Management of glioma: From Evidence to Practice

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Glioma are not all the same

Genetic Pathways to GBM

- **p53 mutations**, 60%,
- **LOH 17p**
- **PDGF overexpression**
- telomerase activity, 20%
- **Astrocytoma II**
- **LOH 19q**
- **Rb alteration**
- telomerase activity, 40%
- **Astrocytoma III**
- **LOH 10q**
- **DCC loss expr**, 50%
- **PDGFR amplification**, <10%
- telomerase activity, 100%

**Mean Survival**
- > 5 years
- 2-5 years
- ≤ 1 year
- > 5 years

**Mean Survival**
- "→ Cave: extrapolation/generalization of results"

- **Primary Glioblastoma**
  - mean age: 55 years

- **Secondary Glioblastoma**
  - mean age: 39 years

Chemotherapy ➔ Systemic Treatments

Chemotherapy
Disposition of the Presentation:  
*Focus on randomized trials*
Clinical scenario 1

- 70 y. o. gentleman
- Inaugural seizure, right parieto-occipital tumor, → partial resection
- → Histology: glioblastoma

Additional information required?

- Performance status: WHO 1 (KPS 80%)

Treatment options?
**EORTC 26981/NCIC CE.3 Phase III Study: Radiation ± Temozolomide**

**Concomitant TMZ/RT**
- 75 mg/m^2^ po qd for 6 weeks,
- then 150-200 mg/m^2^ po qd day 1-5 q 28 days for 6 cycles

**Adjuvant TMZ**
- Weeks 6, 10, 14, 18, 22, 26, 30

**RT Alone**

---

**Temozolomide** 75 mg/m^2^ po qd for 6 weeks, then 150-200 mg/m^2^ po qd day 1-5 q 28 days for 6 cycles

**Focal RT** daily — 30 x 200 cGy
- Total dose 60 Gy

*PCP prophylaxis was required for patients receiving TMZ during the concomitant phase.*
EORTC-NCIC Trial: Updated Survival

<table>
<thead>
<tr>
<th></th>
<th>RT (95% ci)</th>
<th>TMZ/RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.1 (11.2, 13.0)</td>
<td>14.6 (13.2, 16.8)</td>
<td></td>
</tr>
<tr>
<td>10.9% (7.6-14.8)</td>
<td>27.2% (22.2-32.5)</td>
<td></td>
</tr>
<tr>
<td>1.9% (0.6-4.4)</td>
<td>9.8% (6.4-14.0)</td>
<td></td>
</tr>
<tr>
<td>0.63 [0.52-0.75]</td>
<td>p &lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Median OS, mo:

2-yr survival:

5-yr survival:

HR [95% C.I.]:

Number of patients at risk:

Stupp et al. Lancet Oncol 2009, 10:459-466
### Table 1. Demographic Characteristics of the Patients at Baseline.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Radiotherapy (N=286)</th>
<th>Radiotherapy plus Temozolomide (N=287)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>57</td>
<td>56</td>
</tr>
<tr>
<td>Range</td>
<td>23–71</td>
<td>19–70</td>
</tr>
<tr>
<td>Age — no. (%)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50 yr</td>
<td>81 (28)</td>
<td>90 (31)</td>
</tr>
<tr>
<td>≥50 yr</td>
<td>205 (72)</td>
<td>197 (69)</td>
</tr>
<tr>
<td>Sex — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>175 (61)</td>
<td>185 (64)</td>
</tr>
<tr>
<td>Female</td>
<td>111 (39)</td>
<td>102 (36)</td>
</tr>
<tr>
<td>WHO performance status — no. (%)*†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>110 (38)</td>
<td>113 (39)</td>
</tr>
<tr>
<td>1</td>
<td>141 (49)</td>
<td>136 (47)</td>
</tr>
<tr>
<td>2</td>
<td>35 (12)</td>
<td>38 (13)</td>
</tr>
</tbody>
</table>

