Management Of Immune-related Adverse Events Of Immune Checkpoint Inhibitors

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Disclosures

• I have no disclosures
• I declare no conflict of interests
Content

• Introduction to checkpoint inhibitors ICI
• General aspect of immune-related adverse events (irAEs)
• Monotherapy: anti-programmed death 1 (PD-1) “receptor”, anti-programmed death-ligand (PD-L1) and anti-cytotoxic T-lymphocyte–associated antigen (CTLA4)
• Immunotherapies combination: anti-PD-1 + anti-CTLA4
• Management of irAEs
• Refractory irAEs
A Comparison of CTLA-4 and PD-1/PD-L1 pathways: Similarities and Differences

Similarities

- Expressed by activated T cells
- Reduce T-cell proliferation, glucose metabolism, cytokine production, and survival

Differences

<table>
<thead>
<tr>
<th>CTLA-4</th>
<th>PD-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early T-cell responses inhibitor (lymphoid tissues)</td>
<td>Late T-cell responses inhibitor (peripheral tissues and tumor)</td>
</tr>
<tr>
<td>Priming phase</td>
<td>Effector phase</td>
</tr>
<tr>
<td>Expressed by T cells</td>
<td>Expressed by T cells and other immune cells</td>
</tr>
<tr>
<td>CTLA-4 affects Treg functioning</td>
<td>The role of PD-1 on Tregs is unclear</td>
</tr>
<tr>
<td>CTLA-4 ligands expressed by professional antigen-presenting cells</td>
<td>PD-1 ligands can be inducibly expressed on nonimmune cells, including tumor cells</td>
</tr>
<tr>
<td>More frequent and severe irAEs</td>
<td>Fewer irAEs with greater antitumor activity</td>
</tr>
<tr>
<td>CTLA-4 blockade allows for activation and proliferation of more T-cell clones, and reduces Treg-mediated immunosuppression</td>
<td>PD-1 blockade restores the activity of antitumor T cells that have become quiescent</td>
</tr>
</tbody>
</table>
IrAEs can have a delayed onset and prolonged duration compared to adverse events resulting from chemotherapy.

The relationship between irAEs and dose/exposure remains to be fully established.
39 indications: 1L, 2L, 3L et 4L (15 cancer types)

U.S. FDA Approved Immune-Checkpoint Inhibitors (oct 2018)

- Squamous Cell Head & Neck Cancer
  1L/2L nivolumab after platinum chemotherapy
  1L/2L pembrolizumab after platinum chemotherapy

- Malignant Melanoma
  Adjuvant/1L ipilimumab
  1L nivolumab ± ipilimumab
  Adjuvant nivolumab
  1L pembrolizumab

- Merkel Cell Carcinoma
  2L avelumab

- Cutaneous Squamous Cell Carcinoma
  1L cemiplimab

- Hepatocellular Carcinoma
  2L nivolumab after sorafenib

- Adv. Renal Cell Carcinoma
  1L nivolumab plus ipilimumab
  2L nivolumab after anti-angiogenic therapy

- MSI-H or dMMR Cancers
  2L nivolumab in CRC
  2L nivolumab plus ipilimumab in CRC
  2L pembrolizumab in any MSI-H/dMMR cancer

- Cervical Cancer
  2L pembrolizumab CPS ≥ 1

- Small Cell Lung Cancer
  3L nivolumab

- Non-Small Cell Lung Cancer
  1L pembrolizumab TPS ≥ 50%
  1L pembrolizumab + pemetrexed&carboplatin in squamous NSCLC
  1L Pembrolizumab + carboplatin&(nab-)paclitaxel
  2L pembrolizumab TPS ≥ 1%
  2L nivolumab
  2L atezolizumab NSCLC
  Maintenance durvalumab after chemoradiation

- Gastric & GEJ Carcinoma
  3L pembrolizumab after fluoropyrimidine- and platinum-chemotherapy +/- HER2 therapy & CPS ≥ 1

- Classical Hodking Lymphoma
  4L pembrolizumab
  3L nivolumab after auto-HSCT and BV
  4L nivolumab and after auto-HSCT

- PMBC
  3L pembrolizumab

- Locally Adv. or Met. Urothelial Cancer
  1L/2L nivolumab after platinum chemotherapy
  1L/2L pembrolizumab
  1L/2L atezolizumab after platinum chemotherapy
  1L/2L avelumab after platinum chemotherapy
  1L/2L durvalumab after platinum chemotherapy
A broad spectrum of irAEs

- The most lymphocyte-rich organs are those that are most rapidly affected (skin, gut)
- The frequency of irAEs is mainly dependent on the agents used but also on the specific characteristics of individual patients
- The toxicity mimics classical autoimmune diseases but remains different entities on all biological and clinical levels
- The pathological mimicry ≠ classic auto-immune diseases: ICI-related colitis ≠ IBD, ICI-related GBS ≠ GBS, ICI-related hepatitis ≠ AIH
- Treatment by analogy with classical autoimmune diseases
- Growing body of literature on pleomorphic presentations continues to accumulate

