ESMO Guidelines: Management of Toxicities from Immune Checkpoint Inhibitors

John B.A.G. Haanen MD PhD
My disclosures

• I have provided consultation, attended advisory boards, and/or provided lectures for: Pfizer, Bayer, MSD, BMS, IPSEN, Novartis, Roche/Genentech, Neon Therapeutics, Celsius Therapeutics, Gadeta BV, Immunocore, Seattle genetics for which NKI received honoraria

• Through my work NKI received grant support from BMS, MSD, Novartis and Neon Therapeutics
CONTENT OF THIS PRESENTATION

• General aspects of immune related adverse events related to immune checkpoint inhibitors
• Anti-CTLA4 associated
• Anti-PD1/PDL1 associated
• Anti-CTLA4 + anti-PD1/PDL1 associated
• Management of side effects
  – General aspects
  – Specific algorithms
  – Important Practical Questions
  – Take home message
CLINICAL PRACTICE GUIDELINES

Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

J. B. A. G. Haanen¹, F. Carbonnel², C. Robert³, K. M. Kerr⁴, S. Peters⁵, J. Larkin⁶ & K. Jordan⁷, on behalf of the ESMO Guidelines Committee*
<table>
<thead>
<tr>
<th>Drug</th>
<th>Indications</th>
<th>EMA/FDA approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>Metastatic melanoma</td>
<td>EMA + FDA</td>
</tr>
<tr>
<td></td>
<td>Adjuvant therapy stage III melanoma</td>
<td>FDA</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Metastatic melanoma</td>
<td>EMA + FDA</td>
</tr>
<tr>
<td></td>
<td>2(^{nd}) line metastatic NSCLC</td>
<td>EMA + FDA</td>
</tr>
<tr>
<td></td>
<td>2(^{nd}) line metastatic RCC</td>
<td>EMA + FDA</td>
</tr>
<tr>
<td></td>
<td>Classical Hodgkin’s disease(^{a})</td>
<td>EMA + FDA</td>
</tr>
<tr>
<td></td>
<td>Recurrent or metastatic SCCHN(^{p})</td>
<td>EMA + FDA</td>
</tr>
<tr>
<td></td>
<td>Locally advanced or metastatic UCC(^{c})</td>
<td>EMA + FDA</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Metastatic melanoma</td>
<td>EMA + FDA</td>
</tr>
<tr>
<td></td>
<td>2(^{nd}) line metastatic NSCLC (PD-L1 ≥ 1%)</td>
<td>EMA + FDA</td>
</tr>
<tr>
<td></td>
<td>1(^{st}) line metastatic NSCLC (PD-L1 ≥ 50%)</td>
<td>EMA + FDA</td>
</tr>
<tr>
<td></td>
<td>1(^{st}) line metastatic NSCLC in combination with pemetrexed + carboplatin</td>
<td>FDA</td>
</tr>
<tr>
<td></td>
<td>Classical Hodgkin’s disease(^{a})</td>
<td>EMA + FDA</td>
</tr>
<tr>
<td></td>
<td>Locally advanced or metastatic UCC(^{c})</td>
<td>FDA</td>
</tr>
<tr>
<td></td>
<td>MSI-H or MMR deficient metastatic malignancies(^{e})</td>
<td>FDA</td>
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<td>Atezolizumab</td>
<td>Locally advanced or metastatic UCC(^{c})</td>
<td>FDA</td>
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<td></td>
<td>2(^{nd}) line metastatic NSCLC</td>
<td>FDA</td>
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<tr>
<td>Avelumab</td>
<td>Locally advanced or metastatic UCC(^{c})</td>
<td>FDA</td>
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<tr>
<td></td>
<td>Metastatic Merkel cell carcinoma</td>
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<tr>
<td>Durvalumab</td>
<td>Locally advanced or metastatic UCC(^{c})</td>
<td>FDA</td>
</tr>
<tr>
<td>Ipilimumab + nivolumab</td>
<td>Metastatic melanoma</td>
<td>EMA + FDA</td>
</tr>
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</table>
GENERAL ASPECTS

- Adverse events are unwanted effects of immune checkpoint inhibitors
- AEs are most likely the result of the mechanism of action of immune checkpoint inhibitors
- AEs can occur in every organ
- AEs occur more often in skin, colon, liver, thyroid gland, pituitary gland
Finding the balance between efficacy and toxicity

