ESMO 2012
three abstracts...

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ESMO central nervous tumors track

- **Assigned role: discuss three presentations**
  - One on surgery
  - One on CD133
  - One on anti-angiogenesis
- **Unifying factor: it’s all glioblastoma …**
Re-surgery for recurrent glioblastoma: outcome analysis and correlation with *MGMT* status

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Surgery for recurrent glioblastoma: removing the tip of the iceberg?

- Male, 51 yrs
- Surgery for recurrent glioblastoma
- Immediate post-resection MRI: no residual tumor
- Baseline scan 4 weeks later prior to start bevacizumab
- Did the resection benefit the patient?
A retrospective analysis was made for glioblastoma patients treated between 01/2005 and 06/2010.

**Inclusion criteria were:**
- age $\geq 18$;
- ECOG PS 0-2;
- chemotherapy at disease progression after RT/TMZ;
- availability of data about second progression.
Pts characteristics and results

<table>
<thead>
<tr>
<th>MGMT methylation status</th>
<th>Evaluable methylated</th>
<th>Evaluable unmethylated</th>
<th>Population (N=232)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>165</td>
<td>62</td>
<td>103</td>
</tr>
</tbody>
</table>

| Age                     | Median (range)        | 52 (18-77)             |
| Treatment at progression| Re-surgery + chemotherapy | 102 (44%)             |
|                         | Chemotherapy alone    | 130 (66%)              |

Median time between 1st and 2nd surgery was 13.1 months:
- MGMT methylated: 19.3 months
- MGMT unmethylated: 13 months (p=0.001)

OS: 22.4 months
- OS in pts with 2nd surgery: 25.8 months
- OS in pts without 2nd surgery: 18.6 months (p=0.003)

At multivariate analysis, re-surgery DID NOT affect OS (p=0.11) while age (p=0.001), MGMT methylation (p=0.002) and PFS6 (p=0.0001) were significantly correlated.
Is surgery a prognostic marker for improved 6-month PFS or OS in recurrent glioblastoma?

- Two data sets were analyzed.
  - 511 patients enrolled period 1998-2005
  - 247 patients enrolled during 2005-2008,
    - 208 underwent surgery during the clinical trial or immediately prior to study registration.

- No statistically significant difference in PFS6 or OS between the surgery and nonsurgery groups
  - in either data set alone or in the combined data set (P > .45)

Clarke et al, Neuro Oncol 2011;13:1118-24
The ultimate question in glioma surgery

• Candidates for surgery at progression:
  – Young patients, good clinical condition
  – Longer interval from first surgery
  – Smaller, more superficially located lesions in non-eloquent area’s

• Are surgeons improving prognosis?

• Or are they operating good prognosis patients?
Questions and Observations

• How many operated cases were methylated?
• At present most analysis of impact of surgery on outcome focuses on clinical variables
  – Unclear impact of molecular factors
  – If MGMT promoter methylation identifies patients with longer PFS: 2nd surgery more likely
• These data support the hypothesis that surgeons operate favorable prognosis patients
  – Which may be a good thing, if proven effective
A Phase 2 Trial of the Multitargeted Kinase Inhibitor Lenvatinib (E7080) in Patients (pts) With Recurrent Glioblastoma (GBM) and Disease Progression Following Prior Bevacizumab Treatment

D.A. Reardon,1 E. Pan,2 J. Fan,3 J. Mink,3 D. Barboriak,4 J.J. Vredenburgh,4 A. Desjardins,4 K. Peters,4 J.P. O’Brien,3 P. Wen1

1Dana-Farber/Brigham and Women’s Cancer Center, Boston, MA, USA; 2Moffitt Cancer Center, Tampa, FL, USA; 3Eisai Inc, Woodcliff Lake, NJ, USA; 4Preston Robert Tisch Brain Tumor Center, Duke University Medical Center, Durham, NC, USA
Not all anti-VEGF drugs are created alike…

<table>
<thead>
<tr>
<th>compound</th>
<th>VEGF-R-1</th>
<th>VEGFR-2</th>
<th>VEGFR-3</th>
<th>VEGF-A</th>
<th>EGFR</th>
<th>PIGF</th>
<th>C-kit</th>
<th>PDGF-Rβ</th>
<th>ORR</th>
<th>6 mo PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>cediranib</td>
<td>TKI</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15.3%</td>
<td>16.2%</td>
</tr>
<tr>
<td>vandetanib</td>
<td>TKI</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>13%</td>
<td>6.3%</td>
</tr>
<tr>
<td>aflibercept</td>
<td>‘AB’</td>
<td></td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>24%</td>
<td>7.7</td>
</tr>
<tr>
<td>bevacizumab</td>
<td>AB</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>28.2%</td>
<td>42.6%</td>
</tr>
<tr>
<td>pazopanib</td>
<td>TKI</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>vatalanib</td>
<td>TKI</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td>4%</td>
<td>25% (?)</td>
</tr>
<tr>
<td>sunitinib</td>
<td>TKI</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0%</td>
<td>16.7%</td>
</tr>
</tbody>
</table>

