Recent advances in the management of metastatic malignant melanoma – a breakthrough also for elderly patients?

SIOG 2014 Annual, Lisbon, Portugal

Introduction – melanoma in Europe in general:
- In Europe every year approximately 100,000 new melanoma cases (age-standardised rate 11.1 per 100,000) and 22,200 deaths due to melanoma
- Incidence of melanoma rising since early 1970s
- European mean age-standardised survival for skin melanoma ~ 83% (95% CI 82.9–83.6), but women had much better survival than men, survival worse for eastern Europe (generally 50–75%)
- Survival decreased steadily with age in all regions

Introduction – melanoma in the elderly
- Rise in occurrence of melanoma in individuals ≥ 65 years disproportionate
- Advancing age further compounds the risk of developing melanoma
- Clinical presentation and pathological characteristics differ from younger counterparts
- Poor prognostic features such as nodular subtype, histologic ulceration, elevated mitotic rate more common in the elderly
- Paradoxically less likely to have lymph node metastasis than younger patients
- Particular high-risk group: elderly white men, in particular men living alone

Survival curves from the AJCC Melanoma Staging Database:

Useful tool to calculate prognosis: http://melanomaprognosis.org/
Survival in stage IV patients:

- M1a (skin, subcutaneous tissue or distant lymph nodes and normal LDH): 62%
- M1b (metastasis to the lung or with combination of lung and skin or subcutaneous metastases and normal LDH): 53%
- M1c (any other visceral site or at any location with elevated LDH): 33%

→ Median survival 6-9 months, 5-yr survival rate 1-2%


Different ways to attack melanoma:

- Attack directly the melanoma cell
- Stimulate immunosystem to overcome immunoresistance
  - Interleukin-2, interferon-α
  - Anti-CTLA-4 antibodies (ipilimumab, tremelimumab)
  - Anti-PD-1 ab (Nivolumab, Pembrolizumab, CT-011)
  - Anti-PD-L1 ab (BMS936559, MPDL3280A, MEDI4736...)
  - Vaccination Therapy (peptide-based, dendritic cells,...)
  - Adoptive T cell therapy (with TILs)
  - Biochemotherapy
  - Or combination targeted therapy / immunotherapy

Clinicaltrials.gov: 302 recruiting studies for pts with met. melanoma (22-10-14)

The past – low response rate of single agent chemotherapy:

<table>
<thead>
<tr>
<th>Agent</th>
<th>CR + PR (%)</th>
<th>95%CI</th>
<th>Source of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dacarbazine</td>
<td>7-15</td>
<td>NA</td>
<td>&gt; 1 phase III RCT</td>
</tr>
<tr>
<td>Temozolomide</td>
<td>12</td>
<td>9-15</td>
<td>Single phase III RCT</td>
</tr>
<tr>
<td>Carmustine</td>
<td>18</td>
<td>11-25</td>
<td>Phase II trials</td>
</tr>
<tr>
<td>Lomustine</td>
<td>13</td>
<td>9-17</td>
<td>Phase II trials</td>
</tr>
<tr>
<td>Radiation</td>
<td>15.5</td>
<td>NA</td>
<td>Single phase III RCT</td>
</tr>
<tr>
<td>Claplat</td>
<td>23</td>
<td>17-29</td>
<td>Phase II trials</td>
</tr>
<tr>
<td>Carboplatinum</td>
<td>16</td>
<td>5-27</td>
<td>Phase II trials</td>
</tr>
<tr>
<td>Vindesine</td>
<td>13</td>
<td>5-21</td>
<td>Phase II trials</td>
</tr>
<tr>
<td>Vincristine</td>
<td>14</td>
<td>10-18</td>
<td>Phase II trials</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>6-13</td>
<td>4-22</td>
<td>Phase II trials including 1RCT</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>15</td>
<td>9-21</td>
<td>Phase II trials</td>
</tr>
</tbody>
</table>

DTIC was till 2011 the only cytotoxic agent approved for the treatment of advanced melanoma, but: no phase III data to support survival benefit relative to other treatments or even a « best supportive care » group!

