MANAGEMENT OF TOXICITIES FROM IMMUNE CHECKPOINT INHIBITORS

John B.A.G. Haanen MD PhD

ESMO ASIA IO Preceptorship 2018
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 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
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&lt;sup&gt;nd&lt;/sup&gt; line metastatic NSCLC</td>
<td>EMA + FDA</td>
</tr>
<tr>
<td></td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line metastatic RCC</td>
<td>EMA + FDA</td>
</tr>
<tr>
<td></td>
<td>Classical Hodgkin's disease</td>
<td>EMA + FDA</td>
</tr>
<tr>
<td></td>
<td>Recurrent or metastatic SCCHN&lt;sup&gt;13&lt;/sup&gt;</td>
<td>EMA + FDA</td>
</tr>
<tr>
<td></td>
<td>Locally advanced or metastatic UCC&lt;sup&gt;14&lt;/sup&gt;</td>
<td>EMA + FDA</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Metastatic melanoma</td>
<td>EMA + FDA</td>
</tr>
<tr>
<td></td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line metastatic NSCLC (PD-L1 ≥ 1%)</td>
<td>EMA + FDA</td>
</tr>
<tr>
<td></td>
<td>1&lt;sup&gt;st&lt;/sup&gt; line metastatic NSCLC (PD-L1 ≥ 50%)</td>
<td>EMA + FDA</td>
</tr>
<tr>
<td></td>
<td>1&lt;sup&gt;st&lt;/sup&gt; line metastatic NSCLC in combination with pemetrexed + carboplatin</td>
<td>FDA</td>
</tr>
<tr>
<td></td>
<td>Classical Hodgkin's disease</td>
<td>EMA&lt;sup&gt;a&lt;/sup&gt; + FDA&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Locally advanced or metastatic UCC&lt;sup&gt;14&lt;/sup&gt;</td>
<td>FDA</td>
</tr>
<tr>
<td></td>
<td>MSI-H or MMR deficient metastatic malignancies&lt;sup&gt;8&lt;/sup&gt;</td>
<td>FDA</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>Locally advanced or metastatic UCC&lt;sup&gt;14&lt;/sup&gt;</td>
<td>FDA</td>
</tr>
<tr>
<td></td>
<td>2&lt;sup&gt;nd&lt;/sup&gt; line metastatic NSCLC</td>
<td>FDA</td>
</tr>
<tr>
<td>Avelumab</td>
<td>Locally advanced or metastatic UCC&lt;sup&gt;14&lt;/sup&gt;</td>
<td>FDA</td>
</tr>
<tr>
<td></td>
<td>Metastatic Merkel cell carcinoma</td>
<td>FDA</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>Locally advanced or metastatic UCC&lt;sup&gt;14&lt;/sup&gt;</td>
<td>FDA</td>
</tr>
<tr>
<td>Ipilimumab + nivolumab</td>
<td>Metastatic melanoma</td>
<td>EMA + FDA</td>
</tr>
</tbody>
</table>
Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

NCCN Guidelines Version 1.2018
Management of Immunotherapy-Related Toxicities

PULMONARY ADVERSE EVENT(S) | ASSESSMENT/GRADING | MANAGEMENT
---|---|---
Mild (G1) $^{ff}$ |  | • Hold immunotherapy $^{f}$
|  | • Reassess in 1–2 weeks
|  | • H&P
|  | • Pulse oximetry (resting and with ambulation)
|  | • Consider chest imaging (chest CT with contrast [preferred] or chest x-ray)
|  | • Consider repeat chest imaging in 3–4 weeks or as clinically indicated
| Pneumonitis $^{***}$ | Moderate (G2) $^{ggg}$ | • Hold immunotherapy $^{f}$
|  |  | • Consider infectious workup:
|  |  | • Nasal swab for potential viral pathogens
|  |  | • Sputum culture, blood culture, and urine culture
|  |  | • Consider bronchoscopy with bronchoalveolar lavage (BAL) to rule out infection and malignant lung infiltration
|  |  | • Consider chest imaging (chest CT with contrast [preferred] or baseline chest x-ray)
|  |  | • Repeat CT in 3–4 weeks
|  |  | • Recommend infectious evaluation with institutional immunocompromised panel
|  |  | • Consider empiric antibiotics if infection has not yet been fully excluded
|  |  | • Methylprednisolone/prednisone 1–2 mg/kg/day $^{d}$
|  |  | • Monitor every 3–7 days with:
|  |  | • H&P
|  |  | • Pulse oximetry (resting and with ambulation)
|  |  | • If no improvement after 48–72 hours of corticosteroids, treat as grade 3

