Immunotherapie: hoe omgaan met de bijwerkingen, een praktische gids

14de TOGA meeting, Antwerpen
14-10-2016

Dr. Pascal Wolter, M.D.
CHR Verviers
Treatment of cancer in the past:

How to treat cancer?

Surgery

Radiotherapy

Chemotherapy

Treatment modalities in Oncology
Treatment of cancer in 2000:

How to treat cancer?

- Surgery
- Targeted therapies
- Radiotherapy
- Chemotherapy

Treatment modalities in Oncology
Treatment of cancer in 2016:

How to treat cancer?

Surgery
Targeted therapies
Radiotherapy
Immunotherapy
Chemotherapy

Treatment modalities in Oncology
Historical overview of immunology and cancer:

Paul Ehrlich suggests that the immune system can control cancers (1909)

1890s Coley’s toxin

1960s tumor ‘immunosurveillance’ hypothesis by MF Burnet

Search for tumor-associated antigens (TAA) begins
First human TAA recognised in 1991 (MAGE-A1) (P Van der Bruggen et al)

Interleukin-2 approved by FDA 1998 for treatment of advanced metastatic melanoma

Interferon-α approved by FDA (1995) for adjuvant treatment of stage IIB/III melanoma

1995: dendritic cells can present TAA to the adaptive immune system

Ipilimumab approved by FDA/EMEA (03-2011 / 07-2011)

Anti-PD1 and several other immunomodulatory drugs in pipeline

Can the immune system recognize and eliminate malignant tumors?

Historical overview of immunology and cancer:

- **1890s**
  - Coley's toxin
- **1909**
  - Paul Ehrlich suggests that the immune system can control cancers
- **1960s**
  - ‘immunosurveillance’ hypothesis by MF Burnet
  - Search for tumor-associated antigens (TAA) begins
  - First human TAA recognised in 1991 (MAGE-A1) (P Van der Bruggen et al)
- **1975**
  - Interleukin-2 approved by FDA 1998 for treatment of advanced metastatic melanoma
- **1995**
  - Interferon-α approved by FDA (1995) for adjuvant treatment of stage IIB/III melanoma
  - Dendritic cells can present TAA to the adaptive immune system
  - Anti-PD1 and several other immunomodulatory drugs in pipeline

Can the immune system recognize and eliminate malignant tumors?

**YES!**

## Overview of approved immunotherapies in oncology – the past:

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA approval</th>
<th>EMA approval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Indication</td>
<td>Date of approval</td>
</tr>
<tr>
<td>Interferon α-2b</td>
<td>Melanoma adjuvant</td>
<td>12-1995</td>
</tr>
<tr>
<td>Interleukin-2</td>
<td>Advanced melanoma</td>
<td>1998</td>
</tr>
<tr>
<td>Intravesical BCG</td>
<td>Bladder cancer adjuvant (Tis, Ta, T1)</td>
<td>04-08-1998</td>
</tr>
<tr>
<td>Peginterferon alfa-2b (Sylatron®)</td>
<td>Melanoma adjuvant</td>
<td>29-03-2011</td>
</tr>
<tr>
<td>Sipuleucel-T (Provenge®)</td>
<td>CRPC</td>
<td>29-04-2010</td>
</tr>
<tr>
<td>Drugs (2011-2016)</td>
<td>FDA approval</td>
<td>EMA approval</td>
</tr>
<tr>
<td>-------------------</td>
<td>--------------</td>
<td>--------------</td>
</tr>
<tr>
<td></td>
<td>Indication</td>
<td>Date of approval</td>
</tr>
<tr>
<td>Ipilimumab (Yervoy®)</td>
<td>advanced melanoma</td>
<td>25-03-2011</td>
</tr>
<tr>
<td></td>
<td>melanoma adjuvant</td>
<td>28-10-2015</td>
</tr>
<tr>
<td>Nivolumab* (Opdivo®)</td>
<td>Advanced melanoma after ipilimumab</td>
<td>22-12-2015</td>
</tr>
<tr>
<td></td>
<td>Squamous NSCLC (after platinum chemotherapy)</td>
<td>04-03-2015</td>
</tr>
<tr>
<td></td>
<td>Advanced RCC (previously pretreated)</td>
<td>23-11-2015</td>
</tr>
<tr>
<td></td>
<td>Advanced classical HL after auto-TX and Adcetris</td>
<td>17-05-2016</td>
</tr>
<tr>
<td></td>
<td>Non-squamous NSCLC (previously pretreated)</td>
<td>09-10-2015</td>
</tr>
</tbody>
</table>

*CHMP positive opinion ° first approval in Japan in 07/2015
<table>
<thead>
<tr>
<th>Drugs (2011-2016)</th>
<th>FDA approval</th>
<th>EMA approval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Indication</td>
<td>Date of approval</td>
</tr>
<tr>
<td>Pembrolizumab (Keytruda®)</td>
<td>advanced melanoma</td>
<td>04-09-2014 (after ipi) 18-12-2015 (1st)</td>
</tr>
<tr>
<td></td>
<td>Advanced NSCLC</td>
<td>02-10-2015</td>
</tr>
<tr>
<td></td>
<td>HNSCC after platinum</td>
<td>05-08-2016</td>
</tr>
<tr>
<td>T-VEC (Imlygic®)</td>
<td>melanoma lesions in the skin and lymph nodes</td>
<td>27-10-2015</td>
</tr>
<tr>
<td>Combination of Ipi/Nivo</td>
<td>(BRAF V600 wild-type) unresectable or metastatic melanoma</td>
<td>30-09-2015</td>
</tr>
<tr>
<td>Atezolizumab (Tecentriq®)</td>
<td>Recurrent bladder cancer</td>
<td>18-05-2016</td>
</tr>
</tbody>
</table>

