MANAGEMENT OF IMMUNE-RELATED SIDE EFFECTS OF 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
GENERAL ASPECTS

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

Marie Boyle: ‘Cherish’
ANTI-CTLA4

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


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
Checkmate 067: Safety
Onset Grade 3–4 Treatment-Related Select AEs

Larkin J et al ECC 2015
## 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>
</tr>
<tr>
<td>2</td>
<td>77 (25)</td>
</tr>
<tr>
<td>3</td>
<td>15 (5)</td>
</tr>
<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

Boutros et al., Nat Rev Clin Oncol 2016
Immune related AEs

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

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

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

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

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

Grade 2 diarrhea

Grade 3 diarrhea

Grade 1 diarrhea

Right colon

Left colon

Geukes Foppen, Rozeman et al., ESMO Open in press
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 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 with and without vitiligo, exact fisher test

---

**Graphs**

A: First 12 wk of treatment

B: First 20 wk of treatment

Hua et al JAMA Dermatol 2016
Lichen planus

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

Aggravation of pre-existing psoriasis

Courtesy of C Robert
Frequent AE: fatigue

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

Boutros et al Nat Rev Clin Oncol 2016
Hepatitis

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

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

Hofman et al., Eur J Cancer 2016
Endocrine AE

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

Boutros et al Nat Rev Clin Oncol 2016
Pneumonitis

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

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

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

Myasthenia gravis

Zimmer et al., Eur J Cancer 2016
### 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>Colitis/diarrhea</td>
<td>30%</td>
<td>45%</td>
<td>1-2%/13%</td>
<td>12-23%/45%</td>
<td>8%/24%</td>
<td>20%/35%</td>
</tr>
<tr>
<td>Skin/pruritis</td>
<td>14%/22%</td>
<td>26%/24%</td>
<td>15-20%</td>
<td>28-41%/35%</td>
<td>39%/39%</td>
<td>25%/33%</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1.5%</td>
<td>10%</td>
<td>5-10%</td>
<td>16%</td>
<td>16%</td>
<td>20%</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>1%</td>
<td>7%</td>
<td>0.2%</td>
<td>8-12%</td>
<td>10%</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue</td>
<td>9%</td>
<td>11%</td>
<td>20-30%</td>
<td>39%</td>
<td>46%</td>
<td>43%</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>5%</td>
<td>24%</td>
<td>4%</td>
<td>22-32%</td>
<td>10%</td>
<td>18%</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>2%</td>
<td>2-4%</td>
<td>7-11%</td>
<td>10%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>&lt;3%</td>
<td>2-6%</td>
<td>3%</td>
<td>5%</td>
<td></td>
<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

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
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 per severe
  - ICSI to be withheld
- Severe (G3/G4): i.e. > 6 liquid stools per day over baseline or if episodes within 1h of eating
  - Requires hospitalisation and isolation until infection excluded
  - ICSI to be withheld

**Management escalation pathway**
- Symptomatic: No oral fluids, loperamide, avoid high fibre/fermentable 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/colonoscopy to start
    - No improvement in 72h or worsening or development of concern
      - I.V. (methyl)prednisolone 1-2 mg/kg
      - Gastroenterology input and ensure sigmoidoscopy/colonoscopy is requested
      - No improvement in 72h or worsening
        - Infliximab 5 mg/kg
          - (if no peritonitis/sepsis/TP/Peptostreptomyces/IVIA III/IV/CHF)
          - Can repeat 2 weeks later
          - Must have had sigmoidoscopy/colonoscopy prior
          - Other immune-suppressive treatment options: MMF 500-1000 mg bid or tacrolimus

**Assessment and Investigations**
- Baseline investigations: FBC, U/E, LFTs, CRP, TFTs
  - Stool microscopy for leucocytes/ova/parasites, culture, viral PCR, Giardia stool 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 sinister cause
  - Sigmoidoscopy/colonoscopy (+/- biopsy)
  - Contact patient every 72h
  - Repeat baseline bloods at outpatient review

- Inpatients: Test as above, including sigmoidoscopy/colonoscopy
  - Consider CT abdominal/pelvis, repeat Abdominal X-ray as indicated
  - Daily FBC, U/E, LFTs, CRP
  - Review diet (e.g. nothing by mouth, clear fluids, TPM)
  - Early surgical review if bleeding, pain or distension

