Current Topics in Melanoma

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Disclosures

- I have received honoraria and travel support from Bristol-Myers Squibb (BMS)
- I have received honoraria and travel support from Roche
- I have received honoraria from Novartis
- I have served on advisory boards for BMS, Roche, Novartis, and Merck
- Some of the slides in this presentation are the property of BMS and/or Novartis and/or Roche; I have obtained permission to use those slides
- I may mention off-label use of some drugs; any discussion of off-label use has not been supported or encouraged by drug manufacturers
Objectives

• Understanding basic concepts of melanoma classification, diagnosis and management
• Understanding recent advances in management of metastatic disease
• Understanding at a general level the toxicities of new therapies and their management
Background

- Melanoma is projected to account for 3.6% of new cancer cases in Canada
  - But 8% in 15-29 age group and 6% in 30-49 age group
- Incidence rates in some areas are rising among young people (particularly young women)
- About 85% are localized; 10% involve regional nodes; 5% present with distant mets (US SEER data)
- Benefit of adjuvant therapies is uncertain
- Until recently, metastatic disease had poor outcomes, with disease course little modified by available agents
  - In 2015, projected melanoma mortality is 20%; 2/3 of those will be men

Canadian cancer statistics source: Canadian Cancer Society 2015
Lifetime Risk of Developing Melanoma is Increasing

(From CheckPoint module 2A) U.S. statistics.
Classification of Melanoma
Changing Perspectives

- Morphological and anatomical descriptors losing favor
- As molecular biology and genetics advance, new classifications emerge
- New therapies directed at molecular targets
- Continued exploration of relationship between melanoma and immune system
Melanoma Classification

• Classification formerly descriptive
  – Nodular, SSM, lentigo maligna, acral, mucosal, choroidal, etc.
  – These subtypes now have no significant bearing on prognosis or management

• Now interest in identification of characteristic mutations
  – Cutaneous $\rightarrow$ BRAF
  – Mucosal $\rightarrow$ c-KIT
  – Ocular / uveal $\rightarrow$ GNAQ/GNA11

• May eventually have multiple gene “signature”
Management of Non-Metastatic Melanoma: Typical Approaches
Cutaneous Melanoma: Localized

- Early-stage disease
  - Surgery a mainstay
    - Excisional bx → wide ex (+/- SLNB)
  - Typically no adjuvant treatment indicated
Cutaneous Melanoma: Localized

- Synoptic pathology report highlights:
  - Breslow depth
  - Presence of ulceration
  - Mitotic rate
  - Presence of in-transit metastases or satellite lesions
Cutaneous Melanoma: Regional Nodal Metastases

• Surgery as above; may include more extensive node dissection

• Adjuvant interferon could be offered
Mucosal Melanoma

• Staging and treatment protocols not well-established due to rarity
  – Incidence 2 per million vs 150 per million for cutaneous in US
  \(^1\)

• Can arise in any mucosal area, but more commonly:
  – Head and neck (nasal/sinus)
  – Gastrointestinal (anorectal)
  – Genitourinary (vulvovaginal)

• Value of sentinel node biopsy, adjuvant therapy unknown

\(^1\) Mihajlović et al. Int J Clin Exp Pathol 2012;5(8):739-753
Ocular Melanoma

- Incidence 2-8 per million per year in Caucasians
- Multidisciplinary evaluation required
- No proven benefit of any one primary treatment modality over another
  - Can be surgery and/or radiation
- Risk of metastasis increases with increasing thickness of primary tumor
- 50% of patients who develop metastases will have liver metastases only

Cutaneous Melanoma: Adjuvant Interferon

• Considered a standard adjuvant treatment
  – In BC, for resected clinically node-positive patients, but can be prescribed more broadly

• Problems
  – Several randomized trials of varying design, and which provided inconsistent results
  – Subsequent aggregate analyses suggest modest relapse-free and OS benefit, possibly limited to clinically node-positive patients
  – Mucosal, acral, ocular not well represented
  – Toxicity
Adjuvant Treatment - Now

