

ECOG 5204

Intergroup Randomized Phase III Trial of
Postoperative Oxaliplatin, 5-FU and Leucovorin
Versus Oxaliplatin, 5-FU, Leucovorin and
Bevacizumab for Stage II or III Rectal Cancer
Receiving Preoperative Chemoradiation

E5204 Rationale

- Clinical evidence supports the use of adjuvant chemotherapy in rectal cancer following neoadjuvant chemoradiotherapy and surgery
- Oxaliplatin-containing regimens are effective for adjuvant treatment of colon cancer
- Addition of bevacizumab to FOLFOX regimens provides clinical benefit in mCRC
- The role of bevacizumab added to FOLFOX within the adjuvant setting remains unknown

E5204 Trial Schema

Neoadjuvant Tx: Patients on **NSABP R-04** or RT + 5-FU/LV or infusional 5-FU

Stratify:
ECOG PS (0 or 1)
Clinical staging
Prior oxaliplatin*
Prior chemoradiation therapy

R
A
N
D
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M
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Z
E

Arm A:
mFOLFOX6
q2w × 12*

Arm B:
mFOLFOX6 + bevacizumab
q2w × 12*

*Patients can be enrolled in both NSABP-R-04 and E5204

E5204 Objectives

- Primary objective
 - Overall survival
- Secondary objectives
 - Disease-free survival
 - Tolerability and long-term rectal function
 - Evaluate molecular markers of treatment efficacy
 - Correlate tumor molecular prognostic markers with survival

E5204 Trial Design

- Projected accrual
 - 2100 patients
- Stratification
 - ECOG PS 0 or 1
 - Clinical staging
 - ◆ High risk (T3, N+, M0 or T4, any N, M0)
 - ◆ Low risk (T1-2, N+, M0 or T3, N0, M0)
 - Prior oxaliplatin (**NSABP R-04 trial**)
 - Prior radiotherapy dose
 - ◆ 40-50 Gy vs >50-54 Gy pre-op chemoradiation (**NSABP R-04 patients included-follow NSABP R-04 RT Guidelines**)

E5204 Trial Design (cont'd)

- Patients complete questionnaires on bowel function and quality of life at the following time points:
 - Randomization
 - End of treatment (following 12 cycles in Arms A and B)
 - 12 months post-treatment
 - Annually to 5 years post-treatment
- Upon completion of study, patients are followed for 10 years

E5204 Eligibility Criteria

- Age ≥ 18 yrs
- ECOG PS of 0-1
- Histologically confirmed adenocarcinoma of the rectum
- Adequate bone marrow, liver, and kidney function
- Must have undergone concurrent neoadjuvant chemoradiotherapy
 - Neoadjuvant chemoradiotherapy received on protocol NSABP-R-04 allowed provided it met these criteria
 - ◆ No evidence of metastatic disease confirmed within the past 3 months
 - ◆ No evidence of tumor outside of the pelvis
- Must have undergone prior radiotherapy at a dose of 40-50 Gy vs >50-54 Gy pre-op chemoradiation AND received one of the following chemotherapy regimens:
 - Continuous infusion of 5-FU \pm oxaliplatin
 - 5-FU/leucovorin calcium
 - Capecitabine \pm oxaliplatin
 - Oxaliplatin and capecitabine received on NSABP R-04 protocol

E5204 Eligibility Criteria (cont'd)

- No evidence of metastatic disease within the past 3 months
- No significant proteinuria
- No uncontrolled hypertension
- No wounds, ulcers, or bleeding or clotting disorder
- No peripheral vascular disease
- No recent significant traumatic injury
- No history of TIA, CVA, or other arterial thrombotic event
- No existing peripheral neuropathy
- 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

E5204 Treatment Plan

- Arm A: mFOLFOX6*
 - Oxaliplatin 85 mg/m² IV + leucovorin (LV) 400 mg/m² IV for 2 hours on day 1
 - Fluorouracil 400 mg/m² IV bolus (immediately following LV)
 - Fluorouracil 2400 mg/m² IV continuously over 46 hours
 - Treatment repeats 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 repeats q2w for 12 courses in the absence of disease progression or unacceptable toxicity

*Patients who received prior neoadjuvant oxaliplatin on protocol NASBP R-04 receive up to 9 courses of treatment followed by 3 additional courses of leucovorin IV and 5-FU ± bevacizumab.

