CADTH

CADTH REIMBURSEMENT REVIEW

Clinician Input

encorafenib and binimetinib (Braftovi and Mektovi)

Pfizer Canada ULC

Indication: Braftovi (encorafenib): In combination with binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation, as detected by a validated test. Mektovi (binimetinib): In combination with encorafenib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation, as detected by a validated test.

January 15, 2021

CADTH Drug Reimbursement Review
Clinician Group Input Template

CADTH Project Number	PC0232-000
Generic Drug Name (Brand Name)	**encorafenib and binimetinib (Braftovi and Mektovi) – Pfizer Canada**
Indication	**Braftovi (encorafenib): In combination with binimetinib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation. Mektovi (binimetinib): In combination with encorafenib, for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation.**
Name of the Clinician Group	**Ontario Health (Cancer Care Ontario) Skin Cancer Drug Advisory Committee**
Author of the Submission	Dr. Frances Wright, Dr. Teresa Petrella, Dr. Tara Baetz, Dr. Elaine McWhirter, Dr. Marcus Butler
Contact information	Name: Dr. Frances Wright Title: Surgeon/Ontario Cancer Lead (OH-CCO) Email: [redacted] Phone:

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

OH-CCO's Drug Advisory Committees provide timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs (PDRP) and the Systemic Treatment Program.

2. Information Gathering

Please describe how you gathered the information included in the submission.

Via emails and teleconference meeting.

3. Current treatments

3.1. Describe the current treatment paradigm for the disease

Focus on the Canadian context.

Please include drug and non-drug treatments.

Drugs without Health Canada approval for use in the management of the indication of interest may be relevant if they are routinely used in Canadian clinical practice. Are such treatments supported by clinical practice guidelines?

Treatments available through special access programs are relevant.

Do current treatments modify the underlying disease mechanism? Target symptoms?

Response:

Per current SOC – combinations: dabrafenib-trimetinib (D+T), cobimetinib-vemurafenib; vemurafenib is rarely used

4. Treatment goals

4.1. What are the most important goals that an ideal treatment would address?

Examples: Prolong life, delay disease progression, improve lung function, prevent the need for organ transplant, prevent infection or transmission of disease, reduce loss of cognition, reduce the severity of symptoms, minimize adverse effects, improve health-related quality of life, increase the ability to maintain employment, maintain independence, reduce burden on caregivers.

Response:

For Stage IV patients – prolong life

For Stage III-IV patients – improve survival

Improve health-related QoL

5. Treatment gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

Examples:

- *Not all patients respond to available treatments*
- *Patients become refractory to current treatment options*
- *No treatments are available to reverse the course of disease*
- *No treatments are available to address key outcomes*
- *Treatments are needed that are better tolerated*
- *Treatment are needed to improve compliance*

- *Formulations are needed to improve convenience*

Response:

Unmet need –

- To improve compliance (e.g., pyrexia is a common adverse event with D+T, which affects patient's compliance with treatment)
- QoL
- Need therapy that are better tolerated (e.g., less photosensitivity reaction with E+B, less discontinuation due to treatment-related toxicities)

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

Would these patients be considered a subpopulation or niche population?

Describe characteristics of this patient population.

Would the drug under review address the unmet need in this patient population?

Response:

Patients unable to tolerate current SOC

- Prescribers need to be able to switch patients to another combination (i.e., additional treatment options should be available for treatment-related toxicities management)
- If this has less treatment-related toxicities, may be preferentially prescribed
- Reduced toxicities also means less ER/clinic visits

6. Place in therapy

6.1. How would the drug under review fit into the current treatment paradigm?

Is there a mechanism of action that would complement other available treatments, and would it be added to other treatments?

Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy?

Would the drug under review be used as a first-line treatment, in combination with other treatments, or as a later (or last) line of treatment?

Is the drug under review expected to cause a shift in the current treatment paradigm?

Response:

E+B can potentially replace current SOC

E+B would provide an additional treatment option for patients unable to tolerate current SOC.

E+B has a different toxicity profile than current SOC. Prescribers need to be able to switch between agents for toxicity management (able to switch from E+B to D+T and vice versa).

6.2. Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

If so, please describe which treatments should be tried, in what order, and include a brief rationale.

Response:

Clinicians would like to have the flexibility to switch between different combination agents when toxicities occur.

6.3. How would this drug affect the sequencing of therapies for the target condition?

If appropriate for this condition, please indicate which treatments would be given after the therapy has failed and specify whether this is a significant departure from the sequence employed in current practice.

Would there be opportunity to treat patients with this same drug in a subsequent line of therapy? If so, according to what parameters?

Response:

E+B would be another treatment option in addition to current SOC for BRAF V600m melanoma patients.

6.4. Which patients would be best suited for treatment with the drug under review?

Which patients are most likely to respond to treatment with the drug under review?