*CHMP positive opinion
Overview of anti-PD1/L1 agents in clinical development:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Market name</th>
<th>Prior names</th>
<th>Manufacturer</th>
<th>IgG type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>Opdivo®</td>
<td>MDX1106, BMS936558</td>
<td>BMS - ONO</td>
<td>IgG4 fully human AB</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Keytruda®</td>
<td>MK-3745</td>
<td>MSD</td>
<td>IgG4 engineered humanized AB</td>
</tr>
<tr>
<td>Pidilizumab</td>
<td>-</td>
<td>CT-011</td>
<td>Cure Tech</td>
<td>IgG1k fully human AB</td>
</tr>
<tr>
<td>BMS936559</td>
<td>-</td>
<td></td>
<td>BMS - ONO</td>
<td>IgG4 fully human AB</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>Tecentriq®</td>
<td>MPDL3280A, RG7446</td>
<td>Genentech/Roche</td>
<td>IgG1 engineered fully human AB</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>-</td>
<td>MEDI4736</td>
<td>Medimmune</td>
<td>IgG1 engineered fully human AB</td>
</tr>
<tr>
<td>Avelumab</td>
<td>-</td>
<td>MSB0010718C</td>
<td>Merck Serono</td>
<td>IgG1 fully human AB</td>
</tr>
</tbody>
</table>

Clinicaltrials.gov: 353 recruiting studies with anti-PD1/PD-L1 (02-10-16)
Historical overview of treatments for metastatic melanoma:

- DTIC approved by FDA in 1975
- Interleukin-2 approved by FDA in 1998

- Ipilimumab approved by FDA/EMA (03-2011 / 07-2011)
- Pembrolizumab, Nivolumab approved by FDA/EMA (09-2014 / 07-2015; 12-2014 / 07-2015)
- Ipilimumab / Nivolumab approved by FDA/EMA (10-2015 / 04-2016)
- T-VEC approved by FDA/EMA (10-2015)
- Vemurafenib approved by FDA/EMA (08-2011 / 12-2011)
- Dabrafenib approved by FDA/EMA (05-2013 / 06-2013)
- Trametinib approved by FDA/EMA (05-2013 / 04-2014)
- Dabrafenib / Trametinib approved by FDA/EMA (09-2015)
- Vemurafenib / Cobimetinib approved by FDA/EMA (11-2015)

10 new drugs or drug combinations in < 5 years approved by FDA and/or EMA
Overall Survival Metastatic Melanoma

1-year OS Phase 3 Studies

- Ipilimumab: 30-35%\(^1,2\)
- Ipilimumab: 46%\(^3\)
- Ipilimumab: 47%\(^4\)
- Vemurafenib: 56%\(^5\)
- Dabrafenib: 70%\(^6\)
- Nivolumab: 73%\(^7\)
- Pembro 10 mg/kg Q3W\(^a\)
- Pembro 10 mg/kg Q2W\(^a\)
- Dab + Tram
- Vem + Cobi

2-year OS Phase 3 Studies

- Ipilimumab: 24%\(^3\)
- Ipilimumab: 29%\(^4\)
- Vemurafenib: 45%\(^6\)
- Dabrafenib: 58%\(^8\)
- Nivolumab: 51%\(^10\)
- Dab + Tram: 48%\(^11\)

\(^a\)2 mg/kg Q3W is the approved dosing for pembrolizumab in advanced melanoma

Adapted from ©Georgina V. Long 2015

About 20% are still alive with Ipilimumab

Schadendorf D et JCO 2015, 33(17): 1889-94
Study CA209-003: Overall Survival at 5 Years

All Patients (events: 69/107), median and 95% CI: 17.3 (12.5–37.8)

NIVO 3 mg/kg (events: 11/17), median and 95% CI: 20.3 (7.2–NR)

Number of Patients at Risk

<table>
<thead>
<tr>
<th>All Patients</th>
<th>107</th>
<th>86</th>
<th>64</th>
<th>51</th>
<th>49</th>
<th>43</th>
<th>41</th>
<th>36</th>
<th>29</th>
<th>17</th>
<th>15</th>
<th>12</th>
<th>3</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIVO 3 mg/kg</td>
<td>17</td>
<td>15</td>
<td>11</td>
<td>9</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Database lock Oct 2015

Hodi S et al AACR 2016 Annual Meeting (Abstract CT001)
The other side of the coin … immune related adverse events:

### Occurrence of adverse events with Ipilimumab (10 mg/kg)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Any gr (%)</th>
<th>gr. 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin (rash, pruritus)</td>
<td>47-68</td>
<td>0-4</td>
</tr>
<tr>
<td>GI (diarrhea, colitis)</td>
<td>31-46</td>
<td>8-23</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>3-9</td>
<td>3-7</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>4-6</td>
<td>1-5</td>
</tr>
</tbody>
</table>

Toxicities with anti-PD1/PDL1 mAbs less common and less severe in comparison with anti-CTLA-4 mAbs → gr. 3-4 ranging from 7-12% with single agent anti-PD1/PDL1 vs 10-18% with single agent anti-CTLA-4.

Michot JM et al Eur J Cancer 2016 Feb;54:139-48
Systemic Oncology Therapies

**CHEMOTHERAPY**
- Target: rapidly dividing tumour and normal cells
- Adverse events: diverse due to non-specific nature of therapy

**TARGETED THERAPIES**
- Target: specific molecules involved in tumour growth and progression
- Adverse events: reflect targeted nature

**IMMUNO-ONCOLOGY (I/O) THERAPIES**
- Target: immune system
- Adverse events: unique events can occur as a result of immune-system activity

Different spectrum of adverse events with each type of therapy

Although adverse events may have different etiologies, some adverse events with I-O may present like those with other therapies

Require different management strategies
The challenge: finding the right balance ...
Occurrence of ir-adverse events with Ipi and anti-PD1 in melanoma:

<table>
<thead>
<tr>
<th>Type of study</th>
<th>MDX010-20 (ph 3, 676 pts.)</th>
<th>CA184-024 (ph 3, 502 pts.)</th>
<th>Tremelimumab (CA209-066) (ph 3, 655 pts.)</th>
<th>Nivolumab (ph 3, 418 pts.)</th>
<th>MK-3475-006 (ph 3, 834 pts.)</th>
<th>Ipi + Nivo (CA209-067) (ph 3, 945 pts., I/N 313)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (gr) (%)</td>
<td>all gr (%)</td>
<td>all gr (%)</td>
<td>all gr (%)</td>
<td>all gr (%)</td>
<td>all gr (%)</td>
<td>all gr (%)</td>
</tr>
<tr>
<td>Any (ir) event</td>
<td></td>
<td></td>
<td>61.1</td>
<td>74.3</td>
<td>79/73</td>
<td>95</td>
</tr>
<tr>
<td>Skin (rash, pruritis)</td>
<td>43.5</td>
<td>26.7</td>
<td>2.0</td>
<td>15</td>
<td>15/13</td>
<td>40</td>
</tr>
<tr>
<td>Gl (diarrhea, colitis)</td>
<td>29</td>
<td>32.8</td>
<td>4.0</td>
<td>16</td>
<td>2/4</td>
<td>44</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>3.8</td>
<td>29.1</td>
<td>20.7</td>
<td>1</td>
<td>1/2</td>
<td>17</td>
</tr>
<tr>
<td>Endocrine</td>
<td>7.6</td>
<td>2.8</td>
<td>0.0</td>
<td>5</td>
<td>7/3</td>
<td>15</td>
</tr>
<tr>
<td>Pneumon.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>0.4/2</td>
<td>n.r.</td>
</tr>
<tr>
<td>Renal</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>2/4</td>
<td>n.r.</td>
</tr>
</tbody>
</table>