E5204 Assessments

- During chemotherapy
 - History and physical exam
 - Weight, ECOG PS
 - CBC, differential, platelets
 - Serum creatinine
 - SGOT (AST), total bilirubin, alkaline phosphatase
 - Urine protein/creatinine ratio*
- After final treatment
 - History and physical exam
 - ECOG PS
 - Carcinoembryonic antigen (CEA)
 - Colonoscopy or barium enema†
 - FACT-Diarrhea subscale questionnaire
 - Patient Bowel Function/Uniscale questionnaire
 - FACT/GOG-Neurotoxicity subscale questionnaire

*Prior to every third cycle for patients receiving bevacizumab

†1 year after surgery, then recommended every 3 years thereafter

E5204 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

E5204 Endpoints

- Primary endpoint: overall survival
 - Statistical analyses will begin at 25% of 533 events
 - Stratified log-rank test should provide 85% power to detect a 1.30 hazard ratio for overall survival

E5204 Endpoints (cont'd)

- Secondary endpoints
 - Disease-free survival
 - Tolerance of treatment
 - Patterns of failure
 - Evaluation of molecular markers of treatment efficacy
 - Correlation of tumor molecular prognostic markers with survival

E5204 Long-Term Follow-up

- Follow-up schedule
 - Follow-up begins after 12 cycles of therapy (Arms A + B)
 - Follow-up assessments performed every 3 months for patients < 2 years from randomization, every 6 months for patients 2-5 years from randomization, and every 12 months for patients 5-10 years from randomization
- Long-term follow-up includes
 - Carcinoembryonic antigen (CEA)
 - Colonoscopy or barium enema 1 year after surgery, then recommended every 3 years thereafter
 - FACT-Diarrhea subscale questionnaire
 - Patient Bowel Function/Uniscale questionnaire
 - FACT/GOG-Neurotoxicity subscale questionnaire
 - ◆ Bowel function and neurotoxicity measured at randomization, on cycle 4 day 1, 3 months post-chemotherapy, 12 months post-chemotherapy and annually to 5 years post-treatment

E5204 Ancillary Studies

- Assess long-term rectal function
 - Patient Bowel Function/Uniscale questionnaire
 - FACT-Diarrhea subscale questionnaire
- Validate the FACT-Diarrhea subscale questionnaire
- Assess long-term symptoms of oxaliplatin-related neurotoxicity
 - FACT/GOG-Neurotoxicity subscale questionnaire
- Tissue sample collection to assess laboratory correlates

GI Intergroup Participants

- CALGB
- ECOG
- NCCTG
- NSABP
- SWOG

NSABP R-04

NSABP R-04

- Neoadjuvant study conducted in conjunction with **E5204**
- Stage II/III rectal cancer
- 2×2 randomized trial design
- Primary objective: rate of relapse
- Secondary objectives:
 - Clinical complete response
 - Pathologic complete response
 - Correlation of response and prognosis with molecular markers
 - Preoperative QOL (capecitabine vs infusional 5-FU)
 - Toxicity

R-04 investigators are strongly encouraged to refer participants to the **E5204 trial for adjuvant therapy**

R-04 Trial Schema

Stratify:

Participating center

Clinical Tumor Staging (stage II vs III)

Surgical Intent

(sphincter-saving vs non-sphincter-saving)

RANDOMIZE

Arm I:

225 mg/m²/d 5-FU + RT (d1-5)

Arm II:

225 mg/m²/d 5-FU + RT (d1-5)
+ 50 mg/m² Ox (d1)

Arm III:

825 mg/m² PO bid C + RT (d1-5)

Arm IV:

825 mg/m² PO bid C + RT (d1-5)
+ 50 mg/m² Ox (d1)

SURGERY

RT = radiotherapy;
Ox = oxaliplatin;
C = capecitabine.

R-04 Eligibility Criteria

- Age ≥ 18 yrs
- ECOG or Zubrod performance status of 0-1
- Life expectancy ≥ 5 yrs
- Histologically confirmed adenocarcinoma of the rectum
- Distal extent of tumor < 12 cm from anal verge
- No evidence of metastatic disease
- No prior therapy for this disease
- Adequate bone marrow, liver, and kidney function
- No significant cardiovascular disease; adequate upper GI integrity and function; no active IBD; no clinically significant peripheral neuropathy