Total Neoadjuvant Therapy (TNT) and Non-operative Management (NOM) for Rectal Cancer: Are they ready for prime time?

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Disclosures

RenovoRX Advisory Board
2020: Where Are We?

Individualizing therapy:
- Selective use of RT
- Intensifying neoadjuvant therapy
- NOM

Blunt rectal dissection
Trials of Adjuvant CRT
NCI Consensus Statement
German Rectal Study
Addition of Oxaliplatin


Distant
Local
4-6%
20-25%
Individualizing the Management of Rectal Cancer

• Total neoadjuvant therapy (TNT)

• Non-operative management (NOM)

• Selective use of radiotherapy
Intensifying Pre-operative Therapy

- Distant recurrence rates now exceed local recurrence rates
- Over 60% of patients don’t receive adjuvant chemotherapy after surgery in NCDB analysis*
- Benefit of chemotherapy in the adjuvant setting is unclear**
- Move systemic therapy upfront to address micrometastatic disease earlier
- Particularly in high-risk patients
  - node positive disease
  - bulky primary tumors

*Xu Z, Cancer, 2017
Total Neoadjuvant Therapy (TNT)

Can we further improve outcomes by addressing micrometastatic systemic disease as well as the primary tumor with upfront chemotherapy rather than adjuvant chemotherapy?
Total Neoadjuvant Therapy (TNT)

Current Tri-Modality Paradigm for T3-4 or Node + Rectal Cancer

Chemoradiotherapy → pCR ~20% Surgery → Chemotherapy

25-70% DO NOT receive adjuvant systemic chemotherapy

Total Neoadjuvant Therapy (TNT)

New paradigm for T3-4 or Node + Rectal Cancer

• Two phase II studies have evaluated induction chemotherapy followed by CRT in high-risk patients based on MRI
MRI to Risk Stratify Rectal Cancer

- Determine extent of extramural tumor \(^1\)
- Identify risk of CRM positivity \(^2\)

1- Mercury Study group, Radiology, 2007
2- Mercury Study group, British Medical Journal, 2006
High Risk Features

**UK Trial**
- Tumor extending to within 1mm or beyond mesorectal fascia
- T3 low-lying tumor at or below the levators
- Tumor extending ≥ 5 mm into perirectal fat
- T4 or N2

**Spanish Trial**
- Tumors extending to within 2mm or beyond mesorectal fascia
- ≤ 6 cm from anal verge
- cT3 or resectable cT4, any cT3N+

*Chua, Lancet Oncol;2010*  
*Fernandez-Martos, J Clin Oncol;2010*
UK EXPERT Phase II Trial

- 105 pts with poor-risk rectal cancer defined by MRI
- 97 underwent surgery, 20% pCR rate
- 3-year PFS and OS: 68% and 83%
- 3-year RFS after complete resection was 74%

CAPOX x 12 weeks  54 Gy + Capecitabine  TME  CAPOX x 12 weeks

Chua, Lancet Oncol; 2010
Spanish Phase II Randomized Trial

- 108 pts with poor-risk rectal cancer based on MRI

**Treatment Strategies**

1. **Induction CAPOX**
   - X 4 Cycles

2. **Capecitabine**
   - + 5040cGy

3. **Surgery:**
   - TME

4. **CAPOX**
   - X 4 Cycles

5. **Capecitabine**
   - + 5040cGy

6. **Surgery:**
   - TME

*Fernandez-Martos, J Clin Oncol, 2010*
### Spanish Phase II Randomized Trial

- Median follow-up of 70 months

<table>
<thead>
<tr>
<th></th>
<th>Standard Tx N=52</th>
<th>TNT N=56</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pCR</td>
<td>13%</td>
<td>14%</td>
<td>NS</td>
</tr>
<tr>
<td>R0</td>
<td>87%</td>
<td>88%</td>
<td>NS</td>
</tr>
<tr>
<td>G3/4 Toxicity during CRT</td>
<td>29%</td>
<td>23%</td>
<td>NS</td>
</tr>
<tr>
<td>G3/4 Toxicity during Chemo</td>
<td><strong>54%</strong></td>
<td><strong>19%</strong></td>
<td><strong>0.0004</strong></td>
</tr>
<tr>
<td>Compliance to Full Chemo</td>
<td>57%</td>
<td>94%</td>
<td><strong>0.0001</strong></td>
</tr>
<tr>
<td>Any Surgical Complications</td>
<td>45%</td>
<td>51%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Induction Chemotherapy