F. Martins & M. Obeid, Nature Clinical Oncology Reviews, 2019
Kinetics of irAEs (any grade)

- The most lymphocyte-rich organs are those that are most rapidly affected.
- In general anti-PD1 and anti-PDL-1 have similar kinetics of irAEs.
- Time to onset of irAEs any grade with anti-PD-1 monotherapy:
  - Skin (~3\textsuperscript{rd} w)
  - Gastrointestinal (~3-4\textsuperscript{th} w)
  - Hepatic and endocrine (~6-7\textsuperscript{th} w)
  - Neurological (~7-8\textsuperscript{th} w)
  - Lung (9-10\textsuperscript{th}
  - Renal (14-15\textsuperscript{th})
- 85% of patients experienced irAEs within the first 16 weeks of ICI.
- irAEs generally resolved within several weeks, with the shortest time to resolution for GI events.
- Some long-lasting endocrinopathies (hypophysitis).
- Median time to resolution of irAEs of any grade with IMs ranged from 3.3 weeks for hepatic AEs to 28.6 weeks for skin AEs.
Kinetics of irAEs grade>3

Anti-CTL4+ anti-PD-1

F. Martins & M. Obeid, Nature Clinical Oncology Reviews, 2019

- Time to onset of grade 3/4 irAEs with ICI combination
  - Skin (~3rd w)
  - Gastrointestinal (~7th w)
  - Hepatic (~8th w)
  - Lung (~9th)
  - Endocrine (~11.4th w)
  - Renal (16th)

- In general, irAEs in patients receiving combination have an earlier onset compared to the same irAEs in those receiving monotherapies

- Median time to resolution of grade 3/4 AEs was ~ 5 weeks, (excluding endocrinopathies)

- Peaks in grade 3/4 AE burden were observed ~ days 50 and 90.

Sznol M et al JCO 2017
<table>
<thead>
<tr>
<th>Study details</th>
<th>Any adverse events (Grade ≥3 adverse events)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study</strong></td>
<td><strong>Dose, number of patients</strong></td>
</tr>
<tr>
<td></td>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td></td>
</tr>
<tr>
<td>EORTC 18071</td>
<td>10 mg/kg, 3-weekly, N=471</td>
</tr>
<tr>
<td>Hodi et al.184</td>
<td>3 mg/kg, 3-weekly, N=131</td>
</tr>
<tr>
<td>Nivolumab</td>
<td></td>
</tr>
<tr>
<td>CheckMate 066</td>
<td>3 mg/kg, 2-weekly, N=506</td>
</tr>
<tr>
<td>CheckMate 057</td>
<td>3 mg/kg, 2-weekly, N=267</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td></td>
</tr>
<tr>
<td>Keynote-010</td>
<td>2 mg/kg, 3-weekly, N=339</td>
</tr>
<tr>
<td>Keynote-010</td>
<td>10 mg/kg, 3-weekly, N=343</td>
</tr>
<tr>
<td>Keynote-064</td>
<td>200 mg, 3-weekly, N=509</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td></td>
</tr>
<tr>
<td>CheckMate 067</td>
<td>3 mg/kg ipilimumab plus 1 mg/kg nivolumab, 3-weekly, N=313</td>
</tr>
<tr>
<td>CheckMate 214</td>
<td>1 mg/kg ipilimumab plus 3 mg/kg nivolumab, 3-weekly, N=547</td>
</tr>
<tr>
<td>CheckMate 227</td>
<td>1 mg/kg 6-weekly ipilimumab plus 3 mg/kg 2-weekly nivolumab, N=576</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td></td>
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<tr>
<td>Pembrolizumab</td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td></td>
</tr>
</tbody>
</table>

F. Martins & M. Obeid, Nature Clinical Oncology Reviews, 2019

- CheckMate 067, 214 and 227: additive toxicity with combination depends on both the dose and the interval of ICI
- CheckMate 227: the frequency and severity of irAEs are more closer to those of monotherapy
- CheckMate 067 (ipi 3/nivo 1): **colitis (7-8% G3/4) et hepatitis (20% G3/4)**
- Toxicity profile of PD-L1 and PD-1 inhibitors is similar << anti-CTLA4
- Pneumonitis are exceptional with anti-CTLA4, rare with anti-PDL-1 **but 2.5x (+) with anti-PD-1 (Pembrolizumab)**
- Anti PD(L)-1: 2x(-) endocrine and hepatic irAEs (but more severe), <1% with anti-PDL-1
- Neurological irAEs are <1% with anti-PD(L)-1
Comparative safety of immune checkpoint inhibitors: network meta-analysis, 36 head-to-head phase II and III randomised trials (n=15 370):

Pooled incidence of irAEs

<table>
<thead>
<tr>
<th>ICI</th>
<th>G 1-5</th>
<th>G 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab</td>
<td>66.4 %</td>
<td>15.1 %</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>71.8%</td>
<td>14.1 %</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>75.1%</td>
<td>19.8%</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>86.8%</td>
<td>28.6%</td>
</tr>
</tbody>
</table>

- Atezolizumab: hypothyroidism, nausea, and vomiting
- Pembrolizumab: arthralgia, pneumonitis and hepatic toxicities
- Ipilimumab: skin, gastrointestinal and renal toxicities.
- Nivolumab: endocrine toxicities

