First-Line Treatment of BRAF V600 Mutated Metastatic Melanoma with Vemurafenib

(SKIN – Vemurafenib)

Skin Cancer Disease Site Group

Effective: July 2012
Required Update: June 2016
Annual Review: 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 Lead/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 vemurafenib in the first-line treatment of serine threonine protein kinase B-RAF (BRAF) V600 mutated 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.
First-Line Treatment of BRAF V600 Mutated Metastatic Melanoma with Vemurafenib

Protocol Code: SKIN – Vemurafenib

Developed by: Skin Cancer Disease Site Group

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

Treatment Recommendations

The Skin Cancer DSG recommends vemurafenib for the first-line treatment of patients with BRAF V600 mutated metastatic melanoma who meet the inclusion criteria (see below).

Treatment Intent

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

Rationale

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

Vemurafenib, a BRAF inhibitor, has demonstrated promising results as treatment for BRAF V600 mutated metastatic melanoma. The RAF oncogene is mutated in 40-50% of melanomas, and 90% of these mutations are V600E. Vemurafenib exhibits anti-tumour activity by inhibiting BRAF V600 kinase.

Clinical Benefit (Level Ib Evidence see Appendix I)

Support for vemurafenib comes from the BRIM-3 phase III randomized clinical trial comparing vemurafenib and dacarbazine treatment in patients with BRAF V600 mutated metastatic melanoma. Inclusion criteria were an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2, no active brain metastases, BRAF V600 mutated and previously untreated, unresectable stage IIIC or IV metastatic melanoma. A total of 675 patients were randomized to receive either vemurafenib 960 mg orally twice daily (n = 337) or dacarbazine 1000 mg/m² intravenously every 3 weeks (n = 338).
Complete, partial and overall response rates were 0.9%, 47.5% and 48.4%, respectively, for vemurafenib, and 0%, 5.5% and 5.5%, respectively, for dacarbazine. At 6 months, OS was 84% (95% confidence interval [CI], 78 to 89) in the vemurafenib group and 64% (95% CI, 56 to 73) in the dacarbazine group. Median OS was 12.5 months for vemurafenib and 9.5 months for dacarbazine. Median PFS was 5.3 months for vemurafenib and 1.6 months for dacarbazine. Vemurafenib also demonstrated a manageable safety profile with few drug-related discontinuations and was associated with a 63% decrease in hazard of death (p < 0.0001). Vemurafenib is a promising new therapy for patients with BRAF V600 mutated metastatic melanoma and a foundation upon which to build combination therapies.

**Patient Population and Selection Criteria**

**Inclusion criteria**
- Unresectable or metastatic (Stage IIIC or IV) melanoma; **AND**
- Confirmed BRAF V600 mutation positive disease; **AND**
- An ECOG performance status of ≤ 2

**Exclusion criteria**
- Previous systemic therapy for advanced disease
- Unstable central nervous system (CNS) metastases
- Severe hypersensitivity reaction to vemurafenib
- Pregnant or lactating females

**CCMB Formulary Status**

1. **Formulary definition**
   - Restricted
   - Covered under Home Cancer Drug Program

2. **Adjudication process**
   - Complete “Restricted Drug Form – CUTANEOUS DSG” (J:\Pharmacy\FORMS)
   - Approval required by: Skin Cancer DSG Chair or Designate
   - Usual duration of approval: 3 months
Implementation and Safety Considerations

A Health Canada Advisory from August 20, 2013 reported the risks of malignancy progression and drug rash with eosinophilia and systemic symptoms (DRESS Syndrome). Based on its mechanism of action, vemurafenib may cause progression of cancers associated with rat sarcoma (RAS) mutations and should be used with caution in patients with prior or concurrent cancers associated with a RAS mutation. Cases of DRESS syndrome have been reported and were characterized by rash, eosinophilia and systemic involvement (e.g., fever, lymphadenopathy, elevated transaminases and renal insufficiency). The typical time to onset was 7-25 days. Vemurafenib should be permanently discontinued in patients who develop DRESS syndrome.

A Health Canada Advisory from April 7, 2014 reported the risk of drug induced liver injury (DILI). Health care providers are reminded to monitor transaminases, alkaline phosphatase and bilirubin prior to starting treatment and monthly while on vemurafenib. Liver toxicities should be managed by dose reduction, dose interruption or discontinuation.

| Treatment Regimen – Vemurafenib
<table>
<thead>
<tr>
<th>1 cycle = 28 days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
</tr>
<tr>
<td>Vemurafenib</td>
</tr>
</tbody>
</table>

Clinical Monitoring and Follow-Up Recommendations

**Hematology, chemistry and required tests**

- Complete blood count (CBC), electrolytes, liver function tests (LFTs) at baseline and every 4 weeks while on treatment

**Non-hematologic monitoring**

- Blood pressure at baseline and periodically, dermatologic exam at baseline and regularly throughout treatment