Severe (G3–4) $^{hhh}$ | See IMMUNO-14

$^{f}$
$^{g}$
$^{d}$
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
  – Tremelimimumab: human IgG2 mAb
CTLA4 blockade renders T cells in an active state
Immune related Adverse Events associated with anti-CTLA4

- colitis
- hypophysitis
- vitiligo
- dermatitis

Thyroiditis, Hepatitis, Pneumonitis, Nephritis, Meningitis etc.
Auto-immune uveitis

After topical steroid treatment
Ipilimumab Kinetics of AE

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

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 in melanoma

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 (81.8)</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 (94.6)</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 (97.4)</td>
<td>52 of 52 (100)</td>
</tr>
<tr>
<td>Endocrine</td>
<td>15.1 (4.6 to NA)</td>
<td>13 of 21 (61.9)</td>
<td>9 of 16 (56.3)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>4.5 (0.3 to 10.1)</td>
<td>6 of 6 (100)</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 (100)</td>
<td>4 of 4 (100)</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>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>91 (29)</td>
<td>236 (75)</td>
<td>171 (55)</td>
</tr>
<tr>
<td>1</td>
<td>125 (40)</td>
<td>61 (20)</td>
<td>112 (36)</td>
</tr>
<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>Age median (range)</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>58 (30 – 80)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>42 (45)</td>
</tr>
<tr>
<td>Female</td>
<td>51 (55)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of cancer</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>80 (86)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>13 (14)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Immunotherapy</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diarrhea at presentation</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<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>
</tr>
<tr>
<td>Unknown</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Colon perforation</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>3 (3)</td>
</tr>
<tr>
<td>No</td>
<td>90 (97)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ulcers</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>29 (31)</td>
</tr>
<tr>
<td>No</td>
<td>64 (69)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prednisone at start</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Budesonide</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>12 (12)</td>
</tr>
<tr>
<td>No</td>
<td>85 (88)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Infliximab</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>54 (56)</td>
</tr>
<tr>
<td>No</td>
<td>43 (44)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mycophenolic acid</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>3 (3)</td>
</tr>
<tr>
<td>No</td>
<td>94 (97)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tacrolimus</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<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

Geukes 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

Geukes Foppen, Rozeman et al., ESMO Open 2018
Discrepancy between diarrhea and colitis (2)

Grade 2 diarrhea

Grade 1 diarrhea

Grade 3 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</th>
<th>PR</th>
<th>SD</th>
<th>PD</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
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
## Frequencies of irAE for immune checkpoint inhibitors reported

<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><strong>Colitis/diarrhea</strong></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><strong>Skin/pruritis</strong></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><strong>Hypothyroidism</strong></td>
<td>1.5%</td>
<td>10%</td>
<td>5-10%</td>
<td>16%</td>
<td>16%</td>
<td>20%</td>
</tr>
<tr>
<td><strong>Hypophysitis</strong></td>
<td>1%</td>
<td>7%</td>
<td>0.2%</td>
<td>8-12%</td>
<td>10%</td>
<td>-</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>9%</td>
<td>11%</td>
<td>20-30%</td>
<td>39%</td>
<td>46%</td>
<td>43%</td>
</tr>
<tr>
<td><strong>Hepatitis</strong></td>
<td>5%</td>
<td>24%</td>
<td>4%</td>
<td>22-32%</td>
<td>10%</td>
<td>18%</td>
</tr>
<tr>
<td><strong>Pneumonitis</strong></td>
<td>2%</td>
<td>2-4%</td>
<td>7-11%</td>
<td>10%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td>&lt;3%</td>
<td>&lt;3%</td>
<td>2-6%</td>
<td>3%</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td><strong>Neurologic</strong></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><strong>Total (all grades/grade 3-4)</strong></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><strong>Discontinuation</strong></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
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-TNFα)
  • Mycophenolate mofetil
  • Tacrolimus
  • Other → plasmapheresis, anti-thymocyte globulin, IVIG
Algorithm diarrhea and colitis