## Occurrence of ir-adverse events with Ipi and anti-PD1 in NSCLC:

<table>
<thead>
<tr>
<th>Type of study</th>
<th>CA209-017 (ph 3, 272 sqNSCLC pts.)</th>
<th>CA209-057 (ph 3, 582 non-sq NSCLC pts.)</th>
<th>CA209-012 (ph 1, 52 pts.)</th>
<th>Keynote-001 (ph 1, 495 NSCLC pts.)</th>
<th>Keynote--010 (ph 3, 991 NSCLC pts.)</th>
<th>POPLAR (ph 3, 287 NSCLC pts.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any (ir) event</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>all gr (%)</td>
<td>all gr (%)</td>
<td>all gr (%)</td>
<td>70%</td>
<td>9.5%</td>
<td>67%</td>
</tr>
<tr>
<td></td>
<td>gr3/4 (%)</td>
<td>gr3/4 (%)</td>
<td>gr3/4 (%)</td>
<td>9%</td>
<td>0.2%</td>
<td>11%</td>
</tr>
<tr>
<td>Skin (rash, pruritus)</td>
<td>4%</td>
<td>0%</td>
<td>n.r.</td>
<td>9%</td>
<td>0.2%</td>
<td>9/13</td>
</tr>
<tr>
<td>GI (diarrhea, colitis)</td>
<td>8%</td>
<td>0%</td>
<td>8%</td>
<td>8%</td>
<td>0.6%</td>
<td>1%</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>3%</td>
<td>0.6%</td>
<td>4%</td>
</tr>
<tr>
<td>Endocrine</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>6%</td>
<td>0.2%</td>
<td>7%</td>
</tr>
<tr>
<td>Pneumon.</td>
<td>5%</td>
<td>0%</td>
<td>n.r.</td>
<td>6%</td>
<td>1.8%</td>
<td>3%</td>
</tr>
<tr>
<td>Renal</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
<td>n.r.</td>
</tr>
</tbody>
</table>

Kinetics of appearance of immune-related adverse event under Ipilimumab:

<table>
<thead>
<tr>
<th>Type of Immune-Related Adverse Event</th>
<th>Median Time to Onset, wk</th>
<th>Median Time From Onset to Resolution, wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Hepatic</td>
<td>3-9</td>
<td>0.7-2.0</td>
</tr>
<tr>
<td>Gastrointestinal reactions</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Endocrine</td>
<td>7-20</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviations: NR, not reported.

![Graph showing the kinetics of immune-related adverse events](image-url)

Kinetics of appearance of IR-AEs under Nivolumab (in CA209-037):

Villadolid j et al Trans Lung Cancer Res 2015 4 (5):560-75
Pembrolizumab:
Immune-mediated Adverse Reactions
Median Time to Onset and Median Duration\(^1\)

- Median time to onset and median duration of immune-mediated adverse reactions are presented based on 2799 patients with NSCLC and melanoma treated with Pembrolizumab.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Median Time to Onset</th>
<th>Median Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis</td>
<td>3.3 (2 days–19.3 mo)</td>
<td>1.5 (1 day–17.2+ mo)</td>
</tr>
<tr>
<td>Colitis</td>
<td>3.5 (10 days–16.2 mo)</td>
<td>1.3 (1 day–8.7+ mo)</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>1.3 (8 days–21.4 mo)</td>
<td>1.8 (8 days–20.9+ mo)</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>3.7 (1 day–11.9 mo)</td>
<td>4.7 (8 days–12.7+ mo)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>1.4 (1 day–21.9 mo)</td>
<td>2.1 (3 days–15.0+ mo)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>8.5 (1 day–18.9 mo)</td>
<td>NR (2 days–27.7+ mo)</td>
</tr>
<tr>
<td>Nephritis</td>
<td>5.1 (12 days–12.8 mo)</td>
<td>3.3 (12 days–8.9+ mo)</td>
</tr>
</tbody>
</table>

General Management Guidelines for irAEs

1. Signs and Symptoms Present
   - Rule out alternative etiologies
   - Determine severity using NCI CTCAE grading scale

2. No irAE?
   - Manage with symptomatic therapy
   - CONTINUE

3. Yes irAE?
   - Grade 1: Manage with symptomatic therapy
     - CONTINUE
   - Any grade 2 or grade 3 skin toxicities:
     - Administer oral steroid therapy*
       - Consider consulting organ-specific consultant
     - If no improvement to ≤ grade 1 after 1 week, manage as high-grade event
     - SUSPEND
   - Grade 3 non-skin toxicity or any grade 4 toxicity:
     - Treat with high-dose steroid therapy*
       - Consult organ-specific consultant
     - If no improvement
       - DISCONTINUE

Please refer to organ specific guidelines

*e.g. prednisone 1 mg/kg daily, methylprednisolone 2 mg/kg IV or equivalent. Depending on the dose and length of time, if symptoms improve, gradually taper over a minimum of 4 weeks.
Common Terminology Criteria for Adverse Events (CTCAE)

Version 4.0
Published: May 28, 2009 (v4.03: June 14, 2010)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute
Skin toxicity

