# TRIPARTITE

COLORECTAL MEETING 2014

**Impact of mFOLFOX6 Following Chemoradiation on Tumor Response and Surgical Complications in Patients With Locally Advanced Rectal Cancer Treated With Total Mesorectal Excision: Results of a Prospective Trial (NCT00335816)**

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# Background

- The standard treatment of patients with locally advanced rectal cancer (LARC) includes neoadjuvant chemoradiation (CRT), total mesorectal excision (TME), and postoperative adjuvant chemotherapy (ACT)

- A relatively small proportion of patients treated with this protocol have a pathologic complete response (pCR)

- Patients with a pCR to CRT and treated with TME have an improved prognosis compared to non-pCR patients

- The additional benefit of TME in patients that have a complete response to CRT has been questioned

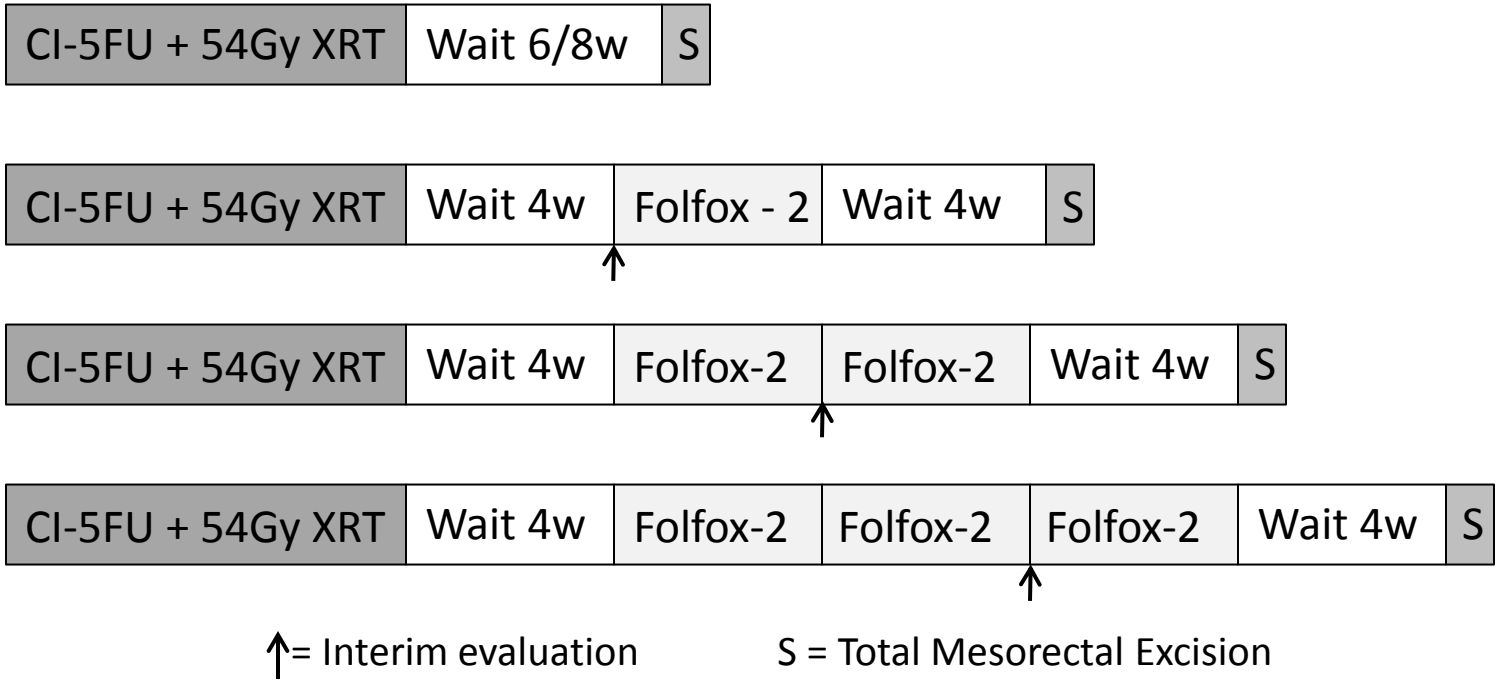
# Objective

- The objective of this study was to increase the proportion of patients responding to neoadjuvant therapy by simultaneously:
  - Delivering the adjuvant chemotherapy before TME
  - Lengthening the interval from the initiation of CRT to TME

