BC Cancer Protocol Summary for Palliative Combination Chemotherapy for Metastatic Colorectal Cancer using Oxaliplatin, Bevacizumab and Capecitabine

***Protocol Code**:* *GICOXB*

***Tumour Group**:* *Gastrointestinal*

***Contact Physician**:* *GI Systemic Therapy*

ELIGIBILITY:

- First line therapy for locally advanced, locally recurrent or metastatic colorectal adenocarcinoma, not curable with surgery or radiation, and for metastatic adenocarcinoma of the appendix or small bowel.
- Second line therapy will be considered only for those patients who have undergone resection of metastasis and therefore were not suitable for first-line therapy with bevacizumab
- No major surgery within 28 days of administration of therapy
- No untreated CNS metastases
- ECOG performance status less than or equal to 2
- Patients who have received single agent capecitabine or fluorouracil treatment first-line as the result of frailty, but who are now well enough to receive combination chemotherapy.
- Patients who have progressed on single agent capecitabine or fluorouracil therapy first-line and treatment escalation/combination chemotherapy is desired.
- Adequate marrow reserve
- Adequate renal and liver function
- Caution in patients with: 1) previous pelvic radiotherapy; 2) recent MI; 3) uncontrolled angina, hypertension, cardiac arrhythmias, congestive heart failure, renal disease including proteinuria, bleeding disorders, previous anthracycline exposure, prior radiation to the chest wall or other serious medical illness
- Caution in patients with recent (less than 6 months) arterial thromboembolic events

EXCLUSIONS:

- Suitable candidate for infusional fluorouracil protocol (GIFFOXB)
- Severe renal impairment (Creatinine Clearance less than 30 mL/min)
- Suspected dihydropyrimidine dehydrogenase (DPD) deficiency (see Precautions)
- Severe pre-existing peripheral neuropathy
- Avoid in patients with congenital long QT syndrome.

TESTS AND MONITORING:

- **Baseline**: CBC and differential, platelets, creatinine, LFTs (bilirubin, ALT, alkaline phosphatase), albumin, sodium, potassium, magnesium, calcium, dipstick or laboratory urinalysis for protein, Blood Pressure measurement and appropriate imaging study. Optional: CEA, CA 19-9.
- **Prior to each cycle**: CBC and differential, platelets, creatinine, LFTs (bilirubin, ALT, alkaline phosphatase), albumin, sodium, potassium, magnesium, calcium, Blood Pressure measurement
  - **Prior to each *even* numbered cycles**: dipstick or laboratory urinalysis for protein
- 24 hour urine for protein if occurrence of proteinuria dipstick urinalysis shows 2+ or 3+ or laboratory urinalysis for protein is greater than or equal to 1g/L
- Blood Pressure measurement to be taken pre and post dose for first 3 cycles only and then pre-therapy with each subsequent visit.
- If clinically indicated: CEA, CA 19-9
- For patients on warfarin, weekly INR until stable warfarin dose established, then INR prior to each cycle.
- Baseline and routine ECG for patients at risk of developing QT prolongation (at the discretion of the ordering physician). See Precautions.

- Quantitative evaluation of disease response status every six to twelve weeks; discontinue therapy if any progression of disease.
- Consider weekly nursing assessment for capecitabine toxicity in first two cycles and when increasing capecitabine dose.

PREMEDICATIONS:
- Antiemetic protocol for high - moderate emetogenic chemotherapy (see SCNAUSEA)
- Counsel patients to avoid cold drinks and exposure to cold air, especially for 3-5 days following oxaliplatin administration.
- **Cryotherapy (ice chips) should NOT be used as may exacerbate oxaliplatin-induced pharyngo-laryngeal dysesthesias.**

TREATMENT:

A Cycle equals -

Drug	Dose	BC Cancer Administration Guidelines
oxaliplatin	130 mg/m^2	IV in 250 to 500 mL of D5W over 2 hours
bevacizumab	7.5 mg/Kg†	IV in 100 mL Normal Saline over 15 minutes‡
capecitabine*	1000 mg/m^2 BID	PO x 14 days

Repeat every 21 days for a maximum of 16 cycles. If there is continued evidence of response or stable disease by imaging or tumour markers, apply for up to 16 additional cycles of chemotherapy and bevacizumab via Compassionate Access Program.

