- Iuchi Toshihiko et al: Tyrosine kinase inhibitors for brain mets of EGRF mutant adenocarcinoma of the lung

- Bruno Chauffert et al: RCT phase II of irinotecan + Bev as neoadjuvant + adj. to TMZ treated unresectable GBM (TEMAVIR ANOCEF) study

- Emeline Tabouret et al: Association of a strong plasma biomarker level with response and survival in patients treated with Bevacizumab for recurrent HGG

Christine Marosi
Medical University of Vienna
Disclosures

Christine Marosi received previously travel support, lecture honoraria and research funding from Roche.
Tyrosine kinase inhibitors without radiation therapy for brain metastases from EGFR-mutant adenocarcinoma of the lung

Toshihiko Iuchi¹, M. Shingyoji², T. Sakaida¹, S. Yokoi³, M. Itakura², K. Kawasaki¹, Y. Hasegawa¹, H. Kageyama³, T. Iizasa²
1. Neurological Surgery, Chiba Cancer Center, Chiba, JAPAN,
2. Thoracic Disease, Chiba Cancer Center, Chiba, JAPAN,
3. Cancer Diagnosis, Chiba Cancer Center Research Institute, Chiba, JAPAN
May radiotherapy be delayed to (certain) patients with brain metastases?

still a hot topic: brain metastases may affect 6% of the population

– ASCO 2006: W.Regine: The evidence favors whole brain radiotherapy
– Radiotherapy remains the mainstay of treatment of patients with BM
  • Gaspar LE et al: The role of whole brain radiation therapy in the management of newly diagnosed brain metastases:
  • Linskey ME, et al: The role of stereotactic radiosurgery in the management of patients with newly diagnosed brain metastases
  • both: J Neurooncology January 2010: systematic reviews and evidence-based clinical practice guideline.
– EORTC Study 22951/26001 Kocher et al: delay of WBRT in good prognostic patients duration of independent SV similar

Kocher M, Soffietti R,
J Clin Oncol. 2011;29):134-41
Treatment

Brain Metastases (EGFR mutant)

Gefitinib

Tm. Progression (intracranial/systemic)

Erlotinib

Tm. Progression (intracranial/systemic)

SRS/SRT and/or WBRT
Lesion Control

MST (95% C.I.)
- Time to 1st. relapse: 10.2m (8.2-16.1m)
- Time to Radiation: 14.9m (12.4-21.3m)
EGFR mutations

Ex19del
- CR: 43%
- PR: 57%
- 21 Cases

Others
- PD: 6%
- SD: 19%
- CR: 13%
- PR: 63%
- 16 Cases

p=0.049
### Adverse Events

**37 Cases**

*No Grade 4 Adverse Event*

**Grade 3 Adverse Events**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis</td>
<td>1</td>
<td>2.7%</td>
</tr>
<tr>
<td>Skin Rash</td>
<td>8</td>
<td>21.6%</td>
</tr>
<tr>
<td>Blood toxicity</td>
<td>2</td>
<td>5.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lymphocytopenia (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrocytopenia (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver dysfunction</td>
<td>4</td>
<td>10.8%</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>0</td>
<td>0.0%</td>
</tr>
</tbody>
</table>
HA-WBRT in conjunction with selective boosting

Metha M, ASCO 2011
Assessments of neurocognitive outcomes after WBRT +/- SRS in patients with brain metastases: 16 studies. 1648 patients

- Biphasic pattern of neurocognitive impairment:
  - Subacute, transient decline with a peak at 4 months
    (31-57% patients impaired at three months)
    > 4 points at MMSE, -2 SD at HVLT, COWA
  - Late delayed irreversible impairment months or years after WBRT, affecting more memory than motor functions
    48-85% patients impaired at 12 months

- Must be balanced against the detrimental cognitive effects of brain disease recurrence

Tallet et al. Radiation Oncology 2012, 7:77
Leukencephalopathy after WBRT + SRS vs SRS alone for metastatic lung cancer

similar initial white matter grading,
at 12 months: 40% grade, and 45% grade 3 white matter changes
at 24 months 25% grade 2 and 70% grade 3 white matter changes in the WBRT group

Monaco EA et al, Cancer June 15, 2012
Leukencephalopathy after WBRT + SRS vs SRS alone for metastatic lung cancer

2 exemplary patients

WBRT + SRS

A

B

C

26.5 months

SRS

D

E

F

22.3 months

Monaco EA et al, Cancer June 15, 2012
TKIs prevented the formation of metachronous brain metastases (B), but not progression of established brain metastases (C) as compared to chemotherapy.
RANDOMIZED MULTICENTER PHASE II TRIAL OF IRINOTECAN AND BEVACIZUMAB AS NEO-ADJUVANT AND ADJUVANT TO TEMOZOLOMIDE-BASED CHEMORADIATION VERSUS CHEMORADIATION FOR UNRESECTABLE GLIOBLASTOMA