Timing of Rectal Cancer Response to Chemoradiation

# Protocol Schema

Four sequential Phase II Trials:




- Simon's two-stage design
- Smallest number of pts needed for a type I error of 5% and power of 90%
- Each SG to reach a 10% increase in pCR before advancing to the next SG

# Methods

- Primary endpoint was pCR
  - assessed by pathologic exam of the surgical specimen
- Surgical difficulty was scored using an arbitrary scale
- Adverse events were recorded according to the NCI Common Toxicity Criteria, version3
- Surgical complications were graded according to Clavien-Dindo
- Comparisons between groups using Fisher's Exact test or Student's T test
- Multivariate analysis using logistic regression

# Patient Attrition

| | SG1 | SG2 | SG3 | SG4 | Total |
|---|---|---|---|---|---|
| **Registered Patients** | **71** | **74** | **71** | **76** | **292** |
| **Non-protocol treatment** | **8** | **1** | **1** | **5** | **15** |
| Local Excision | 2 | | | 3 | |
| Xeloda | 2 | 1 | | | |
| Bolus 5-FU | 1 | | | | |
| Conflicting trial | 1 | | | | |
| Change in therapy | 2 | | | 1 | |
| Surgery non-protocol site | | | | 1 | |
| Unknown | | | 1 | | |
| **Discontinued Treatment** | **2** | **5** | **2** | **6** | **15** |
| Refused surgery | 1 | 3 | 1 | 2 | |
| Metastasis diagnosed before surgery | 1 (liver) | 2 (lung) | | 1 (peritoneum) | |
| Lost to follow-up | | | 1 | | |
| Delayed treatment | | | | 3 | |
| **Death on study** | **1** | **1** | **1** | **0** | **3** |
| Cardiac arrest post-CRT | 1 | | | | |
| Cardiac arrest during FOLFOX | | | 1 | | |
| Cardiopulmonary | | 1 | | | |
| **Eligible Patients** | **60** | **67** | **67** | **65** | **259** |
| Metastasis diagnosed at surgery | 1 (liver) | | 1 (liver) | 1 (ovary) | |

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# Characteristics of Eligible Patients

| | SG1 | SG2 | SG3 | SG4 | P value |
|---|---|---|---|---|---|
| **Number of Patients** | 60 | 67 | 67 | 65 | |
| **Age** | 57 (34-87) | 56 (32-84) | 56 (21-76) | 58 (33-72) | 0.15 |
| **Female** | 23 (38%) | 30 (45%) | 30 (45%) | 24 (37%) | 0.7 |
| **ECOG 0** | 55 (92%) | 60 (90%) | 56 (84%) | 51 (78%) | 0.14 |
| **Clinical Stage** | | | | | 0.29 |
| **II** | 19 (32%) | 12 (18%) | 15 (22%) | 18 (28%) | |
| **III** | 41 (68%) | 55 (82%) | 57 (78%) | 47 (72%) | |
| **Local Staging** | | | | | 0.004 |
| **ERUS** | 57 (95%) | 55 (82%) | 60 (89%) | 47 (72%) | |
| **MRI** | 7 (12%) | 15 (22%) | 16 (23%) | 26 (40%) | |
| **Distance Anal Verge (cm)** | 6.9 (3.0) | 6.2 (3.1) | 7.1 (2.9) | 6.7 (3.4) | 0.42 |
| **Size (cm)** | 4.6 (1.5) | 5.0 (2.0) | 4.6 (1.8) | 5.3 (2.1) | 0.10 |

