De behandeling van het maligne melanoom

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Melanoompunt

Disclosures

Research funding, advisory boards, travel grants for this topic:
- MSD, BMS, Pierre Fabre, Roche
Inhoud voordracht

- Behandeling lokaal beperkt melanoom
- Behandeling gemetastaseerd melanoom
  - Target Therapie
  - Immuuntherapie
  - Andere
- Speciale situaties: Hot news!
  - Adjuvant beleid
  - Hersenuitzaaiingen

Melanoma Therapy 1846 - 2014
Behandeling gelokaliseerde ziekte

Heelkunde: brede excisie!

Micro-staging of Melanoma

1. Sentinel lymph node biopsy (SLNB)
   - Number of tumour-positive nodes highly predictive for survival
   - Used to detect micro-metastases
   - Appropriate for patients in whom neither palpation nor lymph node sonography has suggested the presence of lymph node metastases

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Sentinel lymph node biopsy

- Radioactive substance and/or dye is injected near the tumour
- Injected material detected visually and/or with a probe that detects radioactivity
- Sentinel nodes are the first lymph nodes to take up the material and are removed and checked for cancer cells

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Dummer R. Ann Oncol 2010;21(Suppl. 5):v194-7
NCI. Melanoma Treatment PDQ. Available at: http://www.cancer.gov/cancertopics/pdq/treatment/melanoma/Patient
Richtlijn sentinel klier ESMO

Sentinel LN biopsy in melanoma with a tumour thickness of >1 mm and >0.75 mm and additional risk factors such as ulceration or mitotic rate (pT1b) are recommended for precise staging.

Sentinel LN biopsy should be carried out only in experienced centres.

Wat te doen igv + SN

4 studies mbt nut van resectie alle lymfeklieren…


Conclusie
• Geen winst in overleving
• risico op complicaties
• Van belang prognostisch?
Enkel nog voor geselecteerde patiënten
Among 2100 patients with metastatic melanoma enrolled in phase II trials, the median survival time was 6.2 months [95% confidence interval (CI) 5.9–6.5 months], with 25.5% (95% CI 23.6% to 27.4%) alive at 1 year.
Systeem therapieën bij het MM

- BRAF en MEK inhibitoren
  - Tafinlar/Mekinist
  - Zelboraf/Cotellic
- Immuuntherapie
  - Yervoy (ipilimumab)
  - Opdivo (Nivolumab)
  - Keytruda (Pembrolizumab)
  - Combinaties
- Chemotherapie
  - DTIC, CDDP, Taxol, ...

SITE OF ACTION OF ANTICANCER DRUGS

- **S phase specific**
  - cytarabine
  - 6-mercaptopurine
  - 6-thioguanine
  - methotrexate
  - hydroxyurea
- **G₀ phase**
  - alkylating agents
  - antitumor antibiotics
  - nitrosoureas
  - dacarbazine
  - cisplatin
- **G₂ phase**
  - bleomycin
- **M phase**
  - vinblastine
  - vincristine
  - paclitaxel

etoposide
Welk effect heeft chemotherapie?

| TABLE 4: Selected chemotherapy agents – Results from phase II and phase III trials in melanoma |
|-----------------|-----------------|-----------------|
| Chemotherapy    | Patients (N)    | Objective response rate (%) |
| Alkylation agents |                 |                             |
| Dacarbazine     | 2,470           | 18%                          |
| Temozolomide    | 350             | 15%                          |
| Nitrosoureas    |                 |                             |
| Lomustine       | 270             | 13%                          |
| Fotemustine     | 153             | 24%                          |
| Platinum analog |                 |                             |
| Cisplatin       | 188             | 23%                          |
| Carboplatin     | 43              | 16%                          |
| Microtubule stabilizing/destabilizing | | |
| Paclitaxel      | 65              | 13%                          |
| Docetaxel       | 105             | 11%                          |
| Vincristine     | 52              | 12%                          |
| Vinblastine     | 62              | 13%                          |
| Vindesine       | 273             | 14%                          |

Approval of dacarbazine
Phase 3 trials of chemotherapy, polychemotherapy and biochemotherapy fail to demonstrate improvement in survival
EU approval of ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy

First Phase 3 trial showing improvement in overall survival in pretreated patients (ipilimumab)
Two Phase 3 trials showing improvement in survival in previously untreated patients (ipilimumab and vemurafenib)

Approval of fotemustine (France)


BRAF en MEK-inhibitoren

= doelgerichte therapie!