**Patients 18 to 70 years of age with new and histologically confirmed glioblastoma, World Health Organization [WHO] grade IV, were eligible for the study. Eligible patients had WHO performance status of 2 or less, hematologic, renal, and hepatic function, neutrophil count, ≥1500 per cubic millimeter, <50 years of age or ≤50 years of age, significantly different.
“Remember when shake, rattle and roll meant more than just getting out of bed?”
EORTC 26981/NCIC CE.3
Elderly Patients (60-70 yrs)

Stupp et al. Lancet Oncol 2009
Figures unpublished

Age 60-65 yrs
HR=0.64 (0.43-0.94), p=0.02

Age 65-70 yrs
HR=0.78 (0.50-1.24), p=0.29

<table>
<thead>
<tr>
<th></th>
<th>RT (95%CI)</th>
<th>TMZ/RT (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>11.4 (9.0-13.3)</td>
<td>12.2 (8.6-17.4)</td>
</tr>
<tr>
<td>2-yr survival</td>
<td>8.3% (1.0-15.5)</td>
<td>24.2% (12.7-35.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>RT (95%CI)</th>
<th>TMZ/RT (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>12.0 (9.5-13.3)</td>
<td>10.9 (8.7-18.4)</td>
</tr>
<tr>
<td>2-yr survival</td>
<td>4.9% (0.0-11.2)</td>
<td>17.6% (5.0-30.2)</td>
</tr>
</tbody>
</table>
Nordic Trial Design

RT 60 Gy (2 Gy x 30)

RT 34 Gy (3.4 Gy x 10)

TMZ x 6
(200 mg/ m² d 1–5 q 28d)

342 pts
292 random
3 arms

NOA-08/Methvsalem Trial Design

RT = radiotherapy; TMZ = temozolomide
Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial

Wolfgang Wick, Michael Platten, Christoph Meisner, Jörg Felsberg, Ghazaleh Tabatabai, Matthias Simon, Guido Nikkhah, Kirsten Papsdorf, Joachim P Steinbach, Michael Sabel, Stephanie E Combs, Jan Vesper, Christian Braun, Jürgen Meixensberger, Ralf Ketter, Regine Mayer-Steinacker, Guido Reifenberger, Michael Weller, for the NOA-08 Study Group* of the Neuro-oncology Working Group (NOA) of the German Cancer Society

**Overall Survival**

*MGMT* methylated: **TMZ** longer survival than **RT**

*MGMT* unmethylated: **RT** longer survival than **TMZ**

*Lancet Oncol 2012; 13(7):707-15*
Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial

Annika Malmström, Björn Henning Grenberg, Christine Marosi, Roger Stupp, Didier Frappaz, Henrik Schultz, Ufuk Abacioglu, Björn Tavelin, Benoit Lhermitte, Monika E Hegi, Johan Rosell, Roger Henriksson, for the Nordic Clinical Brain Tumour Study Group (NCBTSG)

Overall survival

**All pts**

- Median overall survival:
  - TMZ 6-8 months
  - 34 Gy 7.5 months
  - 60 Gy 6-9 months

**Age > 70 yrs**

- Median overall survival:
  - TMZ 9-10 months
  - 34 Gy 7-9 months
  - 60 Gy 5.2 months

*MGMT* methylated: **TMZ > RT**

*MGMT* unmethylated: **RT > TMZ**

*Lancet Oncol* 2012; epub
MGMT – A DNA Repair Protein Predicts Outcome
Resistance to Alkylation Agent Chemotherapy – MGMT

INACTIVATION OF THE DNA-REPAIR GENE MGMT AND THE CLINICAL RESPONSE OF GLIOMAS TO ALKYLATING AGENTS


Clinical Trial Substantiates the Predictive Value of O-6-Methylguanine-DNA Methyltransferase Promoter Methylation in Glioblastoma Patients Treated with Temozolomide