† ***The bevacizumab dose should be recalculated for patients who experience more than a 10% change in body weight.***

‡ ***Observe for fever, chills, rash, pruritus, urticaria or angioedema and stop infusion and contact the physician if any of these occur. Infusion reactions should be treated according to severity. If the bevacizumab infusion is restarted then it should be given at an initial rate of 60 minutes or longer.***

If acute hypertension (increase in BP measurement of greater than 20 mm Hg diastolic or greater than 160/100 if previously within normal limits) occurs during bevacizumab infusion – stop treatment. Resume at ½ the original rate of infusion if blood pressure returns to pretreatment range within one hour. If blood pressure does not return to pretreatment range within one hour – hold bevacizumab and subsequent infusions of bevacizumab should be given over 3 hours. Acute hypertension that is symptomatic (e.g. onset of headaches or change in level of consciousness) or BP measurement of greater than 180/110 that does not improve within one hour of stopping bevacizumab is an urgent situation that requires treatment.

Line should be flushed with Normal Saline pre and post dose as bevacizumab should not be mixed with dextrose solutions.

**** Capecitabine is available as 150 mg and 500 mg tablets (refer to Capecitabine Suggested Tablet Combination Table for dose rounding).***

Patients with PICC lines should have a weekly assessment of the PICC site for evidence of infection or thrombosis.

DOSAGE MODIFICATIONS (Sections A, B & C)

Attention: Dose Modifications Guidelines differ for NEUROLOGIC (Table 1) and NON-NEUROLOGIC Toxicities (Table 2).

A. Dose Modifications for NEUROLOGIC Toxicity
B. Dose Modifications for HEMATOLOGIC Toxicity
C. Dose Modifications for NON-HEMATOLOGIC, NON-NEUROLOGIC Toxicity

Neuropathy may be partially or wholly reversible after discontinuation of therapy; patients with good recovery from Grade 3 (not Grade 4) neuropathy may be considered for re-challenge with oxaliplatin, with starting dose one level below that which they were receiving when neuropathy developed

Table 1 - Dose Levels for NEUROLOGIC Toxicity (Section A)

Agent	Dose Level 0 (Starting Dose)	Neurotoxicity Dose Level –1N	Neurotoxicity Dose Level –2N	Neurotoxicity Dose Level –3N
oxaliplatin	130 mg/m^2	100 mg/m^2	65 mg/m^2	Discontinue Therapy

**If patient has both neurologic and non-neurologic toxicity, the final dose of oxaliplatin is the LOWER of the dose adjustments (ie if hematologic toxicity mandates dose –2 reduction (85 mg/m^2) and neurologic toxicity mandates dose –2N reduction (65 mg/m^2), then 65 mg/m2 is given.*

A. Dose Modifications for NEUROLOGIC Toxicity

Toxicity Grade	Duration of Toxicity		Persistent (present at start of next cycle)
	1 – 7 days	greater than 7 days	
Grade 1	Maintain dose level	Maintain dose level	Maintain dose level
Grade 2	Maintain dose level	Maintain dose level	Decrease one neurotoxicity dose level
Grade 3	↓1 neurotoxicity dose level	↓1 neurotoxicity dose level	Discontinue therapy
Grade 4	Discontinue therapy	Discontinue therapy	Discontinue therapy
Pharyngo-laryngeal (see precautions)	Increase duration of infusion to 6 hours	N/A	N/A

Oxaliplatin Neurotoxicity Definitions

Grade 1	Paresthesias/dysesthesias of short duration that resolve; do not interfere with function
Grade 2	Paresthesias / dysesthesias interfering with function, but not activities of daily living (ADL)
Grade 3	Paresthesias / dysesthesias with pain or with functional impairment which interfere with ADL
Grade 4	Persistent paresthesias / dysesthesias that are disabling or life-threatening
Pharyngo-laryngeal dysesthesias (investigator discretion used for grading): Grade 0 = none; Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe	

Table 2 Dose Levels for NON-NEUROLOGIC TOXICITY (Sections B & C)

