Anti-epidermal growth factors in colorectal cancer

By Yoo-Joung Ko, MD, MMSc, SM, FRCPC

HOT SPOT

Background

- Colon cancer is the second leading cause of cancer death in Canada
- Biologic therapies including anti-VEGF and anti-EGFR approaches have been approved in advanced colorectal cancer
- The epidermal growth factor receptor (EGFR) is a member of the HER tyrosine kinase cell surface receptors and is important in regulating a diverse range of cellular processes including cellular proliferation, differentiation and survival
- Dysregulation of the epidermal growth factor pathway is important in many cancers including breast, lung and colon cancer
- Two monoclonal antibodies to the EGFR (Erbitux® and Vectibix®) and two small molecule inhibitors (Iressa® and Tarceva®) are in current clinical use in cancer treatment

EGFR and K-ras

- K-*ras* gene encodes a small G protein that links the ligand-induced EGF receptor activation to activation of MAP kinase intracellular pathway
- Mutations in K-*ras* commonly seen in lung, pancreatic and colon cancer (40%–50%)
- Mutations in K-*ras* result in ligand-independent constitutive activation of the EGFR pathway
- Approximately 40% of patients with colorectal cancer have mutations in K-*ras* and 60% express wild-type K-*ras*
- Colorectal cancer patients with somatic mutations in K-*ras* do not benefit from anti-EGFR treatment
- Mutations in B-*raf* have been detected in patients who do not have K-*ras* mutations, but do not benefit from anti-EGFR therapy

K-ras testing

- Most common mutations are in codons 12 and 13 in exon 2, which account for approximately 90% of K-*ras* mutations
- Approved laboratories use a PCR-based kit (DxS®) to detect seven possible mutations in codons 12 and 13
- Tumour tissue can be from biopsies embedded in paraffin or frozen (either metastatic or primary tumour)

Table One.

	Cetuximab (Erbitux®)	Panitumumab (Vectibix®)
Approved Indication	Cetuximab + Irintocan	Panitumumab monotherapy
Backbone	Chimeric	Human
Class	IgG1	IgG2
Loading Dose	Yes: 400mg/m^2 over 120 min	No
Schedule	Weekly: 250mg/m^2 over 60 min	Q2weekly: 6mg/kg over 60 min or 90 min (if >1000mg)
Premedication	Yes: H1 antagonist 30–60 min prior to first infusion	None

EGFR inhibitors in colorectal cancer

(Table One)

- Cetuximab was approved by Health Canada in 2005
- Panitumumab was approved by Health Canada in 2008

Phase III studies of anti-EGFR therapies in colorectal cancer

(Table Two)

- One study of FOLFIRI with or without cetuximab as first-line therapy demonstrated significant improvement in response rate, progression-free survival and respectability for those who received combined therapy
- A recent randomized trial of FOLFOX +/- panitumumab as first-line therapy demonstrated an improved progression-free survival (9.6 versus 8.0 months), but no difference in overall survival or response rate
- In the second-line setting, a study of FOLFIRI +/- cetuximab showed a better response rate (16% versus 4%), progression-free survival and quality of life, but no difference in overall survival (half crossed over to cetuximab at progression)
- A third-line study of panitumumab versus best supportive care demonstrated an improved progression-free survival and response rate, but not in overall survival due to a preplanned crossover
- A third-line study of cetuximab versus best supportive care demonstrated an improvement in overall survival (9.5 versus 4.8 months) in K-*ras* wild-type patients

Table Two. (Statistically significant results in BOLD)

	Study	RR %	Median PFS/TTP (mos)	Median OS (mos)
1st line	**CRYSTAL (FOLFIRI +/- Cetux)**	**59 vs 43**	**9.9 vs 8.7 (HR=0.68)**	**23.5 vs 20.0 (HR=0.80)**
	OPUS (Rand Phase II FOLFOX +/- Cetux)	**61 vs 37**	7.7 vs 7.2 (HR=0.57)	**?**
	PRIME (FOLFOX4 +/- Pmab) 60% WT *K-RAS*	55 vs 48	**9.6 vs 8.0 (HR=0.80)**	Not reached vs 18.8 (HR=0.83)
2nd line	**EPIC (Iri +/- cetux)**	**16 vs 4**	3.98 vs 2.79 (HR=0.77)	10.71 vs 9.99
	Study 188 (FOLFIRI +/- Pmab) 55% WT *K-RAS*	**35 vs 10**	**5.9 vs 3.9 (HR=0.73)**	14.5 vs 12.5 (HR=0.85)
3rd line	**P-mab (Pmab vs BSC)**	**17 vs 0**	**12.3 vs 7.3 Weeks (HR=0.45)**	**Not reported (Crossover)**
	NCIC CO.17 (Cetux vs BSC)	**NR**	**3.8 vs 1.9 Mos (HR=0.40)**	**9.5 vs 4.8 Mos (HR=0.55)**

Anti-epidermal growth factors in colorectal cancer

HOT SPOT

Side effects

- Fatigue, papulopustular rash, and diarrhea most common side effects
- Rash commonly seen on the face, scalp, trunk, usually within two to three weeks of therapy initiation
- Hypomagnesemia uncommon, but often needs replacement therapy
- Cetuximab rarely associated (<4%) with infusion reactions