Pazopanib Neuro Oncol 2010;12:855-61  
Bevacizumab JCO 2009;27:4733-4740  
Cediranib REGAL data  
Vatalanib Neuro-oncology 2010;12:304-316  
Afiblerecept J Clin Oncol 2011;29:2689-95  
Sunitinib J Neurooncol 2012;110:111-8
Some conclusions from REGAL and other anti-VEGF projects

• Are PFS & ORR valuable endpoints?
  – Trends towards improved PFS, ORR
  – However: not supported by OS signal in the right direction
  – Classical T1 MRI with contrast has limited prediction for the OS endpoint ‘patient benefit’

• 6 mo PFS in phase II of 28% does not translate in OS benefit
  – benchmark for anti-VEGF agents?
2nd line treatment with bevacizumab after failure to anti-VEGF TKR inhibitor

• Two series (n = 24 and n = 14) with recurrent glioblastoma and bevacizumab-containing regimens after failure to anti-VEGF TKR inhibitor
  – 1\textsuperscript{st} series 6 of 24 patients (25\%) had a PR to TKRI treatment, 6-mo PFS was 16.7\%
  – 2\textsuperscript{nd} series on 14 patients: no ORR to TKI

• Response to bevacizumab: ORR 21-29\% PR, PFS-6 12.5-29\%, median OS after start of Bev 5.2 – 7.8 mo

Essentially all GBM recur after initial therapy and the majority of patients do not survive more than 1 year after the diagnosis of recurrent disease (1 y: 20%-25%)\(^1\)

GBMs are highly vascularized tumors and this was a rationale for the evaluation of the antiangiogenic bevacizumab as a treatment

- Single-agent PFS-6 rate = 42.6% and median OS = 9.2 months\(^2\); PFS-6 rate after a bevacizumab-containing regimen in recurrent disease = 2%; median PFS = 37.5 days\(^3\)

Lenvatinib is an antiangiogenic agent that, in addition to inhibiting VEGFRs, inhibits several signaling drivers (ie, FGFRs, PDGFRs, and RET) that may become activated and compensate for VEGFR inhibition\(^4^\text{-}^6\)

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**Primary Endpoint:** 6-month PFS rate
### Patient Demographics

<table>
<thead>
<tr>
<th>Category</th>
<th>Cohort 3 (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, median (range)</td>
<td>52 (27-74)</td>
</tr>
<tr>
<td>Gender, male</td>
<td>18 (56.3)</td>
</tr>
<tr>
<td>Race, white</td>
<td>32 (100)</td>
</tr>
<tr>
<td><strong>Baseline Karnofsky Performance score</strong></td>
<td></td>
</tr>
<tr>
<td>100% = Normal, no complaints; no evidence of disease</td>
<td>3 (9.4)</td>
</tr>
<tr>
<td>90% = Able to carry on normal activity; minor signs or symptoms of disease</td>
<td>11 (34.4)</td>
</tr>
<tr>
<td>80% = Normal activity with effort; some signs or symptoms of disease</td>
<td>12 (37.5)</td>
</tr>
<tr>
<td>70% = Cares for self; unable to carry on normal activity or to do active work</td>
<td>6 (18.8)</td>
</tr>
</tbody>
</table>

*All patients were previously treated (with up to 2 systemic treatments)*
Results and Conclusion

Key conclusion:
- Lenvatinib provided a modest benefit in a difficult-to-treat disease setting with poor prognosis and no effective treatments

Most common AEs were hypertension, 47% (Grade 3: 18.8%; Grade 4: 3.1%); fatigue, 44% (Grade 3: 15.6%; Grade 4: 3.1%); headache, 41%; proteinuria 31% (Grade 3: 6.3%); and diarrhea 31% (no Grade 3 or 4)

<table>
<thead>
<tr>
<th>Tumor Response</th>
<th>N=32</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS-6, %</td>
<td>8.3</td>
</tr>
<tr>
<td>Median PFS, mos (95% CI)</td>
<td>1.87 (0.95-2.73)</td>
</tr>
<tr>
<td>OS-6, %</td>
<td>28</td>
</tr>
<tr>
<td>OS-12, %</td>
<td>11.15</td>
</tr>
<tr>
<td>Median OS, mos (95% CI)</td>
<td>4.11 (3.02-5.88)</td>
</tr>
<tr>
<td>Complete response (CR), n (%)</td>
<td>0</td>
</tr>
<tr>
<td>Partial response (PR), n (%)</td>
<td>0</td>
</tr>
<tr>
<td>Stable disease (SD), n (%)</td>
<td>9 (28.13)</td>
</tr>
<tr>
<td>Progressive disease (PD), n (%)</td>
<td>14 (43.75)</td>
</tr>
<tr>
<td>Unknown, n (%)</td>
<td>9 (28.13)</td>
</tr>
<tr>
<td>Objective response rate (CR + PR)</td>
<td>0</td>
</tr>
</tbody>
</table>
Radiographic Response With Lenvatinib

Case

A. Axial maps of $K_{\text{trans}}$ derived from evaluation of DCE-MRI analyzed using extended Tofts model in patient with glioblastoma before and after single dose of lenvatinib demonstrate 96.3% decreased $K_{\text{trans}}$ in right temporal parietal tumor.

