



**London Health Sciences Centre**  
London Regional Cancer Program

# **Use of Bevacizumab in Advanced Colorectal Cancer**

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## **GI Practice Guideline**

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This guideline is a statement of consensus of the GI Disease Site Team regarding their views of currently accepted approaches to treatment. It is not intended to replace the independent medical judgement of the physician in the context of individual clinical circumstances to determine any patient's care or treatment.

# Table of Contents

## 1.0 BACKGROUND

1.1 Biology.....	4
1.2 Clinical trials in advanced colorectal cancer: efficacy .....	5
1.3 Adverse Events .....	6

## 2.0 ELIGIBILITY AT THE LRCP

2.1 Inclusion Criteria .....	8
2.2 Exclusion Criteria .....	8
2.3 Caution.....	8

## 3.0 TREATMENT

### REGIMENS SUPPORTED AT THE LRCP

3.1 FOLFIRI + bevacizumab .....	9
3.2 FOLFOX-4 + bevacizumab .....	9
3.3 Xelox + bevacizumab .....	9
3.4 Capecitabine + bevacizumab .....	9

## 4.0 MANAGEMENT

4.1 Eligibility .....	9
4.2 Informed consent .....	10
4.3 Monitoring .....	10
4.4 Management of toxicity .....	10
4.4.1 Venous thrombosis.....	10
4.4.2 Arterial thromboembolism.....	10
4.4.3 Proteinuria (1 <sup>st</sup> occurrence).....	10
4.4.4 Proteinuria (2 <sup>nd</sup> and subsequent occurrence) .....	11
4.4.5 Infusion reaction .....	11
4.4.6 Hypertension .....	11
4.5 Discontinuation of bevacizumab.....	12
4.6 Bevacizumab dose adjustments .....	12

## 5.0 LOGISTICS

5.1 Administration .....	13
5.2 Preparation .....	13

## 6.0 IMPACT .....

## 7.0 COSTS AND ACQUISITION PROCESS .....

Authors and Contact .....	15
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## GI Practice Guideline

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### 1.0 Background

#### 1.1 Biology

Cancers require the ingrowth of new blood vessels if they are to grow beyond 1-2 mm, the diffusion limits of oxygen and glucose. This process known as angiogenesis is therefore a therapeutic opportunity. Angiogenesis is mediated by several vascular growth factors, particularly ‘vascular-endothelial growth factor’, or VEGF, released by cancer cells. VEGF binds to specific receptors on endothelial cells, and induces directional growth of new blood vessels, from existing blood vessels to the tumor deposits, along a concentration gradient. Although these vessels are able to supply blood to the growing tumor cells, they are structurally abnormal and ‘leaky’, and prone to bleeding and thrombosis.

Original therapeutic concepts involved disablement, removal or reduction of these blood vessels. However, recently the concept has evolved that if the tissue turgor in the tumor interstitium could be reduced, by reducing the ‘leakiness’ of the endothelial layer, then deliver of any coadministered cytotoxic drugs might be improved. It is now believed that this could be an important mechanism of action of some anti-angiogenic agents.

Irrespective of the precise therapeutic mechanisms, the angiogenic pathways have been an intense focus of drug discovery, with several new agents successfully developed in diverse indications. One of the first was bevacizumab, a recombinant humanized monoclonal antibody to VEGF, which bind and sequesters VEGF, rendering it essentially unavailable for interacting with its receptor(s). Bevacizumab has been, and is, the subject of many clinical trials, and has shown activity in advanced colorectal cancer, as well as in other major and minor cancer types. Bevacizumab was approved by Health Canada’s TPD branch in September 2005 for use in advanced colorectal cancer. Bevacizumab exhibits little activity as a single agent, and data support its use only in the context of chemotherapy.

## 1.2 Clinical Trials in Advanced Colorectal Cancer: efficacy

The benefit of adding bevacizumab to chemotherapy has been established in two randomized phase II studies and two randomized phase III studies:

**Table 1. Randomized trials of bevacizumab in advanced colorectal cancer.**

Author (reference)	Treatment allocated	Evaluable patients	Median survival (months)	1-year overall survival (%)	Median progression-free survival (months)	Tumour response (%)
Hurwitz et al. (9,15)	IFL	411	15.3*	63.4	6.2*	35*
	IFL/BV	402	20.3*	74.3	10.6*	45*
	5-FU / FA / BV	110	18.3	68§	8.8	40
Giantonio et al (10)	FOLFOX4	289	10.7*	44§†	5.5*	9†
	FOLFOX4/BV	290	12.5*	57§†	7.4*	22†
Kabbinavar et al (11)	5-FU/ FA	36	13.8	NR	5.2	17
	5-FU/ FA / BV	68	18.0†		7.4†	32†
Kabbinavar et al (12)	5-FU/ FA	105	12.9	53§	5.5*	15
	5-FU/ FA / BV	104	16.6	63§	9.2*	26

