ESMO ADVANCED COURSE ON LUNG CANCER IN IMMUNOTHERAPY

Management of IO toxicity

John Haanen MD PhD

Zürich, 3-4 July 2019

Netherlands Cancer Institute, Amsterdam
DISCLOSURE OF INTEREST

I have provided consultation, attended advisory boards, and/or provided lectures for: Amgen, AZ/Medimmune, Bayer, BMS, GSK, Ipsen, Merck Serono, MSD, Novartis, Pfizer, Roche/Genentech, Sanofi, Seattle Genetics for which NKI received honoraria.

I am on the SAB of AIMM, Celsius Therapeutics, Immunocore and Neon Therapeutics. Financial compensation goes to NKI.

Through my work NKI received grant support from Bayer, BMS, MSD, Novartis, Neon Therapeutics, Pfizer.
Finding the balance between efficacy and toxicity

Marie Boyle: ‘Cherish’
How much toxicity from IO treatment do we accept?

- Depending on cure rate
- Higher toxicity rate and grade is acceptable in stage IV disease
- In stage II-III disease (depending on tumor type) some patients are cured by surgery or other primary treatment
- Depending on the impact of toxicity on Quality of Life
- Disabling long-term toxicity
- Depending on the grade 3-5 rate
- No good cut-off
- Depending on accepted toxicity of Standard of Care (non-IO)
- Depending on the association between toxicity and efficacy

Tawbi et al., NEJM 2018; Eggermont et al. NEJM 2016; Schlenk et al., Biol Blood Marrow Transpl 2008
Correlation between irAE and efficacy in NSCLC treated with anti-PD-(L)1

<table>
<thead>
<tr>
<th>Study</th>
<th>ICI</th>
<th>n</th>
<th>Grade ≥ 3 irAEs, %</th>
<th>RR, %</th>
<th>PFS, mo</th>
<th>OS, mo</th>
<th>Cycles, n</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>irAEs</td>
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<td>irAE's</td>
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<tr>
<td>Ricciuti et al. 12</td>
<td>Nivolumab</td>
<td>195</td>
<td>7.6</td>
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<td>10.0</td>
<td>5.7</td>
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<tr>
<td>Moor et al. 13</td>
<td>Nivolumab</td>
<td>196</td>
<td>13.2</td>
<td>NR</td>
<td>NR</td>
<td>5.9</td>
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<tr>
<td>Toi et al. 14</td>
<td>Nivolumab</td>
<td>70</td>
<td>NR</td>
<td>57</td>
<td>12</td>
<td>12</td>
<td>3.6</td>
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<tr>
<td>Haratani et al. 15</td>
<td>Nivolumab</td>
<td>134</td>
<td>9</td>
<td>52</td>
<td>28</td>
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<td>4.8</td>
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<tr>
<td>Teraoka et al. 16,b</td>
<td>Nivolumab</td>
<td>43</td>
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<td>17</td>
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<tr>
<td>Sato et al. 17</td>
<td>Nivolumab</td>
<td>38</td>
<td>NR</td>
<td>64</td>
<td>7.4</td>
<td>Not R</td>
<td>1.6</td>
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<tr>
<td>Lisberg et al. c</td>
<td>Pembrolizumab</td>
<td>97</td>
<td>3.1</td>
<td>39.5</td>
<td>8.9</td>
<td>8.2</td>
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<td>Von Pawel et al. 19,b</td>
<td>Atezolizumab</td>
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<td>Kfoury et al. 20</td>
<td>Anti-PD-1/PD-L1</td>
<td>618</td>
<td>Grade ≥2 28.3%</td>
<td>NR</td>
<td>NR</td>
<td>14.2</td>
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<tr>
<td>Toi et al. 21</td>
<td>Anti-PD-1</td>
<td>137</td>
<td>NR</td>
<td>52</td>
<td>13</td>
<td>10.3</td>
<td>3.4</td>
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<tr>
<td>Shafqat et al. 22</td>
<td>Anti-PD-1/PD-L1</td>
<td>157</td>
<td>11.4</td>
<td>NR</td>
<td>NR</td>
<td>24.4</td>
<td>4.2</td>
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</table>
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 progression in patients with and without vitiligo, exact fisher test

Hua et al JAMA Dermatol 2016
Correlation between irAE and efficacy in melanoma treated with anti-PD-1

Pooled analysis of PFS and OS of CheckMate-069 and-067: ipi/nivo
What do we know about IO toxicities?

