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NCIC CLINICAL TRIALS GROUP (NCIC CTG)

A RANDOMIZED PHASE II STUDY OF REOLYSIN IN COMBINATION WITH FOLFOX6/BEVACIZUMAB OR FOLFOX6/BEVACIZUMAB ALONE IN PATIENTS WITH METASTATIC COLORECTAL CANCER

NCIC CTG Protocol Number: **IND.210**

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STUDY ACKNOWLEDGMENT/DISCLOSURE

I understand that this protocol contains information that is confidential and proprietary to Oncolytics Biotech Inc.

I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, and according to Good Clinical Practice and any applicable local regulations. I will make a reasonable effort to complete the study within the time designated. I confirm that I and study personnel participating under my supervision have adequate resources to fulfill their responsibilities as outlined in this protocol. I will maintain documentation of any investigator responsibilities assigned to participating study personnel. I confirm that all data will be submitted in a timely manner and will be accurate, complete and supported by source documents.

I will provide copies of the protocol and access to all information furnished by NCIC CTG and Oncolytics Biotech Inc. to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational product and the study.

I will provide protocol information to my Research Ethics Board (REB), subject to the following condition: The contents of this protocol may not be used in any other clinical trial and may not be disclosed to any other person or entity without the prior written permission of Oncolytics Biotech Inc. and NCIC CTG. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to Oncolytics Biotech Inc. and NCIC CTG of any such disclosure.

I understand that any inventions or discoveries made by any Principal Investigator during the course of this Study which directly relate to the study drug shall be disclosed to CTG and Oncolytics Biotech Inc. and shall become the property of Oncolytics Biotech Inc. However, the Principal Investigator shall retain the right to use any such inventions or discoveries for their own internal research and education.

I understand that I may terminate or suspend enrolment of the study at any time if it becomes necessary to protect the best interests of the study subjects, however I will give prompt notice to NCIC CTG. The study may be terminated at any time by NCIC CTG or Oncolytics Biotech Inc. with or without cause.

Any supplemental information that may be added to this document is also confidential and proprietary to Oncolytics Biotech Inc. and NCIC CTG and must be kept in confidence in the same manner as the contents of this protocol.

_____ _____

Investigator
(printed name and signature)

Date

Protocol Number: NCIC CTG IND.210

CENTRE: _____

TREATMENT SCHEMA

This is an open-label, randomized, non-blinded, phase II clinical study of reolysin day 1-5 (cycles 1, 2, 4, 6, 8 and alternate cycles thereafter) plus q2 weekly FOLFOX6/bevacizumab versus q2 weekly FOLFOX6/bevacizumab as first line palliative treatment for patients with advanced or metastatic colorectal cancer. Prior to the randomized component, 6-9 patients will first be accrued to ensure safety and tolerability of the combination.

SAMPLE SIZE

Up to 100 evaluable patients (50 per arm) will be randomized. The estimated accrual for this study is 8 patients per month. Thus, patient accrual is expected to be completed within 13-15 months.

ELIGIBILITY

All patients:

- Histologically diagnosed colorectal adenocarcinoma
- Paraffin embedded primary (or metastatic) tumour sample available for assessment; patient must have provided informed consent for release of the sample
- Metastatic or advanced disease for which systemic treatment with FOLFOX6/bevacizumab is indicated
- Patients must have measureable disease as per RECIST 1.1
- ECOG performance status 0, 1, 2
- Age $\geq$ 18 years
- No prior chemotherapy regimens for advanced or metastatic disease
- No prior oxaliplatin based or bevacizumab based therapy, but may have had adjuvant fluoropyrimidine-based therapy provided completed at least one year prior to enrolment. Exceptions may be given for low dose chemotherapy given as a radiosensitizer
- No contraindications to treatment with 5FU (for e.g. known DPD deficiency or severe cardiac disease), and no neuropathy > grade 1
- Prior radiation permitted $\geq$ 4 weeks since last dose
- No major surgery within 21 days prior to randomization

Absolute granulocyte count (AGC)	$\geq 1.5 \times 10^9$/L
Platelet count	$\geq 100 \times 10^9$/L
Total bilirubin	$\leq$ 1 x ULN
Serum creatinine	$\leq$ 1.5 x ULN
ALT and AST	$\leq$ 3 x ULN *(If documented liver metastasis, $\leq$ 5xULN)*

- Proteinuria < 2 g/24 hrs
- No significant cardiac (including uncontrolled hypertension) or pulmonary disease, active CNS disease or infection
- No immunosuppressive treatment of known hepatitis or HIV positive patients
- Patients with active or uncontrolled infections, or with serious illnesses or medical conditions, which would not permit the patient to be managed according to the protocol.
- No history of other malignancies, except adequately treated non-melanoma skin cancer or solid tumours with no evidence of disease $\geq$ 3 years.
- No history of central nervous system metastases or untreated spinal cord compression.
- All patients (unless sterile) must use an adequate method of birth control.

PRE-TREATMENT EVALUATIONS

- History, physical exam, hematology, biochemistry, urinalysis and adverse events/baseline symptoms, within 7 days prior to randomization
- Quality of life questionnaire within 14 days prior to randomization
- Blood samples for correlative studies after randomization but prior to first dose of chemotherapy
- Radiology: chest CT; abdominal/pelvic CT; other scans as necessary, within 28 days prior to randomization (within 35 days if negative)

TREATMENT

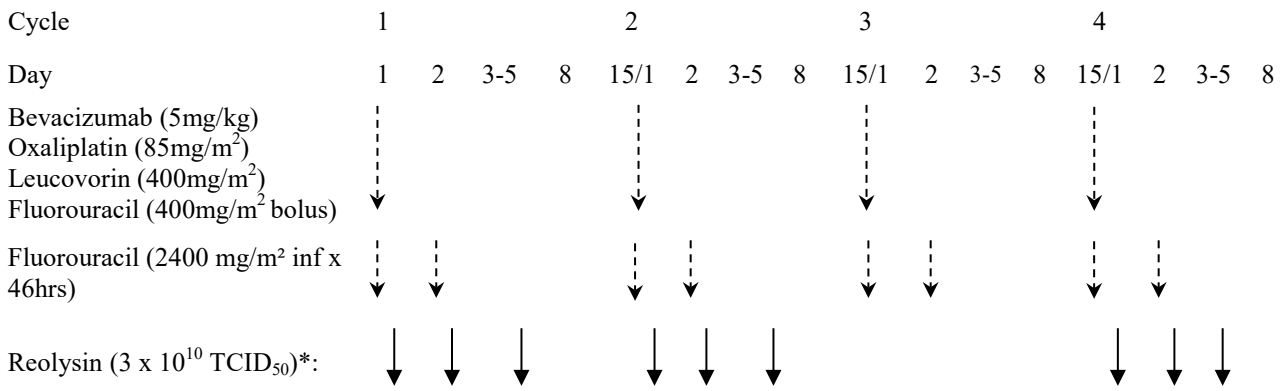
Arm A and safety run in patients:
FOLFOX6/bevacizumab given every 14 days plus reolysin days 1-5 on cycles 1, 2, 4, 6, 8 and alternate cycles thereafter.

Arm B:
FOLFOX6/bevacizumab given every 14 days.

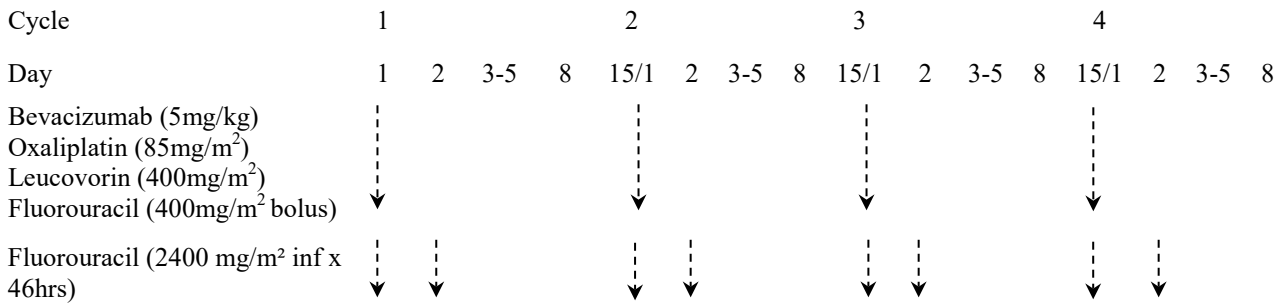
Patients in the randomized component of the study will be randomly assigned to Arm A or Arm B.

DRUG ADMINISTRATION SCHEDULE

Arm A and safety run in:



Arm B:



** dose may be modified dependent on results of safety run component*

ON TREATMENT EVALUATIONS

- Hematology and Biochemistry: weekly for cycles 1 and 2 then day 1 for subsequent cycles
- Urinalysis: each cycle (day 1)
- CEA: end of every 2nd cycle (every 4 weeks)
- Physical exam (weight, blood pressure, heart rate, ECOG PS): Baseline and every cycle (day 1)
- Blood samples for correlative studies: end of cycle 2 and at off treatment
- Radiology: every 8 weeks to assess all sites of disease
- Quality of life: day 1 cycle 5 and at off treatment
- Adverse events: evaluated continuously

DURATION OF TREATMENT

Treatment will continue until:

- Patient experiences progression as defined in section 10.0
- Unacceptable toxicity
- Patient chooses to withdraw

1.0 OBJECTIVES

Six to nine patients will be enrolled initially to confirm the safety and tolerability of the combination (FOLFOX6/bevacizumab/reolysin).

1.1 Primary Objective

To evaluate the effect of reolysin in combination with standard FOLFOX6 chemotherapy on the progression free survival of patients with advanced or metastatic colorectal cancer.

1.2 Secondary Objectives

1.2.1 To determine the tolerability and toxicity of reolysin and FOLFOX6/bevacizumab when given in combination.

1.2.2 To investigate additional potential measures of efficacy including:

- change in CEA levels
- objective response rate
- to evaluate the effect of both treatments on overall survival (OS)

1.2.3 To explore potential molecular factors which may be prognostic, or predictive of response, by assessment of archival tumour tissue and serial blood samples.

1.2.4 To explore the Quality of Life (as measured by the EORTC QLQC30).

2.0 BACKGROUND INFORMATION AND RATIONALE

2.1 Colorectal Cancer

Colorectal cancer (CRC) is the second-leading cause of cancer death in Canada *[Statistics CCS 2011*] and has historically been refractory to most chemotherapeutics. Over the past five years, the introduction of irinotecan and oxaliplatin have enabled patients with advanced colorectal cancer to live longer than before, with a median survival for these patients of over 20 months *[Tournigand 2004]*. Although a number of new effective therapies have been developed for patients with metastatic colorectal cancer, all patients treated in the palliative setting will ultimately succumb to their disease. New treatments are needed.

2.2 Chemotherapy in Metastatic Colorectal Cancer

Oxaliplatin, a third generation cisplatin analogue, is a pivotal component of systemic therapy for metastatic CRC. Two multicenter randomized studies compared 5 fluorouracil/folinic acid (5FUFA) with and without oxaliplatin as first-line treatment for metastatic CRC *[de Gramont 2000; Giacchetti 2000]*. The combination of oxaliplatin to 5FU FA (FOLFOX) demonstrated superior response rates (51% vs 22%, $p<0.0001$; 53% vs 16%, $p< 0.001$) and longer progression-free survival (PFS) (9.0 vs 6.2 months, $p = 0.0003$; 8.7 vs 6.1 months, $p < 0.05$). In a North American Intergroup trial (N9741), FOLFOX4 was superior to irinotecan and bolus 5FUFA (IFL) with respect to response rate, PFS, and overall survival (OS) *[Goldberg 2004]*. In Europe, FOLFOX6 and FOLFIRI have been compared to each other, used sequentially, in the management of patients with advanced colorectal cancer, and there does not appear to be a significant difference in outcome based on the sequence of administration, although the toxicity profiles are dissimilar. Both FOLFIRI and FOLFOX are standard first line chemotherapy options. In some instances, clinical response may permit post-chemotherapy surgical resection with curative intent.

There are numerous published regimens that combine varying doses and schedules of oxaliplatin and 5-FUFA. These combinations have been named FOLFOX 1-7. There is no clear evidence that any one FOLFOX regimen is superior to another. The role of FOLFOX as front-line therapy for patients with advanced or metastatic colorectal cancer is supported by the findings of the N9741 intergroup study. This trial will use the modified FOLFOX6 regimen that has been evaluated in prior clinical trials *[Hochster 2008]*.

2.3 Antiangiogenic Therapy in Metastatic Colorectal Cancer

Inhibition of VEGF with antiangiogenic drugs is thought to improve delivery of chemotherapy via vascular normalization and disruption of tumour vasculature *[Jain 2009]*. Bevacizumab, a monoclonal antibody that binds to VEGF, significantly improves outcomes when added to standard chemotherapy for metastatic colorectal cancer (MCRC) *[Giantonio 2007; Hurwitz 2004; Hurwitz 2005; Kabbinavar 205; Saltz 2008]*. It has been approved for use in untreated patients with advanced colorectal cancer in combination with 5FU-based chemotherapy. In the pivotal first line trial, bevacizumab in combination with IFL compared to IFL alone led to superior response rates, PFS, and OS (20.3 months in the bevacizumab group versus 15.6 months, HR 0.66, $p<0.001$). A meta-analysis of randomized trials comparing chemotherapy plus bevacizumab with chemotherapy alone as first or second line therapy for metastatic CRC detected a significant advantage in favor of the addition of bevacizumab to chemotherapy in terms of OS [HR 0.79; 95% CI 0.69-0.90; $p = 0.0005$], PFS (HR 0.63; 95% CI 0.49-0.81, $p=0.0004$), and response rate (RR 1.50; 95% CI 1.06-2.10, $p=0.02$) *[Welch 2010]*. Bevacizumab does not appear to alter the toxicity profile of chemotherapy, although hypertension and proteinuria are commonly seen. Approximately 3-4% of patients receiving bevacizumab suffer arterial thrombotic events. Bevacizumab in combination with modified FOLFOX6 is a standard chemotherapy option in the first line treatment of metastatic CRC.

