



**Use of Bevacizumab in the
Neoadjuvant Setting for Patients with
Locally Advanced Rectal Cancer**

Neoadjuvant FOLFOX with Bevacizumab but without Pelvic Radiation for Locally Advanced Rectal Cancer

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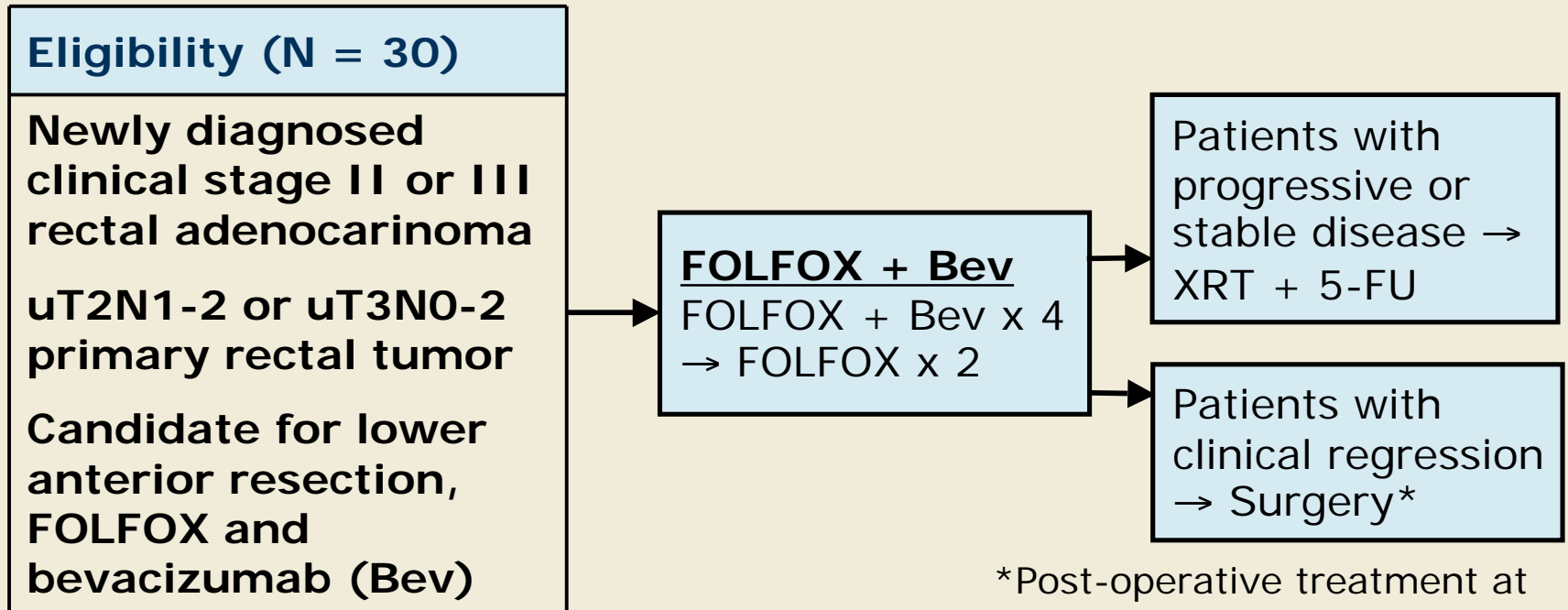
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Introduction

- Standard therapy for locally advanced rectal cancer is 5-FU-based chemotherapy combined with radiation therapy and followed by surgery and adjuvant chemotherapy.
- Although pelvic XRT nearly eliminates the risk of local recurrence (LR), it can be associated with long-term adverse effects on bowel, bladder and sexual functions and can induce myelosuppression.
- Improvements in systemic chemotherapy for patients with Stage III colon cancer and in surgical techniques for patients with rectal cancer have improved patient outcomes.
- **Current study objective:**
 - Assess the feasibility of achieving R0 resection with neoadjuvant FOLFOX plus bevacizumab administered without pelvic XRT in patients with newly diagnosed, locally advanced rectal cancer.

Pilot Study Design

Accrual: 32



XRT = radiation therapy

*Post-operative treatment at discretion of physician.
FOLFOX x 6 recommended; no post-operative Bev provided.

Results

(Mean Follow-Up 18.2 Months)

Event Rate	N	%
R0 resection — all pts	32/32	100
R0 resection, on study	30/30	100
Pts needing pre-op pelvic XRT	0/30	0
Pathologic complete response	8/30	27
Deaths	1/30	3
LR rate	0/30	0
Distant recurrence — all lung	3/30	10

Conclusions

- Neoadjuvant FOLFOX-based chemotherapy without XRT does not appear to compromise the R0 resection rate in patients with locally advanced rectal cancer not requiring abdominoperineal resection.
 - R0 resection rate, all patients accrued (n = 32): 100%
 - R0 resection rate, patients on study (n = 30): 100%
- The pathologic complete response (CR) rate was 27% (8/30 patients).
- These data suggest that appropriately selected patients with locally advanced rectal cancer may forego pelvic XRT without adversely affecting R0 resection and pathologic CR rates.
- Based on these preliminary results, a cooperative group study is planned to examine neoadjuvant FOLFOX without XRT in patients with locally advanced rectal cancer.

Investigator comment on the results of a study of neoadjuvant FOLFOX/bevacizumab without radiation therapy for locally advanced rectal cancer

The standard treatment approach for most patients with locally advanced rectal cancer is neoadjuvant chemoradiation therapy. Most acknowledge that radiation therapy is probably the more toxic component of this treatment, particularly the long-term side effects. I have patients who have radiation proctitis, which is nasty and leads to pain, constant diarrhea and sphincter dysfunction. It would be a paradigm shift if we could utilize highly active systemic therapy without radiation therapy.

Memorial Sloan-Kettering Cancer Center had two interesting pilot studies — one with FOLFOX with bevacizumab and one with FOLFOX alone — and in their series, they had an approximately 30 percent pathologic complete response rate for patients with mid- or higher-rectum adenocarcinomas without radiation therapy, which is as good as it gets when you talk about 5-FU-based neoadjuvant chemoradiation therapy. The critical issue this raises in rectal cancer is the importance of adequate imaging. It is imperative to identify patients who are good candidates — those with T3N0, and perhaps T3N1 disease, but definitely not more than that.

Both ACOSOG and CALGB have proposals in their portfolio right now to test this strategy prospectively in a multicenter setting.

Interview with Axel Grothey, MD, July 9, 2010

Investigator comment on the results of a study of neoadjuvant FOLFOX/bevacizumab without radiation therapy for locally advanced rectal cancer

This study is a potential game changer. The Memorial Sloan-Kettering Group speculated that there were some patients who were currently receiving chemoradiation therapy for rectal cancer who didn't need it. We all agree on that concept, but the challenge is in figuring out which patients don't need radiation therapy to avoid putting them at risk.

The Memorial group treated about 30 patients, and they were aggressive in monitoring them. They did baseline CT scans and pelvic scans and did MRI in the interim to make sure patients had responding disease. If the patients' disease was responding, they were treated essentially with four courses of chemotherapy. The patients went to surgery, and if they had an R0 or a resection of all known disease, that was it. They didn't receive radiation therapy. By all accounts this was a positive study, which suggests that radiation therapy is not necessary for every patient. This is huge because it spares patients a lot of toxicity, but physicians should not take it as a carte blanche to practice this outside of clinical trials, which are currently planned in the cooperative group setting.

Interview with Alan P Venook, MD, June 16, 2010