The past – low response rate of single agent chemotherapy:

- All melanomas are not the same.

Not all melanomas are the same ....

And why did we not move forward?

Un-personalized melanoma care

With 70 phase II trial arms evaluations in 42 trials of inactive agents we would expect at least 3 “positive” trials by chance → problem: offering new agents to unselected patients

And Wissenschaft ist [...] gar nichts anderes als eben das Versessen auf das Finden von Unterschieden! Man könnte ihr Wesen gar nicht besser beschreiben. Für Wissenschaftsmenschen ist rechts wichtiger als das Feststellen von Unterschieden. Wissenschaft heißt Unterscheidungskunst, z.B. an jedem Menschen die Merkmale finden, die ihn von den anderen unterscheiden.

And Science is [...] nothing but the ‘determination to establish differences’. Its essence couldn’t be defined more accurately. For us, the men of science, nothing is so important as establishing differences; science is the art of differentiation. Discovering in every man what distinguishes him from others to know him.
Not all melanomas are the same ...

**BRAF** is only the beginning.

### A Landscape of Driver Mutations in Melanoma

- **BRAF** is only the beginning.
- **Other oncogenes and tumor suppressors thought to be involved in melanomagenesis:**
  - RAC1, PPP6C, SNX31, TACC1, ARID2, STK19 (Hodi et al., Krauthammer et al.)
  - MDM4 (Gembarska et al.)
  - PREX2 (Berger et al.)
  - GRIM3 (Prickett et al.)

And others such as:
- MITF, CDK4, CCND1, ERBB4, AKT1, AKT2, AKT3, NEDD9, MYK, ETV1, PTEN

### Mutational status in melanoma in the elderly:

- **BRAF** mutation associated with younger age, fewer markers of sun damage, higher total nevus counts, histopathologic subtype (SSMM, RMS), presence of mitoses, tumoral location, age at diagnosis ≤ 50 yrs; no association with Breslow or ulceration, no other difference in clinical features (ECOG, LDH, brain met, etc.) between **BRAF**-mutant and **BRAF** wild-type – **BRAFV600K** older?

- **NRAS** status associated with elevated mitotic activity, thickness > 1mm, CNS involvement and shorter melanoma specific survival - **NRAS** mutation = adverse prognostic factor

- Mutant **BRAF** is generally mutually exclusive with the presence of mutant **NRAS**

### BRAF-inhibitors in melanoma - the good news started at ASCO 2009:

- **# 9000** Phase I study of PLX4032: Proof of concept for V600E **BRAF** mutation as a therapeutic target in human cancer.
Improved Survival with BRAF-inhibitors in melanoma:


