American College of Surgeons Clinical Research Program
Surgical Investigators Webinar

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Alliance/ACS Clinical Research Program

• Improve cancer care outcomes through high-quality health services research that leverages the multidisciplinary collaboration and research infrastructure of the Alliance and its partners to generate new knowledge and facilitate the implementation and dissemination of research findings throughout the oncology community

• Improve oncological surgical practice through dissemination of best practices and clinical trial findings

Increase interaction and integration between the Alliance, the ACS, and the Commission on Cancer
An Integrated Model

Alliance for Clinical Trials in Oncology

American College of Surgeons

Dissemination & Implementation Committee: Engagement
Education Committee: Dissemination
Standards Committee: Implementation
Cancer Care Delivery Research: Knowledge Generation

ACS CRP
NCCTG N1048 (PROSPECT) A Phase II/III Trial of Neoadjuvant FOLFOX, with Selective Use of Combined Modality Chemoradiation Versus Preoperative Combined Modality Chemoradiation for Locally Advanced Rectal Cancer Patients Undergoing Low Anterior Resection with Total Mesorectal Excision

NRG GI002 (TNT) Phase II Clinical Trial Platform of Sensitization Utilizing Total Neoadjuvant Therapy in Rectal Cancer

ATOMIC (A021502) Randomized Trial of Standard Chemotherapy Alone or Combined with Atezolizumab as Adjuvant Therapy for Patients with Stage III Colon Cancer and Deficient DNA Mismatch Repair
An NCI Cooperative Group Phase II/III Trial of Neoadjuvant FOLFOX with Selective Use of Combined Modality Chemoradiation for Locally Advanced Rectal Cancer Patients Undergoing Low Anterior Resection with Total Mesorectal Excision
Neoadjuvant Chemotherapy Without Routine Use of Radiation Therapy for Patients With Locally Advanced Rectal Cancer: A Pilot Trial

Deborah Schrag, Martin R. Weiser, Karyn A. Goodman, Mithu Gotten, Ellen Hollywood, Andreas Cernek, Diane L. Redy-Lopes, Mark J. Gollub, Imru Shia, Jose G. Gutierrez, Larissa K. F. Temple, Philip B. Poyn, and Leonard B. Saltz

ABSTRACT

Purpose
Although neoadjuvant chemoradiation achieves low local recurrence rates in clinical stages II to III rectal cancer, it delays administration of optimal chemotherapy. We evaluated preoperative infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX) with bevacizumab with selective rather than consistent use of chemoradiation.

Patients and Methods
Thirty-two patients with clinical stages II to III rectal cancer participated in this single-center phase II trial. All were candidates for low anterior resection with total mesorectal excision (TME). Patients were to receive six cycles of FOLFOX, with bevacizumab included for cycles 1 to 4. Patients with stable/progressive disease were to have radiation before TME, whereas responders were to have immediate TME. Postoperative radiation was planned if R0 resection was not achieved. Postoperative FOLFOX × 6 was recommended, but adjuvant regimens were left to clinician discretion. The primary outcome was R0 resection rate.

Results
Between April 2007 and December 2006, 32 (100%) of 32 study participants had R0 resections. Two did not complete preoperative chemotherapy secondary to cardiovascular toxicity. Both had preoperative chemoradiotherapy and then R0 resections. Of 30 patients completing preoperative chemotherapy, all had tumor regression and TME without preoperative chemoradiotherapy. The pathologic complete response rate to chemotherapy alone was 8 of 32 (25%; 95% CI, 11% to 43%). The 4-year local recurrence rate was 0% (95% CI, 0% to 11%); the 4-year disease-free survival was 84% (95% CI, 67% to 94%).

Conclusion
For selected patients with clinical stages II to III rectal cancer, neoadjuvant chemotherapy and selective radiation does not seem to compromise outcomes. Preoperative Radiation or Selective Preoperative Radiation and Evaluation Before Chemotherapy and TME (PROSPECT), a randomized phase III trial to validate this experience, is now open in the US cooperative group network.