- Trials are underway looking at adjuvant targeted therapy, anti-CTLA4 antibodies, and vaccine (cutaneous melanoma only)
- EORTC 18071\(^1\) – ipilimumab vs placebo (OS data not mature)
  - Evaluated in higher-risk stage 3 melanoma patients post-complete regional node dissection
  - RFS-3 significantly higher for ipi group (46.5 vs 34.8%; \(p=0.0013\))
  - mRFS 26.1 vs 17.1 months
  - 5 deaths in ipi group

• Other trials:
  – BRIM-8: p3 vemurafenib vs placebo in resected BRAF\textsuperscript{V600}\_mutant stage 2C or 3 cutaneous melanoma
  – E1609: p3 ipilimumab vs interferon-\(\alpha_2\) in resected stage 3 and 4 (M1a and M1b only)
  – MAVIS: p3 polyvalent melanoma vaccine (POL-103A) vs placebo in resected stage 2b/c and 3
Progress in Management of Advanced Melanoma
Past Treatments for Metastatic Melanoma

**Treatment**

- Dacarbazine (DTIC)
  - In large randomized trials, Response rate (RR) of <15%

- Temozolomide
  - Similar to DTIC

- IL-2
  - RR of 15-20%
  - A minority are durable responses
  - Highly toxic treatment

**Survival**

- Median OS: 6.2 months
- One year OS: 25.5% (95% CI, 23.6% to 27.4%)

OS=overall survival.

1. Korn, JCO. 2008 Feb 1; 26(4)
Advanced melanoma

- Recent advances include immunotherapy and targeted therapy
- It is now standard to evaluate tumors for $\text{BRAF}^{V600}$ and other mutations
  - 40-60% of cutaneous melanomas will be $\text{BRAF}$ mutated
  - $\text{KIT}$ and $\text{NRAS}$ routinely in near future?
Targeted Therapies: BRAF and MEK inhibition
Mechanism of Action: BRAF and MEK inhibitors

![Diagram showing the mechanism of BRAF and MEK inhibitors](http://gsksource.com/gskprm/en/US/images/gsk_content/TAFMEK/FPB/map-k-pathway/index.html#22)

- **Stimulation of tumor growth**
- **Inhibition of BRAF V600 mutation-positive melanoma cell growth in vitro**
BRIM3 Study Design in Previously Untreated Patients With Metastatic Melanoma

Multicenter, randomized, open-label, Phase 3 study of vemurafenib vs. dacarbazine in previously untreated patients with *BRAFv600E* mutation-positive* unresectable stage IIIIC or IV melanoma1,2

<table>
<thead>
<tr>
<th>Patients</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| • Aged ≥18 years  
• No prior systemic therapy  
• Enrollment: N=675 | **Vemurafenib**  
960 mg BID (n=337)  
vs.  
**Dacarbazine**  
1000 mg/m² IV q3w (n=338) |

**Primary objectives**  
• OS, PFS

**Secondary objectives**  
• BORR, DOR, TTF, safety

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Overall Survival (December 30, 2012 Cut-off) Censored At Crossover

1. Presented by Alex Hauschild as a poster at SMR 2013. Vemurafenib Improves Overall Survival Compared With Dacarbazine in Advanced BRAFV600-Mutated Melanoma: Updated Results From a Phase 3 Randomized, Multicenter Trial.
COMBI-d: Study Design

N = 947 screened

- BRAF V600E/K
- Unresectable stage IIIC/IV
- Treatment naïve
- ECOG PS 0/1
- No brain mets, unless:
  - Treated
  - Stable ≥ 12 weeks

Stratification
- BRAF mut V600E v K
- LDH (>ULN v ≤ ULN)

Primary Endpoint: Investigator-assessed PFS
Secondary Endpoints: OS, overall response rate (ORR), duration of response, safety

Pre-planned interim OS [95 events]

Primary Analysis (PFS) [213 events] Aug 2013
Final Analysis (OS) [222 deaths] Jan 2015

n = 211
Dabrafenib + trametinib
150 mg BID + 2 mg QD

n = 212
Dabrafenib + placebo
150 mg BID + placebo QD

n = 423

COMBI-d: Overall Survival

Dabrafenib

- Died: 123 (58%)
- Median OS = 18.7 mo
  (95% CI: 15.2–23.7)
- HR 0.71 (95% CI: 0.55, 0.92)
  \( P = 0.011 \)