2.4 Reolysin

Reolysin is a Dearing strain of reovirus serotype 3, with demonstrated in vitro and in vivo activity in many cancers including colorectal cancer *[Hirasawa 2002]*. Reovirus has an inherent propensity to preferentially infect and destroy cancer cells through exploitation of activated Ras pathway and downstream elements. It causes virus-mediated cell death due to inhibition of double-stranded RNA-activated protein kinase *[Marcanto 2007; Strong 1998]*. It appears to have minimal human toxicity and its human safety and potential efficacy have been demonstrated with > 360 patients treated on clinical trials to date. In phase I trials, reolysin was well tolerated and dose limiting toxicities were not observed *[Vidal 2008]*. The most common side effect is a flu-like illness. An international randomized phase III trial of reolysin with paclitaxel and carboplatin in head and neck cancers is presently under way.

In preclinical studies, reolysin has cytopathic effect in tumours driven by KRAS mutations or upstream activation of the Ras pathway, both of which are important in colorectal cancer. The Ras oncogene plays an important role in colorectal cancer tumourigenesis *[Shirasawa 1993]*. Activating mutations in the KRAS oncogene are present in 40 to 50% of colorectal cancers *[Vogelstein 1988]*. Ligand binding of the epidermal growth factor receptor (EGFR) leads to a cascade of intracellular events which include activation of the Ras pathway. Expression or up-regulation of EGFR occurs in 60 to 80% of colorectal cancer *[Porebska 2000]*.

Reolysin has preclinical activity against colorectal cancer. In cell proliferation studies in HCT116 colon cancer cells, Reolysin was highly cytopathic against HCT116. HCT116 variants in which Ras was disrupted by homologous recombination demonstrated equivalent sensitivity to reolysin. Reovirus enhanced the cytopathic effects of fluorouracil at every concentration tested *[Wadler 2004]*. Hirasaw et al. evaluated the antitumour activity of Reolysin in preclinical models of colorectal cancer *[Hirasawa 2002]*. Reolysin infected five human colon cancer cell lines (Caco-2, DLD-1, HCT-116, HT-29, and SW48) but not a normal colon cell line (CCD-18-Co). After over 72 hours post infection, > 95% of cancer cell lines were destroyed. Ras activity in the human colon cancer cell lines was elevated compared to normal colon cancer cell lines. Intravenous treatment with reolysin in three different colon tumour xenografts models resulted in significant inhibition of tumour growth. Histological examination of tumours revealed necrosis and fibrosis in reolysin treated mice compared to controls and active viral replication in the tumours.

Transient inhibition of continuous VEGF signaling to tumour-associated endothelium, followed by a recovery period induces a proviral state. B16-VEGF tumours treated in vivo with either sunitinib or bevacizumab became highly susceptible to systemic treatment with reolysin. Combined treatment with Reolysin and antiangiogenic therapy was superior to single agent treatment when reolysin *[Kottke 2011]* was administered after antiangiogenic therapy.

In a window-of-opportunity clinical study, a single cycle of intravenous reolysin was given to patients at a dose of 1×10^{10} $TCID_{50}$ from days 1 to 5, between 6 and 28 days prior to a planned resection of colorectal cancer metastatic to the liver (Adair et al, unpublished data). There were no surgical complications and treatment was well tolerated with no grade 3 or 4 toxicities. There was greater selective expression of reovirus protein in malignant cells compared to either tumour stroma or surrounding normal liver tissue. Tubulin is an indirect marker of replication in viral factories. In four out of six assessable cases, co-localization of reolysin was seen with tubulin in tumour tissue but not in adjacent stroma. Recovery of replicating virus from tumour (but not liver) was achieved in all 4 patients from whom fresh tissue was available. A phase I study of FOLFIRI and reolysin is ongoing (ClinicalTrials.gov identifier NCT01274624).

2.5 Rationale

Reolysin has single agent activity in colorectal non clinical models, and appears to have additive/synergistic effects when combined with 5-FU and bevacizumab in preclinical models. We hypothesize that reolysin added to standard modified FOLFOX6 plus bevacizumab in the first line metastatic setting will demonstrate improved progression-free survival compared to FOLFOX6 plus bevacizumab. As FOLFOX6 is administered every 14 days, and the standard dose of reolysin in other studies is administered every 3 to 4 weeks, reolysin will be given on alternate cycles after cycles 1 and 2 (i.e. cycles 1, 2, 4, 6, 8 etc.)

Formal phase I studies of reolysin in combination with FOLFOX6/bevacizumab have not been conducted. No clinically relevant interactions have been reported with other combinations in the clinical program, and none are expected with the combination being tested in this protocol. To ensure patient safety, a safety run-in of 6 to 9 patients will be conducted; with a provision for dose de-escalation should this be required.

Quality of life (QoL) in this study will be assessed using the EORTC QLQ-C30 questionnaire. This self-administered questionnaire consists of 30 items in which are embedded five functional domains (physical, role, emotional, cognitive and social), three symptom domains and a global assessment. The validity and reliability of this questionnaire have been studied by the EORTC Study Group on Quality of Life *[Aaronson 1993]*. This tool has also been used extensively in previous NCIC CTG trials. It has been demonstrated to be sensitive to detecting clinically and statistically important changes in this patient population *[Jonker 2007]*.

3.0 BACKGROUND THERAPEUTIC INFORMATION

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.0 TRIAL DESIGN

This is an open-label, randomized, non-blinded, phase II clinical study of reolysin day 1-5 (cycles 1, 2, 4, 6, 8 and alternate cycles thereafter) plus q2 weekly FOLFOX6/bevacizumab versus q2 weekly FOLFOX6/bevacizumab as first line palliative treatment for patients with advanced or metastatic colorectal cancer. Prior to the randomized component 6-9 additional patients will be accrued to ensure safety and tolerability of the combination (see protocol section 8.1.1). The study is being conducted by the NCIC Clinical Trials Group, with support of Oncolytics Biotech Inc.

5.0 STUDY POPULATION

Patients will have documented evidence of advanced metastatic colorectal cancer. This study is designed to include minorities as appropriate, but is not designed to measure differences in intervention effects.

5.1 Eligibility Criteria

There will be NO EXCEPTIONS to eligibility requirements at the time of randomization. Questions about eligibility criteria should be addressed PRIOR to randomization.

The eligibility criteria for this study have been carefully considered. Eligibility criteria are standards used to ensure that patients who enter this study are medically appropriate candidates for this therapy. For the safety of the patients, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar diseases, it is important that no exceptions be made to these criteria for admission to the study.

Patients must fulfill all of the following criteria to be eligible for admission to the study:

5.1.1 Patients must have a histological diagnosis of colorectal adenocarcinoma.

5.1.2 All patients must have a formalin fixed paraffin embedded tissue block (from their primary or metastatic tumour) available for translational studies and must have provided informed consent for the release of the block.

5.1.3 Presence of clinically and/or radiologically documented disease. All radiology studies must be performed within 28 days prior to randomization (within 35 days if negative).

All patients must have measurable disease as defined by RECIST 1.1.

The criteria for defining measurable disease are as follows:

Chest X-ray	≥ 20 mm	
CT/MRI scan (with slice thickness of < 5 mm)	≥ 10 mm	→ longest diameter
Physical exam (using calipers)	≥ 10 mm	
Lymph nodes by CT scan	≥ 15 mm	→ measured in short axis

5.1.4 Patients must have advanced and or metastatic disease, for which no curative therapy exists and for which systemic therapy is indicated.

5.1.5 ECOG performance of 0, 1 or 2.

5.1.6 Age ≥ 18 years of age.

5.1.7 *Previous Therapy*

Surgery:
Previous major surgery is permitted provided that it has been at least 21days prior to patient randomization and that wound healing has occurred.

Chemotherapy:
Patients may NOT have received any prior cytotoxic chemotherapy for advanced or metastatic disease. Prior adjuvant fluoropyrimidine-based therapy is permitted provided completed at least one year prior to enrolment and the regimen did not include oxaliplatin or bevacizumab. Exceptions may be made for low dose chemotherapy given as a radiosensitizing agent.

Other Therapy:
Patients may have received other therapies including immunotherapy, or with signal transduction inhibitors, providing that the patient has recovered from all reversible drug related toxicity (with the exception of alopecia) and adequate washout period has been met.

Radiation:
Prior external beam radiation is permitted provided a minimum of 4 weeks has elapsed between the last dose and enrollment to the trial. Exceptions may be made for low dose, non-myelosuppressive radiotherapy after consultation with NCIC CTG.

5.1.8 Laboratory Requirements (must be done within 7 days prior to randomization)

Hematology:		
Granulocytes (AGC)	$\geq$ 1.5 x 10^9/L	
Platelets	$\geq$ 100 x 10^9/L	
Biochemistry:		
Serum creatinine	$\leq$ 1.5 x ULN	
Total bilirubin	$\leq$ 1.0 x ULN	*(unless elevated secondary to conditions such as Gilbert's disease)*
ALT and AST	$\leq$ 3 x ULN	(*Note*: $\leq$ 5 x ULN if documented liver metastasis)
Proteinuria	< 2 g/24 hrs	(screen using spot testing; if $\geq$ grade 2 repeat with mid-stream urine - if still $\geq$ grade 2 then urine collection for 24 hours to confirm< 2 g/24 hrs)

5.1.9 Patient consent must be appropriately obtained in accordance with applicable local and regulatory requirements. Each patient must sign a consent form prior to enrollment in the trial to document their willingness to participate.

Patients who cannot give informed consent (i.e. mentally incompetent patients, or those physically incapacitated such as comatose patients) are not to be recruited into the study. Patients competent but physically unable to sign the consent form may have the document signed by their nearest relative or legal guardian. Each patient will be provided with a full explanation of the study before consent is requested.

5.1.10 Patients must be accessible for treatment and follow-up. Patients registered on this trial must be treated and followed at the participating centre. This implies there must be reasonable geographical limits (for example: 2 hour's driving distance) placed on patients being considered for this trial. (Call the NCIC CTG office (613-533-6430) if questions arise regarding the interpretation of this criterion.) Investigators must assure themselves that the patients registered on this trial will be available for complete documentation of the treatment, adverse events, response assessment and follow-up.

5.1.11 Patient is able (i.e. sufficiently fluent) and willing to complete the quality of life (EORTC QLQ-C30) in either English or French. The baseline assessment must already have been completed. Inability (illiteracy in English or French, loss of sight, or other equivalent reason) to complete the questionnaires will not make the patient ineligible for the study. However, ability but unwillingness to complete the questionnaires will make the patient ineligible. The baseline assessment must be completed within 14 days prior to randomization.

5.1.12 In accordance with NCIC CTG policy, protocol treatment is to begin within 5 working days of patient randomization.

5.2 Ineligibility Criteria

Patients who fulfill any of the following criteria are not eligible for admission to the study:

5.2.1 Patients with a history of other malignancies, except for adequately treated non-melanoma skin cancer or solid tumours curatively treated with no evidence of disease for $\geq$ 3 years. (*Please call NCIC CTG if any questions about the interpretation of this criterion*).

5.2.2 Patients who are on immunosuppressive therapy or have known HIV infection or active hepatitis B or C.

5.2.3 Patients with active or uncontrolled infections or with serious illnesses or medical conditions which would not permit the patient to be managed according to the protocol.

5.2.4 Patients with significant cardiac (including uncontrolled hypertension) or pulmonary disease, or active CNS disease or infection.

5.2.5 Patients are not eligible if they have a known hypersensitivity to the study drug(s) or their components.

5.2.6 Patients with history of central nervous system metastases or untreated spinal cord compression.

5.2.7 Patients who have had prior treatment with oxaliplatin or bevacizumab, who have contraindications to treatment with 5FU (for e.g. known DPD deficiency or severe cardiac disease), and or neuropathy > grade 1.

5.2.8 Patients who are not sterile unless they use an adequate method of birth control.

AMEND #1: 2013-APR-25; ADMIN UPDATE #1: 2014-MAY-23 *(withdrawn)*; AMEND #3: 2014-JUN-16

6.0 PRE-TREATMENT EVALUATION

(See Appendix I)

Investigations		Timing
History and Physical Exam including:	History including: • diagnosis • prior therapy • concurrent illness • concomitant medication Physical Exam including: • height, weight • blood pressure, pulse • performance status • tumour assessment documentation of all measurable and non-measurable disease	Within 7 days prior to randomization
Hematology	• CBC, differential, platelets	
Biochemistry	• serum creatinine • bilirubin • alkaline phosphatase • AST, ALT • LDH • total protein • CEA	
Other Investigations	• Urinalysis (see section 5.1.8) • Pregnancy test* • Quality of life (EORTC QLQC30)**	
Radiology***	• chest CT scan • abdominal/pelvic CT scan • other scans/x-rays as necessary to document disease	Within 28 days prior to randomization (within 35 days if negative)
Correlative Studies	• Archival tissue block (all patients) ♦	Must be confirmed available prior to randomization
	• Blood samples for correlative studies ♦	AFTER randomization but BEFORE first dose of study treatment
Adverse Events♦♦	• Baseline toxicity evaluation (to document residual toxicity from previous therapy and baseline symptoms)	Within 7 days prior to randomization

* For women of childbearing potential only. Required within 7 days prior to randomization.

** Within 14 days of randomization.

*** To ensure comparability, the baseline scans and subsequent scans to assess response must be performed using identical techniques (i.e. scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner).

♦ Samples for correlative studies (archival tissue block, blood, serum, plasma) required for ALL patients. See Section 17.0 and IND.210 Lab Manual for details.

♦♦ Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) *(Appendix V)*.

7.0 ENTRY/RANDOMIZATION PROCEDURES

7.1 Entry Procedures

All randomizations will be done through the NCIC CTG web-based, password-operated Electronic Data Capture (EDC) system. Complete details regarding obtaining a password, accessing the system and registering/randomizing patients will be provided at the time of study activation and will also be included in the "EDC Data Management Guidebook", posted on the IND.210 trial specific web-site. If sites experience difficulties accessing the system and/or registering/randomizing patients please contact the help desk (link in EDC) or the IND.210 Study Coordinator.