Marie Boyle: ‘Cherish’
ANTI-CTLA4

• Currently two drugs are available:
  – Ipilimumab: human IgG1 mAb
  – Tremelimumab: human IgG2 mAb
CTLA4 blockade renders T cells in an active state

Ribas. NEJM 2012
Immune related Adverse Events associated with anti-CTLA4

colitis
	hypophysitis

Thyroiditis
Hepatitis
Pneumonitis
Nephritis
Meningitis etc.

vitiligo
dermatitis
Auto-immune uveitis

After topical steroid treatment
Ipilimumab Kinetics of AE

Time (weeks)

Toxicity Grade

- Rash, pruritis
- Liver toxicity
- Diarrhea, colitis
- Hypophysitis

Weber et al J Clin Oncol 2012
PD1/PDL1 blockade reinvigorates inactivated T cells at the tumor site

Ribas. NEJM 2012
Anti-PD1 Demonstrates Broad Antitumor Activity

[Graphs showing change from baseline in tumor size for various cancer types]

Courtesy of G Long

Anti-PD1 Nivolumab Pooled Safety Analysis
Time to Onset of Select Treatment-related AEs (Any Grade; N = 474)

- Skin (n = 155; 33%): 5.0 (0.1–57.0)
- Gastrointestinal (n = 66; 14%): 7.3 (0.1–37.6)
- Hepatic (n = 19; 4%): 7.7 (2.0–38.9)
- Pulmonary (n = 9; 2%): 8.9 (3.6–22.1)
- Endocrine (n = 36; 8%): 10.4 (3.6–46.9)
- Renal (n = 8; 2%): 15.1 (3.9–26.4)

Weber J et al JCO 2017
Anti-PD1 Nivolumab Pooled Safety Analysis
Kinetics of Onset and Resolution of Immune-related AEs

Incidence

Weber J et al JCO 2017
Combining anti-CTLA4 and anti-PD1/PDL1

Ribas. NEJM 2012
Clinical responses with combination versus monotherapy

Larkin et al. NEJM 2015
Grade 3-4 irAE over time in CheckMate-067

Sznol et al. J Clin Oncol 2018
Checkmate 067: Safety
Onset Grade 3–4 Treatment-Related Select AEs

- Skin (n = 33): 3.1 (IQR, 1.0, 8.0; min-max, 0.1-55.0)
- GI (n = 73): 7.1 (IQR, 4.3, 10.6; min-max, 0.6-48.9)
- Hepatic (n = 76): 8.4 (IQR, 5.2, 12.1; min-max, 2.1-48.0)
- Endocrine (n = 21): 11.4 (IQR, 6.7, 13.6; min-max, 2.9-19.1)
- Pulmonary (n = 6): 9.4 (IQR, 3.7, 19.9; min-max, 3.7-20.6)
- Renal (n = 7): 16.3 (IQR, 4.1, 23.7; min-max, 3.3-29.0)

Time Since Study Initiation (weeks)

Sznol et al. J Clin Oncol 2018
Time to resolution of AEs

<table>
<thead>
<tr>
<th>AE</th>
<th>Median (95% CI)</th>
<th>Overall</th>
<th>Treated With IMs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>3.9 (2.1 to 6.1)</td>
<td>27 of 33</td>
<td>23 of 29 (79.3%)</td>
</tr>
<tr>
<td>GI</td>
<td>3.6 (2.0 to 4.3)</td>
<td>69 of 73</td>
<td>62 of 65 (95.4%)</td>
</tr>
<tr>
<td>Hepatic</td>
<td>4.3 (3.1 to 5.6)</td>
<td>74 of 76</td>
<td>52 of 52 (100%)</td>
</tr>
<tr>
<td>Endocrine</td>
<td>15.1 (4.6 to NA)</td>
<td>13 of 21</td>
<td>9 of 16 (66.3%)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>4.5 (0.3 to 10.1)</td>
<td>6 of 6</td>
<td>5 of 5 (100%)</td>
</tr>
<tr>
<td>Renal</td>
<td>1.9 (0.4 to 3.6)</td>
<td>7 of 7</td>
<td>4 of 4 (100%)</td>
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No. at risk:

