BC Cancer Protocol Summary for Palliative Third Line Treatment of Metastatic Colorectal Cancer Using PANitumumab

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

ELIGIBILITY

Patients must have:

- Metastatic colorectal adenocarcinoma,
- Previous treatment with fluorouracil or capecitabine, irinotecan and oxaliplatin,
- Wild type RAS (tested on primary or metastatic tumour), and
- Wild type BRAF (tested on primary or metastatic tumour)

Patients should have:

- ECOG performance status 0 to 2
- Adequate marrow reserve

Note: patients may receive one of GIAVPANI or GIAVCETIR – not both.

EXCLUSIONS

Patients must not have:

- Mutant RAS or mutant BRAF tumours
- Symptomatic brain metastases, interstitial pneumonitis or pulmonary fibrosis

TESTS:

- Baseline: CBC & Diff, creatinine, ALT, alkaline phosphatase, total bilirubin, albumin, sodium, potassium
- Baseline if clinically indicated: CEA, CA19-9, GGT, magnesium, calcium, ECG
- 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

PREMEDICATIONS:

- Antiemetic protocol for low emetogenicity (see SCNAUSEA). Antiemetics are not usually required.
- Consider preemptive therapy for PANitumumab-induced dermatologic toxicity (see below).

TREATMENT:

A cycle equals -

Drug	Dose	BC Cancer Administration Guideline
PANitumumab	6 mg/kg	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.

Repeat every 2 weeks until either toxicity or disease progression.

DOSE MODIFICATIONS:

1. Dermatologic toxicities:

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	Toxicity (adapted from CTCAE and Melosky et al.)	PANitumumab dose
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	Maintain dose level Consider clindamycin 2% and hydrocortisone 1% in a lotion to be applied topically BID as needed.
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	Maintain dose level 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.
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	Withhold infusion for 2 to 4 weeks: ▪ When improvement to Grade 2 or less, resume at: 1st occurrence: Resume at 100% of previous dose 2nd occurrence: Resume at 80% of previous dose 3rd occurrence: Resume at 60 % of 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.
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	Discontinue treatment.

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. **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 – 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. **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.

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. Van Cutsem E, Peeters M, Siena S, et al: Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol 2007;25:1658-64.
2. Fakih, Marwan: Management of anti-EGFR targeting monocolonal antibody-induced hypomagnesemia. Oncology 2008; 22:74-76.
3. Melosky, B, Burkes, R, Rayson, D, Alcindor, T, Shear, N and Lacouture M: Management of skin rash during EGFR-targeted monoclonal antibody treatment for gastrointestinal malignancies: Canadian recommendations. Curr Oncol 2009; 16:14-24.