CNS metastases and systemic treatment options

Dr WHENHAM Nicolas

BSMO symposium, Friday 24th February 2017
Complete and prolonged response

Salivary duct carcinoma (parotid) with androgen receptor positivity treated with Androgen Deprivation Therapy

January 2010

January 2012
CNS metastases and systemic treatment options

• Brain metastases are only a part of a disseminated disease that require systemic therapy
• Treatment must be function of the primary tumor, histology and molecular biology
CNS metastases and systemic treatment options

• Most clinical trials excluded patients with brain metastases

• Evidence comes from case reports, small series, retrospective analyses and a limited number of prospective phase II trials

• Major flaws in design
  • Multiple histologies, various stages
  • Rarely randomized
  • Small sample sizes
  • Inadequate statistics and endpoints
  • Competing risks

Level I of evidence
What is the best timing for systemic therapies?

- Primary prevention (time until brain metastases)
- Therapy concurrent with WBRT/SRS (« radiation sensitizers »)
- Secondary prevention (time until new metastasis outside the SRS bed)
- Progression after WBRT

Primary tumor

Adjuvant therapies

Metastatic disease

X lines of systemic therapies
For extracranial disease

Brain Metastases

SRS

WBRT

Death

BSC
Gap between enthusiasm with new drugs and real life....

Why do oncologists give chemo at the end of life?...

Median survival only minimally improved in the most recent patients
(from 3.2 to 3.9 months, between 1990 and 2010)
Low 2-year survival rate : 8%

The real impact of systemic therapies (chemotherapy and targeted therapy) is not really known at present in the context of brain metastases
Classical point of view of the oncologist

- FACTORS AFFECTING RESPONSIVENESS
  - Blood brain barrier
  - Chemosensitivity
Blood Brain Barrier

<table>
<thead>
<tr>
<th>Drug</th>
<th>CSF penetration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrosoureas (ACNU, BCNU; CCNU, Fotemustine)</td>
<td>++</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>++</td>
</tr>
<tr>
<td>Thiotepa</td>
<td>+</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>(+)</td>
</tr>
<tr>
<td>Temozolomide</td>
<td>++</td>
</tr>
<tr>
<td>Cyclophosphamide, Ifosfamide</td>
<td>+/-</td>
</tr>
<tr>
<td>Cytosinarabinosid</td>
<td>++</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>+/-</td>
</tr>
<tr>
<td>5-FU</td>
<td>(++)</td>
</tr>
<tr>
<td>Anthracyclins</td>
<td>-</td>
</tr>
<tr>
<td>Liposomal doxorubicine</td>
<td>++</td>
</tr>
<tr>
<td>VM26</td>
<td>+/-</td>
</tr>
<tr>
<td>Etoposide</td>
<td>+/-</td>
</tr>
<tr>
<td>Vincaalkaloids, Taxanes</td>
<td>-</td>
</tr>
<tr>
<td>Topotecan</td>
<td>++</td>
</tr>
<tr>
<td>Cisplatin, Carboplatin</td>
<td>++</td>
</tr>
</tbody>
</table>

++ : CSF concentration 20-30% of serum concentration
+ : CSF concentration 10% of serum concentration
− : CSF concentration <5% of serum concentration

Chamberlain et al. NeuroOncology 2017
Immunotherapy

- Brain is no more considered as a sanctuary

- Brain metastases may contain pre-existing tumor infiltrating lymphocytes

- Immune modulation may allow cytotoxic T cells to penetrate into the microenvironment in the brain resulting in antitumor immunity

- No data of drug penetration (antibodies) in on-treatment human brain tissue

Tumor infiltrating lymphocytes and expression of programmed death ligand 1 (PD-L1) in melanoma brain metastases (Berghoff et al, Histopathol 2014)
Immunotherapy: some key messages

- Checkpoint inhibitors (anti-CTLA-4 and anti-PD1/PDL1) have shown promising results in a small number of early clinical trials concerning non-irradiated (asymptomatic, no steroids) brain metastases from melanoma and NSCLC
Ipilimumab in patients with melanoma and brain metastases: an open-label phase II trial (Margolin et al. Lancet Oncol 2012)

- 72 patients
- Two cohorts:
  - A: 51 asymptomatic patients, not on corticosteroids
  - B: 21 symptomatic patients, taking a corticosteroid
- Ipilimumab 10mg/kg/3w (induction phase) then 10mg/kg/12w
- Two cohorts:
  - A: response rate of 25% (13/51), OS 7.0 months
  - B: response rate of 5% (1/21), OS 3.7 months
Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase II trial (Goldberg et al. Lancet Oncol 2016)