- What has been reported in peer-reviewed journals
  - Phase 1, phase 2, phase 3 and phase 4 trials
  - Expanded access programs
  - Compassionate use or Named Patient Programs
  - Case reports
  - Reports on real-world data
- Eminence-based (personal experience)
- How well are IO toxicities reported in clinical trial?
- What should we look at?
  - Treatment related AE?
  - Immune related AE?
  - All grade toxicity rate?
  - Grade 3-4 toxicity rate?
  - Grade 5 toxicity rate?
  - Treatment discontinuation rate?
  - Treatment delay?
  - Duration of AE (to grade 1 or lower)?
## Checkpoint blockade drug classes and FDA/EMA-approved indications

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Name</th>
<th>Melanoma</th>
<th>NSCLC</th>
<th>RCC</th>
<th>HL</th>
<th>Urothelial</th>
<th>HNSCC</th>
<th>Merkel</th>
<th>MSI-H CRC</th>
<th>Gastric</th>
<th>HCC</th>
<th>MSI-H</th>
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<tbody>
<tr>
<td>CTLA4 blockade</td>
<td>Ipilimumab</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td>Tremelimumab</td>
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<tr>
<td>PD1 blockade</td>
<td>Nivolumab</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
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<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Pembrolizumab</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
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<td></td>
<td>x</td>
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<tr>
<td>PDL1 blockade</td>
<td>Atezolizumab</td>
<td>x</td>
<td></td>
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<td></td>
<td></td>
<td>x</td>
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<td></td>
<td>Durvalumab</td>
<td>x</td>
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<td>Avelumab</td>
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<td></td>
<td></td>
<td>x</td>
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</table>
Increase in frequency of reported ir-endocrinopathies by ICI over the past 15 years

Total Number of Reported Cases of Endocrine Immune-related Adverse Events

- A: Ipilimumab approved
- B: Nivolumab & Pembrolizumab approved

Year

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases</th>
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<tbody>
<tr>
<td>'03</td>
<td>1</td>
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<tr>
<td>'04</td>
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<td>'05</td>
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<td>'09</td>
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<td>'10</td>
<td>23</td>
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<tr>
<td>'11</td>
<td>58</td>
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<tr>
<td>'12</td>
<td>72</td>
</tr>
<tr>
<td>'13</td>
<td>62</td>
</tr>
<tr>
<td>'14</td>
<td>182</td>
</tr>
</tbody>
</table>

Tan et al., Clin Diab Endocrinol 2019
How do we treat IO toxicities?

- Pharma developed algorithms
- 2017: ESMO Guidelines
- 2017: SITC Guidelines
- 2018: ASCO Guidelines
- 2018: NCCN Guidelines

None of the Guidelines are based on outcomes of randomized controlled trials!

- Based on recommendations coming from treatment of auto-immune diseases, organ transplantations
- Empirically obtained data from key opinion leaders in the field
- Based on assumed mechanism of action of IO drugs
How should a patient starting with IO treatment be approached?

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

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

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

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

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

Champiat et al., Ann Oncol 2016
Case

56-year old male patient. No comorbidities (no autoimmune disease)

2007: Superficial spreading melanoma on the back (left side). Breslow: 1.9 mm, no ulceration, pT2a

Nov 2018: bulky irresectable axillary metastases
NRAS Q61 mutation
No brain metastases
Lab: normal LDH
Referred to NKI
PET-CT-scan December 2018
Case

56-year old male patient. No comorbidities (no autoimmune disease)

2007: Superficial spreading melanoma on the back (left side). Breslow: 1.9 mm, no ulceration, pT2a