<table>
<thead>
<tr>
<th>AE</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
<th>21</th>
<th>24</th>
<th>27</th>
<th>30</th>
<th>33</th>
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<tbody>
<tr>
<td>Endocrine</td>
<td>21</td>
<td>17</td>
<td>13</td>
<td>12</td>
<td>12</td>
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<td>7</td>
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<td>GI</td>
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<td>Hepatic</td>
<td>76</td>
<td>51</td>
<td>28</td>
<td>15</td>
<td>8</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Pulmonary</td>
<td>6</td>
<td>3</td>
<td>3</td>
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<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Renal</td>
<td>7</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tr>
<tr>
<td>Skin</td>
<td>33</td>
<td>19</td>
<td>12</td>
<td>10</td>
<td>9</td>
<td>7</td>
<td>7</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

Sznol et al. J Clin Oncol 2018
Checkmate 067 Safety
Number of organs involved

<table>
<thead>
<tr>
<th>Number of organ categories impacted, n (%)*</th>
<th>NIVO+IPI (N=313)</th>
<th>NIVO (N=313)</th>
<th>IPI (N=311)</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>91 (29)</td>
<td>236 (75)</td>
<td>171 (55)</td>
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<tr>
<td>1</td>
<td>125 (40)</td>
<td>61 (20)</td>
<td>112 (36)</td>
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<tr>
<td>2</td>
<td>77 (25)</td>
<td>14 (5)</td>
<td>24 (8)</td>
</tr>
<tr>
<td>3</td>
<td>15 (5)</td>
<td>2 (1)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>5 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*Organ categories: Skin, gastrointestinal, endocrine, hepatic, pulmonary, renal

Larkin J et al ECC 2015
Frequent AE

Incidence per 1000 person-months of all grade and grade 3 to 5 adverse events under immunotherapy using the SAS System. The results include data from the following studies: CA-184-002, KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, CheckMate-037, CheckMate-066, CheckMate-067, and CheckMate-069.
Immune related AEs

Boutros et al., Nat Rev Clin Oncol 2016
Diarrhea/colitis

- More frequent with anti-CTLA4
- Neutrophilic, lymphocytic infiltrate or both
- Beware of infection (C difficile, CMV)

Boutros et al Nat Rev Clin Oncol 2016
Diarrhea/colitis in 93 patients treated with immune checkpoint inhibitors between 2010-2016

<table>
<thead>
<tr>
<th></th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age median (range)</td>
<td>58 (30 – 80)</td>
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<tr>
<td>Gender</td>
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<tr>
<td>Male</td>
<td>42 (45)</td>
</tr>
<tr>
<td>Female</td>
<td>51 (55)</td>
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<tr>
<td>Type of cancer</td>
<td></td>
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<tr>
<td>Melanoma</td>
<td>80 (86)</td>
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<tr>
<td>NSCLC</td>
<td>13 (14)</td>
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<tr>
<td>Immunotherapy</td>
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<tr>
<td>Ipilimumab (3 mg/kg)</td>
<td>44 (46)</td>
</tr>
<tr>
<td>Ipilimumab (10 mg/kg)</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>11 (11)</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Sequential ipilimumab + pembrolizumab</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Sequential ipilimumab + nivolumab</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Combined ipilimumab + nivolumab</td>
<td>12 (13)</td>
</tr>
<tr>
<td>Combined tremelimumab + durvalumab</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Diarrhea at presentation</td>
<td></td>
</tr>
<tr>
<td>Grade I</td>
<td>16 (17)</td>
</tr>
<tr>
<td>Grade II</td>
<td>37 (38)</td>
</tr>
<tr>
<td>Grade III</td>
<td>43 (44)</td>
</tr>
<tr>
<td>Grade IV-V</td>
<td>0 (0)</td>
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<tr>
<td>Unknown</td>
<td>1 (1)</td>
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<tr>
<td>Colon perforation</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3 (3)</td>
</tr>
<tr>
<td>No</td>
<td>90 (97)</td>
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<tr>
<td>Ulcers</td>
<td></td>
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<td>Yes</td>
<td>29 (31)</td>
</tr>
<tr>
<td>No</td>
<td>64 (69)</td>
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<tr>
<td>Prednisone at start</td>
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<tr>
<td>None</td>
<td>5 (5)</td>
</tr>
<tr>
<td>&lt; 1 mg/kg</td>
<td>57 (59)</td>
</tr>
<tr>
<td>1 mg/kg</td>
<td>32 (33)</td>
</tr>
<tr>
<td>&gt; 1 mg/kg</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Budesonide</td>
<td></td>
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<td>Yes</td>
<td>12 (12)</td>
</tr>
<tr>
<td>No</td>
<td>85 (88)</td>
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<td>Infliximab</td>
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<td>Yes</td>
<td>54 (56)</td>
</tr>
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<td>No</td>
<td>43 (44)</td>
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<tr>
<td>Mycophenolic acid</td>
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<td>Yes</td>
<td>3 (3)</td>
</tr>
<tr>
<td>No</td>
<td>94 (97)</td>
</tr>
<tr>
<td>Tacrolimus</td>
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<tr>
<td>Yes</td>
<td>2 (3)</td>
</tr>
<tr>
<td>No</td>
<td>95 (97)</td>
</tr>
</tbody>
</table>