Notes: 5-FU, 5-fluorouracil; BV, bevacizumab; FA, folinic acid; FOLFOX4, infusional 5-FU, bolus FA, oxaliplatin, IFL, bolus 5-FU/FA/CPT-11; NR, not reported. See Table 3 for drug regimen details. \*Data is statistically significant ( $p < 0.05$ ) compared to control. See text for details. †Pooled results of two bevacizumab arms (low-dose, 5 mg/kg and high-dose, 10 mg/kg) presented. ‡Data available from online presentation ASCO 2005. §Estimated from Kaplan-Meier survival curves.

(Welch S et al. The role of Bevacizumab (Avastin™) combined with chemotherapy in the treatment of patients with advanced colorectal cancer: A Clinical Practice Guideline. Program in Evidence-based Case (PEBC), Cancer Care Ontario (CCO). Developed by the Gastrointestinal Cancer Disease Site Group, December 12, 2005)

The key evidence is provided by the two large randomized phase III trials. Bevacizumab 5 mg/kg q2 weekly was added to bolus IFL (irinotecan, 5FU, leucovorin), and compared to IFL alone, in the first line setting. All efficacy parameters improved to an extent that was both statistically and clinically worthwhile: overall survival (20.3 vs 15.6 m,  $p = 0.00003$ ), progression free survival (10.6 vs 6.2 m,  $p < 0.00001$ ) and objective response (45% vs 35%,  $p = 0.0029$ ). (Ref: Hurwitz et al. NEJM 2004; 305: 2335). Adverse event profile will be discussed below.

Bevacizumab 10 mg/kg q2 weekly was added to FOLFOX-4 and compared to FOLFOX-4 alone, in the second line setting. Median survival improved from 10.7 to 12.5 m ( $p = 0.0018$ ) and PFS from 4.8 to 7.2 m ( $p < 0.0001$ ). Response rates improved from 9.2% to 21.8% ( $p < 0.0001$ ).

Two additional randomized phase II studies (Table 1) provided strong evidence that bevacizumab improved survival and PFS, substantially, in patients treated with 5FU + leucovorin (but without irinotecan or oxaliplatin).

The results of another study, NO16966 were presented at ESMO 2006. This study compared XELOX vs FOLFOX, with or without bevacizumab, in a 2 x 2 design in the first line. This study showed that, for PFS, XELOX was as efficacious as FOLFOX-4, and the addition of bevacizumab reduced the risk of progression (9.4 m vs 8.0 m,  $p=0.0003$ , Hazard ratio 0.83). This trial involved over 2000 patients. However in a subgroup analysis, bevacizumab improved the PFS more with XELOX (9.3 m vs 7.4 m,  $p=0.0076$ ) than with FOLFOX (9.4 vs 8.6 m,  $p=0.1871$ ). The doses were as follows: XELOX (capecitabine 1000 mg/m<sup>2</sup> bid x 14 days; oxaliplatin 130 mg/m<sup>2</sup>; bevacizumab 7.5 mg/kg) q3 weekly; and FOLFOX-4 (standard doses + bevacizumab 5 mg/kg) q2 weekly. The side effect burden from bevacizumab was minimal (GI perforation 0.6 vs 0.3%; grade 3/4 arterial thromboembolic events 1.7% vs 1.0%; grade 3/4 proteinuria 0.6% on bevacizumab). The full side effect profile is not available; also, survival data is not available yet.

Therefore, data exists in support of the addition of bevacizumab to FOLFOX, XELOX, IFL, and 5FU-LV in the first line setting, and FOLFOX in the second line setting. There is no setting in advanced colorectal cancer in which bevacizumab has been shown ineffective. No data exists for bevacizumab + FOLFIRI. It is reasonable however, to support the addition of bevacizumab in all situations in advanced colorectal cancer, in appropriate patients, in which chemotherapy with fluoropyrimidines is administered, with or without the addition of irinotecan and oxaliplatin. It is not proposed that bevacizumab be used in any adjuvant setting outside of a clinical trial at this time.