- 36 patients: 18 melanoma – 18 NSCLC
- Asymptomatic (no steroids), brain mets < 2cm
- Pembrolizumab 10mg/kg q 2w
- Response rate
  - Melanoma: 22% (6-month OS 47%)
  - NSCLC: 33% (median OS 7.7 months)
- Concordance of response in systemic disease and brain metastases
- Sustained responses over many months
Immunotherapy: some key messages

- Validation will come with larger studies in different tumor types
- Biomarkers via extra-cerebral biopsies if concordance of response is persistently observed

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Therapy tested</th>
<th>Cancer type</th>
<th>Estimated enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02460068</td>
<td>Multicenter, randomized, phase III</td>
<td>Fotemustine vs. Fotemustine/ipilimumab vs ipilimumab/nivolumab</td>
<td>Melanoma</td>
<td>168</td>
</tr>
<tr>
<td>NCT02621515</td>
<td>Multicenter, phase II</td>
<td>Nivo in symptomatic BM</td>
<td>Melanoma</td>
<td>70</td>
</tr>
<tr>
<td>NCT02320058</td>
<td>Multicenter, phase II</td>
<td>Nivo/ipi followed by nivo</td>
<td>Melanoma</td>
<td>110</td>
</tr>
<tr>
<td>NCT02374242</td>
<td>Multicenter, phase II</td>
<td>Nivo/ipi</td>
<td>Melanoma</td>
<td>75</td>
</tr>
<tr>
<td>NCT02085070</td>
<td>Single-center, phase II</td>
<td>Pembrolizumab</td>
<td>Melanoma, NSCLC</td>
<td>64</td>
</tr>
</tbody>
</table>
Immunotherapy: some key messages

• Several retrospective case series suggest checkpoint inhibitors can be safely combined with radiation therapies *but*
  • we have to follow possible drug-related toxicities such as perilesional edema
  • detrimental effect of concomitant use of steroids
Can immunotherapy potentiate radiation therapy (radio-sensitizing effect) to obtain better intracranial disease control?

Can radiotherapy potentiate immunotherapy (abscopal effect) to achieve better extracranial disease control?

• D’Souza et al, 2016
Ipilimumab and radiation therapy for melanoma brain metastases
Silk et al, Cancer Med 2013

Retrospective analysis of 70 patients

<table>
<thead>
<tr>
<th>OS</th>
<th>No ipilimumab</th>
<th>Ipilimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>5.3m</td>
<td>18.3m</td>
</tr>
<tr>
<td>WBRT</td>
<td>5.3m</td>
<td>3.1m</td>
</tr>
<tr>
<td>SRS</td>
<td>4.0m</td>
<td>19.9m</td>
</tr>
</tbody>
</table>

Stereotactic radiosurgery for melanoma brain metastases in patients receiving ipilimumab: safety profile and efficacy of combined treatment

Retrospective analysis of 46 patients

Patients treated with SRS during or before Ipi had better OS and less regional recurrence (RR) than those treated with SRS after Ipi (1-yr OS 65% vs. 56% vs. 40%, p=0.008; 1-yr RR 69% vs. 64% vs. 92%, p=0.003).