Monika E. Hegi,1,4 Annie-Claire Diserens,1 Sophie Godard,1 Pierre-Yves Dietrich,7 Luca Regli,2 Sandrine Ostermann,5 Philippe Otten,8 Guy Van Melle,6 Nicolas de Tribolet,2,3 and Roger Stupp5

Clin Cancer Res 10:1871-74, 2004
MGMT: Prediction of Benefit From TMZ Treatment

Unmethylated MGMT

Methylated MGMT

Our patient: now fully fit, PS 0 (KPS90-100%)  

- completed 6 adj. cycles, well tolerated
- MRI stable or slightly improved
For how long should we continue treatment?

Duration of maintenance (adjuvant) TMZ:
- 6 months?
- 12 months?
- Until progression?
History

Promising Survival for Patients With Newly Diagnosed Glioblastoma Multiforme Treated With Concomitant Radiation Plus Temozolomide Followed by Adjuvant Temozolomide


J Clin Oncol 20:1375-1382. © 2002

Oncologists: 6 cycles of therapy

Procarbazine, Lomustine, and Vincristine (PCV) Chemotherapy for Anaplastic Astrocytoma: A Retrospective Review of Radiation Therapy Oncology Group Protocols Comparing Survival With Carmustine or PCV Adjuvant Chemotherapy


J Clin Oncol 17:3389-3395. © 1999

Neurologists: 1 year of therapy
Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Roger Stupp, M.D., Warren P. Mason, M.D., Martin H. Hauri, M.D.,
Michael Weller, M.D., Barbara Fisher, M.D., Eberhard H. von Borst, M.D.,
Karl Belanger, M.D., Alba A. Brandes, M.D., Gábor Marosi, M.D.,
Ulrich Bogdahn, M.D., Jürgen Curschmann, M.D., Herbert C. Janzer, M.D.,
Samuel K. Ludwin, M.D., Thieren P. P. Andreesen, Anouk Allgeier, Ph.D.,
Denis Lacombe, M.D., J. Gregory Cloughesy, M.D., Elizabeth Eisenhauer, M.D.,
and René O. Mirimanoff.

Evidence based medicine: up to 6 cycles

Value of prolonged maintenance therapy

- How much benefit do you expect?
- Feasibility (screen 1500 – 2000 pts)?
- Value of the effort
Correlative Evidence

- Up to 12 cycles allowed
- 37% of pts received >6 cycles
- Dose-dense regimen = double dose intensity

Conclusions:
- No improved outcome with dose-dense TMZ
- No improvement over prior EORTC-NCIC trial results
Comparison EORTC26981 (2004) and RTOG 0525 (2011)

EORTC

RTOG

Dead 901
Total 1120

2 yr: 28%
“I’ll have an ounce of prevention.”
Clinical scenario 2

- 45 y. o. lady
- Inaugural seizure, right frontal tumor, → partial resection
- → Histology: anaplastic astrocytoma « with some oligodendroglial features »

- Additional information required ?
- Treatment options ?
Clinical scenario 2

- 45y. o. lady
- Inaugural seizure, right frontal tumor, → partial resection
- → Histology: astrocytoma grade III « with some oligodendroglial features »

Additional information required?
- Histology review, molecular markers

Treatment options?
Anaplastic Glioma (grade III)

- Anaplastic astrocytoma
- Oligodendroglialoma
- Oligo–astrocytoma (mixed)

GBM-O
Pathology Review and Molecular Characterization

- LOH 1p/19q
- *IDH* mutations

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**Histological diagnosis**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of Patients</th>
<th>%</th>
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<tbody>
<tr>
<td>Anaplastic astrocytoma,</td>
<td>97</td>
<td>60</td>
</tr>
<tr>
<td>eligible histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaplastic oligoastrocytoma,</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>eligible histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glioblastoma multiforme</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>Oligodendrogliomas</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Anaplastic oligodendroglioma</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Mixed astrocytoma</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Other gliomas</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>No histology</td>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>
IDH mutations carry a more favorable prognosis

Variable frequency of IDH mutations

- Anaplastic Astrocytoma
  - $P < 0.001$

- Glioblastoma
  - $P = 0.002$

Yan, Parsons … & Bigner. NEJM 2009, 360:765-73
Clinical scenario 2

- 45y. o. lady
- Inaugural seizure, right frontal tumor, → partial resection
- → Histology: astrocytoma grade III « with some oligodendroglial features »

Additional information required?

