ASTRO 2018 : Neuro-Oncologie

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Elevated *MGMT* Gene Expression Is Independently Associated With Worse Overall Survival In NRG Oncology/RTOG 9813

NRG Oncology/RTOG 9813
A phase III study of RT + temozolomide (TMZ) versus RT+nitrosourea (NU) in grade III anaplastic astrocytoma

**Purpose/Objective:** This study sought to determine the prognostic significance of *MGMT* gene expression in NRG Oncology/RTOG 9813.

**Age**
- 1. <50
- 2. ≥50

**KPS**
- 1. 60-80
- 2. 90-100

**Surgery**
- 1. Biopsy
- 2. Resec.

**Arm 1:** RT: 59.4 Gy (1.8 Gy x 33 fractions, 5 days a week x 6 weeks) + TMZ 200 mg/m² daily on days 1-5 of the first week of RT. Repeat TMZ every 28 days for a total of 12 cycles.

**Arm 2:** RT: 59.4 Gy (1.8 Gy x 33 fractions, 5 days a week x 6 weeks) + NU (BCNU 80mg/m² IV days 1-3 every 8 weeks OR CCNU 130mg/m² p.o. every 8 weeks

However, methylation is an upstream regulatory mechanism that leads to gene expression silencing.

**Hypothesis:** Patients with elevated levels of MGMT gene expression would have significantly worse survival rates.
**MGMT** Gene Expression Is A Superior Prognostic Biomarker for Long-Term Survival Over **MGMT** Promoter Methylation in NRG Oncology/RTOG 9813

We found that elevated **MGMT** gene expression is significantly associated with worse overall survival and progression-free survival, independent of **MGMT** promoter methylation and **IDH1** mutation status.
Risk Factors for Progression of Low Grade Glioma Following Gross Total Resection and Observation in the Molecular Era

Management of low risk low grade glioma

- EORTC 22845 “Non-believers trial”
  - Compared to salvage RT, adjuvant RT improves PFS, but not OS
  - At 1 year, seizures better controlled with adjuvant RT

- Phase II RTOG 9802 (Low risk arm)
  - Eligibility: Age <40 and surgeon defined GTR were observed

  - Risk factors for worse PFS were:
    - Preoperative tumor size ≥ 4 cm
    - Astrocytoma or oligoastrocytoma histology
    - Residual tumor greater than 1 cm based on MRI imaging

- We sought to assess which factors predict for progression in the molecular era.
Methods

Results

• Multiple studies demonstrated that IDH1 and IDH2 Wildtype status is associated with exceptionally poor survival
  • In our cohort of imaging confirmed GTR, OS was favorable regardless

• LGG with imaging confirmed GTR followed by no adjuvant treatment have excellent OS regardless of molecular status

• Risk factors for progression in our cohort include:
  • Increasing age at diagnosis
  • Increasing tumor size
  • IDH mutation 1p19q intact
Preservation of Neurocognitive Function with Conformal Avoidance of the Hippocampus during Whole-Brain Radiotherapy for Brain Metastases: Preliminary Results of Phase III Trial NRG Oncology CC001

NRG-CC001: Phase III Trial Memantine and WBRT with or without Hippocampal Avoidance in Patients with Brain Metastases

Basic Eligibility: Brain metastases 5mm outside hippocampus; KPS≥70; 3D MRI scan; hydrocephalus/ventricular distortion excluded; baseline NCF testing