Nivolumab had the best safety profile in lung cancer

Cheng Xu et al, BMJ 2019
The types of fatal irAEs:
- Anti-CTLA-4 antibodies: colitis 70%, hepatitis 16% and pneumonitis 8%
- Anti-PD(L)-1 antibodies: pneumonitis 35%, hepatitis 22%, colitis 17%, neurologic events 15% and myocarditis 8%
- Combination therapies: colitis 37%, myocarditis 25% hepatitis 22%, pneumonitis 14% and myositis 13%

Table 1. Spectrum of Fatal Immune-Related Adverse Events in Viglyze

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ipilimumab (n = 193)</th>
<th>Anti-PD-1/PD-1L (n = 333)</th>
<th>Combination (n = 87)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Types of cancer*</td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Melanoma</td>
<td>136 (96)</td>
<td>50 (18)</td>
<td>49 (66)</td>
<td></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>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 ONCO 2018
Co-occurrence irAEs:
- Myositis and myocarditis (50%)
- Myasthenia gravis and myocarditis (10%)
- Other co-irAEs appeared sporadic

Fatality rates:
- 40% for myocarditis
- Hypophysitis (2%), adrenal insufficiency (3.7%) and colitis (5%)
- 10-17% for other irAEs

Toxicity-related fatality rates:
- 0.36%(anti–PD-1)
- 0.38%(anti–PD-L1)
- 1.08%(anti–CTLA-4)
- 1.23%(PD-1 plus CTLA-4)

Time to symptom onset:
- Myocarditis and hepatic failure: fulminant fashion
- Neurological: protracted fashion
- Median time to fatal toxic effects occurred early after combination (14 vs 40 days)

Wang et al, JAMA ONCO 2018
Management of toxicities from immunotherapy

ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

J. Haenen, F. Carbonnel, C. Robert, K. Kerr, S. Peters, J. Larkin and K. Jordan,
on behalf of the ESMO Guidelines Committee

*For details of author affiliations, correspondence and versions, please see the full version at esmo.org/Guidelines/Supportive-and-Palliative-Care
# General Principles of Management

<table>
<thead>
<tr>
<th>Grade</th>
<th>Management</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Very close monitoring</td>
<td>Corticosteroids generally not needed; usually can continue treatment, but with monitoring</td>
</tr>
<tr>
<td>2</td>
<td>May start oral prednisone 0.5-1.0 mg/kg/d&lt;br&gt;If IV required, start methylprednisolone 0.5-1 mg/kg/d&lt;br&gt;Once AEs improved to ≤ grade 1, start 4- to 6-week steroid taper</td>
<td>Immunotherapy is held during corticosteroid use, but generally may be continued once AEs resolve to ≤ grade 1</td>
</tr>
<tr>
<td>3</td>
<td>Start prednisone 1-2 mg/kg/d, or equivalent dose methylprednisolone&lt;br&gt;If no improvement in 2-3 days, add additional/alternative immunosuppressant&lt;br&gt;Once AEs improved to ≤ grade 1, start 4- to 6-week steroid taper</td>
<td>Hold immunotherapy; if symptoms do not improve within 4-6 weeks, discontinue immunotherapy&lt;br&gt;Consider IV corticosteroids</td>
</tr>
<tr>
<td>4</td>
<td>Start prednisone 1-2 mg/kg/d, or equivalent dose methylprednisolone&lt;br&gt;If no improvement in 2-3 days, add additional/alternative immunosuppressant</td>
<td>Discontinue immunotherapy&lt;br&gt;Continue IV corticosteroids</td>
</tr>
</tbody>
</table>

Colitis/diarrhea

Diarrhea is one of the most frequent GI symptoms
Diarrhea is a symptom of colitis (rectal bleeding, abdo pain)
Colitis and diarrhea can often be confused
Rule out infection and signs of perforation

- Wide spectrum of presentations on endoscopic images:
  - large, deep ulcerations
  - diffuse or patchy erythema
  - inflammatory exudate
  - loss of vascular pattern
  - aphthae
  - edema
  - friability
  - erosions
  - and normal appearance

- Neutrophilic, lymphocytic infiltrate or both

Geukes Foppen et al, ESMO OPEN 2017

Wang et al, Inflamm Bowel Dis 2018
No significant association was found between diarrhea grade and colitis grade.

The correlation between grade of diarrhoea and endoscopic or histological features for severity of colitis is poor.

Patients with higher endoscopic severity scores, ulcers or a pancolitis needed the addition of infliximab more often.

