- Should be routinely investigated in any of these diagnosis

BRAF mutated glioblastoma before and after 4 cycles of combined RAF and MEK inhibition
Glioma state of the art approach in 2018

- WHO 2016: Glioma diagnostics is based on *molecular* analysis
- Low grade IDHwt glioma can have molecular features of glioblastoma
  - Requiring glioblastoma treatment
- Genome wide methylation may allow improved diagnostics
- For methylated glioblastoma: combo temozolomide/lomustine treatment?
- Depatux-M for EGFR amplified glioblastoma?
  - Phase III trial in newly diagnosed ongoing
- Immunotherapy in glioma continues to be ‘promising’
- BRAF/MEK inhibition shows targeted treatment is active in glioma
  - Once the target is relevant