BC Cancer Protocol Summary for the Treatment of Locally Advanced or Metastatic Cutaneous Squamous Cell Carcinoma using Cetuximab

Protocol Code	*SMAVCET*
Tumour Group	*Skin and Melanoma*
Contact Physician	*Dr. Vanessa Bernstein*

ELIGIBILITY:

Patients must have:
- Metastatic (nodal or distant) or locally advanced cutaneous squamous cell carcinoma (CSCC),
- No further options for surgery and radiotherapy, or have contraindications to these therapies, or for whom these therapies would be debilitating or disfiguring, and
- Ineligibility for first-line cemiplimab.

Patients should have:
- Good performance status

Note patients are allowed:
- Retreatment if they did not previously progress while on cetuximab therapy, or
- Switching from chemotherapy to cetuximab or using cetuximab after chemotherapy

EXCLUSIONS:

Patients must not have:
- Previous treatment with cemiplimab

TESTS:

- Baseline: CBC and differential, platelets, magnesium, calcium, albumin, sodium, potassium, creatinine, appropriate imaging
- Prior to each cycle: CBC and differential, platelets, magnesium, calcium, albumin, sodium, potassium, creatinine
- First follow up visit post-treatment: CBC and differential, platelets, magnesium, calcium, albumin, sodium, potassium, creatinine

PREMEDICATIONS:

- diphenhydrAMINE 50 mg PO 30 to 60 minutes prior to EACH cetuximab dose

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
Cycle 1 : cetuximab	400 mg/m^2	IV over 2 hours (use 0.2 micron in-line filter) (maximum infusion rate 10 mg/min) Observe for 1 hour post-infusion*
Cycle 2 and onwards: cetuximab	250 mg/m^2	IV over 1 hour (use 0.2 micron in-line filter) (maximum infusion rate 10 mg/min) Observe for 1 hour post-infusion*

* 1 hour observation period following end of 1st and 2nd cetuximab infusions. Obtain vital signs pre-infusion, halfway through infusion, and 1 hour post-infusion. May discontinue observation period if no infusion reactions occur for 2 consecutive doses.

- Flush cetuximab line post infusion with Normal Saline (0.9% Sodium Chloride)
- 1 cycle = 1 week
- Repeat once weekly until disease progression or unacceptable toxicity.

VITAL SIGNS: Temperature, Pulse, Respiration, and Blood Pressure **pre**-cetuximab infusion, **halfway** through infusion and **one hour post** infusion. Patients are to be observed visually for the first 15 minutes of cetuximab infusion

If patients do not have a significant reaction for 2 consecutive doses of cetuximab, patients do not need vital signs performed one hour post infusion.

DOSE MODIFICATIONS:

1. Dermatologic Toxicity:

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. 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	Cetuximab dose
1	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	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 + minocycline 100 mg PO BID for 1 to 2 weeks or longer as needed.
3	Severe, generalised erythroderma or macular, papular or vesicular eruption	Withhold infusion for 2 to 4 weeks: ▪ When improvement to Grade 2 or less, continue at 50% of original dose; If toxicities do not worsen, escalate by 25% increments of original dose until recommended starting dose is reached ▪ If no improvement, discontinue cetuximab Continue treatment with clindamycin 2% and hydrocortisone 1% in a lotion to be applied topically BID as needed + minocycline 100 mg PO BID for 1 to 2 weeks or longer as needed.
4	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 during treatment and for 2 months following the last dose of cetuximab.

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, paronychia and blisters.