• Median follow-up of 70 months

<table>
<thead>
<tr>
<th></th>
<th>Post-op CAPOX x 4</th>
<th>Pre-op CAPOX x 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 year DFS</td>
<td>64%</td>
<td>61%</td>
</tr>
<tr>
<td>5 year Cum Incidence LR</td>
<td>1.9%</td>
<td>5.3%</td>
</tr>
<tr>
<td>5 year OS</td>
<td>78%</td>
<td>75%</td>
</tr>
</tbody>
</table>

Total Neoadjuvant Therapy at MSKCC

• 61 LARC patients received induction FOLFOX
  – 4 patients achieved an excellent response to chemotherapy alone, declined radiation, proceeded directly to TME

• 57 received chemoradiation (median dose 50Gy)

• 49 patients who underwent TME
  – Median 6.5 cycles of ICT
  – 100% R0 resections
  – pCR in 13 (27%)
  – >90% treatment effect in 23 (47%)

Cercek A, Goodman KA, J Natl Cancer Inst, 2014
TNT Results

• 12 did not to undergo TME
  – 9 had clinical response managed non-operatively
  – 1 refused recommended surgery
  – 1 deferred due to comorbidities
  – 1 developed distant metastatic disease

• A total of 22 patients had either:
  – Pathologic complete response (n=13)
  – Complete clinical response (9)
    • leading to non-operative management
    • 2 local recurrences, salvaged and both NED
    • 7 remain NED without local recurrence

*Cercek A, Goodman KA, J Natl Cancer Inst, 2014*
Updated MSKCC TNT results

- 628 evaluable patients with LARC treated from 6/09 – 3/15

**Flowchart**

**Total Neoadjuvant chemotherapy (TNT) or Chemoradiation with adjuvant chemo**

- **FOLFOX/ CapeOX then CRT**
  - n=308
  - Surgery within 12 mos n=235 (76%)
  - No surgery within 12 mos n=73* (24%)
  - pCR n=44 (19%)
  - Sustained cCR at 12 mos n=67 (92%)

- **CRT with Adjuvant CT**
  - n=320
  - Surgery within 12 mos n=296 (92%)
  - No surgery within 12 mos n=24 ** (8%)
  - pCR n=47 (16%)
  - Sustained cCR at 12 mos n=19 (79%)

*Cercek A, JAMA Oncol, 2018*
Updated MSKCC TNT Results

- Complete response rate = pCR + cCR at 12 months
  - 36% in TNT group
  - 21% in CRT→S→CT

- In TNT group, 67 (22%) 308 pts had sustained cCR and were treated non-operatively beyond 12 months.
  - Of 31 pts with 2 yr follow-up, 27 (87%) had a durable cCR.

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<table>
<thead>
<tr>
<th></th>
<th>TNT N= 249*</th>
<th>CRT with Adjuvant CT N=101*</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 FU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average Percent of Planned Dose Received (%)</td>
<td>95.9%</td>
<td>88.4%</td>
<td>0.003</td>
</tr>
<tr>
<td>Number of cycles administered</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;6 cycles</td>
<td>236 (94.8)</td>
<td>84 (83.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>8 Cycles</td>
<td>235 (94.4)</td>
<td>76 (75.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average Percent of Planned Dose Received (%)</td>
<td>90.4%</td>
<td>73.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Number of cycles administered</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;6 cycles</td>
<td>214 (85.9)</td>
<td>64 (63.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>8 Cycles</td>
<td>195 (78.3)</td>
<td>42 (41.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Where chemotherapy dosing data was available

Cercek A, JAMA Oncol, 2018
NRG-GI002 (TNT) Schema
Non-comparative 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
Locally Advanced Rectal Cancer