Ref. Nr. of pts. Study endpoint Responses Median PFS/OS Safety

<table>
<thead>
<tr>
<th>Ref.</th>
<th>No. of pts.</th>
<th>Study</th>
<th>Median PFS/OS</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapman P NEJM 2011 (BRIM-3)</td>
<td>675 Vemurafenib 337 pts, DTIC 338 pts</td>
<td>Co-primary: PFS/OS Secondary: ORR, DR, safety</td>
<td>VEM vs DTIC CR: 1% vs 0% PR: 48% vs 5% Median time to response: VEM: 1.45 m DTIC: 2.7m</td>
<td>VEM grades 2-4 (%): Arthralgia: 18-3-0% Rash: 10-8-0% Fatigue: 11-2-0% cut SCC: gr. 3 12% Keratoacanthoma: 2-6-0% Hyperkeratosis: 5-1-0% Nausea: 7-1-0% Diarrhea: 5-&lt;1-0%</td>
</tr>
<tr>
<td>Hauschild A Lancet 2012 (BREAK)</td>
<td>250 Dabrafenib (187) vs DTIC (63)</td>
<td>Primary: PFS (invest.) Secondary: PFS (by IRC), OS, ORR, DR, safety</td>
<td>DABR vs DTIC CR: 3 vs 2% PR: 47 vs 5% SD: 42 vs 48% PD: 5 vs 37% Median time to response: DABR: 6.2 wks DTIC: n.r.</td>
<td>DABR grades 2-4 (%): Arthralgia: 5-1-0% Pyrexia: 8-3-0% Fatigue: 5-1-0% cut SCC/KA: 2-4-0% Nausea: 2-0-0%</td>
</tr>
<tr>
<td>Flaherty K NEJM 2012 (METRIC)</td>
<td>322 pts Trametinib (214) vs chemo DTIC or Paclitaxel (108)</td>
<td>Primary: PFS  Secondary: OS, ORR, DR, safety</td>
<td>TRAM vs chemo CR: 2 vs 0% PR: 20 vs 8% SD: 56 vs 31% PD: 18 vs 46% Median duration of response: TRAM: 5.5 m.</td>
<td>TRAM grades 2-4 (%): Rash: 19-8% (gr. 3+4) Diarrhea: 6-0-0% Fatigue: 5-4-0% Peripheral edema: 4-1-0% Acneiform dermatitis: 9-1-0% Hypertension: 3-12-0% Nausea: 2-1-0%</td>
</tr>
</tbody>
</table>

Phase 3 studies with BRAFi / MEKi in melanoma:

VEM in the elderly – results from open label, safety study:

Between 01-03-2011 and 31-01-2013, 3226 pts enrolled; 2965 pts/92% <75 vs 257 pts/8% ≥75 treated with VEM

Age ≥75 associated with increased rate of SAE, increased rate of grade 3 and 4 AE, difference mainly related to increased incidences of cutaneous SCC, keratoacanthoma and QT-prolongation, drug interactions more common

No difference in response and PFS

Improved Survival with Combo of BRAF + MEK-inhibitors:

What about c-KIT and melanoma ....?

• In comparison with classical cutaneous melanomas melanomas arising from mucosal surfaces and from the palms, soles, and nailbeds have been shown to harbor KIT mutations.

• Previous clinical trials testing the efficacy of single-agent imatinib for the treatment of melanoma were disappointing:
  - Two phase II trials did not reveal any objective responses in 41 patients (Ugurel et al, Wyman et al). The authors concluded that imatinib had no therapeutic effect in melanoma and should no longer be investigated.
  - In a third phase II study with 21 melanoma patients there was only one patient with a partial response lasting 12.8 months, interestingly a patient with metastatic acral lentiginous melanoma.

• Carvajal RD JAMA 305(22):2327-2334, 2011
• All 6 responses in tumors with exon 11 L576P or exon 13 K642E mutations

• Case 2:
  - 21-02-2011: 78 yrs, ulcerated pigmented lesion at the left toe, pathologically malignant melanoma, Clark IV, Breslow 3mm, margins invaded
  - 08-04-2011: Wide excision of the melanoma of the left toe, but again no free margins
  - 15-4-2011: Amputation of the left toe
  - 12-2011: diagnosis of intransit- and lungmetastasis
  - In the past: DTIC mono
  - Now: KIT mutational analysis!

• 13-01-2012: KIT mutational analysis confirms mutation of exon 11 (pointmutation: p.Leu576Pro), starts Nilotinib, 2x400 mg/d
• 09-02-2012: PR after 2 cycli, CR in 10-2014