Targeted Medicine

Melanoma cell-signalling pathways
The MAPK and PI3K pathways

Ligand
Receptor tyrosine kinase

Cell proliferation
Cell survival
Mitosis
Migration

Effector proteins
RNA synthesis

Transcription factors
Activation
Translocation

Cell membrane

PI3K
PIPK
NRAS
NRAS
BRAF
BRAF
MEK
MEK
ERK
ERK
AKT
akt
mTOR
mTOR
Raptor
Raptor
Welk effect hebben BRAF inhibitoren?
Vemurafenib efficacy in previously untreated patients

Overall Survival in 1L stage IIIC and IV melanoma: Zelboraf vs DTIC

- Median Progression-free survival tripled in Zelboraf arm (5.6 mo) vs. DTIC (1.6 mo)
- Overall Response Rate 9x higher in Zelboraf arm (48%) vs DTIC (5.5%)
Nevenwerkingen

<table>
<thead>
<tr>
<th>Very Common</th>
<th>Common</th>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1/10</td>
<td>≥1/100 to &lt;1/10</td>
<td>≥1/1000 to &lt;1/100</td>
</tr>
<tr>
<td>Folliculitis</td>
<td>Basal cell carcinoma</td>
<td></td>
</tr>
<tr>
<td>CuSCC, seborrhoeic keratosis, skin papilloma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache, dysgeusia</td>
<td>7th nerve paralysis</td>
<td>Neuropathy peripheral</td>
</tr>
<tr>
<td>Uveitis</td>
<td>Retinal vein occlusion</td>
<td>Vasculitis</td>
</tr>
<tr>
<td>Cough</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea, vomiting, nausea, constipation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Photosensitivity reaction, actinic keratosis, rash, pruritus, hyperkeratosis, erythema, alopecia, dry skin, sunburn</td>
<td>Palmoplantar erythrodysaesthesia syndrome, erythema nodosum, keratosis pilaris</td>
<td>Toxic epidermal necrolysis, Stevens-Johnson syndrome</td>
</tr>
<tr>
<td>Arthralgia, myalgia, pain in extremity, musculoskeletal pain, back pain</td>
<td>Arthritis</td>
<td></td>
</tr>
<tr>
<td>Fatigue, pyrexia, oedema peripheral, asthenia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GGT increase</td>
<td>ALT, alkaline phosphatase &amp; bilirubin increase weight decreased</td>
<td>AST increase</td>
</tr>
</tbody>
</table>

Impact van BRAF en MEK inhibitie
Summary of responses and PFS of single agent BRAFi and BRAFi+MEKi combined therapy

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase</td>
<td>III</td>
<td>III</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>Agent</td>
<td>vemurafenib</td>
<td>dabrafenib</td>
<td>dabrafenib + trametinib</td>
<td>dabrafenib + trametinib</td>
</tr>
<tr>
<td>ORR</td>
<td>48%</td>
<td>50%</td>
<td>54%</td>
<td>76%</td>
</tr>
<tr>
<td>FFS</td>
<td>5.3 months</td>
<td>5.1 months</td>
<td>5.8 months</td>
<td>9.4 months</td>
</tr>
</tbody>
</table>
PFS by Independent Review Facility

- **Vemurafenib + Placebo**
  - PFS events, n: 117
  - Median PFS (95% CI), mo: 6.0 (5.6-7.5)
  - HR (95% CI): 0.60 (0.45-0.79)
  - P value two-sided: 0.0003

- **Vemurafenib + Cobimetinib**
  - PFS events, n: 82
  - Median PFS (95% CI), mo: 11.3 (8.5-NE)

**Graph:**
- **Progression-Free Survival (%)**
- **Time, months**
- **Vemurafenib + cobimetinib (n = 247)**
- **Vemurafenib + placebo (n = 248)**
- **Censored**

---

**coBRIM:**

**Summary of Selected AEs**

- **Vemurafenib + Placebo (V + P; n = 239)**
- **Vemurafenib + Cobimetinib (V + C; n = 254)**

