Immunotherapy in Melanoma, Pseudo-progression, Management of Toxicities
Clinical Case Presentation

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Disclosures

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• Travel accommodation: Astra Zeneca, Bristol-Myers Squibb, Merck, Roche
Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in unresectable or metastatic melanoma

1861 patients treated in 12 studies: 8 phase III, 2 phase III, and 2 observational studies

3yr-OS: 22% (20–24)

OS, overall survival

Pseudo-progression: tumour “flare”

Screening

Week 12
Initial increase in total tumour burden (mWHO PD)

Week 16
Responding

Week 96
Durable and ongoing response without signs of irAEs

irAEs, immune-related adverse events; mWHO, modified World Health Organization; PD, progressive disease

Harmankaya et al. EADO 2009
Pseudo-progression: tumour “flare”

In melanoma, it may occur in 10% to 15% of patients. In epithelial cancers such as NSCLC and HNSCC the rate appears to be closer to 2% to 3%. This incidence calculation may be an underestimation because irRECIST were not evaluated across all patients in these studies.

<table>
<thead>
<tr>
<th>Regimen and Trial</th>
<th>Cancer Type</th>
<th>No. of Evaluable Patients</th>
<th>No. of Responses</th>
<th>Objective Response Rate (%)</th>
<th>Primary Response Criteria</th>
<th>Immune-Related Response Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>Colorectal, melanoma, renal cell</td>
<td>39</td>
<td>3</td>
<td>8</td>
<td>RECIST 1.0</td>
<td>Not reported Not reported Not reported</td>
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<tr>
<td>Brahmer et al</td>
<td>Multiple</td>
<td>135</td>
<td>17</td>
<td>13</td>
<td>RECIST 1.0</td>
<td>Not reported 4 additional Not reported</td>
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<tr>
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<td>Non-small-cell lung</td>
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<td>6</td>
<td>10</td>
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<table>
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<tbody>
<tr>
<td>Lambrolizumab</td>
<td>Hamid et al</td>
<td>117</td>
<td>44</td>
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<td>RECIST 1.1</td>
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<td>Pembrolizumab</td>
<td>Hodi et al</td>
<td>411</td>
<td>115/14/64</td>
<td>40/28</td>
<td>RECIST 1.1</td>
<td>192</td>
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<td></td>
<td>Robert et al</td>
<td>157</td>
<td>41</td>
<td>26</td>
<td>RECIST 1.1</td>
<td>173</td>
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<td>Herbst et al</td>
<td>Multiple</td>
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<td>32</td>
<td>18</td>
<td>RECIST 1.1</td>
<td>Not reported Not reported Not reported</td>
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<tr>
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<td>Non-small-cell lung</td>
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<td>RECIST 1.1</td>
<td>53</td>
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<td>Renal cell</td>
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<td>Bladder</td>
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<td>17</td>
<td>26</td>
<td>RECIST 1.1</td>
<td>Not reported 1 additional Not reported</td>
</tr>
</tbody>
</table>

HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; irRECIST, immune-related Response Evaluation Criteria In Solid Tumours
Pseudo-progression should be considered until disease progression can be confirmed

<table>
<thead>
<tr>
<th>Performance status</th>
<th>DISEASE PROGRESSION</th>
<th>PSEUDO-PROGRESSION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deterioration of performance</td>
<td>Remains stable or improves</td>
</tr>
<tr>
<td>Systemic symptoms</td>
<td>Worsen</td>
<td>May or may not improve</td>
</tr>
<tr>
<td>Symptoms of tumor enlargement</td>
<td>Present</td>
<td>May or may not be present</td>
</tr>
<tr>
<td>Tumor burden</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>Increase</td>
<td>Initial increase followed by a</td>
</tr>
<tr>
<td></td>
<td></td>
<td>response</td>
</tr>
<tr>
<td>New lesions</td>
<td>Appear and increase in size</td>
<td>Appear then remain stable and/or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>subsequently respond</td>
</tr>
<tr>
<td>Biopsy may reveal</td>
<td>Evidence of tumor growth</td>
<td>Evidence of immune cell infiltration</td>
</tr>
</tbody>
</table>
Adverse events of special interest noted with anti-CTLA-4 and anti-PD-1 antibodies alone and in combination

ALT, alanine aminotransferase; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; PD-1, programmed cell death-1

Rare Severe AEs observed with Immune-Checkpoint Inhibitors

Fulminating Myocarditis with Combination Immune Checkpoint Blockade

Incidence of Thyroid-Related Adverse Events in Melanoma Patients Treated With Pembrolizumab

Pembrolizumab-Induced Demyelinating Polyradiculoneuropathy

TO THE EDITOR: Pembrolizumab and nivolumab, two humanized antibodies against programmed cell death 1 (PD-1) receptor, were recently approved for the treatment of unresectable or metastatic melanoma and for other cancers. We report two cases of severe demyelinating polyradiculoneuropathy that occurred after treatment with pembrolizumab for advanced melanoma.

Patient 1 was a 45-year-old woman who was treated with pembrolizumab (2 mg per kilogram of body weight every 3 weeks) for an inoperable recurrent nasal-cavity melanoma. Before the third infusion, she presented with paresthesia and hypoesthesia of all limbs, which was rapidly followed by symmetrical motor weakness in the legs with areflexia and peripheral facial palsy. Pembrolizumab was discontinued, and prednisolone (2 mg per kilogram per day) and intravenous immune globulin were administered. The neurologic symptoms reached their peak within 3 weeks and decreased over the next 2 months.