NSCLC: non-small cell lung cancer

Geuks Foppen, Rozeman et al., ESMO Open 2018
Discrepancy between diarrhea and colitis (1)

Grade 2 diarrhea
No abnormalities on colonoscopy

Grade 3 diarrhea
No abnormalities on colonoscopy
Discrepancy between diarrhea and colitis (2)

Grade 2 diarrhea
Grade 3 diarrhea
Grade 1 diarrhea

Right colon
Left colon

Geukes Foppen, Rozeman et al., ESMO Open 2018
Skin AE

- Pruritus: frequent rarely severe
- Rash: very frequent but poorly described
- Vitiligo seems associated with response to anti-PD1

Boutros et al Nat Rev Clin Oncol 2016
Vitiligo

Hofman et al., Eur J Cancer 2016
Vitiligo and clinical response to pembrolizumab

<table>
<thead>
<tr>
<th>Patient</th>
<th>CR (n%)</th>
<th>PR (n%)</th>
<th>SD (n%)</th>
<th>PD (n%)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitiligo (N=17)</td>
<td>3 (18)</td>
<td>9 (53)</td>
<td>3 (18)</td>
<td>2 (12)</td>
<td>0.002</td>
</tr>
<tr>
<td>Non vitiligo (N=50)</td>
<td>4 (8)</td>
<td>10 (20)</td>
<td>1 (2)</td>
<td>35 (70)</td>
<td></td>
</tr>
<tr>
<td>Total (N=67)</td>
<td>7 (10)</td>
<td>19 (28)</td>
<td>4 (6)</td>
<td>36 (54)</td>
<td></td>
</tr>
</tbody>
</table>

*Complete/partial response versus stable/progressive disease/progression in patients disease/progression in patients with and without vitiligo, exact fisher test

Hua et al JAMA Dermatol 2016
Lichen planus

Hofman et al., Eur J Cancer 2016
Grover’s like eruption upon anti-CTLA4

Aggravation of pre-existing psoriasis

Courtesy of C Robert
Frequent AE: fatigue

- Underestimated by physicians
- Frequent and long lasting
- Unknown etiology (if not due to hormonal disturbances)
- Apart from discontinuation no treatment options

Boutros et al Nat Rev Clin Oncol 2016
Hepatitis

- Usually asymptomatic
- Rule out viral infection
- Auto-Abs often negative
- Biopsies should be performed

Boutros et al Nat Rev Clin Oncol 2016
(peri)portal and lobular hepatitis

Hofman et al., Eur J Cancer 2016
Endocrine AE

- Dysthyroidisms more frequent with anti-PD-1 than CTLA-4
- Hyperthyroidism frequently precedes hypothyroidism
- Hypophysitis induces pan or partial hypopituitarism, more frequent with anti-CTLA-4 or combination
- Long lasting AE requiring replacement therapy

Boutros et al Nat Rev Clin Oncol 2016
Pneumonitis

- More frequent with anti-PD1 than with anti-CTLA-4
- Rarely severe
- Rule out infection
- Prompt CT-scan and lavage

Boutros et al Nat Rev Clin Oncol 2016
Pneumonitis followed by lung fibrosis

Zimmer et al., Eur J Cancer 2016
Neurological irAEs: 2-3% (Spain et al., Ann Oncol 2016)