- 1-yr OS = 68%
- 2-yr OS 42%

Dabrafenib + Trametinib

- Died: 99 (47%)
- Med OS = 25.1 mo
  (95% CI: 19.2–NR)

- 1-yr OS = 74%
- 2-yr OS 51%

Number at risk

- Dabrafenib + trametinib: 211, 208, 200, 187, 174, 159, 144, 135, 124, 112, 106, 103, 88, 53, 21, 3, 0, 0
- Dabrafenib + placebo: 212, 206, 191, 175, 159, 147, 138, 127, 111, 104, 95, 88, 70, 42, 10, 2, 1, 0

Dabrafenib + Trametinib: med follow up 20 mo (range 0-30 mo); Dabrafenib med follow up 16 mo (range 0-32 mo).

COMBI-v: Most common AEs by grade ≥20% of patients (all grades)

<table>
<thead>
<tr>
<th>Preferred term, n (%)</th>
<th>Dabrafenib + trametinib (n=350)*</th>
<th>Vemurafenib (n=349)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Any event</td>
<td>343 (98)</td>
<td>167 (48)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>184 (53)</td>
<td>15 (4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>121 (35)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>112 (32)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Chills</td>
<td>110 (31)</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>101 (29)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Headache</td>
<td>101 (29)</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>101 (29)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>92 (26)</td>
<td>48 (14)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>84 (24)</td>
<td>3 (&lt;1)</td>
</tr>
<tr>
<td>Rash</td>
<td>76 (22)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>30 (9)</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>20 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Hyperkeratosis</td>
<td>15 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>13 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Skin papilloma</td>
<td>6 (2)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Two subjects (dabrafenib + trametinib) and three subjects (vemurafenib) were excluded from safety population because they were randomised but not dosed.
## COMBI-v: BRAFi- or MEKi-related AEs

<table>
<thead>
<tr>
<th>Preferred term, n (%)</th>
<th>Dabrafenib + trametinib n=350</th>
<th>Vemurafenib n=349</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BRAF inhibitor-related adverse events</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>184 (53)</td>
<td>73 (21)</td>
</tr>
<tr>
<td>cuSCC + KA</td>
<td>5 (1)</td>
<td>63 (18)</td>
</tr>
<tr>
<td>Hyperkeratosis</td>
<td>15 (4)</td>
<td>86 (25)</td>
</tr>
<tr>
<td>Skin papilloma</td>
<td>6 (2)</td>
<td>80 (23)</td>
</tr>
<tr>
<td>Hand-foot syndrome†</td>
<td>14 (4)</td>
<td>87 (25)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>20 (6)</td>
<td>137 (39)</td>
</tr>
<tr>
<td>Photosensitivity and sunburn</td>
<td>15 (4)</td>
<td>124 (36)</td>
</tr>
<tr>
<td>Non-cutaneous malignancies</td>
<td>3 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>New primary melanoma</td>
<td>2 (&lt;1)</td>
<td>7 (2)</td>
</tr>
<tr>
<td><strong>MEK inhibitor-related adverse events</strong>#</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>112 (32)</td>
<td>131 (38)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>92 (26)</td>
<td>84 (24)</td>
</tr>
<tr>
<td>Acneiform rash</td>
<td>22 (6)</td>
<td>20 (6)</td>
</tr>
<tr>
<td>Ejection fraction decrease</td>
<td>29 (8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Chorioretinopathy</td>
<td>2 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
</tbody>
</table>

*AEs indicated are those typically associated with BRAF inhibitors; †Hand–foot syndrome includes PPE and palmoplantar keratoderma. # AE’s indicated are those typically associated with MEK inhibitors
CuSCC=cutaneous squamous cell carcinoma; KA=keratoacanthoma.
BRAF/MEK inhibitor toxicity