Brain Metastasis -> Stratify -> RPA Prior Therapy

Randomize

- WBRT 30Gy + Memantine
- HA-WBRT 30Gy + Memantine
<table>
<thead>
<tr>
<th>Test</th>
<th>WBRT+memantine N=256</th>
<th>HA-WBRT+memantine N=259</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HVLT-R Recall</td>
<td>-1.29</td>
<td>-1.31</td>
<td>0.87</td>
</tr>
<tr>
<td>HVLT-R Delayed Recall</td>
<td>-1.29</td>
<td>-1.17</td>
<td>0.37</td>
</tr>
<tr>
<td>HVLT-R Recognition</td>
<td>-0.72</td>
<td>-0.64</td>
<td>0.58</td>
</tr>
<tr>
<td>TMT-A</td>
<td>-1.21</td>
<td>-1.29</td>
<td>0.74</td>
</tr>
<tr>
<td>TMT-B</td>
<td>-3.49</td>
<td>-3.18</td>
<td>0.63</td>
</tr>
<tr>
<td>COWA</td>
<td>-0.82</td>
<td>-0.82</td>
<td>0.94</td>
</tr>
<tr>
<td>CTB Composite</td>
<td>-1.46</td>
<td>-1.40</td>
<td>0.70</td>
</tr>
</tbody>
</table>

- Probability of cognitive failure at 6 months:
  
  **HA-WBRT+MA** 59.5% (50.2-64.9)%
  
  **WBRT+MA** 68.2% (61.8-75.3)%

- Hazard ratio = 0.74 95% CI (0.58-0.95)  
  \( p=0.02 \)
A Radiosensitivity Gene Signature and PD-L1 Status Predict Clinical Outcome of Patients with Glioblastoma Multiforme in The Cancer Genome Atlas (TCGA) Dataset

- To validate the clinical value of radiosensitivity gene signature and PD-L1 status in TCGA-GBM dataset
• The “PD-L1-High-RR group” treated with RT
  • Showed worse OS compared to others
  • Differentially expressed genes in this group were associated with cancer-related immune/inflammatory response and key oncogenic pro-survival signaling pathways.
  • One of epigenetically regulated genes (BAI1) was associated with angiogenesis
  • Infiltrated immune cells promotes immunosuppressive tumor microenvironment.

• Thus, this group might get benefit from anti-PD-1/PD-L1 blockades combined with antiangiogenic drug and RT using immune stimulating dose-fraction schedule

**TREM1**

• “Triggering receptor expressed on myeloid cells 1”
• Myeloid cell activation
• High expression in human GBM → worse OS
GADGET Trial

• Pas d’autorisation de diapos ...

• Abstract publié, papier définitif en attente

• Phase 3 : GK vs Edge SRS
  – End-point :
    • 1) RN (évaluation par IRM +/- Tep MET
    • 2) LC and OS
  – Max 4 méta, max 3 cm
  – GK : isodose 50%, 20 à 24 Gy
  – Edge : isodose ???, 24 Gy

• Résultats :
  – RN : gde 2 : pas de différence ; gde 3 : plus de tox bras GK !!! Pas de p value !!!
  – LC et OS : pas de différence
  – Facteurs de RN indépendant (multi-varié) : volume tumoral
Combining SRS/WBRT with immunotherapy/targeted therapy for brain metastases

Radiosurgery Plus Drug

Perceived Risk

- BRAF
- Taxanes
- Most TKIs
- Methotrexate
- Gemcitabine
- Cisplatin

Doxorubicin
T-DM1
ADCs

No break:
- anti-PD1
- anti-PDL1
- anti-CTLA-4
- capecitabine
- temozolomide
- etoposide
- vincristine
- pemetrexed
- lapatinib
- trastuzumab
- hormonal agents
- bevacizumab
- mTor
- ALK

Break between SRS and Drug
Treatment of Brain Metastases with Stereotactic Radiosurgery and Immune Checkpoint Inhibitors: An International Meta-Analysis of Individual Patient Data

Ipilimumab > Nivolumab/Pembrolizumab
  • SRS + checkpoint inhibitors in metastatic melanoma 2.5x increased risk of RN (Martin, JAMA Onc)
    • SRS + ipilimumab 4.7x increased risk

• 1-Year OS of 56%
• Radionecrosis more common with ipilimumab
• Concurrent over sequential therapy may be associated with improved 1-year OS, 1-year LC, and 1-year regional brain control
• Prospective data are needed
**Molecular Classification**

**IDH wild-type**
- **GBM**
  - MGMT Methylated
    - MGMT Non-methylated
      - less or no benefit from alkylating agent chemo
  - EGFR amplification
    - EGFRvIII mutation
    - clinical trials

