Adjuvant Therapy for Melanoma and Practical Considerations for Immunotherapy

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Adjuvant Therapy for Melanoma
The burden of high-risk disease dwarfs that of advanced melanoma and is an important clinical problem.
Adjuvant Therapy

• The Old
  – Interferon

• The New
  – Ipilimumab

• The Future
# Adjuvant IFN-α Regimens

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Dose</th>
<th>Frequency</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Dose</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 MIU</td>
<td>3 x weekly</td>
<td>18 – 24 months</td>
</tr>
<tr>
<td><strong>Intermediate Dose</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction</td>
<td>10 MIU</td>
<td>5 x weekly</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Maintenance</td>
<td>10 MIU</td>
<td>3 x weekly</td>
<td>12 -24 months</td>
</tr>
<tr>
<td></td>
<td>5 MIU</td>
<td>3 x weekly</td>
<td>24 months</td>
</tr>
<tr>
<td><strong>High Dose</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction</td>
<td>20 MIU/m²</td>
<td>5 x weekly</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Maintenance</td>
<td>10 MIU/m²</td>
<td>3 x weekly</td>
<td>11 months</td>
</tr>
<tr>
<td><strong>Short Course</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction X 1</td>
<td>20 MIU/m²</td>
<td>5 x weekly</td>
<td>4 weeks</td>
</tr>
<tr>
<td><strong>Intermittent</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Induction X 3</td>
<td>20 MIU/m²</td>
<td>20 MIU/m²</td>
<td>5 x weekly for 4 weeks Q 4 months</td>
</tr>
</tbody>
</table>
## Interferon Trials Leading To Regulatory Approval

<table>
<thead>
<tr>
<th>Study/PI</th>
<th>Stage</th>
<th>N</th>
<th>Treatment agent/ dosage/duration</th>
<th>Median Follow up (yr)</th>
<th>Impact on</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RFS</td>
</tr>
<tr>
<td>E1684</td>
<td>T4, N+</td>
<td>287</td>
<td>IFNα2b 20 MU/m2/D IV for 1 month. Then, 10 MU/m2 SC TIW for 11 months vs. Observation</td>
<td>6.9</td>
<td>0.61; p=.001</td>
</tr>
<tr>
<td>E1690</td>
<td>T4, N+</td>
<td>642</td>
<td>IFNα2b 20 MU/m2/D IV for 1 month. Then, 10 MU/m2 SC TIW for 11 months vs. 3 MU/D given SC TIW for 2 years vs. Observation</td>
<td>4.3</td>
<td>0.78; p=.05</td>
</tr>
<tr>
<td>E1694</td>
<td>T4, N+</td>
<td>880</td>
<td>IFNα2b 20 MU/m2/D IV for 1 month. Then 10 MU/m2 SC TIW for 11 months vs. GMK vaccine for 96 wks</td>
<td>1.3</td>
<td>0.75; p=.006</td>
</tr>
<tr>
<td>EORTC 18991</td>
<td>N1-2</td>
<td>1256</td>
<td>PegIFNα2b given SC at 6 µg/kg/week (8 weeks) then 3 µg/kg/week (5 years) vs. Observation</td>
<td>3.8</td>
<td>0.82; P=.011</td>
</tr>
</tbody>
</table>

ASCO 2016

accc-iclio.org
E1684: Updated Efficacy (ITT at 12.6 yr Median Follow-up)

Log-rank test: $P_2 = .02; P_1 = .01$

Treatment groups (N = 286)
- High-dose IFN
- Observation

Overall Survival
Log-rank test: $P_2 = .18; P_1 = .09.$

<table>
<thead>
<tr>
<th>Observation</th>
<th>Total</th>
<th>Dead or relapsed</th>
<th>Alive or relapse-free</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>140</td>
<td>106</td>
<td>34</td>
<td>1.0</td>
</tr>
<tr>
<td>High-dose IFN</td>
<td>146</td>
<td>95</td>
<td>51</td>
<td>1.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Observation</th>
<th>Total</th>
<th>Dead</th>
<th>Alive</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>140</td>
<td>95</td>
<td>45</td>
<td>2.7</td>
</tr>
<tr>
<td>High-dose IFN</td>
<td>146</td>
<td>93</td>
<td>53</td>
<td>3.8</td>
</tr>
</tbody>
</table>
Tweaking Interferon