Skin toxicity management

- Appearance and severity of rash has been associated with tumour response and survival
- Pre-emptive strategy may minimize dose delay or dose reduction given that they are most likely to have clinical benefit
- A randomized study of a pre-emptive strategy decreased the incidence of grade two or higher skin toxicity by more than 50%
- Sun exposure and skin drying products may exacerbate the rash
- 2% topical clindamycin and 1% hydrocortisone in a lotion base for mild to moderate rash
- Oral minocycline 100mg od or doxycycline 100mg od to bid for moderate to severe rash
- For severe painful rash, anti-EGFR therapy may need to be held until improvement

Combination of biologic therapies

- Randomized phase II study of bevacizumab + cetuximab versus bevacizumab + cetuximab + irinotecan demonstrated response rates of 23% and 38% respectively
- PAACE study of oxaliplatin or irinotecan-based chemo + bevacizumb +/- panitumumab had more toxicity in the double biologic arm and decreased PFS
- CAIRO-2 study of XELOX + bevacizumab +/- cetuximab did not demonstrate improved PFS or response rates with double biologics

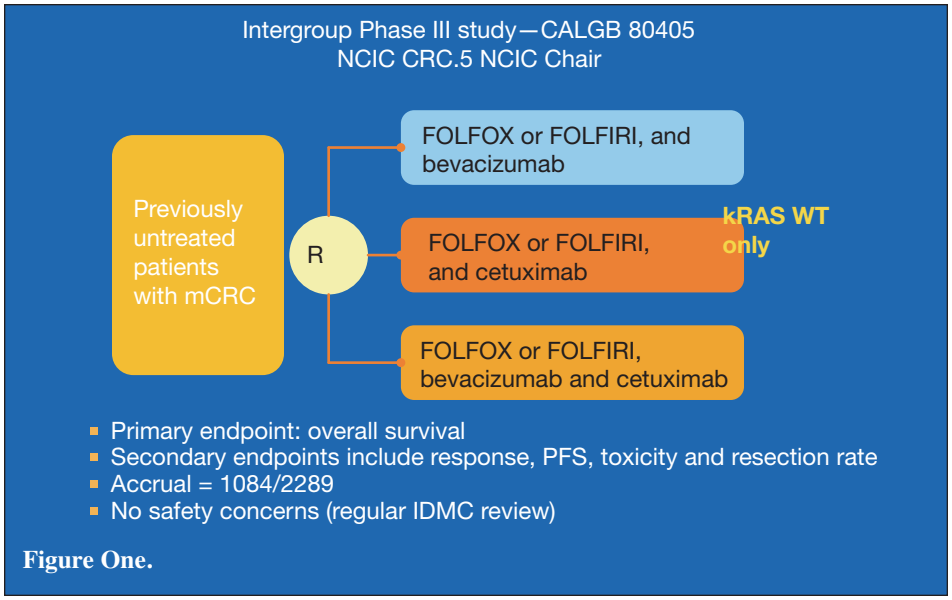

Figure One.

Ongoing studies of anti-EGFR therapies

(Figure One)

- A priority North American trial of chemotherapy (either FOLFOX or FOLFIRI) with cetuximab or bevacizumab has been activated by the National Cancer Institute of Canada
- This study is limited to those with wild-type K-*ras* and the combined biologic arm (cetuximab and bevacizumab with chemotherapy) has been dropped
- This study is powered to assess a survival difference between chemotherapy + bevacizumab and chemotherapy with cetuximab

Conclusion

- Monoclonal antibodies to the epidermal growth factor receptor provide clinical benefit to colorectal cancer patients who have progressed on oxaliplatin and irinotecan-based chemotherapies
- Clinical benefit is limited to those patients who do not have a detectable mutation in K-*ras* (i.e., wild-type)
- K-*ras* testing one tumour tissue must be done prior to initiating therapy
- Two monoclonal antibodies are approved in Canada, one (cetuximab) with irinotecan and the other (panitumumab) as monotherapy
- Rash is a common side effect that can be managed with a pre-emptive strategy
- There is emerging evidence that chemotherapy with an anti-EGFR agent may have a role in the second-line and first-line settings

References

Ciardiello, F., & Tortora, G. (2008). EGFR antagonists in cancer treatment. **N Engl J Med, 358,** 1160–74.

Cutsem, E.V., Kohne, C.H., Hirte, E., et al. (2009). Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. **N Engl J Med, 360,** 1408–17.

Cutsem, E.V., Peeter, M., Siena, S., et al. (2007). Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. **J Clin Oncol, 25,** 1658–1664.

Karapetis, C.S., Khambata-Ford, S., Jonker, D.J., et al. (2008). K-ras mutations and benefit from cetuximab in advanced colorectal cancer. **N Engl J Med, 359,** 1757–65.

Melosky, B., Burkes, R., Rayson, D., et al. (2009). Management of skin rash during EGFR-targeted monoclonal antibody treatment for gastrointestinal malignancies: Canadian recommendations. **Current Oncology, 16**(1), 14–24.

Generously supported by an unrestricted educational grant from Amgen

AMGEN®