Which patients are most in need of an intervention?

Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)?

Response:

Patients with unresectable Stage III or Stage IV BRAF v600m melanoma, including patients previously treated with immunotherapy – these patients were included in the COLUMBUS study.

6.5. How would patients best suited for treatment with the drug under review be identified?

Examples: *Clinician examination or judgement, laboratory tests (specify), diagnostic tools (specify)*

Is the condition challenging to diagnose in routine clinical practice?

Are there any issues related to diagnosis? (e.g., tests may not be widely available, tests may be available at a cost, uncertainty in testing, unclear whether a scale is accurate or the scale may be subjective, variability in expert opinion.)

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)?

Should patients who are pre-symptomatic be treated considering the mechanism of action of the drug under review?

Response:

BRAF molecular testing – this is currently SOC

Treatment decision also based on clinical judgement.

6.6. Which patients would be least suitable for treatment with the drug under review?

Response:

Melanoma patients without BRAF mutations

6.7. Is it possible to identify those patients who are most likely to exhibit a response to treatment with the drug under review?

If so, how would these patients be identified?

Response:

Yes – BRAF mutation testing is routinely done in melanoma patients

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

Are the outcomes used in clinical practice aligned with the outcomes typically used in clinical trials?

Response:

Clinical assessment, imaging, bloodwork, toxicities assessment

6.9. What would be considered a clinically meaningful response to treatment?

Examples:

- *Reduction in the frequency or severity of symptoms (provide specifics regarding changes in frequency, severity, and so forth)*
- *Attainment of major motor milestones*
- *Ability to perform activities of daily living*
- *Improvement in symptoms*
- *Stabilization (no deterioration) of symptoms*

Consider the magnitude of the response to treatment. Is this likely to vary across physicians?

Response:

All of the above except *attainment of major motor milestones*

6.10. How often should treatment response be assessed?

Response:

Clinical assessment – every 4-6 weeks

Imaging – every 2 to 3 months

Bloodwork – every 4-6 weeks

6.11. What factors should be considered when deciding to discontinue treatment?

Examples:

- *Disease progression (specify; e.g., loss of lower limb mobility)*
- *Certain adverse events occur (specify type, frequency, and severity)*
- *Additional treatment becomes necessary (specify)*

Response:

Disease progression and treatment tolerability

6.12. What settings are appropriate for treatment with the drug under review?

Examples: Community setting, hospital (outpatient clinic), specialty clinic

Response:

Take home cancer drug – used in community setting

6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?

If so, which specialties would be relevant?

Response:

NA

7. Additional information

7.1. Is there any additional information you feel is pertinent to this review?

Response:

A significant proportion of patients are unable to tolerate current funded treatment such as D-T due to toxicities.

8. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may

contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   OH-CCO provided secretariat support to the DAC in completing this submission.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician that contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Clinician Information	
Name	*Dr. Frances Wright*
Position	*Surgeon – Sunnybrook Health Sciences Centre*
Date	*15-Jan-2021*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 2

Clinician Information	
Name	*Dr. Teresa Petrella*
Position	*Medical oncologist*
Date	*15-Jan-2021*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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Pfizer	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 3

Clinician Information	
Name	*Dr. Tara Baetz*
Position	*Medical oncologist*
Date	*15-Jan-2021*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration				
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Pfizer	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 4

Clinician Information	
Name	*Dr. Elaine McWhirter*
Position	*Medical Oncologist*
Date	*15-Jan-2021*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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Pfizer	☒	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

Declaration for Clinician 5

Clinician Information	
Name	*Dr. Marcus Butler*
Position	*Medical oncologist*
Date	*15-Jan-2021*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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CADTH

CADTH Drug Reimbursement Review
Clinician Group Input Template

CADTH Project Number	
Generic Drug Name (Brand Name)	**Encorafenib and binimetinib (braftovi and mektovi)**
Indication	**Advanced Melanoma**
Name of the Clinician Group	**Save Your Skin Foundation Medical Advisory Group and Supporters**
Author of the Submission	**Kathy Barnard**
Contact information	Name: Kathy Barnard Title: Founder Email: [redacted] Phone: [redacted]

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

Save Your Skin Foundation Medical Advisory Group and Supporters

www.saveyourskin.ca

2. Information Gathering

Please describe how you gathered the information included in the submission.

Clinician input template distributed by email correspondence

3. Current treatments

3.1. Describe the current treatment paradigm for the disease

Response:

Dabrafenib/trametinib for braf mutant disease with normal LDH and <3 organs with metastases, or if ineligible for immunotherapy. Immunotherapy otherwise or if patient preference given differing toxicity profiles. Single agent PD1 immunotherapy, or ipilimumab/nivolumab if patients: prefer aggressive approach (and willing to risk greater toxicity) for 10% better longer term outcomes, or if brain metastases. Goals either way are for long term disease control and possible cure in a significant minority.