• Lower the dose
• Shorten the duration of HDI – high dose IV only
• Use pegylated IFN – once weekly dosing, lower dose with comparable AUC
Study design: ECOG 1697

Patients with intermediate- and high-risk melanoma

- Defined as T3:
  - Breslow thickness >1.5 mm (AJCC 6th ed)
  - >2.0 mm (AJCC 7th ed)

- or

Any thickness with microscopically positive nodal disease (N1a–N2a)

Postoperative adjuvant IFN alfa-2b
20 MU/m²/day
5 days/week × 4 wks

Observation

Relapse-free survival (n=975)

Median RFS (95% CI), years
Obs (n=481): 7.8 (5.8, 9.8)
IFN (n=494): 7.3 (7.0, 9.5)
p=0.690*

*Stratified log-rank test

Agarwala SS, et al. JCO. January 2017
Adjuvant Therapy

• The Old
  – Interferon

• The New
  – Ipilimumab

• The Future
Ipilimumab (HD) vs Placebo
EORTC 18071/CA184-029: Study Design

Stratification factors:

- Stage (IIIA vs IIIB vs IIIC 1-3 positive lymph nodes vs IIIC ≥4 positive lymph nodes)
- Regions (North America, European countries and Australia)

N=951

Treatment up to a maximum 3 years, or until disease progression, intolerable toxicity, or withdrawal

Primary Endpoint: Recurrence-free Survival (IRC)

- Stratified by stage.
- **Data are not yet mature.**

**Patients Alive Without Relapse (%)**

- **Median: 26.1 mo**
- **Median: 17.1 mo**

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients at Risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>276</td>
<td>205</td>
<td>67</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>260</td>
<td>193</td>
<td>62</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2-Year RFS rate (%)</th>
<th>Ipilimumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>51.5</td>
<td>43.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3-Year RFS rate (%)**</th>
<th>Ipilimumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>46.5</td>
<td>34.8</td>
</tr>
</tbody>
</table>

**HR (95% CI)**

- 0.75 (0.64–0.90)

**Log-rank P value**

- 0.0013

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[accc-iclio.org](http://accc-iclio.org)
EORTC 18071: Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Ipilimumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths/patients</td>
<td>162 / 475</td>
<td>214 / 476</td>
</tr>
<tr>
<td>Hazard ratio (95.1% CI)*</td>
<td>0.72 (0.58 - 0.88)</td>
<td></td>
</tr>
<tr>
<td>Log-rank P value*</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
</table>

*Stratified by stage at randomization

CI = confidence interval; NR = not reached.

Eggermont AMM et al NEJM 2016
### Safety Summary

<table>
<thead>
<tr>
<th></th>
<th>Iplimumab (n = 471)</th>
<th>Placebo (n = 474)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Any AE, %</td>
<td>98.7</td>
<td>54.1</td>
</tr>
<tr>
<td>Treatment-related AE, %</td>
<td>94.1</td>
<td>45.4</td>
</tr>
<tr>
<td>Treatment-related AE discontinuation, %</td>
<td>48.0</td>
<td>32.9</td>
</tr>
<tr>
<td>Any immune-related AE, %</td>
<td>90.4</td>
<td>41.6</td>
</tr>
</tbody>
</table>

- No new deaths due to drug-related AEs compared with the primary analysis
  - 5 patients (1.1%) in the ipilimumab group
    - 3 patients with colitis (2 with gastrointestinal perforations)
    - 1 patient with myocarditis
    - 1 patient had multiorgan failure with Guillain-Barré syndrome
  - No deaths related to study drug in the placebo group
E1609 Phase III Ipilimumab vs IFN

Patients with resectable stage IIIB or III C or IV (M1a or M1b)

N=1500 +

Ipilimumab 10mg/kg

Ipilimumab 3mg/kg

High dose interferon

Primary Endpoint: RFS, OS
Secondary Endpoints: Safety, Quality of life, immunologic correlates of RFS, OS
Completed accrual: 8/2014- Results anticipated: 2018