- In 47-68% of pts receiving ipilimumab, observed after an average of 3.6 weeks, in 34% with nivolumab and 39% with pembrolizumab, typically after 2\textsuperscript{nd} course
- Diffuse, maculopapular rash, with pruritus
- Histopathology: perivascular lymphocytic infiltrate extending deep into the dermis and up to epidermis
- CD4+ and CD8+ T cells in close proximity to apoptotic melanocytes → \textit{\~10\% vitiligo with Pembrolizumab}
- Managed symptomatically (topical or oral steroids), rarely require skipping a dose or discontinuation
- BUT: rare cases of toxic epidermal necrolysis and Stevens-Johnson syndrome have been reported with Ipi, eventually resulting in death

Minkis K et al JAAD 2013; 69:e121-8
Lacouture M et al JAAD 2014, epub
Overall survival in 253 patients receiving immunotherapy from 15 studies.
Grade

1
Macules/papules covering <10% BSA* + asymptomatic or with symptoms**

Grade

2
Macules/papules covering 10-30% BSA* + asymptomatic or with symptoms** + limiting self-care ADL***

Grade

3-4
Macules/papules covering >30% BSA* + asymptomatic or with symptoms** + severe/life threatening symptoms + generalized exfoliative/ ulcerated / bullous rash

Investigations

Mucocutaneous clinical examination

Serum testing for liver, kidney function, typtase, IgE levels

Consider dermatology consult

Consider skin biopsy

Management

• Continue Immunotherapy
• Topical steroids
• Oral antihistamines for pruritus

• Oral prednisone 1mg/kg/day or equivalent
• Oral antihistamines for pruritus

• Hold Immunotherapy
• Oral prednisone 1mg/kg/day or equivalent
• Oral antihistamines for pruritus

• Repeat skin exam
• If develops symptoms treat as higher grade

Follow-up

• If improves to ≤ gr. 1, resume immunotherapy
• After symptoms improve, taper steroids over ≥1 month
• If rash does not improve after 12 weeks from last dose of therapy discontinue immunotherapy.

• If improves to ≤ gr. 1, taper steroids over ≥1 month
• If worsens in 48 hrs, consider additional immunosuppression (infliximab, cyclophosphamide, mycophenolate mofetil) or supportive measures
• If no improvement after 12 weeks from last dose of therapy discontinue immunotherapy.

BSA = Body surface area. ** symptoms as per CTCAE 4.0, i.e. pruritus, burning, tightness. ***ADL = activity of daily living. * additional supportive measures = prophylactic antibiotics, management in the burns unit

Gastrointestinal side-effects:

- Diarrhea in up to 44% of pts receiving ipilimumab, grade 3/4 in 18% with 10 mg/kg; 6-8 weeks after start, only 1-3% with anti-PD1/PDL1.
- Can be associated with colitis, leading to obstruction and bowel perforation.
- Predominantly descending colon.
- Histopathology: neutrophilic infiltrates in 46%, lymphocytic infiltrates in 15%, mixed in 38%.
- Managed symptomatically according algorithm (methylprednisolone 1-2 mg/kg, eventually infliximab 5mg/kg).
- **BUT:** rare cases of perforation resulting in death have been reported with Ipi → early intervention key!

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea (= frequent and watery bowel movements)</td>
<td>Increase of &lt; 4 stools per day over baseline; mild increase in ostomy output compared to baseline</td>
<td>Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline</td>
<td>Increase of &gt; 7 stools per day over baseline; incontinence, hosp indicated; severe increase in ostomy output compared to baseline, limiting self care ADL</td>
<td>Life-threatening consequences, urgent intervention indicated</td>
</tr>
</tbody>
</table>

Kim KW et al AJR 2013
Diarrhea Management Algorithm:

1. Diarrhea or blood in stool
   - Rule out clear non IRAE
     - Yes: Specific treatment
     - No: Continue immunotherapy

2. Grade of diarrhea
   - 1: Treat symptomatically without steroids
     - Yes: Continue immunotherapy
     - No: Resolved to diarrhea ≤ gr. 1
     - Yes: Treat with high dose steroids and taper for at least 1 month
     - No: Treat with oral budesonide or other moderate dose steroid

3. Grade of diarrhea
   - 3-4: Consider endoscopy
     - No: Likely colitis?
       - Yes: Discontinue immunotherapy
       - No: Treat with high dose steroids and taper for at least 1 month

4. If no response in 1 week, consider 5mg/Kg dose of infliximab
Endocrine side-effects:

- Immune-related hypophysitis in 1-6% of patients treated with 3 or 10 mg/kg ipilimumab, 1-6% with anti-PD1/PDL1, recovery in 37-50%
- Problem: nonspecific symptoms such as headache, nausea, vertigo, behaviour change, visual disturbances and weakness occur at an average of 6 weeks after initiation of therapy with Ipilimumab
- MRI can show enlargement or heterogeneity of the pituitary
- Before treatment: determine pituitary, thyroid, adrenal and gonadal status
- Before each dose: thyroid function tests and biochemistry profile, including mineral electrolyte, and hepatic functions
- Median time to resolution of symptoms and the substitution of physiologic doses of hydrocortisone can be longer than 20 weeks with Ipi
- Also possible: isolated thyroid dysfunction (hypothyroidism and/or thyreotoxicosis) or adrenal insufficiency
- As most endocrinopathies can be treated with hormone replacement, discontinuation usually not needed

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroidism (= decreased production of thyroid hormone by the thyroid gland)</td>
<td>Asymptomatic; clinical or diagnostic observations only; intervention not indicated</td>
<td>Symptomatic; thyroid replacement indicated; limiting instrumental ADL</td>
<td>Severe symptoms; limiting self-care ADL; hosp indicated</td>
<td>Life-threatening consequences, urgent intervention indicated</td>
</tr>
</tbody>
</table>

### Presentation of Immune-related Endocrinopathies

<table>
<thead>
<tr>
<th>Endocrinopathy</th>
<th>Presentation</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypophysitis</strong></td>
<td>Clinical symptoms: headache and fatigue</td>
<td>Biochemical tests distinguish between primary adrenal insufficiency (low cortisol or inappropriate cortisol stimulation test; high ACTH) and primary hypothyroidism (low free T4; high TSH)</td>
</tr>
<tr>
<td></td>
<td>Radiographic findings: pituitary enhancement and enlargement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Biochemical findings: low ACTH and TSH due to pituitary dysfunction</td>
<td></td>
</tr>
<tr>
<td><strong>Hyperthyroidism / hypothyroidism</strong></td>
<td>Revealed through routine monitoring of thyroid function (TSH) during immune checkpoint inhibitor therapy</td>
<td>Distinguish primary hypothyroidism (low free T4 and high TSH) from hypophysitis, which can cause secondary hypothyroidism (low free T4 and low TSH)</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>Low cortisol or inappropriate cortisol stimulation test; high ACTH</td>
<td>Potentially serious consequences of adrenal crisis associated with dehydration, hypotension, and electrolyte imbalances (eg, hyperkalemia and hyponatremia)</td>
</tr>
</tbody>
</table>

ACTH = adrenocorticotropic hormone; T4 = thyroxine; TSH = thyroid-stimulating hormone.