Algorithms to guide management of immune-related diarrhea should not be based on the grade of diarrhea.
# Summary of recommendations

## Management

<table>
<thead>
<tr>
<th>Condition</th>
<th>Management Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-severe diarrhoea</td>
<td>Treatment with antidiarrhoeals, fluid and electrolyte supplementation, if required, and ICPIs can be continued</td>
</tr>
<tr>
<td>Persistent grade 2 / severe grade 3-4 / grade 1-2 with alarm symptoms</td>
<td>ICPI discontinuation and initiation of systemic corticosteroids (1 to 2 mg/kg IV daily)</td>
</tr>
</tbody>
</table>
| Response to IV corticosteroids                | Responding (within 3–5 days): switch to the oral form, treatment tapered over 8–12 weeks  
Not responding: switch to infliximab 5 mg/kg (unless contraindicated) |
| Colonic perforation (with or without intra-abdominal abscess) | Emergency subtotal colectomy with ileostomy and endoscopy                           |

## Follow-up and long-term implications

- Corticosteroids or infliximab treatment does not affect response and OS of patients treated with ipilimumab
- Reintroduction of ICPI in patients previously experiencing enterocolitis is associated with a high risk of relapse - discuss on an individual basis
Vedolizumab can be used for the treatment of infliximab-refractory colitis, with favorable outcomes and a good safety profile.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Infliximab + Vedolizumab, No. (%)</th>
<th>Vedolizumab only, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of patients</td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td>Checkpoint inhibitor type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTLA-4</td>
<td>3 (33)</td>
<td>5 (26)</td>
</tr>
<tr>
<td>PD-1/L1</td>
<td>2 (22)</td>
<td>10 (53)</td>
</tr>
<tr>
<td>Combination</td>
<td>4 (44)</td>
<td>4 (21)</td>
</tr>
<tr>
<td>Mean duration of steroid therapy, days (SD)</td>
<td>131 (74)</td>
<td>85 (75)</td>
</tr>
<tr>
<td>Median time from symptom onset to vedolizumab/infliximab therapy, days (IQR)</td>
<td>39 (6-152)</td>
<td>15 (4-74)</td>
</tr>
<tr>
<td>Median no. of vedolizumab doses (IQR)</td>
<td>3 (1-4)</td>
<td>2 (1-4)</td>
</tr>
<tr>
<td>Mean fecal calprotectin level at time of onset µg/g (SD)</td>
<td>268 (244)</td>
<td>346 (290)</td>
</tr>
<tr>
<td>Peak grade of diarrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>5 (55)</td>
<td>10 (53)</td>
</tr>
<tr>
<td>3-4</td>
<td>4 (44)</td>
<td>9 (47)</td>
</tr>
<tr>
<td>Initial endoscopic findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulceration</td>
<td>2 (22)</td>
<td>6 (32)</td>
</tr>
<tr>
<td>Nonulcerative inflammation</td>
<td>4 (44)</td>
<td>9 (47)</td>
</tr>
<tr>
<td>Normal</td>
<td>3 (33)</td>
<td>4 (21)</td>
</tr>
<tr>
<td>Initial histologic findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active features</td>
<td>5 (55)</td>
<td>11 (57)</td>
</tr>
<tr>
<td>Chronic features</td>
<td>1 (11)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Microscopic</td>
<td>3 (33)</td>
<td>7 (37)</td>
</tr>
<tr>
<td>Mean overall duration of disease months (SD)</td>
<td>7 (4)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Mean fecal calprotectin level after vedolizumab therapy µg/g (SD)</td>
<td>253 (344)</td>
<td>165 (133)</td>
</tr>
<tr>
<td>Clinical remission</td>
<td>6 (67)</td>
<td>18 (95)</td>
</tr>
<tr>
<td>Last repeat endoscopic findings¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulceration</td>
<td>0 (0)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Nonulcerative inflammation</td>
<td>2 (22)</td>
<td>5 (26)</td>
</tr>
<tr>
<td>Normal</td>
<td>6 (67)</td>
<td>3 (16)</td>
</tr>
<tr>
<td>Endoscopic remission</td>
<td>4 (44)</td>
<td>5 (26)</td>
</tr>
<tr>
<td>Active features on last repeat histologic analysis¹</td>
<td>6 (67)</td>
<td>6 (32)</td>
</tr>
</tbody>
</table>

Patients who failed infliximab before vedolizumab had a clinical success rate of 67% compared to 95% for patients that did not receive infliximab.

Abu-Sbeih et al., J Immunother Cancer 2018
Early introduction of selective immunosuppressive therapy associated with favorable clinical outcomes in patients with immune checkpoint inhibitor–induced colitis

The early introduction (< 10 day) of infliximab or vedolizumab during the course of irAEs-related colitis without waiting for response to corticosteroids, was associated with:

- a favorable impact on the disease course
- Better response to therapy
- reduced length of hospital stay
- lower IMC recurrence rate
- (colitis recurrence less with vedolizumab vs infliximab)
Fecal lactoferrin and calprotectin are sensitive non-invasive markers of colitis

- The sensitivity of lactoferrin to detect histologic and endoscopic inflammation was 90% and 70% respectively.
- Calprotectin > 150mcg/g of stool had a sensitivity of 68% to detect abnormal endoscopic features, and 86% to detect histological active inflammation.
- The mean fecal calprotectin value was 465mcg/g of stool (SD, 363) in patients with ulceration, whereas in patients with normal endoscopic features, it was 152mcg/g of stool.