INTRODUCTION
The advantage of combined-modality therapy (CMT) in rectal cancer is that it has reduced local pelvic recurrence—a dreaded and morbid event—to rates of <10%. In 2004, a German randomized trial established the superiority of preoperative administration of fluorouracil-based chemoradiotherapy (FUCMT). Subsequently, neoadjuvant FUCMT followed by a total mesorectal excision (TME) and postoperative systemic therapy has been standard practice in North America. Most trials comparing CMT regimens demonstrated that oral capecitabine and parenteral FU have equal efficacy and that intensification with oxaliplatin has an incremental benefit. As a result, the current trimalid therapy paradigm of fluoropyrimidine-containing CMT, then TME, and finally adjuvant systemic therapy, prevails.

Although local recurrence (LR) has been related to a rare complication, distant recurrence rates for stages II to III rectal cancers are still consistently >25% and patients therefore more commonly succumb to rectal cancer as a consequence of
Study Design

• A phase II/III study:
  
  – Randomized phase II of 366 patients with early stopping rule if failure to complete R0 resections or if high rate of Local Recurrence

  – Phase III component to include 644 additional patients
Study Schema with Suggested Post-op Regimens

“Standard Arm”

RANDOMIZE 1:1

Response ≥20%

“Selective Arm”

Response <20%

5FUCMT → TME → FOLFOX x 8*

5FUCMT → TME → FOLFOX x 6*

FOLFOX x 6 → TME → FOLFOX x 6*

FOLFOX x 6 → 5FUCMT → TME → FOLFOX x 4*
Primary Endpoints:
- Randomized Phase II Component
  - R0 Resection Rate
  - Time to local recurrence (TLR)
- Phase III Component: Co-primary endpoints
  - Time to local recurrence (TLR)
  - Disease free survival (DFS)

Secondary Endpoints:
- Pathologic complete response rate (Pcr)
- Overall survival (OS)
- Quality of life (QOL)
- Clinician and patient reported treatment toxicity
- Molecular correlates of response to neoadjuvant therapy
- Adverse Event (AE) Profiles
- Rates of receiving 5FUCMT
Eligibility

- Clinical stage T2N1, T3N0, or T3N1 (stage IIA, IIIA, or IIIB) as determined by operative exam, CT, MRI, or EUS

- Candidate for sphincter preservation TME before neoadjuvant therapy

- No encroachment on the mesorectal fascia based on preoperative imaging or ≥ 4 LN that are more than 10 mm (N2 disease)
Accrual Updates

• Total Accrual = 1130
  • 50 remaining
A Phase II Clinical Trial Platform of Sensitization Utilizing Total Neoadjuvant Therapy (TNT) in Rectal Cancer

NRG Oncology - (NRG-GI002)

Thomas George, MD, FACP
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Director, GI Oncology Program
Associate Director, Clinical Investigation
University of Florida Health Cancer Center
Gainesville, FL

NCT02921256
Current Tri-Modality Paradigm for Rectal Cancer

T3-4 or Node + Rectal Cancer

Chemoradiotherapy → pCR ~20% Surgery → Chemotherapy

25-70% DO NOT receive adjuvant systemic chemotherapy

NRG-GI002 (TNT) Schema
Non-comparative experimental arms

- FOLFOX x 8
- XRT + Capecitabine
- Surgery

V. High Risk
- Bulky
- N2
- Low lying
- APR required

Locally Advanced Rectal Cancer

Additional arms added through protocol amendments

NCT02921256
Eligibility (opposite of PROSPECT study population)