All eligible patients enrolled on the study by the participating treatment centre will be assigned a serial number which must be used on all documentation and correspondence with NCIC CTG.

The following information will be required:

- trial code (NCIC CTG IND.210)
- investigator NCIC CTG user ID
- patient's initials (may be coded), hospital number (if permitted by the local REB)
- informed consent version date, date signed by patient, name of person conducting consent discussion and date signed
- confirmation of the requirements listed in Section 5.0, including dates of essential tests and actual laboratory values

7.2 BSA Calculation

In calculating surface areas, actual heights and weights should be used, that is, there will be no downward adjustment to "ideal" weight.

Note: All eligible patients admitted to the trial will be followed by the coordinating centre. It is the responsibility of the physician in charge to satisfy himself or herself that the patient is indeed eligible before requesting randomization.

7.3 Stratification

Patients will be stratified for the following factors

- *KRAS* mutation status (if known)
- prior adjuvant chemotherapy

8.0 TREATMENT PLAN

Although the NCIC Clinical Trials Group acts as the coordinating agency for the trial, the responsibility for treatment of patients rests with the individual investigator. In accordance with NCIC CTG policy, protocol treatment is to begin within 5 working days of patient randomization.

8.1 Chemotherapy Treatment Plan

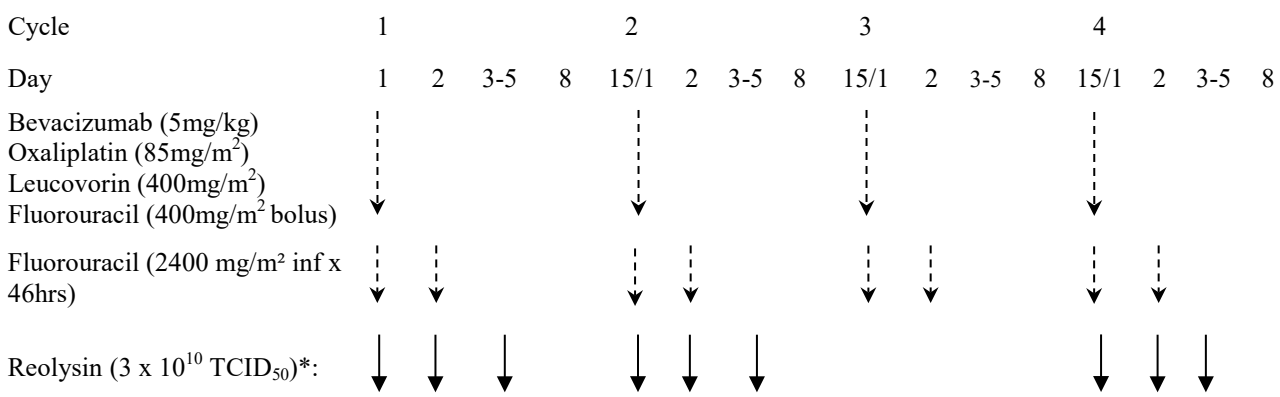
8.1.1 *Drug Administration*

Safety run-in:
Prior to the randomized component of this study, six to nine patients will be enrolled in three participating sites. Initially, one patient will be enrolled at the doses indicated below and observed for 2 weeks. Two additional patients will be enrolled providing no safety concerns (i.e. unexpected severe toxicity) are identified in the initial patient, and observed for 2 weeks. If no safety concerns, 3-6 additional patients will be enrolled prior to the initiation of the randomized component of the trial. If safety concerns are identified, the dose of reolysin will be de-escalated by one dose level (see 8.1.3), an additional 3 patients enrolled, and that chosen as the dose for the randomized component.

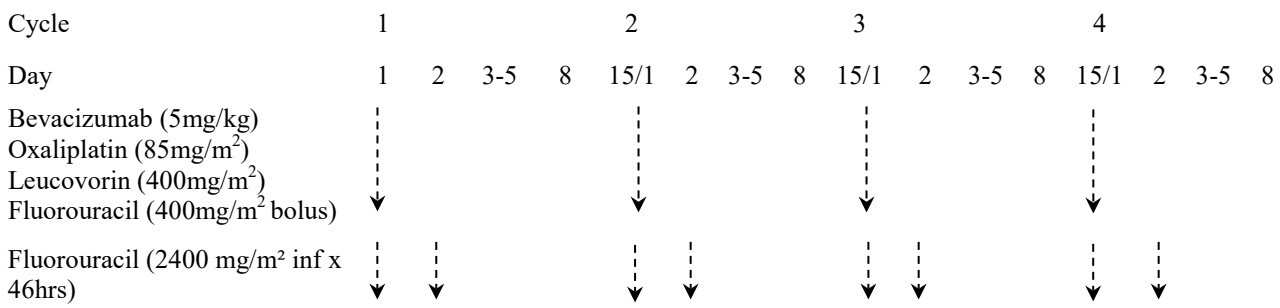
Randomized trial:

Agent(s)	Dose	Route	Duration	Schedule
Bevacizumab	5mg/kg	IV	1 hour	Day 1 every 2 weeks
oxaliplatin	85 mg/m²	IV	2 hours	Day 1 every 2 weeks
leucovorin	400 mg/m²	IV	2 hours (concurrently with oxaliplatin)	Day 1 every 2 weeks
fluorouracil	400 mg/m²	IV	bolus, after leucovorin	Day 1 every 2 weeks
fluorouracil	2400 mg/m²	IV	continuous infusion over 46 hours	Day 1 every 2 weeks
Reolysin	$3x10^{10}$ $TCID_{50}$	IV	1 hour	Days 1–5 (every 2 weeks cycles 1,2,4,6,8 etc)
1 cycle = **2 weeks on study**				

Arm A and safety run in:



Arm B:



** dose may be modified dependent on results of safety run component*

Protocol treatment is to begin within 5 working days of patient randomization. Patients on the FOLFOX-6/bevacizumab-reolysin arm who discontinue one of the protocol therapies for toxicity related to that therapy may continue with the other, at the discretion of the investigator. Cross over is not permitted. Patients who continue treatment with either FOLFOX/bevacizumab or reolysin are considered on study and all evaluations and data submission are required as outlined in sections 9.1 and Appendix IV unless otherwise discussed with the Senior Investigator. Components of the FOLFOX/bevacizumab regimen may be held or discontinued for toxicity but must be discussed with the Senior Investigator.

Reolysin should be administered after chemotherapy on days 1 (i.e. before fluorouracil infusion starts) and 3, and in a separate line on day 2 (during fluorouracil infusion). Centres may use different sequencing of bevacizumab and FOLFOX where the local formulary dictates (e.g. bevacizumab given after cytotoxic chemotherapy but before reolysin).

In the case of short weeks (e.g. a public holiday), the duration of the reolysin schedule may be shortened for that week (i.e. given day 1-4 on Tuesday to Friday).

8.1.2 *Premedication*

All patients will receive antiemetics as per standard centre practice prior to each infusion of chemotherapy.

APAP (acetaminophen) may be used for the prophylaxis or treatment of the flu-like signs and symptoms, especially fever, that are commonly associated with REOLYSIN. The decision about using APAP should be considered for each individual patient, with particular attention to the patient's hepatic status at the time of entry into the trial. Extra caution should be used if there is a history of viral (HBV or HCV) hepatitis and/or a preentry elevation of bilirubin above normal.

If the patient has metastatic cancer in the liver, the impact of the metastases on overall liver function should be considered. If the values for AST and ALT are less than twice the upper limit of normal, APAP may still be used, but careful monitoring of hepatic function should be done.

Given the usual timing of fever and other "flu-like" adverse events associated with REOLYSIN, treatment with APAP should be limited to the days on which REOLYSIN is administered and the day following the last dose of each cycle. When REOLYSIN is administered in combination with bone marrow suppressing chemotherapies, it is recommended not to continue APAP longer in order to prevent the possible "masking" of fever due to infection---especially in the presence of neutropenia.

Dosing of APAP: The recommended dose is 500 or 1000 mg every 6 to 8 hours. The MAXIMUM daily (24-hour) dose must NOT exceed 3000 mg. (NB: Given that there are more than 600 products that contain APAP, it is also essential that patients be warned NOT to use other products containing APAP at the same time)

If used for prophylaxis, it is recommended that the first dose be given 1 to 3 hours following the completion of reolysin infusion on day 1 of the cycle.

NSAID usage should be avoided in patients with known renal dysfunction especially when they are planned for contrast enhanced imaging. Patients should be encouraged to ensure good hydration especially when febrile.

Management of symptoms should take place as necessary (see Section 8.1.3 below). Details of any premedication or concomitant medication given to manage or prevent adverse events should be recorded on case report forms (CRFs).

Diarrhea:
Upon FIRST occurrence of diarrhea, loperamide (Imodium) is recommended at an initial dose of 4 mg (two capsules) followed by 2 mg (one capsule) after each unformed stool. The total daily dose should not exceed 16 mg (eight capsules). For patients who experience either persistent diarrhea(> 24 hours), diarrhea that is still severe (6+ episodes per day) after 12 hours of Imodium, or who exceed the recommended dose of Imodium, treatment with dyphenoxylate and atropine (Lomotil) every 6-8 hours until diarrhea is controlled is recommended.

The addition of Lomotil typically reduces the need for Imodium. The recommended initial dosage of Lomotil is two tablets four times daily or 10 ml (two regular teaspoonfuls) of Lomotil liquid four times daily (20 mg per day). Most patients will require this dosage until initial control has been achieved, after which the dosage may be reduced to meet individual requirements. In patients who required both Imodium and Lomotil for diarrhea control, it is recommended that reduction of Imodium be implemented first.

ADMIN UPDATE #1: 2014-MAY-23 *(withdrawn)*; AMEND #3: 2014-JUN-16; AMEND #4: 2014-NOV-17

Once diarrhea is controlled with either Imodium and/or Lomotil, it is generally recommended that patients continue to use at least one drug as a prophylactic regimen. For patients whose diarrhea was well-controlled with Imodium alone, the recommended treatment regimen is 1 capsule after each regular (non-diarrheal) bowel movement. For patients who required both Imodium and Lomotil to achieve diarrhea control, the recommended regimen is Lomotil 1 tablet every 12 hours, or 2 tablets every 24 hours, with Imodium added as needed. Treatment with Imodium or Lomotil should be avoided in the presence of fever or if the stool is bloody.

8.1.3 *Dose Adjustments*

Doses of each drug/agent used as protocol therapy will be modified for hematologic and other adverse events considered related to that drug/agent; doses of other drugs/agents do not require modification. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE). Doses reduced for toxicity will not be re-escalated.

In general when treatment is held because of *drug related adverse effects* for > 3 weeks without recovery to the degree required for restarting treatment, the patient should go off protocol therapy. Specific details are found in the sections below.

The use of an institution's written standard procedures for dose modification of bevacizumab / FOLFOX6 is permissible. Dose reductions or treatment interruption for reasons other than those described below may be made by the clinical investigator if it is deemed in the best interest of patient safety. Whenever possible, these decisions should first be discussed with the senior investigator. Note: response evaluation must be performed every 8 weeks even if cycles are delayed.

The next cycle should not be given until platelets $\geq$ 75 x 10^9/L and ANC $\geq$ 1.5 x 10^9/L, all other laboratory requirements defined in protocol Section 5.1.8 have been met (including creatinine), and all other toxicity is $\leq$ grade 2.

Suggested dose levels.

Doses of leucovorin do not need reductions after toxicity. It is not anticipated that the dose of reolysin will need to be reduced.

	FOLFOX doses (mg/m^2)			Bevacizumab (mg/kg)	Reolysin ($TCID_{50}$)*
	Oxaliplatin	5FU bolus	5FU infusion		
Starting dose	85	400	2400	5	3x10^{10}
1st dose reduction	65 mg/m^2	320	2000	Not applicable**	1x10^{10}
2nd dose reduction	50 mg/m^2	200	1600		Discontinue
3rd dose reduction	Discontinue				Discontinue

* It is not anticipated that the dose of reolysin will require reduction.
** No dose modification is required. Doses will be held for bevacizumab related toxicities. If toxicity does not resolve, bevacizumab will be discontinued.

Hypertension (Bevacizumab only)

Patients who develop hypertension should have their blood pressure monitored daily until ≤ grade 1. Consult Appendix VI for tables and flow diagrams regarding management.

Grade of Event	Management/Next Dose*
Grade 1	Consider increased BP monitoring
Grade 2 • Persistent mild hypertension (140-149/90-99)	Consider starting or adding a long acting DHP CCB (Table 1 of Appendix VI). Gradually increase dose up to maximum dose until BP control.
• Persistent moderate hypertension (150-179/100-109)	Start/ add long acting DHP CCB (Table 1 of Appendix VI). Gradually increase dose up to maximum dose to control BP. If partial or no control and still in the moderate hypertension range, add an additional drug and increase dose up to maximum dose until BP control. If partial or no control thereafter, and still in the moderate range, **hold** bevacizumab and add an additional drug at increasing dose up to maximum dose until BP control to mild hypertension. Restart bevacizumab only when controlled
Grade 3 • Severe (>180/>110)	<u>If asymptomatic</u>: **Hold** bevacizumab and start immediate antihypertensive therapy with 2 drug combination including at least a DHP CCB (table 1 of Appendix VI). - Increase dose up to maximum dose of both agents until BP control. If control to mild hypertension range, restart bevacizumab. - If partial or no BP control, add another drug and increase dose up to maximum dose until BP control (see Appendix VI). Restart bevacizumab only when controlled <u>If symptomatic</u>: stop bevacizumab, hospitalize with aggressive I.V. therapy as per hypertensive crisis management (see Appendix VI)
Grade 4 • Hypertensive crisis	Discontinue permanently
* Discontinue permanently if hold > 3 weeks	

Proteinuria (Bevacizumab and Reolysin)
Initial screening may be done with urinalysis of spot samples. If protein ≥ grade 2, 24-hour urine collection and urine microscopy is mandatory. A urine specimen should be taken and frozen for virus shedding studies (contact NCIC CTG for instructions).