Symptom Grade

Mild (G1): i.e., < 3 liquid stools per day over baseline, feeling well
ICSI can be continued

Moderate (G2): i.e., 4-6 liquid stools per day over baseline or abdominal pain or blood in stool or nausea or nocturnal episodes
Outpatient management if appropriate
If unwell, manage as severe
ICSI to be withheld

Severe (G3/4): i.e., > 6 liquid stools per day over baseline or if episodes within 1 h of eating
Requires hospitalisation and isolation until infection excluded
ICSI to be withheld

Management escalation pathway

Symptomatic: No oral fluids, loperamide, avoid high fibre/lactose diet

G1 and persists > 14 days or G2 and persists for > 3 days or worsens
Prednisolone 0.5-1 mg/kg (non-enteric coated) or consider oral budesonide 9 mg od if no bloody diarrhoea
Do not wait for sigmoidoscopy/colonoscopy to start

No improvement in 72 h or worsening of absorption concern
Prednisolone 1-2 mg/kg
Gastroenterology input and ensure sigmoidoscopy/colonoscopy is requested
At clinician discretion

No improvement in 72 h or worsening
Inpatient: Test as above, including sigmoidoscopy/colonoscopy
Consider CT abdomen/pelvis, repeat Abdominal X-ray as indicated
Daily FBC, UEC, LFTs, CRP
Review diet (e.g., nothing by mouth, clear fluids, TPM)
Early surgical review if bleeding, pain or distension

Assessment and Investigations

Baseline investigations: FBC, UEC, LFTs, CRP, TFI
Stool microscopy for leukocytes/evidence of parasites, culture, viral PCR, Clostridium difficile toxin and cryptosporidia
Culture for drug-resistant organisms

Outpatients: Baseline tests as above
Consider in case of abdominal discomfort: abdominal X-ray for signs of colitis
Exclude stricture
Sigmoidoscopy/colonoscopy (+/- biopsy)
Contact patient every 72 h
Repeat baseline bloods at outpatient review

Medications

Prednisolone 1-2 mg/kg i.v.
Loperamide 4 mg 1st dose then 2 mg 30 min before each meal and after each loose stool until 12 h without diarrhoea (max. 18 mg/day)

Haanen et al., Ann Oncol 2017
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)
  - Avoid skin irritants, avoid sun exposure, topical emollients recommended
  - Topical steroids (mild strength) cream od +/- oral or topical antihistamines for itch
  - Proceed with treatment

- **Grade 2:** rash covers 10%-30% of BSA (see Figure 4)
  - Supportive management, as above
  - Topical steroids (moderate strength) cream od or clobetasol cream bd +/- oral or topical antihistamines for itch
  - Proceed with ICPI treatment
  - 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 i.e. methylprednisolone 0.5-1 mg/kg and continue to oral steroids on response, wean over 2-4 weeks
    - Recommend ICPI at 6/wk or Q2 after discussion with patient and consultant

- **Grade 3:** rash covers > 30% BSA (see Figure 4) or grade 2 with substantial symptoms
  - As for Grade 1
  - Dermatology review
  - Consider punch biopsy and clinical photography