- Histology review, molecular markers

Treatment options?
Treatment of anaplastic glioma

- Standard of care (historic) → Radiotherapy (approx. 60 Gy)

**RANDOMIZED COMPARISONS OF RADIOTHERAPY AND NITROSOUREAS FOR THE TREATMENT OF MALIGNANT GLIOMA AFTER SURGERY**


The NEW ENGLAND JOURNAL OF MEDICINE 1980; 303:1323-29

- All malignant glioma (no MRI)
- 11% anaplastic glioma
- RT vs Semustine
- Median survival doubled from 4 → 8 mo
Chemotherapy for a chemosensitive disease?

Specific Genetic Predictors of Chemotherapeutic Response and Survival in Patients With Anaplastic Oligodendrogliomas

Multicenter Phase II Trial of Temozolomide in Patients With Anaplastic Astrocytoma or Anaplastic Oligoastrocytoma at First Relapse

Results: Progression-free survival (PFS) at 6 months, the primary protocol end point, was 46% (95% confidence interval, 38% to 54%). The median PFS was 5.4 months, and PFS at 12 months was 24%. The median overall survival was 13.6 months, and the 6- and 12-month survival rates were 75% and 56%, respectively. The objective response rate determined by independent central review of gadolinium-enhanced magnetic resonance imaging scans of the ITT population was 35% (8% complete response [CR], 27% partial response [PR]), with an additional 26% of patients with stable disease (SD). The median PFS for patients with SD was 4.4 months, with 33% progression-free at 6 months.
Anaplastic Glioma (grade III)

Time to 2nd treatment failure = primary endpoint

Sequence of treatment does not matter

Better outcome of oligos independent of tx (sequence)
Anaplastic Glioma (grade III)

Sequence of treatment does not matter

MGMT as a prognostic marker, independent of therapy

R

RT

Chemo-Tx

2nd failure (progression)

Time to 2nd treatment failure = primary endpoint

Wick …& Weller
J Clin Oncol 2009; 27:5874-5880

Time to 1st progression & MGMT

TTF (2nd progression)
Scenario 2: 45 y., anaplastic astrocytoma

Treatment options:

- Small tumor: → Radiotherapy
- Large tumor: → Chemotherapy

Evidence:

- German NOA-04 trial:
  - Treatment sequence dose not matter
    - Primary chemo → RT at progression
    - Primary RT → Chemo at progression
Chemo yes, but which chemo?

Brada et al.  
*J Clin Oncol* 28: 4601-8, 2010

No difference in outcome

Wick et al.  
Scenario 2: 45 y., anaplastic astrocytoma

Treatment options:
- → Radiotherapy
- → Chemotherapy
- → both

Diagnosis:
Anaplastic oligodendroglioma
LOH 1p/19q
PCV Chemotx for Oligos: PFS

van den Bent et al., J Clin Oncol 2006; 24:2715-22
Cairncross et al., J Clin Oncol 2006; 24:2707-14
Oligos: Genetics and Chemo

van den Bent et al., J Clin Oncol 2006; 24:2715-22

Cairncross et al., J Clin Oncol 2006; 24:2707-14
(Neo)adjuvant PCV for oligos: Long-term follow-up

van den Bent et al., ASCO 2012, abstr #2

Cairncross et al, ASCO 2012, abstr #2008b
Overall survival and molecular markers

- non-deleted (n=236)
  - Overall survival
  - HR: 0.83, 95% CI [0.62, 1.10]
  - P = 0.19

