MANAGEMENT OF IMMUNE-RELATED SIDE EFFECTS OF IMMUNE CHECKPOINT INHIBITORS

John B.A.G. Haanen MD PhD
Disclosures

- I have provided consultation, attended advisory boards, and/or provided lectures for: **Pfizer, MSD, BMS, IPSEN, Roche/Genentech, NEON Therapeutics, Novartis** for which NKI received honoraria
- Through my work NKI received grant support from **BMS, MSD, Novartis**
- I declare no conflict of interest
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

Ribas. NEJM 2012
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


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

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>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/colicitis 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>
</tbody>
</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>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>
</tbody>
</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 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

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

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

*Complete/partial response versus stable/progressive disease/progression in patients 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>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></td>
<td></td>
<td>2-6%</td>
<td>3%</td>
<td>5%</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. ICPI 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. ICPI to be withheld.

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

Management escalation pathway

Symptomatic: i.e. oral fluids, loperamide, avoid high fibre/latex 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/colectoscopy to start.

No improvement in 72h or worsening or absorption concern.

Inpatient: Test as above, including sigmoidoscopy/colectoscopy. 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.

At clinician discretion


Assessment and Investigations

Baseline investigations: FBC, UEC, LFTs, CRP. TTFs. Stool microscopy for leukocytes/ova/parasites, culture, viral PCR. Giardia difficile toxin and cryptosporidia. Culture for drug-resistant organisms.

Medications

Imatinib 5 mg/kg (if no perforation/sepsis/TNFalpha xeroderma/IV CD) can repeat 2 weeks later. Must have had transsigmoid/colectoscopy prior.

Other immune suppressive treatment options: MMF 500-1000 mg bid or tacrolimus.

Loperamide 4 mg 1st dose then 2 mg 30mls before each meal and after each loose stool until 12h 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

<table>
<thead>
<tr>
<th>Symptom Grade</th>
<th>Management escalation pathway</th>
<th>Assessment and Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1: skin rash, with or without symptoms, &lt; 10% BSA (see Figure 4)</td>
<td>Avoid skin irritants, avoid sun exposure, topical emollients recommended</td>
<td>Physical examination Exclude other causes, e.g. oral illness, infection, other drug rash</td>
</tr>
<tr>
<td></td>
<td>Topical steroids (mild strength) cream od +/- oral or topical antihistamines for itch Proceed with treatment</td>
<td>As above Consider dermatology referral and skin biopsy</td>
</tr>
<tr>
<td></td>
<td>Supportive management, as above</td>
<td></td>
</tr>
<tr>
<td>Grade 2: rash covers 10%-30% of BSA (see Figure 4)</td>
<td>Topical steroids (moderate strength) cream od (clobetasone) cream bd +/- oral or topical antihistamines for itch Proceed with ICPI treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>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. methylprednisolone 0.5-1 mg/kg and convert to oral steroids on response, wean over 2-4 weeks Recommerce ICPI at G1/mld G2 after discussion with patient and consultant</td>
<td></td>
</tr>
<tr>
<td>Grade 3: rash covers &gt; 30% BSA (see Figure 4) or grade 2 with substantial symptoms</td>
<td>As for Grade 1 Dermatology review Consider punch biopsy and clinical photography</td>
<td></td>
</tr>
<tr>
<td>Grade 4: skin sloughing &gt; 30% BSA (see Figure 4) with associated symptoms (e.g. erythema, purpura, epidermal detachment)</td>
<td>As for Grade 1 Dermatology review Punch biopsy Clinical photography</td>
<td></td>
</tr>
</tbody>
</table>
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 hypoadrenalinism, 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

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

- MRI pituitary protocol (also exclude brain metastases), visual field assessment
  - Replace cortisol and/or thyroid per guide below**
  - MRI pituitary protocol
  - Refer to endocrinologist

Further management

- 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

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
  - Polynreurnoradiculopathy (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>Discontinued for Tox(^a)</th>
<th>No Discontinuation for Tox(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIVO+IPI DC ((n = 176))</td>
<td>NIVO+IPI no DC ((n = 233))</td>
</tr>
<tr>
<td><strong>Median PFS, months</strong></td>
<td><strong>HR (99.5% CI)</strong></td>
</tr>
<tr>
<td><strong>(95% CI)</strong></td>
<td><strong>0.74 (0.56, 0.98), (P &lt; 0.04)</strong></td>
</tr>
</tbody>
</table>

- Median PFS: 16.7 (10.2, NA) vs. 10.8 (5.9, 23.0)
- HR: 0.74 (0.56, 0.98), \(P < 0.04\)

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><strong>ORR, % (95% CI)</strong></td>
<td>68.2 (60.8, 75.0)</td>
</tr>
<tr>
<td><strong>P value for comparison</strong></td>
<td>0.0200</td>
</tr>
</tbody>
</table>

### Best overall response, %

<table>
<thead>
<tr>
<th></th>
<th>NIVO+IPI</th>
<th>NIVO+IPI</th>
</tr>
</thead>
<tbody>
<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)

<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
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)\(^1\)

<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</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>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 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

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

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

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

And same for Anti-PD1 → Ipilimumab*

* Bowyer et al, BJC 2016

Courtesy 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?
52 Patients with mild-mod autoimmune disease Treated with anti-PD1

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatologic</td>
<td>27</td>
<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

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>Condition</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

20 (38%) Auto-immune flare on anti-PD1

- 14 Rheumatologic
- 3 Dermatology
- 1 Endocrine
- 2 Haematologic

Managed with oral steroids, SSA and IVIg (1)

Courtesy of G Long

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

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

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

*IS = immunosuppression at start

Courtesy of G Long

Menzies A et al., Annals Onc 2016
Take home messages
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!