**Assessment of treatment response**

- Imaging every 3 months
Common or Clinically Important Adverse Events §3,6-8
(Refer to individual drug monographs for full details of adverse events)

<table>
<thead>
<tr>
<th>Effect</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia</td>
<td>Musculoskeletal pain (56%)</td>
</tr>
<tr>
<td>Rash</td>
<td>Rash (41%) – may be severe</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Fatigue (46%)</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>Photosensitivity (41%)</td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td>Elevated LFTs (12%)</td>
</tr>
<tr>
<td>Cutaneous squamous cell carcinoma</td>
<td>Reported in up to 27% of patients and usually occurred early in the course of treatment, with a median time to the first appearance of 7 to 8 weeks</td>
</tr>
<tr>
<td>New primary melanoma</td>
<td>Reported in 2% of patients</td>
</tr>
<tr>
<td>Skin papilloma</td>
<td>Skin papilloma (21-31%, severe &lt; 1%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>Nausea, vomiting (38%)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>Alopecia (38-45%, severe &lt; 1%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3% of patients</td>
</tr>
</tbody>
</table>

* See Appendix III CTCAE v.4.0
## Precautions

<table>
<thead>
<tr>
<th>Precaution</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary malignancies</td>
<td>Cutaneous squamous cell carcinoma is reported with an incidence of 26%. New primary melanomas are reported in 2% of patients. Other RAS mutated cancers have also been reported.</td>
</tr>
<tr>
<td>QTc prolongation</td>
<td>QTc prolongation is common but severe in 2% of patients. Vemurafenib is not recommended in patients with pre-existing QTc prolongation (&gt; 500 ms) and those with QTc exceeding 500 ms during treatment.</td>
</tr>
</tbody>
</table>

## Dose Modifications

### Dose levels
- 960 mg po BID
- 720 mg po BID
- 480 mg po BID

### Grade 1 or 2 (tolerable)
- Continue with 960 mg orally, twice daily

### Grade 2 (intolerable) or Grade 3
- 1<sup>st</sup> appearance: Hold until resolved to Grade 1 and restart at 720 mg orally, twice daily
- 2<sup>nd</sup> appearance: Hold until resolved to Grade 1 and restart at 480 mg orally, twice daily
- 3<sup>rd</sup> appearance: Discontinue permanently

### Grade 4
- 1<sup>st</sup> appearance: Discontinue permanently for skin reaction, hypersensitivity or life-threatening organ toxicity. Other toxicity, discontinue or hold until resolved to Grade 1 and restart at 480 mg orally, twice daily
- 2<sup>nd</sup> appearance: Discontinue permanently
### Drug Interactions

(Refer to product monograph for complete list of possible drug interactions)

<table>
<thead>
<tr>
<th>Drug-drug interactions</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dextromethorphan</strong></td>
<td>Increases dextromethorphan area under the curve (AUC), monitor for toxicity.</td>
</tr>
<tr>
<td><strong>Midazolam</strong></td>
<td>Decreases midazolam AUC, monitor for decreased midazolam effect.</td>
</tr>
<tr>
<td><strong>Warfarin</strong></td>
<td>Increases warfarin AUC, monitor international normalized ratio (INR).</td>
</tr>
<tr>
<td><strong>Drugs associated with QTc prolongation and/or torsades de pointes</strong></td>
<td>Should be avoided.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug-food interactions</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grapefruit, starfruit, Seville oranges</strong></td>
<td>May increase plasma level of vemurafenib.</td>
</tr>
</tbody>
</table>
References


CCMB Contributors

Miss. Lisa Havixbeck, BSc (Pharm)
Mrs. Kristi Hofer, BSc (Pharm), Senior Pharmacist, Operations

Contact Physician

Dr. Ralph PW Wong, Medical Oncologist, Skin Cancer Disease Site Group

Approved By

Dr. Ralph PW Wong, Medical Oncologist
Chair, WRHA/CCMB Oncology Pharmacotherapeutic Subcommittee

Dr. Vallerie Gordon, Medical Oncologist
Lead and Advisory Panel Chair, CCMB Clinical Practice Guidelines Initiative

We gratefully acknowledge the support of CancerCare Manitoba, the CancerCare Manitoba Foundation and the Provincial Oncology Clinical Practice Guidelines Initiative.
## Appendix I

### Levels of Evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Evidence obtained from meta-analysis of randomised controlled trials</td>
</tr>
<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>
</table>

## Appendix II

### ECOG Performance Status Scale

<table>
<thead>
<tr>
<th>0</th>
<th>Fully active, able to carry on all pre-disease activities without restriction (Karnofsky 90-100)</th>
</tr>
</thead>
<tbody>
<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>
</tr>
</tbody>
</table>

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>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.</td>
</tr>
<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.