**Bar Chart:**
- Grade 1
- Grade 2
- Grade 3
- Grade 4

- **AEs:**
  - Cutaneous SCC
  - Keratoacanthoma
  - QT prolongation
  - Serous retinopathy
  - Decreased ejection fraction
Immunotherapy = T cell kills a tumor

Presented By Michael Postow at 2017 ASCO Annual Meeting
Tumor

Tumors can be hard to see
Tumors expressing antigens

Tumor recognized as foreign

Presented By Michael Postow at 2017 ASCO Annual Meeting
T cells in tumor microenvironment

T cell attack
The Immune System Recognizes and Eliminates Cancer via Multiple, Complex Mechanisms

Immune Checkpoint Inhibitor Ipilimumab

Ipi: fully human, monoclonal antibody that blocks cytotoxic T-lymphocyte antigen-4 (CTLA-4) to augment antitumor immunity.
YERVOY™ monotherapy increased median overall survival by 4 months over the control arm (10 months vs. 6 months, HR=0.66; [0.51-0.87]; p=0.0026)

Kaplan-Meier analysis of survival

Potential changes in tumour burden with YERVOY™

Majority of responders
Conventional response
Slow, steady decline in tumor burden

Minority of responders
Late response after initial progression
New lesion appears and then declines along with target lesion

Baseline
12 weeks
First assessment
Later assessments

Adapted from Hodi et al. 2010
Adapted from Wolchok et al. 2009
Gastrointestinal
- Signs and symptoms such as:
  - Diarrhoea
  - Abdominal pain
  - Blood or mucus in stool
  - Bowel perforation
  - Peritoneal signs
  - Ileus

Skin
- Symptoms such as:
  - Pruritus
  - Rash

Neurologic
- Symptoms such as:
  - Unilateral or bilateral weakness
  - Sensory alterations
  - Paraesthesia

Endocrine
- Signs and symptoms such as:
  - Fatigue
  - Headache
  - Mental status changes
  - Abdominal pain
  - Unusual bowel habits
  - Hypotension
  - Abnormal thyroid function tests and/or serum chemistries

Liver
- Signs such as:
  - Abnormal liver function
  - Tests (e.g. elevated AST, ALT or total bilirubin)

Other adverse reactions
- Including ocular manifestations
CTLA-4 Immune Checkpoint Pathway Inhibition Using Iplimumab: Pooled OS Data From Melanoma Patients

- In a pooled analysis of 12 studies, an OS plateau starts at approximately 3 years with follow-up of up to 10 years in some patients

N=1861
Median OS, months (95% CI): 11.4 (10.7–12.1)*
3-year OS rate, % (95% CI): 22 (20–24)*

*Iplimumab was given at different doses and lines of therapy, and using different schedules across the 12 studies.

Schachter J, et al. ECOG Congress. 2013. A43.39A

Presented by: F. Stephen Hodi, MD

Anti PD1
Winst van Anti PD1 versus ipilimumab

Phase III
Nivolumab vs chemotherapy  
Pembrolizumab vs ipilimumab

ORR 35-42%
Grade ≥ 4 AE 15-17%
Anti-PD1 are superior to chemotherapy and to ipilimumab

Robert et al NEJM 2015  
Robert et al NEJM 2015

Long term effect of pembrolizumab
Keynote 006 OS (Median Follow-Up, 33.9 mo)

<table>
<thead>
<tr>
<th>Arm</th>
<th>Events, n</th>
<th>HR (95% CI)</th>
<th>Median, mo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>278</td>
<td>0.70 (0.58-0.86)</td>
<td>32.3 (24.5-NR)</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>155</td>
<td>—</td>
<td>15.9 (13.3-22.0)</td>
</tr>
</tbody>
</table>

Robert et al ASCO 2017
Wat bij combinatie van immuuntherapie?

Overall Survival (Co-Primary Endpoint)

- Median OS, months (95% CI):
  - NIVO (286): 20.0 (17.6-24.4)
  - Ipilimumab (186): 16.9 (13.0-21.1)
  - NIVO+Ipilimumab (283): 22.2 (19.2-25.3)
  - Ipilimumab (186): 16.9 (13.0-21.1)

- HR (95% CI):
  - NIVO (286) vs. Ipilimumab (186): 0.55 (0.42-0.72)
  - NIVO+Ipilimumab (283) vs. Ipilimumab (186): 0.64 (0.49-0.81)

- 2-year OS rates were similar to results from the phase II CheckMate 069 trial of NIVO+Ipilimumab (64%) and the phase CheckMate 066 trial of NIVO monotherapy (58%).