15 patients SRS during Ipi
- CNS bleeding in 2 patients (13%)
- Seizure in 2 patients (13%)
- Need for steroids > 2 weeks in 5 patients (33%)
- Increase of treated tumor in 50% (vs 13% if SRS after Ipi)
<table>
<thead>
<tr>
<th>Study phase</th>
<th>Institution/group</th>
<th>ClinicalTrials.gov ID</th>
<th>Disease site</th>
<th>Cohorts</th>
<th>Planned accrual</th>
<th>IT mechanism</th>
<th>Est. completion date</th>
<th>Primary outcome measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Multi-institutional (CheckMate548)</td>
<td>NCT02667587</td>
<td>Newly diagnosed glioblastoma</td>
<td>Nivolumab + temozolomide + RT vs. placebo + temozolomide + RT</td>
<td>n = 320</td>
<td>anti-PD-1</td>
<td>May 2017</td>
<td>OS</td>
</tr>
<tr>
<td>III</td>
<td>Multi-institutional (CheckMate498)</td>
<td>NCT02617589</td>
<td>Newly diagnosed glioblastoma</td>
<td>Nivolumab + RT vs. temozolomide + RT</td>
<td>n = 550</td>
<td>anti-PD-1</td>
<td>October 2019</td>
<td>OS</td>
</tr>
<tr>
<td>II</td>
<td>Ludwig Institute for Cancer Research</td>
<td>NCT02336165</td>
<td>Newly diagnosed, recurrent glioblastoma</td>
<td>MEDI4736 vs. MEDI4736 + standard RT vs. MEDI4736 + bevacizumab</td>
<td>n = 108</td>
<td>anti-PD-1</td>
<td>July 2017</td>
<td>OS, PFS</td>
</tr>
<tr>
<td>I/II</td>
<td>Northwestern University</td>
<td>NCT02530502</td>
<td>Newly diagnosed glioblastoma</td>
<td>RT + temozolomide + pembrolizumab → temozolomide</td>
<td>n = 50</td>
<td>anti-PD-1</td>
<td>March 2018</td>
<td>Dosage, PFS, OS</td>
</tr>
<tr>
<td>I</td>
<td>H. Lee Moffitt Cancer Center</td>
<td>NCT02313272</td>
<td>Recurrent glioma</td>
<td>HFSRT + pembrolizumab + bevacizumab</td>
<td>n = 32</td>
<td>anti-PD-1</td>
<td>June 2017</td>
<td>Dosage</td>
</tr>
<tr>
<td>I</td>
<td>MD Anderson Cancer Center</td>
<td>NCT02696993</td>
<td>NSCLC BM</td>
<td>Nivolumab + SRS; nivolumab + WBRT; nivolumab + ipilimumab + SRS; nivolumab + ipilimumab + WBRT</td>
<td>n = 130</td>
<td>anti-PD-1; anti-CTLA-4</td>
<td>April 2020</td>
<td>Dosage; PFS</td>
</tr>
<tr>
<td>II</td>
<td>Grupo Español Multidisciplinar de Melanoma (GEM)</td>
<td>NCT02115139</td>
<td>Melanoma BM</td>
<td>Ipilimumab + WBRT</td>
<td>n = 66</td>
<td>anti-CTLA-4</td>
<td>October 2016</td>
<td>1-year survival rate</td>
</tr>
<tr>
<td>II</td>
<td>University of Michigan Cancer Center</td>
<td>NCT02097732</td>
<td>Melanoma BM</td>
<td>Ipilimumab → SRS → ipilimumab vs. SRS → ipilimumab</td>
<td>n = 40</td>
<td>anti-CTLA-4</td>
<td>May 2017</td>
<td>Local control rate</td>
</tr>
<tr>
<td>I</td>
<td>Thomas Jefferson University</td>
<td>NCT01703507</td>
<td>Melanoma BM</td>
<td>Ipilimumab + WBRT vs. ipilimumab + SRS</td>
<td>n = 24</td>
<td>anti-CTLA-4</td>
<td>November 2017</td>
<td>Dosage</td>
</tr>
<tr>
<td>I</td>
<td>Sidney Kimmel Comprehensive Cancer Center</td>
<td>NCT01950195</td>
<td>Melanoma BM</td>
<td>Ipilimumab + SRS</td>
<td>n = 30</td>
<td>anti-CTLA-4</td>
<td>December 2016</td>
<td>Adverse events and safety</td>
</tr>
<tr>
<td>II</td>
<td>University Hospital, Lille</td>
<td>NCT02662725</td>
<td>Melanoma BM</td>
<td>Ipilimumab + SRS</td>
<td>n = 73</td>
<td>anti-CTLA-4</td>
<td>December 2015</td>
<td>OS</td>
</tr>
</tbody>
</table>

Current clinical trials of immunotherapy with radiation for primary and metastatic CNS malignancy.

Rational for combination
What about consequences of delayed onset of response and inflammatory treatment effects observed with immunotherapy?

D’Souza et al
Frontiers in Oncology 2016
Oncogen-driven targeted therapies

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>ONCOGEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC</td>
<td>EGFR</td>
</tr>
<tr>
<td>NSCLC</td>
<td>ALK</td>
</tr>
<tr>
<td>Breast</td>
<td>HER2</td>
</tr>
<tr>
<td>Melanoma</td>
<td>BRAF</td>
</tr>
</tbody>
</table>
Lung Cancer

• 25-40% NSCLC develop brain metastasis during the course of the disease

• TKIs against active oncogenes are effective in brain metastases (EGFR mutation and ALK gene rearrangements)


<table>
<thead>
<tr>
<th></th>
<th>EGFR mutated</th>
<th>ALK rearranged</th>
<th>EGFR/ALK negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy prior to TKI</td>
<td>56%</td>
<td>38%</td>
<td>100%</td>
</tr>
<tr>
<td>ORR (CR+PR)</td>
<td>81%</td>
<td>84%</td>
<td>33%</td>
</tr>
<tr>
<td>OS</td>
<td>52months</td>
<td>74months</td>
<td>25months</td>
</tr>
<tr>
<td>TKI upfront subgroup</td>
<td>PR 13/13</td>
<td>CR 4/18 and PR 14/18</td>
<td>n.a.</td>
</tr>
</tbody>
</table>
## Prognosis

