Practice Guideline: Systemic Therapy Summary

Second-Line Treatment of Metastatic Melanoma with Ipilimumab

(SKIN – Ipilimumab)

Skin Cancer Disease Site Group

Effective: July 2012
Updated: June 2015
ACKNOWLEDGEMENT AND SPONSORSHIP DISCLAIMERS

There are no relevant conflicts of interest to disclose.
Preface

This document has been prepared by the Winnipeg Regional Health Authority/CancerCare Manitoba (WRHA/CCMB) Oncology Pharmacotherapeutic (P&T) Subcommittee’s Systemic Therapy Summaries Working Group, as a means of disseminating drug information and formulary decisions made by the Subcommittee. The CCMB Provincial Pharmacy Program, Provincial Oncology Drug Program (PODP) and Clinical Practice Guidelines Initiative (CPGI) have contributed to the development of this summary.

Systemic Therapy Summaries (STS) are being developed for drugs/or indications where the P&T Subcommittee, based on scientific data, has accepted clinical benefit. The P&T Subcommittee Chair and the CPGI Medical Director/Advisory Panel Chair approve all STS documents.

The content of this STS was in large part adapted from the Formulary Addition Request submitted to the P&T Subcommittee by the CCMB Skin Cancer Disease Site Group (DSG), July 2012. This document will be reviewed, and updated as necessary, once in every twelve-month period; unless emerging evidence from scientific research dictates otherwise.

Purpose

This document is intended as a guide to facilitate the safe and effective clinical use of ipilimumab in the second-line treatment of metastatic melanoma.

For this purpose, it may be used by qualified and licensed healthcare practitioners involved with the care of oncology patients, which may include (but is not limited to): physicians, nurses, and pharmacists at CancerCare Manitoba, Community Cancer Programs Network (CCPN) sites and WRHA Community Oncology Program sites.

Disclaimer

Use of this document should not preclude the practitioner’s independent clinical judgment, nor should it replace consultation with the oncologist.

It is the responsibility of the practitioner to develop an individualized treatment plan for each patient under his/her care, and ideally this should take place within the context of a multidisciplinary team. The unique needs and preferences of the patient and the family should always be reflected in the plan of care.

This document is not a comprehensive drug monograph. Practitioners must refer to other sources for complete drug information.
Second-Line Treatment of Metastatic Melanoma with Ipilimumab

Protocol Code: SKIN – Ipilimumab

Developed by: Skin Cancer Disease Site Group

Date of Presentation to P&T Subcommittee: July 17, 2012

Treatment Recommendation

The Skin Cancer DSG recommends second-line treatment of metastatic melanoma with ipilimumab for patients who meet the inclusion criteria (see below).

Treatment Intent

- Non-curative
- Improve overall survival (OS) and progression-free survival (PFS)

Rationale

In Canada, melanoma is the 8th most common cancer and the 12th most common cause of cancer. The median age of diagnosis is between 45 and 55 and it is the leading cause of cancer deaths among women between 25 and 30 years of age. The treatment of patients with metastatic melanoma remains disappointingly ineffective. The most widely used single-agent is dacarbazine and it yields response rates of 7-12% using various dose schedules. Other single-agents, and various combinations of these agents, also elicit activity in this disease, but the reported response rates are generally no more encouraging than with dacarbazine alone, and there is no impact on survival.

Ipilimumab is a fully human anti-CTLA-4 monoclonal antibody (IgG1) specific to the Cytotoxic T Lymphocyte-associated Antigen 4 (CTLA-4) expressed on T cells.1,2 CTLA-4 binds B7.1 and B7.2 and mediates a negative signal, which triggers inhibition of T cell activity.3,4 Blockade of the CTLA-4 receptor on T-cells through anti-CTLA-4 inhibits the negative signal and enhances T cell activity.5,6 Ipilimumab has demonstrated clinical benefit in the treatment of metastatic melanoma.

Clinical Benefit7 (Level Ib Evidence see Appendix I)

Support for ipilimumab in the treatment of metastatic melanoma comes from the MDX010-20 study, a randomized, double blind, phase III study. A total of 676 patients with previously treated metastatic melanoma were randomized to receive ipilimumab administered with (n = 403) or without (n = 137) a glycoprotein 100 (gp100) peptide vaccine or gp100 alone (n = 136). Patients that had stable disease for 3 months after week 12 or a confirmed partial or complete response were offered re-induction therapy with their assigned treatment regimen after disease progression occurred.
Median OS, the primary endpoint, was 10.0 months for ipilimumab plus gp100 (hazard ratio [HR] for death in comparison to gp100 alone, 0.68; \( p < 0.001 \)), 10.1 months for ipilimumab alone (HR for death in comparison to gp100 alone, 0.66; \( p = 0.003 \)), and 6.4 months for gp100 alone. Median PFS was 2.76 months for ipilimumab plus gp100, 2.86 months for ipilimumab alone and 2.76 months for gp100 alone.

