LOCALISED MELANOMA RESECTED:
ADJUVANT THERAPY FOLLOWED BY SYSTEMIC RELAPSE

CLINICAL CASE DISCUSSION

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DISCLOSURE

HONORARIA AS SPEAKER, CONSULTANCY OR ADVISORY ROLE:
Bristol-Myers Squibb, Roche, Amgen, Merck Sharp & Dohme, Novartis, GlaxoSmithKline, Pierre-Fabre

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STOCK OWNERSHIP: None
Stage III Management Guidelines:
- SNB
- CLND
- Adjuvant treatment

CLND, complete lymph node dissection; SNB, sentinel node biopsy
Algorithm for stage I-III

Criteria for Sentinel Node Biopsy (SNB)

- SNB is recommended for staging in AJCC 8th edition stages pT1b (thickness >0.8 mm or <0.8 mm with ulceration) or higher [II,B]
  
- SNB is not recommended for stage pT1a (thickness <0.8 mm)

1. Han JCO 2013; 2. Sondak ASCO Educational Book 2017

No Complete Lymph Node Dissection (CLND) for SNB +

- For positive SNB patients, avoiding CLND is justified based on the results of the MSLT-II and DeCOG-SLT trials. The control arm of that trial is not standard observation, but US-based follow-up, which should be the strategy proposed to the patient [I, A].

Criteria for adjuvant:

- Patient with SNB deposit of more than 1 mm are candidate for adjuvant [I, A].
Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma


**CONCLUSIONS**

Immediate completion lymph-node dissection increased the rate of regional disease control and provided prognostic information but did not increase melanoma-specific survival among patients with melanoma and sentinel-node metastases. (Funded by the National Cancer Institute and others; MSLT-II ClinicalTrials.gov number, NCT00297895.)
Important:
• The control arm is not simple clinical follow-up, but active US-based surveillance every 4 months!

CLND, complete lymph node dissection; H&E, hematoxylin & eosin staining; IHC, immunohistochemistry; LM, lymphatic mapping; MSLT, multicentre selective lymphadenectomy trial; RT-PCR, reverse-transcriptase-polymerase-chain-reaction; SL, sentinel lymphadenectomy; SN, sentinel node
Results from MSLT-II: no benefit to radical lymphadenectomy

A

B

No. at Risk

Dissection

Observation

Years after Randomization

P=0.55

No. at Risk

Subgroup 1

744 682 581 441 326 214 144 92 53 21 6

Subgroup 2

820 751 639 482 348 241 163 109 64 34 8

Subgroup 3

80 77 73 69 63 61 47 36 30 18 7

Subgroup 4

111 105 95 82 77 63 54 42 31 21 5

Faries, NEJM 2017

RT-PCR, reverse-transcriptase-polymerase-chain-reaction

ESMO 2019 | Barcelona | September 29th 2019
Overview of key adjuvant checkpoint blockade trials

ECOG-1609: Phase III, 1673 pts
- Ipi 10 vs ipi 3 vs HD INF-α2b
- Population: stage III B-C, IV M1a-b
- Endpoint: I, RFS & OS; II, QoL
- Adult accrual completed
- HR RFS/OS: 1.0⁴/NA

EORTC-18071: Phase III, 951 pts
- Ipi 10 mg/kg vs placebo
- Population: stage III A³-C
- Endpoint: I, RFS; II, DMFS and OS
- mRFS/mOS: 28 vs 17 / 87 vs NR
- HR RFS/OS: 0.75/0.72

Checkmate 915: Phase III, 900 pts
- Ipi 1 + nivo vs nivo
- Population: stage IIIB – D, IV
- Endpoint: RFS
- Accrual completed
- Results expected in 12/2020

SWOG S1404: Phase III, 1378 pts
- Ipi 10 vs. pembro vs. HD IFN-α
- Population: stage IIIA (N2a) – C, IV
- Endpoint: OS/RFS in PD-L1+
- Accrual completed
- Results expected in 05/2020

Checkmate-238: Phase III, 800 pts
- Ipi 10 mg/kg vs nivo 3 mg/kg
- Population: stage III B-C, IV NED
- Endpoint: I, RFS; II, OS
- mRFS/mOS: NA/NA
- HR RFS/OS: 0.57/NA