Agent	Dose Level 0 (Starting dose)	Dose Level -1	Dose Level -2	Dose Level -3
oxaliplatin	130 mg/m^2	100 mg/m^2	85 mg/m^2	Discontinue Therapy
capecitabine	1000 mg/m^2 bid	750 mg/m^2 bid	500 mg/m^2 bid	Discontinue Therapy

B. Dose Modifications for HEMATOLOGIC Toxicity

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	**ANC (x10^9/L)**	**oxaliplatin**	**capecitabine**
▪ If ANC less than 1.2 on Day 1 of cycle, hold treatment. Perform weekly CBC, maximum of 2 times. ▪ If ANC is greater than or equal to 1.2 within 2 weeks, proceed with treatment at the dose level noted across from the **lowest ANC** result of the delayed week(s). ▪ If ANC remains less than 1.2 after 2 weeks, discontinue treatment.	1	greater than or equal to 1.2	Maintain dose level	Maintain dose level
	2	1.0 to less than 1.2	Maintain dose level	Maintain dose level
	3	0.5 to less than 1.0	↓ 1 dose level	↓ 1 dose level
	4	less than 0.5	↓ 2 dose levels	↓ 2 dose levels
	Grade 4 neutropenia & greater than or equal to Grade 2 fever		↓ 2 dose levels	↓ 2 dose levels
	Grade	**Platelets (x10^9/L)**	**oxaliplatin**	**capecitabine**
▪ If platelets less than 75 on Day 1 of cycle, hold treatment. Perform weekly CBC, maximum of 2 times. ▪ If platelets greater than or equal to 75 within 2 weeks, proceed with treatment at the dose level noted across from the **lowest platelets** result of the delayed week(s). ▪ If platelets remain less than 75 after 2 weeks, discontinue treatment.	1	greater than or equal to 75	Maintain dose level	Maintain dose level
	2	50 to less than 75	Maintain dose level	Maintain dose level
	3	10 to less than 50	↓ 1 dose level	↓ 1 dose level
	4	less than 10	↓ 2 dose levels	↓ 2 dose levels

C. Dose Modifications for NON-HEMATOLOGIC, NON-NEUROLOGIC Toxicity

If Grade 2, 3 or 4 toxicities occur, daily administration of capecitabine should be immediately interrupted until these symptoms resolve or decrease in intensity to grade 1.

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	**Diarrhea**	**oxaliplatin**	**capecitabine**
▪ If diarrhea greater than or equal to Grade 2 on Day 1 of any cycle, hold treatment. Perform weekly checks, maximum 2 times. ▪ If diarrhea is less than Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the **highest** Grade experienced. ▪ If diarrhea remains greater than or equal to Grade 2 after 2 weeks, discontinue treatment.	1	Increase of 2-3 stools/day, or mild increase in loose watery colostomy output	Maintain dose level	Maintain dose level
	2	Increase of 4-6 stools, or nocturnal stools or mild increase in loose watery colostomy output	Maintain dose level	Maintain dose level
	3	Increase of 7-9 stools/day or incontinence, malabsorption; or severe increase in loose watery colostomy output	Maintain dose level	↓ 1 dose level
	4	Increase of 10 or more stools/day or grossly bloody colostomy output or loose watery colostomy output requiring parenteral support; dehydration	↓ 1 dose level	↓ 2 dose levels*
	Grade	**Stomatitis**		
▪ If stomatitis greater than or equal to Grade 2 on Day 1 of any cycle, hold treatment. Perform weekly checks, maximum 2 times. ▪ If stomatitis is less than Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the **highest** Grade experienced. ▪ If stomatitis remains greater than or equal to Grade 2 after 2 weeks, discontinue treatment.	1	Painless ulcers, erythema or mild soreness	Maintain dose level	Maintain dose level
	2	Painful erythema, edema, or ulcers but can eat	Maintain dose level	Maintain dose level
	3	Painful erythema, edema, ulcers, and cannot eat	Maintain dose level	↓ 1 dose level
	4	As above but mucosal necrosis and/or requires enteral support, dehydration	↓ 1 dose level	↓ 2 dose levels*