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopic findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>42 (70)</td>
<td>4 (36)</td>
</tr>
<tr>
<td>Normal</td>
<td>18 (30)</td>
<td>7 (64)</td>
</tr>
<tr>
<td>Histological findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>54 (90)</td>
<td>8 (73)</td>
</tr>
<tr>
<td>Normal</td>
<td>6 (10)</td>
<td>3 (27)</td>
</tr>
</tbody>
</table>

Abu-Sbeih et al., J Immunother Cancer 2018
Five consistent radiological subtypes (no pathognomonic involvement)

Overall incidence:
- Higher risk with PD-1 vs CTLA-4 inhibitors
  - < 2% with nivolumab
  - < 4% with pembrolizumab
  - (<1% with PDL-1 inhibitors)
  - CheckMate 067 (7%) vs (3%) CheckMate 227
  - is more frequent in the first-line setting

By tumor type
- All grade: NSCLC and RCC 4.1% vs melanoma 1.6%
- Grade > 3: NSCLC 1.8% vs melanoma 0.2%
- (similar rates in Nishino et al JAMA Onco 2016)

- COP-like pneumonitis $\rightarrow$ severe GGO type
- GGO-like $\rightarrow$ interstitial appearances
- COP-like more common (44%) among NSCLC vs 6% other cancers
- No association: radiological entities and survival
- Association between COP-like and the introduction of IM
- Co-occurrence in 50 % of patients: rash skin 20%, colitis (14%), endocrinopathies (7%)

<table>
<thead>
<tr>
<th>Radiologic Subtypes</th>
<th>Representative Image</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptogenic organizing pneumonia-like (n = 5, 19%)</td>
<td><img src="image1.png" alt="Image" /></td>
<td>Discrete patchy or confluent consolidation with or without air bronchograms</td>
</tr>
<tr>
<td>Ground glass opacities (n = 10, 37%)</td>
<td><img src="image2.png" alt="Image" /></td>
<td>Discrete focal areas of increased attenuation</td>
</tr>
<tr>
<td>Interstitial (n = 6, 22%)</td>
<td><img src="image3.png" alt="Image" /></td>
<td>Increased interstitial markings, interlobular septal thickening</td>
</tr>
<tr>
<td>Hypersensitivity (n = 2, 7%)</td>
<td><img src="image4.png" alt="Image" /></td>
<td>Centrilobular nodules  Tree-in-bud micronodularity</td>
</tr>
<tr>
<td>Pneumonitis not otherwise specified (n = 4, 15%)</td>
<td><img src="image5.png" alt="Image" /></td>
<td>Mixture of nodular and other subtypes</td>
</tr>
</tbody>
</table>

Naidoo et al., J Clin Oncol 2017
Clinical Outcomes and Mortality Associated With high grade pneumonitis (infection)

Table 3. Pneumonitis Management and Outcomes

<table>
<thead>
<tr>
<th>Highest CTCAE Grade</th>
<th>Treatment Hold</th>
<th>Oral Corticosteroids</th>
<th>Intravenous Corticosteroids</th>
<th>Additional Immunosuppression*</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15 (83)</td>
<td>2 (12)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>17</td>
</tr>
<tr>
<td>2</td>
<td>0 (0)</td>
<td>10 (71)</td>
<td>4 (29)</td>
<td>0 (0)</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>0 (0)</td>
<td>2 (20)</td>
<td>4 (40)</td>
<td>0 (0)</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (100)</td>
<td>0 (0)</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (100)</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>14</td>
<td>9</td>
<td>6</td>
<td>43</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Highest CTCAE Grade</th>
<th>Completely Resolved</th>
<th>Improved</th>
<th>Worsened</th>
<th>Unknown</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>17</td>
</tr>
<tr>
<td>2</td>
<td>10 (71)</td>
<td>3 (21)</td>
<td>0 (0)</td>
<td>1 (8)</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>4 (40)</td>
<td>2 (20)</td>
<td>4 (40)</td>
<td>0 (0)</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>1 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (100)</td>
<td>0 (0)</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
<td>5</td>
<td>5</td>
<td>1</td>
<td>43</td>
</tr>
</tbody>
</table>

- Pneumonitis improved/resolved in:
  - 100% of grade 1
  - 93% of grade 2
  - 64% of grade 3/4 → additional immunosuppression beyond corticosteroids
- 50% of grade 3/4: pejoration despite therapeutic escalation with high-dose iv corticosteroids, infliximab, and cyclophosphamide
- The main etiology of death: infectious complications

Naidoo et al., J Clin Oncol 2017
Risk factor of worsening clinical outcomes:
- current vs former smokers
- underlying lung conditions vs no lung conditions

Incidence risk (without prior chest radiation therapy)
- pneumonitis occurred in 35.1% of patients with a fibrosis score $\geq 1$
- (vs only in 5.8% patients with a fibrosis score of 0)

Yamaguchi et al. 2018
Prophylaxis Considerations With Prolonged Corticosteroid Use
Immune-related thyroid toxicity

- Most common endocrine toxicity from ICI
- Incidence 1-5% with CTLA-4 inhibition, 5-10% with PD(L)-1 inhibition, 10-20% with combination
- Median time to onset for thyrotoxicosis ~ 21 days for combination vs 47 days for monotherapy
- Same median time to onset for hypothyroidism with mono vs combination therapy ~ 65 days
- High dose steroids do not improve outcome for immune-related thyroid disorders, no difference in:
  - Duration of thyrotoxicosis
  - Time to conversion to hypothyroidism
  - Time to onset of hypothyroidism
Immune-related thyroid toxicity