4. Treatment goals

4.1. What are the most important goals that an ideal treatment would address?

Response:

Similar or better outcomes as with dabrafenib/trametinib, for same target population but with lesser (and different) difficult toxicities. Thus, improved survival, quality of life, response rates.

5. Treatment gaps (unmet needs)

5.1. Considering the treatment goals in Section 4, please describe goals (needs) that are not being met by currently available treatments.

Response:

Given the long term nature of therapy, the VERY frequent toxicities of dabrafenib/trametinib are very challenging to treat and difficult for patients (mostly high grade fevers/chills, and rarely ocular/cardiac toxicity). We would prefer agents with similar or better efficacy but without those toxicities; this proposed treatment would be safer and our doublet of choice for most braf mutated cases.

5.2. Which patients have the greatest unmet need for an intervention such as the drug under review?

Response:

The need is mostly met but the toxicities of current therapies can be daunting. We would expect lesser toxicity at the same price with this newer treatment. There would be an unmet need for patients who might not be compliant with reporting/monitoring and management of toxicities of current treatments (dabrafenib/trametinib). This new treatment would apply to the entire current dab/tram population (new incident cases, we would not usually switch patients unless their toxicities were unmanageable).

6. Place in therapy

6.1. How would the drug under review fit into the current treatment paradigm?

Response:

Switch from current dabrafenib/trametinib if refractory fevers or other non ocular toxicities noted

Otherwise, this would replace our first or 2nd line use of dabrafenib/trametinib.

6.2. Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with the drug under review. Please provide a rationale from your perspective.

Response:

Toxicities of such treatments are best avoided altogether if possible so we would not recommend the use of dabrafenib/trametinib or vemurafenib/cobimetinib "first". We already use immunotherapy "first" in appropriate patients and this new option would not change that.

6.3. How would this drug affect the sequencing of therapies for the target condition?

Response:

We would sequence with immunotherapies exactly as we do now, either before encorafenib/binimetinib (1st line enco/bini) or after (as 2nd line), replacing our previous niche for dabrafenib/trametinib

6.4. Which patients would be best suited for treatment with the drug under review?

Response:

All patients now considered for dabrafenib/trametinib therapy. BRAF V600 mutated melanoma either as first line or 2nd line therapy (before or after immunotherapy)

6.5. How would patients best suited for treatment with the drug under review be identified?

Response:

Precisely as they are now for dabrafenib/trametinib patient selection. BRAF V600 mutated melanoma (advanced or unresectable). Ideally, normal LDH and < 3 organs with metastases, UNLESS pt not felt to be candidate for immunotherapy. ECOG PS should not be limited to 0-1 since pts can benefit extremely rapidly from cancer symptoms even if "sicker" (because of disease symptoms).

6.6. Which patients would be least suitable for treatment with the drug under review?

Response:

Cases without V600 mutations. Responses have been reported in the literature for V600 mutations other than "E" or "K" mutations and despite the lack of level I evidence for those variants, Rx should be permitted for those cases.

6.7. Is it possible to identify those patients who are most likely to exhibit a response to treatment with the drug under review?

Response:

Precisely as they are now for dabrafenib/trametinib patient selection. BRAF V600 mutated melanoma (advanced or unresectable). Ideally, normal LDH and < 3 organs with metastases, UNLESS pt not felt to

be candidate for immunotherapy. ECOG PS should not be limited to 0-1 since pts can benefit extremely rapidly from cancer symptoms even if "sicker" (because of disease symptoms).

6.8. What outcomes are used to determine whether a patient is responding to treatment in clinical practice?

Response:

Measureable tumour response by clinical and radiographic assessments.

6.9. What would be considered a clinically meaningful response to treatment?

Response:

Improvement of symptoms and stable disease or measureable response of lesions by examination or imaging

6.10. How often should treatment response be assessed?

Response:

Clinically every 4 weeks initially then as required, sometimes every 3 months. Radiographically at least every 3 months.

6.11. What factors should be considered when deciding to discontinue treatment?

Response:

True progression by RECIST criteria, or high grade or refractory toxicities (as per the clinical trial protocol)

6.12. What settings are appropriate for treatment with the drug under review?

Response:

Any setting if under the care of a licensed medical oncologist.

6.13. For non-oncology drugs, is a specialist required to diagnose, treat, and monitor patients who might receive the drug under review?

Response:

Not applicable

7. Additional information

7.1. Is there any additional information you feel is pertinent to this review?

Response:

The clinical benefit in terms of better toxicity profile is very significant and this would likely be our agent(s) of choice.

8. Conflict of Interest Declarations

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Declaration for Clinician 1

Clinician Information	
Name	*Dr Sandeep Sehdev*
Position	*Medical oncologist*
Date	*18-12-2020*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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Novartis	☒	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