*** If treatment with capecitabine is discontinued, then oxaliplatin is also discontinued.**

Prior to a Cycle (Day 1)	Toxicity		Dose Level For Subsequent Cycles	
	Grade	Palmar-Plantar Erythrodysesthesia (Hand-Foot Skin Reaction)	oxaliplatin	capecitabine
▪ If hand-foot skin reaction is greater than or equal to Grade 2 on Day 1 of any cycle, hold treatment. Perform weekly checks, maximum 2 times. ▪ If hand-foot skin reaction is less than Grade 2 within 2 weeks, proceed with treatment at the dose level noted across from the **highest** Grade experienced. ▪ If hand-foot skin reaction remains greater than or equal to Grade 2 after 2 weeks, discontinue treatment.	1	Skin changes (eg, numbness, dysesthesia, paresthesia, tingling, erythema) with discomfort not disrupting normal activities	Maintain dose level	Maintain dose level
	2	Skin changes (eg, erythema, swelling) with pain affecting activities of daily living	Maintain dose level	Maintain dose level
	3	Severe skin changes (eg, moist desquamation, ulceration, blistering) with pain, causing severe discomfort and inability to work or perform activities of daily living	Maintain dose level	↓ 1 dose level

Renal dysfunction:

Creatinine Clearance mL/min	Capecitabine Dose only
greater than or equal to 50	100%
30 to less than 50	75%
less than 30	Discontinue Therapy

Cockcroft-Gault Equation:

$$\text{Estimated creatinine clearance (mL/min)} = \frac{N\,(140 - \text{age})\,\text{wt (kg)}}{\text{serum creatinine (micromol/L)}}$$

N = 1.23 male
N = 1.04 female

Proteinuria:
There are 3 different measures of proteinuria that may be used to assess the need for modification of Bevacizumab therapy – urine dipstick analysis (measured in + values), laboratory urinalysis for protein (measured in g/L) and 24 hour urine collections for protein (measured in g/24 hours)

Urine dipstick analysis or laboratory urinalysis for protein should be performed at baseline and then prior to each even numbered cycle of therapy:

Degree of Proteinuria	
Neg or 1+ dipstick or less than 1 g/L laboratory urinalysis for protein	Administer bevacizumab dose as scheduled
2+ or 3+ dipstick or greater than or equal to 1 g/L laboratory urinalysis for protein	Administer bevacizumab dose as scheduled. Collect 24-hour urine for determination of total protein within 3 days before the next scheduled bevacizumab administration. ***Adjust bevacizumab treatment based on the table below.***
If urine dipstick shows 4+ at baseline or during treatment	Withhold bevacizumab and proceed with 24 hour urine collection

24-Hour Urine Total Protein (G/24 hours)	**Bevacizumab Dose**
less than or equal to 2	100%
greater than 2-4	Hold dose and recheck 24 hour urine every 2 weeks, resume therapy when less than or equal to 2g/24 hour
greater than 4	Discontinue Therapy

Hypertension:

Blood Pressure (mm Hg)	Bevacizumab Dose
less than or equal to 160/100	100%
greater than 160/100	100% Notify physician and start or adjust antihypertensive therapy*
Hypertensive Crisis	Discontinue Therapy

- **Antihypertensive therapy may include hydroCHLOROthiazide 12.5-25 mg PO once daily, ramipril (ALTACE®) 2.5-5 mg PO once daily, or amlodipine (NORVASC™) 5-10 mg PO once daily.**

PRECAUTIONS:

1. **Platinum hypersensitivity** can cause dyspnea, bronchospasm, itching and hypoxia. Appropriate treatment includes supplemental oxygen, steroids, epinephrine and bronchodilators. Vasopressors may be required. (see table below) For Grade 1 or 2 acute hypersensitivity reactions no dose modification of oxaliplatin is required and the patient can continue treatment with standard hypersensitivity pre-medication:

   45 minutes prior to oxaliplatin:

   - dexamethasone 20 mg IV in 50 mL NS over 15 minutes

   30 minutes prior to oxaliplatin:

   - diphenhydrAMINE 50 mg IV in NS 50 mL over 15 minutes and famotidine 20 mg IV in NS 100 mL over 15 minutes (Y-site compatible)

   Reducing infusion rates (e.g., from the usual 2 hours to 4-6 hours) should also be considered since some patients may develop more severe reactions when rechallenged, despite premedications.