<table>
<thead>
<tr>
<th>Subtype of NSCLC</th>
<th>Median OS with BM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular unselected NSCLC</td>
<td>3-15months</td>
</tr>
<tr>
<td>ALK-positive</td>
<td>26-27months</td>
</tr>
<tr>
<td>EGFR-mutated</td>
<td>14-17months</td>
</tr>
<tr>
<td><em>Wild-type</em></td>
<td>6-12months</td>
</tr>
<tr>
<td>KRAS-mutated</td>
<td>6-7months</td>
</tr>
</tbody>
</table>

### Score GPA

<table>
<thead>
<tr>
<th>Score GPA</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&gt;60y</td>
<td>50-59y</td>
<td>&lt;50y</td>
</tr>
<tr>
<td>KPS</td>
<td>&lt;70</td>
<td>70-80</td>
<td>&gt;80</td>
</tr>
<tr>
<td>Num BM</td>
<td>&gt;3</td>
<td>2-3</td>
<td>1</td>
</tr>
<tr>
<td>Extra CNS</td>
<td>yes</td>
<td>-</td>
<td>no</td>
</tr>
</tbody>
</table>

0-1.0 -> 3.0months  
1.5-2.0 -> 5.5months  
2.5-3.0 -> 9.4months  
3.5-4.0 -> 14.8months  
Sperduto, 2012

Mak 2015, Wang 2015
**EGFR** (10% among Caucasians)

- Prospective studies (in selected patients) with upfront erlotinib or gefitinib alone at the time of diagnosis of BM in EGFR-TKI naïve patients have demonstrated objective response rates of 70% to 89%

- EGFR-TKIs are more effective at penetrating the blood-brain barrier than conventional chemotherapy but first-generation TKIs have again limited CSF concentrations

- Third-generation EGFR TKIs are in various phases of clinical investigation, better CNS penetration, ex. AZD-3759 (Zeng et al)
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>EGFR TKI</th>
<th>Concurrent Local Treatment</th>
<th>N, characteristics</th>
<th>ORR</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iuchi et al</td>
<td>Phase II</td>
<td>Gefitinib</td>
<td>none</td>
<td>41 Japanese patients</td>
<td>87%</td>
<td>21.9months</td>
</tr>
<tr>
<td>Kim et al</td>
<td>Phase II</td>
<td>Gefitinib or Erlotinib</td>
<td>none</td>
<td>31 Korean, non-smoker, EGFR mutant patients</td>
<td>96%</td>
<td>18.8months</td>
</tr>
<tr>
<td>Welsh et al</td>
<td>Phase II</td>
<td>Erlotinib</td>
<td>WBRT</td>
<td>40 patients</td>
<td>86%</td>
<td>11.8months</td>
</tr>
<tr>
<td>Lee et al</td>
<td>Phase II</td>
<td>Erlotinib</td>
<td>WBRT</td>
<td>40 patients EGFR-wt, multiple BM</td>
<td>-</td>
<td>3.4months</td>
</tr>
<tr>
<td>Ceresoli et al</td>
<td>Phase II</td>
<td>Gefitinib</td>
<td>none</td>
<td>41 patients</td>
<td>27%</td>
<td>5months</td>
</tr>
<tr>
<td>Sperduto et al</td>
<td>Phase III</td>
<td>Erlotinib</td>
<td>WBRT plus SRS</td>
<td>41 patients</td>
<td>-</td>
<td>6.1months</td>
</tr>
<tr>
<td>Hoffknecht et al</td>
<td>Retrospective</td>
<td>Afatinib</td>
<td>-</td>
<td>35 evaluable patients pretreated with 1st-line EGFR TKI</td>
<td>35%</td>
<td>-</td>
</tr>
<tr>
<td>Grommes et al</td>
<td>Phase I/II</td>
<td>High-dose Erlotinib</td>
<td>none</td>
<td>9 patients pretreated with 1st-line EGFR TKI</td>
<td>78%</td>
<td>12months</td>
</tr>
</tbody>
</table>
EGFR TKI ready for prime-time?