- Manufacturer prescribing information contains toxicity management info
- Typical strategies:
  - Supportive care
  - Dose interruption and subsequent reduction
  - Steroids
- Rechallenge is often possible, but in some cases should not be attempted
  - Eg, ILD, some grade 3-4 toxicities
- In some cases, one drug can be continued but not the other
  - Eg, discontinuation of MEK inhibitor but possible continuation of BRAF inhibitor if significant EF decrease or symptomatic CHF
Targeted Therapies: KIT inhibition
c-KIT Mutation in Melanoma

Journal of Investigative Dermatology (2008) 128, 2575–2595
KIT inhibition

- KIT mutation seems to be more relevant than KIT amplification
- Melanoma phenotypic subtypes most likely to demonstrate KIT mutation are:
  - Mucosal (1.5% overall incidence; 15-40% mutation incidence)
  - Acral (2-3% incidence; 10-35% mutation incidence)
  - Chronically sun-damaged (high incidence; 15% mutation incidence)
- There are no phase 3 studies
- While KIT inhibitor therapy use is accepted in KIT-mutated tumors, its use would be considered off-label

KIT inhibition

- Response rates vary from 15-40%
- Responses may be more likely in patients whose tumors have particular KIT mutations
  - Eg, mutations in exons 11, 13, and 17
- Median PFS tends to be just a few months, but may be longer in responding patients
- If the best means of identifying suitable patients can be determined, a randomized trial is needed

Checkpoint Inhibitors
Checkpoint Inhibitors

• Currently two classes:
  – Anti-CTLA-4 antibodies
  – Anti-PD-1 antibodies
Immuno-oncology: Blocking CTLA-4 and PD-1 Pathways with Monoclonal Antibodies

CTLA-4 pathway blockade

PD-1 pathway blockade

T-cell activation (cytokines, lysis, proliferation, migration to tumour)


CTLA-4=cytotoxic T-lymphocyte antigen-4; PD-1=programmed cell death 1; PD-L1/2=PD ligand 1/2; TCR=T cell receptor.
MDX-020: Pivotal Phase III Trial

First phase III trial to demonstrate overall survival advantage in metastatic melanoma

Overall Survival was the Primary Endpoint in this Trial

Also presented at ASCO 2010 (Plenary Session, Abstract #4)
Long-Term Survival with Ipilimumab in Melanoma

Pooled Analysis: Phase III and Phase II Trials

- 10 prospective trials and two retrospective, observational studies (n = 1861)

Median OS: 11.4 months
(95% CI, 10.7-12.1 months)

3-year survival rate: 22%
(95% CI, 20% to 24%)

Pooled Analysis: Phase III, Phase II Trials and EAP

- 12 clinical investigations (n = 1861)
- US EAP (n = 2985)

Median OS: 9.5 months
(95% CI, 9.0-10.0 months)

3-year survival rate: 21%
(95% CI, 20% to 22%)
Nivolumab Improved Overall Survival vs. Dacarbazine in Melanoma

Patients who died, n/N

Median OS mo (95% CI)

Nivolumab 50/210 NR

Dacarbazine 96/208 10.8 (9.3–12.1)

NR = not reached.

Based on 5 August 2014 database lock.

Follow-up since randomization: 5.2–16.7 months.
Pembrolizumab Showed Improved OS (RECIST v1.1) vs. Ipilimumab in Melanoma

### Overall Survival (%)

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Median (95% CI) mo</th>
<th>Rate at 12 mo</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab 10 mg/kg Q2W</td>
<td>NR</td>
<td>74.1%</td>
<td>0.63 (0.47-0.83)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Pembrolizumab 10 mg/kg Q3W</td>
<td>NR</td>
<td>68.4%</td>
<td>0.69 (0.52-0.90)</td>
<td>=0.0036</td>
</tr>
<tr>
<td>Ipilimumab 3 mg/kg IV Q3W x 4 doses</td>
<td>NR (12.7-NR)</td>
<td>58.2%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**No. at Risk**

- Pembrolizumab, Q2W: 279, 266, 248, 233, 219, 212, 177, 67, 19, 0
- Pembrolizumab, Q3W: 277, 266, 251, 238, 215, 202, 158, 71, 18, 0
- Ipilimumab: 278, 242, 212, 188, 169, 157, 117, 51, 17, 0