Degree of proteinuria	Bevacizumab dosing	Reolysin dosing
Grade 1	Administer bevacizumab dose as scheduled	Administer reolysin dose as scheduled
Grade 2	Administer bevacizumab dose as scheduled. - Collect 24 hour urine for total protein* within 3 days prior to the next scheduled bevacizumab administration.	Hold dose until results of urine microscopy are available. • If no evidence of glomerulonephritis on microscopy, - Administer reolysin doses as scheduled** - Collect 24 hour urine for total protein* within 3 days prior to start of the next cycle • If active sediment (suggestive of glomerulonephritis), - Hold dose - Collect 24-hour urine for protein immediately. - Investigate further (nephrology consult) May restart** when protein <2.0 g/24 hrs AND no evidence of glomerulonephritis
Grade 3	Discontinue therapy	

* 24 hr urine for protein
- If < 2g/24hours, administer as scheduled
- If 2-3.4g/24hrs, hold dose and recheck 24 hour urine prior to each cycle, resume therapy when < 2g/24 h

** If initial reolysin dose(s) are held due to urine screening, remaining reolysin doses that cycle may be given if protein result is <2g/24h.

Dose reductions for Neurotoxicity (Oxaliplatin only)
Only the dose of oxaliplatin should be modified for neurotoxicity. There is evidence that infusions of calcium gluconate and magnesium sulphate prior to and following oxaliplatin may reduce the incidence and severity of oxaliplatin induced peripheral neuropathy. Concomitant therapy with calcium gluconate and magnesium sulphate is permitted at the discretion of the investigator. Caution is warranted in patients with known hypercalcemia or those receiving therapy with digitalis or thiazide diuretics.

Adverse Event Grade	Duration of Toxicity		Persistent (present at start of next cycle)
	1 – 7 days	> 7 days	
Grade 1	No Change	No Change	Maintain dose level
Grade 2	No Change	No Change	Reduce 65mg/m^2
Grade 3	No Change	Reduce 65mg/m^2	Discontinue oxaliplatin
Grade 4	Discontinue oxaliplatin		Discontinue oxaliplatin
Pharyngolaryngeal dysesthesia	Hold infusion and observe the patient. Check oxygen saturation; if normal, an anxiolytic agent may be given. May restart at a slower. Increase duration of infusion to 6 hours for subsequent cycles.		

Dose Reductions for Other Hematological and Non-Hematological Toxicity (All Agents)

Worst toxicity with previous cycle or during therapy	FOLFOX6 *	Bevacizumab	Reolysin
Grade 4 ANC ≥ 7 days or ≥ G3 platelets	Hold until recovery * and reduce by 1 DL	**	**
Febrile neutropenia or thrombocytopenic bleeding	Hold until recovery * and reduce by 1 DL	**	**
Delay in next cycle by 2-3 weeks *** or 2 x 1 week delays	Hold until recovery * and reduce by 1 DL	**	**
Other grade 3 non-hematologic or intolerable grade 2 toxicity related to FOLFOX6	Hold until recovery * reduce by one DL	**	**
Gastrointestinal perforation or wound dehiscence requiring medical intervention, arterial or venous thromboemboli	Hold until recovery*. Consider discontinuing if grade 4.	Discontinue	Hold until recovery
Grade 3 or 4 skin toxicity	Hold until recovery and reduce fluorouracil by 1 DL *	**	**
Grade 3 or 4 Hypersensitivity	Discontinue causal agent	**	**
Pneumonitis, RPLS	Discontinue	Discontinue	**
Other grade 4 non-hematologic	Discontinue	Discontinue	Discontinue

* Do not retreat until the ANC is ≥ 1.5 x 10^9/L, the platelet count is ≥ 75 x 10^9/L, creatinine has returned to ≤ 1.5 x ULN and other non-hematologic toxicity ≤ grade 2.

** Hold start of next cycle until able to receive FOLFOX; no dose modification required

*** Discontinue if delay > 3 weeks

8.2 Duration of Therapy

Treatment will continue until the criteria for removal from protocol treatment have been met (see Section 12.0).

8.3 Concomitant Therapy

8.3.1 *Permitted*

- Other supportive and palliative care (e.g. pain control) as required throughout the study.
- Growth factors may be used according to centre policy but cannot be used in place of protocol defined dose adjustments or delays. Please consult NCIC CTG in the case of patients experiencing multiple delays as exceptions may be made for patients who are benefiting from protocol therapy..
- Anti-emetics or anti-diarrheal agents as required (see section 8.1.2).
- APAP (acetaminophen) may be used for the prophylaxis or treatment of the flu-like signs and symptoms especially fever, that are commonly associated with reolysin as described in section 8.1.2. Given that there are more than 600 products that contain APAP, it is also essential that patients be warned NOT to use other products containing APAP.

8.3.2 *Not permitted*

- Other anti-cancer therapy or investigational therapy.
- The use of NSAIDs should be avoided by patients with symptoms or risk factors for renal dysfunction and those with fever, dehydration, or prior to administration of contrast agents used in imaging.

9.0 EVALUATION DURING AND AFTER PROTOCOL TREATMENT

All patients entered on study must be evaluated according to the schedule outlined in Appendix I with documentation submitted according to the schedule in Appendix IV.

9.1 Evaluation During Protocol Treatment

Investigations		Timing
Physical Exam** including:	• history • weight • ECOG performance status • clinical tumour measurements • blood pressure • heart rate (pulse)	Day 1 each cycle*
Hematology**	• CBC, differential, platelets	Weekly for cycle 1 and 2 and then day 1 each cycle and as clinically indicated
Biochemistry**	• serum creatinine • bilirubin • alkaline phosphatase • AST, ALT • LDH • total protein	Weekly♦♦♦♦ for cycle 1 and 2, then day 1 each cycle and as clinically indicated
	• CEA	End of every second cycle (every 4 weeks)
Radiology***	• chest CT • abdominal/pelvic CT • other scans as necessary to follow known disease	Every 8 weeks****
Other Investigations**	• urinalysis ♦	Day 1 each cycle and as clinically indicated
Correlative Studies♦♦	• Blood samples for correlative studies	End of cycle 2 and at end of last cycle
Quality of Life**	• EORTC QLQ-C30	Day 1 cycle 5 and at off treatment
Adverse Events♦♦♦	Patients must be evaluated continuously for adverse events	

* Physical exam must be conducted by physician on participant list prior to reolysin contained cycles. For FOLFOX/bevacizumab cycles only, physical exam may be delegated according to centre policy. Person evaluating patients per protocol must be delegated that responsibility by PI and be on the participants list.

** Timing of Day 1 Assessments: Pre-treatment blood draws, physical exams, urinalysis and QoL may be done one working day prior to treatment if necessary (e.g. Friday for treatment on Monday, or to accommodate holidays). NOTE: labs do NOT need to be repeated on day 1 cycle 1.

*** To ensure comparability, baseline X-rays/CT/MRI/bone scans and subsequent X-rays/CT/MRI bone scans to assess response must be performed using identical technique (i.e. scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner).

**** Maintain schedule even if cycles are delayed.

♦ Initial screening may be done by dipstick. If protein ≥ grade 2, 24 hour urine collection and urine microscopy is mandatory. A urine specimen should be taken and frozen for virus shedding studies (contact NCIC CTG for instructions)

♦♦ Samples for correlative studies (blood, serum, plasma) required for ALL patients. See Section 17.0 and the Lab Manual for details.

♦♦♦ Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) (Appendix V).

♦♦♦♦ Day 8 Cycle 1 and 2 only: bilirubin, ALP, AST, ALT, LDH.

9.2 Evaluation After Protocol Treatment

All patients will be seen at 4 weeks after the end of last cycle date. Thereafter, continued follow-up is not required for patients who go off protocol treatment with progressive disease, except to document ongoing toxicities (until resolved to ≤ grade 2) and late toxicities (including second malignancies) and death. For patients who go off protocol treatment before progression is documented OR have objective CR, PR, or SD ongoing, follow-up and a Follow-Up Report will be required every 3 months until relapse/progression (see Appendix I for investigations to be performed). Death Report will be required for all patients. Due within 2 weeks of knowledge of death (see Appendix IV - Documentation for Study).

Investigations		Timing
History and Physical Exam:	• Blood pressure • ECOG performance status • tumour assessment (including clinical tumour measurement if applicable)	Four weeks after completion of protocol treatment
Laboratory Investigations	• CBC, differential, platelets • serum creatinine • bilirubin • alkaline phosphatase • AST and ALT • LDH • total protein • urinalysis*	Four weeks after completion of protocol treatment Every three months thereafter *only if ongoing protocol related toxicity until resolved to ≤ grade 2*
	• CEA	Four weeks after completion of protocol therapy Every three months thereafter until relapse/PD; *ONLY for patients with CR, PR, or SD ongoing*
Correlative Studies	• Blood sample	Four weeks after completion of protocol therapy if not done at off treatment
Radiology**	• as required to follow measureable disease, and as clinically indicated	Every three months thereafter until relapse/PD;. *ONLY for patients with CR, PR, or SD ongoing*
Quality of Life	• EORTC QLQ-C30	At four week evaluation if not completed at off treatment
Adverse Events	AEs graded according to the CTCAE (Appendix V)	Four weeks after completion of protocol treatment (See Appendix IV) Every three months thereafter *only if ongoing protocol related toxicity until resolved to ≤ grade 2*

* Initial screening may be done by dipstick. If protein ≥ grade 2, 24 hour urine collection and urine microscopy is mandatory. A urine specimen should be taken and frozen for virus shedding studies (contact NCIC CTG for instructions).

** To ensure comparability, baseline X-ray/CT/MRI bone scan and subsequent X-ray/CT/MRI/bone scan to assess response must be performed using identical technique (i.e. scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner). Either CT or MRI may be used for baseline and subsequent imaging, but the same imaging modality must be used for baseline and subsequent scans for each individual patient.

10.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

10.1 Definitions

10.1.1 *Evaluable for Toxicity*

All patients will be evaluable for toxicity from the time of their first treatment with reolysin or FOLFOX6/bevacizumab.

10.1.2 *Evaluable for RECIST Response*

All patients with measurable disease at baseline who have had their disease re-evaluated will be considered evaluable for response. Patients on therapy for at least this period and who meet the other listed criteria will have their response classified according to the definitions set out below *[Eisenhauer 2009]*. Patients should have response evaluations performed at least once while on study or within 4 weeks of last dose.

In some trials, late responses (i.e. after 6-8 cycles) have been observed.

10.1.3 *Evaluable for Quality of Life Response*

All patients who have completed the baseline questionnaire and at least one subsequent time point will be evaluable.

10.2 Objective Response and Evaluation Endpoints

Response and progression will be evaluated in this study using the revised international criteria (1.1) proposed by the RECIST (Response Evaluation Criteria in Solid Tumours) committee.

10.2.1 *Measurable Disease*

Measurable *tumour lesions* are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$ 20 mm with chest x-ray and as $\geq$ 10 mm with CT scan or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component $\geq$ 10 mm by CT scan). *Malignant lymph nodes* must be $\geq$ 15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumour measurements must be recorded in millimetres (or decimal fractions of centimetres). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

10.2.2 *Non-measurable Disease*

All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

10.2.3 *Target Lesions*

When more than one measurable tumour lesion is present at baseline all lesions up to *a maximum of 5 lesions total* (and a maximum of *2 lesions per organ*) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. Note that pathological nodes must meet the criterion of a short axis of ≥ 15 mm by CT scan and only the *short* axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed (see 10.2.4). At baseline, the sum of the target lesions (longest diameter of tumour lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

10.2.4 *Non-target Lesions*

All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered *non-target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as “present” or “absent”.

10.2.5 *Objective (RECIST 1.1) Response Definition*

All patients will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below:

Complete Response (CR): disappearance of *target* and *non-target* lesions and normalization of tumour markers. Pathological lymph nodes must have short axis measures < 10mm (Note: continue to record the measurement even if < 10mm and considered CR). Residual lesions (other than nodes < 10mm) thought to be non-malignant should be further investigated (by cytology or imaging) before CR can be accepted. Confirmation of response is not required.

Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumour lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non target lesions must be non-PD. Confirmation of response is not required.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on study. Minimum duration of stable disease is 4 weeks.

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as reference the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥ 5mm. Appearance of new lesions will also constitute progressive disease (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumour burden has increased sufficiently to merit discontinuation of treatment or where the tumour burden appears to have increased by at least 73% in volume. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

Table: Time Point response: Integration of Target, Non-Target and New lesions into response assessment:

Target Lesions	Non-Target Lesions	New Lesions	Overall Response at this time point
Target lesions ± non target lesions			
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not all evaluated	No	PR
PR	Non-PD/ not all evaluated	No	PR
SD	Non-PD/ not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Any	PD
Any	PD	Any	PD
Any	Any	Yes	PD
Non target lesions ONLY			
No Target	CR	No	CR
No Target	Non-CR/non-PD	No	Non-CR/non-PD
No Target	Not all evaluated	No	NE
No Target	Unequivocal PD	Any	PD
No Target	Any	Yes	PD
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.			

Best Response:
In this trial confirmation of response is NOT required.

10.2.6 *Response Duration*

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

10.2.7 *Stable Disease Duration*

Stable disease duration will be measured from the time of start of treatment until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

11.0 SERIOUS ADVERSE EVENT REPORTING

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for Adverse Event (AE) reporting (version can be found in Appendix V). All appropriate treatment areas should have access to a copy of the CTCAE. A copy of the CTCAE can be downloaded from the CTEP web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

All serious adverse events (SAE) defined as per ICH guidelines (see below) and other adverse events must be recorded on case report forms. In addition, all "reportable" serious adverse events are subject to expedited reporting using the NCIC CTG SAE form. The term 'reportable SAE' is used in the definitions which follow to describe those SAEs which are subject to expedited reporting to NCIC CTG.

