Management of glioblastoma: The road towards stratified cancer care
ESMO, Vienna, 29 September 2012
How do we select targets for intervention?

- Proliferation? Migration? Invasion?
- Understand tumor biology and interfere with tumor-related processes?
- Understand glioma biology and interfere with glioma-related processes?
- Consider genetic or expression signatures?
- Glioma targets or host targets?
The Hallmarks of Cancer

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Molecular targets of antiangiogenic therapies investigated in glioblastoma

Fig. 2. Molecular targets of antiangiogenic therapies investigated in glioblastoma. ANG indicates angiopoietin; CKII indicates casein kinase II; eNOS indicates endothelial nitric oxide synthase; ERK indicates extracellular signal-regulated kinases; FAK indicates focal adhesion kinase; GSK3β indicates glycogen synthase kinase 3β; MEK indicates mitogen-activated protein kinase kinase; mTOR indicates mammalian target of rapamycin; PDGF(R) indicates platelet-derived growth factor (receptor); PIIK indicates phosphatidylinositol 3-kinase; PKC indicates protein kinase C; PLCγ indicates phospholipase Cγ; and VEGF(R) indicates vascular endothelial growth factor (receptor).
Antiangiogenic therapies for glioblastoma may not have to target proper endothelial cells.
Astrocyte or glial precursor cell

-9p21 ($CDKN2A$, $p14^{ARF}$)
-13q ($RB1$)

TP53 mutation (≈25%)

-10 (≈70%)

PTEN mutation (≈30%)

$MGMT$ promoter methylation (≈40%)

Gene amplification (≈50%):
- $EGFR$
- $CDK4$
- $MDM2$
- $MDM4$

or other genes

TP53 mutation (≈60%)

$MGMT$ promoter methylation (60-70%)

IDH-1 mutation (≈70%)

+ 7
+ 19
+ 20

Astrocytoma
WHO grade II

-9p21 ($CDKN2A$)
-13q ($RB1$)
-19q13.3

Anaplastic astrocytoma
WHO grade III

Primary glioblastoma
WHO grade IV

-10q (≈70%)

PTEN mutation (<5%)

Secondary glioblastoma
WHO grade IV

IDH-1 mutation (≈5%)
Are the genetic changes that are associated with the development of gliomas relevant for the clinical course and response to current standards of care?
Astrocytoma
- WHO grade II

Anaplastic astrocytoma
- WHO grade III
- TP53 mutation (≈60%)
  - 9p21 (CDKN2A)
  - 13q (RB1)
  - 19q13.3

Secondary glioblastoma
- WHO grade IV
- 10q (≈70%)
- PTEN mutation (<5%)
  + 7q
  + 12p
  - 9p21 (CDKN2A, p14 ARF)
  - 10 (≈70%)
  - PTEN mutation (≈30%)
  - 13q (RB1)
- IDH-1 mutation (≈70%)
  MGMT promoter
  + 7q

Astrocyte or glial precursor cell

Are the genetic changes that are associated with the development of gliomas relevant for the clinical course and response to current standards of care?

No, but we could still target them specifically …

Primary glioblastoma
- WHO grade IV

Secondary glioblastoma
- WHO grade IV

Gene amplification (≈50%):
- EGFR
- CDK4
- MDM2, MDM4
- TP53 mutation (≈25%)
  + 7
  + 19
  + 20

MGMT promoter methylation (≈40%)

IDH-1 mutation (≈5%)
  MGMT promoter methylation (60-70%)
Astrocyte or glial precursor cell

-9p21 (CDKN2A, p14ARF)
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-9p21 (CDKN2A)
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PTEN mutation (<5%)

Gene amplification
(≈50%):
EGFR, CDK4,
MDM2, MDM4,
or other genes

TP53 mutation (≈60%)
MGMT promoter methylation (60-70%)