- 1p/19q co-deleted (n=80)
  - Overall survival
  - HR: 0.56, 95% CI [0.31, 1.03]
  - P = 0.059

van den Bent et al. Proc ASCO 2012, abstr # 3
Glioblastoma

- Radiation therapy combined with temozolomide followed by 6 cycles of temozolomide remains the standard of care for fit patients with GBM

- In elderly patients:
  - Standard RT over 6 weeks appears to be inadequate for elderly patients (>70 yrs). A hypofractionated schedule should be preferred
  - Exclusive chemotherapy with TMZ may be an adequate treatment in elderly patients with a methylated MGMT
Take Home Messages

- Grade III gliomas
  - IDH mutation status identifies patients with a better prognosis

- In oligodendrogliomas, 1p/19q co-deletion is a prognostic and predictive marker.
  - Longer survival for co-deleted oligo’s with (PCV-) chemotherapy given early in the course of disease (adjuvant or neo-adjuvant).
  - No benefit of adjuvant PCV in non-deleted anaplastic astrocytomas.
Disposition of the Presentation: *Focus on randomized trials*

- Glioblastoma
  - Newly diagnosed
    - Standard TMZ/RT, duration of adjuvant TMZ
    - Dose-dense vs standard dosing
    - Elderly
    - Role of MGMT
- Anaplastic Glioma
- Recurrent Glioma
Clinical scenario 1

- 65 y. o. gentleman
- right fronto-parietal tumor, → partial resection → Histology: glioblastoma
- Treatment with TMZ/RT → TMZ
- Recurrence/progression after cycle 5

- Additional information required ?
- Treatment options ?
Glioma Therapy

Resectable

Unresectable

\( S_x \) \( D_x \) \( B_x \)

1st line

\( TMZ/RT \rightarrow TMZ \)

Comparison:
EORTC-NCIC
NEJM 2005

1st Recurrence

Treatment options?

Comparison:
5 wks
7 months
8 months
15 months
GBM (glioma) recurrence: Treatment options

- Repeat surgery ± Gliadel®
- Re-irradiation (experimental)
- Chemotherapy:
  - FDA/EMEA approved: Temozolomide, Carmustine, Lomustine
  - Only FDA: Bevacizumab (Avastin®)
  - Irinotecan (CPT11)
  - Carboplatin
  - EGFR inhibitors
Progression-free survival

- Temozolomide
- Procarbazine

PFS_{6mo}:
- Temozolomide: 21% vs. Procarbazine: 8%
- P = 0.008

Prior chemo:
- n = 65 TMZ
- n = 73 PCZ
- \( {\text{OS}}_{\text{median}} \) TMZ 6.6 mo vs. PCZ 5.9 mo

No prior chemo:
- n = 37 TMZ
- n = 35 PCZ
- \( {\text{OS}}_{\text{median}} \) TMZ 7.5 mo vs. PCZ 5.3 mo

Yung et al. Br J Cancer 2000; 83: 588-593
Lomustine (CCNU) is an active agent (confirmed in 2009)

Enza CCNU

Progression-free survival

<table>
<thead>
<tr>
<th></th>
<th>Enza</th>
<th>CCNU</th>
<th>p-value</th>
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<tbody>
<tr>
<td>PFS6</td>
<td>11%</td>
<td>19%</td>
<td>0.13</td>
</tr>
<tr>
<td>RR</td>
<td>2.9%</td>
<td>4.3%</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Overall survival

<table>
<thead>
<tr>
<th></th>
<th>Enza</th>
<th>CCNU</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (95% CI)</td>
<td>ENZ 6.60 (5.22 to 7.75)</td>
<td>LOM 7.13 (6.01 to 8.80)</td>
<td>HR (95% CI), 1.20 (0.88 to 1.65)</td>
</tr>
</tbody>
</table>
**VEGF Inhibition**  
*(recurrent glioma)*

