Melanoma Systemic Therapy: A Primary Care Perspective

March 28th, 2018
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Medical Oncology
Trillium Health Partners
Lifetime Risk of Developing Melanoma


1/1500    1/600    1/250    1/150    1/100    1/74    1/65    1/58   1/50   1/40

aUS Statistics
# Life Years Lost to Cancers (US SEER Data, 1975-2012)

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Life Years Lost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testis</td>
<td>36.8</td>
</tr>
<tr>
<td>Cervix uteri</td>
<td>26.7</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>22.3</td>
</tr>
<tr>
<td>Brain &amp; CNS</td>
<td>22.1</td>
</tr>
<tr>
<td>Breast (female)</td>
<td>19.0</td>
</tr>
<tr>
<td>Ovary</td>
<td>17.7</td>
</tr>
<tr>
<td>Oral cavity / pharynx</td>
<td>17.5</td>
</tr>
<tr>
<td>Liver &amp; IBD</td>
<td>17.4</td>
</tr>
<tr>
<td>Corpus &amp; uterus, NOS</td>
<td>17.2</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>17.1</td>
</tr>
<tr>
<td>Stomach</td>
<td>16.4</td>
</tr>
<tr>
<td>Esophagus</td>
<td>16.1</td>
</tr>
<tr>
<td>Leukemia</td>
<td>15.8</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>15.5</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>15.4</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>15.2</td>
</tr>
<tr>
<td>Pancreas</td>
<td>14.9</td>
</tr>
<tr>
<td>Non-Hodgkin...</td>
<td>14.0</td>
</tr>
<tr>
<td>Myeloma</td>
<td>13.7</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>11.4</td>
</tr>
<tr>
<td>Prostate</td>
<td>9.8</td>
</tr>
</tbody>
</table>

US Data show that melanoma is the #1 cancer killer of women in the 25-30 age range and #2 among women aged 30-35.

Melanoma Incidence rates

*Rising at 3 to 5% per year*

Rate per 100,000 standardized to the world population

Melanoma Key Facts

• 7,500 Canadians will be diagnosed this year

• 90% of melanomas are caused by exposure to UV light including tanning beds
Types of Melanoma

- Cutaneous 91.2%
- Ocular 5.2%
- Mucosal 1.3%
- Unknown 5.3%

Median OS: 6.2 months

- 25.5% alive at 1 year
- Only ~10% alive at 24 months

Survival data from 42 phase II trials with over 2100 stage IV patients

1 yr survival 25%

Overall Survival Metastatic Melanoma

1-year OS Phase III Studies

<table>
<thead>
<tr>
<th>Year</th>
<th>DTIC</th>
<th>Ipilimumab</th>
<th>Vemurafenib</th>
<th>Dabrafenib</th>
<th>Nivolumab</th>
<th>Pembrolizumab</th>
<th>Dab + Tram</th>
<th>Vem + Cobi</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990</td>
<td>25-35%</td>
<td>46%</td>
<td>47%</td>
<td>56%</td>
<td>70%</td>
<td>71%</td>
<td>71% Pembrolizumab</td>
<td>74% Dab + Tram</td>
</tr>
<tr>
<td>2010</td>
<td>15% 2-year OS</td>
<td>24%</td>
<td>29% Ipilimumab</td>
<td>45% Dabrafenib</td>
<td>58% Nivolumab</td>
<td>53% Dab + Tram</td>
<td>48% Vem + Cobi</td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>22% Ipilimumab</td>
<td>42% Nivolumab (Ph I)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2012</td>
<td>18% Ipilimumab</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>2013</td>
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<tr>
<td>2014</td>
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<tr>
<td>2015</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2016</td>
<td>XX% Pembrolizumab (Ph III)</td>
<td>XX% Dab + Tram (Ph III)</td>
<td>XX% Pembrolizumab (Ph I)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes:
- Dabrafenib (Dab)
- Ipilimumab (Ipi)
- Nivolumab (Nivo)
- Pembrolizumab (Pembro)

Presented by Georgina Long at 2016 ASCO Annual Meeting
Overall Survival Metastatic Melanoma