EORTC 1325: Phase III, 1019 pts
- Pembro 200 mg vs placebo
- Population: stage III A³-C
- Endpoint: I, RFS; II, DMFS and OS
- mRFS/mOS: NA/NA
- HR RFS/OS: 0.57/NA

Checkmate 915: Phase III, 900 pts
- Ipi 1 + nivo vs nivo
- Population: stage III B–C
- Endpoint: RFS
- Accrual completed
- Results expected in 12/2020

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¹Eggermont, NEJM 2016; ²Weber, NEJM 2017; ³Eggermont NEJM 2018; ⁴Tarhini, ASCO 2017; Time in months, NA: Not Available, NR: Not Reached. ⁵Excluding LN mets. < 1mm and in transit metastasis w/o nodal disease; ⁶also Keynote-054; ⁷AJCC 8th classification
## Comparison of stage subgroup eligibility criteria

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Stage - AJCC 7th Edition (All patients NED)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>IIC</td>
</tr>
<tr>
<td>EORTC 18071</td>
<td>Ipilimumab 10 versus placebo</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC 1325</td>
<td>Pembrolizumab versus placebo</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Checkmate 238</td>
<td>Ipilimumab 10 versus nivolumab</td>
<td>✓</td>
</tr>
<tr>
<td>ECOG 1609</td>
<td>Ipilimumab 10 versus ipilimumab 3 versus HD INF-α2b</td>
<td>✓</td>
</tr>
<tr>
<td>BRIM-8</td>
<td>Vemurafenib versus placebo</td>
<td>✓</td>
</tr>
<tr>
<td>COMBI-AD</td>
<td>Dabrafenib + trametinib versus placebo</td>
<td>✓</td>
</tr>
</tbody>
</table>

AJCC, American Joint Committee on Cancer; EMA, European Medicines Agency; FDA, Food and Drug Administration; HD INF-α2b, high-dose interferon-α2b; NED, no evidence of disease; SN sentinel node.
Key efficacy landmarks in the adjuvant setting of melanoma

**EORTC 18071**
- Ipilimumab 10 mg/kg vs placebo,
- Stage IIIA-C; RFS HR 0.76, OS HR 0.72

**Checkmate 238**
- Ipilimumab 10 mg/kg vs nivolumab,
- Stage IIIB-C + IV; RFS HR 0.66, OS HR NA

**EORTC 1325**
- Pembrolizumab vs placebo,
- Stage IIIA-C; RFS HR 0.57, OS HR NA

**COMBI-AD**
- Dabrafenib + trametinib vs placebo
- Stage IIIA-C; RFS HR 0.49, OS HR 0.57

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Adjuvant in melanoma: important data are still missing!

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>HR RFS</th>
<th>HR DMFS</th>
<th>HR OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC 18071</td>
<td>Ipilimumab 10 mg versus placebo</td>
<td>0.76</td>
<td>0.76</td>
<td>0.72</td>
</tr>
<tr>
<td>EORTC 1325</td>
<td>Pembrolizumab versus placebo</td>
<td>0.57</td>
<td>0.53</td>
<td>NA</td>
</tr>
<tr>
<td>Checkmate 238</td>
<td>Ipilimumab 10 versus nivolumab</td>
<td>0.65</td>
<td>0.73</td>
<td>NA</td>
</tr>
<tr>
<td>ECOG 1609</td>
<td>Ipilimumab 10 versus ipilimumab 3 versus HD INF-α2b</td>
<td>1.0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>BRIM-8</td>
<td>Vemurafenib versus placebo</td>
<td>0.54 (IIIC-IIIB)</td>
<td>0.8 (IIIC)</td>
<td>NA</td>
</tr>
<tr>
<td>COMBI-AD</td>
<td>Dabrafenib + trametinib versus placebo</td>
<td>0.47</td>
<td>0.51</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Stage III patients from these trials were required to have complete lymph node dissection!

How do we integrate those results in a post MSLT-2/DeCOG8,9 trial era?