11.1 Definition of a Reportable Serious Adverse Event

- All serious adverse events related to protocol treatment (reolysin and/or folfox/bevacizumab) regardless of whether they are unexpected or not, occurring during the treatment period and within 30 days after the last protocol treatment administration, must be reported in an expedited manner. Any late serious adverse event occurring after this 30-day period which is unexpected and related to protocol treatment must also be reported in an expedited manner (see Section 11.2 for reporting instructions).
- A serious adverse event (SAE) is any adverse event that at any dose:
  - results in death
  - is life-threatening
  - requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospital admissions for study drug administration, transfusional support, scheduled elective surgery and admissions for palliative or terminal care)
  - results in persistent or significant disability or incapacity
  - is a congenital anomaly/birth defect

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the events listed above.

11.2 Serious Adverse Event Reporting Instructions

All reportable serious adverse events must be reported using a web-based Electronic Data Capture (EDC) system being used for this trial. For details about accessing the EDC system and completing the on-line SAE report form, please refer to the NCIC CTG Generic Data Management Guidebook for SAE Reporting posted on the IND. 210 section of the NCIC CTG website (www.ctg.queensu.ca).

Within 24 hours:	Complete preliminary Serious Adverse Event Report and submit to NCIC CTG via EDC system.
Within 7 days:	Update Serious Adverse Event Report as much as possible and submit report to NCIC CTG via EDC system.

AMEND #1: 2013-APR-25; ADMIN UPDATE #1: 2014-MAY-23 *(withdrawn)*; AMEND #3: 2014-JUN-16

EDC SAE web application interruption:

In the rare event that internet connectivity to the EDC SAE system is disrupted, please print and complete a paper copy of the SAE Report, available from the trial specific website.

FAX paper SAE Report to:

Ashley Theis, Study Coordinator
NCIC Clinical Trials Group
Fax No.: 613-533-2411

Please use the same timelines for submission as for direct EDC reporting.

Once internet connectivity is restored, the information that was FAXED to NCIC CTG on the paper SAE Report must also be entered by the site into the EDC SAE web application.

Local internet interruption:

If you are unable to access the EDC SAE system, and cannot access a paper copy of the SAE Report from the trial website, please phone the IND trial team (613-533-6430) to obtain a copy of the SAE Report by FAX. Once completed, the report must be FAXED back to NCIC CTG as indicated above. Once internet connectivity is restored, the information that was FAXED to NCIC CTG on the paper SAE Report must also be entered by the site into the EDC SAE web application.

In cases of prolonged internet interruptions, please contact the NCIC CTG Safety Desk for further instructions (613-533-6430).

11.3 NCIC CTG Responsibility for Reporting Serious Adverse Events to Health Canada

The NCIC CTG will provide expedited reports of SAEs to Health Canada (Office of Clinical Trials and the Biologics and Genetics Therapies Directorate) for those events which meet regulatory requirements for expedited reporting, i.e. events which are BOTH serious AND unexpected, AND which are thought to be related to protocol treatment (or for which a causal relationship with protocol treatment cannot be ruled out).

11.4 NCIC CTG Reporting Responsibility to Oncolytics Biotech Inc.

Oncolytics Biotech Inc. will be notified of all serious adverse events reported to Health Canada. NCIC CTG as sponsor will determine regulatory reportability in Canada.

11.5 NCIC CTG and Oncolytics Biotech Inc. Reporting Responsibilities

Oncolytics Biotech Inc. will report all reolysin regulatory reportable serious adverse events from non-NCIC CTG trials (Safety Updates) to Health Canada and also provide to NCIC CTG within the timelines outlined in the contract. NCIC CTG will review these events to determine which meet the criteria (serious, unexpected, drug related) for IND.210 investigator distribution.

11.6 Reporting Safety Reports to Investigators

NCIC CTG will notify Investigators of all Safety Reports (Serious Adverse Events (SAEs) from this trial and Safety Updates (SUs) from other clinical trials) that are reportable to regulatory authorities in Canada as reported to the NCIC CTG. This includes all serious events that are unexpected and related (i.e. possibly, probably, or definitely) to protocol treatment. The reports will be posted to the NCIC CTG trial IND.210 web-based safety monitoring utility.

Investigators must notify their Research Ethics Boards (REBs) of events which involve corrective action(s) to be taken as a result of the event(s) such as protocol and/or informed consent changes. The date of REB Submission for these SAEs and SUs will need to be entered into the NCIC CTG trial IND.210 web based safety monitoring utility and documentation of REB submission must be retained in the study binder on site. The REB submission template provided by NCIC CTG can be used to assist with tracking, submission, filing and monitoring.

The submission of events to your ethics board should be done as soon as possible (we suggest within 30 days). REB submissions greater than 90 days from the date of notification will be regarded as delinquent and a major deficiency will be assigned. These safety reports are to be filed in the trial files on site.

12.0 PROTOCOL TREATMENT DISCONTINUATION AND THERAPY AFTER STOPPING

12.1 Criteria for Discontinuing Protocol Treatment

Patients may stop protocol treatment in the following instances:

- Intercurrent illness, which would, in the judgement of the investigator, affect assessments of clinical status to a significant degree, and require discontinuation of protocol therapy.
- Unacceptable toxicity as defined in Section 8.0.
- Objective tumour progression or disease recurrence as defined in section 10.
- Request by the patient.
- Completion of therapy as outlined below. Efforts should be made to maintain the investigations schedule and continue follow-up, even if patients discontinue protocol treatment prematurely and/or no longer attend the participating institution.

12.2 Duration of Protocol Treatment

(see Section 10.0 for response definition)

- In the absence of serious or unmanageable toxicity or disease progression, patients may continue on therapy.
- Patients randomized to the FOLFOX6/bevacizumab/reolysin arm may continue on FOLFOX6/ bevacizumab or reolysin, if the other component of protocol treatment was discontinued due to unacceptable toxicity, at the discretion of the investigator; cross over is not permitted. Patients who continue treatment with either FOLFOX/Bevacizumab or reolysin are considered on study and all evaluations and data submission are required as outlined in sections 9.1 and Appendix IV unless otherwise discussed with the Senior Investigator.

12.3 Therapy After Protocol Treatment is Stopped

Further treatment, if any, is at the discretion of the investigator.

12.4 Follow-up Off Protocol Treatment

All patients will be seen at 4 weeks after completion of protocol therapy. Thereafter, continued follow-up is not required for patients who go off protocol treatment with progressive disease, except to document ongoing toxicities (until resolved to $\leq$ grade 2) and late toxicities (including second malignancies) and death. For patients who go off protocol treatment before progression is documented OR have objective CR, PR, or SD ongoing, follow-up and a Follow-Up Report will be required every 3 months until relapse/progression (see Appendix I for investigations to be performed). If the patient starts new anticancer therapy, contact the study coordinator to discuss whether further follow-up is required. Death Report will be required for all patients. Due within 2 weeks of knowledge of death (see Appendix IV - Documentation for Study).

13.0 CENTRAL REVIEW PROCEDURES AND TISSUE COLLECTION

13.1 Central Radiology Review

At the conclusion of the trial, a central review of scans may be carried out if any responses have been claimed. For purposes of reporting, the results of both local and central radiology reviews will be included.

13.2 Central Pathology Review

There will be no central pathology review for this study.

13.3 Tissue Collection

Archival tissue samples will be collected on all patients for correlative studies. *See Section 17.0 for complete details.*

14.0 STATISTICAL CONSIDERATIONS

14.1 Objectives and Design

This is an open label multicentre randomized phase II trial to determine the anti-tumour activity of reolysin in patients with colorectal cancer.

The expected progression free survival for FOLFOX6/bevacizumab is 8.5 months. The clinical trial will accrue up to 100 evaluable patients (50 per arm). Patients will have an equal probability of receiving reolysin plus FOLFOX6/bevacizumab or FOLFOX6/bevacizumab alone. Six to 9 additional patients will be accrued in a safety run in to evaluate the safety and tolerability of the combination.

Patients will be stratified for the following factors

- *KRAS* mutation status (if known at the time of randomization – if unknown will be corrected for at the time of the primary analysis)
- prior adjuvant chemotherapy

14.2 Primary Endpoints and Analysis

The primary objective of the study is progression free survival (progression is defined in Section 10). Secondary endpoints include evaluation of:

- Changes in CEA levels
- Objective response rate
- The effect of both treatments on overall survival (OS)
- Potential prognostic or predictive molecular factors by assessment of archival tumour tissue or blood samples.
- Quality of Life

14.3 Sample Size and Duration of Study

Accrual and Analysis:
The clinical trial will accrue up to 100 evaluable patients (50 per arm) in around 13 months. Final analysis will be performed when 50 PFS events are observed, which is projected at the time after all patients are followed for at least 6 months. One-sided log-rank test adjusting for stratification factors at randomization will be used the compare the PFS between two treatment groups.

Since the survival data was immature at the time of the primary analysis, an additional analysis with a focus on overall survival will be performed when 80 deaths are observed.

Significance Level and Power:
The expected progression free survival for FOLFOX6/bevacizumab is 8.5 months. With a total sample size of 100 accrued in around 13 months and followed for 6 months, we will have 80% power to detect a difference between two treatment groups in PFS from 8.5 to 15.5 months (i.e. hazard ratio of 0.55) with a one-sided alpha 0.1.

The number of deaths (80) required for the final analysis of OS will enable us to detect a hazard ratio of 0.62 with 80% power and a one-sided 0.1 alpha level which is corresponding to an increase of median survival from 15 months for patients on FOLFOX6/bevacizumab to 24.2 months for patients on reolysin plus FOLFOX6/bevacizumab.

Accrual and Duration of Study:
The estimated monthly accrual for this study is 8 patients a month. Thus, patient accrual is expected to be completed within 13 months. Additional 6 months is required to allow the PFS data to mature.

The estimated event rate of survival is around 3 per month and therefore, 6 to 8 more months of follow-up would be required to observe number of events required for final analysis of survival.

14.4 Safety Monitoring

Adverse events will be monitored on an ongoing basis by the central office and their frequencies reported annually at investigators' meetings.

14.5 Quality of Life

The quality of life of patients will be assessed using EORTC QLQ-C30. The EORTC QLQ-C30 is a self-administered cancer specific questionnaire with multi-dimensional scales. It consists of both multi-item scales and single item measures, including five functional domains, a global quality of life domain, three symptom domains, and six single items. Questionnaire compliance rates will be ascertained for each group at each measurement time point. Scoring of the EORTC QLQ-C30 data will be completed following the procedures recommended by the EORTC Study Group on Quality of Life. For each domain or single item measure a linear transformation will be applied to standardize the raw score to range between 0 and 100 and the mean and standard deviation of the baseline scores and changes from baseline at each of post-baseline assessments will be calculated. The Wilcoxon test will be used to compare the differences in change scores from baseline between the two groups. Time to definitive quality of life deterioration, defined a priori as a 10 unit or greater deterioration from baseline scores, for EORTC QLQ-C30 physical function and global QoL scores will be the primary analyses for quality of life and analysed by log-rank test and Kaplan-Meier methodology. The Hockberg procedure will be used to adjust for multiple testing *[Hochberg 1988]*. It has been shown that 10 unit change is a degree of change that is perceptible and meaningful to patients *[Osoba 1998]*. The standard NCIC CTG QOL Response Analysis categorizing patients as either having improved, stable, or worsened QOL will also be performed *[Osoba 2005]*. In this analysis, a change score of 10 points from baseline is defined a priori as clinically relevant. For functional scales and global health status, patients will be considered to have QOL improvement if reporting a score 10- points or better than baseline at any time of QOL assessment. Conversely, patients will be considered worsened if reporting a score minus 10-points or worse than baseline at any time of QOL assessment without any improvement. Patients whose scores fall between 10-point changes from baseline at every QOL assessment will be considered as stable. In contrast to functional scales, for the determination of patient's QOL response, classification of patients into improved and worsened categories will be reversed for symptom scales. Other exploratory QoL evaluations will be completed as appropriate.

15.0 PUBLICATION POLICY

15.1 Authorship of Papers, Meeting Abstracts, Etc

15.1.1 The results of this study will be published. Prior to trial activation, the chair will decide whether to publish the trial under a group title, or with naming of individual authors. If the latter approach is taken, the following rules will apply:

- The first author will generally be the chair of the study.
- A limited number of the members of the NCIC Clinical Trials Group and Oncolytics Biotech Inc., may be credited as authors depending upon their level of involvement in the study.
- Additional authors, up to a maximum of 15, will be those who have made the most significant contribution to the overall success of the study. This contribution will be assessed, in part but not entirely, in terms of patients enrolled and will be reviewed at the end of the trial by the study chair.

15.1.2 In an appropriate footnote, or at the end of the article, the following statement will be made:

> "A study coordinated by the NCIC Clinical Trials Group. Participating investigators included: (a list of the individuals who have contributed patients and their institutions)."

15.2 Responsibility for Publication

It will be the responsibility of the Study Chair to write up the results of the study within a reasonable time of its completion. If after a period of six months following study closure the manuscript has not been submitted, the central office reserves the right to make other arrangements to ensure timely publication.

Dissemination of Trial Results

NCIC CTG will inform participating investigators of the primary publication of this trial. The complete journal reference and, if where publicly available, the direct link to the article will be posted on the Clinical Trial Results public site of the NCIC CTG web site (http://www.ctg.queensu.ca).

15.3 Submission of Material for Presentation or Publication

Material may not be submitted for presentation or publication without prior review by Oncolytics Biotech Inc., the NCIC CTG Senior Investigator, Senior Biostatistician, Study Coordinator, and approval of the Study Chair. Individual participating centres may not present outcome results from their own centres separately. Supporting groups and agencies will be acknowledged.

16.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

16.1 Regulatory Considerations

All institutions in Canada must conduct this trial in accordance with International Conference on Harmonization-Good Clinical Practice (ICH-GCP) Guidelines.