1-year OS Phase III Studies

- **DTIC**
  - 25–35%
- **Ipilimumab**
  - 1990: 15%
  - 2010: 24%
  - 2011: 22%
  - 2012: 18%
  - 2013: 45%
  - 2014: 58%
  - 2015: 53%
  - 2016: 64%
- **Ipilimumab**
  - 1990: 25–35%
  - 2010: 46%
  - 2011: 47%
  - 2012: 56%
  - 2013: 70%
  - 2014: 71%
  - 2015: 71%
  - 2016: 73%
- **Vemurafenib**
  - 1990: 25–35%
  - 2010: 46%
  - 2011: 47%
  - 2012: 56%
  - 2013: 70%
  - 2014: 71%
  - 2015: 71%
  - 2016: 73%
- **Dabrafenib**
  - 1990: 25–35%
  - 2010: 46%
  - 2011: 47%
  - 2012: 56%
  - 2013: 70%
  - 2014: 71%
  - 2015: 71%
  - 2016: 73%
- **Nivolumab**
  - 1990: 25–35%
  - 2010: 46%
  - 2011: 47%
  - 2012: 56%
  - 2013: 70%
  - 2014: 71%
  - 2015: 71%
  - 2016: 73%
- **71% Pembrolizumab**
  - 1990: 25–35%
  - 2010: 46%
  - 2011: 47%
  - 2012: 56%
  - 2013: 70%
  - 2014: 71%
  - 2015: 71%
  - 2016: 73%
- **74% Dabrafenib + Trametinib**
  - 1990: 25–35%
  - 2010: 46%
  - 2011: 47%
  - 2012: 56%
  - 2013: 70%
  - 2014: 71%
  - 2015: 71%
  - 2016: 73%
- **75% Vemurafenib + Cobimetinib**
  - 1990: 25–35%
  - 2010: 46%
  - 2011: 47%
  - 2012: 56%
  - 2013: 70%
  - 2014: 71%
  - 2015: 71%
  - 2016: 73%
- **73% Nivolumab + Ipilimumab (Phase II)**
  - 1990: 25–35%
  - 2010: 46%
  - 2011: 47%
  - 2012: 56%
  - 2013: 70%
  - 2014: 71%
  - 2015: 71%
  - 2016: 73%
Overall Survival Metastatic Melanoma
1-year OS Phase III Studies

DTIC
25–35%

1990
15%
2-year OS

3-year OS
22% Ipi

5-year OS
18% Ipi

1990
24%
29% Ipi

2010
46% Ipi

2011
47% Ipi

2012
56% Vem

2013
70% Dab

2014
71% Nivo

2015
71% Pembrolizumab
74% Dab + Tram
75% Vem + Cobimetinib
73% Nivo + Ipi (Ph II)

2016
64% Nivo + Ipi (Ph II)

Pembrolizumab Q2W and Q3W 10mg/kg:
Dab= dabrafenib; Ipi= ipilimumab; Nivo= nivolumab; Pembro= pembrolizumab; Tram= trametinib; Vem= vemurafenib

Presented By Georgina Long at 2016 ASCO Annual Meeting
Therapeutic Approaches for Advanced Melanoma

Targeted Therapy

MAP kinase pathway inhibition

- BRAF inhibitors
  - Vemurafenib
  - Dabrafenib
- MEK inhibitors
  - Trametinib
  - cobimetinib

Tumour cell proliferation and survival

ImmunoTherapy

Antitumour immune response

- Anti-CTLA-4
  - Ipilimumab
- Anti-PD-1
  - Nivolumab
  - Pembrolizumab

Driver Oncogenic Mutations Define Clinically Relevant Melanoma Molecular Subsets

Arising from Skin Without Chronic Sun Damage
- 40% BRAF
- 20% NRAS
- 0% KIT

Arising from Skin With Chronic Sun Damage
- 10% BRAF
- 10% NRAS
- 2% KIT

Arising from Mucosal Surfaces
- 5% BRAF
- 15% NRAS
- 20% KIT

Arising from Acral Surfaces
- 15% BRAF
- 15% NRAS
- 15% KIT

Uveal Melanoma
- 25% GNAQ
- 55% GNA11

Curtin et al. NEJM 2005; Curtin et al. JCO 2006; Van Raamsdonk et al., NEJM 2010
Mechanisms of Action of Targeted Therapies Modulating the MAP Kinase Pathway

**BRAF inhibitors**
- Dabrafenib
- Vemurafenib
- Encorafenib

**MEK inhibitors**
- Trametinib
- Cobimetinib
- Binimetinib

**BRAF**
- BRAF<sub>V600E</sub>

**MEK**
- MEK

**ERK**
- ERK

Pathway activation and tumor progression

Olszanski AJ. J Manag Care Spec Pharm 2014; 20(4):346-56.v
Pooled Overall Survival: Dabrafenib + Trametinib
(N = 617)

Median (95% CI), mo
25.6 (23.1, 34.3)

1-yr
74%

2-yr
53%

5-yr
28-30%
Dabrafenib + Trametinib: BRAF V600 Melanoma

Week 0

Week 8

Presented by Georgina V. Long

Presented By Georgina Long at 2016 ASCO Annual Meeting
Key Adverse Events with Targeted Therapies in Advanced Melanoma

- Pyrexia
- Photosensitivity
- Other skin toxicities
- Arthralgia
Examples of Photosensitivity Reactions with Vemurafenib

Photos courtesy of Dr. Joël Claveau.
Other Potential Adverse Skin Effects with Targeted Therapies

Follicular hyperkeratotic rash

Keratoacanthomas

Photos courtesy of Dr. Joël Claveau.
Other Potential Adverse Skin Effects with Targeted Therapies

Photos courtesy of Dr. Joël Claveau.