- Biopsy proven stage II or III rectal adenocarcinoma
- ECOG PS 0-2
- The tumor must be locally advanced (by any ONE):
  - distal location: cT3-4 ≤ 5 cm from the anal verge, any N (as defined by measurement on MRI, ERUS/pelvic CT scan or palpable on DRE)
  - bulky: any cT4 with the majority of tumor < 12 cm from the anal verge or evidence that the tumor is adjacent to (defined as within 3 mm of) the mesorectal fascia on MRI or ERUS/pelvic CT scan
  - high risk for metastatic disease with >4 regional lymph nodes (cN2)
  - not a candidate for sphincter-sparing surgical resection prior to neoadjuvant therapy (as planned by the primary surgeon)

- Stage of the primary tumor may be determined by endoscopic ultrasound or MRI (MRI is preferred).
- Adequate untreated tumor specimen must be available for mutational profiling.
TNT Endpoints

Primary = NAR Score

Secondary
- pCR & cCR rates
- OS and DFS
- Toxicity
- Rate of negative circ margin
- Rate of local recurrence
- Rate of sphincter preservation/function/QOL
- Compliance & treatment completion rates
- Molecular predictors of response & distant failure

Any arm/hypothesis meeting the pre-specified endpoint will move into a “solo” and definitive RCT

NCT02921256; PI – George TJ
TNT Primary Objective

To demonstrate an absolute improvement in Rectal Neoadjuvant Response Score (NAR) of 4.7 Reduction from 14.32 (contemporary studies) to 9.62

Corresponding to a ~20% reduction of HR for death and 3-4% increase in 5 year OS (near doubling of pCR and/or downstaging)

n=79 evaluable patients in each arm

Yothers G, et al.; J Clin Oncol 32:5s, 2014 (suppl; abstr 3533)
Types of DNA damage and repair

Cause of damage:
- Radio- and chemotherapy
- UV light
- Replication errors
- Alkylating agents

Type of damage:
- Double-strand breaks
- Bulky adducts
- Insertions
- Deletions
- O6-alkylguanine
- Single-strand breaks

Repair Enzymes:
- DNA-PK, ATM
- XP, polymerases
- MSH2, MLH1
- AGT
- PARP

Chemotherapy
X-rays

Direct reversal (AGT)
Base excision repair (BER)
NRG-GI002 (TNT) Schema
Non-comparative experimental arms

V. High Risk
- Bulky
- N2
- Low lying
- APR required

Locally Advanced Rectal Cancer

FOLFOX x 8 → XRT + Capecitabine → Surgery

FOLFOX x 8 → XRT + Capecitabine + Veliparib → Surgery

FOLFOX + ? x 8 → XRT + Capecitabine → Surgery

Additional arms added through protocol amendments

NCT02921256
NRG-GI002: TNT Platform Design A Cumulative

- Fastest enrolling rectal cancer study in U.S.
- First arm enrollment is complete
- New arm just activated Aug 2018
- Several additional arms in development
- New hypotheses welcomed!
XRT as a Catalyst for Immunotherapy

• PD-1 inhibition is very active in (MSI-H) mCRC

• Goal: Overcome IO resistance in MSS with XRT
  – XRT increases tumor PD-L1 expression, increases TILs and reduces FOXP3 in CRC
  – XRT + anti-PD-1 is active in CRC xenografts
  – XRT + anti-PD-1 stimulates tumor-specific Tcells

NRG-GI002 (TNT) Schema
Non-comparative experimental arms

- V. High Risk
- Bulky
- N2
- Low lying
- APR required

Locally Advanced Rectal Cancer

Now Open

Additional arms added through protocol amendments

FOLFOX x 8
XRT + Capecitabine
Surgery

FOLFOX x 8
XRT + Capecitabine + Veliparib
Surgery

FOLFOX x 8
XRT + Capecitabine + Pembrolizumab
Surgery

FOLFOX x 8
XRT + Capecitabine + ?
Surgery

Arm PI – O. Rahma

NCT02921256
Correlative Studies

- Surgical procedure outcomes & sphincter function
- Circulating and tumor-based biospecimen collection with post-hoc prognostic and predictive biomarker analysis planned
- MRI imaging to correlate with pathologic findings
Correlative Studies supported through CTEP & U10