Myasthenia gravis

Zimmer et al., Eur J Cancer 2016
<table>
<thead>
<tr>
<th></th>
<th>Ipi 3 mg/kg</th>
<th>Ipi 10 mg/kg</th>
<th>Anti-PD1</th>
<th>Ipi + nivo</th>
<th>Ipi + pembro</th>
<th>Ipi -&gt; anti-PD1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colitis/diarrhea</td>
<td>30%</td>
<td>45%</td>
<td>1-2%/13%</td>
<td>12-23%/45%</td>
<td>8%/24%</td>
<td>20%/35%</td>
</tr>
<tr>
<td>Skin/pruritis</td>
<td>14%/22%</td>
<td>26%/24%</td>
<td>15-20%</td>
<td>28-41%/35%</td>
<td>39%/39%</td>
<td>25%/33%</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1.5%</td>
<td>10%</td>
<td>5-10%</td>
<td>16%</td>
<td>16%</td>
<td>20%</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>1%</td>
<td>7%</td>
<td>0.2%</td>
<td>8-12%</td>
<td>10%</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9%</td>
<td>11%</td>
<td>20-30%</td>
<td>39%</td>
<td>46%</td>
<td>43%</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>5%</td>
<td>24%</td>
<td>4%</td>
<td>22-32%</td>
<td>10%</td>
<td>18%</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>2%</td>
<td>2-4%</td>
<td>7-11%</td>
<td>10%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>&lt;3%</td>
<td>2-6%</td>
<td>3%</td>
<td>5%</td>
<td></td>
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<tr>
<td>Neurologic</td>
<td>&lt;1%</td>
<td>4.5%</td>
<td>&lt;1%</td>
<td>&lt;5%</td>
<td>1%</td>
<td>-</td>
</tr>
<tr>
<td>Total (all grades/grade 3-4)</td>
<td>63%/18%</td>
<td>79%/34%</td>
<td>70-85%/10-20%</td>
<td>96%/54-57%</td>
<td>95%/42%</td>
<td>88%/38%</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>19%</td>
<td>31%</td>
<td>5-10%</td>
<td>39%</td>
<td>27%</td>
<td>15%</td>
</tr>
</tbody>
</table>

Management of Immune-related Adverse Events

- Patient Education
- Clear Notification Pathway for Patients
- Infrastructure and Sub-specialty Consultants

1. Identify Toxicity Early
2. Treat Early and Aggressively → Algorithms
   - Start with corticosteroids
3. Oncologist-led Management
Algorithms

Haanen et al., Ann Oncol 2017
General Principles

• Low Grade
  • Monitor closely (grade 1 and 2)
  • Delay therapy (grade 2)

Moderate Grade?

• High Grade → Immunosuppression
  • Cease checkpoint inhibitor, consult sub-specialty and consider hospitalisation
  • Systemic corticosteroids
  • Infliximab (anti-TNF$\alpha$)
  • Mycophenolate mofetil
  • Tacrolimus
  • Other → plasmapheresis, anti-thymocyte globulin, IVIG
Management of irAE: diarrhea/colitis

- Grade 1 diarrhea:
  - Observation
  - Start loperamide
  - Continue treatment

- Grade 2 diarrhea/colitis
  - Withhold treatment
  - Culture stools (a.o. C difficile)
  - Budesonide or oral prednisolone
  - Schedule colonoscopy

- Grade 3 or 4 diarrhea/colitis
  - Withhold treatment
  - Culture stools
  - Perform colonoscopy
  - High dose steroids
  - If no improvement within 2-5 days escalate immunosuppression
  - Infliximab -> tacrolimus
  - In case of severe diarrhea/colitis admit patient!
  - Taper slowly
Algorithm for skin toxicity

**Symptom Grade**

- Grade 1: skin rash, with or without symptoms, < 10% BSA (see Figure 4)
- Grade 2: rash covers 10%-30% of BSA (see Figure 4)
- Grade 3: rash covers > 30% BSA (see Figure 4) or grade 2 with substantial symptoms
- Grade 4: skin sloughing > 30% BSA (see Figure 4) with associated symptoms (e.g., erythema, purpura, epidermal detachment)

**Management escalation pathway**

- Avoid skin irritants, avoid sun exposure, topical emollients recommended
- Topical steroids (mild strength) cream od +/- oral or topical antihistamines for itch
- Supportive management, as above
- Topical steroids (moderate strength) cream od or (clobetasol) cream bd +/- oral or topical antihistamines for itch
- Withhold ICPI
- Topical treatments as above (potent)
- Initiate steroids:
  - If mild to moderate: 0.2-1 mg/kg prednisolone od for 3 days then wean over 1-2 weeks; or
  - If severe: iv. methylprednisolone 0.5-1 mg/kg and convert to oral steroids on response, wean over 2-4 weeks
- Recommence ICPI at 1/4 of Q2 after discussion with patient and consultant
- Lv. (methyl)prednisolone 1-2 mg/kg
  - Seek urgent dermatology review
  - Discontinue ICPI treatment