### 1.3 Adverse Events

Bevacizumab has a well documented and novel set of side effects. These influence eligibility (vide infra) and require monitoring and specific management. Generally, these are mild-moderate but can occasionally be serious and even lethal. The following is a representative table:

**Table 2. Adverse events reports in randomized trials of bevacizumab in advanced colorectal cancer.**

	Hurwitz (3)		Giantonio (10)		Kabbinar (11)†			Kabbinar (12)†	
	IFL (n=397)	IFL+BV (n=393)	FOLFOX4 (n=289)	FOLFOX4+BV (n=290)	5FU/FA (n=35)	5FU/FA/BV 5 mg/kg (n=35)	5FU/FA/BV 10 mg/kg (n=32)	5FU/FA (n=104)	5FU/FA/BV (n=100)
All grade III/IV toxicity	74%	65%*	NR	NR	64%	74%	78%	71%	87%
60-day all-cause mortality	5%	3%	4%	6%	NR	NR	NR	14%	5%
Leukopenia Grade III/IV	31%	37%	NR	NR	3%	6%	3%	7%	6%
Diarrhea Grade III/IV	25%	32%	NR	NR	37%	29%	31%	40%	39%
Neuropathy Grade III/IV	NR	NR	8%	18%	NR	NR	NR	NR	NR
Hypertension Any Grade III/IV	8% 2%	22%* 11%*	NR 2%	NR 6%*	3% 0%	11% 9%	28% 25%	6% 3%	32% 16%
Thrombosis Any Grade III/IV	16% NR	19% NR	NR 2.5%	NR 3%	9% 3%	25% 14%	13% 6%	18% NR	18% NR
Hemorrhage Grade III/IV	3%	3%	<1%	3%*	0%	0%	9%	3%	5%
Proteinuria Any Grade III/IV	22% <1%	27% <1%	NR 0	NR 1%	11% NR	23% NR	28% NR	19% 0	38% 1%
GI perforation	0	1.5%	0	1%	NR	NR	NR	0	2%

Notes: 5FU=5fluorouracil, FA=folinic acid, IFL=bolus 5-FU/FA+ irinotecan. FOLFOX4=infusional 5-FU, bolus FA + oxaliplatin, BV=bevacizumab (see Table 3 for regimen details). NR=not reported.

\*Denotes p<0.05 in comparison to control group.

†Description of statistical significance not published.

(Welch S et al. *ibid*)

The product monograph alerts patients and physicians to a range of side effects, some common, some less common. Common side effects include diarrhea, vomiting, and leucopenia which may simply reflect the associated chemotherapy, but which might also be slightly increased by bevacizumab. Bevacizumab-specific side effects include hypertension, proteinuria, thromboembolic events, hemorrhage and gastrointestinal perforation. Grades 3/4 hypertension can be expected in about 10-15% of patients, and proteinuria (almost always grades 1/2) in an extra 20%. Hypertension does require treatment; the proteinuria rarely requires cessation of bevacizumab and does not cause long-term kidney damage. Major hemorrhage is rare (1-2%) but mild epistaxis is common (an extra 5-30%). The extra risk of venous thromboembolism seems small but arterial thromboembolic events do seem to occur at a somewhat higher rate on bevacizumab (~2-5% extra); age >65 years may be a risk factor. Gastrointestinal

perforation occurs with a small but increased incidence (about 1.5%) and may be fatal; pre-disposing features seem to include tumor remaining in the GI tract, and other causes of abdominal inflammation. The incidence of delayed wound healing seems negligible but this may relate to exclusion of patients with recent surgery from the trials.

Health Canada October 24, 2006 updated Safety Information: Rare cases of hypertensive encephalopathy have been reported. Avastin should be permanently discontinued in patients who develop hypertensive encephalopathy. There have been reports of patients treated with Avastin developing Reversible Posterior Leukoencephalopathy Syndrome (RPLS), which can present with seizures, headache, altered mental status, visual disturbance or cortical blindness, with or without associated hypertension. RPLS may be reversible if recognized and treated promptly. In patients developing RPLS, treatment of specific symptoms, including control of hypertension, if present, is recommended along with discontinuation of Avastin. For further details visit [www.rochecanada.com/pdf/avastinHPE.pdf](http://www.rochecanada.com/pdf/avastinHPE.pdf)

Management of side effects see (Section 4.0)