NR=not reached
Nivolumab Plus Ipilimumab in a Concurrent Regimen in Patients with Advanced Melanoma Showed 79-88% OS at 2 Years

- Data from a phase 1 trial (CA209-004) of nivolumab plus ipilimumab on a concurrent or sequenced regimen
- 62% of patients had grade 3/4 AEs on the concurrent regimen; there were no new safety signals and most events were manageable using standard protocols
- Historical 1-year survival rates with ipilimumab and nivolumab monotherapy in patients with advanced melanoma were 45.6% (phase 3) and 62% (phase 1), respectively

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aData from separate, noncomparative trials; use cross-trial comparisons with caution in the absence of data from a randomized, comparative trial.

Q3W, every 3 weeks.

Checkpoint Inhibitor Response Patterns
Therapies that affect the immune system may not induce a measurable impact on tumour growth immediately after administration\(^1\)

Response to I-O Therapy is a Multi-step Process that May Impact Response Kinetics

<table>
<thead>
<tr>
<th>I-O Start(^2)</th>
<th>Immune cell activation and proliferation</th>
<th>Effect on tumour</th>
<th>Effect on survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Days to Weeks</td>
<td>Several Weeks</td>
<td>Several Months</td>
</tr>
</tbody>
</table>

Initial I-O therapy administration

- Immune activation and T-cell proliferation start early on after initial I-O administration
- Clinically measurable immune-mediated antitumour effects occur over weeks to months
- Potential effect on survival may occur several months after initial I-O administration

Potential Tumour Response Patterns to Therapy

Response in baseline lesions typically seen with chemotherapy, but also I-O therapies and targeted therapies. Captured by existing RECIST and WHO criteria.

“Stable disease”: Slow, steady decline in tumour volume seen with chemotherapy, targeted and I-O therapies. Captured by existing RECIST and WHO criteria.

Graphs for illustrative purposes showing responses to ipilimumab in advanced melanoma.

Potential Tumour Response Patterns to Therapy

Response after initial increase in tumour volume; novel and specific to I-O therapy RECIST or WHO criteria may not be appropriate to assess

Reduction in tumour burden after appearance of new lesions; novel and specific to I-O therapy, RECIST or WHO criteria may not be appropriate to assess

Some vaccines may not follow similar patterns of response as other I-O therapies

Pseudo-progression: Inflammation Causes Swelling, May Appear as Tumour Growth or New Lesions Upon Imaging

Considerations when evaluating true progression vs. pseudo-progression

<table>
<thead>
<tr>
<th>May indicate progression</th>
<th>May indicate pseudo-progression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Performance status</strong></td>
<td></td>
</tr>
<tr>
<td>Deterioration of performance</td>
<td>Remains stable or improves</td>
</tr>
<tr>
<td><strong>Systemic symptoms</strong></td>
<td></td>
</tr>
<tr>
<td>Worsen</td>
<td>May or may not improve</td>
</tr>
<tr>
<td><strong>Symptoms of tumour enlargement</strong></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>May or may not be present</td>
</tr>
<tr>
<td><strong>Tumour burden</strong></td>
<td></td>
</tr>
<tr>
<td>Increase</td>
<td>Increase followed by response</td>
</tr>
<tr>
<td>Baseline</td>
<td>Appear then remain stable and/or subsequently respond</td>
</tr>
<tr>
<td>New lesions</td>
<td></td>
</tr>
<tr>
<td>Increase</td>
<td></td>
</tr>
<tr>
<td>Appear and increase in size</td>
<td></td>
</tr>
<tr>
<td><strong>Biopsy may reveal</strong></td>
<td></td>
</tr>
<tr>
<td>Evidence of tumour growth</td>
<td>Evidence of T-cell infiltration</td>
</tr>
</tbody>
</table>