Non-comparative experimental arms

FOLFOX x 8
- XRT + Capecitabine
- Surgery

FOLFOX x 8
- XRT + Capecitabine + Veliparib
- Surgery

FOLFOX x 8
- XRT + Capecitabine + Pembro
- Surgery

FOLFOX + ? x 8
- XRT + Capecitabine + ?
- Surgery

Additional arms added through protocol amendments
Timing of Surgery

What is the appropriate interval after treatment to assess response?
Timing of Evaluation of pCR: GRECCAR-6

• A multicenter, randomized, controlled trial to evaluate the effect of interval (7 or 11 weeks) between neoadjuvant CRT and surgery on complete pathological response in rectal cancer

• 265 T3/4 or N+ rectal ca patients from 24 centers enrolled 10/2012 – 2/2015

• No difference in pCR rates
  – 15% v. 17.3%

• 11 wk group had more:
  – Medical complications
  – Worse rate of complete TME’s

Lefevre JH, J Clin Oncol, 2016
Adding Chemotherapy (TNT approach)

“TIMING STUDY”

<table>
<thead>
<tr>
<th>Group</th>
<th>Response</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>Continuous infusion fluorouracil + radiotherapy</td>
<td>Total mesorectal excision</td>
</tr>
<tr>
<td>Group 2</td>
<td>Continuous infusion fluorouracil + radiotherapy</td>
<td>Rest</td>
</tr>
<tr>
<td></td>
<td>mFOLFOX6 (two cycles)</td>
<td>Rest</td>
</tr>
<tr>
<td>Group 3</td>
<td>Continuous infusion fluorouracil + radiotherapy</td>
<td>Rest</td>
</tr>
<tr>
<td></td>
<td>mFOLFOX6 (four cycles)</td>
<td>Rest</td>
</tr>
<tr>
<td>Group 4</td>
<td>Continuous infusion fluorouracil + radiotherapy</td>
<td>Rest</td>
</tr>
<tr>
<td></td>
<td>mFOLFOX6 (six cycles)</td>
<td>Rest</td>
</tr>
</tbody>
</table>

Response: Pathologic complete response (pCR)

Garcia-Aguilar, Lancet Oncol, 2015
German Phase II Study: CAO/ARO/AIO-12

- A multicenter, randomized, Phase II trial to evaluate the effect of sequencing of therapy for rectal cancer
German Phase II Study: CAO/ARO/AIO-12

- CRT-related grade 3+ toxicity was lower (37% v 27%) and compliance with CRT higher in group B – consolidation group
- CT-related toxicity was lower and compliance with CT higher in Group A – induction group
- pCR rate in IIT population – 17% in Group A, 25% in Group B
- The longer interval between completion of CRT and surgery in Group B (median 90 v 45 days in Group A) did not increase surgical morbidity

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TNT Group A (n = 142)</th>
<th>TNT Group B (n = 142)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathologic stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ypT0N0</td>
<td>27 (19)</td>
<td>38 (27)</td>
</tr>
<tr>
<td>I</td>
<td>48 (34)</td>
<td>31 (22)</td>
</tr>
<tr>
<td>IIA</td>
<td>29 (20)</td>
<td>37 (26)</td>
</tr>
<tr>
<td>IIIB</td>
<td>0 (0)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>IIC</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>IIIB/C</td>
<td>11 (7)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>IV</td>
<td>24 (17)</td>
<td>20 (14)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>NAR score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>37 (26)</td>
<td>50 (35)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>71 (50)</td>
<td>62 (44)</td>
</tr>
<tr>
<td>High</td>
<td>32 (23)</td>
<td>26 (18)</td>
</tr>
<tr>
<td>Missing</td>
<td>2 (1)</td>
<td>4 (3)</td>
</tr>
</tbody>
</table>

Fokas E, J Clin Oncol, 2019
TNT: Short Course RT

Rapido Trial

• High risk rectal cancer population
• 920 pts randomized 6/11-6/16
  – 302 were cT4
  – 828 were cN+, of whom 621 - cN2
• median time between randomization and surgery was 15.9 wks for arm A and 25.3 wks for arm B
• 19% had a ypT0N0

Marijnen C, Proceedings of ESTRO, 2017
Washington University Phase II Trial of SCRT

76 pts with cT3 (91%) or T4 (9%) Rectal Cancer

5Gy x 5

FOLFOX x 4 cycles

Surgery: TME

6-8 cycles of post-op Chemo Optional

Washington University Phase II Trial of SCRT
Non-operative Therapy

Can surgery be avoided in the setting of complete clinical response to preoperative treatment?
Paradigm shift?