But: high toxicity of the combination

<table>
<thead>
<tr>
<th>Grade 3/5 AE</th>
<th>Discontinuation for AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipiplimumab 3mg/kg</td>
<td>19%</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>13%</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>13%</td>
</tr>
<tr>
<td>Ipiplimumab + nivolumab</td>
<td>57%</td>
</tr>
</tbody>
</table>

Acierno et al. ESMO 2016, Acierno et al. NEJM 2017; Rhein et al JAMA 2016; Atkinson et al. SOR 2015; Wolchok et al. NEJM 2017

Ipiplimumab + nivolumab:
pooled data from Checkmate 067 and 069

- PFS and OS not significantly different between the patients who discontinued for AE during the induction period and those who did not discontinue

Schadendorf et al J Clin Oncol 2017
Hot news!

- Adjuvante behandelingen
- Hersenuitzaaiingen

Adjuvant treatment with ipilimumab

Eggermont et al NEJM 2016
Adjuvante behandeling

CA209-238: Study Design

- Patients with high-risk, completely resected stage III/IIIC or stage IV melanoma
- NIVO 3 mg/kg IV Q2W and IPI pexaflor IV Q2W for 4 doses then Q4W from week 24
- IPI 10 mg/kg IV Q2W for 4 doses then Q4W from week 24 and NIVO pexaflor IV Q2W

Enrollment period: March 30, 2015 to November 30, 2015

Follow-up

Maximum treatment duration of 1 year

Primary Endpoint: RFS

Legend: P value <0.0001
## Safety Summary

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>NIVO (n = 452)</th>
<th>IPi (n = 453)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Any AE</td>
<td>436 (97)</td>
<td>110 (25)</td>
</tr>
<tr>
<td>Treatment-related AE</td>
<td>385 (85)</td>
<td>65 (14)</td>
</tr>
<tr>
<td>Any AE leading to</td>
<td>44 (10)</td>
<td>21 (5)</td>
</tr>
<tr>
<td>discontinuation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment-related AE leading to discontinuation</td>
<td>35 (8)</td>
<td>16 (4)</td>
</tr>
</tbody>
</table>

- There were no treatment-related deaths in the NIVO group.
- There were 2 (0.4%) treatment-related deaths in the IPi group (marrow aplasia and colitis), both >100 days after the last dose.
09/2016: progression frontal left metastasis with edema and dysarthria, with right occipital progressive disease

- Resection frontal metastasis: pathology metastatic melanoma, NRAS mutation
- 10/2016: stable disease
- Partial adrenal insufficiency: start Medrol, intolerance hydrocortisone

12/2016: relapse in operation zone with dural thickening and progression of metastasis right occiput
Conclusie

Belangrijke vooruitgang in behandeling
Genezing van ST IV????
10/2013 Relapse locally in skin transplant
- Broad excision 7.5 cm x 4.8 cm x 1 cm
- NGS: BRAF wild type, NRAS mutation
07/2014 Metastatic lymph node left groin
- Groin complete lymph node extirpation
- 3/13 lymph nodes metastatic involvement
02/2015 Vomiting and headache: Solitary brain metastasis parasellair right
08/2015 new brain met left frontal: refusal of surgery or RT

11/2015 brain metastasis frontal left progressive and more symptoms
   Refusal surgery, Stereotactic radiosurgery 16 Gray

03/2016: bleeding in meta left frontal: start Medrol
06/2016 new asymptomatic metastatic brain lesion right occiput: SRS 20 Gray

09/2016 progression frontal left metastasis with edema and dysarthria, with right occipital progressive disease
  Resection frontal metastasis: pathology metastatic melanoma, NRAS mutation
10/2016: stable disease
  Partial adrenal insufficiency: start Medrol, intolerance hydrocortisone

12/2016: relapse in operation zone with dural thickening and progression of metastasis right occiput
Efficacy and Safety of Nivolumab Plus Ipilimumab in Patients with Melanoma Metastatic to the Brain: Results of the Phase II Study CheckMate 204