Clinicaltrials.gov
Adjuvant Therapy

• The Old
  – Interferon

• The New
  – Ipilimumab

• The Future
# PD1 Pathway Inhibitor Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>TNM Stage</th>
<th>Therapy</th>
<th>Dose and Schedule – Treatment Arm</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>CheckMate 238*</td>
<td>800</td>
<td>IIIB, IIIC, IV</td>
<td>Nivolumab Vs. Ipilimumab</td>
<td>Nivo 3 mg/kg IV v Ipilimumab 10 mg/kg</td>
<td>RFS</td>
</tr>
<tr>
<td>KEYNOTE-054</td>
<td>900</td>
<td>IIIA [&gt; 1 mm met], IIIB, IIIC</td>
<td>Pembrolizumab Vs. Placebo</td>
<td>Pembrolizumab 200 mg IV on q 3 w33kw for up to 1 year</td>
<td>RFS, RFS in PDL1+</td>
</tr>
<tr>
<td>S1404</td>
<td>1378</td>
<td>IIIA(N2), IIIB, C, IV</td>
<td>Pembrolizumab Vs. HD IFN or HD Ipi</td>
<td>Pembro 200 mg IV Q3 wks x 1 yr vs HD IFN regimen or Ipi 10 mg/kg</td>
<td>RFS, OS in all and PDL1+</td>
</tr>
</tbody>
</table>

* Completed accrual 10/15
Is adjuvant therapy more effective than treatment in the metastatic setting?

**EORTC 1325/ KEYNOTE 054**

- **TUMOR MATERIAL**
  - SAFETY → UNBLINDING
  - PEMBROLIZUMAB 200 mg IV Q3 wks 1 year
  - PLACEBO IV Q3wks 1 year

- **SCREENING**
  - 900 eligible patients

- **RECURRENT**

- **PART 1: ADJUVANT PART**
  - RFS

- **PART 2: AFTER 1ST RECURRENTION**
  - DMFS/OS

**Stratification factors:**
- * Surgery if clinically indicated and tumor material obtained from surgery or biopsy.
- ** Recurrence > 6 months after completion of 1 year pembrolizumab treatment
- *** After recurrence, patients assigned to placebo arm will be offered to crossover to pembrolizumab
<table>
<thead>
<tr>
<th>Study</th>
<th>No of Pts</th>
<th>TNM Stage</th>
<th>Therapy</th>
<th>Dose and Schedule – Treatment Arm</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMBI-AD</td>
<td>852</td>
<td>III (BRAF V600E/K)</td>
<td>Dabrafenib + Trametinib Vs. Placebo</td>
<td>Dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) orally for 12 months</td>
<td>RFS</td>
</tr>
<tr>
<td>BRIM 8</td>
<td>725</td>
<td>IIIC, III (BRAF V600; Cobas)</td>
<td>Vemurafenib Vs. Placebo</td>
<td>Vemurafenib 960 mg orally twice daily for 52 weeks</td>
<td>RFS</td>
</tr>
</tbody>
</table>
Adjuvant Therapy Summary

- IFN is still a standard option for many patients.
- Ipilimumab (high dose) is also an option but no data comparing it to IFN. High toxicity (is it justifiable in the adjuvant setting?)
- Should we await data for adjuvant anti PD-1?
- BRAF targeted adjuvant therapy for BRAF+ patients?
Practical Considerations for Immunotherapy
Unique Practical Aspects of Immunotherapy

• **Response Assessment**
  – Unique response patterns
  – Timing of imaging

• **Toxicity Recognition and Management**
Immune-Related Patterns of Response with anti-CTLA4:
Melanoma Response After the Appearance and Subsequent Disappearance of New Lesions

3 mg/kg Ipilimumab Q3W X 4

Pre-treatment

Week 36: Still Regressing

Week 12: Progression

“Pseudoprogression”
“Tumor Flare”