**Patient Population and Selection Criteria**

**Inclusion criteria**

- Unresectable or metastatic (Stage IIIC or IV) melanoma; **AND**
- An Eastern Cooperative Oncology Group (ECOG) performance status of less than or equal to 1; **AND**
- Anticipated life expectancy of greater than 3 months; **AND**
- Received at least one line of systemic therapy for advanced melanoma; **OR**
- Intolerance to a previous line of systemic therapy for advanced melanoma

**Exclusion criteria (Initial Therapy)**

- Unstable central nervous system (CNS) metastases
- Severe immune-based reaction to ipilimumab
- Pregnant or lactating females

**Exclusion criteria (Re-Induction Therapy)**

- Less than a partial response to previous (most recent) course of ipilimumab; **AND/OR**
- Disease relapse or progression within 3 months of any previous course of ipilimumab

**CCMB Formulary Status**

1. **Formulary definition**
   - Restricted

2. **Adjudication process**
   - Complete “Restricted Drug Form-CUTANEOUS DSG” (\( J:\Pharmacy\FORMS \))
   - Approved required by: P&T Chair or Designate
   - Usual Duration: 4 doses

3. **Restrictions**
   - Administration is permitted at CCP sites under the direction of the attending Cutaneous DSG oncologist
Implementation and Safety Considerations

- Additional resources will need to be available for monitoring of side effects.
- Systemic immunosuppressants, including systemic corticosteroids, should be avoided (except for treatment of immune-mediated adverse reactions) as they could interfere with the pharmacodynamic activity of ipilimumab.
- Monitor 1 hour post-infusion.

### Treatment Regimen – SKIN – Ipilimumab

1 cycle = 3 weeks

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>CCMB Administrative Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>3 mg/kg, q3 weeks for 4 doses</td>
<td>IV in 100 mL normal saline (NS) over 90 minutes&lt;br&gt;(Final Concentration range of 1-4 mg/mL)&lt;br&gt;Attach paclitaxel tubing&lt;br&gt;Flush line with NS post-infusion</td>
</tr>
</tbody>
</table>
Clinical Monitoring and Follow-Up Recommendations

Hematology, chemistry and required tests

- At baseline and before each dose:
  - Complete blood count (CBC), liver function tests (LFTs), electrolytes and thyroid function

Clinical toxicity assessment

- Monitor for immune-related adverse events (e.g., diarrhea, bowel perforation, hypophysitis, adrenal insufficiency, other endocrinopathies, hepatic, ocular, skin or neuropathic effects, fatigue)

Assessment of treatment response

- Repeat imaging after 4 doses to assess response
- In the event of tumour progression on diagnostic imaging and in the absence of clinical deterioration, repeat imaging in 4-6 weeks is indicated
### Common or Clinically Important Adverse Events*11

(Refer to individual drug monographs for full details of adverse events)

<table>
<thead>
<tr>
<th>Immune Breakthrough Events (IBEs)</th>
<th>Immune-mediated adverse events are likely based on the mechanism of action. A correlation has been shown with clinical response and IBEs. IBEs are usually linked to drug exposure and are reversible. They are manageable with established therapies (i.e., corticosteroids). Treatment algorithms for some IBEs and criteria for dose modification due to adverse events are established.</th>
</tr>
</thead>
</table>
| **Dermatologic** | • Common IBE<sup>2,8,10</sup>  
• Mostly low-grade<sup>2</sup>  
• Rash, pruritus and vitiligo<sup>2,10</sup>  
• Resolves with symptomatic therapy or corticosteroids<sup>10</sup>  
• Frequently associated with T cell infiltrate<sup>2,8</sup> |
| **Gastro-intestinal (GI)** | • Diarrhea is a frequent IBE<sup>8,10</sup>  
• Most cases are mild or moderate (Grade 1-2) but fatalities have been reported  
• Watery to frank blood  
• Biopsy usually demonstrates inflammatory colitis  
• Management algorithm established  
• Most cases respond to either symptomatic treatment or steroids  
• Can rarely lead to GI perforation (less than 1%) requiring surgery<sup>8</sup> |
| **Endocrinopathy** | • Hypophysitis, adrenal insufficiency (including adrenal crisis), and hyper- or hypothyroidism  
• Fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, hypotension  
• Median time to onset of moderate to severe immune-mediated endocrinopathy was 11 weeks and ranged up to 19.3 weeks after initiation of ipilimumab  
• Median number of doses prior to onset was 4 doses  
• Treated with systemic steroids |
### Hepatitis

- Abnormal LFTs, jaundice, tiredness
- Moderate (Grade 2) aspartate aminotransferase (AST), alanine aminotransferase (ALT) or total bilirubin elevation treated with dose delays
- Severe, life-threatening (Grade 3-4) AST, ALT or total bilirubin treated with systemic corticosteroids