## **2.0 ELIGIBILITY AT THE LRCP**

### **2.1 Inclusion Criteria**

- advanced colorectal cancer
- suitable for fluoropyrimidine based chemotherapy, with or without oxaliplatin and irinotecan
- first or >first line chemotherapy

### **2.2 Exclusion Criteria**

- known hypersensitivity to any components of bevacizumab such as Chinese hamster ovary cell products or recombinant human or humanized antibodies.
- pregnant or lactating females (urine test confirmation required)
- pediatric patients
- within 28 days after major surgery, or until the surgical wound is fully healed
- untreated central nervous system (CNS) metastases: brain metastases
- uncontrolled hypertension, >150/100
- “advanced” atherosclerotic disease

### **2.3 Caution**

- history of arterial thromboembolic events or age >65 is associated with an increased risk of arterial thromboembolic events during therapy.
- prior or recent arterial thromboembolic events
- fully anticoagulated patients

- tumor still in situ
- congestive heart failure; prior anthracycline exposure and/or prior radiation to the chest increase risk for developing CHF.
- any other risk factor for GI perforation, eg. active ulceration, diverticulitis, etc.
- patients with a history of hypertension may be at increased risk for the development of proteinuria.
- Safety and efficacy has not been studied in patients with hepatic impairment.
- Safety and efficacy has not been studied in renally impaired patients.

### 3.0 TREATMENT

#### REGIMENS SUPPORTED AT THE LRCP

- 3.1 FOLFIRI + bevacizumab 5 mg/kg q2 weekly  
(Standard doses of FOLFIRI) Reference: Canadian Product Monograph.
- 3.2 FOLFOX – 4 modified + bevacizumab 5/g/kg q2 weekly 1<sup>st</sup> Line Therapy
- 3.3 FOLFOX-4 modified + bevacizumab 10 mg/kg q2 weekly 2<sup>nd</sup> Line Therapy  
Standard doses of FOLFOX-4m reference: Giantonio BJ et al. High-dose bevacizumab in combination with FOLFOX4 improves survival in patients with previously treated advanced colorectal cancers. Results from the Eastern Cooperative Oncology Group (ECOG) study E3200. 2005 ASCO Gastrointestinal Cancers Symposium; Abstract 169a.
- 3.4 XELOX + Bevacizumab 7.5 mg/kg, q3 weekly. (also called Capox + Bevacizumab) Standard doses of XELOX. reference: Hochster HS et al. Safety and Efficacy of bevacizumab (Bev) when added to oxaliplatin/fluoropyrimidine (O/F) regimens as first-line treatment of metastatic colorectal cancer (mCRC): TREE 1&2 Studies. J Clin Oncol 2005; 23 (16 Suppl): Abstract 3515.
- 3.5 Capecitabine + bevacizumab 7.5 mg/kg q3 weekly.  
Capecitabine dose 1000 mg/m<sup>2</sup> bid.

### 4.0 MANAGEMENT

The particular toxicities of bevacizumab require attention to be paid to eligibility, informed consent, monitoring, treatment and dose adjustment/discontinuation.

#### 4.1 Eligibility

The above studies have generally been designed to exclude patients perceived to be at higher than average risk for the specific side effects of bevacizumab. Therefore, they have excluded patients with poorly controlled hypertension (eg. >150/100), with significant proteinuria (>500 mg/24h), with a history of thromboembolic or hemorrhagic events, or on full anticoagulation or on antiplatelet drugs (ASA ≤325 mg excepted). Also, patients with open wounds or within 28 days of surgery have been excluded.

Although LRCP physicians should be free to exercise clinical judgment to make exceptions, they should be aware that the generally manageable toxicity profile reported in these studies applies to a selected population. Any exceptions should be managed with caution.

#### 4.2 Informed Consent

It is not our practice to provide detailed risk/benefit information, in writing, to patients going on standard care, off a clinical trial. However, LRCP physicians should discuss the risks of bevacizumab so that patients are made fully aware. On the other hand, these risks should not be unnecessarily over-stated, especially to those at average risk. Likewise nurses should be thoroughly familiar with the risk profile and monitoring policies. Patients should be particularly counseled about the significance of abdominal pain as a possible accompaniment of GI perforation, and the need for urgent medical evaluation; and also to promptly report any features of arterial or venous thromboembolic events (eg. stroke, suspected myocardial ischemia, deep vein thrombosis, or possible pulmonary embolus), and/or significant hemorrhage. Patients should also be aware that the usual side effects of chemotherapy might be more severe on bevacizumab, although there is currently some uncertainty about this. Females of childbearing potential must be counseled that bevacizumab may be highly teratogenic.