- **Bevacizumab** + CPT11  
  - *Vredenburgh et al.*  
  - *Clin Cancer Res 2007*

- **Cediranib**  
  - *Batchelor et al.*  
  - *Cancer Cell 11:83-95, 2007*

  - Day -1  
  - +1  
  - +27

- **Gd-MRI**

- **T2 FLAIR**

- **Permeability**
**Bevacizumab ± CPT 11 “BRAIN” trial**

**Design:**

→ Randomized Phase II

- **Recurrent GBM** (1st or 2nd Relapse; n=167)
- Stratification by:
  - KPS: 70-80, 90-100
  - 1st, 2nd relapse

1:1

- **Bevacizumab** (n=85)
- **Bevacizumab / CPT11** (n=82)

At PD

Optional: Bev +CPT-11

**1º Endpoint(s):**

- % alive + progression-free at 6 mo
- % alive at 6 mo
Bevacizumab at PD: add CPT11

Friedman et al.
JCO 27: 4733-40, 2009

Waterfall plot of tumor regression

RR 28%

RR 38%
Progression-free survival

- BV (n = 85) median PFS 4.2 months (95% CI, 2.9 to 5.8)
- BV + CPT-11 (n = 82) median PFS 5.6 months (95% CI, 4.4 to 6.2)

Overall survival

- BV (n = 85) median OS 9.2 months (95% CI, 8.2 to 10.2)
- BV + CPT-11 (n = 82) median OS 8.7 months (95% CI, 8.0 to 9.4)

Friedman et al.
JCO 27: 4733-40, 2009
REGAL Study (Cediranib)
Randomized phase III in recurrent GBM

Stratified by
- Age (>65) and
- Resection (salvage sx)

- Primary endpoint:
  - PFS

- 2° endpoints:
  - OS, PFS6, RR
PFS: based on central review T1 + T2/FLAIR

Batchelor on behalf of REGAL investigators. LBA#7, ESMO 2010

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Events</th>
<th>Median PFS</th>
<th>HR vs lom (95% CI)</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Ced</td>
<td>131</td>
<td>111 (85%)</td>
<td>85 days</td>
<td>1.02 (0.72, 1.45)</td>
<td>0.738</td>
</tr>
<tr>
<td>Ced + lom</td>
<td>129</td>
<td>99 (77%)</td>
<td>125 days</td>
<td>0.75 (0.53, 1.07)</td>
<td>0.153</td>
</tr>
<tr>
<td>Pla + lom</td>
<td>65</td>
<td>46 (71%)</td>
<td>47 days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The number of patients at risk denotes the number of patients event-free at the beginning of the period

HR = hazard ratio
Overall survival (OS)

Batchelor on behalf of REGAL investigators. LBA#7, ESMO 2010

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Events</th>
<th>Median OS</th>
<th>HR vs lom (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ced</td>
<td>131</td>
<td>86 (66%)</td>
<td>8.0 months</td>
<td>1.43 (0.96, 2.13)</td>
<td>0.112</td>
</tr>
<tr>
<td>Ced + lom</td>
<td>129</td>
<td>77 (60%)</td>
<td>9.4 months</td>
<td>1.14 (0.76, 1.71)</td>
<td>0.512</td>
</tr>
<tr>
<td>Pla + lom</td>
<td>65</td>
<td>34 (52%)</td>
<td>9.8 months</td>
<td></td>
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</tr>
</tbody>
</table>

*The number of patients at risk denotes the number of patients event-free at the beginning of the period

HR = hazard ratio
TMZ is the agent of first choice in chemotherapy-naive patients.

Nitrosoureas remain a valid treatment in malignant glioma.

VEGF pathway inhibitors:
- failed to prolong survival in recurrent GBM
- the value of inducing radiological response and reduction of peritumoral edema is however undisputed.
Thank you for your attention