- Patient germline DNA
- Imaging assessments
- Tumor sample
- Blood

Correlative studies include:
- Serial biopsies w/ associated plasma collected prospectively & consistently as part of this clinical trial platform
- Full exon sequencing, proteomics, metabolomics, circulating tumor DNA analyses
- Considering PDX-model generation in a subset for additional correlative studies
- Other hypothesis-driven concepts that are intervention-specific (e.g., “HRD-like” for PARPi, TILs for PD-1, etc.)
- Ultimate goal is to define predictors of response/resistance for validation in subsequent registration studies

* TNT Plus sites only
Questions
Alliance A021502 (ATOMIC) - Randomized Trial of Standard Chemotherapy Alone or Combined with Atezolizumab as Adjuvant Therapy for Patients with Stage III Colon Cancer and Deficient DNA Mismatch Repair

Frank Sinicrope, MD – Study Chair
Kabir Mody, MD – Study Co-Chair
Walter Peters, MD – Study Co-Chair

December 14, 2017
Study Overview: Background
Background – Immune Checkpoints

- The PD-1/PD-L1 pathway acts to protect tumor cells from immune attack by T cells which can be circumvented by checkpoint inhibitors.

- Targeting PD-1 with pembrolizumab or nivolumab for treatment of refractory metastatic colorectal cancers with deficient DNA mismatch repair (d-MMR) produced frequent and durable responses. These data led to FDA approval of both drugs for d-MMR tumors.

Background – Atezolizumab

- Atezolizumab is a monoclonal antibody that binds to PD-L1 and blocks its interaction with PD-1, thereby enhancing T-cell activity against tumor cells.

- Atezolizumab is well tolerated with no dose-limiting toxicities; data include a phase I trial of atezolizumab plus bevacizumab +/- FOLFOX.

- Atezolizumab is FDA-approved for treatment of platinum-resistant metastatic non-small cell lung cancer (NSCLC) and locally advanced or metastatic urothelial cancer.
Background – Checkpoint Inhibitor + Chemotherapy

- Atezolizumab was shown to enhance the efficacy of platinum-containing chemotherapy in NSCLC (IMpower150, ESMO ImmunoOnc 2017).

- Oxaliplatin has been shown to induce immunogenic tumor cell death.

- We hypothesize that atezolizumab can enhance the efficacy of standard adjuvant FOLFOX chemotherapy for stage III colon cancer with d-MMR.
Background–Deficient (d)-Mismatch Repair (MMR)

- d-MMR results in microsatellite instability (MSI).
- d-MMR tumors are hypermutated with abundant neoantigens that trigger tumor infiltrating lymphocytes (TILs); factors associated with response to checkpoint inhibitors.
- d-MMR cancers include both sporadic and hereditary, e.g. Lynch Syndrome types.
- About 12% of stage III colon cancers show d-MMR or MSI.
- NCCN Guidelines recommend d-MMR or MSI testing of all newly diagnosed CRC cases.
Study Overview: Trial Design
Trial Design – Schema

- **Stratification Factors:** T, N stage, tumor location

- **Dosing Schedule (one cycle = 2 weeks):**
  - Atezolizumab 840 mg IV q2 weeks
  - Oxaliplatin 85 mg/m² IV q2 weeks
  - Leucovorin 400 mg/m² IV q2 weeks
  - Fluorouracil 400 mg/m² IV bolus + 2400 mg/m² IV q2 weeks

* One cycle of mFOLFOX6 is allowed prior to registration

# dMMR status assessed via local or reference lab testing of MMR proteins by IHC
Trial Design – Objectives

- **Primary**: to determine whether atezolizumab combined with FOLFOX and its continuation as monotherapy can significantly improve *disease-free survival (DFS)* vs FOLFOX alone in patients with stage III colon cancers and d-MMR.

- **Secondary**: impact of addition of atezolizumab to FOLFOX on *overall survival* vs FOLFOX alone.