Frequency (%) of mutations in kinase signaling pathways in melanoma subtypes

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Cutaneous</th>
<th>Acral</th>
<th>Mucosal</th>
<th>Uveal</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF</td>
<td>40-60</td>
<td>15-20</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>NRAS</td>
<td>15-20</td>
<td>10-15</td>
<td>5-10</td>
<td>&lt;1</td>
</tr>
<tr>
<td>c-KIT (mut)</td>
<td>&lt;2</td>
<td>10-20</td>
<td>10-20</td>
<td>5-10</td>
</tr>
<tr>
<td>c-KIT (ampl)</td>
<td>&lt;1</td>
<td>20-30</td>
<td>20-30</td>
<td>1-10</td>
</tr>
<tr>
<td>GNAQ</td>
<td>&lt;1</td>
<td>1-10</td>
<td>1-10</td>
<td>&lt;1</td>
</tr>
<tr>
<td>ERBB4</td>
<td>1-2 (::)</td>
<td>::</td>
<td>::</td>
<td>::</td>
</tr>
<tr>
<td>PTEN</td>
<td>10-20</td>
<td>10-20</td>
<td>10-20</td>
<td>1-2</td>
</tr>
<tr>
<td>FGFR3</td>
<td>10-20</td>
<td>10-20</td>
<td>10-20</td>
<td>1-2</td>
</tr>
<tr>
<td>AKT1/3</td>
<td>1-2 (::)</td>
<td>::</td>
<td>::</td>
<td>::</td>
</tr>
</tbody>
</table>

Carvajal RD JAMA 305(22):2327-2334, 2011

03.11.2014
NRAS in melanoma:

- NRAS identified as melanoma oncogene already in 1984 by Albino et al.
- Mutations in NRAS, K Ras and HRas present in 25%, 5% and 1% of melanomas
- >80% of NRAS mutations = point mutation leading to substitution of glutamine to leucine at position 61 (exon 2); mutations at positions 12 and 13 (exon 1) less frequently
- Mutations at position 61 are associated impaired GTPase activity and the locking of the Ras protein into its activated (GTP-association) conformation

NRAS mutant melanoma – MEK-inhibitors: MEK162

- MEK162 = an ATP noncompetitive, selective inhibitor of MEK1 and MEK2
- open label, phase II study in patients (pts) with BRAFV600E and NRAS mt advanced cutaneous melanoma.
- MEK162 administered orally at a starting dose of 45 mg twice daily
- 68 pts: 42 BRAF-mt and 24 NRAS mt, among 29 BRAF mt and 13 NRAS mt pts evaluable for efficacy
- 2 confirmed and 6 unconfirmed partial responses (PRs) and 13 pts with stable disease (SD) were recorded in the BRAF arm and 3 confirmed PRs, 3 unconfirmed PR and 13 pts with SD recorded in the NRAS arm.

Different ways to attack melanoma:

- Attack directly the tumor
- Stimulate immunity to overcome immunosuppression
  - Interferon-2, interferon-1, anti-CTLA-4 antibodies
  - Imatinib, temozolomide, anti-angiogenic therapy

- Biochemotherapy
- Or combination targeted therapy + immuno-therapy
  - BRAF inhibitors (vemurafenib, dabrafenib), MEK inhibitors (trametinib, cobimetinib), CDK4/6 inhibitors (LEE011, palbociclib, LY2835219), PD-1/PD-L1, checkpoint inhibitors

- Vaccination therapy (peptide-based, dendritic cells, others)
- Adoptive T-cell therapy (with TILs)

Clinicaltrials.gov: 302 recruiting studies for pts with met. melanoma (22-10-14)

Improved Survival with Ipilimumab in melanoma:

- Kaplan-Meier Curves for Clinical Trial in Black population. Red vs OS = 16.8 months (95% CI 14.5 to 19.1) in the ipilimumab group vs 10.4 months (95% CI 9.4 to 11.4) in the dacarbazine arm group at 6 months (95% CI 5.5 to 6.7) is the ipilimumab gain.
- Ipilimumab FDA approved for the treatment of patients with unresectable or metastatic melanoma (25 March 2011), NDA approval on 14 July 2011 for the treatment of patients with previously-treated unresectable (inoperable) or metastatic melanoma

Can the immune system recognize and eliminate malignant tumors?

