Adjuvant Melanoma Therapy: European Perspectives

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The need for adjuvant treatment
Melanoma primary tumor thickness differs around the world

- Germany: 0.7 mm
- Australia: 0.7 mm
- Poland: 2.6 mm
- Russia: 5.5 mm
- Latin America (Brazil): ???
Melanoma capitals of the world

- according to incidence rates:
  Australia → USA → Germany
- according to absolute numbers:
  USA → Germany → other countries
- according to death rates:
  China/Russia/USA → Germany → Australia
Why Adjuvant Treatment?

Survival of High-Risk Melanoma

High Risk Patients:
- Higher Recurrence Rate
- Relatively Poor Survival

After 3 years

High Risk Patients:
- Higher Recurrence Rate and Relatively Poor Survival
## Survival of stage III melanoma pts

### AJCC 5-Year Survival by Lymph Node Tumor Burden and Primary Tumor Ulceration (Stage III)

<table>
<thead>
<tr>
<th>Ulceration</th>
<th>Number of Nodal Micromets</th>
<th>Number of Nodal Macromets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2-3</td>
</tr>
<tr>
<td>Absent</td>
<td>81.5±1.9 (777)</td>
<td>73.2±3.7 (246)</td>
</tr>
<tr>
<td>Present</td>
<td>56.6±2.9 (531)</td>
<td>53.9±4.2 (223)</td>
</tr>
</tbody>
</table>
Adjuvant Radiotherapy

• Multicenter study: Australia and New Zealand Melanoma Trials Group (ANZMTG); Trans-Tasman Radiation Oncology Group (TROG)

• Eligible: ≥ 1 Parotid gland LNs, ≥ 2 neck/axillary LNs, ≥ 3 groin LNs oder ≥ 3cm (in diameter for head/neck LNs resp. ≥ 4cm for groin LNs) or extracapsular extension

• Schedule: Randomization to 20x 2.4 Gy (for a total of 48Gy) or observation alone

Adjuvant radiotherapy

- Multicenter study: Australia and New Zealand Melanoma Trials Group (ANZMTG); Trans-Tasman Radiation Oncology Group (TROG)
- Randomization: total of 250 pts. (2002-2007)
- Median follow-up time: 40 months
- Local relapses: 20/109 (RT) vs. 34/108 (control)
  HR=0.56; p=0.041
- Relapse-free survival: 70 (RT) vs. 73 cases
  HR=0.91; p=0.56
- Overall survival: 59 (RT) vs. 47 cases;
  2.6 years (RT) vs. 3.9 years; HR=1.37; p=0.12

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New interdisciplinary German guideline

May 2013:

Adjuvant radiotherapy needs to be discussed in presence of
3+ macrometastases and/or extracapsular extension of LNs

## Adjuvant IFN-α schedules in Europe

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Dose</th>
<th>Frequency</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low dose (as approved)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 MIU</td>
<td>3 x weekly</td>
<td>18 months</td>
</tr>
<tr>
<td><strong>Intermediate dose (EORTC, Nordic group)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initiation</td>
<td>10 MIU</td>
<td>5 x weekly</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Maintenance</td>
<td>10 MIU</td>
<td>3 x weekly</td>
<td>12 months</td>
</tr>
<tr>
<td></td>
<td>or</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 MIU</td>
<td>3 x weekly</td>
<td>24 months</td>
</tr>
<tr>
<td><strong>High dose (as approved)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initiation</td>
<td>20 MIU/m²</td>
<td>5 x weekly</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Maintenance</td>
<td>10 MIU/m²</td>
<td>3 x weekly</td>
<td>11 months</td>
</tr>
</tbody>
</table>
Adjuvant Interferon Treatment in Europe

L = low dose
H = high dose
H1m = high 1 month
I = intermediate
P = pegylated
0 = no dose
Duration of treatment:

Low-dose IFN longer than 18 months?
IFNα2a - 18 versus 60 months

(Hauschild et al, J Clin Oncol 2009)
IFNα2a - 18 versus 60 months
(Hauschild et al, J Clin Oncol 2009)
Intermittent high-dose intravenous interferon alpha 2b (IFNa2b) for adjuvant treatment of stage III malignant melanoma: Final analysis of a randomized phase III DeCOG-trial (MM-ADJ-5)