- **Secondary**: to assess the adverse event profile and safety of each treatment arm (using CTCAE and PRO-CTCAE).
Trial Design – Statistical Analyses

- Primary endpoint is DFS.
  - Target Hazard Ratio = 0.60 (equivalent to achieving DFS of 84% at 3-year mark for atezolizumab arm [2-sided alpha = 0.05, 90% power]); N = 700 patients
  - Interim analyses at 50% and 75% of events
  - Total number of DFS events required = 165

- Secondary endpoints are OS, immune-related and other adverse events, and QOL.

- Toxicity monitoring via CTCAE v4.0, PRO-CTCAE (Patient Reported Outcomes Measurement System), and HRQOL (Health-related Quality of Life) Instruments.
Trial Design – Patient Impact

- The addition of atezolizumab to FOLFOX has the potential to significantly reduce colon cancer recurrence and prolong DFS vs FOLFOX alone (i.e., current SOC).

- Using patient reported adverse events provides additional and valuable information on treatment safety (i.e., PRO-CTCAE considers emotional aspects and unreported side effects).
Trial Design – Eligibility Summary

- Curative resection of stage III colon adenocarcinoma with d-MMR.
- Tumor evaluation for d-MMR:
  - MMR protein expression (MLH1, MSH2, MSH6, or PMS2) by IHC.
    - Even if MSI-H by PCR is known, d-MMR by IHC is still required.
  - Local testing is acceptable. If NA, then tissue can be sent to a site-selected reference lab for MMR testing by IHC.
- Mandatory submission of FFPE tumor tissue to enable retrospective central confirmation of d-MMR by IHC.
  - Central confirmation is not for eligibility.
Trial Design – Eligibility Summary (continued)

- ECOG Performance Status: 0-2
- One cycle of mFOLFOX6 may be given prior to registration.
  - Allows additional time for a patient to decide whether or not to participate, and for sufficient time to obtain a local MMR IHC result while the patient starts treatment.
- For patients who are randomized to Arm 1 (mFOLFOX6 + atezolizumab) and had received Cycle 1 of mFOLFOX6 prior to registration, atezolizumab will begin with Cycle 2 of mFOLFOX6.
Trial Design – Adjuvant Treatment Duration

- Regardless of IDEA study results, the duration of adjuvant mFOLFOX6 treatment on A021502 is 6 months. Justification is based upon:
  - No data exists in IDEA for adjuvant treatment duration (3 vs 6 months) in d-MMR colon cancers.
  - Risk stratification used in IDEA that is based upon T and N stage is unknown among d-MMR cancers.
  - A021502 is a FDA registration trial and uniformity of treatment is optimal.
Trial Design – Additional Key Issues

- FFPE tumor tissue submission to the central lab required for all patients.
  - Tissue submission must be accompanied by electronically-completed, printed A021502 Requisition Form.
    - Fillable PDF can be found on study-specific Alliance and CTSU websites.
- A021502 is an FDA Registration trial and thus includes the following:
  - Central and on-site monitoring
  - Collection of major and critical protocol deviations via Medidata Rave®
  - Utilization of the centralized Delegation Task Log (DTL) via the CTSU
## Trial Design – Biospecimen Collection

<table>
<thead>
<tr>
<th>Time Window</th>
<th>Prior to treatment</th>
<th>3 weeks after treatment initiation</th>
<th>2 mo. after Cycle 5 (i.e., cycle 9), Day 1</th>
<th>6 months after end of adjuvant Rx</th>
<th>Time of recurrence</th>
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</thead>
<tbody>
<tr>
<td>Mandatory Submissions for All Patients Registered to the A021502 Main Study:</td>
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<tr>
<td>Tissue</td>
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<tr>
<td>Optional Submissions for Patients Registered to the PP1 and/or ST1 Substudies:</td>
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- Each specimen type has a separate consent question for optional future correlative science studies.