Anal Cancer

Definitive surgery
(before 1970’s)

Preoperative chemoradiation
(1970’s)

Definitive chemoradiation
(Present)

Distal rectal cancer

Definitive surgery
(before 1990’s)

Preoperative chemoradiation
(Present)

Definitive chemoradiation
(Present)
Rationale for NOM

• Radical rectal resection associated with significant toxicity:
  – Surgical complications in ~30%
  – Peri-op mortality up to 3%
  – Permanent or temporary stoma
  – Impaired bowel function
  – Late complications:
    • Bowel obstruction
    • Incisional hernias
    • Urinary incontinence
    • Sexual dysfunction

• Is surgery always necessary?

### NOM: Brazilian Data

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>361 patients, 99 with clinical CR (27%)</td>
<td></td>
</tr>
<tr>
<td>Mean followup:</td>
<td>60 months</td>
</tr>
<tr>
<td>Local recurrence:</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>4 surgical salvage</td>
</tr>
<tr>
<td></td>
<td>1 brachytherapy salvage</td>
</tr>
<tr>
<td></td>
<td>No subsequent recurrence</td>
</tr>
<tr>
<td></td>
<td>Mean interval to recurrence: 52 months</td>
</tr>
<tr>
<td>Pelvic recurrence:</td>
<td>0%</td>
</tr>
<tr>
<td>Distant metastasis:</td>
<td>8%</td>
</tr>
<tr>
<td>5-year OS:</td>
<td>93%</td>
</tr>
</tbody>
</table>

Habr-Gama J Gastrointest Surg 2006
54 Gy + 5-FU/leuc bolus x 3 →
5-FU/leuc bolus x 3

70 Eligible patients with distal rectal cancer

69 Concluded CRT

1 Died during chemotherapy

22 (32%) Incomplete clinical response

29 (43%) Incomplete response

33 (49%) Immediate or salvage surgery

8* (17%) Early regrowth *(only 7 underwent salvage)

47 (68%) Initial clinical complete response

47 (68%) Initial clinical complete response

39 (57%) Sustained clinical complete response (after 12 mo. f/u)

3-yr OS + DFS = 94% and 75%

3-yr OS + DFS = 90% and 72%

4 (10%) Late local recurrence

35 (51%) No radical surgery required

Habr-Gama A, Dis Colon Rectum, 2013
NOM: Dutch Data

• Prospective cohort study of “watch and wait” approach
• Patients with LARC treated with CRT from 2004-2014
  – Standard 50.4 Gy + capecitabine (n=95) or 5 Gy x 5 with longer duration to surgery (n=5)
• Response assessed 6-8wks post-treatment
  – MRI, Endoscopy
• Clinical CR or “near cCR”: no residual tumor or fibrosis only on MRI/small residual ulcer or scar on endoscopy; no palpable tumor on DRE
• Initial report: 21/196 (11%) patients fulfilled these criteria
• Long-term outcomes report: 100 patients

Maas M, J Clin Oncol, 2011
15/100 had local regrowth in lumen (n = 12) or in a lymph node (n = 3)
3 were in TEM pts, all had ypT2
2/15 had synchronous DM
12/13 were salvaged with standard surgery
1/13 had a pelvic exenteration

NOM for ypT2 after TEM not recommended
NOM: Dutch Data

- Median follow-up of 41 months
- 3-yr distant metastasis–free survival was 97%
- 3-yr disease-free survival was 81%

3-yr local regrowth–free survival = 85%
3-yr OS = 97%

NOM: Danish Dose-escalation Trial

- 60 Gy/30 fx to primary tumor
- 50 Gy/30 fx to regional nodes
- Concurrent UFT
- 5 Gy brachy boost

- LR rate: 15.5%
- Low rate of late toxicity

Appelt, Lancet Oncol, 2015
NOM: MSKCC Experience

- Retrospective review of stage I-III rectal cancer pts treated at MSKCC between 2006 – 2015