Hussein Tawbi,1 Peter Forsyth,2 Alain Algazi,3 Omid Hamid,4 F. Stephen Hodi,5 Stergios Moschos,6 Nikhil Khushalani,2 Rene Gonzalez,7 Christopher Lao,6 Michael Postow,9 Michael B. Atkins,10 Marc Ernstoff,11 Igor Puzanov,11 Ragini Kudchadkar,12 Reena Thomas,13 Ahmad Tarhini,14 Joel Jiang,15 Alexandre Avila,15 Sheena Demelo,15 Kim Margolin16

1University of Texas, MD Anderson Cancer Center, Houston, TX, USA; 2Moffitt Cancer Center and Research Institute, Tampa, FL, USA; 3University of California-San Francisco, San Francisco, CA, USA; 4The Angeles Clinic and Research Institute, Los Angeles, CA, USA; 5Dana-Farber Cancer Institute, Boston, MA, USA; 6University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC, USA; 7University of Colorado Comprehensive Cancer Center, Aurora, CO, USA; 8University of Michigan, Ann Arbor, MI, USA; 9Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA; 10Georgetown-Lombardi Comprehensive Cancer Center, Washington DC, USA; 11Roswell Park Cancer Institute, Buffalo, NY, USA; 12Winship Cancer Institute of Emory University, Atlanta, GA, USA; 13Stanford University Hospital, Palo Alto, CA, USA; 14University of Pittsburgh Medical Center, Pittsburgh, PA, USA; 15Bristol-Myers Squibb, Princeton, NJ, USA; 16Department of Medical Oncology, City of Hope, Duarte, CA, USA.

Abstract Number 9507

Trial Design

• Induction
  - NIVO 1 mg/kg Q3W × 4 + IPI 3 mg/kg Q3W × 4

• Maintenance
  - NIVO 3 mg/kg Q2W

Treat until progression or unacceptable toxicity (maximum of 24 months) a

Key eligibilities

- ≥ 1 measurable, unirradiated MBM (0.5-3.0 cm)
- Prior SRT in ≤ 3 MBM
- Previous treatment with BRAFi/MEKi permitted

Q2W = every 2 weeks; Q3W = every 3 weeks

aPatients with grade 3-4 adverse events (AEs) during NIVO+IPI induction could resume NIVO when toxicity resolved; all patients who discontinued proceeded to follow-up

Original planned enrollment of 110 asymptomatic patients

Exclusion criteria included neurological symptoms; steroids > 10 days; WBRT; prior treatment with checkpoint inhibitors; leptomeningeal disease
### Demographic and Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (N = 75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>53 (71)</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>59 (22–79)</td>
</tr>
<tr>
<td>BRAF mutation, n (%)</td>
<td>41 (55)</td>
</tr>
<tr>
<td>NRAS mutation, n (%)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>LDH &gt; ULN, n (%)</td>
<td>31 (41)</td>
</tr>
<tr>
<td>LDH &gt; 2x ULN, n (%)</td>
<td>11 (15)</td>
</tr>
<tr>
<td>Prior systemic cancer therapy, n (%)</td>
<td>12 (16)</td>
</tr>
<tr>
<td>Dabrafenib/Trametinib</td>
<td>6 (8)</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Prior SRT, n (%)</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Median of median target lesion diameters, mm (IQR)</td>
<td>9.0 (6.5–14.0)</td>
</tr>
<tr>
<td>Target lesions, n (%)</td>
<td></td>
</tr>
<tr>
<td>1-2 lesions</td>
<td>59 (79)</td>
</tr>
<tr>
<td>&gt;3 lesions</td>
<td>16 (21)</td>
</tr>
</tbody>
</table>

IQR = interquartile range

### Response to Treatment – All Patients (N = 75)

<table>
<thead>
<tr>
<th>Best overall response, n (%)</th>
<th>Global</th>
<th>Intracranial</th>
<th>Extracranial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>4 (5)</td>
<td>16 (21)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Partial response</td>
<td>36 (48)</td>
<td>25 (33)</td>
<td>32 (43)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>4 (5)</td>
<td>4 (5)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Progressive disease*</td>
<td>18 (24)</td>
<td>18 (24)</td>
<td>16 (21)</td>
</tr>
<tr>
<td>Not evaluableb</td>
<td>13 (17)</td>
<td>12 (16)</td>
<td>20 (27)</td>
</tr>
</tbody>
</table>

Objective response rate, % (95% CI)

