American College of Surgeons Clinical Research Program

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American College of Surgeons Clinical Research Program
Surgical Investigators Webinar

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Presenters: Martin Weiser, MD
Thom George, MD
Rectal Cancer - NCCTG N1048: 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

Rectal Cancer – TNT G001A: Phase II Clinical Trial Platform of Sensitization Utilizing Total Neoadjuvant Therapy (TNT) in Rectal Cancer
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
PROSPECT

Preoperative Radiation Or Selective Preoperative radiation and Evaluation before Chemotherapy and TME

N1048-CALGB81001-ACOSOGZ6052

Full protocol available on CTSU Website (www.ctsu.org)
Endorsed by SWOG, ECOG, NCIC, RTOG, NSABP, SAKK

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


ABSTRACT

Purpose
Although neoadjuvant chemoradiotherapy 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) 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 2008, 32 (100%) of 32 study participants had R0 resections. Two did not complete preoperative chemotherapy secondary to cardiovascular toxicity. Both had preoperative chemoradiomotherapy and then R0 resections. Of 30 patients completing preoperative chemoradiotherapy, all had tumor regression and TME without preoperative chemoradiotherapy. The pathologic complete response rate to chemoradiation 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.

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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 capcitabine and parenteral FU have equal efficacy and that intensification with oxaliplatin has no incremental benefit. As a result, the current trimodality 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

FOLFOX x 6 → 5FUCMT → TME → FOLFOX x 8*

Response ≥20%

TME → FOLFOX x 6*

“Selective Arm”

Response <20%

FOLFOX x 6 → 5FUCMT → TME → FOLFOX x 4*

*Post-op chemo is suggested; # of cycles & regimen may be modified (modification is not a protocol violation)
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 \( \geq 4 \) LN that are more than 10 mm (N2 disease)
Accrual Updates

• Total Accrual = 915
  (as of 11/17/2017)

Phase 2 portion completed
A Phase II Clinical Trial Platform of Sensitization Utilizing Total Neoadjuvant Therapy (TNT) in Rectal Cancer

NRG Oncology - (NRG-GI002)

PI: Thomas George, MD
Presenter: Y. Nancy You, MD

NCT02921256
Financial Disclosures

Research Support (Institution):

Astrazeneca
Bayer
Bristol-Myers Squibb
Merck
Lilly
Incyte

Consultant:

Bayer
Merck
Background

- Advances from rectal cancer trial results have plateaued over the past decade
- Attempts to improve pCR and survival have failed
- Sphincter preservation remains out of reach for a large proportion of patients
- Neoadjuvant therapy has been our greatest recent success for patients
Current Tri-Modality Paradigm for Rectal Cancer

T3-4 or Node + Rectal Cancer

Chemoradiotherapy → pCR ~20% → Chemotherapy

25-70% DO NOT receive adjuvant systemic chemotherapy

Adjust the Paradigm

T3-4 or Node + Rectal Cancer

Chemotherapy → Chemoradiotherapy → Surgery
NRG-GI002 (TNT) Schema
Non-comparative Phase II experimental arms

Locally Advanced Rectal Cancer

FOLFOX x 8 → XRT + Capecitabine → Surgery

Create a clinical trial **platform** through which innovative hypotheses can be tested with a high degree of certainty/refinement before moving into a definitive study

Additional arms added through protocol amendments

FOLFOX + ? → XRT + Capecitabine → Surgery

NCT02921256
Types of DNA damage and repair

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

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
- Recombinational repair (HR, NHEJ)
- Nucleotide-excision repair
- Mismatch repair
- Direct reversal (AGT)
- Base excision repair (BER)
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

Locally Advanced Rectal Cancer

FOLFOX x 8 → XRT + Capecitabine → Surgery

FOLFOX x 8 → XRT + Capecitabine + Veliparib → Surgery

FOLFOX x 8 → XRT + Capecitabine + Pembrolizumab → Surgery

Additional arms added through protocol amendments

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

NRG Oncology™

Coming soon

NCT02921256
Eligibility (opposite of PROSPECT study population)