Nov 2018: bulky irresectable axillary metastases
NRAS Q61 mutation
No brain metastases
Lab: LDH normal, S100b: 1.73 μg/L (ULN: 0.10 μg/L)
Referred to NKI

Discussed in Multidisciplinary Team: advise: start ipilimumab + nivolumab

Dec 2018: start ipi 3 mg/kg + nivo 1 mg/kg
Jan 2019: 2\textsuperscript{nd} course ipi/nivo: no side effects of treatment
Lab: S100b: 2.49 μg/L; LDH 316 U/L (ULN 250 U/L)

1 week later: Nausea, loss of appetite, especially coffee, headaches under control with paracetamol.
Started to cough once in while, dry, not productive. On physical exam: no abnormalities
Works 40 hrs/week, but more tired in the evenings

2 weeks later: slow deterioration, weight loss of 10 kg as of start of treatment
Worked now 50%. More tired. Dyspnea on exertion, no cough, no diarrhea, no abdominal pain, no rash.
Lab: further increase in S100b and LDH, rest including hormonal axes normal
3\textsuperscript{rd} ipi + nivo was given, but because of likelihood of disease progression, PET was performed
PET/CT evaluation after 2 courses of ipilimumab/nivolumab
PET: more or less stable disease of left axillary metastases
Inflamed lower lung lobes
Symmetric mediastinal lymphadenopathy
Pleural effusion
Inflamed upper and lower GI tract, pancreas

Now also complaints of diarrhea, more nausea and increased shortness of breath.
Oxygen saturation: 91%
Lab: S100b stable: 4.56 μg/L and LDH 346 U/L, no other abnormalities

Multiple grade 1-2 (clinically) immune related adverse events:
• Upper GI tract
• Colitis
• Pancreatitis
• Pneumonitis
• Sarcoid-like disease
Case

Started with prednisone 1 mg/kg (100 mg)

1 week later: Diarrhea gone (normal stools); regained appetite, dyspnea more or less the same (Oxygen saturation: 95%)

Steroids were tapered after 2 weeks of high dose

During tapering he started complaining of dry and irritated eyes
S100b: 8.91 mg/L
sLDH: 689 U/L

Haanen, unpublished
Potential mechanism by which immune related adverse events develop

Postow et al., NEJM 2018
Increasing T cell activity against antigens that are present in tumors and healthy tissue

Postow et al., NEJM 2018; Berner et al., JAMA Oncol 2019;
Preexisting autoantibodies

**Autoantibody Development under Treatment with Immune-Checkpoint Inhibitors**

Emma C. de Moel¹, Elisa A. Rozeman², Ellen H. Kapiteijn³, Els M.E. Verdegaal³, Annette Grummels⁴, Jaap A. Bakker⁴, Tom W.J. Huizinga¹, John B. Haanen²,³, René E.M. Toes¹, and Diane van der Woude¹

**Pre-ipilimumab auto-antibody (AA) negative pts**

- 127 pts treated with ipilimumab
- 19% developed AA
- Mostly anti-TPO and anti-TG
- 15/19 (79%) pts that developed AA had irAE
- 46/80 (57%) pts with no AA developed irAE
- No correlation with specific AA and organ-specific irAE
Direct binding of anti-CTLA-4 to CTLA-4 expressed on normal tissue

Hypophysitis Secondary to Cytotoxic T-Lymphocyte—Associated Protein 4 Blockade

*Insights into Pathogenesis from an Autopsy Series*

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**Table 2** Distribution of Hormone-Secreting and CTLA-4—Expressing Pituitary Cells by Double Indirect Immunofluorescence in the Gland from Autopsy Case 6