IDH-1 mutation (≈70%)
+ 7
+ 12p
+ 19
+ 20

Astrocytoma WHO grade II

Anaplastic astrocytoma WHO grade III

Primary glioblastoma WHO grade IV

Secondary glioblastoma WHO grade IV

MGMT promoter methylation (≈40%)

IDH-1 mutation (≈5%)
-10q (≈70%)
PTEN mutation (<5%)
Astrocyte or glial precursor cell

**Astrocytoma**
- WHO grade II
  - TP53 mutation (≈60%)
  - MGMT promoter methylation (60-70%)
  - 9p21 (CDKN2A, p14<sup>ARF</sup>)
  - 10q (PTEN)
  - 13q (RB1)

**Anaplastic astrocytoma**
- WHO grade III
  - IDH-1 mutation (≈70%)
  - MGMT promoter methylation (≈40%)
  - 9p21 (CDKN2A)
  - 10q (PTEN)
  - 13q (RB1)

**Primary glioblastoma**
- WHO grade IV
  - Gene amplification (≈50%): EGFR, CDK4, MDM2, MDM4, TP53 mutation (≈25%)
  - 7
  - 19
  - 20
  - 7q
  - 12p
  - 19q13.3

**Secondary glioblastoma**
- WHO grade IV
  - IDH-1 mutation (≈5%)
  - MGMT promoter methylation (60-70%)
  - 10q (≈70%)
  - PTEN mutation (<5%)
O\textsuperscript{6}-Methylguanin-methyltransferase (MGMT, AGAT), a DNA repair enzyme, counteracts the effect of alkylating agents:
**MGMT** promoter methylation in malignant gliomas: ready for personalized medicine?

Michael Weller, Roger Stupp, Guido Reifenberger, Alba A. Brandes, Martin J. van den Bent, Wolfgang Wick and Monika E. Hegi


- **Unmethylated** *MGMT* promoter
  - *MGMT* gene is active
  - Transcription/translation
  - Chemosensitivity

- **MGMT** promoter methylation
  - Methylation of *MGMT* gene is inactive
  - Transcription/translation blocked
  - Chemosensitivity
Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma


MGMT Gene Silencing and Benefit from Temozolomide in Glioblastoma

Monika E. Hegi, Ph.D., Annie-Claire Dierens, M.Sc., Thierry Gorlia, M.Sc., Marie-France Hamou, Nicolas de Tribolet, M.D., Michael Weller, M.D., Johan M. Kros, M.D., Johannes A. Hainfellner, M.D., Warren Mason, M.D., Luigi Mariani, M.D., Jacoline E.C. Bromberg, M.D., Peter Hau, M.D., René O. Meimounoff, M.D., J. Gregory Cairncross, M.D., Robert C. Janzer, M.D., and Roger Stupp, M.D.

Temozolomide (one week on/one week off) vs radiotherapy in the primary treatment of anaplastic astrocytoma and glioblastoma in older patients: a randomized phase III study

Histology

Temozolomide

Radiotherapy

Radiotherapy

Temozolomide

3 9 12 27 30 33 weeks

TMZ 100 mg/m² po/day for 7 days every 14 days until failure of therapy, to be adjusted in 25-mg steps

Focal radiotherapy daily — 30 x 1.8-2 Gy to a total 54–60 Gy
TMZ is not inferior to RT

Figure 2: Kaplan-Meier analysis of overall and event-free survival
(A) Overall survival. (B) Event-free survival presented as non-proportional curves, which are deemed non-problematic in the context of non-inferiority. RT=radiotherapy. TMZ=temozolomide. HR=hazard ratio.
MGMT is a prognostic biomarker
MGMT is a predictive biomarker
Astrocytoma or glial precursor cell

-9p21 (CDKN2A, p14ARF)
-13q (RB1)

TP53 mutation (≈25%)

-10 (≈70%)
PTEN mutation (≈30%)

TP53 mutation (≈60%)

MGMT promoter methylation (60-70%)