2. Allergic/Hypersensitivity Reactions:

Grade	Description (NCI-CTC)	Management	Cetuximab Dose
1	Transient rash, drug fever lower than 38^{o} C	Decrease infusion rate by 50%	Maintain 50% reduction in infusion rate
2	Urticaria, drug fever greater than 38^{o} C and/or asymptomatic bronchospasm	Stop cetuximab infusion. Administer bronchodilators. Resume infusion at 50% once reaction has resolved or decreased to Grade 1	1st occurrence – maintain 50% reduction in rate. At second occurrence of more than or equal to grade 2 despite slower rate, discontinue.
3	Symptomatic bronchospasm requiring parenteral medication with or without urticaria; allergy-related edema/angioedema	Stop cetuximab and disconnect infusion tubing. Administer epinephrine, bronchodilators, antihistamines, glucocorticoids, iv fluids, vasopressors and oxygen as indicated.	Discontinue cetuximab
4	Anaphylaxis	same as for Grade 3	

3. Hypomagnesemia:

Dose Modifications and Management of Cetuximab Hypomagnesemia
Serious cases may be symptomless 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

Consider oral supplementation as tolerated for all grades.

Grade	Serum Magnesium	Management
1	0.5 mmol/L to LLN	Continue cetuximab. Consider daily oral magnesium replacement. If unable to supplement orally, magnesium sulfate 2 g IV.
2	0.4 to 0.49 mmol/L	Continue cetuximab and initiate daily oral magnesium replacement (if able to supplement orally) and magnesium sulfate 5 G IV in 100 mL NS over 3 hours every 2 weeks.
3	0.3 to 0.39 mmol/L	If symptomatic - hold cetuximab until improved to Grade 2. If asymptomatic – increase supplementation to magnesium sulfate 5 G IV in 100 mL NS over 3 hours weekly
4	Less than 0.3 mmol/L	Hold cetuximab until asymptomatic and improved to Grade 2 – increase supplementation to magnesium sulfate 5 G 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 complex	Each 250 mg tablet contains 250 mg	1 tablet twice daily
Magnesium glucoheptonate	Each 15 ml 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:

Hypersensitivity: Cetuximab infusion associated symptoms, usually occur with the first dose (90%) but may be associated with subsequent doses. Grade 1 or 2 infusion reactions occur in up to 19% of patients receiving cetuximab alone. These may consist of chills, fever and dyspnoea. Grade 3 or 4 reactions usually occur within minutes of the first infusion and are characterized by bronchospasm, urticaria and hypotension. Mild infusion reactions are managed by slowing the infusion and antihistamine therapy.

Severe **infusion reactions** occur in 3% of patients and are rarely (fewer than 1 in 1000) fatal. They are managed by immediate and permanent discontinuation of the infusion and appropriate emergency medical therapy with adrenaline, corticosteroids, IV antihistamines, bronchodilators and oxygen. Refer to BC Cancer Protocol Summary for Management of Infusion-Related Reactions to Systemic Therapy Agents (SCDRUGRX).

Interstitial lung disease has been reported with EGFR inhibitors. Treatment should be withheld if patients with pre-existing lung disease experience worsening respiratory symptoms. If pneumonitis or lung infiltrates are confirmed, treatment should be discontinued.

Call Dr. Vanessa Bernstein or tumour group delegate at 250-519-5570 or 1-800-670-3322 with any problems or questions regarding this treatment program.

References:

1. Maubec E, Petrow P, Scheer-Senyarich I, et al. Phase II study of cetuximab as first-line single-drug therapy in patients with unresectable squamous cell carcinoma of the skin. J Clin Oncol. 2011 Sep 1;29(25):3419-26.
2. Reigneau M, Robert C, Routier E, et al. Efficacy of neoadjuvant cetuximab alone or with platinum salt for the treatment of unresectable advanced nonmetastatic cutaneous squamous cell carcinomas. Br J Dermatol. 2015 Aug;173(2):527-34.
3. Foote MC, McGrath M, Guminski A, et al. Phase II study of single-agent panitumumab in patients with incurable cutaneous squamous cell carcinoma. Ann Oncol. 2014 Oct;25(10):2047-2052.
4. Eli Lilly Canada Inc. ERBITUX® product monograph. Toronto, Ontario; 10 Jan 2018.