Patient 2 was an 85-year-old woman with metastatic melanoma with an NRAS Q61L mutation, who was treated sequentially with four injections of ipilimumab (3 mg per kilogram), binimetinib, and then pembrolizumab (2 mg per kilogram every 3 weeks). Between the sixth and seventh infusions of pembrolizumab, she presented with paresthesias of the arms and neck.

Pneumonitis in Patients Treated With Anti-Programmed Death-1/Programmed Death Ligand 1 Therapy

AE, adverse event
Case presentation

- 45-year-old lady, PS 0
- Medical history significant for allergy to pollen
- No autoimmune disease
- No concomitant medications
- 2011: WLE + SLN for stage IIIB nodular melanoma of the R arm, BRAF<sup>wt</sup>
- Jan 2015: R axillary nodal and hepatic relapse
- Feb 2015: ipilimumab 3 mg/kg i.v. q3 weeks for 3 cycles, stopped for diarrhoea grade 3, resolved with oral steroids
- Partial response

i.v., intravenous; PS, performance status; SLN, sentinel lymph node biopsy; WLE, wide local excision; WT, wild type
Q1. How do you proceed?

1. Surveillance

2. Proceed to cycle 4 of ipilimumab

(one answer)
Q1. How do you proceed?

1. Surveillance ✓

2. Proceed to cycle 4 of ipilimumab
Case presentation

June 2015: follow-up CT TAP shows pulmonary, nodal, and cutaneous recurrence

CT TAP, computed tomography of thorax, abdomen and pelvis
Q2. What is the recommended treatment approach?

1. Re-induction with ipilimumab

2. Start anti-PD-1 as 2nd line immunotherapy

(one answer)
Q2. What is the recommended treatment approach?

1. Re-Induction with ipilimumab

2. Start anti-PD-1 as 2nd line immunotherapy ✓
Q3. What kind of blood check prior to anti-PD-1?

1. CBC + liver/kidney function, electrolytes
2. CBC + liver/kidney function, electrolytes, thyroid function, HBV, HCV, HIV serology
3. CBC + liver/kidney function, electrolytes, thyroid function

(one answer)
Q3. What kind of blood check prior to anti-PD-1?

1. CBC + liver/kidney function, electrolytes
2. CBC + liver/kidney function, electrolytes, thyroid function, HBV, HCV, HIV serology ✓
3. CBC + liver/kidney function, electrolytes, thyroid function
Case presentation

• 2 days post-cycle 5 of anti-PD-1, the patient reports profound fatigue, loss of appetite, chills, diarrhea grade 1.
• No fever, no skin rush or pruritus
• Clinical evaluation: unremarkable
• Blood work shows elevated TSH (grade 3) and decrease fT4 (grade 3), normal fT3  ➔ Symptomatic hypothyroidism
• CT-TB shows: partial response, no signs of hypophysitis
Q4. How do you proceed?

1. Stop anti-PD-1 treatment
2. Start thyroid replacing therapy, continue anti-PD1 treatment, and follow up thyroid function monthly
3. Start thyroid replacing therapy and continue treatment
Q4. How do you proceed?

1. Stop anti-PD-1 treatment
2. Start thyroid replacing therapy, continue anti-PD1 treatment, and follow up thyroid function monthly ✓
3. Start thyroid replacing therapy and continue treatment
Case presentation

• After 8 cycles of anti-PD-1, the patient reports fatigue, dry cough, and dyspnea at rest.

Grade 3 pneumonitis

PD-1, programmed cell death-1

Courtesy of Pr Keilholz, Charité Comprehensive Cancer Center
Q5. How do you proceed?

1. Monitor symptoms daily, start oral steroids, and delay anti-PD-1 treatment
2. Monitor symptoms daily, add prophylactic antibiotics and delay anti-PD-1 treatment
3. Hospitalize, introduce i.v. steroids, add prophylactic antibiotics, permanently discontinue anti-PD-1 treatment
Q5. How do you proceed?

1. Monitor symptoms daily, start oral steroids, and delay anti-PD-1 treatment
2. Monitor symptoms daily, add prophylactic antibiotics and delay anti-PD-1 treatment
3. Hospitalize, introduce i.v. steroids, add prophylactic antibiotics, permanently discontinue anti-PD-1 treatment ✓
The patient was started on i.v. steroids and symptoms improved after 1 week.

Anti-PD1 treatment was permanently discontinued.

Given the PR, she was followed without further therapy until new disease progression.

i.v., intravenous; PD-1, programmed cell death-1; PR, partial response

Courtesy of Pr Keilholz, Charité Comprehensive Cancer Center
I-O therapy: Safety Considerations

- Toxicity results from increased or excessive immune activity
- Early diagnosis and appropriate management essential to minimize life-threatening complications
- Unless an alternative etiology identified, consider all signs and symptoms
- Systemic steroids may be required for management
- Can be severe or life-threatening, may involve various organs

Immune-related AEs

Patient and physician education for early recognition

AE, adverse event; I-O, immuno-oncology
Thank you!