*Postow MA. ASCO Educational Book. 2015;75-83.*
Endocrinopathy Management Algorithm:

Suspect endocrinopathy (based on clinical signs and symptoms¹)

Suspect adrenal crisis

Yes

Suspect Adrenal Crisis:
1. Rule out sepsis
2. If strong suspicion of adrenal crisis (e.g. severe dehydration, hypotension, shock, ... ) then start stress dose IV steroids (with mineralocorticoid activity), fluids, consult endocrinologist
3. If symptoms suggestive of endocrinopathy but patient not in crisis, then wait for lab results before starting steroid therapy

No

1. Check endocrine labs² (before starting steroids)
2. MRI head with pituitary cuts
3. Visual field testing if appropriate
4. Consider endocrinologist consult

Results abnormal

Yes

Rule out other etiologies for patient symptoms
Initiate more frequent patient follow-up
Repeat endocrine labs in 1-3 weeks

No

Initiate short course of high dose steroids to reverse inflammation
Initiate appropriate hormone replacement to reverse endocrinopathy
Consult endocrinologist as needed

If lab and radiologic results are negative but symptoms persist:
Consult endocrinologist
Considering MRI brain in 1 months

Long term follow-up:
Taper high dose steroids
Continue hormone replacement as needed
Monitor endocrine labs

¹ Possible clinical signs & symptoms: headache, visual field defects, fatigue, weakness, asthenia, anorexia, nausea and vomiting, lethargy, amenorrhea, fever, coma, hypotension, hyponatremia

² suggested endocrine lab work
1. TSH, free T4, T3
2. ACTH, AM serum cortisol, if abnormal ACTH stimulation test
3. LH, FSH, testosterone, prolactin

Upon resolution or adequate treatment of endocrinopathy patients may continue immunotherapy with appropriate replacement
Patients may require chronic hydrocortisone replacement
Beware of complete discontinuation of steroid use due to prolonged adrenal suppression
Hepatotoxicity:

- Has been observed in 3-9% patients treated with ipilimumab, <5% with anti-PD1/PDL1, higher in HCC pts.; in combi with Ipi and other targeted agents or chemotherapy → significant rate of hepatotoxicity with Ipi/DTIC and Ipi/vemurafenib
- With Ipi ~8-12 weeks after starting therapy
- Usually asymptomatic increase of transaminases and bilirubin
- Rule out viral hepatitis, disease progression or other drug-related causes
- Liver function tests before treatment and before each dose, every three months thereafter
- Median time to resolution 0.7-2 weeks with Ipi

<table>
<thead>
<tr>
<th>Alanine aminotransferase increased</th>
<th>&gt;ULN - 3.0 x ULN</th>
<th>&gt;3.0 - 5.0 x ULN</th>
<th>&gt;5.0 - 20.0 x ULN</th>
<th>&gt;20.0 x ULN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition: A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.</td>
<td></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alkaline phosphatase increased</th>
<th>&gt;ULN - 2.5 x ULN</th>
<th>&gt;2.5 - 5.0 x ULN</th>
<th>&gt;5.0 - 20.0 x ULN</th>
<th>&gt;20.0 x ULN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition: A finding based on laboratory test results that indicate an increase in the level of alkaline phosphatase in a blood specimen.</td>
<td></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aspartate aminotransferase increased</th>
<th>&gt;ULN - 3.0 x ULN</th>
<th>&gt;3.0 - 5.0 x ULN</th>
<th>&gt;5.0 - 20.0 x ULN</th>
<th>&gt;20.0 x ULN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition: A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood bilirubin increased</th>
<th>&gt;ULN - 1.5 x ULN</th>
<th>&gt;1.5 - 3.0 x ULN</th>
<th>&gt;3.0 - 10.0 x ULN</th>
<th>&gt;10.0 x ULN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition: A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Grade

1
• Asymptomatic AST or ALT ≤ 2.5xULN*
• Total Bilirubin ≤ 1.5xULN

2
• AST or ALT > 2.5xULN and ≤ 5xULN
• Total Bilirubin > 1.5xULN and ≤ 3xULN

3-4
• AST or ALT > 5xULN
• Total Bilirubin > 3xULN

Investigations

Standard liver function tests (LFT)

Exclude viral and other drug-induced hepatitis

Consider radiologic evaluation to exclude malignant causes

Management

• Continue Immunotherapy if asymptomatic
• Monitor LFT routinely until resolution

• Withhold immunotherapy
• Oral prednisone 1mg/kg/day or equivalent
• Monitor LFT daily

• Discontinue Immunotherapy
• IV methylprednisolone 2-4 mg/kg/day or equivalent
• Monitor LFT daily

Follow-up

• If LFT worsens or develops symptoms, treat as higher grade

• If symptoms resolve and LFT improves to ≤ grade 1, resume immunotherapy at next dose
• After improvement taper steroids over ≥1 month with weekly LFT

• After symptoms and LFT improve to baseline taper steroids over ≥1 month with weekly LFT
• If no response within 3 days consider additional immunosuppression (infliximab, cyclophosphamide, mycophenolate mofetil)

* ULN = upper limit of normal
Pneumonitis:

- In <10% with anti-PD1/PDL1, higher in NSCLC pts.; 3 treatment related deaths in ph. 1 nivolumab studies, most likely less with Ipi alone
- With Ipi more sarcoid-like granulomatous reactions → CAVE: enlarged LN under Ipi → if possible take a biopsy!
- Timing of development wide range (between 7.4 and 24.3 months after start therapy)
- Usually shortness of breath, cough, fever or chest pain, can also be asymptomatic
- Rule out infectious diseases, disease progression or other drug-related causes
- High resolution CT and bronchoscopy indicated, eventually lung function testing
- Severe cases require hospitalization and intravenous corticosteroids, sometimes infiliximab or MMT

