BC Cancer Protocol Summary for the Treatment of BRAF V600E - Mutated Metastatic Colorectal Cancer using PANitumumab and Encorafenib

***Protocol Code*:**	*UGIAVPANEN*
***Tumour Group*:**	*Gastrointestinal*
***Contact Physician*:**	*GI Systemic Therapy*

ELIGIBILITY:

Patients must have:
- Metastatic colorectal cancer,
- BRAF V600E mutation (tested on primary or metastatic tumor),
- Progression after one or more lines of systemic therapy in the metastatic setting, and
- BC Cancer "Compassionate Access Program" request approval prior to treatment

Patients should have:
- Adequate hematologic, hepatic, and renal function
- Life expectancy of 3 months or more

Note:
- Patients who are currently receiving GIAVPANI (started prior to 1 Dec 2022) prior to identification of BRAF V600E mutation may switch to UGIAVPANEN if all other eligibility criteria are met
- Patients who previously received GIFFIRPAN or GIFFOXPAN prior to identification of BRAF V600E mutation may receive UGIAVPANEN if all other eligibility criteria are met

EXCLUSIONS:

Patients must not have:
- Symptomatic brain metastases
- Symptomatic interstitial pneumonitis or pulmonary fibrosis

CAUTIONS:

- Patients with baseline greater than 3 loose BM per day (in patients without colostomy or ileostomy)
- Uncontrolled electrolyte abnormalities (e.g., hypokalemia, hypomagnesemia, hypocalcemia)
- Uncontrolled hypertension

TESTS:

- Baseline: CBC & Diff, creatinine, ALT, alkaline phosphatase, total bilirubin, albumin, sodium, potassium, blood pressure
- Baseline if clinically indicated: CEA, CA19-9, GGT, magnesium, calcium, ECG, dermatologic evaluation, ophthalmology consult
- Prior to each cycle: CBC & Diff, creatinine, total bilirubin, ALT, magnesium
- If clinically indicated: CEA, CA19-9, alkaline phosphatase, albumin, calcium, GGT, sodium, potassium, ECG, ophthalmology consult
- Consider dermatologic evaluation at week 8 (assess for secondary malignancies, including cutaneous squamous cell carcinoma, new primary melanoma, and noncutaneous malignancies); monitoring beyond 8 weeks can be performed by the oncologist or dermatologist every 12 weeks

PREMEDICATIONS:

- Antiemetic protocol for low emetogenicity (see SCNAUSEA).
- Consider preemptive therapy for PANitumumab-induced dermatologic toxicity (see below).

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
PANitumumab	6 mg/kg on Day 1	IV in 100 mL NS over 1 hour using a 0.2 micron in-line filter If tolerated, administer over 30 minutes in subsequent cycles.
encorafenib	300 mg daily continuously	PO

Repeat every 2 weeks until disease progression or unacceptable toxicity.

DOSE MODIFICATIONS:

If either encorafenib or PANitumumab is discontinued, the other medication should also be discontinued.

Dose Levels for encorafenib:

Dose Level	Encorafenib Dose
100%	300 mg
First Reduction	225 mg
Second Reduction	150 mg Discontinue if unable to tolerate

1. Dermatologic toxicity:
PANitumumab

As a class, EGFR Inhibitors are characterized by cutaneous adverse effects, most commonly a papulopustular reaction involving the skin of the face and upper torso. This can leave the skin vulnerable to bacterial overgrowth and serious infection which may require aggressive interventions.

A well characterized clinical course has been identified. Within week 1 of treatment patients experience sensory disturbance with erythema and edema. During weeks 1 to 3 (median time of 14 days after start of therapy) the papulopustular eruption manifests, followed by crusting at week 4. Despite effective treatment for rash, erythema and dry skin may persist in the areas previously affected during weeks 4 to 6. Most patients exhibit some degree of partial improvement during therapy and the rash generally resolves completely and without scarring following cessation of therapy (median time of 84 days after the last dose.)

Consideration should be given to preemptive or reactive treatment of EGFR Inhibitor skin toxicity. **Preemptive therapy** includes doxycycline (or minocycline) 100 mg PO BID and clindamycin 2%/hydrocortisone 1% skin lotion at cycle 1 for the first six weeks. Preemptive therapy was compared to reactive management and resulted in decreased grade ≥ 2 skin toxicity and decreased impairment in quality of life.

Reactive management is summarized below.

