# BC Cancer Protocol Summary for Combined Cetuximab and Radiation Treatment for Locally Advanced Squamous Cell Carcinoma of the Head and Neck

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| ***Protocol Code*** | *HNLACETRT* |
| ***Tumour Group*** | *Head and Neck* |
| ***Contact Physician*** | *Dr. Cheryl Ho* |
| | *Dr. John Wu* |

**ELIGIBILITY:**

- Stage III and IV squamous cell carcinoma of the hypopharynx, oropharynx, oral cavity, supraglottic or larynx including head and neck primary unknown with cervical lymphadenopathy
- ECOG Performance status 0-2
- Suitable for radical irradiation
- Not eligible for concurrent chemotherapy with CISplatin

**TESTS:**

- Baseline: CBC & Diff, magnesium, calcium, albumin, sodium, potassium, phosphate, creatinine
- Baseline (optional results do not have to be available to proceed with treatment) HBsAg, HBcoreAb, HBsAb
- Baseline, if clinically indicated: ALT, HB viral load
- Prior to each treatment: CBC & Diff, magnesium, calcium, albumin, sodium, potassium, phosphate, creatinine
- First follow up visit post-treatment: CBC & Diff, magnesium, calcium, albumin, sodium, potassium, phosphate, creatinine
- If clinically indicated: ALT, HBV viral load

**PREMEDICATIONS:**

- diphenhydrAMINE 50 mg PO 30 to 60 minutes prior to cetuximab
- If required: hydrocortisone 100mg IV 30-60 minutes prior to cetuximab

## TREATMENT:

| Drug | Dose | BC Cancer Administration Guideline |
|---|---|---|
| cetuximab (first dose) | 400 mg/m$^2$ (loading dose) on day **minus** 7 from radiation start date | IV over 2 hours (use 0.2 micron in-line filter) (maximum infusion rate 10 mg/min) Observe for 1 hour post-infusion** |
| | ***THEN*** | |
| cetuximab (subsequent dose) | 250 mg/m$^2$ on days 1, 8, 15, 22, 29 and 36 with concurrent radiation* | IV over 1 hour (use 0.2 micron in-line filter) (maximum infusion rate 10 mg/min) Observe for 1 hour post-infusion** |

* cetuximab may be given on:

- days 1, 8, 15, 22 and 29 if radiation is given over 5 weeks, or
- days 1, 8, 15, 22, 29, 36 and 43 if radiation is given over 7 weeks

** 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 with normal saline at end of infusion.

**VITAL SIGNS:** Temperature, Pulse, Respiration, 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
Flush cetuximab line post infusion with Normal Saline (0.9% Sodium Chloride)

IF patients have a significant infusion reaction with their first dose of cetuximab a reasonable period of observation should be undertaken before initiation of radiotherapy with subsequent cycles.

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.

**Hydration Day 22 + Day 36:**
See magnesium replacement recommendations below.

**DOSE MODIFICATIONS:**

**1. Severe Acneiform Rash (greater than grade 3 rash by NCI-CTC criteria):**

| *Occurrence* | *Cetuximab* | *Outcome* | *Cetuximab Dose* |
|---|---|---|---|
| 1st | Delay infusion 1 to 2 weeks | Improvement | Continue at 250 mg/m$^2$ |
| | | No Improvement | Discontinue cetuximab |
| 2nd | Delay infusion 1 to 2 weeks | Improvement | Reduce dose to 200 mg/m$^2$ |
| | | No Improvement | Discontinue cetuximab |
| 3rd | Delay infusion 1 to 2 weeks | Improvement | Reduce dose to 150 mg/m$^2$ |
| | | No Improvement | Discontinue cetuximab |
| 4th | Discontinue Cetuximab | | |

There is NO evidence, consensus opinions or recommendations for the management of these drug-induced rashes. However, for general management of acne-like rash consider the clindamycin 2% and hydrocortisone 1% in a Nutraderm lotion or in an ointment, to be applied topically TID prn.

For more serious rashes consider adding an antibiotic such as minocycline 100 mg PO BID for 1-2 weeks or longer as needed.

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.

**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. |

| Grade | Description (NCI-CTC) | Management | Cetuximab Dose |
|---|---|---|---|
| 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.

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| 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 |

**RADIOTHERAPY**
To be given under the direction of the treating Radiation Oncologist. The timing of radiation in relation to cetuximab is not critical. It is important to observe a patient for 60 minutes following cetuximab infusion in case of adverse reactions.

**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 Hypersensitivity Guidelines.

**Cardiopulmonary arrest** and/or sudden death have been reported in 2% of patients treated with concurrent radiation. Monitor serum magnesium, potassium and calcium during and after treatment in patients with a history of coronary artery disease, congestive heart failure, or arrhythmias.

**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.

**Hepatitis B Reactivation:** All head and neck cancer patients undergoing chemoradiation should be screened for hepatitis B reactivation risk. Patients with a positive result may require antiviral prophylaxis during treatment and for several months after treatment completion, in addition to close monitoring. Management should be reviewed with an appropriate specialist.

**Call Dr. Cheryl Ho or Dr. Jonn Wu or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.**

## References:


1. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous cell carcinoma of the head and neck. N Engl J Med 2006;354:567-78.
2. Vermorken JB, Ricard MD, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008;359:1116-27.
3. Thomas M. Cetuximab: Adverse event profile and recommendations for toxicity management. *Clin J Oncol Nurs.*2005;9:332-8.
4. Hansen N, Chandiramani DV, Morse MA, *et al.* Incidence and predictors of cetuximab hypersensitivity reactions in a North Carolina academic medical centre. *J Oncol Pharm Practice* 2011;17:125-30.
5. Personal Communication: Kaur N (Medical Information Officer). Bristol Myers Squibb Canada: 29 Sep 2011.
6. Lenz, HJ. Management and preparedness for infusion and hypersensitivity reactions. *Oncologist* 2007;12:601-9.
7. Product Monograph. Erbitux (cetuximab). Branchburg, NJ: ImClone LLC, distributed by Bristol-Myers Squibb Canada, Montreal, Canada. Jan 2014.