New options for newly diagnosed and recurrent glioblastoma

EORTC-EANO-ESMO conference
Trends in Central Nervous System Malignancies
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New treatment options in GBM

Overview

Newly diagnosed glioblastoma
• Tumor-Treating Fields (TTFields)

Recurrent glioblastoma
• Immune checkpoint inhibition
• Targeted therapy based on patient selection
TTF in glioblastoma

Background

• Tumor-Treating Fields are low amplitude alternating (100 – 300kHz) electric fields

• The generated electric field shall interfere with mitosis => TTF may target primarily dividing tumor cells

• As a result cell proliferation and viability are reduced
• Single-use transducer arrays deliver NovoTTF Therapy through the scalp
NovoTTF in glioblastoma

Trial design: EF14

Tumor Treating Fields (>18h day) until 2nd progression (or max 24 months) until 2nd progression

Concomitant TMZ/RT

Adjuvant TMZ

Stratification:
- Resection: complete vs partial vs biopsy
- MGMT methylation status

2:1

max 7 weeks

weeks
NovoTTF in glioblastoma

Trial design: EF14

- Age ≥18 years
- Histologically proven newly diagnosed glioblastoma (WHO grade IV)
- Have completed standard TMZ/RT
  - absence of tumor progression post TMZ/RT!
- Karnofsky Performance Status ≥ 70%
- Interval since last day of RT: ≥ 29 days, < 49 days
- Stable or decreasing dose of steroids (last 7 days)
- Supratentorial tumors
- No significant comorbidities
- No implanted electrical devices (e.g. pacemakers)
- Normal organ function
NovoTTF in glioblastoma  
**Trial design: EF14**

<table>
<thead>
<tr>
<th>Endpoints:</th>
<th>Statistics</th>
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<tbody>
<tr>
<td><strong>1°:</strong></td>
<td></td>
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<tr>
<td>- Progression-free survival <em>(ITT population)</em></td>
<td>- Randomization 2 : 1</td>
</tr>
<tr>
<td><strong>2°:</strong></td>
<td>- Power 80%, p &lt; 0.05 (2-sided)</td>
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<tr>
<td>- Overall survival <em>(as treated patients)</em></td>
<td>- HR PFS &lt; 0.78, HR OS &lt; 0.76</td>
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<tr>
<td>- PFS6</td>
<td>- 700 patients / 4 yrs</td>
</tr>
<tr>
<td>- Survival at 1 + 2 yrs</td>
<td>- (630 pts + 10% for lost to follow-up)</td>
</tr>
<tr>
<td>- Quality of life</td>
<td>- Planned Interim analysis on</td>
</tr>
<tr>
<td></td>
<td>- first 315 patients with min. follow-up of 18 months</td>
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<tr>
<td></td>
<td>- PFS 0.0139</td>
</tr>
<tr>
<td></td>
<td>- OS only tested if PFS significant</td>
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NovoTTF in glioblastoma
No major TTF-related toxicity

<table>
<thead>
<tr>
<th></th>
<th>TTF/TMZ (N=203)</th>
<th>TMZ (N=101)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Grade 1 + 2</td>
<td>Grade 3 + 4</td>
</tr>
<tr>
<td>PROCEDURAL COMPLICATIONS</td>
<td>49%</td>
<td>7%</td>
</tr>
<tr>
<td>DEVICE SITE REACTION</td>
<td>43%</td>
<td>2%</td>
</tr>
<tr>
<td>NERVOUS SYSTEM DISORDERS</td>
<td>47%</td>
<td>22%</td>
</tr>
<tr>
<td>CONVULSION</td>
<td>15%</td>
<td>7%</td>
</tr>
<tr>
<td>STATUS EPILEPTICUS</td>
<td>&lt;1%</td>
<td></td>
</tr>
<tr>
<td>PSYCHIATRIC DISORDERS</td>
<td>33%</td>
<td>4%</td>
</tr>
<tr>
<td>SKIN TISSUE DISORDERS</td>
<td>24%</td>
<td></td>
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</tbody>
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Stupp et al. SNO meeting 2014
EF-14 trial
Progression-free survival (ITT)

<table>
<thead>
<tr>
<th></th>
<th>TTF/TMZ</th>
<th>Adj. TMZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>7.1 mo</td>
<td>4.0 mo</td>
</tr>
<tr>
<td>95% CI</td>
<td>5.9 – 8.2</td>
<td>3.0 – 4.3</td>
</tr>
<tr>
<td>from diagnosis</td>
<td>10.9 mo</td>
<td>7.9 mo</td>
</tr>
<tr>
<td>Log rank</td>
<td></td>
<td>p = 0.0014</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td></td>
<td>0.63</td>
</tr>
</tbody>
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Stupp et al. SNO meeting 2014
EF-14 trial
Overall survival (ITT)

Stupp et al. SNO meeting 2014
TTF in glioblastoma

Conclusions

• TTF is overall well tolerated

• TTF prolongs PFS and OS in patients with newly diagnosed glioblastoma

• Based on the results of the interim analysis, the trial was stopped

• Final results need to be awaited

• Currently no coverage by health care insurances in most countries
Recurrent glioblastoma

Immune checkpoint inhibition

- Immune checkpoint receptors: molecules such as CTLA-4 or PD-1 which reduce T cell activity

- Inhibition of these "checkpoint molecules" may boost immune responses against a tumor

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

  => Various ongoing trials in other tumor entities, e.g. renal cancer, lung cancer...
Nivolumab vs. Bevacizumab

Checkmate 143

Screening & Randomization

First recurrence of glioblastoma following TMZ-based chemoradiation

1:1 Randomization (n = 220)

TREATMENT

Treatment arm N:
Nivolumab 3mg/kg every 2 weeks

Treatment arm B:
Bevacizumab 10 mg/kg every 2 weeks

Follow-Up

Treatment until progression or intolerable toxicity

Primary endpoint: Overall survival

Secondary endpoints: OS 12 PFS ORR
PD-1 inhibition
Pseudoprogression vs. progression

4 weeks after start of anti-PD-1 regimen

Weathers and Gilbert, J Neurooncol 2014
PD-1 inhibition

Pseudoprogression vs. progression

8 weeks after start with nivolumab

=> immune Response Assessment in Neuro-Oncology (iRANO)
FGF receptor (FGFR): A new therapeutic target?