Week 20: Regression

Still Regressing

Ipilimumab Heterogeneous Response Patterns

- 4 distinct response patterns associated with favorable OS

# Response Assessment: RECIST vs. irRC

<table>
<thead>
<tr>
<th>Category</th>
<th>RECIST v1.1¹</th>
<th>mWHO²</th>
<th>irRC³</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Measurement: tumor burden</strong></td>
<td>• <strong>Unidimensional</strong>: Sum Longest Diameter</td>
<td>• <strong>Bidimensional</strong>: Sum Product Diameter (SPD)</td>
<td>• <strong>Bidimensional</strong>: SPD</td>
</tr>
<tr>
<td>Complete Response (CR)</td>
<td>• Disappearance of all target and non-target lesions</td>
<td>• ≥ 50% ↓ in tumor burden compared to baseline</td>
<td>• ≥ 50% ↓ in tumor burden compared to baseline²</td>
</tr>
<tr>
<td></td>
<td>• Confirmation required</td>
<td>• Confirmation required</td>
<td>• Confirmation required</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>• ≥ 30% ↓ in tumor burden compared to baseline</td>
<td>• ≥ 50% ↓ in tumor burden compared to baseline</td>
<td>• ≥ 50% ↓ in tumor burden compared to baseline²</td>
</tr>
<tr>
<td></td>
<td>• Confirmation required</td>
<td>• Confirmation required</td>
<td>• Confirmation required</td>
</tr>
<tr>
<td>Progressive Disease (PD)</td>
<td>• ≥ 20% + 5 mm absolute ↑ in tumor burden compared to nadir</td>
<td>• ≥ 25% ↑ in tumor burden compared to nadir</td>
<td>• ≥ 25% ↑ in tumor burden compared to baseline, nadir, or reset baseline³</td>
</tr>
<tr>
<td></td>
<td>• New lesion</td>
<td>• New lesion</td>
<td>• New lesions added to tumor burden</td>
</tr>
<tr>
<td></td>
<td>• No confirmation required</td>
<td>• No confirmation required</td>
<td>• Confirmation required</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>• Neither PR nor PD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


[accc-iclio.org](http://accc-iclio.org)
Association of Overall Survival With Tumor Response

- Of the 196 patients with PD by RECIST v1.1, the 51 patients (26%) with non-PD by irRC had favorable OS compared with the 145 patients with PD by both criteria.
- A landmark analysis showed similar results.

<table>
<thead>
<tr>
<th>Time, months</th>
<th>PD by RECIST v1.1 and irRC</th>
<th>PD by RECIST v1.1, non-PD by irRC</th>
<th>Non-PD by RECIST v1.1 and irRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>215</td>
<td>51</td>
<td>145</td>
</tr>
<tr>
<td>2</td>
<td>215</td>
<td>51</td>
<td>122</td>
</tr>
<tr>
<td>4</td>
<td>213</td>
<td>46</td>
<td>79</td>
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<tr>
<td>6</td>
<td>207</td>
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<td>8</td>
<td>179</td>
<td>32</td>
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<td>10</td>
<td>153</td>
<td>24</td>
<td>30</td>
</tr>
<tr>
<td>12</td>
<td>92</td>
<td>12</td>
<td>19</td>
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<td>14</td>
<td>68</td>
<td>7</td>
<td>13</td>
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<tr>
<td>16</td>
<td>58</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>18</td>
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<td>1</td>
<td>3</td>
</tr>
<tr>
<td>20</td>
<td>14</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>22</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>24</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Immune Checkpoint Blockade

Key Points About Evaluating Activity

• Antitumor activity may appear to be delayed compared to response times associated with cytotoxic therapies; **imaging every 12 weeks**.

• Patients may experience response after the appearance of progressive disease.

• Development of progressive disease should be confirmed prior to discontinuation of therapy.

• Development of small lesions in the presence of other responsive lesions may be clinically insignificant.

• Durable stable disease may be indicative of response.