• Temptation is to use EGFR-TKI alone as first-line treatment
  • not delay extracranial disease treatment
  • potentially avoiding the toxicities of local therapies

• Ongoing trials investigating the use of upfront TKI:
  • for example, erlotinib with WBRT given at initial presentation or disease progression in patients with EGFR-mutant lung adenocarcinoma who develop BM (clinicaltrials.gov ID NCT01763385)
Retrospective data on 50 patients

Erlotinib alone and radiotherapy after progression: OS 19 months

Upfront WBRT/SRS + erlotinib (after 1-2 weeks): OS 34 months

Key message
use of upfront EGFR-TKI and deferral of RT may result in inferior OS
-> need for randomized trials
ALK (only 2-7%)

- Recent multicenter analysis of ALK-positive NSCLC with CNS disease reported a median survival time of 49.5 months (!) from the onset of brain metastases. Favorable prognostic factors in this study included the absence of extracranial metastases and a high Karnofsky performance score (Johung, 2016)

- Poor CNS penetration of crizotinib (first-line therapy)
- Prior to peripheral tumor resistance, up to 40% to 50% of patients on crizotinib may initially develop brain metastases
- Second-generation ALK inhibitors (ceritinib, alectinib, brigatinib, lorlatinib) have more activity in the brain in part because of improved BBB penetration

87 patients
16 patients with baseline CNS disease
Primary endpoint: % objective response

**Best overall CNS response to alectinib** This waterfall plot illustrates the best overall intracranial responses among 16 patients with baseline measurable CNS disease according to the IRC. Four patients achieved a complete response (CR), and eight patients achieved a partial response (PR). The remaining four patients had stable disease (SD) as their best response. Asterisks indicate those patients who did not receive prior radiation therapy for their CNS disease.
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>ALK TKI</th>
<th>Prior therapy</th>
<th>N, characteristics</th>
<th>ORR (CR+PR)</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costa et al</td>
<td>retrospective</td>
<td>Crizotinib</td>
<td>60% WBRT</td>
<td>275 patients, asymptomatic BM</td>
<td>33%</td>
<td>74% at 6mo</td>
</tr>
<tr>
<td>Shaw et al</td>
<td>Phase I</td>
<td>Ceritinib</td>
<td>79% ALK inhibitor</td>
<td>74 patients</td>
<td>35%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Gadgeel et al</td>
<td>Phase II</td>
<td>Alectinib</td>
<td>81% WBRT Chemo and crizotinib</td>
<td>21 patients</td>
<td>52%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Ou et al</td>
<td>Phase II</td>
<td>Alectinib</td>
<td>crizotinib</td>
<td>34 patients</td>
<td>57%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Gandhi et al</td>
<td>Phase II</td>
<td>Alectinib</td>
<td>crizotinib</td>
<td>16 patients</td>
<td>69%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Camidge et al</td>
<td>Phase II</td>
<td>Brigatinib</td>
<td>All therapies allowed</td>
<td>12 patients</td>
<td>50%</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
## Breast Cancer

<table>
<thead>
<tr>
<th></th>
<th>Risk of BM at ten years</th>
<th>% BM in case of metastatic disease</th>
<th>Median time before BM</th>
<th>Median survival from diagnosis of BM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>0.7%</td>
<td>7.6%</td>
<td>47.4m</td>
<td>10.0 months</td>
</tr>
<tr>
<td>Luminal B</td>
<td>12%</td>
<td>10.8%</td>
<td>54.4m</td>
<td>22.9 months</td>
</tr>
<tr>
<td>HER2+</td>
<td>12%</td>
<td>25-49%</td>
<td>35.8m</td>
<td>17.9 months</td>
</tr>
<tr>
<td>Triple-negative</td>
<td>7%</td>
<td>25-46%</td>
<td>27.5m</td>
<td>7.3 months</td>
</tr>
</tbody>
</table>

HR are lost or altered in > 50% when BM occur

- Simultaneous progression of extracranial disease
- Often with stable extracranial disease In the *trastuzumab - era*

Chemotherapy?

• Old case series
  • 100 patients with brain metastases from breast cancer
  • variety of chemotherapy regimens
  • objective response rate of 50 percent with median duration of response of 7 months
  • But patients were untreated compared with the current era (<10% adjuvant chemotherapy)
**HER2**

- **Trastuzumab:**
  - poor CNS penetration in the context of an intact BBB (high molecular weight)
  - several studies have suggested that trastuzumab may cross the BBB in the context of BM (breakdown of the BBB) and responses of brain metastases have been reported in the clinic, but prospective clinical trial data are lacking.