Grade	Rash (definitions adapted from CTCAE and Melosky et al.)
1	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness OR Macular or papular eruption or erythema with no associated symptoms
2	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL; papules and/or pustules covering > 30% BSA with or without mild symptoms OR Macular or papular eruption or erythema with pruritus or other symptoms that are tolerable or interfere with daily life
3	Papules and/or pustules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated OR Severe, generalised erythroderma or macular, papular or vesicular eruption
4	Life-threatening consequences; papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated OR Generalized exfoliative, ulcerative or blistering skin toxicity

Recommended Management for Rash

Grade	Occur-ence	PANitumumab Dose	Encorafenib Dose	Other Management
1	Any	Maintain dose level	Maintain dose level	Consider clindamycin 2% and hydrocortisone 1% in a lotion to be applied topically BID as needed.
2	First	Maintain dose level	Continue treatment at current dose. If no improvement within 2 weeks: delay encorafenib until improved to less than or equal to Grade 1. 1st occurrence: Resume encorafenib at previous dose	Consider clindamycin 2% and hydrocortisone 1% in a lotion to be applied topically BID as needed and minocycline 100 mg PO BID for 1 to 2 weeks or longer as needed.
	Second		Recurrent Grade 2: Restart encorafenib at reduced dose	
3	First	Withhold infusion for 2 to 4 weeks. When improvement to Grade 2 or less, resume at: 1st occurrence: Resume at 100% of previous dose	Delay encorafenib until less than or equal to Grade 1. 1st occurrence: Resume encorafenib at previous dose	Continue treatment with clindamycin 2% and hydrocortisone 1% in a lotion to be applied topically BID as needed and minocycline 100 mg PO BID for 1 to 2 weeks or longer as needed
	Second	2nd occurrence: Resume at 80% of previous dose	Recurrent Grade 3: Restart encorafenib at reduced dose	
	Third	3rd occurrence: Resume at 60 % of previous dose		
4	Any	Discontinue PANitumumab	Discontinue encorafenib	Clindamycin 2% and hydrocortisone 1% in a lotion to be applied topically BID as needed and minocycline 100 mg PO BID for 1 to 2 weeks or longer as needed Consider prednisone 0.5 mg/kg PO daily. Upon improvement, taper prednisone

The prevention or management of EGFR inhibitor related skin toxicities not only improves or maintains patient quality of life, it prevents dose reduction or discontinuation of potentially effective therapy.

It is recommended that patients wear sunscreen and a hat and limit sun exposure as sunlight can exacerbate any skin reactions.

Activities and skin care products that dry the skin should be avoided such as long, hot showers, alcohol-based or perfumed skin care products. Greasy ointments should be avoided. Frequent moisturizing with alcohol-free emollient creams is recommended.

This rash is distinct from acne vulgaris and therefore, other topical acne treatments should not be applied.

Other less frequent manifestations are: dry skin, pruritus, fissures, palmar-plantar rash, hyperkeratosis, telangiectasia, hyperpigmentation, and blisters.

2. Uveitis:

Severity	Encorafenib
Grade 1	Hold encorafenib until Grade 0. Resume at same dose.
Grade 2 or 3	Hold encorafenib until Grade 0 or 1. Once recovered, restart at next lower dose.
Grade 4	Permanently discontinue encorafenib

- Patients should be referred to an ophthalmologist for diagnosis and treatment. Do not refer to an optometrist.
- Do not start steroid eye drops before the ophthalmologic assessment.
- If symptoms compatible with uveitis, appropriate to contact your regional ophthalmologist on-call to request urgent assessment.

3. QT prolongation:

QTc prolongation. In milliseconds (ms)	Encorafenib
First occurrence QTc greater than 500 ms And Less than or equal to 60 ms increase from baseline	Hold encorafenib. When QTc less than or equal to 500 ms, resume at reduced dose.
Second occurrence QTc greater than 500 ms And Less than or equal to 60 ms increase from baseline	Discontinue encorafenib
Any occurrence QTc greater than 500 ms And Greater than 60 ms increase from baseline	Discontinue encorafenib

4. Hepatotoxicity during treatment:

AST or ALT elevation	Encorafenib	Dose Once Recovered
Grade 2	Continue treatment. If no improvement within 2 weeks: ▪ delay encorafenib until improved to less than or equal to Grade 1 or to baseline level	Resume encorafenib at previous dose
Grade 3	Delay encorafenib until improvement to less than or equal to Grade 1 or to baseline level	First occurrence: Restart encorafenib at reduced dose
		Recurrent Grade 3: Consider discontinuing encorafenib
Grade 4	Permanently discontinue encorafenib Or Delay encorafenib If improvement to less than or equal to Grade 1 or to baseline levels	First occurrence: Restart encorafenib at reduced dose

5. Hypomagnesemia

Serious cases may be asymptomatic and have been reported greater than 6 weeks after initiation of treatment. Symptoms include severe weakness and fatigue. Concern is cardiac arrhythmias which may be associated with hypokalemia. Magnesium levels should be monitored closely and regular infusions of Magnesium Sulfate as well as oral supplementation may be required. Monitoring of potassium and calcium may also be required.