- Paul Quintessential role: 1990s
  - Immunological surveillance

- Immune system monitoring and recognition of self vs non-self

- Cytokine system: T-cell activation, T-cell suppression, T-cell regulation

Iplilimumab: Mechanism of Action

- CD8+ T-cells
- CTLA4
- TCR
- MHC
- APC
- T-cell activation
- T-cell inhibition
- T-cell potentiation

Historical overview of immunology and cancer:

- Search for tumor-associated antigens by Janeway TAA recognized in 1891 (MAGE-A1 by Dr. B. Breslin et al)
- Interleukin-2 approved by FDA 1989 for advanced melanoma metastases
- Ipilimumab approved by FDA 2011 for advanced melanoma metastases

- APC
- T-cells
- T-cell activation
- T-cell inhibition
- T-cell potentiation

About 20% are still alive with Ipilimumab

Ipilimumab in the elderly – results from Italian EAP:
- Between 06-2010 and 01-2012, 855 pts enrolled
- 662 pts/77% <70 vs 193 pts/23% >70 treated with Ipilimumab; 27 pts/3% ≥80, median age 75 (range: 71-88)
- 132 pts (68%) received all 4 doses
- irBORR and irDCR similar in pts >70 years in comparison with pts <70
- 1- and 2-year survival 38% and 22%
- Increased age does not compromise tolerability of ipilimumab, but no data in very elderly

<table>
<thead>
<tr>
<th>Number of patients, n (%)</th>
<th>&gt;70 years</th>
<th>≤70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>irCR</td>
<td>4 (2)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>irPR</td>
<td>24 (13)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>irSD</td>
<td>44 (23)</td>
<td>7 (27)</td>
</tr>
<tr>
<td>irPD</td>
<td>116 (62)</td>
<td>18 (69)</td>
</tr>
<tr>
<td>irBORR</td>
<td>28 (15)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>irDCR</td>
<td>72 (38)</td>
<td>8 (31)</td>
</tr>
</tbody>
</table>

Treatment related AEs by at least 2% of pts

<table>
<thead>
<tr>
<th></th>
<th>Any grade</th>
<th>Gr 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>11 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>19 (10)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 (5)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Liver toxicity</td>
<td>3 (2)</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>

Can we do better than with Ipilimumab ... anti-PD-1/-PD-L1?

Anti-PD-1 and anti-PD-L1 antibodies:
- Topalian et al.: phase I study to assess safety, antitumor activity and PK of BMS-936558 (Nivolumab) = fully human IgG4 blocking antibody against PD-1
  - Results: 296 pts, gr. 3 toxicity in 14%, mainly irAE (colitis, hepatitis, hypophysitis, thyroiditis), 3 deaths due to pneumonitis
  - Clinical activity in 104 melanoma pts: 26 CR (with 0.1 to 10.0 mg/kg) ranging from 19 to 41% per dose level!
- Brahmer et al.: phase I study to assess safety and adverse-event profiles of BMS-388860 = fully human IgG4 blocking antibody that inhibits binding of PD-L1 to both PD-1 and CD80.
  - Results: 207 pts, grade 3/4 toxicity in 9% of pts
  - Clinical activity in 55 melanoma pts: ORR in 4/52 , responses sometimes time-limited
- Conclusion: antibodies blocking PD-1 or PD-L1 are likely to provide a new benchmark for antitumor activity in immunotherapy, expression of PD-L1 as biomarker for response to PD-1 axis inhibitors?