- Global: 53 (41–65)
- Intracranial: 55 (43–66)
- Extracranial: 49 (38–61)

Clinical benefit rate*, % (95% CI)

- Global: 59 (47–70)
- Intracranial: 60 (48–71)
- Extracranial: 52 (40–64)

*Continued and unconfirmed progressive disease
Includes unconfirmed responses
* Clinical benefit rate = complete response + partial response + stable disease > 4 months

Presented By: [Name] at 2017 ASCO Annual Meeting
Intracranial PFS rate at 6 mo - 67%

Presented By Hussein Taday at 2017 ASCO Annual Meeting
### Treatment-related Nervous System AEs

<table>
<thead>
<tr>
<th>n (%)</th>
<th>All treated patients (N = 75)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
</tr>
<tr>
<td>Patients with an event</td>
<td>28 (37)</td>
</tr>
<tr>
<td>Headache</td>
<td>19 (25)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Aphasia</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Seizure</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Brain edema</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Carpal tunnel syndrome</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Peripheral motor neuropathy</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Polyneuropathy</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Syncope</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Tremor</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Visual field defect</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

- Median time to onset of grade 3−4 nervous system AEs was 33 days (n=6)
- Median time to resolution of grade 3−4 nervous system AEs was 4 days (3/3)
A Randomized Phase 2 Study of Nivolumab or Nivolumab plus Ipilimumab in Patients with Melanoma Brain Metastases: The Anti-PD1 Brain Collaboration (ABC)


Study Design

- Melanoma Brain Metastases ≥ 5mm & < 40mm
- No previous
  - Anti-CTLA-4
  - Anti-PD-1 or -PD-L1 agents
  - Previous BRAFi+MEKi allowed
  - ECOG PS 0-2
  - No serious autoimmune disease
  - No corticosteroids (Cohort C < 10mg prednisone allowed)

Primary Endpoint: Intracranial Response Rate ≥ week 12
Secondary Endpoints: Extracranial Response Rate, Overall Response Rate, PFS (intracranial, extracranial, overall), OS

R 1:1

A
- No prior local brain Rx & asymptomatic
- n=30
- Nivolumab 1mg/kg + Ipilimumab 3mg/kg Q2W x4
- Nivolumab 3mg/kg Q2W

B
- No prior local brain Rx & asymptomatic
- n=30
- Nivolumab 3mg/kg Q2W

C
- Previously treated or symptomatic or leptomeningeal, with MRI progression
- n=15
- Nivolumab 3mg/kg Q2W
# Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>A: Ipi+Nivo N=26</th>
<th>B: Nivo N=25</th>
<th>C: Nivo+* N=16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>61 (29-76)</td>
<td>62 (31-86)</td>
<td>54 (28-73)</td>
</tr>
<tr>
<td>Sex, male n (%)</td>
<td>22 (85%)</td>
<td>19 (76%)</td>
<td>11 (69%)</td>
</tr>
<tr>
<td>ECOG performance status, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>6 (23%)</td>
<td>9 (36%)</td>
<td>7 (44%)</td>
</tr>
<tr>
<td>2</td>
<td>1 (4%)</td>
<td>0</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>LDH &gt; ULN, n (%)</td>
<td>11 (42%)</td>
<td>14 (58%)</td>
<td>6 (38%)</td>
</tr>
<tr>
<td>V600 BRAF mutation-positive, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>12 (46%)</td>
<td>14 (58%)</td>
<td>13 (81%)</td>
</tr>
<tr>
<td>Target brain metastases, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>5 (19%)</td>
<td>5 (20%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>2-4</td>
<td>9 (35%)</td>
<td>15 (60%)</td>
<td>7 (44%)</td>
</tr>
<tr>
<td>&gt;4</td>
<td>12 (40%)</td>
<td>5 (20%)</td>
<td>8 (50%)</td>
</tr>
<tr>
<td>Extracranial metastases, n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior BRAFi+MEKi</td>
<td>6 (23%)</td>
<td>6 (24%)</td>
<td>12 (75%)</td>
</tr>
<tr>
<td>Prior local brain therapy</td>
<td>0</td>
<td>0</td>
<td>16 (100%)</td>
</tr>
</tbody>
</table>

*Leptomeningeal, previous local treatment or symptoms

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# Best Intracranial RECIST Response