### Overview of PFS outcome per stage subgroup:

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>IIC</th>
<th>IIIA</th>
<th>IIIB</th>
<th>IIIC</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC 18071¹</td>
<td>Ipilimumab 10 mg versus placebo</td>
<td>SN &gt; 1mm, HR 0.98</td>
<td>HR 0.75</td>
<td>HR 1.00, 1-3 n</td>
<td>HR 0.48, ≥ 4 n</td>
<td></td>
</tr>
<tr>
<td>EORTC 1325²</td>
<td>Pembrolizumab versus placebo</td>
<td>SN &gt; 1mm, HR 0.38</td>
<td>HR 0.58</td>
<td>HR 0.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Checkmate 238³</td>
<td>Ipilimumab 10 versus nivolumab</td>
<td>HR 0.68</td>
<td>HR 0.68</td>
<td>HR 0.68</td>
<td>HR 0.66 M1a/b, HR 0.78 M1c²</td>
<td></td>
</tr>
<tr>
<td>ECOG 1609</td>
<td>Ipilimumab 10 versus ipilimumab 3 versus HD INF-α2b</td>
<td>HR NA</td>
<td>HR NA</td>
<td>M1a-b, HR NA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRIM-8⁴</td>
<td>Vemurafenib versus placebo</td>
<td>HR 0.0-NE</td>
<td>SN &gt; 1mm, HR 0.52</td>
<td>HR 0.63</td>
<td>HR 0.8</td>
<td></td>
</tr>
<tr>
<td>COMBI-AD⁵</td>
<td>Dabrafenib + trametinib versus placebo</td>
<td>SN &gt; 1mm, HR 0.44</td>
<td>HR 0.50</td>
<td>HR 0.45</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data not randomized head to head, should not be compared directly;
¹Eggermont, NEJM 2016; ²Eggermont NEJM 2018; ³Weber, NEJM 2017; ⁴Maio, Lancet Oncol 2018; ⁵Long, NEJM 2017;
Stage IV Management Guidelines:
- Immunotherapies
- Targeted therapies
Algorithm for inoperable stage III-IV

First line TKI is limited to selected patients
- Rapidly evolutive disease, need for quick response, no time to allow safe delivery of 1st line IO

IO rechallenge can be an option in selected patients
- In retrospective series, ipilimumab or ipilimumab+nivolumab shows around 20% ORR after PD-1 failure

BRAF/MEKi are the preferred second line option
- Cave: toxicity! Long half life of checkpoints inhibitors!

Ref. Cutaneous melanoma; ESMO Clinical practice guidelines for diagnosis, treatment, follow-up 2019

BRAFi, BRAF inhibitor; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; IO, immuno-oncology; MEKi, MEK inhibitor; ORR, overall response rate; PD-1, programmed cell death 1; TKI, tyrosine kinase inhibitor; T-VEC, talimogene laherparepvec
Low level of evidence points to IO as the first line choice

- Targeted therapies provide better early outcome...

- ... but immuno-oncology curves are crossing at around 14 months \(^1\) ...

- ... and the difference seems to increase with time

\(^1\) Ugurel, *EJC* 2017
Guidelines for patients failing adjuvant treatment?

A multicenter analysis of melanoma recurrence following adjuvant anti-PD1

Carina Owen, James MG Larkin, Alexander N Shoushtari, Matteo S Carlino, Christian U Blank, Belinda Lee, Joanna Mangana, Victoria Atkinson, Michael Millward, Farzana Zaman, Arissa Young, Muhammad Adrian Khattak, Sapna P Patel, Christoph Hoeller, Peter Hersey, Dharmisha Chauhan, David J Palmieri, Serigne Lo, Alexander M Menzies, Georgina V Long
Escapes on or following adjuvant PD-1 blockade

- Data are are just emerging on this new patient population\(^1\)
- No guidelines exist yet
- Aspects will be addressed in an upcoming ESMO Melanoma Consensus paper