   The practice of rechallenging after severe life-threatening reactions is usually discouraged, although desensitization protocols have been successful in some patients. The benefit of continued treatment must be weighed against the risk of severe reactions recurring. The product monograph for oxaliplatin lists rechallenging patients with a history of severe HSR as a contraindication. Various desensitization protocols using different dilutions and premedications have been reported. Refer to SCOXRX: BC Cancer Inpatient Protocol Summary for Oxaliplatin Desensitization for more information.

1. **Pharyngo-laryngeal dysesthesia** is an unusual dysesthesia characterized by an uncomfortable persistent sensation in the area of the laryngopharynx without any objective evidence of respiratory distress (i.e. absence of hypoxia, laryngospasm or bronchospasm). This may be exacerbated by exposure to cold air or foods/fluids. If this occurs during infusion, stop infusion immediately and observe patient. Rapid resolution is typical, within minutes to a few hours. Check oxygen saturation; if normal, an anxiolytic agent may be given. The infusion can then be restarted at a slower rate at the physician's discretion. In subsequent cycles, the duration of infusion should be prolonged (see Dose Modifications above in the Neurological Toxicity table).

Clinical Symptoms	**Pharyngo-laryngeal Dysesthesia**	**Platinum Hypersensitivity**
Dyspnea	Present	Present
Bronchospasm	Absent	Present
Laryngospasm	Absent	Present
Anxiety	Present	Present
O_2 saturation	Normal	Decreased
Difficulty swallowing	Present (loss of sensation)	Absent
Pruritus	Absent	Present
Cold induced symptoms	Yes	No
Blood Pressure	Normal or Increased	Normal or Decreased
Treatment	Anxiolytics; observation in a controlled clinical setting until symptoms abate or at physician's discretion	Oxygen, steroids, epinephrine, bronchodilators; Fluids and vasopressors if appropriate

2. **QT prolongation and torsades de pointes** are reported with oxaliplatin: Use caution in patients with history of QT prolongation or cardiac disease and those receiving concurrent therapy with other QT prolonging medications. Correct electrolyte disturbances prior to treatment and monitor periodically. Baseline and periodic ECG monitoring is suggested in patients with cardiac disease, arrhythmias, concurrent drugs known to cause QT prolongation, and electrolyte abnormalities. In case of QT prolongation, oxaliplatin treatment should be discontinued. QT effect of oxaliplatin with single dose ondansetron 8 mg prechemo has not been formally studied. However, single dose ondansetron 8 mg po would be considered a lower risk for QT prolongation than multiple or higher doses of ondansetron, as long as patient does not have other contributing factors as listed above.
3. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
4. **Gastrointestinal perforations and wound dehiscence**: Can be fatal. Typical presentation is reported as abdominal pain associated with symptoms such as constipation and vomiting. Bevacizumab should be discontinued in patients with gastrointestinal perforation or wound dehiscence requiring medical intervention.
5. **Hemorrhage**: Bevacizumab has been associated with hemorrhage. Cases of CNS hemorrhage, some with fatal outcome, have been observed. Patients should be monitored for signs and symptoms of CNS bleeding. If Grade 3/4 hemorrhage occurs, discontinue bevacizumab. Patients with significant bleeding diatheses should not receive bevacizumab. Platelet inhibitory medications such as NSAIDS (including ASA at doses greater than 325 mg/day) should be discontinued prior to institution of bevacizumab. COX-2 inhibitors are permissible. **For patients on warfarin, see Thrombosis (for bevacizumab) and Drug Interactions (for capecitabine).**
6. **Thrombosis**: A history of arterial thromboembolic events or age greater than 65 years is associated with an increased risk of arterial thromboembolic events with bevacizumab. If Grade 3 thromboembolic event or incidentally discovered pulmonary embolus arises, hold Bevacizumab for 2 weeks, then consider resumption of bevacizumab if risks of tumour-related hemorrhage are judged low AND the patient is on a stable dose of anticoagulant. If a second Grade 3 thrombosis occurs, or if a Grade 4 thrombosis occurs, discontinue bevacizumab. Patients on warfarin should have INR checked frequently, at least once per cycle, while receiving bevacizumab. In patients on warfarin with an elevated INR, it is recommended to **hold the bevacizumab if INR is greater than 3.0**
7. **Proteinuria**: Has been seen in all clinical trials with bevacizumab to date and is likely dose-dependent. If proteinuria of greater than or equal to 2g/24 hr persists for more than 3 months, consider further investigations - possibly a renal biopsy.
8. **Hypertension**: Has been seen in all clinical trials with bevacizumab to date and is likely dose-dependent. The most commonly used therapies are Calcium Channel Blockers, ACE Inhibitors and Diuretics. Blood pressure should be monitored through routine vital signs evaluations. If hypertension is poorly controlled with adequate medication, discontinue bevacizumab.
9. **Reversible Posterior Leukoencephalopathy Syndrome**: Rarely, patients may develop seizures, headache, altered mental status, visual disturbances, with or without associated hypertension consistent with RPLS. May be reversible if recognized and treated promptly.
10. **Congestive Heart Failure**: Has been reported in up to 3.5% of patients treated with bevacizumab. Most patients showed improvement in symptoms and/or LVEF following appropriate medical therapy.
11. **Myocardial ischemia and angina occurs rarely in patients receiving fluorouracil or capecitabine.** Development of cardiac symptoms including signs suggestive of ischemia or of cardiac arrhythmia is an indication to discontinue treatment. If there is development of cardiac symptoms patients should have urgent cardiac assessment. Generally re-challenge with either fluorouracil or capecitabine is not recommended as symptoms potentially have a high likelihood of recurrence which can be severe or even fatal. Seeking opinion from cardiologists and oncologists with expert knowledge about fluorouracil / capecitabine toxicity is strongly advised under these circumstances. The toxicity should also be noted in the patient's allergy profile.
12. **Diarrhea:** Patients should report mild diarrhea that persists over 24 hours or moderate diarrhea (4 stools or more per day above normal, or a moderate increase in ostomy output). If patient is taking capecitabine, it should be stopped until given direction by the physician. Mild diarrhea can be treated with loperamide (eg. IMODIUM®) following the manufacturer's directions or per the BC Cancer Guidelines for Management of Chemotherapy-Induced Diarrhea. Note that diarrhea may result in increased INR and the risk of bleeding in patients on warfarin.