Grade	Serum Magnesium	Management
1	0.5 mmol/L to less than LLN	Continue PANitumumab. Consider daily oral magnesium replacement
2	0.4 to less than 0.5 mmol/L	Continue PANitumumab and initiate daily oral magnesium replacement and magnesium sulfate 5 G IV in 100 mL NS over 3 hours every 2 weeks
3	0.3 to less than 0.4 mmol/L	if symptomatic - hold PANitumumab until improved to Grade 2. If asymptomatic – increase supplementation to magnesium sulfate 5G IV in 100 mL NS over 3 hours weekly
4	Less than 0.3 mmol/L	Hold PANitumumab until asymptomatic and improved to Grade 2 – increase supplementation to magnesium sulfate 5G IV in 100 mL NS over 3 hours twice weekly.

Oral preparations of magnesium may be poorly tolerated resulting in poor compliance due to potential for diarrhea. Diarrhea is dose dependent. Combination product with calcium may reduce incidence of diarrhea.

Magnesium Preparation	Elemental Magnesium content	Dosage
Magnesium complex	Each 250 mg tablet contains 250 mg	1 tablet twice daily
Magnesium glucoheptonate	Each 15ml of 100 mg/mL solution contains 76.8 mg	15 to 30 mL up to 4 times daily
Magnesium oxide	Each 420 mg tablet contains 252 mg	1 tablet twice daily
Calcium/Magnesium	Each 333/167 tablet contains 167 mg	1 tablet 3 times daily

PRECAUTIONS:

1. **PANitumumab Hypersensitivity Reactions (HSR)**: severe infusion reactions, including anaphylactic reactions, bronchospasm and hypotension have occurred with the administration of PANitumumab in approximately 1% of patients, very rarely with a fatal outcome. Late onset HSR have also occurred and it is recommended that patients be warned of this possibility.
2. **Interstitial Lung Disease:** has been observed with EGFR inhibitors. Interstitial lung disease and interstitial pneumonitis are rare (<1% for PANitumumab). Worsening of preexisting lung conditions is also reported with PANitumumab. Investigation of acute symptoms is warranted and PANitumumab should be withheld in the event of onset or worsening of respiratory symptoms. If pneumonitis or lung infiltrates are confirmed, treatment should be discontinued.
3. **Secondary Malignancies**, such as cutaneous squamous cell carcinoma (cuSCC), new primary melanoma, and non-cutaneous malignancies have been reported with encorafenib. Regular dermatologic evaluation is recommended throughout treatment and for up to 6 months following treatment discontinuation. Advise patients to promptly report any new skin lesions. Suspicious skin lesions should be excised. Permanently discontinue encorafenib for development of RAS mutation-positive non-cutaneous malignancies.
4. **Hemorrhage** has occurred in patients receiving encorafenib in combination with EGFR inhibitor. Delay treatment with encorafenib for any recurrent grade 2 or first occurrence of grade 3 or higher hemorrhage. Delay, reduce doses, or discontinue encorafenib based on the severity of event.
5. **Severe Diarrhea and Dehydration:** PANitumumab should be withheld until resolution. Acute renal failure has been observed in patients with severe diarrhea and dehydration receiving PANitumumab. In addition to the risk of diarrhea induced dehydration, patients on warfarin are at risk for an elevation in INR and an increased risk of bleeding.
6. **Ocular Toxicities** including uveitis, iritis, iridocyclitis, and retinal pigment epithelial detachment have been reported with encorafenib. PANitumumab has been associated with keratitis and corneal perforation. Contact lens use may increase risk for keratitis. Assess patient during treatment for new or worsening visual disturbances. Patients reporting new or worsening visual disturbances such as diminished central vision, blurred vision, or loss of vision should be promptly (i.e., within 24 hours) referred for ophthalmological evaluation. Refer to uveitis table, above.
7. **QT prolongation:** QTc prolongation has been observed with encorafenib; monitor ECG and electrolytes in patients with known risk factors and correct hypokalemia and/or hypomagnesemia prior to treatment, and as clinically indicated. Refer to table, above.
8. **Drug interactions**: Encorafenib is a substrate of CYP3A4. Avoid concurrent use with moderate of strong CYP3A4 inhibitors if possible. If coadministration with strong or moderate CYP3A4 inhibitors is necessary, reduce encorafenib dose. Refer to BC Cancer Drug Manual for more information.

9. **Hypertension**: Hypertension or worsening of pre-existing hypertension may occur during treatment with encorafenib. Monitor at baseline and throughout treatment

Call the GI Systemic Therapy physician at your regional cancer centre or the GI Systemic Therapy Chair Dr. Theresa Chan at (604) 930-2098 with any problems or questions regarding this treatment program.

References:

1. CADTH Reimbursement Recommendation. Encorafenib (Braftovi). Canadian Journal of Health Technologies; July,2021;1(7)
2. Kopetz S, Grothey A, Yaeger R, et al. Encorafenib, Binimetinib, and Cetuximab in *BRAF* V600E-Mutated Colorectal Cancer. N Engl J Med. 2019 Oct 24;381(17):1632-1643.
3. Melosky B, Burkes R, Rayson D, et al. Management of skin rash during EGFR-targeted monoclonal antibody treatment for gastrointestinal malignancies: Canadian recommendations. Curr Oncol. 2009 Jan;16(1):16-26.