Agarwala SS. *Semin Oncol*. 2015.
Unique Practical Aspects of Immunotherapy

• Response Assessment
  – Unique response patterns
  – Timing of imaging

• Toxicity Recognition and Management
Select Immune-related Adverse Reactions

- hypophysitis
- thyroiditis
- adrenal insufficiency
- enterocolitis
- dermatitis
- pneumonitis
- hepatitis
- pancreatitis
- motor & sensory neuropathies
- arthritis

Ipilimumab adverse reaction management guide.
Timing of Immune-related AEs

PD-1 Blockade With Nivolumab

Kinetics of irAEs in Melanoma

Approximate proportion of patients (%)

Time (weeks)

0  10  20  30  40

Skin
Gastrointestinal
Endocrine
Hepatic
Pulmonary
Renal

Management of irAEs Overview

- Responsibility of all healthcare providers
- Early reporting by patients with close monitoring, and early intervention by healthcare providers
- Provide thorough and continuous patient education about the signs and symptoms of irAEs
- Assess for signs and symptoms of irAEs before each cycle of immunotherapy
- Know management algorithm specific to each irAE
  - Safety profiles of immunosuppressants
- Monitor and manage toxicities of immunosuppressants
  - Hyperglycemia and diabetes
  - Opportunistic infection
Immunotherapy-Associated Dermatitis

Back:
- Confluent red rash

Right upper arm:
- Vacuolar changes (magnification x20)

Back:
- Papular lesions (Close up)

Anti-CD8 staining:
- Extensive epidermal exocytosis (magnification x20)

Colitis and Enteritis

• Colonoscopy
  – Multifocal circumscribed erythematous lesions

• Histopathology
  – Predominantly chronic inflammation
  – Eosinophils and focal active cryptitis
# Management of Gastrointestinal AEs

<table>
<thead>
<tr>
<th>Grade</th>
<th>No Colostomy</th>
<th>Colostomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Increase of &lt;4 stools per day (over baseline)</td>
<td>Mild increase in ostomy output (over baseline)</td>
</tr>
<tr>
<td>2</td>
<td>Increase of 4 – 6 stools per day</td>
<td>Moderate increase in output</td>
</tr>
<tr>
<td>3</td>
<td>Increase of &gt;7 stools per day</td>
<td>Severe increase in output</td>
</tr>
<tr>
<td></td>
<td>Incontinence</td>
<td>Limiting self care ADL</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening</td>
<td>Life-threatening</td>
</tr>
<tr>
<td></td>
<td>Urgent intervention indicated</td>
<td>Urgent intervention indicated</td>
</tr>
</tbody>
</table>

- **Increase oral fluids**
- **Hold immunotherapy**
- **As G2 plus:**
  - Admit, IV hydration
  - Steroids 1–2mg/kg per day prednisolone (or equiv)
  - If no improvement in 2–3d: add infliximab 5mg/kg (NB. Infliximab contraindicated with sepsis or perforation)
  - Sigmoidoscopy and biopsy
  - When G1, taper steroids over minimum 1m (Up to 3ms for severe cases)
  - Infliximab may be re-administered at 2 and 6weeks
- **As G3 pus:**
  - Permanently discontinue immunotherapy
  - Involve gastroenterologist
  - Involve surgical team

CTCAE v4.0

Pulmonary Toxicities

- **Pneumonitis**  NSCLC (5-8%) > melanoma (2%)
  - Median time to onset 2.1 months
  - Median time to resolution 1.4 months

- Cough, dyspnoea, ‘LRTI’
# Management of Pneumonitis

<table>
<thead>
<tr>
<th>Grade</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| 1: Asymptomatic | • Hold immunotherapy  
• Steroids (e.g. prednisone 1mg/kg/day or equivalent)  
• Re-assess 3 weeks: continue treatment if completely resolved |
| 2: Symptomatic, limiting ADLs | As G1 plus:  
• Consider admission  
• Prednisone 1–2mg/kg/day PO or equivalent  
• Empiric antibiotics if suspicious for concurrent infection  
• Re-assess every 1–3 days  
• If improving taper steroids, continue treatment if symptoms resolve |

CTCAE v4.0

Adapted from London Cancer Alliance Acute Oncology clinical guidelines, April 2016
## Management of Pneumonitis

<table>
<thead>
<tr>
<th>Grade</th>
<th>Management</th>
</tr>
</thead>
</table>
| 3: Symptomatic, limiting self-care ADLs | - Discontinue immunotherapy permanently  
- Hospitalize  
- High dose steroids (methylprednisolone 1g/day IV)  
- Prophylactic antibiotics  
- Consider bronchoscopy with biopsy  
- Re-assess daily  
- If not improving after 48h or worsening, consider infliximab, mycophenylate, or immunoglobulins  
- If improving, taper steroids |
| 4: Life threatening | As G3 plus:  
- Intensive care input                                               |
Hepatotoxicity