#### 4.3 Monitoring

Patients should be seen at clinic according to the usual schedule of the accompanying chemotherapy regimen. Additional visits can be arranged if necessary. At these visits, the usual evaluations should occur, but blood pressure and proteinuria (dipstick) should also be routinely assessed. In patient who go directly to the chemotherapy suite for alternate cycles, the BP and dipstick for proteinuria should be assessed there prior to treatment and the responsible physician informed if the BP is >150/100 and/or there is proteinuria >1+. In the event there is particular concern about a patient, then arrangements should be made for the family doctor to assess BP and/or proteinuria more frequently.

#### 4.4 Management of Toxicity

##### 4.4.1 Venous thrombosis

If superficial, continue bevacizumab.

If grades 3 or 4 DVT, hold for 2 weeks; restart bevacizumab after 2 weeks if therapeutic dose anticoagulation is stabilized, if no grade 3 or 4 hemorrhage has occurred, and if the tumor does not appear to abut on any major vessel.

##### 4.4.2 Arterial thromboembolism

Discontinue bevacizumab.

#### 4.4.3 Proteinuria (first occurrence)

<2+: Continue bevacizumab as planned.

2+ or 3+: Administer as planned, but collect 24-hour urine. If  $\leq 2$  G/24h, proceed as scheduled; if  $> 2$  G/24h omit and repeat next cycle; delay bevacizumab until proteinuria  $\leq 2$  G/24h.

Nephrotic syndrome: Permanently discontinue bevacizumab.

1+ or 2+: Continue as planned.

3+: Administer as planned but then collect 24h urine. If  $\geq 2$  G/24h, delay until  $< 2$  F/24h; if  $< 2$  G/24h, proceed with bevacizumab.

Nephrotic: Permanently discontinue bevacizumab.

#### 4.4.4 Infusion Reaction

There has been no reported increased incidence of this. If it occurs, it should be managed in the standard way. There is no data on re-challenge, and so clinical judgment should be employed.

#### 4.4.5 Hypertension Monitoring and recommendations: (Reference:BC Cancer Guidelines)

1. Acute hypertension during bevacizumab infusion. During the first three cycles of bevacizumab, blood pressure should be checked before treatment, midway during treatment and at the end of treatment.
  - If acute hypertension (increase by  $>20$ mmHG diastolic or  $>160/100$  if previously within normal limits) occurs during bevacizumab infusion, stop bevacizumab and resume at a slower rate if blood pressure returns to the pretreatment range within one hour.
  - If blood pressure does not return to baseline within one hour, bevacizumab should be held. Subsequent infusion of bevacizumab should be given at a slower rate (2-3 hours).
  - Acute hypertension that is symptomatic (e.g. onset of headaches or change in level of consciousness) or grade 3 hypertension ( $\geq 180/110$ ) that does not improve after one hour of stopping bevacizumab is an urgent situation requiring treatment. If the pulse rate is  $>65$ , labetalol may be given; if the pulse rate is  $<65$ , hydralazine may be used. Consultation with a cardiologist or emergency room physician is recommended for advice about therapy and monitoring.

2. Hypertension during course of treatment with bevacizumab. Patients treated with bevacizumab should have their blood pressure monitored every 2-3 weeks while on therapy.

<b>Hypertension</b>	<b>Systolic</b>	<b>Diastolic</b>
Grade 1 (mild)	140-159	90-99
Grade 2 (moderate)	160-179	100-109
Grade 3 (severe)	$\geq 180$	$\geq 110$

- Grade 2: Stop bevacizumab temporarily and start oral antihypertensive mediation. (SEE Appendix 1) If hypertension is controlled with blood pressure returning to pretreatment level or  $< 160/100$ , restart bevacizumab and continue to monitor blood pressure.
- Grade 3: Bevacizumab therapy should be interrupted until adequate control is achieved by antihypertensive medications. If hypertension is uncontrolled after one month, bevacizumab therapy should be discontinued.
- Hypertensive crisis: Discontinue bevacizumab.