<table>
<thead>
<tr>
<th>Antibody stainings</th>
<th>Total endocrine cells</th>
<th>Hormone-positive cells*</th>
<th>CTLA-4—positive cells*</th>
<th>Double-positive cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH and CTLA-4</td>
<td>116</td>
<td>64 (55)</td>
<td>1 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>PRL and CTLA-4</td>
<td>110</td>
<td>22 (20)</td>
<td>2 (1.8)</td>
<td>0</td>
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<tr>
<td>ACTH and CTLA-4</td>
<td>92</td>
<td>13 (14)</td>
<td>1 (1.1)</td>
<td>0</td>
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<tr>
<td>FSH and CTLA-4</td>
<td>114</td>
<td>12 (10)</td>
<td>3 (2.6)</td>
<td>2</td>
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<tr>
<td>LH and CTLA-4</td>
<td>106</td>
<td>6 (6)</td>
<td>2 (1.9)</td>
<td>2</td>
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<tr>
<td>TSH and CTLA-4</td>
<td>128</td>
<td>5 (4)</td>
<td>1 (0.8)</td>
<td>1</td>
</tr>
</tbody>
</table>
Increasing levels of inflammatory cytokines

LETTER TO THE EDITOR

Interleukin-6 as one of the potential mediators of immune-related adverse events in non-small cell lung cancer patients treated with immune checkpoint blockade: evidence from a case report

Abdul Rafeh Naqash, Li V. Yang, Edward J. Sanderlin, Druid C. Atwell and Paul R. Walker

Postow et al., NEJM 2018; Naquash et al., Acta Oncologica 2018
Immune related Adverse Events associated with anti-CTLA4

colitis

Thyroiditis
Hepatitis
Pneumonitis
Nephritis
Meningitis
e etc.

hypophysitis

dermatitis

Haanen, unpublished, with patient consent
### irAE Kinetics of ipilimumab

<table>
<thead>
<tr>
<th>Study details</th>
<th>Any-grade adverse events (grade ≥3 adverse events)</th>
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<tbody>
<tr>
<td><strong>Study</strong></td>
<td><strong>Diarrhea</strong></td>
</tr>
<tr>
<td>EORTC 18071</td>
<td>41.2% (9.8%)</td>
</tr>
<tr>
<td>[REF 13]</td>
<td></td>
</tr>
<tr>
<td>Hodi et al 199</td>
<td>27.5% (4.6%)</td>
</tr>
<tr>
<td>3 mg/kg, 3-weekly (131)</td>
<td></td>
</tr>
</tbody>
</table>

#### Toxicity Grade

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

**Time (weeks)**

- 0
- 2
- 4
- 6
- 8
- 10
- 12
- 14

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Weber et al J Clin Oncol 2012  
Martins et al., Nat Rev Clin Oncol 2019
### irAE kinetics of anti-PD-(L)1

<table>
<thead>
<tr>
<th>Study details</th>
<th>Any-grade adverse events (grade ≥3 adverse events)</th>
<th>Dose (n)</th>
<th>Diarrhoea</th>
<th>Colitis</th>
<th>Pulmonary</th>
<th>Rash</th>
<th>Neurological</th>
<th>Endocrinopathy</th>
<th>Hepatic</th>
<th>Renal</th>
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<tbody>
<tr>
<td><strong>Nivolumab</strong></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>CheckMate 066 (REF.⁵⁰)</td>
<td></td>
<td>3 mg/kg, 2-weekly (206)</td>
<td>16% (1%)</td>
<td>1% (0.5%)</td>
<td>1.5% (0%)</td>
<td>15% (0.5%)</td>
<td>–</td>
<td>7.3% (1%)</td>
<td>3.4% (1.5%)</td>
<td>1.9% (0.5%)</td>
</tr>
<tr>
<td>CheckMate 057 (REF.⁵⁰)</td>
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<td>3 mg/kg, 2-weekly (287)</td>
<td>8% (1%)</td>
<td>1% (0.3%)</td>
<td>4.9% (1.4%)</td>
<td>9% (3.5%)</td>
<td>0.3% (0.3%)*</td>
<td>10.5% (0%)</td>
<td>10.8% (1.4%)</td>
<td>2% (0%)</td>
</tr>
<tr>
<td><strong>Pembrolizumab</strong></td>
<td></td>
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</tr>
<tr>
<td>KEYNOTE-010 (REF.⁵⁰)</td>
<td></td>
<td>2 mg/kg, 3-weekly (339)</td>
<td>7% (1%)</td>
<td>1% (1%)</td>
<td>5% (2%)</td>
<td>9% (0.3%)</td>
<td>–</td>
<td>15% (1%)</td>
<td>0.3% (0.3%)</td>
<td>–</td>
</tr>
<tr>
<td>KEYNOTE-010 (REF.⁵⁰)</td>
<td></td>
<td>10 mg/kg, 3-weekly (343)</td>
<td>6% (0%)</td>
<td>1% (0.3%)</td>
<td>4% (2%)</td>
<td>13% (0.3%)</td>
<td>–</td>
<td>16.5% (2%)</td>
<td>1% (0%)</td>
<td>–</td>
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<tr>
<td>KEYNOTE-054 (REF.⁵⁰)</td>
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<td>200 mg, 3-weekly (509)</td>
<td>19.1% (0.8%)</td>
<td>3.7% (2%)</td>
<td>4.7% (0.8%)</td>
<td>16.1% (0.2%)</td>
<td>–</td>
<td>23.4% (1.8%)</td>
<td>1.8% (1.4%)</td>
<td>0.4% (0.4%)</td>
</tr>
</tbody>
</table>