This trial is being conducted under a Clinical Trial Application (CTA) with Health Canada. As a result, the conduct of this trial must comply with Division 5 of the Canadian Regulations Respecting Food and Drugs (Food and Drugs Act).

16.2 Inclusivity in Research

NCIC CTG does not exclude individuals from participation in clinical trials on the basis of attributes such as culture, religion, race, national or ethnic origin, colour, mental or physical disability (except incapacity), sexual orientation, sex/gender, occupation, ethnicity, income, or criminal record, unless there is a valid reason (i.e. safety) for the exclusion.

In accordance with the Declaration of Helsinki and the Tri-Council Policy Statement (TCPS), it is the policy of NCIC CTG that vulnerable persons or groups will not be automatically excluded from a clinical trial (except for incompetent persons) if participation in the trial may benefit the patient or a group to which the person belongs.

However, extra protections may be necessary for vulnerable persons or groups. It is the responsibility of the local investigator and research ethics board (REB) to ensure that appropriate mechanisms are in place to protect vulnerable persons/groups. In accordance with TCPS, researchers and REBs should provide special protections for those who are vulnerable to abuse, exploitation or discrimination. As vulnerable populations may be susceptible to coercion or undue influence, it is especially important that informed consent be obtained appropriately.

Centres are expected to ensure compliance with local REB or institutional policy regarding participation of vulnerable persons/groups. For example, if a vulnerable person/group would be eligible for participation in a NCIC CTG clinical trial under this policy but excluded by local policy, it is expected that they would not be enrolled in the trial. It is the centre's responsibility to ensure compliance with all local SOPs.

It is NCIC CTG's policy that persons who cannot give informed consent (i.e. mentally incompetent persons, or those physically incapacitated such as comatose persons) are not to be recruited into NCIC CTG studies. It is the responsibility of the local investigator to determine the subject's competency, in accordance with applicable local policies and in conjunction with the local REB (if applicable).

Subjects who were competent at the time of enrolment in the clinical trial but become incompetent during their participation do not automatically have to be removed from the study. When re-consent of the patient is required, investigators must follow applicable local policies when determining if it is acceptable for a substitute decision maker to be used. NCIC CTG will accept re-consent from a substitute decision maker. If this patient subsequently regains capacity, the patient should be re-consented as a condition of continuing participation.

16.3 Obtaining Informed Consent

It is expected that consent will be appropriately obtained for each participant/potential participant in an NCIC CTG trial, in accordance with ICH-GCP section 4.8. The centre is responsible for ensuring that all local policies are followed.

Additionally, in accordance with GCP 4.8.2, NCIC CTG may require that participants/potential participants be informed of any new information may impact a participant's/potential participant's willingness to participate in the study.

Based upon applicable guidelines and regulations (Declaration of Helsinki, ICH-GCP), a participating investigator (as defined on the participants list) is ultimately responsible, in terms of liability and compliance, for ensuring informed consent has been appropriately obtained. NCIC CTG recognizes that in many centres other personnel (as designated on the participants list) also play an important role in this process. In accordance with GCP 4.8.5, it is acceptable for the Principal Investigator to delegate the responsibility for conducting the consent discussion.

NCIC CTG requires that each participant sign a consent form prior to their enrollment in the study to document his/her willingness to take part. NCIC CTG may also require, as indicated above, that participants/potential participants be informed of new information if it becomes available during the course of the study. In conjunction with GCP 4.8.2, the communication of this information should be documented.

NCIC CTG allows the use of translators in obtaining informed consent. Provision of translators is the responsibility of the local centre. Centres should follow applicable local policies when procuring or using a translator for the purpose of obtaining informed consent to participate in a clinical trial.

In accordance with ICH-GCP 4.8.9, if a subject is unable to read then informed consent may be obtained by having the consent form read and explained to the subject.

16.4 Discontinuation of the Trial

If this trial is discontinued for any reason by the NCIC CTG all centres will be notified in writing of the discontinuance and the reason(s) why. If the reason(s) for discontinuance involve any potential risks to the health of patients participating on the trial or other persons, the NCIC CTG will provide this information to centres as well.

If this trial is discontinued at any time by the centre (prior to closure of the trial by the NCIC CTG), it is the responsibility of the principal investigator to notify the NCIC CTG of the discontinuation and the reason(s) why.

Whether the trial is discontinued by the NCIC CTG or locally by the centre, it is the responsibility of the principal investigator to notify the local Research Ethics Board and all clinical trials subjects of the discontinuance and any potential risks to the subjects or other persons.

16.5 Retention of Patient Records and Study Files

All essential documents must be maintained as per C.05.012 and in accordance with ICH-GCP.

The Principal Investigator must ensure compliance with the Regulations and the GCP Guideline from every person involved in the conduct of the clinical trial at the site.

Essential documents must be retained for 25 years following the completion of the trial at the centre (25 years post final analysis, last data collected, or closure notification to REB, whichever is later), or until notified by NCIC CTG that documents no longer need to be retained.

In accordance with GCP 4.9.7, upon request by the monitor, auditor, REB or regulatory authority, the investigator/institution must make all required trial-related records available for direct access.

NCIC CTG will inform the investigator/institution as to when the essential documents no longer need to be retained.

16.6 Centre Performance Monitoring

This study is eligible for inclusion in the Centre Performance Index (CPI).

Forms are to be submitted according to the schedule in the protocol. There are minimum standards for performance.

16.7 On-Site Monitoring/Auditing

NCIC CTG site monitoring/auditing will be conducted at participating centres in the course of the study as part of the overall quality assurance program. The monitors/auditors will require access to patient medical records to verify the data, as well as essential documents, standard operating procedures (including electronic information), ethics and pharmacy documentation (if applicable).

As this trial is conducted under a CTA with Health Canada, your site may be subject to an inspection by the Health Canada Inspectorate.

Oncolytics Biotech Inc. has reserved the right to audit participating centres. Audits may only be conducted after consultation with NCIC CTG.

16.8 Case Report Forms

A list of forms to be submitted, as well as expectation dates, are to be found in Appendix IV.

This trial will use a web-based Electronic Data Capture (EDC) system for all data collection except for Quality of Life. For details of accessing the EDC system and completing the on-line Case Report Forms please refer to the "Registration/Randomization and Data Management Guidebook" posted on the IND.210 area of the NCIC CTG web-site (www.ctg.queensu.ca).

17.0 TRANSLATIONAL RESEARCH STUDIES

This trial is one of four phase II trials conducted by NCIC CTG with a total of more than 400 patients planned for accrual and as such will create a rich resource to validate putative biomarkers as well as explore discovery of new markers related to the use of biologic therapies for cancer. Prognostic biomarkers are of interest, as are biomarkers that may provide evidence of a pharmacodynamic effect of reolysin. The identification of predictive markers is an important step in allowing patient selection to optimize treatment choices, and ideally would lead to personalized and cost effective therapies

	Tumour*	Paxgene (DNA)*	Plasma*	Serum*
Baseline	✓	✓	✓	✓
End Cycle 2			✓	✓
Off treatment			✓	✓
Additional samples	✓			
* each has mandatory AND optional planned/potential assays				

17.1 Correlative Studies of Archival Paraffin Embedded Tumour Samples– *All patients*

The collection of a representative block of the diagnostic tumour tissue to enable correlative studies is an important part of this trial. Prognostic biomarkers are of interest, as are biomarkers that may provide evidence of a pharmacodynamic effect of reolysin. The identification of predictive markers is an important step in allowing patient selection to optimize treatment choices, and ideally would lead to personalized and cost effective therapies. For this reason, ***collection of a representative tumour block from a biopsy taken prior to study entry, is a mandatory part of this study***. All additional tumour samples from biopsies that may be taken during and/or at end of study should also be submitted. Centres who are unable to submit the block immediately MUST consult NCIC CTG prior to randomizing a patient as the routine submission of unprepared slides is not acceptable (NCIC CTG will explore whether submission of cores, blocks for immediate return, or dipped slides may be an acceptable alternative)

Reovirus depends upon aberrant EGFR/RAS signaling for its replication and cytotoxic activity *[Thirukkumaran 2009]*. Aberrant pathway activation is reported in several malignancies including lung, prostate, colon and breast cancers. In the setting of lung cancer (NSCLC), it has been demonstrated that selection of patients with KRAS or EGFR mutated/amplified tumors led to a clinical benefit rate of 90% for therapy with a Reovirus PLUS paclitaxel/carboplatin combination *[Villalona-Calero 2011]*. Although RAS mutation is not proposed to be an initiating event in the malignant evolution of prostate cancer, and observed KRAS mutation rate in primary prostate cancer samples is low *[Moul 1992]*, in vivo studies have implicated cross-talk between the PTEN/PI3K/AKT pathway and the mitogen activated protein kinase pathway which may predispose to reovirus susceptibility *[Kinkade 2008]*. Furthermore, recent data has shown that ras/raf pathway alterations in CRPC metastases (as opposed to primary tissue) were seen in up to 90% of cases with a KRAS mutation rate of 32% *[Taylor 2010]*. While the rationale for reoD in mCRPC is predicated on factors outlined above that are independent of the RAS/MEK/ERK pathway, these specific observations would support both the evaluation of reovirus in this population and the interrogation of KRAS as a potential predictive marker. Further, EGFR alterations are reported in 30-40% of CRPC samples *[de Muga 2010]* and so this is another potential predictive marker for reovirus therapy in this cohort. In patients with breast cancer, EGFR expression is common, although KRAS is mutated in only a minor fraction of breast tumors (5%). In advanced colorectal cancer, KRAS somatic mutations predict resistance to monoclonal antibodies targeting epidermal growth factor receptor (EGFR).

Myeloid-derived suppressor cells (MDSCs) expand during cancer, inflammation and infection, and suppress T-cell responses. Their presence in the tumor microenvironment has been suggested to have a causative role in promoting tumor-associated immune suppression. Preliminary data suggest that they may be prognostic. COX2 is a key factor in the activation of MDSC, through regulation of arginase 1, iNOS and prostaglandin E2 (PGE2). In an in vivo model of RCC, sunitinib decreases MDSC (measured as decrease in splenic MDSC) which was associated with an enhanced adaptive anti-tumor response to reolysin (preliminary data from Dr. Morris). In ovarian cancer models, treatment with reolysin had antitumor activity and was associated with decreased frequency of MDSC *[Gujar 2013]*. Shojaei et al. reported that accumulation of MDSC (CD11b+Gr1+ cells) in tumours renders them refractory to anti-angiogenic blockage by VEGF antibodies *[Shojael 2007]*. We hypothesize that antitumor activity of reolysin will be associated with decreased frequency of MDSC and in trials that contain bevacizumab, bevacizumab will decrease MDSC and enhance adaptive anti-tumor response to reolysin *[Adair 2012]*. Quantification of MDSCs can be conducted using IHC methods.

Planned studies (mandatory)

1. Assays for Common Tumour Based Mutations.

   OncoCarta (Sequenom) mass spectrometry mutation profiling will be performed as a generic screen for tissue mutations, including EGFR exons 18, 19, 20 and 21 as well as KRAS codons 12, 13 and 61 and Braf.

2. Assays for Copy Number

   FISH will be used to evaluate gene copy number for selected genes relevant for the tumour type being studied, including EML4-ALK FISH for lung cancer patients and PTEN FISH for prostate cancer patients

3. Immunohistochemical assays.

   Assays planned include ALK for lung cancer patients and Myeloid Derived Suppressor Cells (MDSC) *[Gabrilovich 2009]*.

Future banking (optional)

This trial is one of four phase II trials conducted by NCIC CTG with a total of more than 400 patients planned for accrual. A pooled tumour bank, from consenting patients will be created and other exploratory correlative studies conducted.

Directions

At the same time that the baseline form is submitted, an original tumour block should be sent to the NCIC CTG Pathology Coordinator. Centres should contact NCIC CTG if they are unable to submit a tumour block, as sufficient tissue is required for the assays described above. Upon receipt, the NCIC CTG pathology coordinator will then send appropriate material, along with information regarding NCIC CTG protocol number and an assigned unique tumour bank ID number to the research laboratory(ies) where these assays will be done.

Ship tumour block along with a copy of the completed Archival Tumour Tissue Submission Form to:

Shakeel Virk
Pathology Coordinator NCIC Clinical Trials Group
Richardson Labs Bldg, 4th Floor
88 Stuart St.
Queen's University
Kingston, ONK7L 3N6
Tel: 613-533-2906
Fax: 613-548-2486
Email: virk@cliff.path.queensu.ca

17.2 Correlative Studies of Serum and Plasma Samples – *All patients*

The NCIC CTG is interested in exploring the use of surrogate tissues such as serum and plasma in evaluating potential prognostic or predictive biomarkers, or as evidence of pharmacodynamic effects of reolysin. The collection of these samples in these four large phase II trials, with matching tissue based biomarkers is an important objective of these trials. Blood, , serum and plasma samples will be collected and banked for planned and future studies from all patients. In this study, samples will be taken at baseline, end of cycle 2 and at off treatment.

Collection and shipping details will be provided in the Laboratory Manual at start up.

Planned studies (mandatory)

1. KRAS and EGFR mutations

   An 8.5 mL blood sample will be drawn at baseline and collected into PAXgene Blood DNA tubes. Samples will be batched and shipped to Chi Lab in Vancouver for further analysis. RT-PCR will be undertaken on isolated DNA to detect the 3 most frequent KRAS (codon 12, 13 and 61) and EGFR (exons 18 and 21) mutations EntroGen, Tarzana, CA, USA).

2. Serum cytokines, autoimmune/reactive antibodies, anti-viral responses, metabolomics

   A growing body of knowledge derived from pre-clinical investigations has strongly implicated anti-tumour and anti-viral immune responses as key contributors to the anti-tumour effects of oncolytic reovirus. Therefore, we will evaluate these parameters using serum from patients treated with reolysin. Serological responses (cytokines, antibodies and metabolites) provide rich sources of correlative data that can be used to understand the biological consequences of this novel therapy and may provide important biomarkers that will facilitate future patient management.

