DISCLOSURES

• Personal financial compensation from Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, AstraZeneca, EtheRNA, CryoStorage for public speaking, consultancy and participation in advisory board meetings

• My institution (UZ Brussel) received research funding related to research projects conducted by my team from Pfizer, Novartis, Roche, Merck-Serono
Epidemiology

- Melanoma = 1 out of 3 diagnoses of all brain metastases\(^1\)
- 15-20% at initial diagnosis of stage IV melanoma
- Clinical diagnosis in 10-40% advanced melanoma
- 50-73% at autopsy\(^2\)

\(\text{Incidence proportion with brain metastasis at diagnosis (\%)}\)

\[\text{Cancer type}\]

\(^1\) Carlino, MS et al. PHAMOUS Study, SMR 2010.

Natural Prognosis

Median survival of 3-7 months\(^3\)
Cause of death in 20-55% of advanced melanoma patients
Direct cause of death in 95% of cases diagnosed with MBM (high risk for spontaneous hemorrhage)
Kaplan-Meier curves for survival by graded prognostic assessment group for patients with melanoma brain metastases

Sperduto P W et al. JCO 2012;30:419-425

481 patients

BRAF/NRAS-mutation status is an independent prognostic factor in metastatic melanoma

677 patients:
- 47% BRAF V600mut
- 20% NRAS Q61/G12/G13mut
- 32% BRAFwt & NRASwt
- 4% BRAFmut & NRASmut

CNS metastasis at diagnosis:
- 24% BRAF V600mut
- 23% NRASmut
- 12% BRAFwt & NRASwt

Melanoma metastasis to the brain
Is it a time dependent event?

- 159 pts recruited in immunotherapy studies at UZ Brussel
- Median follow-up: 40 months
- Incidence of MBM: 25% (41 pts)
- Patients already suffering from brain metastases at initiation of immunotherapy had a better OS than patients who developed brain metastases after immunotherapy

The development of brain metastases is an event that occurs relatively late in the natural course of the disease, most likely related to the emergence of a subclonal melanoma cell population with homing capacity to the brain.

Loco(regional) Treatment for Melanoma Brain Metastases

- Neurosurgical resection
  - Immediate reduction of mass effect
  - Hematoma
- Radiosurgery/Stereotactic RT
  - Small, solitary- or small no. of MBM
  - Pancranial RT (e.g. 10x3 Gy)
Loco(regional) Treatment for Melanoma Brain Metastases

- **Neurosurgical resection**
  - Immediate reduction of mass effect

- **Radiosurgery/Stereotactic RT**
  - Small, asymptomatic MBM
  - Solitary- or low (#?) no. of MBM
  - Radiosurgery (frame(less))

- **Pancranial RT (e.g. 10x3 Gy)**
  - Ineffective

---

- 331 randomized (7+7 melanoma patients)

- WBRT and stRT boost improved functional autonomy (KPS) for all patients and survival for patients with a single unresectable brain metastasis
11

27/01/2017
22/03/2017
21/03/2018
20/6/2018
04/01/2020

Conclusions

After local treatment of one to three melanoma brain metastases, adjuvant WBRT does not provide clinical benefit in terms of distant intracranial control, survival, or preservation of performance status.

J Clin Oncol 37, © 2019 by American Society of Clinical Oncology

Case Illustration

Male patient 1963

2011: melanoma (trunk, Breslow 3.27 mm, N1a(sn-bilateral))
Bilateral axillary CLND (N0)
09/2016: resection solitary lung metastasis (BRAF V600mut)
10/2016: PET+ sc meta, start pembrolizumab
CR
2/2017: PD CNS; surgery, 4x ipilimumab
Resume anti-PD-1
3/2018: solitary new metastasis, frameless radiosurgery (1x 20Gy)
01/2020: PS 0, nivolumab continued
Temozolomide for MBM

- 7-9% BORR in pts with MBM
- Median OS
  - 3.5 mths (117 not previously treated)
  - 2.2 mths (34 previously treated)

78y male stIV-M1c

March ‘11
March’13

24 cycles Temozolomide

1 Boogerd et al., Cancer 2007; 2 Agarwala SS et al. JCO 2004
BOR in BREAK-MB and BREAK-3

No prior brain treatment: Cohort A
BRAF**V600E** mutation-positive patients maximal intracranial target lesion reduction