- **Lapatinib:**
  - small molecule inhibitor HER2/EGFR > better bioavailability in the CNS
  - lapatinib plus capecitabine is currently the best established systemic therapy option for brain metastases

- **Pertuzumab:**
  - no data except clinical cases, in particular BM excluded from clinical trials supporting combination of trastuzumab, pertuzumab and taxanes as recommended first-line

- **T-DM1 (trastuzumab plus emtansine):**
  - Retrospective analysis of EMILIA trial: protective efficacy similar to that of lapatinib + capecitabine against BM
  - Bartsch et al
    - 10 patients: highly pretreated patients with progressive BM
    - 3/10 partial response; 2/10 stable disease (>6months)

Kirsch et al, JCO 2005
**LANDSCAPE trial**
45 patients, previously untreated brain metastases, HER2-positive
Phase II, single-arm
lapatinib (1250 mg daily) plus capecitabine (2000 mg/m² on days 1 to 14 of a 21-day cycle)
Bachelot et al, Lancet Oncol 2013

**Overall survival at 6 months : 91%**
Median OS : 17 months

For women with brain metastases from HER2-positive disease, the administration of systemic therapy may delay the use of WBRT in LANDSCAPE trial : median time to radiotherapy was 8.3 months

**median time to progression : 5.5 months**

**ORR (PR) : 66%**

**median time to progression : 5.5 months**
Melanoma

• Low incidence of BM in stage I/II but some late CNS relapse

• Risk of BM in advanced melanoma (stage IV) increases with disease duration: 20-30% by 1 year and 30-40% by 3 years

• High propensity for spontaneous hemorrhage

• Historical very poor prognosis

• Classical prognosis instruments (RPA, GPA) don’t take into account new effective systemic melanoma therapy.
Chemotherapy


• Temozolomide (known to definitively cross BBB) induce responses in only 7% of melanoma brain metastasis patients
CTLA-4 and PD-1 inhibitors

- **Ipilimumab** (Margolin et al)
  - 51 patients
  - asymptomatic BM without corticosteroid
  - ORR 16% - CNS disease control rate 24%
  - 2y survival 26%

- **Ipilimumab + Fotemustine** (DiGiacomo et al)
  - Median OS: 12.7 months in BM patients

- Checkpoint inhibitors and melanoma: intracranial response rate 26% (ESMO 2016, abstract 1114)

- Several trials are ongoing to specifically investigate safety and efficacy of checkpoint inhibitors in melanoma brain metastases
Targeted therapies

BRAF and/or MEK inhibitors

40-60% of melanoma harbor a BRAF *driver* mutation (BRAF V600)

BRAF inhibitors are associated with quick-onset regressions

Efficacy is improved when used in combination with MEK inhibitor
Two-Cohort Open-Label Study of Dabrafenib in Patients With Brain Metastases

Screened (N = 325)
Enrolled (n = 172)

- Metastatic melanoma
- Centrally confirmed BRAF V600E mutation
- Asymptomatic brain metastases
- No prior treatment with MEK or BRAF inhibitors

Cohort A (n = 89)
(no prior brain treatment)

Cohort B (n = 83)
(prior brain treatment)

Dabrafenib 150 mg bid

No prior brain treatment: Cohort A

- ORR: 39%
- DCR: 81%
- Overall DCR: 80%

Prior brain treatment: Cohort B

- ORR: 31%
- DCR: 89%
- Overall DCR: 83%

Kirkwood et al., 2012.
### Table: Clinical Trials of BRAF Inhibitors for BM

<table>
<thead>
<tr>
<th>Study</th>
<th>Number and type of patients</th>
<th>Any prior local therapy for BM</th>
<th>Targeted therapy</th>
<th>ORR (CR+PR)</th>
<th>Median duration of intracranial response</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long et al</td>
<td>139 patients BRAF-V600E mutant</td>
<td>47%</td>
<td>Dabrafenib</td>
<td>68%</td>
<td>4.6months</td>
<td>7.6months</td>
</tr>
<tr>
<td>Long et al</td>
<td>33 patients BRAF-V600K mutant</td>
<td>54%</td>
<td>Dabrafenib</td>
<td>28%</td>
<td>3.8months</td>
<td>5.0months</td>
</tr>
<tr>
<td>Dummer et al</td>
<td>24 patients BRAF-V600 mut Symptomatic BM</td>
<td>NR</td>
<td>Vemurafenib</td>
<td>42%</td>
<td>4.4months</td>
<td>5.3months</td>
</tr>
<tr>
<td>Kefford et al</td>
<td>146 patients BRAF mut</td>
<td>38%</td>
<td>Vemurafenib</td>
<td>19%</td>
<td>3.8months</td>
<td>8.0months</td>
</tr>
</tbody>
</table>

- **Serious skin toxicity with the combination of BRAF inhibitors and radiotherapy**
- Dual BRAF and MEK inhibition is now established as the standard of care -> waiting data about efficacy in patients with BM
Renal Cell Carcinoma

• BM : 3.5-17% of RCC
• Median OS : 10.7 months (OS rates 1y:48%, 2y:30%, 3y:12%), Shuch et al, 2008
• Rare (2%) without lung or bone metastases
• Most significant prognostic factors are performance status and the number of BM, not histology
Anti-VEGF therapy is not associated with an increased frequency of intracerebral bleeding (Carden et al, NeuroOncology, 2008)