DEFINITIVE RESULTS OF THE TEMAVIR ANOCEF STUDY

B. Chauffert
Medical Oncology, University Hospital, Amiens
FRANCE
**Study design**

**EXPERIMENTAL GROUP : B/I**

- Neo-adjuvant
  - BVZ 10 mg/kg
  - IRI 125 mg/m²
  - D1, D15, D29 & D43

- 2 months
- Therapeutic break-up
  - 1st MRI

- Chemoradiation
  - 3D-RT 60 Gy: 2Gy/fraction x 30
  - TMZ 75mg/m²/day
  - BVZ: 10mg/kg every 2 weeks

- 6 weeks
- Therapeutic break-up
  - 2nd MRI

- Adjuvant
  - BVZ: 10 mg/kg
  - IRI: 125 mg/m²
  - Every 2 weeks
  - MRI every 2 months

**CONTROL GROUP**

- Chemoradiation
  - 3D-RT 60 Gy: 2Gy/fraction x 30
  - TMZ 75mg/m²/day

- 6 weeks
- Therapeutic break-up
  - 1st MRI

- 6 months
- Adjuvant
  - TMZ 150-200 mg/m²/day
  - X 5 days/month
  - MRI every 2 months

Patients were randomly assigned to experimental arm or control arm (1/1 ratio), and stratified by:

- Mini Mental Status (MMSE) : < 27 vs ≥ 27
- Neurological Status: 0,1 or 2 vs 3,4
- Gender men vs women
- Age: < 50 ans vs ≥ 50 ans
- Center

**BVZ: bevacizumab, IRI: Irinotécan, TMZ: Témozolomide, MRI: Magnetic Resonance Imaging**

neoadjuvant phase delays begin of RT by 3 months + delay since biopsy
## Grade III-IV toxicities (%)

<table>
<thead>
<tr>
<th></th>
<th>Experimental group: B/I (60pts)</th>
<th>Control group (60 pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall toxicities</strong></td>
<td>46.3</td>
<td>37.7</td>
</tr>
<tr>
<td><strong>Hematological</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>8.8</td>
<td>9.3</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>1.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Anemia</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3.5</td>
<td>14.8</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>12.3</td>
<td>13.0</td>
</tr>
<tr>
<td><strong>Non Hematological</strong></td>
<td>40</td>
<td>27.8</td>
</tr>
<tr>
<td>Other infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomatitis</td>
<td>8.8</td>
<td>3.7</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>1.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Renal</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>0.0</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Data presented above were censored the 31st of August 2012, two years follow-up is still ongoing.
Kaplan Meier analysis was performed as secondary objective with an expected PFS at 6 months expected to be $\geq 66\%$. 

![Graph showing Progression Free-Survival (PFS)](image-url)

- **Experimental group**
- **Control group**

At 6 months, the survival rate is 65.01% [51.18\%: 75.82\%].
Comments

• Thanks ANOCEF!
  You don’t avoid difficult questions
• „negative“ trial does just not meet the goals designed by youself (before)
  – impact of delaying RT in the experimental group
  – impact of cross over
• acceptable toxicity – interesting QoL data: how is systemic toxicity, e.g. hypertension, diarrhea, skin rash perceived and managed by glioma patients and their relatives
  – How many patients stopped early in the experimental arm?
• Impressive TTP and OS data in a difficult patient population
  – Mc Namara: OS in patients with GBM and biopsy 4.5 mo, max: 6.3mo
• How would you design this trial today?
ASSOCIATION OF A STRONG CANDIDATE BIOMARKER PLASMA LEVEL WITH RESPONSE AND SURVIVAL IN PATIENTS TREATED WITH BEVACIZUMAB FOR RECURRENT HIGH GRADE GLIOMA

Emeline Tabouret
F. Boudouresque, M. Barrié, M. Matta, C. Boucard, A. Loundou, M. Ouafik, O. Chinot
1. Neurooncology, AP-HM Timone,
2. Umr 911, 3. Santé Publique, AMU, Marseille
FRANCE
Circulating markers of angiogenesis, inflammation and coagulation in patients with glioblastoma
Reynes et al. J NeuroOncol 2011;102:35-41