### Neuropathies

- Sensory neuropathy – unilateral or bilateral weakness, sensory alternations, paresthesia
- Moderate (not interfering with daily activities); treated with dose delay
- Severe (Grade 3-4) Interfering with daily activities, severe motor or sensory neuropathy, Guillain-Barre syndrome or myasthenia gravis; permanently discontinue ipilimumab, institute medical intervention as appropriate for management of severe neuropathy; consider initiation of systemic corticosteroids

### Ocular manifestations

- Uveitis, iritis or episcleritis – administer corticosteroid eye drops
- Permanently discontinue ipilimumab for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy

### Other immune-mediated adverse reactions

- Nephritis
- Pneumonitis
- Meningitis
- Pericarditis
- Hemolytic anemia

* See Appendix III CTCAE v.4.0
### Precautions

| Immune-related adverse reactions | Ipilimumab may cause severe and fatal immune-mediated adverse reactions, which may affect multiple organ systems including GI, hepatic, skin, nervous, endocrine or others. While most of these reactions occurred during the induction period, in some cases onset began months after the last dose. Close monitoring, prompt diagnosis and appropriate management are essential to minimize life-threatening complications. |

### Dose Modifications

| Any moderate immune-mediated adverse reactions | Withhold scheduled dose  
For patients with complete or partial resolution of adverse reactions (Grade 0-1), and who are receiving less than 7.5 mg prednisone or equivalent per day, resume ipilimumab at a dose of 3 mg/kg every 3 weeks until administration of all 4 planned doses or 16 weeks from first dose, whichever occurs earlier |

| Persistent moderate adverse reactions or inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day | Permanently discontinue ipilimumab |

| Severe or life-threatening adverse reactions | Permanently discontinue ipilimumab for the following:  
- Colitis with abdominal pain, fever, ileus, or peritoneal signs, increase in stool frequency (7 or more over baseline), stool incontinence, need for intravenous hydration for more than 24 hours, GI hemorrhage and GI perforation  
- AST or ALT greater than 5 x upper limit of normal (ULN) or total bilirubin greater than 3 x ULN  
- Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous or hemorrhagic manifestations  
- Severe motor or sensory neuropathy, Guillain-Barré syndrome or myasthenia gravis  
- Severe immune-mediated reactions involving any organ system (e.g., nephritis, pneumonitis, pancreatitis, non-infectious myocarditis)  
- Immune-mediated ocular disease that is unresponsive to topical immunosuppressive therapy |
### Drug Interactions

| Drug-drug interactions | Systemic immunosuppressants (i.e., systemic corticosteroids) – should be avoided (except for treatment of immune-mediated adverse reactions) as they could interfere with the pharmacodynamic activity of ipilimumab. |
References


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Appendix I

<table>
<thead>
<tr>
<th>Levels of Evidence</th>
<th>Description</th>
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<tbody>
<tr>
<td>Ia</td>
<td>Evidence obtained from meta-analysis of randomised controlled trials</td>
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<tr>
<td>Ib</td>
<td>Evidence obtained from at least one randomised controlled trial</td>
</tr>
<tr>
<td>IIa</td>
<td>Evidence obtained from at least one well-designed controlled study without randomisation</td>
</tr>
<tr>
<td>IIb</td>
<td>Evidence obtained from at least one other type of well-designed, quasi-experimental study</td>
</tr>
<tr>
<td>III</td>
<td>Evidence obtained from well-designed, non-experimental descriptive studies, such as comparative studies, correlation studies and case studies</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities</td>
</tr>
</tbody>
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## Appendix II

### ECOG Performance Status Scale

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
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<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease activities without restriction (Karnofsky 90-100)</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physical strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework or office work (Karnofsky 70-80)</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about greater than or equal to 50% of waking hours (Karnofsky 50-60)</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair greater than or equal to 50% of waking hours (Karnofsky 30-40)</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled, cannot carry on any self-care, totally confined to bed or chair (Karnofsky 10-20)</td>
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Appendix III

### Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

**Publish Date: 18 May 2009**

<table>
<thead>
<tr>
<th>Grades</th>
<th>Description</th>
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<tbody>
<tr>
<td>Grade 1</td>
<td>Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.</td>
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<tr>
<td>Grade 2</td>
<td>Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.</td>
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<tr>
<td>Grade 3</td>
<td>Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Life-threatening consequences; urgent intervention indicated.</td>
</tr>
<tr>
<td>Grade 5</td>
<td>Death related to AE.</td>
</tr>
</tbody>
</table>

A semi-colon indicates ‘or’ within the description of the grade.  
A single dash (-) indicates a grade is not available.  
Not all grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for grade selection.

**Grade 5**: Grade 5 (Death) is not appropriate for some AEs and therefore is not an option

**Activities of Daily Living (ADL):**
* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
** Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