<table>
<thead>
<tr>
<th>Phase I/II studies with anti-VEGF therapy (up to 2007)</th>
<th>N patients</th>
<th>CNS bleeding N (%)</th>
<th>Outside CNS bleeding (≥grade 3) N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain Metastases EXCLUDED</td>
<td>1711</td>
<td>2 (&lt;1%)</td>
<td>44 (3%)</td>
</tr>
<tr>
<td>Brain Metastases INCLUDED</td>
<td>524</td>
<td>1 (&lt;1%)</td>
<td>8 (2%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Randomized trials with anti-VEGF therapy (up to 2007)</th>
<th>N patients</th>
<th>CNS bleeding N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain Metastases EXCLUDED</td>
<td>5476</td>
<td>9 (&lt;1%)</td>
</tr>
<tr>
<td>Brain Metastases INCLUDED</td>
<td>312</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trials with anti-VEGF therapy (up to 2007)</th>
<th>N patients</th>
<th>CNS bleeding N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Targeted at active brain metastases</td>
<td>121</td>
<td>0</td>
</tr>
<tr>
<td>In high grade gliomas</td>
<td>199</td>
<td>0</td>
</tr>
</tbody>
</table>
Toxicity

- Toxicities related to a multimodality treatment of patients with BM from RCC.

<table>
<thead>
<tr>
<th>Study Patients (N)</th>
<th>Target therapy</th>
<th>RT locoregional treatment n (%)</th>
<th>CNS toxicity Type N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bastos et al. [2014] 53</td>
<td>Su, So, Beva, pazopanib, axitinib</td>
<td>36 (55)</td>
<td>Brain metastasis haemorrhage 3 (5)</td>
</tr>
<tr>
<td>12</td>
<td>Eve, tem</td>
<td>18 (28)</td>
<td>Radiation necrosis 2 (3)</td>
</tr>
<tr>
<td>Verma et al. [2011] 41</td>
<td>no TKI</td>
<td>47 (58)</td>
<td>Radiation necrosis 4 (9)</td>
</tr>
</tbody>
</table>

Combination of radiotherapy and TT seems to be safe (Staehler et al, BJUI 2010)

ESMO guidelines (Escudier et al. 2016) : Adequate control of brain metastases before initiation of anti-VEGF therapy is recommended (expert opinion)

- Staehler et al. [2011] 51 | Su, So | 51 (100) | Brain haemorrhage 2 (0.04) Convulsions 3 (5.8) |
- Vickers et al. [2013] 106 | Su, So, Beva, tem | 86 (81) - |

BM, brain metastasis; RCC, renal cell carcinoma; CNS, central nervous system; RT, radiotherapy; Su, sunitinib; So, sorafenib; paz, pazopanib; Beva, bevacizumab; Eve, everolimus; Tem, temsirolimus.
## Efficacy

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Drug</th>
<th>ORR (PR+CR)</th>
<th>Clinical benefit (ORR +SD&gt;3m)</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gore et al</td>
<td>Expanded access trial (324 patients)</td>
<td>sunitinib</td>
<td>9%</td>
<td>42%</td>
<td>5.3 months</td>
<td>8.2 months</td>
</tr>
<tr>
<td>Sternberg et al</td>
<td>Expanded access trial (58 patients)</td>
<td>sunitinib</td>
<td>4%</td>
<td>39%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Lim et al</td>
<td>6 patients (without local therapy)</td>
<td>sunitinib</td>
<td>33%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Matrana et al</td>
<td>Retrospective database (n=15)</td>
<td>pazopanib</td>
<td>13%</td>
<td>60%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Bastos et al</td>
<td>Retrospective database (n=53)</td>
<td>Anti-VEGF(R) (So, su, beva, pazo, axitinib)</td>
<td>NR</td>
<td>NR</td>
<td>3.4 months</td>
<td>12.2 months</td>
</tr>
<tr>
<td>Stadler et al</td>
<td>Retrospective database (n=50)</td>
<td>sorafenib</td>
<td>4%</td>
<td>72%</td>
<td>NR</td>
<td>12.5 months</td>
</tr>
<tr>
<td>Vickers et al</td>
<td>Retrospective database (n=106)</td>
<td>su (72%), so (22%), beva, tem</td>
<td>31%</td>
<td>45%</td>
<td>NR</td>
<td>14.4 months</td>
</tr>
</tbody>
</table>
METEOR Trial
Randomized phase III trial
Cabozantinib versus Everolimus after anti-VEGFR therapy
Choueiri et al, NEJM november 2015

Brain metastases adequately treated with radiotherapy and/or surgery and stable for at least 3 months before randomization included.