B. Corresponding reformatted axial contrast-enhanced T1-weighted 3D fast low-angle shot (3D FLASH) images show decrease in the size of contrast-enhancing abnormality at the corresponding time points (pre-lenvatinib, post-lenvatinib, 81.7% decrease in lesion volume).

Results: 16 patients performed DCE-MRI. 33% reduction in mean $K_{\text{trans}}$ was observed in 10 patients (63%) and a significant decrease in lesion volume (mean reduction: 33%, $P=0.00287$) was found 1 day after therapy, indicating L affected tumor vascularity and vascular permeability.
Some observations

• Most anti-VEGF agents do not come close to the results in recurrent glioblastoma observed with bevacizumab
• Bevacizumab still not fully evaluated
• Results in 2nd line anti-VEGF agents worse
• Recurrent glioblastoma after bevacizumab still stage in which most drugs are likely to fail
Association between cancer stem cells and CD133+ blood vessels in glioblastoma multiforme

Jana Jaal, MD, PhD

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Tartu University Hospital, Hematology and Oncology Clinic
CD133 (prominin-1): markers of stem cells?

- Originally described as a marker of hematopoietic CD34+ progenitor cells
- Antibody for CD133 recognizes certain glycosylated epitopes (AC133, AC14)
- Rapid down regulation during cell differentiation
  - or only the AC133 epitope and not the CD133 protein???

- Cancer stem cells: capacity to self-renew, driving tumor growth and generate tumor cell progeny that form tumor bulk
  - More resistant against radiotherapy and chemotherapy
- Does expression of CD133 epitopes AC133 and AC141 define Brain Tumor Stem Cells? Unresolved issue …

Kemper et al, Canc Res 2010;70:719, Bidlingmaier J Molmed 2008;86:1025-32
The expression of CD133 predicts poor prognosis in glioma

• Several studies have shown prognostic significance of CD133 expression in glioma
  – Both CD133+ proportion and CD133+ expression in clusters
  – Stem cell related expression signature related to poor survival in GBM treated with RT/TMZ

• Series of 44 glioblastoma patients
  – CSC generation and CD133+/Ki67+ prognostic for progression and poor outcome

What is the source of endothelial cells in glioblastoma?

• Usual hypothesis: derived from bone marrow stem cells, endothelial precursor cells

• Alternative: blood vessels originating from tumor stem cells?
  – In glioblastoma: copious CD133+ or Nestin+ blood vessels in regions with CD133+ or Nestin+ cells
  – Niches with CD133+/nestin+ GSC with blood vessels distributed around the surroundings
  – GSC can co-express CD133, Nestin and CD31

CD133+ stem cells and CD133+ blood vessels

Photos illustrate low (A) and high (B) proportions of CD133+ GBM stem cells in GBM tissue.

Photos depict CD133+ blood vessels (0= no staining, figure 2A; 1= weak staining, figure 2B; 2= moderate staining, figure 2C; 3= strong staining, figure 2D). **A significant association was found between the proportion of CD133+ stem cells and the number of CD133+ blood vessels (p=0.004).** Moreover, a correlation between the number of CD133+ blood vessels and the endothelial CD133 staining intensity was detected (p<0.001).
Kaplan-Meier analysis of overall survival (OS) according to CD133+ stem cell proportion

Median survival of patients with low (<median) and high (≥median) proportion of GBM stem cells were 9.0 months (95% CI 7.6-10.5) and 12.0 months (95% CI 9.3-14.7) respectively (p=0.02).
In summary

- A significant association was found between the proportion of CD133+ stem cells and the number of CD133+ blood vessels (p=0.004).

- Moreover, a correlation between the number of CD133+ blood vessels and the endothelial CD133 staining intensity was detected (p<0.001).

- In multivariate analysis, the proportion of CD133+ GBM stem cells emerged as a significant independent predictor for overall survival.

- Favourable CD133+ expression has to be taken into account in the strategies under preclinical or clinical development for GBM stem cell targeting.
Some observations

- Role of CD133+ for identification of BTSC still matter of debate
- Prognostic role of CD133 expression in most studies
- Intriguing interplay between BTSC and endothelial cells
  - Exchange of proteines?
  - GCS participating to endothelial cell formation?