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage (AJCC 8(^{th}))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
<td>6</td>
<td>4%</td>
</tr>
<tr>
<td>IIIB</td>
<td>42</td>
<td>31%</td>
</tr>
<tr>
<td>IIIC</td>
<td>66</td>
<td>49%</td>
</tr>
<tr>
<td>IIID</td>
<td>5</td>
<td>4%</td>
</tr>
<tr>
<td>IV</td>
<td>17</td>
<td>12%</td>
</tr>
<tr>
<td>Adjuvant Tx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivo</td>
<td>58</td>
<td>43%</td>
</tr>
<tr>
<td>Pembro</td>
<td>39</td>
<td>29%</td>
</tr>
<tr>
<td>Niv/ipi</td>
<td>20</td>
<td>15%</td>
</tr>
<tr>
<td>Niv +/- ipi</td>
<td>19</td>
<td>14%</td>
</tr>
</tbody>
</table>

\(^1\) Owen, ASCO 2019

\[\text{% Recurrence-free survival} = \frac{\text{Number of patients without recurrence}}{\text{Total number of patients}} \times 100\]

\[\text{Months since adj-PD1 initiation} = \begin{cases} 0 & \text{adjuvant PD1 initiation} \\ i & \text{months since init.} \end{cases} \]

\[\text{Recurrence rate} = \frac{\text{Number of patients who recurred}}{\text{Total number of patients}} \times 100\]

\[\text{Recurrence during adj-PD1 (ON)} = 71\% \]

\[\text{Recurrence after adj-PD1 (OFF)} = 29\% \]
Efficacy of 1\textsuperscript{st} line metastatic treatment in adjuvant PD-1 failures\textsuperscript{1}

<table>
<thead>
<tr>
<th>Timing of initial recurrence</th>
<th>Systemic treatment</th>
<th>N</th>
<th>CR/PR</th>
<th>SD</th>
<th>PD</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ON adj-PD1</td>
<td>Ipilimumab +/-anti-PD1</td>
<td>33</td>
<td>8</td>
<td>5</td>
<td>20</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td>BRAF/MEKi</td>
<td>23</td>
<td>18</td>
<td>5</td>
<td>0</td>
<td>78%</td>
</tr>
<tr>
<td></td>
<td>Anti-PD1 + novel agent</td>
<td>9</td>
<td>1</td>
<td>1</td>
<td>7</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td>Anti-PD1</td>
<td>6</td>
<td>0</td>
<td>1</td>
<td>5</td>
<td>0%</td>
</tr>
<tr>
<td>OFF adj-PD1</td>
<td>Ipilimumab +/-anti-PD1</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td>BRAF/MEKi</td>
<td>10</td>
<td>9</td>
<td>0</td>
<td>1</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td>Anti-PD1 + novel agent</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>Anti-PD1</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>40%</td>
</tr>
</tbody>
</table>

\textsuperscript{1} Owen, ASCO 2019
Stage III and IV Melanoma Management: still a lot of unsolved questions!
The new ESMO guidelines will be complemented by a ESMO consensus paper.

ESMO Melanoma Clinical Practice Guidelines - 2019 Edition

- Evidence based guidelines with
  - Level of Evidence (LoE)
  - Grade of Recommendation (GoR)
- Based on
  - Primary clinical data from clinical trials and meta-analyses
- Awaiting publication in Annals of Oncology September 2019


- Consensus recommendation from an expert panel
  - Level of agreement among panelists on predetermined key questions
- Based on
  - Immature / insufficient clinical data
  - Clinical experience / expertise
- Publication expected late 2019 / early 2020
Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

O. Michielin¹, A. van Akkooi², P. Ascierto³, R. Dummer⁴ & U. Keilholz⁵, on behalf of the ESMO Guidelines Committee*

¹Department of Oncology, University Hospital Lausanne, Lausanne, Switzerland; ²Department of Surgical Oncology, Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, the Netherlands; ³Istituto Nazionale Tumori IRCCS Fondazione “G. Pascale”, Napoli, Italy; ⁴Department of Dermatology, Skin Cancer Centre, University Hospital Zürich, Zürich, Switzerland; ⁵Charité Comprehensive Cancer Centre, Charité-Universitätsmedizin Berlin, Berlin, Germany.

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Awaiting Publication in Annals of Oncology

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THANK YOU FOR YOUR ATTENTION!

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