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis (= inflammation focally or diffusely affecting lung parenchyma)</td>
<td>Asymptomatic; clinical or diagnostic observations only; intervention not indicated</td>
<td>Symptomatic; medical intervention indicated; limiting instrumental ADL</td>
<td>Severe symptoms; limiting self-care ADL; oxygen indicated</td>
<td>Life-threatening; respiratory compromise; urgent intervention indicated</td>
</tr>
</tbody>
</table>

**Grade**

1. Asymptomatic
   - Radiologic changes only

2. Mild/moderate new symptoms

3-4
   - Severe life-threatening new symptoms
   - Worsening hypoxia

**Investigations**

- Radiologic imaging (high resolution CT chest)
- Microbial assessment where necessary
- Consider pulmonary/infec-
  tious disease consults and bronchoscopy

**Management**

- Continue Immunotherapy
- Monitor for symptoms every 3 days

- Withhold immunotherapy
- Monitor for symptoms daily
- Oral prednisone 1mg/kg/day or equivalent

- Discontinue Immunotherapy
- Hospitalization
- IV methylprednisolone 2-4 mg/kg/day or equivalent
- Prophylactic antibiotics

**Follow-up**

- Repeat CT every cycle
- If develops symptoms treat as higher grade

- If symptoms to ≤ grade 1 within 3 days of supportive care, *resume immunotherapy at next dose*
  - If persistent beyond 3 days, discontinue immunotherapy
  - After improvement taper steroids over ≥1 month

- After symptoms improve to ≤ grade 1 or baseline taper steroids over ≥6 weeks
  - If worsens in 48 hrs consider additional immunosuppression (infliximab, cyclophosphamide, mycophenolate mofetil)

Neurological Toxicity Management Algorithm:

**Grade**
- Grade 1
- Grade 2
- Grade 3-4 (sensory)
- Grade 3-4 (motor)

**Investigations**
- Radiologic imaging (CT / MRI of brain and / or spine)
- Rule out non-inflammatory causes
- Consider neurology consult (lumbar puncture, EMG, ...)

**Management**
- Grade 1:
  - Continue Immunotherapy if considered related
  - IV methylprednisolone 1-2 mg/kg/day or equivalent
- Grade 2:
  - Discontinue Immunotherapy if considered related
  - IV methylprednisolone 1-2 mg/kg/day or equivalent
- Grade 3-4 (sensory):
  - Discontinue Immunotherapy regardless of relationship
  - IV methylprednisolone 1-2 mg/kg/day or equivalent
- Grade 3-4 (motor):
  - Discontinue Immunotherapy regardless of relationship
  - IV methylprednisolone 1-2 mg/kg/day or equivalent

**Follow-up**
- Grade 1:
  - Continue monitoring
  - If develops symptoms treat as higher grade
- Grade 2:
  - Withhold immunotherapy
  - Monitor for symptoms daily
  - Treat symptoms per local guideline
- Grade 3-4 (sensory):
  - After symptoms improve to ≤ grade 2 or baseline taper steroids over ≥4 weeks
  - If worsens consider IV Ig or additional immunosuppression (infliximab, cyclophosphamide, mycophenolate mofetil)
- Grade 3-4 (motor):
  - After symptoms improve to ≤ grade 2 or baseline taper steroids over ≥4 weeks
  - If worsens consider IV Ig or additional immunosuppression (infliximab, cyclophosphamide, mycophenolate mofetil)
Other immune related adverse effects:

- Renal toxicity (tubolointerstitial nephritis)
- Pancreatitis (can be monitored without immunosuppressive therapy → asymptomatic elevated grade 3 lipase do not need discontinuation!)
- Neuropathy (Guillain-Barré syndrome, Myasthenia gravis-like syndrome, enteric neuropathy, aseptic meningitis)
- Sarcoid-like syndrome
- Episcleritis /Uveitis
- Others: hemophilia A, DRESS (drug rash with eosinophilia and systemic symptoms),
The five pillars of immunotherapy toxicity management:

**PREVENT**
- Know the immune-toxicity spectrum
- Identify dysimmunity risk factors
- Inform patients and their healthcare providers

**ANTICIPATE**
- Baseline check-up
- On-treatment follow-up
- Off-treatment follow-up

**MONITOR**
- Resolution kinetic
- Relapse, recurrence
- Immunosuppression complications

**TREAT**
- Symptomatic treatment
- Patient information
- Discuss:
  - Immunotherapy suspension?
  - Refer to organ specialist?
  - Corticosteroids?
  - Other immunosuppressive drugs?

**DETECT**
- Baseline values = reference values
- Eliminate progression
- Always consider dysimmune toxicities

S. Champiat et al. Ann Oncol 2016;annonc.mdv623
Recommendations for Patient/Caregiver Education

General Educational Points

• Vigilance¹
• Prompt symptom reporting¹
• Advise emergency HCPs about anticancer medication²
  • Show patient wallet card
• Do not take over the counter dietary supplements¹
  • Unless approved by HCP

Educational Points for Follow-up Visits¹

• Reinforce importance of early detection and prompt reporting
• Confirm patient’s ability to verbalize important symptoms
• Procedure for AE reporting or seeking medical attention when office is closed
• Symptoms may occur weeks to months after infusion

Use patient monitoring checklist³

---

Ask patients if they are experiencing any of the following symptoms:

- diarrhea
- abdominal pain/cramping
- nausea/vomiting
- changes in bowel movements
- blood in stool

- rash
- itch
- changes to color of skin

- weakness in hands and feet
- difficulty standing or walking
- tingling or numbness

- fatigue
- headache
- unusual bowel habits
- cognitive problems

Consider potential toxicity and contact provider:

- GI
- Dermatologic
- Neurologic
- Endocrine

General symptoms that may require follow-up:
- fever, vision changes, difficulty sleeping, changes in appetite, difficulty performing daily activities, respiratory distress, pain, coughing
Figure 2. Analyses of the impact of steroid use on ipilimumab responses

- Steroids prior to response
- No steroids prior to response

<table>
<thead>
<tr>
<th>Condition</th>
<th>With Steroids</th>
<th>Without Steroids</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/PR/SD</td>
<td>25.4% (29/114)</td>
<td>24.3% (33/138)</td>
</tr>
<tr>
<td>PD or Unknown*</td>
<td>74.6% (85/114)</td>
<td>75.7% (103/136)</td>
</tr>
</tbody>
</table>