   Serum will be prepared within 2 hours of phlebotomy and stored at –20 C. At the end of the study, sera will be shipped to the Bramson lab on dry ice where they will be subject to a variety of analyses. Anti-viral antibodies will be measured using an in vitro neutralizing antibody assay. Anti-tumour antibodies will be characterized using a phage-display methodology with a phage expression library derived from a collection of human tumors. Serum cytokines will be analyzed using the Luminex MAGPIX platform. Finally, metabolic changes associated with treatment will be measured in sera using liquid chromatography-mass spectrometry.

   NOTE: It would be preferable to store the materials at –80 C. However, if –80 C freezers are not available at all study sites, -20C freezers are acceptable for short-term storage.

Exploratory studies (optional)

1. Evaluation of exosome for potential biomarkers and viral elements

   It has been demonstrated that prostate cancer cells secrete exosomes (membrane-bound vesicles containing proteins, mRNA and microRNAs derived from the donor cell cytoplasm) which can be isolated from the bloodstream. Serum samples will be collected at baseline, end of cycle 2 and end of treatment will be batched and shipped to NCIC CTG Tumour Bank. If the exosome assays and analyses in the reolysin NCIC CTG Prostate trial (IND.209) are promising, similar assays will be performed. Exosomes will be extracted from each sample using differential sucrose assisted centrifugation. Exosome abundance will be evaluated by Nanosight technology. Exosome content will be determined using Western Blotting, Mass Spectroscopy (for protein analysis) and quantitative PCR and micro-arrays (for transcriptome analysis).

2. Evaluation of plasma for microRNA as potential biomarkers

   Several studies have identified circulating microRNAs (miRNA) as non-invasive markers of malignancy. miRNA are small RNA molecules of 21-23 nucleotides that bind with imperfect complementarity to sequences in specific mRNA targets and typically silence their expression and have been implicated in tumour progression by modulating oncogenic and tumour suppressor pathways. In prostate cancer, several circulating miRNAs have been identified as having prognostic and predictive potential, including association with development of castration resistant disease such as with miR-141, miR-375, and miR-126 *[Selth 2012]*. This study will explore known circulating oncogenic miRNA profiles by low-density PCR arrays and correlate with treatment outcomes.

3. Evaluation of plasma or serum

   Potential studies include: serum EGFR extracellular domain (ECD), serum HER2 ECD, E-cadherin ELISAs, TGF-a and HGF.

Please refer to the Correlative Studies Manual for complete instructions.

18.0 REFERENCES

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APPENDIX I - PATIENT EVALUATION FLOW SHEET

Required Investigations	Pre-study (within 7 days prior to randomization, or as noted)	Day 1 each cycle	Weekly cycles 1 and 2 then day 1 each cycle	End cycle 2	Day 1 of cycle 5	Every 8 weeks	4 Weeks; then every 3 Months until Relapse/PD/ death
History & Physical Exam[1]							
Weight	X	X					
Performance Status	X	X					4 weeks ONLY
Clinical tumour measurements	X					X	X (if applicable)
Blood pressure, heart rate	X	X					4 weeks ONLY
Hematology & Biochemistry[1]							
CBC, differential, platelets	X		X				X
Serum creatinine, bilirubin, ALP, AST, ALT, LDH, total protein	X	X	X[2]				X
CEA	X					X[3]	X
Other Investigations							
Pregnancy test, *in women of childbearing potential only*	X						
Urinalysis[1]	X[4]	X[5]					X[5]
Quality of Life	X[6]				X		X[7] (at off treatment)
Radiology[8]							
Chest CT Abd./ Pelvic CT scan Other as clinically indicated	X (within 28 days prior to randomization; 35 if negative)					X	X
Correlative Studies[9]							
Archival tissue block (all patients)	Available prior to randomization						
Blood samples	X (AFTER randomization but BEFORE cycle 1 day 1)			X			X (at off treatment)
Adverse Events							
Adverse Events/ Baseline Symptoms[10]	Within 7 days prior to randomization		Continuously each visit				X

1 Timing of Day 1 Assessments: Pre-treatment blood draws, physical exams, urinalysis and QoL may be done one working day prior to treatment if necessary (e.g. Friday for treatment on Monday, or to accommodate holidays). NOTE: labs do NOT need to be repeated D1C1.
2 Biochemistry: Day 8 cycle 1 and 2 only: bilirubin, ALP, AST, ALT, and LDH.
3 CEA must be done end of every second cycle (every 4 weeks).
4 For protein screen using spot testing; if ≥ grade 2 repeat with mid-stream urine - if still ≥ grade 2 then urine collection for 24 hours to confirm < 2g/24hrs.
5 Initial screening may be done by dipstick. If protein ≥ grade 2, 24 hour urine collection and urine microscopy is mandatory. A urine specimen should be taken and frozen for virus shedding studies (contact NCIC CTG for instructions).
6 Within 14 days of randomization.
7 At 4 week post visit if not done at time off treatment.
8 All patients will be seen at 4 weeks. Thereafter, continued follow-up is not required for patients who go off protocol treatment with progressive disease, except to document toxicities and death. For patients who go off protocol treatment with CR, PR or SD ongoing, follow-up will be required every 3 months until relapse/progression.
9 See section 17.
10 Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) *(Appendix V)*.

APPENDIX II - PERFORMANCE STATUS SCALES/SCORES

PERFORMANCE STATUS CRITERIA

Karnofsky and Lansky performance scores are intended to be multiples of 10.

ECOG (Zubrod)		Karnofsky		Lansky*	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

* The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

APPENDIX III - DRUG DISTRIBUTION, SUPPLY AND CONTROL

Drug Distribution

Full details on Drug Distribution will be posted on the IND.210 website.

Reolysin will be supplied by Oncolytics to the distributor, and sent from the distributor to participating centres.

Drug Labelling

Drug for this study has been labelled in accordance with Health Canada regulations.

Initial Drug Supply

Once a centre is locally activated (following receipt and review of all required documentation), the NCIC CTG will authorize a start-up supply of reolysin to be shipped directly to the centre. The drug will be shipped to the centre within 5 working days of local activation. Note: Shipment will not be made on Fridays and weekends.

Drug accountability forms will be posted on the trial website.

Drug Ordering (Re-supply)

Subsequent requests for more drug should be made by authorized personnel at each centre as directed on the supplied NCIC Request for Drug Shipment form. The drug re-order form can be found on the IND.210 website.

Please allow sufficient time for shipment of drug.

Note: Shipment will not be made on Fridays and weekends. Drug accountability and drug re-order forms will be posted on the trial website for pharmacists to download.

Drug Accountability

The investigational products are to be prescribed only by the investigator and co-investigators on the participants list. Under no circumstances will the investigator allow the drug to be used other than as directed by the protocol. Accurate records must be maintained accounting for the receipt of the investigational product and for the disposition of the product (Drug Accountability Log).

Drug Destruction

Expired/used study drug may be destroyed as per local standard operating procedures. Destruction of expired/used drug must be documented on the Drug Accountability Log and a copy of the destruction certificate kept on file in the pharmacy. Instructions for return or destruction of unused drug will be supplied at the time of expiry and at trial closure.

** PLEASE NOTE **
DRUG FROM THIS SUPPLY IS TO BE USED ONLY
FOR PATIENTS REGISTERED ON THIS STUDY

Study drug shipped to participating centres may be transferred from the main hospital pharmacy to a satellite pharmacy, provided separate drug accountability records are maintained in each pharmacy. Investigational agent may NOT however, be transferred to pharmacies or physicians outside the participating centre.

APPENDIX IV - DOCUMENTATION FOR STUDY

Follow-up is required for patients from the time of randomization and will apply to all eligible and ineligible patients. This trial will use a web-based Electronic Data Capture (EDC) system for all data collection including SAE reporting *(see Section 11.0 for details regarding SAE reporting)*. For details about accessing the EDC system and completing the on-line Case Report Forms please refer to the Data Management Guidebook posted on the IND.210 area of the NCIC CTG web-site (www.ctg.queensu.ca).

Electronic Case Report Form	**To be Completed/Submitted Electronically:**	**Supporting Documentation to be sent by MAIL****
BASELINE REPORT	Due within 2 weeks of patient randomization. Note: Eligibility Checklist must be completed at time of randomization to confirm eligibility.	Copy of consent form signature page(s); relevant operative, pathology and radiology reports.
TREATMENT REPORT	To be completed every 2 weeks (i.e. after each reporting period). Due within 2 weeks of end of reporting period. This report documents treatment, adverse events, investigations and response assessment for each reporting period.	Relevant radiology reports
QUALITY OF LIFE	To be completed within 14 days prior to randomization, on day 1 of cycle 5 and at off treatment	Original QoL questionnaire
CORRELATIVE STUDIES	See section 17.0. To be completed and submitted with the tumour block at time of Baseline folder completion and with correlative samples at time of shipping.	Archival Tissue Submission Form & Request for Payment Form Correlative Sampling Form
END OF TREATMENT REPORT	To be completed when patient permanently discontinues the treatment agent. Due within 2 weeks of end of protocol treatment.	
4 WEEK POST TREATMENT REPORT	To be completed once on all patients, 4 weeks after going off protocol treatment. Due within 2 weeks after contact with patient.	Relevant radiology reports
FOLLOW-UP REPORT	Continued follow-up is not required for patients who go off protocol treatment with progressive disease, except to document ongoing toxicities (until resolved to ≤ grade 2) and late toxicities (including second malignancies). For patients who go off protocol treatment with response or stable disease ongoing, Follow-up Report to be completed every 3 months until relapse/progression. Due within 2 weeks after contact with patient.	Relevant radiology reports.
RELAPSE/ PROGRESSION REPORT	To be completed at the time of disease relapse or progression. Due within 2 weeks after contact with patient.	Relevant radiology reports if not previously submitted for another folder.
DEATH REPORT	Required for all patients.* Due within 2 weeks of knowledge of death.	Autopsy report, if done.
SERIOUS ADVERSE EVENT (SAE) REPORT	All reportable serious adverse events must be reported as described in Section 11.0. Preliminary NCIC CTG Serious Adverse Event Report due within 24 hours. Updated NCIC CTG Serious Adverse Event Report due within 7 days.	All relevant test reports; admission, discharge summaries/notes.

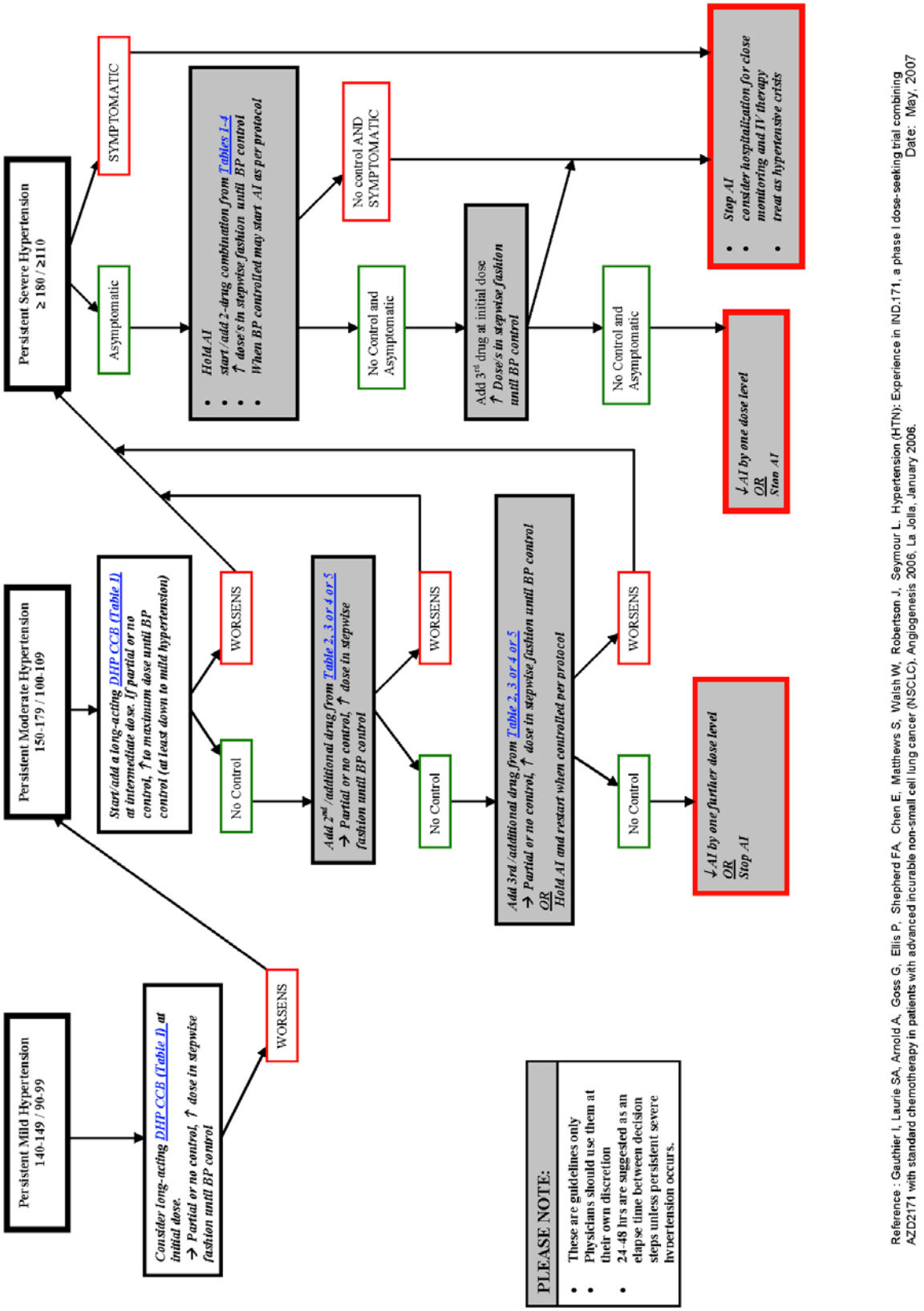
* Note: It is the investigator's responsibility to investigate and report the date/cause of death of any patient who dies during this period. Any death that occurs during protocol therapy or within 30 days after last dose must also be reported as a Serious Adverse Event as described in Section 11.