**Steroid wean duration**
- Moderate: wean over 2-4 weeks
- Severe: wean over 4-6 weeks
- Stooling > 4 weeks:
  - Consider PJP prophylaxis, regular random blood glucose, WBC level, start calcium/Vitamin D supplement

---

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)
- **Grade 2:** rash covers 10-30% of BSA (see Figure 4)
- **Grade 3:** rash covers > 30% BSA (see Figure 4) or grade 2 with substantial symptoms
- **Grade 4:** skin sloughing > 30% BSA (see Figure 4) with associated symptoms (e.g., erythema, purpura, epidermal detachment)

**Management Escalation Pathway**

- **Avoid skin irritants**, avoid sun exposure, topical emollients recommended
- **Topical steroids (mild strength) cream od +/- oral or topical antihistamines for itch**
- **Supportive management, as above**
- **Topical steroids (moderate strength) cream od or clobetasol cream bd +/- oral or topical antihistamines for itch**
- **Withhold ICPI**
- **Topical treatments as above (potent)**
  - Initiate steroids: If mild to moderate 0.5-1 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 convert to oral steroids on response, wean over 2-4 weeks
  - Recommend ICPI at 6/1/mld Q2 after discussion with patient and consultant
- **Grade 4:** skin sloughing > 30% BSA (see Figure 4) with associated symptoms (e.g., erythema, purpura, epidermal detachment)

**Assessment and Investigations**

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

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

- Grade 1 pruritus/rash
  - Cooling ointment
  - Antihistamine

- Grade 2 rash
  - Involve dermatologist
  - Start topical steroids
  - Cooling ointment

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

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

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

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

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

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

**Management escalation pathway**
- 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 NSAIDs)
  - Withhold ICPI

- 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

- 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 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 thyroid 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
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
  – Polynreneradiculopathy (Guillain-Barre (-like) syndrome
  – Myasthenia gravis
  – Myelitis transversa
• Involve neurologist! : rule out other causes of neurologic deficit (MRI, spinal fluid, EMG, antibodies)
• Admit patient
• Start systemic steroids
• Depending on diagnosis: plasmapheresis, IVIG, (rituximab??)
Important Practical Questions

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

- 59 (97%) of responses were maintained

Presented By Caroline Robert at 2016 ASCO Annual Meeting
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?
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 (95% CI)</td>
<td>16.7 (10.2, NA)</td>
<td>10.8 (5.9, 23.0)</td>
</tr>
<tr>
<td>HR (99.5% CI)</td>
<td>0.74 (0.56, 0.98), P &lt; 0.04</td>
<td></td>
</tr>
</tbody>
</table>

Discontinued for Tox\textsuperscript{a}
No Discontinuation for Tox\textsuperscript{b}

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

<table>
<thead>
<tr>
<th></th>
<th>NIVO+IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Discontinued due to AEs (n = 176)</td>
</tr>
<tr>
<td>ORR, % (95% CI)</td>
<td>68.2 (60.8, 75.0)</td>
</tr>
<tr>
<td>(P) value for comparison</td>
<td>0.0200</td>
</tr>
</tbody>
</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>
</tr>
<tr>
<td>Progressive disease</td>
<td>13.1</td>
</tr>
<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>
</thead>
<tbody>
<tr>
<td>Overall Response</td>
<td>31.4%</td>
<td>48.6%</td>
</tr>
</tbody>
</table>

Not Observed with Ipilimumab Monotherapy

Weber et al JCO 2017

¹Courtesy of G Long
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)

**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></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Weber et al JCO 2016 in press
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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>colitis</td>
<td>47 (70%)</td>
</tr>
<tr>
<td>endocrine</td>
<td>13 (19%)</td>
</tr>
<tr>
<td>dermatologic</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>rheumatic</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>hepatitis</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>neurologic</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>ocular</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>hematologic</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

And same for Anti-PD1 → Ipilimumab*

Recurrence 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
• 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 Category</th>
<th>Count</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 crohns 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

Menzies A et al., Annals Onc 2016

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

- Rheumatologic (13 Rheumatoid arthritis) 27 (52%)
- Dermatologic (6 psoriasis) 8 (15%)
- Gastrointestinal (3 Crohn's disease) 6 (12%)
- Neurologic 5 (10%)
- Endocrine 4 (8%)
- Respiratory 2 (4%)
- Haematologic 2 (4%)

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
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!