*Including patients who had SD followed by PD
CR= complete response; PR= partial response; SD= stable disease; PD= progressive disease
Overview of Resolution of Grade 3/4 Regimen-associated imARs in Patients Managed Using Established Guidelines (CheckMate 067)\(^1\)

- Most grade 3/4 imARs were effectively managed using established guidelines\(^1\)

<table>
<thead>
<tr>
<th>imAR organ category(^a)</th>
<th>NIVO + IPI (n = 313)</th>
<th>NIVO (n = 313)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with resolution of imARs, n (%)</td>
<td>Median time to resolution, weeks (range)</td>
</tr>
<tr>
<td>Skin</td>
<td>12 (86)</td>
<td>3.4 (0.7–53.0+)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>41 (98)</td>
<td>3.0 (0.3–33.1+)</td>
</tr>
<tr>
<td>Endocrine</td>
<td>5 (46)</td>
<td>NE (1.6–46.6+)</td>
</tr>
<tr>
<td>Hepatic</td>
<td>38 (100)</td>
<td>4.1 (0.3–26.0)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>2 (100)</td>
<td>4.2 (1.1–7.3)</td>
</tr>
<tr>
<td>Renal</td>
<td>3 (100)</td>
<td>1.7 (0.4–3.6)</td>
</tr>
</tbody>
</table>

- Similar data were reported from the CheckMate 069 phase 2 trial\(^2\)

NA = not available.

Specific situations:

- **Safety of pembrolizumab in pts who stopped Ipi due to irAEs, abstract e22023, ASCO 2015:** 10 pts with MM: “pts who stop ipi due to irAEs may have different irAEs emerge when receiving pembro; experiencing a severe irAE from ipi does not preclude a pt from subsequently receiving pembro.

- **Toxicity of Ipi in pts progressing under anti-PD1, abstract 9059 at ASCO 2015:** 10 pts with MM, 1/10 of pts achieved a PR, 3/10 pts experienced grade3/4 immune related adverse events (irAE), CAVE: cases of severe and unusual irAEs (eg pneumonitis) observed!

- **Ipilimumab in MM pts with pre-existing auto-immune disorders, abstract 9019 at ASCO 2015:** Of 12 pts, 5 had baseline rheumatoid arthritis, 3 had psoriasis/psoriatic arthritis, 1 had systemic lupus erythematosus, 1 had Crohn’s disease, 1 had transverse myelitis, and 1 had sarcoidosis. Ten (83%) had previously received corticosteroids or other systemic therapy for their AD, including 5 ongoing at the time of Ipi initiation (low-dose prednisone in 2 pts and hydroxychloroquine in 3). Following Ipi, 6 pts (50%) had symptomatic worsening or flares of their AD; all resolved with short courses of corticosteroids and none required additional immune suppression. Grade 3-5 irAEs were observed in 5 pts (42%) including colitis (n = 2), hypophysitis (n = 2), and acute angle glaucoma (n = 1). One treatment-related death occurred, presumably from colitis and possibly hypophysitis (no laboratory confirmation) following dose 3 of Ipi. ORR was 17% (2/12 pts)
Ipilimumab and surgery / radiotherapy:

- **Abstract 8583: Surgery for patients receiving ipilimumab: Safety profile and immunological insights (Gyorki DE et al):**
  - Surgery is safe in patients receiving ipi. Immune modulation caused by CTLA-4 blockade does not appear to impact wound healing, even in the bowel. In carefully selected patients metastectomy may be appropriate for breakthrough metastases. The high percentage of T regulatory cells and low T effector cells in the progressive tumors suggests a mechanism of immune escape.

- **See also: Immunologic correlates of the abscopal effect in a patient with melanoma (Postow MA et al. N Engl J Med 2012;366:925-931).**
  - Case report of the abscopal effect (= clearance of nonirradiated tumors after localized radiation therapy) in a patient with melanoma treated with ipilimumab and radiotherapy. Temporal associations were noted: tumor shrinkage with antibody responses to the cancer-testis antigen NY-ESO-1, changes in peripheral-blood immune cells, and increases in antibody responses to other antigens after radiotherapy.
Integration of Immuno-Oncology and palliative care:

- Overwhelming enthusiasm for immunotherapeutics in several tumor types, but:
  - Not all patients will have benefit, responses can be heterogeneous, lack of predictive biomarkers of response and/or toxicity
  - Only a small of patients with enlarging or new lesions will subsequently experience an immune-related response, but: these can be associated with durable benefit measured in years
  - On the other hand: treatment beyond progression can also mean continuation of futile treatment, slowing the transition to “end of life care (EOLC)” and contributing to patient suffering, for example restriction to use supportive medications such as steroids because of concerns about reducing the efficacy of immunotherapy.
  - Challenge of maintaining hope while establishing of realistic expectations
  - Even more difficult in resource-constrained environment
  - More research needed on QoL, palliative care and survivor ship research in the era of immuno-oncology
Changing the face of melanoma
... the modern melanoma patient:
# Disclosure of potential conflict of interests:

<table>
<thead>
<tr>
<th>Employment or leadership positions</th>
<th>Consultant or Advisory Role</th>
<th>Stock ownership</th>
<th>Honoraria</th>
<th>Research funding</th>
<th>Other remuneration</th>
</tr>
</thead>
<tbody>
<tr>
<td>no</td>
<td>No personal renumeration</td>
<td>no</td>
<td>no</td>
<td>Pfizer GSK</td>
<td>No travel grants</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bayer Novartis</td>
<td></td>
</tr>
</tbody>
</table>

Dr. Pascal Wolter, CHR Verviers East Belgium, Centre d’Oncologie et d’Hématologie  
[Email](mailto:pascalwolter@hotmail.com), +32 87 21-1111 or -2987
Casus 1:

- 09-2013: klier- en galblaasmetastasen, vermoeden longmetastasen
- 18-10-2013: inclusie CHECKMATE studie vergelijking van de immunotherapie Ipilimumab/placebo vs Nivolumab/placebo vs Ipilimumab/Nivolumab.
Casus 1:

- 31-10-2013: na eerste toediening ontwikkelen van droge hoest, urticariële rash en subfebrilitas, op CT massieve progressie thv miliaire longmetastasen (dd: pseudoprocessie, dd: pneumonitis)
Questions – What do you do?