For DeCOG, skin cancer centers: Buxtehude¹, Kiel², Berlin³, Heidelberg⁴, Homburg⁵, Mainz⁶, Hamburg⁸, Essen¹⁰, Hannover¹², Bochum¹³, Oldenburg¹⁴, Münster¹⁵, Köln¹⁶, Dresden¹⁷, Ulm¹⁸, Darmstadt¹⁹, Germany, Salzburg⁹, Austria; Zürich¹¹, Switzerland

For Hellenic Melanoma Group: Athens⁷, Greece
DeCOG: adjuvant phase III trial

**Arm A**
Standard high-dose IFN alfa-2b

- IV phase
- SC phase
- 48 weeks
- 3 x 10 MU/m² per week
- IFN alfa-2b

*(IV phase: 4 weeks 5 x 20 MU/m² IFN alfa-2b)*

**Arm B**
Intermittent high-dose IV IFN alfa-2b

- IV phase
- Interruption
  - week 1-4
  - week 5-16
  - week 17-20
  - week 21-32
  - week 33-36
  - week 37-52
- IV phase
- Interruption

*(IV phase: 4 weeks 5 x 20 MU/m² IFN alfa-2b)*
Overall Survival

HR: 1.016 (95%-CI: 0.77 to 1.34)

p=0.91
Quality of Life, EORTC QLQ-C30

LQ-Score (Mean)

Week

20MU/m² IV
10MU/m² SC

0 4 8 12 16 20 24 28 32 36 40 44 48 52
Willingness to tolerate mild to moderate side effects for a minimum RFS benefit of...

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Percentage of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5%</td>
<td>29% (of pts.)</td>
</tr>
<tr>
<td>5-10%</td>
<td>14%</td>
</tr>
<tr>
<td>10-15%</td>
<td>15%</td>
</tr>
<tr>
<td>15-20%</td>
<td>18%</td>
</tr>
<tr>
<td>&gt; 20%</td>
<td>24%</td>
</tr>
</tbody>
</table>
HD-IFN: patients’ perspectives

severe side effects

„at least 50% of our subjects were willing to endure severe side effects for an absolute improvement in 5-year RFS of 10% or more...“

„GERMALATOX“ study in Germany

• Evaluating the willingness of German melanoma patients to tolerate treatment-related toxicities
• Recruitment of 200 melanoma patients with less than 1mm tumor thickness and 100 physicians
• Participants: 10 German skin cancer centers of excellence
• Initiation: 4th Quarter 2012
• Sponsor: Merck (USA), MSD (Germany)
• PI: Dr. Katharina Kähler (Kiel)
FDA News Release (March 2011)

„FDA approves Sylatron® (pegylated IFNa2b) for stage III melanoma“

Future for melanoma approval of Cylatron in Europe is uncertain
Adjuvant melanoma treatment: German Recommendations 2013

• Stage II > 2.0 mm tumor thickness, sentinel lymph node negative: discussion of low-dose IFNα, 3 MU TIW for 18 months (approved indication)

• Stage III melanoma including SN-positive patients: high-dose IFNα or alternatively IFNα“ (approved indications)

• Pegylated IFNα only with EMA approval!

• Alternative: referral to clinical trials
Transformational Results in Patients with Ulceration and III-N1 Disease
EORTC 18991

**RFS**

- Number of patients at risk:
  - Observation: 70, 90, 41, 27, 22, 6
  - Peg-IFN alfa: 64, 96, 54, 43, 35, 11

**DMFS**

- Number of patients at risk:
  - Observation: 67, 90, 48, 30, 25, 6
  - Peg-IFN alfa: 58, 96, 66, 47, 41, 13

- **p=0.06**  **HR=0.72** (99% CI: 0.46, 1.13)
- **p=0.02**  **HR=0.65** (99% CI: 0.41, 1.04)

Eggermont et al. ASCO 2011. Abstract #8506b
Transformational Results in Patients with Ulceration and III-N1 Disease
EORTC 18991

