

CODE: IRINO-CETUXIMAB

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A		REGIMEN NAME	IRINOTECAN-CETUXIMAB Chemotherapy
Cancer		Colorectal Cancer	Palliative intent
Regimen Category		<u>Core, Restricted CCO:</u> Standard therapy endorsed by the Disease Site Group and a regimen which requires eligibility confirmation for reimbursement by CCO New Drug Funding Program.	
Rationale and Uses		Third-line treatment of EGFR-expressing metastatic colorectal cancer in patients with wild-type KRAS after failure of oxaliplatin and irinotecan-containing chemotherapy regimens.	

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B		DRUG REGIMEN		
<u>CETUXIMAB</u>		400 mg/m ²	IV over 2 hours (max rate 10 mg/min)	Week 1
		then		
		250 mg/m ²	IV over 1 hour (max rate 10 mg/min)	Week 2 and then weekly thereafter
		and ONE of the following*		
<u>IRINOTECAN Q Week x 4</u>		125 mg/m ²	IV over 90 minutes	Days 1, 8, 15, 22 (4 weeks on, 2 weeks off)
OR				
<u>IRINOTECAN Q2W</u>		180 mg/m ²	IV over 90 minutes	Day 1 only
OR				
<u>IRINOTECAN Q3W</u>		350 mg/m ²	IV over 90 minutes	Day 1 only
* When cetuximab and irinotecan are scheduled to be administered in the same week, irinotecan should be administered after the cetuximab infusion.				

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C**CYCLE FREQUENCY**

CETUXIMAB REPEAT EVERY 7 DAYS

AND

IRINOTECAN Q Week x 4 REPEAT EVERY 42 DAYS

OR

IRINOTECAN Q 2 Weekly REPEAT EVERY 14 DAYS

OR

IRINOTECAN Q 3 Weekly REPEAT EVERY 21 DAYS

Continue until evidence of disease progression or unacceptable toxicity

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D**PREMEDICATION AND SUPPORTIVE MEASURES**

ANTIEMETIC REGIMENS:

[HESKETH LEVEL 4](#)

- *Unless contraindicated, atropine 0.25-1mg IV or SC may be given for cholinergic adverse effects (early diarrhea)*
- *Prophylactic atropine may be considered in patients experiencing cholinergic symptoms*
- *Diarrhea (abdominal cramp = diarrhea) may be severe and delayed with Irinotecan; use loperamide 4mg at the onset of diarrhea, then 2mg q2h until patient is diarrhea-free for 12 hours*
- *An H₁ antagonist (e.g. 50 mg of diphenhydramine IV) is recommended with each dose of cetuximab*

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E DOSE MODIFICATION

Should not be used in patients with poor performance status (3 or 4). Doses should be modified according to the protocol by which the patient is being treated. The following recommendations are in use at some centres.

Patients should not be retreated with irinotecan until recovery from GI toxicity (without loperamide for at least 24 h) has occurred, platelets $\geq 100 \times 10^9/L$, and ANC $\geq 1.5 \times 10^9/L$. All dose adjustments should be made based on the worst preceding toxicity.

Suggested dose levels for Irinotecan

Regimen	Drug	Starting dose (mg/m ²)	Dose level -1 (mg/m ²)	Dose Level -2 (mg/m ²)
Weekly x 4	Irinotecan	125	100	75
Q2W	Irinotecan	180	140-150	110-120
Q3W	Irinotecan	350	300	250

Irinotecan: Dose Modification for Toxicity

Toxicity grade ³	Suggested dose During treatment course of Weekly schedule ²	At start of subsequent course ¹	
		Weekly schedule ²	Q2W or Q3W schedule ²
1	No change	No change	No change
2	↓ 1 dose level	Diarrhea alone – no change	Diarrhea alone – no change
		Hematologic alone – no change	Hematologic alone – no change
		Other ³ : ↓ 1 dose level	Other ³ : ↓ 1 dose level
3	Omit, then ↓ 1 dose level when \leq grade 2	↓ 1 dose level	↓ 1 dose level
4 or febrile neutropenia	Omit, then ↓ 2 dose levels when \leq grade 2	↓ 2 dose levels	↓ 1 dose level

¹ Relative to the starting dose used in the previous cycle.

² Patients should not be retreated until GI toxicity resolved (without loperamide for at least 24 h), platelets $\geq 100 \times 10^9/L$, and ANC $\geq 1.5 \times 10^9/L$. If patient has not recovered after a 2-week delay, consider discontinuing treatment.

³ Excludes alopecia, anorexia, and fatigue

E**DOSE MODIFICATION (continued)**Cetuximab: Dosage Modification for Dermatologic Toxicity and Related Disorders

Grade 3 or 4 Acneiform Rash	Action	Outcome	Cetuximab
1st occurrence	Delay infusion 1 to 2 weeks	Improvement	Continue at 250mg/m ²
		No improvement	Discontinue
2 nd occurrence	Delay infusion 1 to 2 weeks	Improvement	Reduce: 200mg/m ²
		No improvement	Discontinue
3 rd occurrence	Delay infusion 1 to 2 weeks	Improvement	Reduce: 150mg/m ²
		No improvement	Discontinue
4 th occurrence	Discontinue		

Cetuximab: Infusion Rate Modification for Infusion Reactions

Mild to moderate infusion reactions can be managed with slowing the infusion rate of cetuximab and with continued use of antihistamine medications (e.g. diphenhydramine) in subsequent doses.

Grade	Infusion rate
Grade 1 or 2	5 mg/min
Grade 3 or 4	Discontinue

Other Toxicities

Hold cetuximab and irinotecan for onset of symptoms suggesting pneumonitis. Investigate and discontinue permanently if confirmed.

Hepatic Impairment

Transaminases	Bilirubin	Irinotecan
	1-1.5 x ULN	Consider ↓
> 3 X ULN*	2-4 X ULN	Omit
	≥ 4 X ULN	Omit

*or 5 x ULN with liver metastases

Renal Impairment

The kidney is not a major route of excretion for irinotecan and cetuximab; no dose adjustment anticipated to be required.

Dosage in the elderly

Consider reducing starting dose by 25 mg/m² (Weekly x 4) or 50 mg/m² (Q3W) for patients > 70 years. Monitor patients ≥ 65 years carefully.

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F**ADVERSE EFFECTS**

Refer to Cetuximab and Irinotecan drug monographs for full details of adverse effects.

Most Frequently Occurring Adverse Effects

- Myelosuppression ± infection
- Diarrhea (early and late onset), dehydration
- Abdominal pain/cramping
- Nausea and vomiting
- Fatigue, anorexia
- Increased bilirubin/liver enzymes
- Rash, paronychia
- Headache
- Infusion reactions (may be severe)
- Hypomagnesemia

Less common but may be severe or life-threatening

- Thromboembolism
- Pancreatitis, cholecystitis
- Pneumonitis
- Hemorrhage, including GI
- Colitis, ileus, typhlitis
- GI perforation, obstruction

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G**INTERACTIONS**

Refer to Cetuximab and Irinotecan drug monographs for full details.

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H**DRUG ADMINISTRATION AND SPECIAL PRECAUTIONS**

Refer to Cetuximab and Irinotecan drug monographs for full details.

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OTHER NOTES

Diarrhea can be severe, with either immediate or delayed onset. Patients must be instructed in the use of loperamide as treatment for diarrhea, and must have a supply of this drug upon starting Irinotecan treatments.

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