1. I stop the immunotherapy immediately
2. I go on with the immunotherapy
3. I go on with immunotherapy but I start corticosteroids
4. I don't know
Casus 1:

- 31-10-2013: na eerste toediening ontwikkelen van droge hoest, urticariële rash en subfebrilitas, op CT massieve progressie thv miliaire longmetastasen (dd: pseudoprogressie, dd: pneumonitis)
Immuno-oncology – Patterns of Response in Melanoma

Typical Patterns of Response Observed with Immuno-oncology

- **Majority of responders**
  - Conventional
  - Slow, steady decline in tumour burden

- **Minority of responders**
  - Late response after initial progression
  - New lesions appear and then decline along with target lesion

---

Current Chemotherapy Response Criteria may not adequately capture the clinical activity of Ipilimumab.


Fig. 1. Patterns of response to ipilimumab observed in advanced melanoma. Shown are the four response patterns observed in advanced melanoma patients treated with ipilimumab at 10 mg/kg in the CA184-008 and CA184-022 studies. A, response in baseline lesions; B, “stable disease” with slow, steady decline in total tumor volume; C, response after initial increase in total tumor volume; D, reduction in total tumor burden after the appearance of new lesions. SPD, sum of the product of perpendicular diameters. N, tumor burden of new lesions (C and D). T, top line, total tumor burden; mid line, tumor burden of baseline lesions; bottom line, tumor burden of new lesions. Triangles, ipilimumab dosing time points; dashed lines, thresholds for response or PD/irPD.
Table 1. Comparison between WHO criteria and the irRC

<table>
<thead>
<tr>
<th></th>
<th>WHO</th>
<th>irRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>New, measurable lesions (i.e., ≥5 × 5 mm)</td>
<td>Always represent PD</td>
<td>Incorporated into tumor burden</td>
</tr>
<tr>
<td>New, nonmeasurable lesions (i.e., &lt;5 × 5 mm)</td>
<td>Always represent PD</td>
<td>Do not define progression</td>
</tr>
<tr>
<td>Non-index lesions</td>
<td>Changes contribute to defining BOR of CR, PR, SD, and PD</td>
<td>Contribute to defining irCR (complete disappearance required)</td>
</tr>
<tr>
<td>CR</td>
<td>Disappearance of all lesions in two consecutive observations not less than 4 wk apart</td>
<td>Disappearance of all lesions in two consecutive observations not less than 4 wk apart</td>
</tr>
<tr>
<td>PR</td>
<td>≥50% decrease in SPD of all index lesions compared with baseline in two observations at least 4 wk apart, in absence of new lesions or unequivocal progression of non-index lesions</td>
<td>≥50% decrease in tumor burden compared with baseline in two observations at least 4 wk apart</td>
</tr>
<tr>
<td>SD</td>
<td>50% decrease in SPD compared with baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions</td>
<td>50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir</td>
</tr>
<tr>
<td>PD</td>
<td>At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)</td>
<td>At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 wk apart</td>
</tr>
</tbody>
</table>

Casus 2:

- 04-2008: diagnose acraal lentigineus maligne melanoma thv de linker hiel, Breslow 2,7 mm, Clark level III, pT3a,
- 05-2008: brede resectie (2cm marge), correctie huiddefect dmv full thickness graft genomen uit rechter lies, sentinelklierbiopsie positief, gevolgd door een iliacofemoraal links (2/6 klieren positief)
- 07-2009: opstarten adjuvant Intron A tot half juli 2009 buiten studieverband
- 09-2009: diagnose van in transit metastasen thv de linker dij en lies.
- 10-2009: huidexcisie met subcutis in linker lies, bij APO: verspreide metastasen
- 11-2009: aanvullend radiotherapie tot 60 Gy in 30 fracties
- 01-2010: gunstige respons van de intransit metastasen in bestraal gebied, maar nieuwe metastasen mediaal van net bestralingsveld.
- 02-2010: resectie van in transit metastasen thv de linker dij en lies
- 03-2010: opnieuw resectie van in transit metastasen thv de linker dij
- 04-2010: start systemische chemotherapie oov DTIC in monotherapie oov van verdere lokale en niet resecabele ziekteprogressie, onder de chemotherapie regressie van de meeste noduli
- 08-2010: toename van 2 letseals aan de rand van het vroegere bestraalde gebied, bestraling met rechtstreeks elektronenveld (25 Gy in 5 zittingen)
- 10-2010: multiple recidieven in transit letseals melanoom
- 7-11-2010: geïsoleerde lidmaat perfusie linkerbeen, op iliacaal niveau, met profylactische klierrevidement, zonder tumor.
- 19-05-2011: ziekteprogressie met ontstaan van multiple klier- en subcutane metastasen, tevens levermetastasen, start Ipilimumab ikv expanded access program
Case 2:

Skin (left) and long metastasis (right) before (upper) and after 12 weeks (lower) of Ipilimumab.

CT scan of the lung at baseline

CT scan of the lung at week 12
Questions – What do you do?

1. I stop the immunotherapy immediately and give another treatment
2. I go on with the immunotherapy
3. I go on with immunotherapy but I resect the progressing lesions
4. I don’t know
Casus 3:

- 08-1994 (♀, * 1931): excisie superficieel spreidend melanoma dorsaal aan de enkel, Clark level IV, dikte meting volgens Breslow 2,9 mm.
- tussen 2010 en 2011: recidiverende intransit metastasen waarvoor resectie en geïsoleerde lidmaatperfusie met Melphalan
- 09-2013: intransit-, klier- en longmetasasen
- 04-10-2013: inclusie CHECKMATE studie vergelijking van de immunotherapie Ipilimumab/placebo vs Nivolumab/placebo vs Ipilimumab/Nivolumab.
- 20-11-2013: opname op spoedgevallen voor kortademigheid en lage saturaties
Questions – What is your diagnosis / treatment?

1. Early progression under immunotherapy, I stop the immunotherapy
2. Must be pseudoprogression, I go on with the immunotherapy
3. Most likely pneumonitis, I stop immunotherapy and start immediately corticosteroids
4. I don’t know
Questions?