** Supporting documents should be mailed immediately after the report they refer to has been submitted electronically.

APPENDIX V - NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for Adverse Event (AE) reporting. All appropriate treatment areas should have access to a copy of the CTCAE. A copy of the CTCAE can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

APPENDIX VI - MANAGEMENT OF ANGIOGENESIS INHIBITOR (AI)-INDUCED HYPERTENSION



Reference : Gauthier I, Laurie SA, Arnold A, Goss G, Ellis P, Shepherd FA, Chen E, Matthews S, Walsh W, Robertson J, Seymour L. Hypertension (HTN): Experience in IND.171, a phase I dose-seeking trial combining AZD2171 with standard chemotherapy in patients with advanced incurable non-small cell lung cancer (NSCLC). Angiogenesis 2006, La Jolla, January 2006.
Date: May, 2007

Table 1. Dihydropyridine calcium-channel blockers

Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism?
Nifedipine XL	30 mg po qd	60 mg po qd	90 mg po qd	CYP 3A4 substrate
Amlodipine	2.5 mg po qd	5 mg po qd	10 mg po qd	CYP 3A4 substrate
Felodipine	2.5 mg po qd		10 mg po qd	CYP 3A4 substrate + inhibitor

Table 2: Selective β blockers

Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism?
Metoprolol	25 mg po bid	50 mg po bid	100 mg po bid	CYP 2D6 substrate
Atenolol	25 mg po qd	50 mg po qd	100 mg po qd	**No**
Acebutolol	100 mg po bid	200mg-300 mg po bid	400 mg po bid	Yes (possibly cyp 450)
Bisoprolol	2.5 mg po qd	5-10 mg po bid	20 mg po qd	Yes (possibly cyp 450)

Table 3. Angiotensin Converting Enzyme Inhibitors (ACEIs)

Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism?
Captopril	12.5 po tid	25 mg po tid	50 mg po tid	CYP 2D6 substrate
Enalapril	5 mg po qd	10-20 mg po qd	40 mg po qd	CYP 3A4 substrate
Ramipril	2.5 mg po qd	5 mg po qd	10 mg po qd	Yes (possibly cyp 450)
Lisinopril	5 mg po qd	10-20 mg po qd	40 mg po qd	No
Fosinopril	10 mg po qd	20 mg po qd	40 mg po qd	Yes (possibly cyp 450)
Rarely used:				
Perindopril	4mg po qd	none	8mg po qd	**Yes but not cyp-450**
Quinapril	10mg po qd	20 mg po qd	40 mg po /qd	**No**

Table 4. Angiotensin II Receptors Blockers (ARBs)

Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism?
Losartan	25mg po qd	50 mg po qd	100 mg po qd	CYP 3A4 substrate
Candesartan	4mg po qd	8-16 mg po qd	32mg po qd	CYP 2C9 substrate
Irbesartan	75mg po qd	150 mg po qd	300 mg po qd	CYP 2C9 substrate
Telmisartan	40 mg po qd	none	80 mg po qd	**Yes but not per cyp-450**
Valsartan	80 mg po qd	none	160mg po qd	**Yes but not per cyp-450**

Table 5. α and β blocker

Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism?
Labetolol	100 mg po bid	200 mg po bid	400 mg po bid	CYP 2D6 substrate and inhibitor

NB. Agents in bold characters are suggested as optimal choices to avoid or minimize potential drug-interactions

APPENDIX VII - QUALITY OF LIFE ASSESSMENT

Introduction

The assumption that control of symptoms will automatically improve quality of life is probably true but hasn't yet been tested, especially in determining how certain symptoms may or may not affect quality of life. Current literature reveals interesting things; two in particular are:

- additional and useful information may be obtained from quality of life measurements
- a growing consensus that the goal of medical care today for most patients is the preservation of function and well-being in everyday life.

We have reached the stage where the collection of information about psychological distress, social disruption, emotional trauma and painful side-effects is not only necessary but a routine component in many protocols.

Quality of life data can be used in a variety of ways:

- to try to achieve the best possible outcome for patients
- to evaluate the extent of change in the quality of life of an individual or group across time
- to evaluate new treatments and technologies
- to support approval of new drug applications
- to try to provide the best value for health care dollars
- to compare costs and benefits of various financial and organizational aspects of health care services

In the future, approval of not only drugs but also new therapies or methods of delivery will most likely be based on a combination of quality of life, survival, response, and adverse event data.

Instructions for Administration of a Quality of Life Questionnaire. The instructions below are intended as a guide for the administration of the Quality of Life questionnaire.

1. Preamble

   Quality of life data are collected for research purposes, and will usually not be used for the patient's individual medical care. The assessment is in the form of a self report questionnaire. Therefore, it must be completed by the patient only, without translation, coaching or suggestions as to the "correct" answer by relatives or health care personnel.

   The usual scheduled times to obtain the questionnaires are as follows:

   - pre-randomization or pre-registration (baseline)
   - during treatment
   - during follow-up

   The information provided by the patient in the completed questionnaire is confidential and should not be discussed with or shown to anyone who is NOT mentioned in the consent form signed by the patient.

   If a particular question has not been answered, please document the reason(s) in the appropriate space on the questionnaire. If the whole questionnaire has not been completed, please document the reason(s) on the appropriate case report forms.

2. Pretreatment Assessment

   It should be explained to the patient that the purpose of the questionnaire is to assess the impact of treatment on different areas of the patient's life, e.g.: psychological distress, social disruption, side-effects, et cetera.

   The CRA should collect the questionnaire as soon as it has been completed, check to see that each question has been answered and gently remind the patient to answer any inadvertently omitted questions. If a patient states that s/he prefers not to answer some questions and gives a reason(s), the reason(s) should be noted on the questionnaire. If a specific reason is not given, this also should be noted on the questionnaire.

3. Assessments During Treatment

   The quality of life questionnaire should be given to the patient before being seen by the doctor, and prior to treatment on the day of treatment, as required by the schedule in the protocol. If the patient does not have a doctor visit scheduled, or if it was not possible for the patient to complete the questionnaire before being seen by the doctor, s/he should still complete the questionnaire prior to treatment.

4. Assessments During Follow-up

   The quality of life questionnaire should be given to the patient before being seen by the doctor, on follow-up visits as required by the schedule.

A patient may, on occasion, be reluctant to complete the questionnaire because they feel unwell. In that case, you may express sympathy that things are below par, but state that this is exactly the information we require if we are to understand more about how quality of life is affected. You may also remind them that it takes only a few minutes to complete.

It defeats the whole purpose of the assessment if it is delayed until the patient feels better!

5. What If . . .

   The patient should complete the questionnaires at the clinic. The exception is that the design of some trials may require the patient to take the questionnaire home with them after leaving the clinic, and complete it on the specific day, because a return visit to the clinic is not scheduled.

   There may be circumstances when the patient does not complete the questionnaire as required in the clinic. Three situations are described below. In these cases, it is beneficial if quality of life data can still be collected.

   A. The patient leaves the clinic before the questionnaire could be administered, or someone forgets to give the questionnaire to the patient.

      Contact the patient by phone informing him or her that the questionnaire was not completed. Ask the patient if s/he is willing to complete one:
      If yes, mail a blank questionnaire to the patient, and make arrangements for return of the questionnaire in a timely fashion. Record the date it was mailed and the date received on the questionnaire.

If this is not feasible, then ask the patient if s/he is willing to complete a questionnaire over the phone. If the patient agrees, read out the questions and range of possibilities, and record the answers. Make a note on the questionnaire that the questionnaire was completed over the phone.

If no, note the reason why the questionnaire was not completed on the appropriate case report form.

B. The patient goes on an extended vacation for several months and won't attend the clinic for regular visit(s).

Ensure that the patient has a supply of questionnaires, with instructions about when to complete them, and how to return them. If it is known beforehand, give the patient blank questionnaires at the last clinic visit; if the extended absence is not known in advance, mail the blank questionnaires to the patient. Written instructions may help ensure that the patient stays on schedule as much as possible.

C. The patient does not want to complete the questionnaire in clinic.

Should the patient not wish to answer the questionnaire in the clinic but insists on taking it home, and failing to comply with the patient's wishes is likely to result in the questionnaire not being completed at all, then the patient may take the questionnaire home with instructions that it is to be completed the same day. When the questionnaire is returned, the date on which the questionnaire was completed should be noted and a comment made on the questionnaire as to why the patient took it away from the clinic before completion.

6. Waiving the Quality of Life Component

The only time that we will not require a patient to complete the quality of life questionnaires is if s/he is not literate in either English or French (or other languages that the questionnaire may be available in). In other words, if the assistance of a translator is required to comprehend the questions and reply, the questionnaires should not be completed. Translation of the questions is not acceptable. Please indicate on questionnaire.

7. Unwillingness to Complete Quality of Life Questionnaire

If a patient speaks and reads English or French (or other languages that the questionnaires may be available in), but does not wish to complete the questionnaires then s/he is NOT eligible and should NOT be put on study.

8. Inability to Complete Quality of Life Questionnaire (for reason other than illiteracy in English or French)

An eligible patient may be willing but physically unable to complete the questionnaires, because of blindness, paralysis, etc. If the patient is completing the QOL assessment in the clinic, the questionnaire should be read to them and the answers recorded by a health care professional (e.g. preferably the clinical research associate assigned to the trial, but another clinic nurse, a doctor or social worker who is familiar with the instructions for administering the questionnaires would be acceptable). If the patient is completing the questionnaire at home, and a telephone interview by the clinical research associate is not possible, then a spouse or friend may read the questions to the patient and record the answers. However, this method should be a last resort, and the spouse or friend should be instructed to not coach or suggest answers to the patient. Whichever method is used, it should be recorded on the questionnaire.

If these special arrangements are not possible or feasible, then the patient would not be required to complete the questionnaires, and this should be reported on the appropriate case report form.

Quality of Life Questionnaire – ENGLISH

NCIC CTG Trial: **IND.210**

This **page** to be completed by the Clinical Research Associate

Patient Information

NCIC CTG Patient Serial No: _____ Hospital No.: _XXXXXXXXX_ *(if permitted by REB)* Patient Initials: ____ ____ ____ (first-middle-last)

Institution: _____ Investigator: _____

Scheduled time to obtain quality of life assessment: please check (3)

☐ Prior to randomization

During chemotherapy:

☐ Day 1 cycle 5

Off Treatment:

☐ Off Study ☐ week 4 *(only if not completed at time off study)*

Were ALL questions answered? ___ Yes ___ No If no, reason: _____

Was assistance required? ___ Yes ___ No If yes, reason:_____

Where was questionnaire completed: ☐ home ☐ clinic ☐ another centre

Comments: _____

_____

Date Completed: __ __ __ __ - __ __ __ - __ __
yyyy mmm dd

PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.

NCIC CTG use only

Logged: _____	Study Coord: _____	Res Assoc: _____	Data Ent'd:	Verif:
_____ - ____ - ____	_____ - ____ - ____	_____ - ____ - ____	_____	_____

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

European Organization for Research and Treatment of Cancer (EORTC)

Quality of Life Questionnaire (IND.210)

We are interested in some things about you and your health. Please answer all the questions **yourself** by circling the number that best applies to you. There are no 'right' or 'wrong' answers. Choose the best **single** response that applies to you. The information that you provide is for research purposes and will remain strictly confidential. The individuals (e.g. doctors, nurses, etc.) directly involved in your care will not usually see your responses to these questions -- if you wish them to know this information, please bring it to their attention.

	Not At All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in a bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
During the past week:	**Not At All**	**A Little**	**Quite a Bit**	**Very Much**
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4

Please go on to the next page

EORTC QLQ-C30 (Core 30 Questionnaire Version 3.0 © copyright 1995 EORTC Quality of Life Study Group. All rights reserved.)

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

During the past week:	**Not At All**	**A Little**	**Quite a Bit**	**Very Much**
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4

Please go on to the next page

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

During the past week:	Not At All	A Little	Quite a Bit	Very Much
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you.

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very Poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very Poor						Excellent

Please check to make sure you have answered all the questions.

Please fill in your initials to indicate that you have completed this questionnaire: _____

Today's date (Year, Month, Day): _____

Thank you.

AMEND #1: 2013-APR-25; ADMIN UPDATE #1: 2014-MAY-23 *(withdrawn)*; AMEND #3: 2014-JUN-16

LIST OF CONTACTS

PATIENT RANDOMIZATION

All patients must be randomized as described in Section 7.0 before any treatment is given.

	Contact	Tel. #	Fax #
STUDY SUPPLIES Data Management Guidebook, Protocol, Safety Information	Available on NCIC CTG Website: http://www.ctg.queensu.ca under: Clinical Trials	613-533-6430	613-533-2411
PRIMARY CONTACTS FOR GENERAL PROTOCOL RELATED QUERIES (including eligibility questions and protocol management)	Ashley Theis Study Coordinator NCIC CTG Email: atheis@ctg.queensu.ca or: Lesley Seymour Director, NCIC CTG Investigational New Drug Program Email: lseymour@ctg.queensu.ca		
STUDY CHAIRS	Dr Patricia Tang Email: patricia.tang@albertahealthservices.ca	403-521-3688	403-283-1651
	Dr Derek Jonker Email: djonker@ottawahospital.on.ca	613-737-7700 x 70168	613-247-3511
SERIOUS ADVERSE EVENT REPORTING See protocol Section 11.0 for details of reportable events.	Dr. Lesley Seymour NCIC CTG Investigational New Drug Program or Ashley Theis Study Coordinator NCIC CTG	613-533-6430	613-533-2411
DRUG ORDERING	See Appendix III and trial website at http://www.ctg.queensu.ca under: Clinical Trials		
ELECTRONIC DATA CAPTURE (EDC) (technical support)	NCIC CTG Help Desk Home Page https://scooby.ctg.queensu.ca/helpdesk/ Email Support Staff at: support@ctg.queensu.ca		