

ECOG 5202

A Randomized Phase III Study Comparing 5-FU, Leucovorin and Oxaliplatin Versus 5-FU, Leucovorin, Oxaliplatin and Bevacizumab in Patients With Stage II Colon Cancer at High Risk for Recurrence to Determine Prospectively the Prognostic Value of Molecular Markers

Clinical Background

- The 5 year overall survival rate for patients with stage II colon cancer is between 75% and 80%
- Defining a specific high risk group of patients with stage II disease that may benefit from adjuvant chemotherapy remains a challenge
- Retrospective analysis of molecular prognostic factors suggest that there may be subsets of patients with stage II disease who are at higher risk of recurrence
- Prognostic markers to identify these patients have not been validated in prospective trials
- Treatment options are evolving
 - Role of biologics in adjuvant therapy

Oxaliplatin-Based Chemotherapy in Early-Stage Colon Cancer

Study	Regimen	Stage	3-Year DFS (%)		P value
			Control	Test	
MOSAIC¹		II/III	72.9	78.2	0.002
N=2248 (40% stage II 60% stage III)	Infusional 5-FU ± OX	II	84.3	87.0	NR
		III	65.3	78.2	NR
NSABP C-07²					
N=2407 (21% stage II 79% stage III)	Bolus 5-FU ± OX	II/III	71.6	76.5	<0.004

- In both trials, major toxicity issues attributed to oxaliplatin included grade 3 neuropathy (≥8%), which was reduced after 1 year (≤1%)

5-FU = 5-fluorouracil; DFS = disease-free survival; OX = oxaliplatin.

1. Andre et al. *N Engl J Med*. 2004;350:2343.

2. Wolmark et al. *J Clin Oncol*. 2005;23:16S. Abstract 3500.

Survival Benefit in Metastatic Colorectal Cancer With Bevacizumab + Chemotherapy

	AVF2107g ¹			E3200 ²		
	IFL + placebo (n=411)	IFL + bevacizumab (n=402)	HR	FOLFOX-4 (n=292)	FOLFOX-4 + bevacizumab (n=293)	HR
Median OS (mo)*	15.6	20.3	0.66	10.8	13.0	0.75
PFS (mo)†	6.2	10.6	0.54	4.5	7.5	0.52

- Impact of bevacizumab in adjuvant therapy in CRC is currently under investigation

* $P < 0.001$; † $P \leq 0.0001$.