- Biopsy proven stage II or III rectal adenocarcinoma
- Majority of tumor < 12cm from the anal verge
- 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 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
- Correlative molecular and radiographic predictors of response and distant failure
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)
Rectal Cancer Trial Endpoints

pCR is all or nothing
Tumor Regression Grade is inconsistent

<table>
<thead>
<tr>
<th>Score</th>
<th>Dworak, et al. (score 0–4) [23]</th>
<th>American Joint Committee on Cancer (score 0-3) [26]</th>
<th>Mandard, et al. (score 1–5) [27]</th>
<th>Memorial Sloan Kettering CC (score 1–3) [29]</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRG 0</td>
<td>Minimal tumor response to treatment</td>
<td>No residual tumor cells</td>
<td>–</td>
<td>No residual tumor cells</td>
</tr>
<tr>
<td>TRG 1</td>
<td>Fibrosis in &lt;25 % of tumor</td>
<td>Single or small group of cells</td>
<td>No residual tumor cells</td>
<td>–</td>
</tr>
<tr>
<td>TRG 2</td>
<td>Fibrosis in 25–50 % of tumor</td>
<td>Cancer with fibrotic response</td>
<td>Rare cancer cells</td>
<td>No residual tumor cells</td>
</tr>
<tr>
<td>TRG 3</td>
<td>Fibrosis in &gt;50 % of tumor</td>
<td>Minimal tumor response to treatment</td>
<td>Fibrosis &gt; residual cancer</td>
<td>86–99 % tumor response</td>
</tr>
<tr>
<td>TRG 4</td>
<td>No residual tumor cells</td>
<td>–</td>
<td>Residual cancer &gt; fibrosis</td>
<td>≤85 % tumor response</td>
</tr>
<tr>
<td>TRG 5</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

TRG tumor regression grade
NAR Score

Developed to include more relevant downstaging parameters than just pCR

\[
NAR = \frac{\left[5 \ pN - 3(cT - pT) + 12\right]^2}{9.61}
\]

Where \(cT\) in \{1, 2, 3, 4\},
\(pT\) in \{0, 1, 2, 3, 4\},
\(pN\) in \{0, 1, 2\}

Validated in NSABP R-04
Externally validated in secondary cohort

Yothers G, et al. ASCO 2014 #3533
Raissouni S, et al. ASCO 2014 #3532
NAR Score Summary

NAR Score outperforms pCR at predicting DFS and OS in clinical trials using neoadjuvant therapy for rectal cancer.

It similarly performs well at predicting DFS and OS in trials using pre-op chemo and chemoRT (TNT).

NCI-approved short-term endpoint for phase II clinical trial performance.

Yothers G, et al. ASCO 2014 #3533
Raissouni S, et al. ASCO 2014 #3532
Stats

• Each experimental arm is independently evaluated against a continuously enrolling control arm.

• Primary Endpoint:
  – One-sided type I error of Alpha = 0.10; Type II error of Beta = 0.20 (Power = 80%)

• Evaluable sample size is 79 per arm (87 patients per arm to allow for a 10% drop out rate)

Any experimental arm reaching these pre-specified statistically significant endpoints, in the context of no new safety concerns, would meet criteria for moving forward into a definitive phase III randomized controlled clinical trial.
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

Radiographic assessments

Tumor sample

Plasma

Chemotherapy

Chemoradiotherapy

Surgery

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 intervention-specific hypothesis-driven concepts (e.g., “HRD-like” for PARPi, immunoscore for PD1, etc.)
- Ultimate goal is to define predictors of response/resistance for validation in subsequent registration studies

* TNT Plus sites only
Huge Thanks!

Top Enrolling Centers

- UC Davis
- Univ of Florida
- Spectrum Health (MI)
- Missouri Baptist
- NYU-Perlmutter CC
- Case Western/Clev Clinic
- Ohio NCORP
- Univ of Oklahoma
- Abington/Thomas Jefferson
- Sanford Clinic (SD)
- Vanderbilt
Study Leadership Team

- PI – Thomas George, MD, FACP
- RadOnc Chair – Theodore Hong, MD
- Colorectal Surgery Chair – Marcia Russell, MD
- Pathology Chair – Katherine Pogue-Geile, PhD
- Translational Chair - Nancy You, MD, MHSc, FACS
- Radiology Chair – Marc J. Gollub, MD, FACR
- Stats Chair – Greg Yothers, PhD
- Protocol Officer – Sam Jacobs, MD
- Medical Physics – William Parker, MSc
- ALLLIANCE Co-PI – Osama Rahma, MD
- ECOG-ACRIN Co-PI – Namrata (Neena) Vijayvergia, MD
- SWOG Co-PI – Lisa Kachnic, MD
Study Status

- Protocol activated October 2016 via CTSU
- Enrolling at/ahead of schedule
- Open to all NCTN participating sites
- Additional study arms to be added through protocol amendments thereafter
  - Several in active development

Novel hypotheses, agents and new investigators are encouraged to submit additional arms for future inclusion

NRG-GI002 (TNT Study); NCT02921256; PI – George TJ