- Usually permanent toxicity requiring long-term thyroid hormone replacement
- Treatment for thyrotoxicosis is supportive care (β-blockers)
- Does not require interruption in treatment with immunotherapy
- Close monitoring is recommended due to high incidence and evolution from thyrotoxicosis to hypothyroidism
- Important to differentiate primary vs secondary hypothyroidism (rule out hypophysitis)

**CLINICAL PRACTICE GUIDELINES**

**Immune-related toxicities - endocrinopathies**

**IODI monitoring and management: Thyroid function (cont'd)**

- Elevated TSH, FT4, T3, T7s
  - Baseline abnormal values do not preclude treatment; discuss with endocrinologist if asymptomatic

- Normal TSH, FT4, T3, T7s
  - If symptoms, consider thyroid autoantibodies

- Low TSH, FT4, T3, T7s
  - If symptoms, treat with exogenous hormone

**CLINICAL PRACTICE GUIDELINES**

**Immune-related toxicities - endocrinopathies**

**IODI monitoring and management: Thyroid function**

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  - Baseline abnormal values do not preclude treatment; discuss with endocrinologist if asymptomatic

- Normal TSH, FT4, T3, T7s
  - If symptoms, consider thyroid autoantibodies

- Low TSH, FT4, T3, T7s
  - If symptoms, treat with exogenous hormone

**Hypothyroidism**

- Low TSH with elevated T3 or T4 > 10 with normal T4
- Treatment: L-thyroxine (3-5 μg/kg/day based on clinical history and serum TSH)
- Continue IODI

**Hypothyroidism** (thyroiditis, Graves's disease)

- Investigations: anti-TSH receptor Ab, anti-TPO Ab, nuclear medicine thyroid uptake scan
- Treatment: replacement or subtotal thyroidectomy based on symptoms and cause
- If anti-TSH receptor Ab-positive
  - Patients treated with L-thyroxine
  - Consider propranolol 0.5 mg/kg/day

- If unwell, withhold IODI and consider restarting when symptom controlled
Hypophysitis → central adrenal insufficiency

- The median time to onset of hypophysitis after initiation of ipilimumab treatment was 9 weeks (range, 5–36 weeks)
- G 3/4 in up to one-third of cases
- Fatality rates: Hypophysitis (2%), adrenal insufficiency (3.7%)
- Incidence 1-16% with CTLA-4 inhibition, very rare % with PD(L)-1 inhibition, 8% with combination
- Non specific symptoms: fatigue, headache, vision changes, multiple endocrinopathies
- Lab abnormalities: low TSH/FT4, low Na
- 2 Major complications: adrenal insufficiency (hypotension, syncope, extreme fatigue, weakness, dizziness) and pituitary enlargement
- Clinicians should have high index of suspicion
- Pituitary MRI
High-Dose Corticosteroid Does Not Improve the Outcome of Ipilimumab Related Hypophysitis

Table 4. The effect of HDS on the frequency of resolution of ipilimumab-related adverse effects

<table>
<thead>
<tr>
<th>Condition</th>
<th>No HDS</th>
<th>HDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pituitary enlargement</td>
<td>5/6</td>
<td>6/9</td>
</tr>
<tr>
<td>Secondary adrenal insufficiency</td>
<td>0/10</td>
<td>0/12</td>
</tr>
<tr>
<td>Secondary hypothyroidism</td>
<td>8/9</td>
<td>6/13</td>
</tr>
<tr>
<td>Secondary hypogonadism</td>
<td>5/8</td>
<td>2/7</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>5/5</td>
<td>7/8</td>
</tr>
</tbody>
</table>

- No significant difference of resolution with or without HDS
- Pituitary enlargement, hypogonadism, hypothyroidism and hyponatremia are reversible (73%, 64%, 45%, and 92% respectively)
- Adrenal insufficiency is irreversible
- HDS for ipilimumab-related hypophysitis is associated with reduced survival in melanoma patients

Le Min et al, Clin Can Res 2014

Le Min et al, Clin Can Res 2014

Le Min et al, Clin Can Res 2014

Le Min et al, Clin Can Res 2014

Le Min et al, Clin Can Res 2014

Faje et al, Cancer 2018
Pituitary enlargement is one of the major complications, because the enlarged pituitary may compress the optic chiasm and cause visual field deficits. HDS only for adrenal crisis. Or symptoms due to enlarged pituitary, otherwise avoid.

