ESMO Guidelines: Management of toxicities from Immune Checkpoint inhibitors

John B.A.G. Haanen MD PhD
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>
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<tr>
<td>Nivolumab</td>
<td>Metastatic melanoma</td>
<td>EMA + FDA</td>
</tr>
<tr>
<td></td>
<td>2\textsuperscript{nd} line metastatic NSCLC</td>
<td>EMA + FDA</td>
</tr>
<tr>
<td></td>
<td>2\textsuperscript{nd} line metastatic RCC</td>
<td>EMA + FDA</td>
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<tr>
<td></td>
<td>Classical Hodgkin's disease\textsuperscript{a}</td>
<td>EMA + FDA</td>
</tr>
<tr>
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<td>Recurrent or metastatic SCCHN\textsuperscript{b}</td>
<td>EMA + FDA</td>
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<tr>
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<td>Locally advanced or metastatic UCC\textsuperscript{c}</td>
<td>EMA + FDA</td>
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<td>Pembrolizumab</td>
<td>Metastatic melanoma</td>
<td>EMA + FDA</td>
</tr>
<tr>
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<td>2\textsuperscript{nd} line metastatic NSCLC (PD-L1 $\geq$ 1%)</td>
<td>EMA + FDA</td>
</tr>
<tr>
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<td>1\textsuperscript{st} line metastatic NSCLC (PD-L1 $\geq$ 50%)</td>
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<td>1\textsuperscript{st} line metastatic NSCLC in combination with pemetrexed + carboplatin</td>
<td>FDA</td>
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<tr>
<td></td>
<td>Classical Hodgkin's disease</td>
<td>EMA\textsuperscript{a} + FDA\textsuperscript{d}</td>
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<td></td>
<td>Locally advanced or metastatic UCC\textsuperscript{c}</td>
<td>FDA</td>
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<tr>
<td></td>
<td>MSI-H or MMR deficient metastatic malignancies\textsuperscript{e}</td>
<td>FDA</td>
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<td>Atezolizumab</td>
<td>Locally advanced or metastatic UCC\textsuperscript{c}</td>
<td>FDA</td>
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<td></td>
<td>2\textsuperscript{nd} line metastatic NSCLC</td>
<td>FDA</td>
</tr>
<tr>
<td>Avelumab</td>
<td>Locally advanced or metastatic UCC\textsuperscript{c}</td>
<td>FDA</td>
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<td>Metastatic Merkel cell carcinoma</td>
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<td>Durvalumab</td>
<td>Locally advanced or metastatic UCC\textsuperscript{c}</td>
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<tr>
<td>Ipilimumab + nivolumab</td>
<td>Metastatic melanoma</td>
<td>EMA + FDA</td>
</tr>
</tbody>
</table>
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
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

Weber et al J Clin Oncol 2012
PD1/PDL1 blockade reinvigorates inactivated T cells at the tumor site
Anti-PD1 Demonstrates Broad Antitumor Activity

![Graphs showing change from baseline in tumor size for different cancer types.](image)

**Melanoma** (N=655) KEYNOTE-001

**NSCLC** (N=262) KEYNOTE-001

**H&N** (N=132) KEYNOTE-012

**Urothelial** (N=33) KEYNOTE-012

**Gastric** (N=39) KEYNOTE-012

**TNBC** (N=32) KEYNOTE-012

**cHL** (N=29) KEYNOTE-013

**Mesothelioma** (N=25) KEYNOTE-028

**Ovarian** (N=26) KEYNOTE-028

**SCLC** (N=20) KEYNOTE-028

**Esophageal** (N=23) KEYNOTE-028

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

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>All treated patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NIVO+IPI (N=313)</td>
</tr>
<tr>
<td>0</td>
<td>91 (29)</td>
</tr>
<tr>
<td>1</td>
<td>125 (40)</td>
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<tr>
<td>2</td>
<td>77 (25)</td>
</tr>
<tr>
<td>3</td>
<td>15 (5)</td>
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<tr>
<td>&gt;3</td>
<td>5 (2)</td>
</tr>
</tbody>
</table>

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

Larkin J et al ECC 2015
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)
Diarrhea/colitis in 93 patients treated with immune checkpoint inhibitors between 2010-2016