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=40)</th>
<th>Controls (n=60)</th>
<th>comment</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>COAGULATION</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prothrombin factors 1&amp;2 (nmol/l)</td>
<td>0.42 ± 0.5</td>
<td>0.2 ± 0.05</td>
<td>x2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tissue factor (pg/ml)</td>
<td>154 ± 93</td>
<td>153 ± 59</td>
<td>=</td>
<td>NS</td>
</tr>
<tr>
<td>Endogenous thrombin generation (UI/ml)</td>
<td>10.9 ± 3.4</td>
<td>8.7 ± 2.4</td>
<td>+25%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>INFLAMMATION</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>3.5 ± 7.1</td>
<td>0.7 ± 0.4</td>
<td>x7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TNFalpha (pg/ml)</td>
<td>1.1 ± 0.9</td>
<td>0.6 ± 0.2</td>
<td>x2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>300 ± 156</td>
<td>232 ± 31</td>
<td>+25%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sialic acid (mg/dl)</td>
<td>71 ± 22</td>
<td>55 ± 10</td>
<td>+40%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>17 ± 26.6</td>
<td>1.8 ± 2.7</td>
<td>x10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>ANGIOGENESIS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VEGF (pg/ml)</td>
<td>268 ± 186</td>
<td>123 ± 64</td>
<td>x2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>sVEGF-R1 (pg/ml)</td>
<td>89 ± 29</td>
<td>77 ± 17</td>
<td>+15%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Thrombospondin-1 (ug/ml)</td>
<td>47 ± 14</td>
<td>46 ± 10</td>
<td>=</td>
<td>NS</td>
</tr>
</tbody>
</table>
matrix metalloproteinases

- conserved in evolution from hydra to man
- depend on metal ions (zinc) for catalytic activity
- degrade structural proteins of the extracellular matrix & cell surface proteins, thus involved in signalling & motility

MMP-2: gelatinase A
expression significantly elevated
in glioma cells WHO II-IV
involved in glial invasion & angiogenesis

MMP-9: gelatinase B
expressed in blood vessels
at proliferating margins of glioma
Involved in neoangiogenesis

matrix metalloproteinases and glioma

- 640 hits in PUB Med
- involved in cell motility, invasiveness and angiogenesis – potential targets or markers?

A complete compilation of matrix metalloproteinase expression in human malignant gliomas

Carsten Hagemann, Jelena Anacker, Ralf-Ingo Ernestus, Giles H Vince
Results (cohort 1): **MMP 9** baseline level

<table>
<thead>
<tr>
<th></th>
<th>Low MMP9 N=13</th>
<th>High MMP9 N=12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Non-Responders</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Response rate</td>
<td>61.5%</td>
<td>33.3%</td>
</tr>
<tr>
<td>PFS (months)</td>
<td>8.2</td>
<td>3.7</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.4-15.0</td>
<td>2.9-4.6</td>
</tr>
<tr>
<td>OS (months)</td>
<td>12.3</td>
<td>6.9</td>
</tr>
<tr>
<td>95% CI</td>
<td>0-26.1</td>
<td>4.6-9.3</td>
</tr>
</tbody>
</table>

Overall Survival

- HR: 3.487, p = 0.015

Progression-Free Survival

- HR: 4.290, p = 0.007

OK
cohort 2 showed no effect - so no other cohorts, no hypothesis on MMP-9?
### Results (cohort 1): MMP 2 baseline level

- **ROC**
  - **AUC 0.827 (0.624-0.947)**
  - **p = 0.0017**
  - **Cut-off (227,2)**
  - **Se = 83.3 (51.6-97.9)**
  - **Sp = 92.31 (64.99-81)**

#### Cohort 3: without Bevacizumab

<table>
<thead>
<tr>
<th></th>
<th>Low MMP2</th>
<th>High MMP2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Responders</strong></td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td><strong>Non-Responders</strong></td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td><strong>Response rate</strong></td>
<td>15.4%</td>
<td>83.3%</td>
</tr>
<tr>
<td><strong>PFS (months)</strong></td>
<td>3.0</td>
<td>5.9</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>2.5-3.5</td>
<td>4.0-7.8</td>
</tr>
<tr>
<td><strong>OS (months)</strong></td>
<td>7.3</td>
<td>12.8</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>5.2-9.4</td>
<td>10.4-15.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Low MMP2</th>
<th>High MMP2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N = 17</strong></td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td><strong>N = 3</strong></td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td><strong>Response rate</strong></td>
<td>24%</td>
<td>3%</td>
</tr>
<tr>
<td><strong>PFS (months)</strong></td>
<td>3.1</td>
<td>7.7</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>1.0-5.1</td>
<td>4.0-11.4</td>
</tr>
<tr>
<td><strong>OS (months)</strong></td>
<td>5.8</td>
<td>8.9</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>3.0-8.5</td>
<td>3.2-14.6</td>
</tr>
</tbody>
</table>
MMP-2: elevated plasma levels

- acute coronary infarction
- acute coronary syndrome
- aortic dilatation
- emphysema, COPD
- infectious meningitis
- breast cancer, lung cancer
- bladder cancer
- viral liver disease
- acute pulpitis
- psoriasis
- venous ulcers
- macula degeneration
- arthritis, rheumatic diseases
- direct inguinal hernia
- any inflammatory reaction

A single blood level – in 15 patients! – is not suitable to define „high level of MMP-2“ as a predictive marker given the lack of specificity. But this remains an interesting finding & kinetics could be informative.
Thank you for your attention

any questions?