Hormone replacement as indicated.
## Additional irAEs to Consider

<table>
<thead>
<tr>
<th>irAE</th>
<th>Presentation</th>
<th>Management</th>
</tr>
</thead>
</table>
| **Additional endocrinopathies**     | • Dehydration  
• Hypotension and/or shock | • IV corticosteroid therapy and fluids  
• Balance electrolytes and manage hypotension/shock |
| (eg, adrenal insufficiency)          |                                                                              |                                                                              |
| **Skin events**                      | • Rash appears erythematous, reticular, and maculopapular  
• Located across limbs and trunk | • Supportive care (eg, topical corticosteroids, cold compresses, oatmeal baths)  
• Oral corticosteroids for grade 3/4  
• Systemic corticosteroids (severe cases that do not respond to oral steroids) |
| (eg, rash, pruritus, dermatitis)     |                                                                              |                                                                              |
| **Hematologic toxicities**           | • Abnormal CBC panel                                                         | • Supportive care with corticosteroids  
• Transfusion of blood, as needed  
• Corticosteroids |
| (eg, neutropenia, thrombocytic purpura, autoimmune hemolytic anemia) |                                                                              |                                                                              |

Friedman CF. *JAMA Oncol.* 2016;2:1346-1353.
### Additional irAEs to Consider (cont)

<table>
<thead>
<tr>
<th>irAE</th>
<th>Presentation</th>
<th>Management</th>
</tr>
</thead>
</table>
| **Hepatitis** [a,b] | • Asymptomatic increases in AST, ALT, GGT, or bilirubin  
• Diffuse T-cell infiltrate  
• Biopsy to confirm diagnosis | • High-dose corticosteroid therapy               |
| **Pancreatitis** [c]  | • Upper abdominal or back pain  
• Elevated amylase and lipase  
• Inflamed pancreas on imaging may or may not be present | • High-dose corticosteroid therapy               |
| **Renal failure** [d]  | • Increase in creatinine levels  
• May have rash  
• Renal biopsy to confirm diagnosis | • Corticosteroid therapy and monitor creatinine levels |

---

[a] Friedman CF. *JAMA Oncol.* 2016;2:1346-1353;  
Additional irAEs to Consider (cont)

<table>
<thead>
<tr>
<th>irAE</th>
<th>Presentation</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic events[a] (eg, Guillain-Barre syndrome, chronic immune demyelinating polyneuropathy, encephalitis)</td>
<td>• Weakness, numbness, fevers, nausea, headache, confusion</td>
<td>• High-dose corticosteroid therapy and/or plasmapheresis depending on presentation</td>
</tr>
<tr>
<td>Cardiac events[b]</td>
<td>• Myocarditis, cardiomyopathy, cardiac arrest, HF, myocardial fibrosis</td>
<td>• Corticosteroid therapy and cardiac care</td>
</tr>
</tbody>
</table>

---

Steroid refractory or severe irAEs: “personalized” approach

- Absence of reliable biomarkers
- Very fragile patients
- Limited survival
- Co-morbidities
- Pro-tumor effect of non-selective IS

Personalized approach:
- Selective immunosuppression
- Without compromising the immunotherapy
- No or less pro-tumor effect
- Inhibiting key inflammatory mediator

Diagram:
- Cancers
- Cytokines
- Predominant immune infiltrate type
- Selective immunosuppression
- irAEs
"Shut-off strategy"
Avoid non selective immunosuppression as 1L or 2L
Blockade of the IL-6/IL-17 axis if failure of anti-IL-6 therapy

- For a predominant T-cell infiltrate → anti-IL-6 blockade
- For a prominent B and plasma cell infiltrate → anti-B-cell strategy (anti-CD20 and anti-B-cell activating factor [BAFF] blockade)
- For a predominant neutrophilic and monocytic features +/- granulomatous → anti-TNFα strategy

Figure 2: Algorithms for personalized shut-off treatment of steroid-refractory or rapidly evolving immune-related adverse events
F. Martins et al., & M. Obeid, Lancet Oncology, 2019
New therapeutic perspectives to manage refractory immune checkpoint-related toxicities

Figure 1: Immunosuppressive drugs that can be used to treat immune-related adverse events and their targets

F. Martins et al., & M. Obeid, Lancet Oncology, 2019
A severe case of refractory esophageal stenosis induced by nivolumab and responding to tocilizumab

Horisberger et al., Journal for Immunotherapy of Cancer, 2018
A severe case of neuro-Sjögren's syndrome induced by pembrolizumab

«Do novo» induced connectivite tissue disease
Treated by rituximab (anti-CD20 therapy)

Fig. 3 Line graph showing the kinetic evolution of laboratory parameters of the patient including hemoglobin (g/l), total bilirubin (μmol/l), total IgG (g/l) and erythrocyte sedimentation rate (mm/h) (x-axis showing time in months since the initiation of therapy)
Reintroducing ICIs should be made on an individual basis, taking into account the clinical setting and specific clinical needs of each patient.

Permanent discontinuation of ICIs is advocated in patients with high-grade ocular, hepatic, pancreatic and/or pulmonary irAEs.