![Graph showing toxicity grade over duration of treatment](image_url)
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) weeks
- Gastrointestinal (n = 66; 14%): 7.3 (0.1–37.6) weeks
- Hepatic (n = 19; 4%): 7.7 (2.0–38.9) weeks
- Pulmonary (n = 9; 2%): 8.9 (3.6–22.1) weeks
- Endocrine (n = 36; 8%): 10.4 (3.6–46.9) weeks
- Renal (n = 8; 2%): 15.1 (3.9–26.4) weeks
Anti-PD1 Nivolumab Pooled Safety Analysis
Kinetics of Onset and Resolution of Immune-related AEs

Incidence

Approximate Proportion of Pts (%) vs. Weeks

Skin: Red line
Gastrointestinal: Blue line
Endocrine: Gray line
Hepatic: Cyan line
Pulmonary: Green line
Renal: Black line

Weber J et al J Clin Oncol 2017
Grade 3-4 irAE over time in CheckMate-067: ipi/nivo and nivolumab vs ipilimumab

Sznol et al. J Clin Oncol 2018
# irAE kinetics of anti-CTLA-4 + anti-PD-(L)1

<table>
<thead>
<tr>
<th>Study details</th>
<th>Dose (n)</th>
<th>Any-grade adverse events (grade ≥3 adverse events)</th>
<th>Neurological</th>
<th>Endocrinopathy</th>
<th>Hepatic</th>
<th>Renal</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Diarrhoea</td>
<td>Colitis</td>
<td>Pulmonary</td>
<td>Rash</td>
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<td><strong>Ipilimumab plus nivolumab</strong></td>
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<tr>
<td>CheckMate 067 (REF.⁴⁸)</td>
<td>3 mg/kg ipilimumab plus 1 mg/kg nivolumab, 3-weekly (313)</td>
<td>45% (9%)</td>
<td>13% (8%)</td>
<td>7% (1%)</td>
<td>30% (3%)</td>
<td>34% (6%)</td>
</tr>
<tr>
<td>CheckMate 214 (REF.¹⁷)</td>
<td>1 mg/kg ipilimumab plus 3 mg/kg nivolumab, 3-weekly (547)</td>
<td>27% (4%)</td>
<td>–</td>
<td>–</td>
<td>22% (1%)</td>
<td>–</td>
</tr>
<tr>
<td>CheckMate 227 (REF.¹⁹)</td>
<td>1 mg/kg 6-weekly ipilimumab plus 3 mg/kg 2-weekly nivolumab (576)</td>
<td>16.3% (1.6%)</td>
<td>1% (0.5%)</td>
<td>3% (2%)</td>
<td>16.7% (1.6%)</td>
<td>–</td>
</tr>
</tbody>
</table>

**Toxicity grade**

- **Colitis**
- **Endocrinopathy**
- **Nephritis**
- **Liver toxicity**
- **Skin, rash or pruritus**
- **Pneumonitis**