1. Avastin® (bevacizumab) PI. June 2006.
 2. Giantonio, B et al. *J Clin Oncol*. 2005;23:16S. Abstract 2

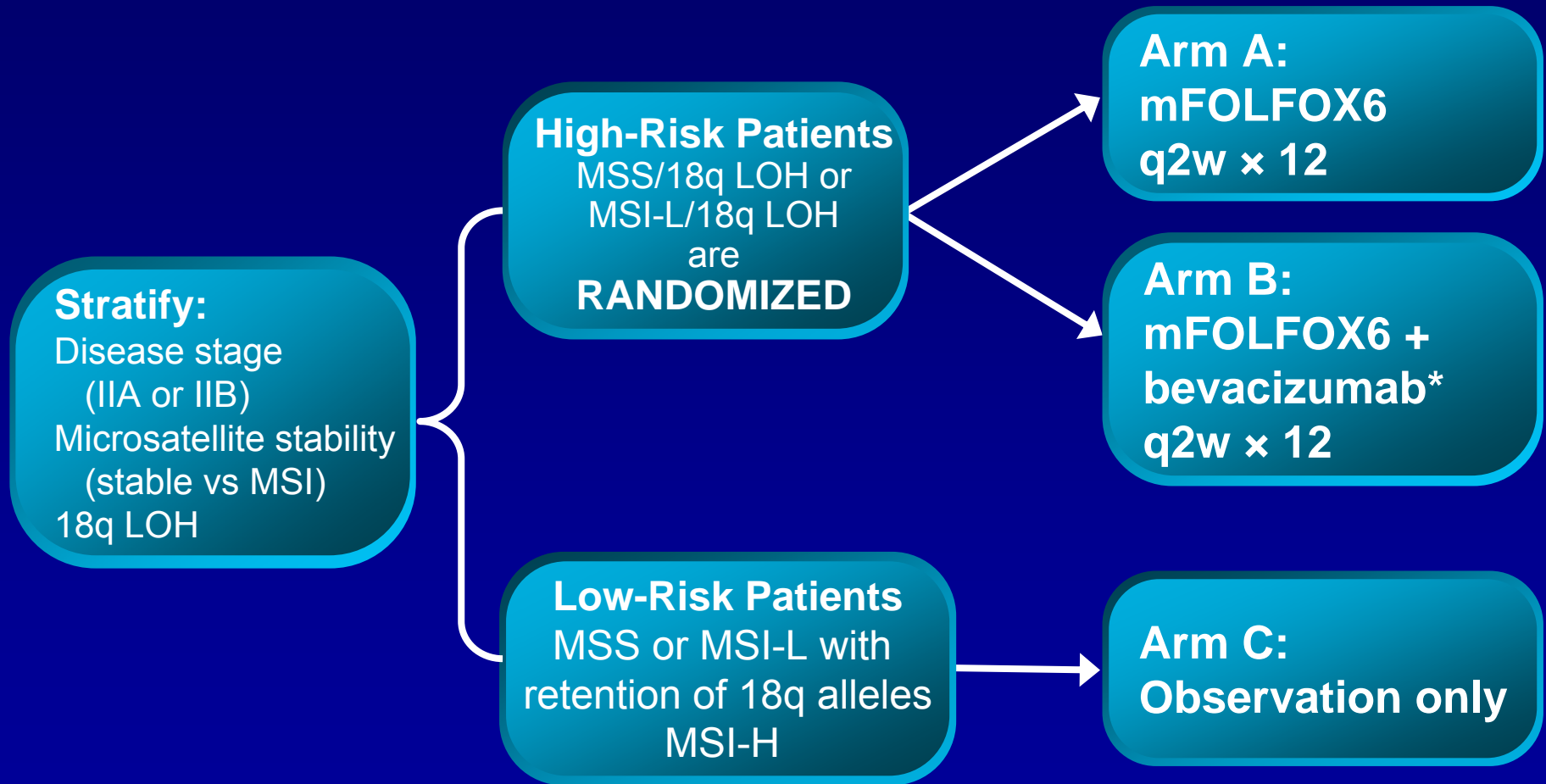
Molecular Prognostic Factors in Early-Stage Colon Cancer Patients

- Adverse prognostic factor: 18q LOH
 - Associated with alterations in apoptotic regulators (*DCC*, *Smad4*)
 - Lower survival rates seen in reported studies
- Favorable prognostic factor: microsatellite instability (MSI)
 - Fewer metastases and longer survival seen in patients with high levels of MSI

E5202 Rationale

- FOLFOX regimens are effective for adjuvant treatment of colon cancer
- Addition of bevacizumab to chemotherapy has demonstrated clinical benefit in mCRC
- Molecular prognostic factors may identify certain populations of patients with stage II disease who may benefit from adjuvant treatment
- These markers must be prospectively validated
- This trial will answer several outstanding questions that are critically important to the treatment of stage II colon cancer
 - E5202 represents the first trial in which patients with colon cancer are selected prospectively for adjuvant therapy based on molecular marker status
 - This trial will also assess the role of chemotherapy and biologics in the treatment of patients with high-risk stage II disease

E5202 Trial Schema



MSI-L = low-level microsatellite instability

MSI-H = high-level microsatellite instability

*Bevacizumab continued for an additional 6 months

E5202 Objectives

- Primary objective
 - 3-year disease-free survival of high-risk patients
- Secondary objectives
 - Overall survival
 - Toxicity profile
 - Tumor biologic correlation with survival

E5202 Trial Design: Sample Submission

- Tumor and normal tissue sample required for enrollment
 - Samples must be formalin-fixed paraffin blocks or unstained histologic sections
 - Submission time points are crucial
 - ◆ Received no later than 50 days following surgery
 - ◆ Received within 5 days of trial registration
 - Surgeons at participating institutions should be aware of timeline in order to introduce patients to trial
 - ◆ Critical given timeline of tissue collection

E5202 Eligibility Criteria

- Age ≥ 18
- ECOG performance status of 0-2
- Histologically confirmed stage II (T3-4, N0, M0) adenocarcinoma of the colon
- Surgical resection of primary tumor within past 28-50 days
 - Tumor and normal tissue sample submitted by day 50
 - Patient to begin therapy no later than day 60
- Distal extent of tumor ≥ 12 cm from anal verge
- Tumor specimen for evaluation of MSI and 18q status
- Adequate bone marrow, liver, and kidney function

E5202 Eligibility Criteria (cont'd)