Example of Evolution of Response to CTLA-4 Inhibition

Screening

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

Week 16: Responding

Week 96: Durable and ongoing response without signs of irAEs

irAE = immune-related adverse events
Harmankaya K, et al. Presented at the World Meeting of Interdisciplinary Melanoma/Skin Cancer Centers: November 19 - 21, 2009; Berlin, Germany.
Checkpoint Inhibitor
Toxicity
Key Considerations on Management of Immune-related Events

Result from enhanced or excessive immune activity

Early diagnosis and appropriate management is essential

Health care team and patient education for early recognition

Can be severe or life-threatening, may involve various organs

Multidisciplinary team approach is required for optimal management

Delayed irAEs may occur

Unless an alternate etiology has been identified, consider all symptoms and signs as potential irAE

Patients should be instructed to report potential AEs as soon as possible

Systemic high-dose corticosteroids* may be required for severe events

*with or without additional immunosuppressive therapy
Bristol-Myers Squibb. YERVOY (ipilimumab) Immune-related Adverse Reactions (IrAR) Management Guide and online Tool at https://www.yervoy.co.uk/
## Immune Related Adverse Events with Checkpoint Inhibition are Uncommon

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Phase of study</th>
<th>Most frequent toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Any grade</td>
</tr>
<tr>
<td><strong>Ipilimumab</strong></td>
<td>CTLA-4</td>
<td>I, II, III</td>
<td>Gastrointestinal Dermatologic</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>15.3-35.1%</td>
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<td></td>
<td></td>
<td></td>
<td>43.5%</td>
</tr>
<tr>
<td><strong>Nivolumab</strong></td>
<td>PD-1 or PD-L1</td>
<td>I, II, III</td>
<td>Rash</td>
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<td></td>
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<td>Pruritus</td>
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<td>Diarrhoea</td>
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<td>Fatigue</td>
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<td>Pneumonitis</td>
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<td>Headache</td>
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<td>Asthenia</td>
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<td>Dyspnea</td>
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<td></td>
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<td>Anemia</td>
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<td><strong>Pembrolizumab</strong></td>
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<td><strong>MPDL3280A</strong></td>
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<td><strong>MEDI4736</strong></td>
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</tbody>
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Kinetics of irAEs: Example for Ipilimumab

Kinetics of irAEs: Example for Nivolumab

Time to onset of select treatment-related AEs (any grade; n = 474)

- **Skin** (n = 155; 33%): Median time to onset = 5.0 weeks (0.1–57.0)
- **Gastrointestinal** (n = 66; 14%): Median time to onset = 7.3 weeks (0.1–37.6)
- **Hepatic** (n = 19; 4%): Median time to onset = 7.7 weeks (2.0–38.9)
- **Pulmonary** (n = 9; 2%): Median time to onset = 8.9 weeks (3.6–22.1)
- **Endocrine** (n = 36; 8%): Median time to onset = 10.4 weeks (3.6–46.9)
- **Renal** (n = 8; 2%): Median time to onset = 15.1 weeks (3.9–26.4)

Median time to onset for treatment-related select AEs ranged from 5.0 weeks for skin AEs to 15.1 weeks for renal AEs.

Circles represent median; bars signify ranges. The kinetics of AEs presented on the slide are for melanoma but may not reflect the kinetics of AEs in other tumor types. Weber JS, et al. Presentation at ASCO 2015.
Stepwise Approach to Using I-O Agents in Clinic

- Initiate treatment according to prescribing Product Monograph
- Careful ongoing clinical assessment is necessary for early identification of irAEs
- irAEs can be severe or life-threatening if not identified early
- irAEs can occur any time
- Keep in mind that toxicity does not equal response
- Early recognition is key
- Consider all symptoms and signs as potential irAE
- Refer to organ-specific algorithms for the management of irAEs
The majority of immune-related AEs are manageable and reversible with drug interruption corticosteroid.