**Assessment and Investigations**

- Physical examination
  - Exclude other causes, e.g., oral illness, infection, other drug rash
- As above
  - Consider dermatology referral and skin biopsy
- As for Grade 1
  - Dermatology review
  - Consider punch biopsy and clinical photography
- As for Grade 1
  - Dermatology review
  - Punch biopsy
  - Clinical photography

Haanen et al., Ann Oncol 2017
Management of irAE: skin

• Grade 1 pruritus/rash
  – Cooling ointment
  – Antihistamine

• Grade 2 rash
  – Involve dermatologist
  – Start topical steroids
  – Cooling ointment

• Grade 3 or 4 rash
  – Involve dermatologist
  – Start systemic steroids
  – Admit patient in case of Stevens-Johnson syndrome or TEN
Algorithm for ir hepatitis

Haanen et al., Ann Oncol 2017
Management of irAE: hepatitis

- Grade 1 AST/ALT elevation
  - Monitor closely
  - Withhold next dose of checkpoint inhibitor

- Grade 2 hepatitis
  - Withhold treatment
  - Rule out viral hepatitis
  - Start systemic steroids
  - Closely monitor AST/ALT

- Grade 3 or 4 hepatitis
  - Rule out viral hepatitis
  - Start systemic steroids (prednisone 2 mg/kg)
  - Monitor closely, if no improvement add mycophenolate mofetil
  - Escalate in case no improvement with tacrolimus or ATG
  - Infliximab?
  - Taper slowly under close monitoring
Algorithm for hypophysitis

Symptoms
- Severe mass effect symptoms, i.e. severe headache, any visual disturbance or severe hypopituitarism, i.e. hypotension, severe electrolyte disturbance

Management escalation pathway
- Initiate iv. (methyl)prednisolone 1 mg/kg after sending bloods for pituitary axis assessment*
  - Analgesia as needed for headache (discuss with neurologist if resistant to paracetamol and NSAIKS)
  - Withhold ICPi

Further assessment and management
- MRI pituitary protocol also exclude brain metastases
  - Consider formal visual field assessment (if abnormal patient to inform driver licensing agency)
  - Aim convert to prednisolone and wean as symptoms allow over 4 weeks to 5 mg
  - Do not stop steroids
  - Refer to endocrinologist
  - Monitor TFTs

Moderate symptoms, i.e. headache but no visual disturbance
- Fatigue/mood alteration but haemodynamically stable, no electrolyte disturbance

- Oral prednisolone 0.5-1 mg/kg od after sending pituitary axis assessment
  - If no improvement in 48h, treat as severe with iv. (methyl)prednisolone as above
  - Withhold ICPi

- MRI pituitary protocol (also exclude brain metastases), visual field assessment
  - Wean steroids based on symptoms over 2-4 weeks to 5 mg prednisolone
  - Do not stop steroids
  - Refer to endocrinologist
  - Monitor TFTs

Vague symptoms
- (e.g. mild fatigue, anorexia), no headache
- Asymptomatic

- Await pituitary axis to confirm diagnosis but warn patients to seek urgent review if unwell
  - Continue ICPi with appropriate HRT**

Patient education (with assistance of a nurse practitioner):
- “Sick day rules”, prescription and education for use of IM steroid if required
- Consider alert card or bracelet

Replace cortisol and/or thyroxine per guide below**

MRI pituitary protocol

Haanen et al., Ann Oncol 2017
Management of irAE: endocrinopathy

• Hypothyroidism:
  – Substitute with levothyroxine and monitor

• Hyperthyroidism:
  – Most often precedes hypothyroidism
  – If symptomatic treat with beta blocker
  – Consult endocrinologist
  – Steroids rarely required (unless thyroiditis)

• Hypophysitis (diagnosis by MRI brain or lab abnormalities)
  – In symptoms due to swelling (headache, diplopia, dizziness): start steroids
  – If low in TSH, ACTH, LH: substitute: levothyroxine, hydrocortisone, testosterone
  – Consult endocrinologist (long term substitution required)
Algorithm for pneumonitis

Haanen et al., Ann Oncol 2017
Management of irAE: pneumonitis

• In case of sudden onset dyspnea on exertion (and infiltrate on chest X-ray): rule out infectious pneumonia
  – Sputum culture
  – BAL (and culture + cytology) (involve pulmonologist)
  – CT-chest (rule out other causes like pulmonary embolism)
  – Pulmonary function tests and repeat over time