Prior brain treatment: Cohort B
BRAF**V600E** mutation-positive patients maximal intracranial target lesion reduction

Dabrafenib: Maximum tumor percent change from baseline investigator-assessed
ORR 53%

DTIC: Maximum tumor percent change from baseline investigator-assessed
ORR 19%

Survival in BREAK-MB and BREAK-3

Treatment: 4 doses of 10 mg/kg ipilimumab, q3 wks; q12w if no PD at 24w
No unexpected ipilimumab related AE
## Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial

**Kim Margolin, Marc S Ellisoff, Oswald Haas, Donald Lawrence, David McDermott, Igor Puzaan, Jakob D Winkler, Joseph I Clark, Marie Sirois, Theodore F Logen, Jon Richards, Tracy Michene, Ayees Baloghi, Kevin N Miller, F Stephen Hodi**

### Table 2: Disease control and objective response after 12 weeks

<table>
<thead>
<tr>
<th></th>
<th>Cohort A (n=51)</th>
<th>Cohort B (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mWHO</td>
<td>irRC</td>
</tr>
<tr>
<td>Global disease control</td>
<td>9 (18%)</td>
<td>8 (16%)</td>
</tr>
<tr>
<td>CNS disease control</td>
<td>12 (24%)</td>
<td>13 (25%)</td>
</tr>
<tr>
<td>Non-CNS disease control</td>
<td>14 (27%)</td>
<td>14 (25%)</td>
</tr>
<tr>
<td>Global objective response</td>
<td>5 (10%)</td>
<td>6 (11%)</td>
</tr>
<tr>
<td>CNS objective response</td>
<td>8 (16%)</td>
<td>8 (16%)</td>
</tr>
<tr>
<td>Non-CNS objective response</td>
<td>7 (14%)</td>
<td>34 (10%)</td>
</tr>
</tbody>
</table>

Data are n (%) (95% CI). mWHO: modified WHO criteria. irRC: immune-related response criteria.

**Hodi et al NEJM 2010: mOS 10,0mths; 2yOS 23%**
Case report : Post radiation necrosis of the brain during successful ipilimumab therapy

At first diagnosis (March 2009) 1 y post stRT (March 2010) 2 y post stRT CR outside the CNS Post-surgery = Necrosis 6 months post surgery


Case report : Post radiation necrosis of the brain during successful dabrafenib therapy

February 2012 -Radiosurgery (20Gy) - Start Dabrafenib for PD outside CNS + 6mths CR outside CNS + 9mths CR outside CNS
Of the 142 patients, 43 (30.7%) patients had MBM at initiation pembrolizumab. Of these, 31 (72.1%) were treated with SRS, 8 (18.6%) with WBRT while 4 (9.3%) had no prior local therapy. Of patients treated with RT, 28 (71.1%) received RT before the initiation of pembrolizumab. 5 (12.8%) patients developed a new symptomatic pseudotumoral lesion at a median time of 11.15 months; range 8-46, after the RT. In all patients, the diagnosis of RNB was radiologically confirmed. The RNB was treated with corticosteroids in two patients, bevacizumab in two patients, and surgery in three symptomatic patients. The diagnosis was histologically confirmed in the patients treated with surgery.
Prospective Phase II Clinical Trials on Melanoma Brain Metastases presented at the 2017 ASCO AM

Dabrafenib plus trametinib in patients with BRAFV600-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial

Figure 2: Confirmed radiographic response in intracranial target lesions in cohort A (A), cohort B (B), cohort C (C), and cohort D (D)
METHODS
In this open-label, multicenter, phase 2 study, patients with metastatic melanoma and at least one measurable, non-irradiated brain metastasis (tumor diameter, 0.5 to 3 cm) and no neurologic symptoms received nivolumab (1 mg per kilogram of body weight) plus ipilimumab (3 mg per kilogram) every 3 weeks for up to four doses, followed by nivolumab (3 mg per kilogram) every 2 weeks until progression or unacceptable toxic effects.
55 to 22% ORR
Overall Survival

- Total N\(^o\) Events, n (%):
  - A: Nivo+Ipi N=35: 16 (46%)
  - B: Nivo N=25: 15 (60%)
  - C: Nivo N=16: 13 (81%)
- Med. OS, mo (95% CI):
  - A: 32.8 (11.9 - NR)
  - B: 26.1 (6.93 - NR)
  - C: 5.1 (1.8 - NR)
- 3-yr OS rate, % (95% CI):
  - A: 49% (32-75)
  - B: 42% (26-88)
  - C: 19% (7-52)

