BCCA Protocol Summary for the Treatment of BRAF V600 Mutation-Positive Unresectable or Metastatic Melanoma Using daBRAFenib

Protocol Code
USMAVDAB

Tumour Group
Skin and Melanoma

Contact Physician
Dr. Kerry Savage

ELIGIBILITY:
- BRAF V600 mutation-positive unresectable or metastatic melanoma
- ECOG 0 or 1
- If brain metastases are present, patients should be asymptomatic or stable
- A BCCA “Compassionate Access Program” request with appropriate clinical information for each patient must be approved prior to treatment
- Note: only one anti-BRA/MEK targeted treatment will be funded (daBRAFenib, trametinib, or combination)

EXCLUSIONS:
- Active central nervous metastases
- Long QT syndrome
- QT-interval longer than 480 milliseconds
- acute coronary syndrome, coronary angioplasty, placement of stents, or cardiac arrhythmia (other than sinus arrhythmias) within the previous 24 weeks
- abnormal cardiac valve morphology grade 2 or higher on ECHO cardiography, or known cardiac metastases

TESTS:
- Baseline: CBC and diff, platelets, creatinine, electrolytes, calcium, magnesium, alkaline phosphatase, ECG
- During treatment:
  - Prior to each cycle: creatinine, electrolytes, calcium, magnesium, alkaline phosphatase
  - ECG: every 4 weeks (prior to each cycle) for the first 12 weeks, then every 12 weeks and after dose modification
  - Dermatologic evaluation: at week 8 (assess for other skin cancers and new primary melanoma); monitoring beyond 8 weeks can be performed by the oncologist or dermatologist every 12 weeks

PREMEDICATIONS:
- Antiemetic protocol for low emetogenicity (see SCNAUSEA). Antiemetics are not usually required.
TREATMENT:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BCCA Administration Guideline</th>
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</thead>
<tbody>
<tr>
<td>daBRAFenib</td>
<td>150 mg BID</td>
<td>PO</td>
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</table>

- Repeat every 4 weeks (1 cycle = 4 weeks) until disease progression or unacceptable toxicity develops.

DOSE MODIFICATIONS:

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Dosing</th>
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<tbody>
<tr>
<td>First reduction</td>
<td>100 mg twice daily</td>
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<tr>
<td>Second reduction</td>
<td>75 mg twice daily</td>
</tr>
<tr>
<td>Third reduction</td>
<td>50 mg twice daily</td>
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<tr>
<td>If unable to tolerate 50 mg twice daily</td>
<td>Discontinue</td>
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</tbody>
</table>

1. Febrile drug reaction

<table>
<thead>
<tr>
<th>Fever</th>
<th>Management</th>
</tr>
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<tbody>
<tr>
<td>38.5 to 40°C</td>
<td>Hold until fever resolves, then resume at same or reduced dose level</td>
</tr>
<tr>
<td>Greater than 40°C or any fever with complications due to rigors, hypotension, dehydration or renal failure</td>
<td>Hold until toxicity is grade 0-1, then resume at one lower dose level</td>
</tr>
</tbody>
</table>

CAUTION:

1. **Non-infectious fever**: can occur with or without severe rigors or chills, dehydration, hypotension or renal failure.
2. **Secondary malignancies**: include cutaneous squamous cell carcinoma (CuSCC), new primary melanoma and malignancies associated with RAS mutations (colorectal and pancreatic adenocarcinoma). CuSCC is managed with simple excision and dose modification or interruption is not recommended.
3. **QT prolongation**: has been associated with daBRAFenib and it should be used with caution in patients at increased risk of torsade de pointes.
4. **Hyperglycemia**: may occur and patients with diabetes or hyperglycemia should be monitored closely.
5. **Pancreatitis**: has been reported in <1% of patients. Unexplained abdominal pain should be promptly investigated to include measurement of serum amylase and lipase.
6. **Uveitis**: including iritis was observed in 1% of patients. Monitor patients for visual signs and symptoms (such as change in vision, photophobia, and eye pain) during therapy.
7. **Drug Interaction**:
   - Concomitant use of QT-prolonging medications should be avoided if possible.
- Caution should be exercised when used with medications predominantly metabolized by CYP3A4.

8. **Renal failure**: is reported in patients on dabrafenib monotherapy and may be associated with pyrexia and/or dehydration. Monitor serum creatinine and other evidence of renal function during treatment and in events of severe pyrexia.

Call Dr. Kerry Savage or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

Date activated: 1 Dec 2014

Date revised: 1 Jul 2017 (Test and precautions updated)

**REFERENCES:**