• High suspicion of pneumonitis:
  – Withhold treatment
  – Admit patient (depending on severity)
  – Start systemic steroids (1-2 mg/kg prednisone)
  – Escalate in case of deterioration: infliximab, MMF, tacrolimus
Management of irAE: neurologic manifestations

- Many possibilities of neurological irAEs:
  - Aseptical meningitis
  - Mononeuritis
  - Polynneuroradiculopathy (Guillain-Barre (-like) syndrome
  - Myasthenia gravis
  - Myelitis transversa
- Involve neurologist! : rule out other causes of neurologic deficit (MRI, spinal fluid, EMG, antibodies)
- Admit patient
- Start systemic steroids
- Depending on diagnosis: plasmapheresis, IVIG, (rituximab??)
Important Practical Questions

• Can treatment be continued after immune-related grade 3-4 toxicity?
  • Special cases – patients with CR
• Does toxicity predict response and outcome?
• Do immune-modulators used to treat toxicity affect efficacy?
• Does toxicity with Anti-CTLA4 predict toxicity with Anti-PD1 and vice versa?
• Can people with auto-immune disease be given checkpoint inhibitors?
Complete Responders Who Stopped Pembrolizumab for Observation (N = 61)

- 59 (97%) of responses were maintained

Total bar length represents the time to the last scan.
Analysis cutoff date: Sep 18, 2015.
Important Practical Questions

• Can treatment be continued after immune-related grade 3-4 toxicity?
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• Does toxicity predict response and outcome?
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### Pooled Ipi + Nivo Melanoma (067 + 069)
Progression-Free Survival by Discontinuation due to Toxicity

<table>
<thead>
<tr>
<th></th>
<th>NIVO+IPI DC (n = 176)</th>
<th>NIVO+IPI no DC (n = 233)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median PFS, months (95% CI)</strong></td>
<td>16.7 (10.2, NA)</td>
<td>10.8 (5.9, 23.0)</td>
</tr>
<tr>
<td><strong>HR (99.5% CI)</strong></td>
<td>0.74 (0.56, 0.98), *P &lt; 0.04</td>
<td></td>
</tr>
</tbody>
</table>

\*PFS per Investigator (Months)

Schadendorf et al  EADO 2016
## Pooled Ipi + Nivo Melanoma (067 + 069) Best Overall Response

<table>
<thead>
<tr>
<th></th>
<th>NIVO+IPI</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Discontinued due to AEs (n = 176)</td>
<td>Did not discontinue due to AEs (n = 233)</td>
<td></td>
</tr>
<tr>
<td><strong>ORR, % (95% CI)</strong></td>
<td>68.2 (60.8, 75.0)</td>
<td>50.2 (43.6, 56.8)</td>
<td></td>
</tr>
<tr>
<td><strong>P value for comparison</strong></td>
<td>0.0200</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Best overall response, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Complete response</strong></td>
<td>17.6</td>
<td>12.0</td>
<td></td>
</tr>
<tr>
<td><strong>Partial response</strong></td>
<td>50.6</td>
<td>38.2</td>
<td></td>
</tr>
<tr>
<td><strong>Stable disease</strong></td>
<td>15.9</td>
<td>10.7</td>
<td></td>
</tr>
<tr>
<td><strong>Progressive disease</strong></td>
<td>13.1</td>
<td>27.0</td>
<td></td>
</tr>
<tr>
<td><strong>Unable to determine</strong></td>
<td>2.8</td>
<td>12.0</td>
<td></td>
</tr>
</tbody>
</table>

Schadendorf et al  EADO 2016
Pooled Nivolumab Safety Study in Melanoma (N= 576)\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>All Patients N=576</th>
<th>Any Select AE N=409</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall Response</strong></td>
<td>31.4%</td>
<td>48.6%</td>
</tr>
</tbody>
</table>

Not Observed with Ipilimumab Monotherapy

Weber et al JCO 2017
Important Practical Questions

• Can treatment be continued after immune-related toxicity?
  • Special cases – patients with CR
• Does toxicity predict response and outcome?
• Do immune-modulators used to treat toxicity affect efficacy?
• Does toxicity with Anti-CTLA4 predict toxicity with Anti-PD1 and vice versa? Can people with auto-immune disease be given checkpoint inhibitors?
**Pooled Nivolumab Safety Study in Melanoma (N= 576)**