Waiting for data on this subgroup
Immunotherapy?

CheckMate 025 trial
Randomized, open-label, phase III study
Nivolumab versus Everolimus in pretreated RCC
Motzer et al, NEJM November 2015

BM excluded
-> NO DATA
Germ Cell Cancer

• Rare, between 0.4 and 4% of metastatic GCC
• More common with choriocarcinoma, high propensity for spontaneous hemorrhage
• Considered as poor prognosis but curable

<table>
<thead>
<tr>
<th>BRAIN METASTASES in GCC</th>
<th>SURVIVAL (&gt;3 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At the time of initial diagnosis Prior to first-line chemotherapy</td>
<td>43-86%</td>
</tr>
<tr>
<td>Relapse only in the brain after achieving complete response to chemotherapy</td>
<td>39-44%</td>
</tr>
<tr>
<td>During or after chemotherapy that failed to achieve complete response</td>
<td>2-26%</td>
</tr>
</tbody>
</table>

Other adverse prognostic factors are:
- Presence of liver or bone metastases
- Beta-hCG > 5000 IU/L
- AFP > 100 ng/mL
Germ Cell Cancer

**Group 1** (brain metastases prior to initial chemotherapy):

- **standard-dose systemic chemotherapy (BEP or VIP)**
  - To control systemic disease and brain metastases
  - Cisplatin and Etoposide penetrate the brain in the presence of metastases
  - Careful observation if complete response
  - Surgical excision (preferred) and/or focal RT if residual disease

**Group 2** (solitary brain metastasis as the only site of relapse after chemotherapy)

- Surgical resection and/or stereotactic radiosurgery +/- chemotherapy

**Group 3** (brain metastases at relapse after initial chemotherapy)

- salvage high-dose or standard-dose chemotherapy followed by resection and/or SRS of residual masses
- WBRT in palliative care
Germ Cell Cancer

• Brain metastases of disseminated Germ Cell Cancer remain a chemo-sensitive disease
• Rare condition, potentially curable, multidisciplinary approach
  • EXPERTISE CENTERS NEEDED
• Risk of CNS hemorrhage with use of initial chemotherapy due to
  • Highly vascular nature of choriocarcinomas
  • High sensitivity and rapid necrotic response of GCC to chemotherapy
What is optimal management approach to the CNS metastases?

- Performance status
- Histology (and molecular data)
  - primary tumor
  - (or metastases)
- Systemic cancer burden
- Previous treatments
- Comorbidities
- Number, size and location of BM
- Willingness of the patient

Treatment of brain metastases should be integrated within the global care project
Multidisciplinary Discussion

- Systemic therapies are not indisputable first-line therapy in BM
- Two exceptions: GCC and SCLC (very chemosensitive diseases)
- Local control remains important
  - For now, the standard-of-care treatment for newly diagnosed BM remains, in the majority of cases: upfront RT (SRS) followed by systemic therapy
  - Systemic therapy in selected cases is a reasonable option to postpone WBRT
  - Concomitant therapy not recommended (outside clinical trials)
Strategy guided by life expectancy

- If poor performance status: privilege Best Supportive Care
- If possible (very) long life expectancy (GPA, specific diseases)
  - Secondary prevention (after surgery/SRS)
  - Alternative to WBRT

Strategy guided by the primary tumor (histology)

- What are again the options at the time of onset of brain metastases?
- Choose the best available drug!

Strategy guided by the extracranial disease

- Consider brain as a sanctuary if extracranial metastases are controlled and brain local control possible with surgery/SRS
- Consider brain as only a part of a disseminated disease if extracranial progression
WHAT WE HAVE

- A few single-arm phase 2 studies especially focused on targeted therapies in NSCLC, breast or melanoma and on checkpoint inhibitors in NSCLC or melanoma

SYSTEMIC THERAPIES MAY HAVE INTRACRANIAL ACTIVITY

WHAT WE WAIT

- Large prospective, randomized, phase 3 trials specifically dedicated to patients with brain metastases

REAL IMPACT OF SYSTEMIC THERAPIES?
BEST SEQUENCE WITH LOCAL THERAPIES?
Best supportive care is not only an option...

- Control of peritumoral edema and increased intracranial pressure
- The management and prevention of venous thromboembolic disease
- Treatment of seizures
- ....

- Benefit of early integrated palliative care in patients with newly diagnosed incurable cancer (Temel et al, JCO 2016)
THANK YOU

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Pr Jean-François BAURAIN
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Pr François DUHOUX
Pr Yves HUMBLET
Dr Filomena MAZZEO
Dr Marc VAN DEN EYNDE