Transforming Fusions of FGFR and TACC Genes in Human Glioblastoma


The brain tumor glioblastoma multiforme (GBM) is among the most lethal forms of human cancer. Here, we report that a small subset of GBMs (3.3%; 3 of 97 tumors examined) harbors oncopgenic chromosomal translocations that fuse in-frame the tyrosine kinase coding domains of fibroblast growth factor receptor (FGFR) genes (UGFR1 or 2AF) to the transforming acidic coiled-coil (TACC) coding domains of TACC1 or TACC2, respectively. The FGFR-TACC fusion protein displays oncopgenic activity when introduced into astrocytes or stereotactically transduced in the mouse brain. The fusion protein, which localizes to mitotic spindle poles, has constitutive kinase activity and induces mitotic and chromosomal segregation defects and triggers aneuploidy. Inhibition of FGFR kinase corrects the aneuploidy, and oral administration of an FGFR inhibitor prolongs survival of mice harboring intracranial FGFR3-TACC3-initiated glioma. FGFR-TACC fusions could identify a subset of GBM patients who would benefit from targeted FGFR kinase inhibition.

Chromosomal translocations leading to production of oncogenic fusion proteins are critical events in the pathogenesis of human cancer (1-3). To examine whether such alternations are present in the tumor glioblastoma multiforme (GBM), we used massively parallel, paired-end sequencing of expressed transcripts (RNA-seq) to detect gene fusions in short-term cultures of glioma stem cells (GSCs) freshly isolated from nine patients with primary GBMs. Using TX-Fuse, a methodology that detects split reads and split inserts (see supplementary materials and methods sections and fig S1A), we discovered six rearrangements (all of which were intrachromosomal) that gave rise to in-frame fusion transcripts (table S1). We validated five of these fusion predictions by direct sequencing of polymerase chain reaction (PCR) products spanning the fusion breakpoint (Fig. 1A and fig. S1, B to E).

In Fig. 1A and B, we show the prediction and cDNA sequence validation, respectively, for the fusion that gave the highest read support involving fibroblast growth factor receptor 3 (FGFR3) fused in-frame with transforming acidic coiled-coil (TACC3) in GSC-1123 and GBM-1123 primary tumor. The cDNA contained an open reading frame coding for a protein of 1,048 amino acids resulting from the in-frame fusion of the FGFR3 N terminus (residues 1 to 758) with the TACC3 C terminus (residues 549 to 836) (Fig. 1C and fig. S2A). FGFR3 is a member of the FGFR receptor tyrosine kinase (TK) family (-12), whereas TACC3 belongs to the evolutionarily conserved TACC gene family, which also includes TACC1 and TACC2. The distinctive feature of TACC proteins is a coiled-coil domain at the C terminus, known as the TACC domain, which mediates localization to the mitotic spindle (3, 9).

TACC proteins are hypothesized to be oncogenic in several human tumors, including GBMs (7, 8). In the predicted fusion protein, the intracellular TK domain of FGFR3 is fused upstream of the TACC domain of TACC3 (Fig. 1C). Exon-specific gene expression analysis from the RNA-seq coverage in GSC-1123 and quantitative reverse transcription PCR showed that the expression of the fused FGFR3-TACC3 exons is higher in GSC-1123 than in other GSCs or the normal brain (0- to 130-fold) (fig. S2, B and C). The FGFR3-TACC3 fusion protein was abundantly expressed in GSC-1123 and GBM-1123, and
CBGJ398X2201 trial
Targeting FGFR in glioblastoma

- BGJ398 is a highly potent and selective pan-FGFR inhibitor
- First in class compound
- Patient selection strategy: FGFR translocation or activating mutation
CBGJ398X2201 trial
Targeting FGFR in glioblastoma

CBGJ398X2201: a phase 2, multicenter, open-label study of BGJ398 in patients with recurrent resectable or unresectable glioblastoma

- Patients with recurrent glioblastoma
- Primary endpoint: PFS-6

**Eligible patients**

**GROUP 1 (non-surgical)**
unresectable disease N ~24
BGJ398 125 mg p.o.

**GROUP 2 (surgical)**
resectable disease N ~10
Pre-Surgery
BGJ398 125 mg p.o.
SURGERY
BGJ398 125 mg p.o.

Prescreening for FGFR1,2,3,4 mutated/translocated
EORTC SPECTA
Screening Patients for Efficient Clinical Trial Access

Screen and Treat

**SPECTAplatforms**
- SPECTAcolor
- SPECTAbrain
- SPECTAmel
- SPECTAlung
- SPECTApros

**SPECTApath**
- PathoBiology
- Biobanking
- Scientific/operational support

**SPECTAforum**
- Patient representatives
- Industry
- Regulators
- Technology companies
- Governments
- Payers

**SPECTAreg**
- Competent bodies
- Regulatory affairs research
EORTC SPECTA
Screening Patients for Efficient Clinical Trial Access

Molecular Screening Platform

- Standard treatment (no open trial)
- 1st line trial
- Standard treatment
- 2nd line trial
- First line
- Third line
- Second line
- 3rd line trial
- First line
- Standard treatment (no open trial)

Academia investment

Industry cooperation