<table>
<thead>
<tr>
<th></th>
<th>All Patients N=576</th>
<th>Any Select AE N=409</th>
<th>Grade 3/4 Select AE N=18*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR</strong></td>
<td>31.4%</td>
<td>48.6%</td>
<td><strong>27.8%</strong></td>
</tr>
<tr>
<td><strong>Med. Duration Response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*57 patients of 576 (10%) experienced any Grade 3/4 Adverse event

Weber et al JCO 2017

**Needs investigation**
Important Practical Questions

• Can treatment be continued after immune-related toxicity?
  • Special cases – patients with CR
• Does toxicity predict response and outcome?
• Do immune-modulators used to treat toxicity affect efficacy?
• Does toxicity with Anti-CTLA4 predict toxicity with Anti-PD1 and vice versa?
• Can people with auto-immune disease be given checkpoint inhibitors?
67 Patients With Immune Toxicity Due to Ipilimumab

- colitis: 47 (70%)
- endocrine: 13 (19%)
- dermatologic: 4 (6%)
- rheumatologic: 3 (4%)
- hepatitis: 3 (4%)
- neurologic: 2 (3%)
- ocular: 2 (3%)
- hematologic: 1 (1%)

And same for Anti-PD1 → Ipilimumab*

No 65 (97%)
Yes 2 (3%)

Recurrent Tox

No 44 (66%)
Yes 23 (34%)

Other Tox

*Courtesy of G Long
Menzies A et al., Annals Onc 2016
Bowyer et al BJC 2016
Important Practical Questions

• Can treatment be continued after immune-related toxicity?
  • Special cases – patients with CR
• Does toxicity predict response and outcome?
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• Can people with auto-immune disease be given checkpoint inhibitors?
52 Patients with mild-mod autoimmune disease Treated with anti-PD1

<table>
<thead>
<tr>
<th>Disease Type</th>
<th>Number (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatologic</td>
<td>27 (52%)</td>
</tr>
<tr>
<td>(13 Rheumatoid arthritis)</td>
<td></td>
</tr>
<tr>
<td>Dermatologic</td>
<td>8 (15%)</td>
</tr>
<tr>
<td>(6 psoriasis)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>(3 Crohn's disease)</td>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Endocrine</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Respiratory</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Haematologic</td>
<td>2 (4%)</td>
</tr>
</tbody>
</table>

20 (38%) On immune-modulator at anti-PD1 start

Courtesy of G Long

Menzies A et al., Annals Onc 2016
52 Patients with mild-mod autoimmune disease treated with anti-PD1

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatologic</td>
<td>27</td>
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<td>4</td>
<td>8%</td>
</tr>
<tr>
<td>Respiratory</td>
<td>2</td>
<td>4%</td>
</tr>
<tr>
<td>Haematologic</td>
<td>2</td>
<td>4%</td>
</tr>
</tbody>
</table>

- **20 (38%)** On immune-modulator at anti-PD1 start
- **20 (38%)** Auto-immune flare on anti-PD1
  - 14 Rheumatologic
  - 3 Dermatology
  - 1 Endocrine
  - 2 Haematologic

Managed with oral steroids, SSA and IVIg (1)

Courtesy of G Long

Menzies A et al., Annals Onc 2016
52 patients mild-mod autoimmune disease treated with anti-PD1

- ORR 17/52 = 33%
- Median PFS 6.2 mo
- Median DoR and OS not reached

<table>
<thead>
<tr>
<th></th>
<th>CR/PR</th>
<th>SD/PD</th>
<th>ORR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flare</td>
<td>7</td>
<td>13</td>
<td>35%</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>No Flare</td>
<td>10</td>
<td>22</td>
<td>31%</td>
<td></td>
</tr>
<tr>
<td>On IS*</td>
<td>3</td>
<td>17</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>Not on IS*</td>
<td>14</td>
<td>18</td>
<td>44%</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*IS = immunosuppression at start

Courtesy of G Long
Menzies A et al., Annals Onc 2016
Take home messages
Know the immune-toxicity spectrum
Identify dysimmunity risk factors
Inform patients and their healthcare providers

PREVENT

Resolution kinetic
Relapse, recurrence
Immunosuppression complications

MONITOR

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

ANTICIPATE

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

TREAT

Baseline values = reference values
Eliminate progression
Always consider dysimmune toxicities

DETECT

Immune related AEs (AEs of specific interest)

Every organ can be involved
Severity can vary from grade 1 – 5
Requires immediate action
Hold further treatment (depending on severity)
Involve organ specialist
Start immunosuppression (depending on severity)
Careful follow-up warranted
Taper immunosuppression

As a medical oncologist: be in the lead!