<table>
<thead>
<tr>
<th>Intracranial Response, n (%)</th>
<th>A: Ipi+Nivo N=25</th>
<th>B: Nivo N=25</th>
<th>C: Nivo+* N=16</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>4 (15%)</td>
<td>3 (12%)</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>7 (27%)</td>
<td>2 (8%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>SD</td>
<td>2 (8%)</td>
<td>1 (4%)</td>
<td>4 (25%)</td>
</tr>
<tr>
<td>PD</td>
<td>12 (46%)</td>
<td>18 (72%)</td>
<td>11 (69%)</td>
</tr>
<tr>
<td>NE*</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>0</td>
</tr>
</tbody>
</table>

- Median duration of intracranial response not reached in any arm

NE = Not Evaluable
*1% who deceased prior to wk 12 + PD
*2Leptomeningeal, previous local treatment or symptoms

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Intracranial Progression Free Survival

Summary

- Nivolumab combined with ipilimumab or nivolumab alone have activity in active, asymptomatic melanoma brain metastases, without prior local therapy
  - Nivo+Ipi Intracranial: Response Rate = 42%; 6-month PFS 46%
  - Nivo alone Intracranial: Response Rate = 20%; 6-month PFS 29%

- Activity is high when nivo+ipi given upfront
  - Nivo+Ipi: Intracranial Response Rate = 50%

- Intracranial and extracranial responses were mostly concordant
COMBI-MB

A Phase 2 Study of Combination Dabrafenib and Trametinib in Patients With BRAF V600-Mutant Melanoma Brain Metastases

Intracranial Response

Overall intracranial response (CR + PR) for Cohort A (n = 76) is 58%, Cohort B (n = 16) is 59%, and Cohort C (n = 16) is 59%

Intracranial disease control (CR + PR + SD) for Cohort A (n = 76) is 59% (95% CI 46-69), Cohort B (n = 16) is 14% (95% CI 8-24), Cohort C (n = 16) is 12% (95% CI 6-20), and Cohort D (n = 17) is 10% (95% CI 5-17).

Intracranial duration of response:
- Events, n/N (%): Cohort A 39/44 (90%), Cohort B 6/9 (67%), Cohort C 4/7 (57%), Cohort D 8/10 (80%)
- Median (95% CI), mo: Cohort A 6.5 (4.0-10.3), Cohort B 7.3 (3.6-12.6), Cohort C 8.3 (1.3-15.9), Cohort D 4.5 (2.8-5.9)

Median (95% CI), %: Cohort A 62 (45-76), Cohort B 73 (28-93), Cohort C 67 (19-90), Cohort D 13 (1-43)

Preliminary Overall Survival

Overall survival rates for Cohort A (n = 76), Cohort B (n = 16), Cohort C (n = 16), and Cohort D (n = 17).

- Median OS (95% CI), mo: Cohort A 10.8 (8.7-13.4), Cohort B 24.3 (17.9-30.0), Cohort C 19.7 (16.4-22.9), Cohort D 11.5 (8.2-22.4)

Cohort B: Asymptomatic with prior local therapy.
Conclusions

- First report of a phase 2 trial evaluating BRAFi + MEKi in patients with melanoma brain metastases
- Clinical benefit and tolerability were achievable with dabrafenib + trametinib in some patients with BRAF V600-mutant melanoma metastasized to the brain
  - IR rate of 56% (95% CI, 46%-69%) in cohort A patients; primary endpoint was met
  - Median duration of OR (eg, 6.5 months in cohort A) was generally shorter than that observed in patients without melanoma brain metastases (12-14 months)\(^9\)
  - No unexpected safety issues were observed with the combination
- These results support:
  - Use of dabrafenib + trametinib as a treatment option for patients with brain metastases
  - Need for continued research to improve outcomes in this advanced melanoma population

Patient developed 3 months after initiation of treatment

- Vomiting, confusion, fever and anorexia
- Brain imaging: response of brain mets
- Hyponatremia
- Adrenal insufficiency
  - Start Hydrocortison
  - Solu cortef once IV
- Asymptomatic hyperthyroidie

Evaluation 5/2017: central response, no new lesions on pet
Evaluation 8/2017: stable disease

Conclusion

Progression central metastasis
No local therapy possible
Durable response with symptomatic brain mets and corticosteroids