#### 4.5 Discontinuation of Bevacizumab

Bevacizumab should be discontinued permanently in the following events:

- GI perforation
- Major arterial thromboembolic event
- Uncontrollable hypertension
- Pregnancy
- Major bleeding event unless there is good reason to believe it will not re-occur
- Major infusion reaction
- Development of brain metastases
- Financial hardship

Bevacizumab should be temporarily discontinued in the event of:

- DVT
- Surgery
- There is a need to institute anticoagulation therapy (eg. atrial fibrillation)

#### 4.6 Bevacizumab Dose Adjustments

In the E3200 ECOG study of FOLFOX  $\pm$  bevacizumab 10 mg/kg, dose reductions to 5 mg/kg were allowed for: hypertension, bleeding and thrombosis of  $\leq$  grade 2; proteinuria of  $> 2$  G/24h that resolved to 500 mg/24h; and liver function abnormalities ( $\geq$  grade 3) that resolved to  $\leq$  grade 1. These dose reductions occurred in 55.8% of patients on the FOLFOX + bevacizumab arm. Overall survival and PFS were recently reported as not being compromised (Giantonio BJ

et al. J Clin Oncol 2006 ASCO Annual Meeting Proceedings (Post Meeting Edition) 24 (185), June 20 suppl: 3538).

Note these reductions were ALLOWED, but apparently NOT MANDATED. It should be noted that both PFS and overall survival were numerically but not significantly better in those who did have dose reductions.

It seems, therefore, that, in the event of moderate toxicities, a dose reduction from 10 mg/kg to 5 mg/kg is a reasonable policy. In regimens using other doses of bevacizumab (eg. 7.5 mg/kg or 5 mg/kg), clinical judgment should be employed but dose reduction should be available as one option for the management of mild-moderate side effects.

Dose reduction might also be considered in the event of financial hardship.

## **5.0 LOGISTICS**

### **5.1 Administration**

The initial bevacizumab dose should be administered over 90 minutes as an IV infusion. If well tolerated, the second should be given over 60 minutes. If this is also well tolerated, all subsequent administrations should be over 30 minutes. (Reference: Canadian Product Monograph)

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

Bevacizumab should not be administered as an IV push or bolus. Initial dose is to be administered following chemotherapy. All subsequent doses can be given before or after chemotherapy. (Avastin Product Monograph, Sept 2005)

Based on BC Cancer Protocols, avastin is given before 5FU pump infusion in Folfiri and Folfax and after oxaliplatin in Xelox (capox). The line must be flushed before and after bevacizumab infusions, as it cannot be given with dextrose or glucose solutions.

### **5.2 Preparation**

Avastin is available as a single use, preservative free, clear glass vials with butyl rubber stopper containing 25mg/mL as either a 100mg/4mL vial or 400mg/16mL vial. It should be prepared by a healthcare professional using aseptic technique. Withdraw the necessary amount for the dose and dilute in a total volume of

100mL of sterile pyrogen free 0.9% sodium chloride. It cannot be administered with dextrose or glucose solutions.

Unused vials are stored at 2-8 degrees C. Protect from light.

## 6.0 IMPACT

Estimates for the use of Bevacizumab can be drawn from actual data for 2005-06 as shown below. It is anticipated that approximately 40% of such patients will become, or present as, metastatic, and in a steady state situation one could expect this to be the proportion of patients who could be offered this drug. Since very few of the PUKs would likely be candidates, we could assume about (543 x 0.4) 200+ patients of whom perhaps 5% could afford or have third party insurance for the drug. The impact, therefore, is unlikely to be more than 10-20 patients per year, outside of clinical trials, until third party insurers, and patterns of their utilization, take on a larger role.

Site Group	Site Sub-Group (based on ICD10 codes)	New Cases to Centre in Report Period	Seen by RAD	Seen by SYS	Seen by SUR	Seen by PO
	Small Intestine	37	2	37	1	0
	Colon	311	59	281	30	0
	Rectosigmoid Junction	16	10	14	4	0
	Rectum, Anus	179	160	149	21	1
	Primary Unknown	105	55	71	38	0
<b>sum</b>		<b>648</b>	<b>286</b>	<b>550</b>	<b>94</b>	<b>1</b>

Given as a q 2 weekly schedule, over thirty minutes administration time, and continuing for 20 months, at most this amounts to 240 hours of administration per year (20 pts x 0.5 hours x 24 infusions), or 30 chair-days, at what appears to be an over-estimate in the assumptions. This would be offset by the administration fee of \$250 per session, or \$60,000.

## 7.0 COSTS AND ACQUISITION PROCESS

The cost is \$5.00/mg. 100mg vial - \$500.00, 400mg - \$2000.00.

Acquisition cost depends on patient's private drug plan. They will need to verify with their plan if the drug is covered. DIN # 02270994.

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