- Squamous cell Carcinoma
- Plantar hyperkeratosis
## Other Adverse Events of Note with Targeted Therapies

<table>
<thead>
<tr>
<th>AE</th>
<th>Observations / considerations&lt;sup&gt;1-3&lt;/sup&gt;</th>
</tr>
</thead>
</table>
| **Ophthalmologic** | • Most common ocular toxicity with BRAFi: **uveitis** (~1% of patients)  
                      • Easily managed with temporary dose interruption, ophthalmology review, course of topical steroids                                                                                                                     |
| **Cardiac**      | • Decrease in left ventricular systolic ejection fraction dysfunction has been observed (usually asymptomatic)  
                      • Peripheral edema suggestive of heart failure should prompt cardiac workup / referral                                                                                                                                           |
|                  | • Possible **prolongation of the QTc interval**  
                      • Avoid, if possible, concomitant use of BRAFi with products known to prolong QTc interval or able to induce torsades de pointes                                                                                     |

# Health Canada-Approved Indications: Combined Targeted Therapies for Advanced Melanoma

<table>
<thead>
<tr>
<th>Agents</th>
<th>Mechanism</th>
<th>Current Canadian Indication</th>
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<tr>
<td>Dabrafenib + trametinib</td>
<td>BRAF inhibitor + MEK inhibitor</td>
<td>For the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation</td>
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Immunotherapy
T-Cell Checkpoint Regulation: An Evolving Approach to Cancer Therapy

- T-cell responses are regulated through a complex balance of inhibitory (“checkpoint”) and activating signals.

- Tumours can dysregulate these pathways, and consequently the immune response.

- Targeting these pathways is an evolving approach to cancer therapy.

Activating receptors
- CD28
- OX40
- CD137

Inhibitory receptors
- CTLA-4
- PD-1
- TIM-3
- LAG-3

Agonistic antibodies

Antagonistic (blocking) antibodies

T-cell stimulation

IPILIMUMAB

NIVOLUMAB
PENBROLIZUMAB
Evolution of a response to Ipilimumab

Screening

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

Week 16: Responding

Week 96: Durable & ongoing response without signs of IRAEs

Harmankaya et al. EADO 7th World Congress of Melanoma 2009.
IPILIMUMAB

Primary Analysis of Pooled OS Data:
1861 Patients that Received Ipilimumab

Median OS (95% CI): 11.4 (10.7, 12.1)
3-year OS rate (95% CI): 22% (20, 24%)

Patients at risk
Ipilimumab 1861 839 370 254 192 170 120 26 15 5 0
Primary Analysis of Pooled OS Data: 1861 Patients that Received Ipilimumab

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

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

Patients at risk
Ipilimumab 1861 839 370 254 192 170 120 26 15 5 0
PD-1 Antibodies

- Pembrolizumab
- Nivolumab
- Nivo-Ipi

Adapted from *N Engl Med.* 2012;366(26):2517
Nivolumab Greatly Improved Overall Survival vs. Dacarbazine


Based on August 5, 2014 database lock.

Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Dacarbazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>210</td>
<td>208</td>
</tr>
<tr>
<td>1-yr OS</td>
<td>73%</td>
<td>42%</td>
</tr>
<tr>
<td>HR</td>
<td>0.42 (99.79% CI, 0.25-0.73; P &lt; 0.0001)</td>
<td></td>
</tr>
<tr>
<td>(Boundary for statistical significance 0.0021)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Follow-up since randomization: 5.2-16.7 months.
Pembrolizumab Showed Improved OS (RECIST v1.1) vs. Ipilimumab at the First Interim Analysis

B  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
Metastatic Melanoma: 1 year survival

Survival data from 42 phase II trials with over 2100 stage IV patients

Median survival: 6.2 months
Metastatic Melanoma: 1 year survival

Survival data from 42 phase II trials with over 2100 stage IV patients

Median survival 6.2 mo.
Nivolumab: Time to Response
Nivolumab: Immune Response after Treatment discontinued
Immune-Related AEs with PD-1 Inhibitors

If not vigilant, may result in more serious immune-related adverse events.