<table>
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<tr>
<th></th>
<th>No. (%)</th>
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<th>No. (%)</th>
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<td>Gender</td>
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<tr>
<td>Male</td>
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<tr>
<td>Female</td>
<td>51 (55)</td>
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<td>Type of cancer</td>
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<td>Melanoma</td>
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<td>NSCLC</td>
<td>13 (14)</td>
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<td>Immunotherapy</td>
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<td>Ipilimumab (3 mg/kg)</td>
<td>44 (46)</td>
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<td>Nivolumab</td>
<td>11 (11)</td>
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<td>Pembrolizumab</td>
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<tr>
<td>Sequential ipilimumab + pembrolizumab</td>
<td>7 (7)</td>
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<td>Sequential ipilimumab + nivolumab</td>
<td>2 (2)</td>
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<tr>
<td>Combined ipilimumab + nivolumab</td>
<td>12 (13)</td>
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<tr>
<td>Combined tremelimumab + durvalumab</td>
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<td>Diarrhea at presentation</td>
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<td>Grade I</td>
<td>16 (17)</td>
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<td>Grade II</td>
<td>37 (38)</td>
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<td>Grade III</td>
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<td>Grade IV-V</td>
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<td>Colon perforation</td>
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<td>Prednisone at start</td>
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<tr>
<td>&gt; 1 mg/kg</td>
<td>57 (59)</td>
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<tr>
<td>&lt; 1 mg/kg</td>
<td>32 (33)</td>
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</tr>
<tr>
<td>&gt; 1 mg/kg</td>
<td>3 (3)</td>
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<td>Budesonide</td>
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<td>Yes</td>
<td>12 (12)</td>
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<td>No</td>
<td>85 (88)</td>
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<td>Infliximab</td>
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<td>No</td>
<td>43 (44)</td>
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<td>Mycophenolic acid</td>
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<tr>
<td>Yes</td>
<td>3 (3)</td>
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</tr>
<tr>
<td>No</td>
<td>94 (97)</td>
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</tr>
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<td>Tacrolimus</td>
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</tr>
<tr>
<td>Yes</td>
<td>2 (3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>95 (97)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NSCLC: non-small cell lung cancer
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 1 diarrhea

Grade 2 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>
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</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 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
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>
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<tr>
<td>Hypophysitis</td>
<td>1%</td>
<td>7%</td>
<td>0.2%</td>
<td>8-12%</td>
<td>10%</td>
<td>-</td>
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<tr>
<td>Fatigue</td>
<td>9%</td>
<td>11%</td>
<td>20-30%</td>
<td>39%</td>
<td>46%</td>
<td>43%</td>
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<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>
<td>-</td>
</tr>
<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

Symptom Grade

- **Grade 1:**
  - ALT or AST > ULN-3x ULN
  - Continue treatment

- **Grade 2:**
  - ALT or AST 3-5x ULN
  - Withhold ICPI treatment
  - If rising ALT/AST when re-checked, start oral prednisolone 1 mg/kg

- **Grade 3:**
  - ALT or AST 5-20x ULN
  - Cease treatment
  - ALT/AST < 400 and normal bilirubin/INR/albumin: oral prednisolone 1 mg/kg
  - ALT/AST > 400 or raised bilirubin/INR/low albumin: i.v. (methyl)prednisolone 2 mg/kg

- **Grade 4:**
  - ALT or AST > 20x ULN
  - i.v. (methyl)prednisolone 2 mg/kg
  - Permanently discontinue treatment

Management escalation pathway

- If > ULN-3x ULN repeat in 1 week

Assessment and Investigations

- Re-check LFTs/INR/albumin every 3 days
- Review medications, e.g. statins, antibiotics and alcohol history
- Perform liver screen: Hepatitis A/B/C serology, Hepatitis E PCR, anti-ANA/SMA/LKM/SLA/LP/LG, iron studies
- Consider imaging for metastases/clot

- As above; daily LFTs/INR/albumin
- Perform US with Doppler
- Low threshold to admit if clinical concern

- As above; hepatology consult
- Consider liver biopsy

Steroid wean:
- G2: once G1, wean over 2 weeks; re-escalate if worsening; treatment may be resumed once prednisolone ≤ 10 mg
- G3/4: once improved to G2, can change to oral prednisolone and wean over 4 weeks; for G3, rechallenge only at consultant discretion

Worsening despite steroids:
- If on oral change to i.v. (methyl)prednisolone
- If on i.v. add MMF 500-1000 mg bd
- If worse on MMF, consider addition of tacrolimus
- A case report has described the use of anti-thymocyte globulin in steroid + MMF-refractory fulminant hepatitis [31]
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

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 (potent) cream bd +/- oral or topical antihistamines for itch
- Proceed with ICPI treatment

**Grade 3:** rash covers > 30% BSA (see Figure 4) or grade 2 with substantial symptoms
- Withhold ICPI
- Topical treatments as above (potent)
- Initiate steroids:
  - If mild to moderate: 0.5-1 mg/kg prednisolone od for 3 days then wean over 1-2 weeks;
  - Or if severe: i.v. (methyl)prednisolone 0.5-1 mg/kg and convert to oral steroids on response, wean over 2-4 weeks
- Recomence ICPI at G1/mild G2 after discussion with patient and consultant

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

Management escalation pathway

**Assessment and Investigations**

- Physical examination
  - Exclude other causes, e.g. viral 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

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 hypoadrenalism, 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*
2. Analgesia as needed for headache (discuss with neurologist if resistant to paracetamol and NSAID’s)
3. 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 or consult endocrinologist
- Monitor TFTs