Surveillance: Endoscopy/imaging Q3 mos for 1st year, Q4 mos for the 2nd year, then Q6 mos for a total of 5 years

Smith JJ, JAMA Oncol, 2019
NOM: MSKCC Local Regrowth

- Median F/U = 33 months for 113 in WW
  - 91: no local regrowth
  - 22: local regrowth (median time - 11.2mos)
    - 19 endoluminal
    - 3 extraluminal

Salvaged = 22

Local excision n = 2

TME LAR (n = 9)

APR (n = 11)

5 yr rate of local regrowth = 21%

5 yr rate of rectal preservation in cCR group = 82%

Smith JJ, JAMA Oncol, 2019
• WW group significantly older than pCR group (median age 67 v. 57 yrs)
• 9 pts (8%) in WW group v. 5 pts with pCR (4%) developed distant metastases
• 8/22 patients (36%) with local regrowth in WW group developed distant metastases, only 1/91 (1%) with no local regrowth had DM (P < .001)
NOM: UK Experience

- Oncological Outcomes after Clinical Complete Response in Patients with Rectal Cancer (OnCoRe) was a propensity-score matched cohort analysis
  - 259 rectal cancer pts, 228 → surgical resection, 31 cCR → WW
  - 98 pts added to WW from registry = 129 pts underwent WW

3-year actuarial rate of local regrowth = 38% (36 of 41 non-metastatic cases were salvaged)
NOM: Meta-analysis

- 23 studies including 867 patients
- Median follow-up of 12 – 68 months
- Pooled 2-year local regrowth was 15.7%
- 95% with regrowth had salvage therapies
- No significant difference in cancer-specific mortality, disease-free survival, or overall survival with WW as compared to surgery

*Dossa F, Lancet Gastroenterol Hepatol. 2017*
NOM: International Watch and Wait Database

• 1009 rectal cancer pts from 47 institutions in 15 countries treated with WW
• 880 with cCR included in analysis
  – Majority T3 and N+, received 50Gy
  – Local regrowth occurred in 213 pts: 2 yr rate of 25%, 88% occurred within first 2 yrs
  – 3 yr DM rate = 8%
  – 5 yr DSS was 94% and 5 yr OS was 85%

van der Valk MJM, Lancet, 2018
OPRA: Phase II Randomized Multi-institutional Trial of NOM

Distal Rectal Cancer MRI staging

Randomization

Arm 1 (Induction) INCT
FOLFOX / CapeOX (16-18 weeks)
Interval Evaluation DRE-Endoscopy – MRI *
CRT (5.5 weeks)
FOLFOX / CapeOX (16-18 weeks) Restaging DRE – Endoscopy ± Biopsy - MRI
Clinical stable disease or progression TME
Clinical partial or complete response NOM

Arm 2 (Consolidation) CNCT
CRT (5.5 weeks)
Interval Evaluation DRE-Endoscopy – MRI *
FOLFOX / CapeOX (16-18 weeks)

Primary endpoint: 3-year disease-free survival
OPRA Institutions

- Lead Institution: MSKCC

Participating Institutions:

- Cleveland Clinic
- Colon & Rectal Surgery, Omaha
- John Muir Health
- Oregon Health & Science University
- St. Joseph Hospital
- St. Paul’s Hospital
- University of Calgary
- University of Colorado
- University of California, San Francisco
- University of California, Irvine
- University of Chicago
- University of Rochester, New York
- University of South Florida
- University of Vermont
- University of Washington Medical Center
- Washington Hospital Center
- Washington University
## OPRA Follow up for NOM patients