Skin
- Dermatitis exfoliative
- Erythema multiforme
- Stevens Johnson Syndrome
- Toxic Epidermal Necrolysis

Eye 1%
- Uveitis
- Iritis

Hepatic 1%
- Autoimmune Hepatitis

Gastrointestinal (GI)
- Colitis 5 -10%
- Enterocolitis
- Necrotizing colitis
- GI perforation

Endocrine – 10%
- Hypothyroidism
- Hyperthyroidism
- Adrenal insufficiency
- Hypophysitis
- Thyroditis

Pulmonary
- Pneumonitis 5%
- Interstitial lung disease
- Acute interstitial pneumonitis

Renal 1%
- Nephritis, autoimmune
- Renal failure

Neurologic 1%
- Autoimmune neuropathy
- Demyelinating Polyneuropathy
- Guillain-Barre
- Myasthenia Gravis like syndrome

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- Dermatitis exfoliative
- Erythema multiforme
- Stevens Johnson Syndrome
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- Renal failure

Neurologic 1%
- Autoimmune neuropathy
- Demyelinating Polyneuropathy
- Guillain-Barre
- Myasthenia Gravis like syndrome
Kinetics of Immune-related AEs with Anti-PD-1 Therapy (Nivolumab)

Time to onset of select treatment-related AEs

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

Circles represent median; bars signify ranges.
MRI: Hypophysitis
Diffuse mild enlargement of the pituitary gland and pituitary stalk
Immunotherapy induced Pneumonitis
Vitiligo with anti-PD1 in melanoma patients

Hua et al JAMA Dermatol 2016
Repigmentation of hair with anti-PD1 or anti-PDL1
14 patients

Riviera et al JAMA Dermatol 2017
Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma

# Immunotherapy for Advanced Melanoma

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
<th>Canadian Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab (Yervoy®)¹</td>
<td>Anti-CTLA-4</td>
<td>Treatment of unresectable or metastatic melanoma</td>
</tr>
<tr>
<td>Nivolumab (Opdivo®)²</td>
<td>Anti-PD-1</td>
<td>Treatment of unresectable or metastatic melanoma</td>
</tr>
<tr>
<td>Pembrolizumab (Keytruda®)³</td>
<td>Anti-PD-1</td>
<td>Treatment of unresectable or metastatic melanoma</td>
</tr>
<tr>
<td><strong>Combination</strong></td>
<td><strong>Indication</strong></td>
<td></td>
</tr>
<tr>
<td>Ipilimumab + nivolumab⁴</td>
<td></td>
<td>Treatment of unresectable or metastatic melanoma</td>
</tr>
</tbody>
</table>

Stage III Melanoma & Adjuvant Systemic Therapy

No Adjuvant Therapy
- Risk of Recurrence @ 5 years: 70%
- Risk of Death @ 5 years: 45%

Interferon¹
- Risk of Recurrence @ 5 years: ~64%
- Risk of Death @ 5 years: ~41%
- HR 0.83 vs placebo

Ipilimumab²
- Risk of Recurrence @ 5 years: 59%
- Risk of Death @ 5 years: 35%
- HR 0.72 vs placebo

Nivolumab³
- Risk of Recurrence @ 5 years: ~38%
- Risk of Death @ 5 years: ~38%
- HR 0.65 vs ipilimumab

Dabrafenib+Trametinib⁴
- Risk of Recurrence @ 5 years: ~37%
- Risk of Death @ 5 years: ~26%
- HR 0.47 vs placebo

Risk of no adjuvant therapy at 5 years from Eggermont et al. NEJM 2016. The % shown for drug therapies determined from the risk reduction (HR).

Presented by Georgina V Long, MIA
Overall Survival in Melanoma

- BRAFi + MEKi
- Anti-PD1 +/- Anti-CTLA4
- Anti-CTLA4

70–75% or 47%

Time from randomisation, months

OS, proportion alive

Overall Survival in Melanoma

OS, proportion alive

Time from randomisation, months

Overall Survival in Melanoma

- BRAFi + MEKi
- Anti-PD1 +/- Anti-CTLA4
- Anti-CTLA4

64%
55-60%
~50%
70-75%
47%

58%
52%
~40-45%

Time from randomisation, months

OS, proportion alive


Presented by Georgina V Long, MIA
Future Directions
The landscape of T cell activating and inhibitory receptors

- Activating receptors: CD28, OX40, GITR, CD137, CD27, HVEA
- Inhibitory receptors: CTLA-4, PD-1, TIM-3, BTLA, LAG-3, TIGIT
- Agonistic antibodies
- Blocking antibodies
- T-cell stimulation
Take Home Points

- Melanoma incidence is rising: Sun Protection counseling is critical
- Molecular testing determines treatment options
- Targeted agents for BRAF positive melanoma oral agents with excellent tolerability
- Immunotherapy is here to stay!

Do we have curative treatment for Metastatic Melanoma?