Astrocytoma WHO grade II

IDH-1 mutation (≈70%)
+ 7q
+ 12p

Anaplastic astrocytoma WHO grade III

Gene amplification (≈50%):
EGFR, CDK4,
MDM2, MDM4,
or other genes

-9p21 (CDKN2A)
-13q (RB1)
-19q13.3

Primary glioblastoma WHO grade IV

IDH-1 mutation (≈5%)

MGMT promoter methylation (≈40%)

-10q (≈70%)
PTEN mutation (<5%)

Secondary glioblastoma WHO grade IV
Fig. 1. Schematic of the epidermal growth factor receptor (EGFR)vIII truncation. The EGFRvIII variant receptor is characterized by a deletion of exons 2–7 of the wild type (Wt) EGFR gene. This results in an in-frame truncation of amino acids (AA) 6 to 273 in the extracellular domain of the full length protein, yielding a constitutively active variant receptor that can not bind ligand. The EGFRvIII also contains a novel glycine residue inserted at the fusion junction.
Immunologic Escape After Prolonged Progression-Free Survival With Epidermal Growth Factor Receptor Variant III Peptide Vaccination in Patients With Newly Diagnosed Glioblastoma

John H. Sampson, Amy B. Heindeliger, Gary E. Archer, Kenneth D. Aldape, Allen H. Friedman, Henry S. Friedman, Mark E. Gillens, James E. Vescio, Sam V. McLaughlin, Duane A. Mitchell, David F. Barden, Raymond Swanson, Robert J. Schmitting, Werinui Shu, James J. Vredenburgh, and Darod D. Bigner

J Clin Oncol 26:4722-4729. © 2010 by American Society of Clinical Oncology

Table 2. EGFRVIII Immunohistochemistry Before and After Vaccination

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NOTE: Percent negative after vaccine is 82% (95% CI, 48% to 97%) or ratio of 11; binomial test $P < .001$.

Abbreviation: EGFRVIII, epidermal growth factor receptor variant III.

Fig 3. Epidermal growth factor receptor (EGFR) and EGFR variant III (EGFRVIII) immunohistochemistry of a patient with glioblastoma multiforme (GBM). Staining with (A) EGFR and (B) EGFRVIII before vaccine. (C) Preservation of EGFR staining but (D) specific loss of EGFRVIII staining at recurrence after vaccination.
Fig 4. Immune response correlates. Overall survival (OS) from histologic diagnosis for all patients for whom serum was available to test for epidermal growth factor receptor variant III (EGFRvIII)–specific antibody titers (n = 14; left) and delayed-type hypersensitivity (DTH; n = 17; right). The blue line shows patients with EGFRvIII–specific immune responses, and the gold line shows patients without EGFRvIII–specific responses. Left: The median OS for the six patients who developed EGFRvIII–specific antibody responses was 47.7 months (95% CI, 20.8 to ∞ months). For the eight patients who did not develop antibody responses, the OS was only 22.8 months (95% CI, 21.0 to 34.9 months). After adjustment for age, Karnofsky performance status, and methylguanine methyltransferase methylation, the OS from vaccination of the patients who developed antibody responses was found to be greater (hazard ratio, 0.08; 95% CI, 0.007 to 0.93; P = .043). Right: The median OS for the three patients who developed DTH responses specific for PEPvIII (a 13-amino-acid peptide with an additional terminal cysteine that spans the EGFRvIII mutation) has not been reached at 50 months. For the 14 patients who did not develop DTH responses to PEPvIII, the OS was 23.1 months (95% CI, 21.0 to 44.1 months). Patients who developed PEPvIII DTH responses had a significantly longer OS (P = .03).
EORTC 26112-22115
Trial Design

Adjuvant TMZ/Placebo ➤ P Maintenance

• RT/TMZ completed
• EGFRvIII mutation
• Tumor ≤ 2 cm

Adjuvant TMZ/Rindopepimut ➤ R Maintenance

• Double-blind vaccination
• Priming: 2 injections, 2 weeks post RT/TMZ
• During adjuvant TMZ: 1 injection day 22 each cycle
• Maintenance: 1 weekly injection