Martins et al., Nat Rev Clin Oncol 2019
Checkmate 067: Safety
Onset Grade 3–4 Treatment-Related Select AEs

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

Sznol et al. J Clin Oncol 2018
<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%)</th>
<th>Anti-PD-1/PD-L1</th>
<th>Combination</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Iplilimumab (n = 193)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Types of cancer³</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>136 (96)</td>
<td>50 (18)</td>
<td>49 (66)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>0 (0)</td>
<td>152 (54)</td>
<td>17 (23)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5 (4)</td>
<td>78 (28)</td>
<td>8 (11)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of fatal irAE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colitis</td>
<td>135 (70)</td>
<td>58 (17)</td>
<td>32 (37)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>15 (8)</td>
<td>115 (35)</td>
<td>12 (14)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>31 (16)</td>
<td>74 (22)</td>
<td>19 (22)</td>
<td>.23</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>10 (5)</td>
<td>3 (1)</td>
<td>2 (2)</td>
<td>.01</td>
</tr>
<tr>
<td>Cardiac</td>
<td>3 (2)</td>
<td>27 (8)</td>
<td>22 (25)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Myositis</td>
<td>1 (0.5)</td>
<td>22 (7)</td>
<td>11 (13)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Nephritis</td>
<td>1 (0.5)</td>
<td>7 (2)</td>
<td>3 (4)</td>
<td>.19</td>
</tr>
<tr>
<td>Adrenal</td>
<td>8 (4)</td>
<td>6 (2)</td>
<td>3 (4)</td>
<td>.26</td>
</tr>
<tr>
<td>Neurologic</td>
<td>11 (6)</td>
<td>50 (15)</td>
<td>7 (8)</td>
<td>.003</td>
</tr>
<tr>
<td>Hematologic</td>
<td>3 (2)</td>
<td>14 (4)</td>
<td>2 (2)</td>
<td>.22</td>
</tr>
<tr>
<td>Other (skin, thyroid, diabetes, other gastrointestinal)</td>
<td>13 (7)</td>
<td>24 (8)</td>
<td>7 (8)</td>
<td>.93</td>
</tr>
<tr>
<td>Other clinical features</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time to irAE, days</td>
<td>40</td>
<td>40</td>
<td>14</td>
<td>.01</td>
</tr>
<tr>
<td>&gt;1 concurrent irAE, %</td>
<td>27 (14)</td>
<td>51 (15)</td>
<td>24 (28)</td>
<td>.01</td>
</tr>
<tr>
<td>Reporting year</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2014 or before</td>
<td>98 (51)</td>
<td>3 (1)</td>
<td>2 (2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2015</td>
<td>45 (23)</td>
<td>20 (6)</td>
<td>9 (10)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2016</td>
<td>21 (11)</td>
<td>88 (28)</td>
<td>17 (20)</td>
<td>.001</td>
</tr>
<tr>
<td>2017</td>
<td>26 (13)</td>
<td>192 (58)</td>
<td>44 (51)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2018 (up to January 15)</td>
<td>3 (2)</td>
<td>30 (9)</td>
<td>15 (17)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Wang et al., JAMA Oncol 2018
Incidence of fatal irAE and fatality rates

Fatal irAE occur following ICI at a rate of 0.3 to 1.3%

Wang et al., JAMA Oncol 2018
Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy:

New NCCN Guidelines: Recognition and Management of Immunotherapy-Related Toxicity

Presented by John A. Thompson, MD
Management of Immunotherapy-Related Toxicities, Version 1.2019

MANAGEMENT OF IMMUNE CHECKPOINT INHIBITOR TOXICITIES: A REVIEW AND CLINICAL GUIDELINE FOR EMERGENCY PHYSICIANS

EXPERT CONSENSUS DOCUMENT

Management guidelines for paediatric patients receiving chimeric antigen receptor T cell therapy