- **Astrocytoma**

**IDH mutated**
- **1p/19q intact**
  - **Astrocytoma**
    - g-CIMP
    - **TP53** mutation
    - ATRX mutation
  - 2^o GBM
    - CDKN2A/CDKN2B deletion
    - Chr. 10q loss

- **1p/19q deleted**
  - **Oligodendroglioma**
    - g-CIMP
    - CIC mutation
    - TERT mutation
Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D., Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D., Karl Belanger, M.D., Alba A. Brandes, M.D., Christine Marosi, M.D., Ulrich Bogdahn, M.D., Jürgen Curschmann, M.D., Robert C. Janzer, M.D., Samuel K. Ludwin, M.D., Thierry Gorlia, M.Sc., Anouk Allgeier, Ph.D., Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D., and René O. Mirimanoff, M.D., for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group

2005

TMZ/RT 14.6 (13.2–16.8)
RT alone 12.1 (11.2–13.0)

Hazard ratio for death 0.63
(95% CI 0.52–0.75)
P<0.001

Radiotherapy
Radiotherapy plus temozolomide

Patients Alive (%)

Radiotherapy alone
Radiotherapy + temozolomide

Short-Course Radiation plus Temozolomide in Elderly Patients with Glioblastoma


Median age 73 yrs (range 65-90 yrs)

2017

Median Overall Survival (mo) (95% CI)
Radiotherapy + Temozolomide 9.3 (8.3–10.3)
Radiotherapy Alone 7.6 (7.0–8.4)

Hazard ratio for death 0.67 (95% CI 0.56–0.80)
P<0.001
Tumor Treating Fields prolongs Progr.-free survival

<table>
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<tr>
<th>Progr.-free</th>
<th>TTFields/TMZ</th>
<th>TMZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>6.7 mo</td>
<td>4.0mo</td>
</tr>
<tr>
<td></td>
<td>6.1 – 8.1</td>
<td>3.8 – 4.4</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.63 (CI 0.52 – 0.76)</td>
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<td>P-value</td>
<td>0.00005</td>
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Overall survival

<table>
<thead>
<tr>
<th>Survival</th>
<th>TTFields/TMZ</th>
<th>TMZ</th>
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</thead>
<tbody>
<tr>
<td>Median</td>
<td>20.9 mo</td>
<td>16.0 mo</td>
</tr>
<tr>
<td>95% CI</td>
<td>19.3 – 22.7</td>
<td>14.9 – 18.4</td>
</tr>
<tr>
<td>2-year</td>
<td>43.1 %</td>
<td>30.7 %</td>
</tr>
<tr>
<td>95% CI</td>
<td>(38.7 – 48.0)</td>
<td>(25.1 – 37.5)</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.63 (CI 0.53 – 0.76)</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>0.00006</td>
<td></td>
</tr>
</tbody>
</table>
Bevacizumab → no improvement in survival

Newly diagnosed GBM

- Strat. hazard ratio, 0.88 (95% CI, 0.76-1.02)
- P=0.10 by log-rank test

Placebo+RT-TMZ

Bevacizumab+RT-TMZ

Recurent GBM

- HR 0.95 (95% CI 0.74–1.21)
- P=0.650

8.6 mo

9.1 mo

Wick et al for EORTC. NEJM 2017;377:1954-63

Chinot et al for AvaGlio. NEJM 2014;370:709-22

Gilbert et al for RTOG. NEJM 2014, 370:699-708
Lomustine (CCNU) remains the reference treatment in recurrent glioma

Phase III Study of Enzastaurin Compared With Lomustine in the Treatment of Recurrent Intracranial Glioblastoma

Median OS (95% CI)
- ENZ 6.60 (5.22 to 7.76)
- LOM 7.13 (6.01 to 8.80)
- HR (95% CI): 1.20 (0.88 to 1.65)
- Log rank P = .25

Phase III Randomized Trial Comparing the Efficacy of Cediranib As Monotherapy, and in Combination With Lomustine, Versus Lomustine Alone in Patients With Recurrent Glioblastoma

Overall Survival (%)


J Clin Oncol 31:3212-3218, 2013