- Mainly asymptomatic AST and/or ALT rise
- Occasionally: pyrexia, bilirubin elevation

**Initial approach**

- Exclude new / progressive liver metastases
- Review medications and alcohol intake

Adapted from London Cancer Alliance Acute Oncology clinical guidelines, April 2016
# Management Hepatotoxicity

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
<th>Management Plan</th>
</tr>
</thead>
</table>
| 1     | AST/ALT ≤3 x ULN  
BR ≤1.5 x ULN | • Continue immunotherapy  
• Investigations as listed |
| 2     | AST/ALT = 3-5 x ULN  
BR = x1.5-3 ULN | • Hold immunotherapy  
• Prednisolone 1–2mg/kg/day or IV equivalent Or  
• If patient is well, re-check liver function every 2 days and initiate steroids if no improvement or worsening.  
• Taper steroids over 4 weeks once G1 or baseline |
| 3     | AST/ALT = 5-20 x ULN  
BR = 3-10 x ULN | • As G2 plus:  
• Prednisolone 1–2mg/kg/day or IV equivalent  
• Consider permanent discontinuation of immunotherapy |
| 4     | AST/ALT >20 ULN  
BR > 10 x ULN | • As G3 plus:  
• Hepatology review  
• Permanently discontinue immunotherapy  
• Consider mycophenylate |

CTCAE v4.0

Adapted from London Cancer Alliance Acute Oncology clinical guidelines, April 2016

Endocrine Disorders: Pituitary and Thyroid

- **Incidence:** Commoner with anti-CTLA-4 (4%) than anti-PD1 (<1%)

- **Symptoms:** Fatigue, headache, visual, arthralgia, behaviour
  Often vague and non-specific

- **Investigations**
  ↓ ACTH  ↓ TSH  ↓ GH
  ↓ FSH  ↓ LH  ↓ PRL

- **Grading:** None!
Hypophysitis - Imaging
Management of Hypophysitis

1. Hold immunotherapy

2. Endocrinology input

3. Acute phase: corticosteroids (≈MP 1-2mg/kg/day) may limit hypophysitis

4. Hormone replacement (thyroxine, hydrocortisone) as needed

5. Immunotherapy may be re-started after corticosteroid taper

Adapted from London Cancer Alliance Acute Oncology clinical guidelines, April 2016
Less Common Toxicities of Immunotherapy

Ocular (<1%)
- Uveitis, episcleritis, conjunctivitis (anti-CTLA4)

Neurological
- Guillaine-Barre syndrome, myaesthenia gravis, PRES

Cardiac
- Myocarditis, heart failure
Management of irAEs

- Describe signs and symptoms, including complications if not treated promptly
- Emphasize early recognition and prompt reporting
- Discuss preventative measures, if applicable
- Instruct patient to present agent-specific wallet card to all healthcare providers
- Stress adherence with corticosteroid therapy
- Provide supportive care instructions
- Enforce early reporting of worsening condition

Patient and Caregiver Education

• Whom to call
• Why to call
• When to call
• Where to call (MUST HAVE 24/7 clinician availability)

The Immuno-Oncology Framework

- Improved Clinical Endpoints
- Reliable Immunological Methods
- New Response Criteria
- Biomarkers
- Regulatory Interactions
- Side Effect Management
- Regulatory Guidance
- Integration into Clinical Practice
- Clinical Development

Immuno-Oncology

Oncoimmunology 1:3, 334-339; May/June 2012;
Practical Considerations: Summary

• Immunotherapy requires a team approach
  – Physician, nurse, patient, family

• Unique response patterns may occur
  – Allow time for treatment to work
  – Pseudoprogression

• Toxicity recognition and management is unique
  – Patient education
  – Steroids as needed
  – Follow guidelines
Questions?
Thank you for participating in the ICLIO Webinar. Presentation slides and archived recording will be available at accc-icl.io.org.