# Treatment Characteristics

| | SG1 | SG2 | SG3 | SG4 | P value |
|---|---|---|---|---|---|
| **Number of Patients** | 60 | 67 | 67 | 65 | |
| **Radiation therapy** | | | | | |
| Cumulative Dose (Gy), mean (sd) | 51 (3) | 52 (3) | 52 (2) | 51 (2) | 0.17 |
| Unscheduled Interruptions | 9 (15%) | 16 (24%) | 15 (22%) | 3 (5%) | 0.09 |
| **Sensitizing Chemotherapy (5-FU)** | | | | | |
| Cumulative Dose ($mg/m^2$ $X10^3$), mean (sd) | 9.5 (1.3) | 10.1 (1.2) | 9.3 (0.7) | 9.4 (0.4) | 0.21 |
| Unscheduled Interruptions | 16 (27%) | 24 (36%) | 20 (30%) | 17 (26%) | 0.73 |
| Dose Reductions | 9 (15%) | 9 (14%) | 8 (12%) | 10 (15%) | 0.99 |
| **FOLFOX** | | | | | |
| Number of cycles, mean (sd) | N/A | 1. 7 (0.7) | 3.5 (1.1) | 5.0 (2.1) | 0.0001 |

# Adverse Events During Neoadjuvant Therapy

| | SG1 | SG2 | SG3 | SG4 | Total |
|---|---|---|---|---|---|
| **Number of Patients** | 60 | 67 | 67 | 65 | 259 |
| **Chemoradiation** | | | | | |
| Grade 3 | 24 (40%) | 19 (28%) | 18 (27%) | 7 (11%) | 68 (26%) |
| Grade 4 | | 1 (1) | 2 (3%) | 3 (5%) | 6 (2%) |
| **FOLFOX** | | | | | |
| Grade 3 | N/A | 2 (3%) | 12 (18%) | 18 (26%) | 26 (13%) |
| Grade 4 | N/A | 1 (1%) | | 5 (8%) | 6 (3%) |

**Most Common AEs During CRT**

| | |
|---|---|
| Diarrhea | (6%) |
| Lymphopenia | (6%) |
| Proctitis | (3%) |
| Fatigue | (2%) |
| Hand-Foot syndrome | (3%) |

**Most Common AEs During FOLFOX**

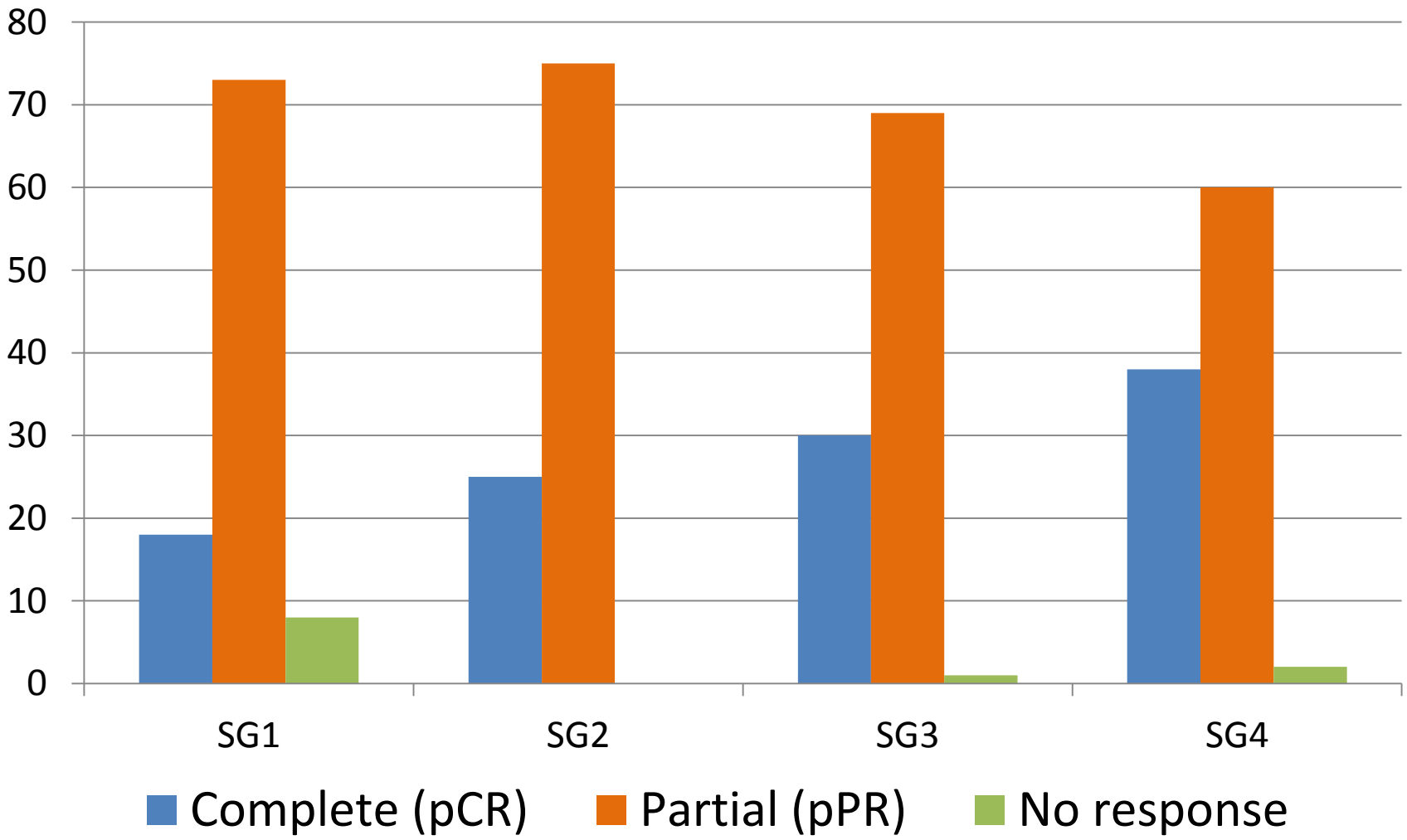
| | |
|---|---|
| Neutropenia | (6%) |
| Lymphopenia | (4%) |
| Leukopenia | (3%) |