**2011 OVERALL SURVIVAL**

- **Observation**
- **Peg-IFN alfa**

<table>
<thead>
<tr>
<th>Observation</th>
<th>Peg-IFN alfa</th>
</tr>
</thead>
<tbody>
<tr>
<td>61</td>
<td>46</td>
</tr>
<tr>
<td>90</td>
<td>96</td>
</tr>
<tr>
<td>68</td>
<td>78</td>
</tr>
<tr>
<td>41</td>
<td>57</td>
</tr>
<tr>
<td>32</td>
<td>51</td>
</tr>
<tr>
<td>6</td>
<td>16</td>
</tr>
</tbody>
</table>

- p=0.006
- HR=0.59 (99% CI 0.35, 0.97)
- Median OS: 3.7 yrs vs > 9 yrs
Primary Tumor Ulceration
EORTC 18081
Randomized Phase 3 Trial Ulcerated Primary Melanoma

2 yrs PEG-Intron* vs Observation
1000 Patients
Interferon benefits (RFS): Hazard ratios

- HDI (4 trials): 0.80 (-20% risk)
- IDI (2 trials): 0.82 (-18% risk)
- LDI (7 trials): 0.81 (-19% risk)
- PegIFN (1 trial): 0.82 (-18% risk)

Relapse-free survival benefits
(OS benefits significantly smaller)
Current Adjuvant Melanoma Trials

...that could potentially change standards of care in 2013 - 2016
MAGE-3 ASCI
(MAGE-A3 found in 50% of melanomas)

- MAGE-A3 screening
- Predictive signature to MAGE-A3 ASCI
Phase III study – “DERMA”
ADjuvant immunotherapy with MAGE-A3 in melanoma

- Melanoma with macroscopic LN involvement
- Resected MAGE-A3 (+) Stage IIIB/C Melanoma
- Randomization
  - Placebo
  - MAGE-A3 ASCI

13 administrations over 27 months
1300 patients – double-blind, randomized trial

Recruitment completed in June 2011
EORTC 18071 Ipilimumab

Melanoma
Stage III (TxN1-3M0)
(N = 950)

Lymph node dissection

Randomisation within 56 days (1:1)

Arm A: Ipilimumab (N=475)
Induction: 4 inf. over 12 weeks
Maintenance: 1 inf every 12 w. for 3 years or distant mets

Arm B: Placebo (N=475) as Arm A

Recruitment completed in June 2011
Adjuvant ipilimumab vs. HDI (ECOG 1609)

High-risk, resected, stage III/IV melanoma

*(Estimated n=1000)*

**Stratification**: AJCC Staging (IIIB vs. IIIC vs. M1a vs. M1b)

**Ipilimumab**

**Induction**: IV over 90 minutes on day 1; then q21 days (total 4 courses).

**Maintenance**: (beginning on week 24): IV over 90 minutes on day 1; then q90 days (max. 4 courses).

**High-dose IFN-α2b**

**Induction**: IV days 1-5, 8-12, 15-19, and 22-26.

**Maintenance**: SQ days 1, 3, and 5. Then q week x 48 weeks.
Which of the following drugs provides the greatest hope for the future of adjuvant therapy apart from interferons?

- Adjuvant bevacizumab (UK trial)
- Adjuvant ASCI (MAGE-A3 vaccine)
- Adjuvant ipilimumab (Yervoy)
- Adjuvant vemurafenib (Zelboraf)
- Adjuvant dabrafenib plus trametinib
Conclusions

- Prolongation of OS is doubtless the aim of an adjuvant treatment, but obviously difficult to achieve with interferons.
- Prolongation of DFS is a meaningful goal for patients if the treatment is well tolerated.
- Clinical trials on new promising agents like Ipilimumab and MAGE-3 ASCI are mandatory, but however patients are difficult to convince if IFN treatment is used in the routine.
- The existing treatment alternatives (LDI, HDI) and a „wait and see“ policy with a regular follow-up alone should be discussed with patients...
Muito obrigado pelo seu amável convite ao Brasil. Gostaria muito de voltar!

Minha antiga médica residente Elisabeth gostaria voltar ao Brasil também, pudessem convidar-lá como tradutora na próxima vez?
www.worldmelanoma2013.com

8th World Congress of Melanoma

9th Congress of the European Association of Dermatooncology (EADO)
7th Interdisciplinary Melanoma/Skin Cancer Centers Meeting
3rd European Post-Chicago Melanoma Meeting 2013

July 17–20, 2013
Hamburg, Germany
Congress Center Hamburg (CCH)