13. **Dihydropyrimidine dehydrogenase (DPD) deficiency** may result in severe and unexpected toxicity – stomatitis, diarrhea, neutropenia, neurotoxicity – secondary to reduced drug metabolism. This deficiency is thought to be present in about 3% of the population.
14. **Possible drug interaction with capecitabine and warfarin** has been reported and may occur at any time. For patients on warfarin, weekly INR during capecitabine therapy is recommended until a stable warfarin dose is established. Thereafter, INR prior to each cycle. Consultation to cardiology/internal medicine should be considered if difficulty in establishing a stable warfarin dose is encountered. Upon discontinuation of capecitabine, repeat INR weekly for one month.
15. **Possible drug interaction with capecitabine and phenytoin and fosphenytoin** has been reported and may occur at any time. Close monitoring is recommended. Capecitabine may increase the serum concentration of these two agents.
16. Oxaliplatin therapy should be interrupted if symptoms indicative of **pulmonary fibrosis** develop – nonproductive cough, dyspnea, crackles, rales, hypoxia, tachypnea or radiological pulmonary infiltrates. If pulmonary fibrosis is confirmed oxaliplatin should be discontinued.
17. **Extravasation**: Oxaliplatin causes irritation if extravasated. Refer to BC Cancer Extravasation Guidelines.
18. **Venous Occlusive Disease** is a rare but serious complication that has been reported in patients (0.02%) receiving oxaliplatin in combination with fluorouracil. This condition can lead to hepatomegaly, splenomegaly, portal hypertension and/or esophageal varices. Patients should be instructed to report any jaundice, ascites or hematemesis immediately.
19. Oxaliplatin therapy should be interrupted if **Hemolytic Uremic Syndrome (HUS)** is suspected: hematocrit is less than 25%, platelets less than 100,000 and creatinine greater than or equal to 135 micromol/L. If HUS is confirmed, oxaliplatin should be permanently discontinued.

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:

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