# Surgical Results

| | SG1 | SG2 | SG3 | SG4 | P value |
|---|---|---|---|---|---|
| **Number of Patients** | 60 | 67 | 67 | 65 | |
| **Weeks from start of CRT to surgery,** mean (SD) | 14.2 (4.3) | 17.1 (2.9) | 21.0 (2.7) | 25.2 (4.0) | 0.0001 |
| **Weeks from end of CRT to surgery,** mean (SD) | 8.5 (4.2) | 11.1 (2.9) | 15.4 (2.6) | 19.3 (4.2) | 0.0001 |
| **Sphincter-saving surgery,** N (%) | 46 (77%) | 50 (75%) | 50 (75%) | 44 (67%) | 0.68 |
| **R0 resection,** N (%) | 59 (98%) | 67 (100%) | 64 (96%) | 65(100%) | 0.089 |
| **# nodes examined,** median (range) | 12 (2-31) | 14 (2-30) | 13 (2-30) | 11 (1-47) | 0.2 |
| **Technical Difficulty *,** mean+/-SD | 4.6 (2.7) | 4.9 (2.8) | 5.1 (2.5) | 4.8 (2.4) | 0.8 |
| **EBL (ml),** median (range) | 200 (50-1200) | 225 (25-1500) | 200 (50-1000) | 150 (0-1000) | 0.62 |

(*) Arbitrary scale from 1 (easy) to 10 (difficult)

# Pathologic Tumor Response



# Surgical Complications
## (Clavien-Dindo Grading)

| | SG1 | SG2 | SG3 | SG4 |
|---|---|---|---|---|
| Patients | 60 | 67 | 67 | 65 |
| Grade I | 16 (27%) | 18 (27%) | 16 (24%) | 14 (22%) |
| Grade II | 6 (10%) | 12 (18%) | 13 (19%) | 16 (24%) |
| Grade IIIa | 2 (3%) | 2 (3%) | 1 (1%) | 5 (8%) |
| Grade IIIb | 6 (10%) | 2 (3%) | 2 (3%) | 2 (3%) |
| Grade 4a | 2 (3%) | 1 (1%) | | |
| Any surgical complication | 28 (47%) | 32 (48%) | 35 (52%) | 28 (43%) |

Most common Grade III and IV complications were anastomotic leak and pelvic abscess