---

**Moderate symptoms, i.e. headache but no visual disturbance**

- Fatigue/mood alteration but haemodynamically stable, no electrolyte disturbance

**Management escalation pathway**

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

**Further assessment and management**

- 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

---

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

**Management escalation pathway**

1. Await pituitary axis to confirm diagnosis but warn patients to seek urgent review if unwell
2. Continue ICPI with appropriate HRT**

**Further assessment and management**

- 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)
Algorithm for pneumonitis

**Symptom Grade**
- **Grade 1:** Radiographic changes only
  - Ground glass change, non-specific interstitial pneumonia
- **Grade 2:** Mild/moderate new symptoms
  - Dyspnea, cough, chest pain
- **Grade 3 or 4:** Severe new symptoms
  - Now/worrisome hypoxia
  - Life threatening
  - Difficulty in breathing, ARDS

**Management escalation pathway**
- Consider delay of treatment
- Monitor symptoms every 2-3 days
- If worsening: treat as grade 2 or 3-4

**Assessment and Investigations**

**Baseline indications:**
- Chest X-ray
- Bloods (FBC/U/E/LFTs/FFTs/Ca/ESR/CRP)
- Consider sputum sample and screening for viral, opportunistic or specific bacterial (Mycoplasma, Legionella) infections depending on the clinical context

**Without ICI**
- Start Ab if suspicion of infection
  - (fever, CRP, neutrophil counts)
- If no evidence of infection or no improvement with Ab after 48h add in prednisolone 1 mg/kg/day orally
- Consider Pneumocystis prophylaxis depending on the clinical context
- High resolution CT +/- bronchoscopy and BAL pending appearances

**Outpatient Monitoring:**
- Monitor symptoms daily
- Baseline indications, as above plus:
  - Repeat chest X-ray weekly and baseline bloods
  - Lung function tests including TLC
  - If no improvement after 48h of oral prednisolone, manage as per Grade 3

**Discontinue ICI**
- Admit patient, baseline tests as above
  - (methylprednisolone: iv 2–4 mg/kg/day)
- High resolution CT and respiratory review
  - +/- bronchoscopy and BAL pending appearances
- Over with empiric Ab
- Discuss escalation and ventilation

**If not improving or worsening after 48h:**
- Add infliximab 5 mg/kg or MMF if concurrent hepatic toxicity
- Continue with i.v. steroids: wean as clinically indicated

**Once improved to baseline:**
- Grade 2: wean oral steroids over at least 8 weeks, taper to symptomatics
- Grade 3/4: wean steroids over at least 8 weeks

**Steroid considerations:**
- Calcium & Vitamin D supplementation as per local guidelines
- Pneumocystis prophylaxis: cotrimoxazole 480 mg bd MW/F or tinidazole if cotrim allergy

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
  - Polynreuroradiculopathy (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)

Presented By Caroline Robert at 2016 ASCO Annual Meeting

- 59 (97%) of responses were maintained

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

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

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

Schadendorf et al  EADO 2016
Pooled Ipi + Nivo Melanoma (067 + 069)

Best Overall Response

<table>
<thead>
<tr>
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<th>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>
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<tr>
<td>( P ) value for comparison</td>
<td>0.0200</td>
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</table>

Best overall response, %

<table>
<thead>
<tr>
<th></th>
<th>NIVO+IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>17.6</td>
</tr>
<tr>
<td>Partial response</td>
<td>50.6</td>
</tr>
<tr>
<td>Stable disease</td>
<td>15.9</td>
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<tr>
<td>Progressive disease</td>
<td>13.1</td>
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<tr>
<td>Unable to determine</td>
<td>2.8</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>
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<tbody>
<tr>
<td>Overall Response</td>
<td>31.4%</td>
<td>48.6%</td>
</tr>
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</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)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>ORR</td>
<td>31.4%</td>
<td>48.6%</td>
<td>27.8%</td>
</tr>
<tr>
<td>Med. Duration Response</td>
<td>NR</td>
<td>22 mo</td>
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</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?
  • 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*

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

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

*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
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52 Patients with mild-mod autoimmune disease Treated with anti-PD1

<table>
<thead>
<tr>
<th>Disease Category</th>
<th>Number (Percent)</th>
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<tbody>
<tr>
<td>Rheumatologic</td>
<td>27 (52%)</td>
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<tr>
<td>(13 Rheumatoid arthritis)</td>
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<tr>
<td>Dermatologic</td>
<td>8 (15%)</td>
</tr>
<tr>
<td>(6 psoriasis)</td>
<td></td>
</tr>
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<td>Gastrointestinal</td>
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<tr>
<td>(3 Crohns disease)</td>
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<tr>
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<tr>
<td>Haematologic</td>
<td>2 (4%)</td>
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</tbody>
</table>

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

Menzies A et al., Annals Onc 2016

Courtesy of G Long
52 Patients with mild-mod autoimmune disease treated with anti-PD1

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<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>
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<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
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!