- **Grade 4:** skin sloughing > 30% BSA (see Figure 4) with associated symptoms (e.g. erythema, purpura, epidermal detachment)
  - L.V. methylprednisolone 1-2 mg/kg
  - Seek urgent dermatology review
  - Discontinue ICPI treatment

**Management escalation pathway**

**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
  - 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**

1. **Initiate i.v. (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 NSAI DS)
   - Withhold ICPi

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

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

**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 to convert to prednisolone and wean as symptoms allow over 4 weeks to 5 mg
- Do not stop steroids
- Refer to or consult endocrinologist
- Monitor TFTs

- 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 or consult endocrinologist
- Monitor TFTs

- Replace cortisol and/or thyroxine per guide below**
- MRI pituitary protocol
- Refer to endocrinologist

**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

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)
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?
- 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

Presented By Caroline Robert at 2016 ASCO Annual Meeting
Important Practical Questions

• Can treatment be continued after immune-related grade 3-4 toxicity?
• **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 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>Median PFS, months</td>
<td>16.7 (10.2, NA)</td>
<td>10.8 (5.9, 23.0)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (99.5% CI)</td>
<td>0.74 (0.56, 0.98)</td>
<td>P &lt; 0.04</td>
</tr>
</tbody>
</table>

Schadendorf et al  EADO 2016
Safety Summary from Checkmate-067

<table>
<thead>
<tr>
<th>Patients reporting event</th>
<th>NIVO+IPI (n = 313)</th>
<th>NIVO (n = 313)</th>
<th>IPI (n = 311)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3/4</td>
<td>Any grade</td>
</tr>
<tr>
<td>Treatment-related AE, %</td>
<td>95.8</td>
<td>59.1</td>
<td>86.3</td>
</tr>
<tr>
<td>Treatment-related AE leading to discontinuation, %</td>
<td>40.3</td>
<td>30.4</td>
<td>12.5</td>
</tr>
<tr>
<td>Treatment-related death, n (%)</td>
<td>2 (0.6)</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>

- No new safety signals were observed with the additional follow-up
- No additional deaths due to study drug toxicity were reported since the prior analysis
  - Previously reported treatment-related deaths were cardiomyopathy and liver necrosis for NIVO+IPI (n = 1 each and both occurred >100 days after last treatment), neutropenia for NIVO (n = 1), and colonic perforation for IPI (n = 1)
- Patients who discontinued NIVO+IPI during induction due to a treatment-related AE had similar 4-year PFS (35%) and OS (54%) to patients in the overall population (37% and 53%, respectively)

Presented by Hodi at ESMO 2018
Pooled Ipi + Nivo Melanoma (067 + 069)
Best Overall Response

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

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

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

Not Observed with Ipilimumab Monotherapy

Courtesy of G Long Weber et al JCO 2017
Important Practical Questions

- Can treatment be continued after immune-related toxicity?
- 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)\(^1\)

**Needs investigation**

<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>27.8%</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
Important Practical Questions

• Can treatment be continued after immune-related toxicity?
• 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*

- Recurrent Tox
  - No: 65 (97%)
  - Yes: 2 (3%)

- Other Tox
  - No: 44 (66%)
  - Yes: 23 (34%)

* Bowyer et al. BJC 2016
Important Practical Questions

• Can treatment be continued after immune-related toxicity?
• 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?**
52 Patients with mild-mod autoimmune disease Treated with anti-PD1

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

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>Type</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatologic (13 RA)</td>
<td>27</td>
<td>52%</td>
</tr>
<tr>
<td>Dermatologic (6 psoriasis)</td>
<td>8</td>
<td>15%</td>
</tr>
<tr>
<td>Gastrointestinal (3 CD)</td>
<td>6</td>
<td>12%</td>
</tr>
<tr>
<td>Neurologic</td>
<td>5</td>
<td>10%</td>
</tr>
<tr>
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<td>8%</td>
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<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></td>
</tr>
<tr>
<td>No Flare</td>
<td>10</td>
<td>22</td>
<td>31%</td>
<td>&gt;0.05</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!