**MSKCC study response evaluation forms**

<table>
<thead>
<tr>
<th></th>
<th>Complete Response</th>
<th>Near Complete Response</th>
<th>No Response</th>
</tr>
</thead>
</table>
| **Endoscopy**    | ❑ Flat, white scar
❑ Telangiectasia
❑ No ulcer
❑ No nodularity                  | ❑ Irregular mucosa
❑ Small mucosal nodules or minor mucosal abnormality
❑ Superficial ulceration
❑ Mild persisting erythema of the scar | ❑ Visible tumor                                               |
| **Digital Rectal**
Exam              | ❑ Normal                                                                              | ❑ Smooth induration or minor mucosal abnormalities          | ❑ Palpable tumor nodules                                                 |
| **MRI-T2W**      | ❑ Normal appearing bowel wall without any fibrosis in the tumor bed
❑ Only dark T2 signal, no intermediate T2 signal
❑ No visible lymph nodes or very few, small (<5mm nodes) | ❑ Mostly dark T2 signal, some remaining intermediate signal AND/OR
❑ Partial regression of lymph nodes | ❑ More intermediate than dark T2 signal, no T2 scar AND/OR
❑ No regression of lymph nodes |
| **MRI-DW**       | ❑ No visible signal on B800-B1000 AND/OR
❑ Uniform, linear signal in wall above tumor is acceptable | ❑ Significant regression of signal on B800-B1000 | ❑ Insignificant regression of signal on B800-B1000 |
Brazilian Follow up for NOM patients

Habr-Gama A, Dis Colon Rectum, 2013
Challenges Predicting a pCR

• Surgery is still the only means of reliably detecting a pCR
• Clinical response is not always predictive of pathologic response
• Clinical evaluations are limited in their ability to distinguish post-RT changes from residual disease
  – DRE, endoscopic assessment, EUS, CT, MRI and PET
• Biopsy after CRT difficult to interpret
  – Positive biopsy - unknown clinical significance of few viable cells
  – Negative biopsy could be sampling error
Challenges Predicting Nodal Involvement

- Baseline nodal staging is inaccurate in rectal cancer.

- Primary tumor response is not always predictive of lymph node response.
  - 7% of pathologic CR in primary tumor have pathologically positive mesorectal nodes in MSKCC series.

Fernández-Esparrach G, Gastrointest Endosc, 2011
Stipa Ann Surg Oncol 2004
Emerging Therapeutic Model

- Neoadjuvant CRT
- Neoadjuvant CT
- No cCR
- cCR
- Surgery
- NOM
- Response assessment
  - Functional MRI/CT/PET
  - Biomarkers?
Emerging Therapeutic Model

Options for Investigator-Initiated Trials in Radiation Oncology

- Neoadjuvant CT
- Neoadjuvant CRT
  - cCR
  - No cCR
- Surgery
- NOM

Targeted agents
Immunotherapy
RT dose escalation

Response assessment
Functional MRI/CT/PET
Biomarkers?
Can radiotherapy be avoided in a subset of patients after a good clinical response to neoadjuvant chemotherapy?
• 32 patients enrolled
  – 17/32 (53%) were female, Clinical stages T2-3, N0-2
  – 2 patients withdrawn after cycle 1-2 (MI and cardiac rhythm disturbance attributed to infusional 5FU)
  – 30 completed induction therapy and surgery without RT
  – Median age of 30 patients: 51 years (26 – 81 years)

Of 32 patients accrued
– 32/32 had R0 resections
– 8/32 (25%) had a pCR
– 1/32 post-op death
– 0/32 have had LR
– 3/32 have had distant recurrence (pulmonary mets)
  • 1 patient has died

PROSPECT Trial

“Standard Arm”

RANDOMIZE 1:1

1000 pts

Response ≥20%

Response <20%

“Selective Arm”

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

FOLFOX x 6 -> TME -> FOLFOX x 6

5FUCMT → TME → FOLFOX x 2
TNT: Ready for Prime Time?

- Pre-operative therapy remains standard of care for T3+ or N+ rectal cancer
  - Reduces local recurrence risk
  - Allows for sphincter preservation
- Moving chemotherapy to pre-operative setting
  - Improves compliance and tolerability
  - May improve long-term DFS but need larger study to determine this
  - Optimal sequencing still unknown
- TNT included in NCCN guidelines
NOM: Ready for Prime Time?

- Non-operative management for distal rectal cancers may be possible in highly selected patients
- Attempts to intensify neoadjuvant therapy with goal of increasing pCR rates
  - Induction or consolidative chemotherapy
  - Increasing RT dose per Danish Study
  - Adding new radiosensitizers, targeted agents, immunotherapy
- Recommended to treat on protocol if possible and in patients who can be compliant with close follow-up
- Developing the follow-up to OPRA trial through NCTN
Thank you!