- **Switch from ipi → anti-PD-1:** relatively safe
  - Recurrence of initial ipi irAEs 3% (but 34% new irAEs with 21% G 3/4)

- **Retreatment from anti-PD(L)-1 → anti-PD(L)-1**
  - Less safe (but feasible)
    - Recurrent/new events in 52% of patients
      - 26% recurrence of the initial irAE
      - 26% developed a new irAE
      - Recurrent/new irAEs were more common among those requiring initial hospitalization
Dyspnoea, cough and heart palpitations should advocate a full clinical work-up

Serum creatine kinase and troponin levels should be monitored, and their elevation should raise the suspicion of myositis and/or myocarditis

Box 1 | Key points in the management of patients with irAEs

- A decision to reintroduce immune-checkpoint inhibitors (ICIs) following discontinuation owing to immune-related adverse events (irAEs) should be made on an individual basis, taking into account the clinical setting and specific clinical needs of each patient.
- Neurological irAEs should be managed conservatively, and rechallenge should be attempted only in patients with corticosteroid-sensitive and fully resolved peripheral neuropathies or myasthenia gravis. By contrast, patients who have had even mild encephalitis should not be re-exposed to ICIs.
- Permanent discontinuation of ICIs is advocated in patients with high-grade ocular, hepatic, pancreatic and/or pulmonary irAEs. Rechallenge with an anti-cytotoxic T lymphocyte antigen 4 (CTLA-4) antibody is contraindicated owing to a high risk of relapse and/or bowel perforations in patients with severe colitis.
- A rigorous clinical examination, including an assessment of each patient’s baseline bowel movements, is advised before ICI initiation.
- Abdominal pain, diarrhoea and/or rectal bleeding should prompt a thorough clinical work-up including the elimination of infectious causes, such as Clostridium difficile infection. Biopsy samples should be obtained for pathological description and molecular analyses.
- Grade ≥2–3 colitis indicates a need to withhold ICIs and start steroid therapy immediately. Infliximab should be considered in the absence of symptomatic improvements within 2–5 days. Delayed endoscopic examination is correlated with an increased risk of treatment-refractoriness.
- Hospitalization should be considered in patients with grade ≥3 irAEs and tailored regarding comorbidities, frailty status and kinetics of evolution in patients with lower-grade irAEs.
- Tapering of steroids should be considered after 48 hours of consistent symptom improvement and extended over 4–6 weeks to avoid flare phenomena related to the long half-life of ICIs.
- Certain symptoms such as dyspnoea, cough and heart palpitations should advocate a full clinical work-up including the exclusion of infectious pneumonia, tumour progression, pulmonary embolism, cardiac events and pleural carcinomatosis.
- Grade 1 pneumonitis indicates a need for ICI withholding, with close clinical follow-up until resolution of symptoms. Corticosteroids should be initiated in the absence of clinical improvement. Grade ≥2 disease indicates a need for corticosteroids in addition to ICI withholding. Infliximab and/or cyclophosphamide should be considered for refractory pneumonitis, taking into account the limited effectiveness and high risks of infection with this approach.
- A personalized immunosuppression strategy, involving monoclonal antibodies targeting key inflammatory cytokines, should be considered for patients with steroid-refractory irAEs.
- Symptom control and instauration of hormone substitution therapy (or anti-thyroid medication in patients with Graves disease) should be ensured before resuming ICI treatment in patients with endocrine irAEs.
- Asymptomatic biochemical abnormalities, such as elevations of serum creatinine, liver enzyme and/or troponin/creatine kinase levels, should prompt a full clinical work-up. ICIs can potentially be resumed after parameter normalization followed by close monitoring. Electrolyte disturbances should raise suspicions of endocrine irAEs (hypophysitis or adrenalitis) or renal complications.

F. Martins & M. Obeid, Nature Clinical Oncology Reviews, 2019
Baseline

### Box 3 | Proposed surveillance strategy for irAEs

**General pretreatment assessments**

- Performance status: including weight, height and BMI
- Cardiovascular function: including heart rate, blood pressure, electrocardiography, serum cardiac troponin and creatine kinase levels, N-terminal prohormone of brain natriuretic peptide (NT-proBNP), blood electrolytes and chest radiography
- Kidney function: including estimated glomerular filtration rate, urine spot analysis for proteinuria, creatinuria, calciuria, natriuria and protein to creatinine ratio
- Liver function: including total serum bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), γ-glutamyl transferase (GGT) and alkaline phosphatase (ALP) levels
- Immune function and/or infection status: including serum C-reactive protein (CRP), erythrocyte sedimentation rate and complete blood counts, screening for antinuclear antibodies, complement C3 and/or C4, HIV-1 or HIV-2, hepatitis B virus, hepatitis C virus and/or hepatitis E virus, human T lymphotropic virus (HTLV-1) and/or HTLV-2 (if endemic), dosage and immunosubtraction or immunofixation of immunoglobulin G (IgG), IgA and IgM
- Endocrine function: including serum levels of cortisol and adrenocorticotropic hormone (ACTH) (at 8 am), luteinizing hormone (LH), follicle-stimulating hormone (FSH), oestradiol, testosterone, thyroid-stimulating hormone (TSH) and free T4
- Gastrointestinal function: monitoring of pretreatment bowel movements, faecal lactoferrin and calprotectin

**Storage of pretreatment serum samples**

---

**Multidisciplinary approach**

- Baseline assessment
- Ongoing assessment of potential toxicity
- Patient education
- Development of Immune Toxicity clinics & management protocol
- Collaboration with supportive services
  - Emergency department
  - Primary care providers
  - Specialists
  - Visiting Nurses
It is always a challenging problem to preserve this delicate balance.