Kris M. Mahadeo¹,²⁰*, Sajad J. Khazal¹, Hisham Abdel-Azim², Julie C. Fitzgerald³,²⁰, Agne Taraseviciute⁴, Catherine M. Bollard⁵, Priti Tewari⁶, Christine Duncan⁷,²⁰, Chani Traube⁸,²⁰, David McCall¹, Marie E. Steiner⁹,²⁰, Ira M. Cheifetz¹⁰,²⁰, Leslie E. Schilsky³,²⁰, Rachel M. Miller¹, John M. Shuster¹², Peter D. Rege²⁰
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
Algorithm for hepatitis

Haanen et al., Ann Oncol 2017
Algorithm diarrhea and colitis

Symptom Grade

Mild (GI): ≤ 3 liquid stools per day over baseline, feeling well
ICP can be continued

Moderate (G2): ≤ 4-5 liquid stools per day over baseline or abdominal pain or blood in stool or nausea or nocturnal episodes
Outpatient management is appropriate
If unwell, manage as per severe
ICP to be withheld

Severe (G3A): > 6 liquid stools per day over baseline or it episodes within 1h of eating
Requires hospitalisation and isolation until infection excluded
ICP to be withheld

Management escalation pathway

Symptomatic: Oral fluids, leprotamine, avoid high fibrous 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 diarrhea
Do not wait for sigmoidoscopy or colonoscopy to start

No improvement in 72h or worsening or abscess concerns

Lax (methyl)prednisolone 1-2 mg/kg
Gastroenterology input and ensure sigmoidoscopy is requested

At clinician discretion

Assessment and investigations

Baseline investigations: FBC, UEC, LFTs, CRP, TFTs
Stool microscopy for leucocytes/ova/worms, culture, viral PCR, C-diffidium slide test
Cryptosporidium and endoscopy
Culture for drug-resistant organisms

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

Inpatients:
- Test as above, including sigmoidoscopy or colonoscopy
- Consider 57 abdomen/palp, erect Abdominal X-ray as indicated
- Daily FBC, UEC, LFTs, CRP
- Review diet (e.g. nothing by mouth, clear fluids, TPN)
- Early surgical review if bleeding, pain or distension

Infection: ≤ 5 mm/L
(Five per cent blood/autops/TVs, hepatitis, HIV/HAV/CMV
CRP)
Must have had transfusion/sigmoidoscopy/colonoscopy prior
Other immunosuppressive treatment options: MMF 500-1000 mg od or tacrolimus

Methylprednisolone 1-2 mg/kg iv.
Loperamide 4 mg 1st dose then 2 mg every 4h until
each meal and after each loose stool until 12h
without diarrheia (max 16 mg/day)

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-TNFα)
  - Mycophenolate mofetil
  - Tacrolimus
  - Other → plasmapheresis, anti-thymocyte globulin, IVIG
New therapeutics to manage refractory immune related adverse events
Prophylactic TNF blockade uncouples efficacy and toxicity in dual CTLA-4 and PD-1 immunotherapy

Elisabeth Perez-Ruiz, Luna Minute, Itziar Otano, Maite Alvarez, Maria Carmen Ochoa, Virginia Belsue, Carlos de Andrea, Maria Esperanza Rodríguez-Ruiz, Jose Luis Perez-Gracia, Ivan Marquez-Rodas, Casilda Llacer, Martina Alvarez, Vanesa de Luque, Carmen Molina, Alvaro Teijeira, Pedro Berraondo, & Ignacio Mel...
Important Practical Questions

• 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?
• Can patients with organ transplants be treated with checkpoint inhibitors?
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 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., J Clin Oncol 2017
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
Clinically significant toxicities with combination IT and anti-PD-1 resumption

Pollack et al., Ann Oncol 2018
Management of toxicities from immune checkpoint blockade

Take home messages

Risk assessment (AID, organ transplant etc)
Every organ can be involved
Severity can vary from grade 1 – 5
Requires immediate action
Hold further treatment (depending on severity)
Consult organ specialist if necessary
Start immunosuppression (depending on severity)
Careful follow-up warranted
Taper immunosuppression

As a (medical) oncologist: be in the lead!
Thank you for your attention

Questions?