# Relevant Factors Associated with pCR
## Univariate Analysis

| Parameter | pCR | Non-pCR | p-value |
|---|---|---|---|
| Age (years), mean (SD) | 57 (10) | 57 (11) | 0.8890 |
| Gender (%) | M (29%)<br>F (28%) | M (71%)<br>F (72%) | 0.9646 |
| AJCC Clinical Stage (%) | II (31%)<br>III (28%) | II (69%)<br>III (72%) | 0.5328 |
| Size (cm), mean (SD) | 4.7 (0.2) | 5.0 (0.2) | 0.3769 |
| Distance from anal verge (cm), mean (SD) | 6.9 (3.3) | 6.7 (3.1) | 0.6560 |
| Radiation Dose (cGy), mean (SD) | 5109 (226) | 5140 (283) | 0.3963 |
| Number of Cycles of FOLFOX, mean (SD) | 3.5 (2.0) | 3.3 (2.0) | 0.0552 |
| Weeks from start of CRT to surgery, mean (SD) | 20.5 (5.5) | 19.1 (5.3) | 0.0344 |
| Weeks from end of CRT to surgery, mean (SD) | 14.7 (5.6) | 13.3 (5.2) | 0.0342 |
| Group (%) | SG1 (19)<br>SG2 (25)<br>SG3 (30)<br>SG4 (40) | SG1 (81)<br>SG2 (75)<br>SG3 (70)<br>SG4 (60) | 0.0436 |

# Tumor Response by Center

| Center ID | Patients Treated | pCR |
|---|---|---|
| 01 | 27 | 44% |
| 02 | 27 | 37% |
| 07 | 20 | 22% |
| 11 | 22 | 14% |
| 12 | 49 | 27% |
| 13 | 20 | 40% |
| 14 | 20 | 45% |
| 15 | 20 | 25% |
| All centers with < 20 patients each | 54 | 17% |

p= 0.05

- Different centers accrued different numbers of patients in each SG
- Differences between centers could not be explained by SG alone

# Multivariate Analysis

- Model with all potentially relevant factors
- Strongly correlated factors (time and cycles of FOLFOX) introduced separately into the model

| Parameter | p |
|---|---|
| Days from start of CRT | **0.03** |
| Center | **0.01** |
| Radiation total dose | 0.17 |
| Distance from anal verge | 0.47 |
| Size (cm) | 0.34 |
| AJCC disease stage | 0.39 |

| Parameter | p |
|---|---|
| Total FOLFOX dose | **0.01** |
| Center | 0.08 |
| Radiation total dose | 0.22 |
| Distance from anal verge | 0.48 |
| Size (cm) | 0.42 |
| AJCC disease stage | 0.52 |

Cycles of FOLFOX was the strongest predictor for pCR

# Summary

- Delivering chemotherapy at systemic doses after CRT and delaying TME increases the pCR rates without increasing the technical difficulty of the operation or the risk of surgical complications
- Baseline tumor characteristics did not influence the pCR rate
- Tumor progression during neoadjuvant therapy is uncommon

# Summary

- We observed differences in the pCR rate between centers that could not be explained by patient baseline characteristics or treatment group alone
- The study design:
  - Does not allow simultaneous assessment of the contribution of the length of treatment and the cycles of FOLFOX to pCR
  - BUT, the number of cycles of FOLFOX seems to be the most important predictor of pCR

# Discussion

Delivering systemic chemotherapy before TME:

- Contributes to enhance tumor response, increasing the number of potential candidates for watch and wait

- May contribute to improved survival by
  - Increasing the proportion of patients completing the prescribed adjuvant chemotherapy
  - Addressing the risk of distant metastasis earlier in the overall treatment plan

# Participating Institutions

- University of South Florida, Tampa, FL
- University of Vermont, Burlington, VT
- University of California, San Francisco, CA
- Washington Hospital Center, Washington DC
- John Muir Health Systems, CA
- St. Joseph Hospital, Orange County, CA
- Washington University, St. Louis, MO
- University of California, Irvine, CA
- Colon and Rectal Surgery Associates, Omaha, NE
- Oregon Health & Science University, Portland, OR
- University of Chicago, IL
- Center Cleveland Clinic, Cleveland, OH
- City of Hope, California, CA
- University of Minnesota, Minneapolis, MN
- Western Pennsylvania Hospital, Pittsburg, PA
- University of Calgary, Alberta, Canada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