- No significant proteinuria
- No uncontrolled hypertension
- No wounds, ulcers, bleeding, or clotting disorders
- No peripheral vascular disease
- No recent significant traumatic injury
- No history of TIA, CVA, or other arterial thrombotic events
- No existing peripheral neuropathy
- No prior radiotherapy or systemic therapy for this cancer
- No prior surgery or open biopsy within 28 days
- No prior core biopsy or other minor procedure except placement of a vascular access device within 7 days
- No concurrent halogenated antiviral agents (for high-risk patients only)

E5202 Treatment Plan

- Arm A: mFOLFOX6
 - Oxaliplatin 85 mg/m² IV + LV 400 mg/m² IV for 2 hours on day 1
 - 5-FU 400 mg/m² IV bolus (following LV)
 - 5-FU 2400 mg/m² IV continuously over 46 hours (following bolus 5-FU)
 - Treatment duration: q2w for 12 courses in the absence of disease progression or unacceptable toxicity
- Arm B: mFOLFOX6 + bevacizumab
 - Chemotherapy as outlined for Arm A + bevacizumab 5 mg/kg IV infusion over 30-90 minutes
 - Treatment duration: q2w for 12 courses in the absence of disease progression or unacceptable toxicity
 - Patients receive bevacizumab alone for 12 additional courses in the absence of disease progression or unacceptable toxicity
- Arm C: Observation
 - Observation only (per Arm C parameters)

E5202 Assessments

- During chemotherapy
 - History and physical exam
 - Weight, ECOG PS
 - Drug toxicity assessment
 - CBC, differential, platelets
 - Serum creatinine[†]
 - SGOT (AST), total bilirubin[†]
 - Urine protein/creatinine ratio[‡]
 - Blood pressure
- 6 weeks after final treatment*
 - History and physical exam
 - Weight, ECOG PS
 - Drug toxicity assessment
 - SGOT (AST), total bilirubin[†]
 - Carcinoembryonic antigen (CEA) titer

*For Arm A and Arm B only.

[†]As clinically indicated.

[‡]Performed every other cycle for Arm B (bevacizumab-containing arm) only.

E5202 Expected Toxicities*

FOLFOX, bevacizumab expected toxicities:

- Nausea and vomiting
- Peripheral neuropathy
- Cold sensitivity
- Myelosuppression
- Diarrhea, mucositis, stomatitis
- Skin rash, dermatitis
- Hypertension
- Proteinuria
- Arterial thrombotic events

*For complete listing of toxicities, please refer to full protocol available at www.ctsu.org.

E5202 Endpoints

- Primary endpoint: DFS
 - Statistical analyses will be conducted at 9 interim analyses beginning with 120 events
 - Estimated 88% power to detect a 37% difference (absolute difference of 5% at 3 years) in median DFS using a 1-sided stratified log-rank test

E5202 Endpoints (cont'd)

- Secondary endpoint: OS
 - Comparison between Arm A and Arm B
 - ◆ Estimated 84% power to detect a 37% difference (absolute difference of 5% in 5 years) in median OS using a one-sided stratified log-rank test
 - Comparison between Arms A/B and Arm C
 - ◆ Estimated 95% power to detect differences in median OS using an unadjusted 2-sided log-rank test
- Additional secondary endpoints
 - Toxicity profiles
 - Tumor biologic characteristics correlation with survival of patients treated with these regimens

E5202 Long-Term Follow-up

- Follow-up assessments schedule
 - Follow-up begins after completion of chemotherapy or every 3 months within 2 years* from step 2 randomization, every 6 months for patients 3-5 years from randomization, and annually thereafter
- Long-term follow-up includes
 - Carcinoembryonic antigen (CEA) titer
 - Colonoscopy recommended at 1 year post-op, then every 3 years thereafter
 - Biopsy (if indicated)

*For Arm A, follow up is every 3 months for 1.5 year following chemotherapy; for Arm B, follow up is every 3 months for 1 year following chemotherapy; for Arm C, follow up is every 3 months for 2 years.

E5202 Correlative Studies

- Correlate tumor biologic characteristics with survival of patients treated with test regimens
 - Microsatellite stability
 - 18q LOH
- All tissue from study to be archived by ECOG coordinating center and assessed for biologic characteristics by MD Anderson laboratories
- Tissue from studies will be archived for future assessment

Surgeon Participation in E5202 Recruitment

- Participation of general and oncology surgeons is crucial for the timely recruitment of patients
- This study allows credit for enrolling patients to both the recruiting surgeon as well as the treating physician
- For E5202 surgery referral form please refer to <https://members.ctsu.org/DocumentList.asp?ID=102&num=E5202&DocType=10>

GI Intergroup Participants

- CALGB
- ECOG
- NCCTG
- NSABP
- SWOG