Other anti-PD-1 antibodies:
- Hamid et al.: phase II study to assess safety and antitumor activity MK-3475 = fully human IgG4 kappa blocking antibody against PD-1
  - Results: 135 pts (48 prior Ipi, 87 no prior Ipi), 10 mg/kg every 2 wks or every 3 wks or 2 mg/kg every 3 weeks, gr. 3 toxicity in 13%, mainly irAE (colitis, hepatitis, hypophysitis, thyroiditis), 4% pneumonitis (all grade), one death due to myocardial infarction
  - Clinical activity in 57 melanoma pts: total population 38% confirmed objective response, 44% unconfirmed (based on RECIST), duration of response 1.9 -10.8 months, median PFS > 7 months

Hamid O et al NEJM 2013; 369:134-44

Combination of Ipilimumab and Nivolumab:
- Wolchok et al.: phase I study to assess safety and antitumor activity of combination of Ipilimumab and Nivolumab
  - Results: concurrent and sequential therapy with nivolumab and ipilimumab, ORR (WHO) for all patients in the concurrent-regimen group was 49%. Evidence of clinical activity in 65%: MTD: nivolumab at a dose of 1 mg per kilogram of body weight and ipilimumab at a dose of 3 mg per kilogram, 53% of patients had an objective response
  - Grade 3 or 4 adverse events related to therapy occurred in 53% of patients in the concurrent-regimen.
- CONCLUSIONS: Concurrent therapy with nivolumab and ipilimumab had a manageable safety profile and rapid and deep tumor regression in a substantial proportion of patients.

Wolchok JD et al NEJM 2013; 369:122-33
Algorithm for the treatment of patients with metastatic melanoma:

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... brave new world: the costs of ipilimumab, vemurafenib ...:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Price per month</th>
<th>Price per treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab (Yervoy®)</td>
<td>~7,500€</td>
<td>~90.000€/year</td>
</tr>
<tr>
<td>Vemurafenib (Zelboraf®)</td>
<td>~8,800€</td>
<td>~105.000€/year</td>
</tr>
<tr>
<td>Dabrafenib (Tafinlar®)</td>
<td>~7,000€</td>
<td>~91.000€/year</td>
</tr>
<tr>
<td>trametinib (Mekinist®)</td>
<td>~8,700$</td>
<td>~91.000$/year</td>
</tr>
<tr>
<td>Combination D/T</td>
<td>~16.000$</td>
<td>~192.000$/year</td>
</tr>
<tr>
<td>Pembrolizumab (Keytruda®)</td>
<td>~12.500$</td>
<td>~150.000$/year</td>
</tr>
<tr>
<td>Nivolumab (Opdivo®)</td>
<td>~12.000$</td>
<td>~143.000$/year</td>
</tr>
<tr>
<td>Combination I/N</td>
<td>~19.500$</td>
<td>~243.000$/year</td>
</tr>
</tbody>
</table>

How to move forward to improve oncological care for elderly melanoma patients?

- Improve awareness for melanoma in elderly patients / implementation of screening programs for elderly patients
- Develop strategies to reduce general underutilization of currently achievable therapeutic options (surgery)
- Validate Comprehensive Geriatric Assessment in elderly melanoma patients – assess possible impact on treatment decisions
- Better understanding of “immunosenescence” – development of predictive biomarkers for clinical benefit in elderly melanoma patients treated with immunotherapy
- Inclusion of elderly melanoma patients in clinical trials, but implementation GCA
- Develop guidelines for elderly melanoma patients

Conclusions:

- Are recent advances in the management of metastatic malignant melanoma also a breakthrough also for elderly patients? YES
- No aspect of management of older patients with melanoma should be driven by chronological age alone
- Patient preference, comorbidities and potential toxicities should guide management decisions
- Patients should be closely monitored, with prompt interventions for toxicity
- Urgent need to establish multidisciplinary oncological and geriatric approach in daily routine
- More research / clinical trials for elderly melanoma patients needed

Disclosures of potential Conflict of Interest:

- Employment or leadership positions
- Consultant or Advisory Role
- Stock ownership
- Honoraria
- Research funding
- Other remuneration

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If you are already planning your holidays after your retirement ...

... be careful in the sun!
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Marjan Garmyn

Department of Surgical Oncology, UZ Leuven:
Marguerite Stas

Department of General Medical Oncology, UZ Leuven:
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Pascal Wolter

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Stijn Aerts