Presented by Georgina V Long  @ProfGLongMIA

Treatment-Related Adverse Events

- Treatment-related AEs, n (%):
  - A: Ipi+Nivo N=35: 34 (97%)
  - B: Nivo N=25: 17 (68%)
  - C: Nivo N=16: 8 (50%)
- Grade 3/4 treatment-related AEs, n (%):
  - A: 19 (54%)
  - B: 5 (20%)
  - C: 2 (13%)
- Treatment-related SAE, n (%):
  - A: 16 (46%)
  - B: 1 (4%)
  - C: 2 (13%)
- Discontinuation due to AE\(^*\):
  - A: 5 (14%)
  - B: 1 (4%)
  - C: 0 (0%)

- No new or unexpected AEs
- 4/76 (5%) pts had neurological SAE: 1 radionecrosis\(^*\), 1 seizure, 2 headache
- No deaths due to treatment-related AE

\(^*\) Pts with grade 3/4 treatment related AE in Cohort A were allowed to continue nivolumab monotherapy if recovered and deemed due to ipilimumab
\(^*\) PI in cohort C, prior SRS

Presented by Georgina V Long  @ProfGLongMIA
Case presentation

- 74-year-old male patient
- Prior history of BRAF V600mut primary melanoma on right shoulder
- Nov 2017: diagnosis stage IV-M1c melanoma (metastases to LLN, lung, liver and skeleton)

• What to do?
Case presentation

• Start nivolumab (3 mg/kg Q2w)
• Dec 2017: rapid increase of symptoms (pain, anorexia, weakness) during first 4w on nivolumab.
• Deterioration of blood values: LDH: 8966 U/L (ULN 618 U/L), CRP 76.4 mg/l (ULN 5 mg/l)
• What to do?

Case presentation

• Switch to Dabrafenib/Trametinib
• Symptom improvement after 4 days of therapy
• Stop pain medication after 1w of therapy
• Recovery of activity level, appetite
• One short episode of pyrexia (self-limited, 2 days of treatment interruption) after 3w of therapy
• Up to March 2019: uneventful evolution, dabrafenib/trametinib continued at full dose, full recovery of activity level
### Case presentation

- **Switch to Dabrafenib/Trametinib**
- **Symptom improvement after 4 days of therapy**
- **Stop pain medication after 1w of therapy**
- **Recovery of activity level, appetite**
- **One short episode of pyrexia (self-limited, 2 days of treatment interruption) after 3w of therapy**
- **Up to March 2019: uneventful evolution, dabrafenib/trametinib continued at full dose, full recovery of activity level**
- **March 2019: diagnosis of multiple (asymptomatic) brain metastases on whole body 18F-PET/CT**
- **What to do?**

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### Case presentation

- **Start ipilimumab/nivolumab, Q3w x4**
- **Stereotactic radiation therapy** with True Beam system (single fraction of 20 Gy at 80% isodose on 18 brain metastases, 3 days methylprednisolone following RT)
- **April 2019: transient problems reading/writing**
- **May 2019: silent hypophysitis with associated hypopituitarism.** Hormone substitution therapy initiated (Hydrocortisone 20+10mg, levothyroxine 125µ/d). Spontaneous recovery of testosterone levels at follow-up
- **May 2019: recovery of KPS 100%**
- **Favorable evolution on MRI of the brain and CMR on whole-body 18F-FDG/PET**
- **June 2019: treatment continued with nivolumab 240mg iv Q2w**
- **August 2019: switch to nivolumab 480mg Q4w up to present**
- **Uneventful evolution up to latest follow-up (KPS 100%)**
Take Home Messages

• Treatment of patients with MBM
  – Requires a multidisciplinary approach
    (incl. neuro-radiologist, neurosurgeon,
    radiation- and medical oncology with
    expertise)
• New active medical treatment options
  have become available
  – BRAFi/MEKi in BRAF V600mut
    melanoma: high ORR, irrespective of
    tumor burden, suboptimal duration of
    response
  – PD-1/CTLA-4 inhibition: encouraging
    activity/durability in patients with low
    tumor burden CNS involvement
• Post (radiation) treatment necrosis of
  the brain