**Steroid taper is generally required over at least one month.**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Management</th>
<th>Continue the drug?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (gr 1)</td>
<td>Monitor closely</td>
<td>Continue (except for pneumonitis consider delay)</td>
</tr>
</tbody>
</table>
| Moderate (gr 2) | Symptomatic management  
Monitor closely  
Oral corticosteroids if persistent toxicity | Delay the dose  
Resume IO drug when AEs resolve to grade ≤ 1 or baseline                      |
| High (gr 3-4) | Administer high dose IV Corticosteroids  
Symptomatic management  
Monitor closely  
Involve specialist consultant* | Discontinue I-O Drug permanently  
(Delay in some situations)                                                          |

*In the event of grade 3 or 4 toxicity for practitioners in non-tertiary centres, consult with an oncologist or consider transfer to a tertiary centre*
GI Adverse Event Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

**Grade of Diarrhea/Colitis**
(NCI CTCAE v4)

**Grade 1**
- **Diarrhea**: < 4 stools/day over baseline; **Colitis**: asymptomatic

**Grade 2**
- **Diarrhea**: 4-6 stools per day over baseline; IV fluids indicated < 24 hrs; not interfering with ADL
- **Colitis**: abdominal pain; blood in stool

**Grade 3-4**
- **Diarrhea (G3)**: ≥ 7 stools per day over baseline; incontinence; IV fluids ≥ 24 hrs; interfering with ADL
- **Colitis (G3)**: severe abdominal pain, medical intervention indicated, peritoneal signs
- **G4**: life-threatening, perforation

**Management**
- **Grade 1**
  - Continue I-O therapy
  - Symptomatic treatment
- **Grade 2**
  - Delay I-O therapy
  - Symptomatic treatment
- **Grade 3-4**
  - Discontinue I-O therapy
  - 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent
  - Add prophylactic antibiotics for opportunistic infections
  - Consider lower endoscopy

**Follow-up**
- **Grade 1**
  - Close monitoring for worsening symptoms
  - Educate patient to report worsening immediately
  - If worsens:
    - Treat as Grade 2 or 3-4
- **Grade 2**
  - If improves to grade 1:
    - Resume I-O therapy
  - If persists > 5-7 days or recurs:
    - 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent
    - When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy
  - If worsens or persists > 3-5 days with oral steroids:
    - Treat as Grade 3-4
- **Grade 3-4**
  - If improves:
    - Continue steroids until Grade 1, then taper over at least 1 month
  - If persists > 3-5 days, or recurs after improvement:
    - Add infliximab 5 mg/kg (if no contraindication).
    - Note: Infliximab should not be used in cases of perforation or sepsis.

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
Summary
Metastatic Melanoma: Historically

- Diagnosis of unresectable metastatic melanoma
  - Dacarbazine / TMZ
  - Interleukin-2?
  - 2nd-line chemo?
    - Clinical trial
    - BSC
Metastatic Melanoma: Today

- Diagnosis of unresectable metastatic melanoma
- BRAF mutation testing (multiplex testing?)
  - Checkpoint inhibition
  - BRAFi +/- MEKi
  - Checkpoint inhibition
  - DTIC/TMZ
  - Clinical trial BSC
Conclusion

• Many aspects of melanoma management are changing

• New treatments offer substantial improvements over previous options and new hope, but at the potential cost of considerable toxicity
  – Education, monitoring, and early intervention are important

• Future strategies may feature less toxicity
# Genetic Testing in Melanoma: Prevalence of Mutations and Testing Recommendations

<table>
<thead>
<tr>
<th>Melanoma Subtype</th>
<th>Mutations, %</th>
<th>Testing Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BRAF</td>
<td>NRAS</td>
</tr>
<tr>
<td>Cutaneous (non-CSD)</td>
<td>45</td>
<td>15-20</td>
</tr>
<tr>
<td>Cutaneous (CSD)</td>
<td>5-30</td>
<td>10-15</td>
</tr>
<tr>
<td>Acral</td>
<td>10-15</td>
<td>10-15</td>
</tr>
<tr>
<td>Mucosal</td>
<td>5</td>
<td>5-10</td>
</tr>
<tr>
<td>Uveal</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>From an unknown primary</td>
<td>50</td>
<td>20</td>
</tr>
</tbody>
</table>

* Gene expression profiling and monosomy 3 analysis of primary uveal melanomas have been used as prognostic tests for metastatic risk; these tests currently do not have a defined role in patients with metastatic disease.