MANAGEMENT OF LOCALLY ADVANCED RECTAL CANCER: MEDICAL ONCOLOGY PERSPECTIVE

Joleen Hubbard, MD

Gastrointestinal Oncologist
Deputy Director of Clinical Research and Academic Affairs
Allina Health Cancer Institute
Associate Professor of Medical Oncology
Mayo Clinic, Rochester, MN

MINNESOTA SOCIETY OF CLINICAL ONCOLOGY

DISCLOSURE OF RELEVANT FINANCIAL RELATIONSHIP(S) WITH INELIGIBLE COMPANIES

- Advisory Boards: Bayer, Merck, BeiGene, Incyte
- Research Funding (to institution): Merck, Boston biomedical, Treos Bio, Senhwa pharmaceuticals, Bayer, Incyte, TriOncology, Seattle Genetics, Hutchison MediPharma, Pionyr Immunotherapeutics, Trovogene, G1 Therapeutics, Roche

REFERENCES TO OFF-LABEL USAGE(S) OF PHARMACEUTICALS OR INSTRUMENTS

- Nothing to disclose

CASE 1

61 yo male presented to ED with 2-month history of increased frequency of bowel movements (10-12/day), pain with defecation, 20-pound weight loss. CT A/P: thickening of the distal rectum with no evidence of metastatic disease. Colonoscopy: mass 6 cm from anal verge. Biopsy: moderately differentiated adenocarcinoma. CT chest negative. Pelvic MRI: T3N1 lesion. Next best step in management?

A. Long course chemoradiation
B. Short course radiation
C. FOLFOX
D. FOLFIRINOX

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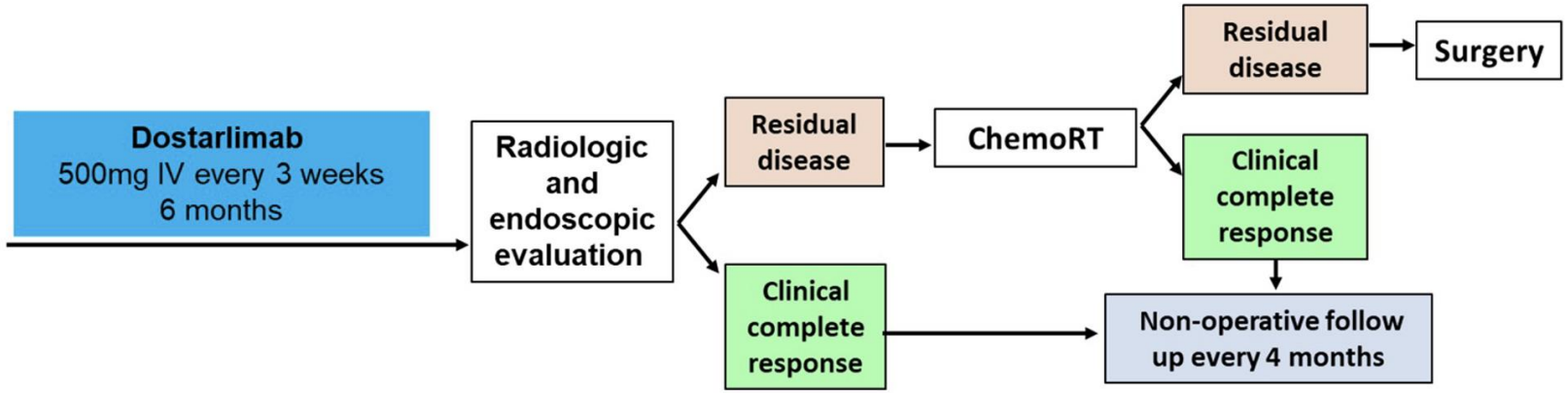
E. **Await mismatch repair (MMR) testing**

Trick Question!!

IMMUNOTHERAPY IN MSI-H/dMMR RECTAL CANCER NEOADJUVANT SETTING

- 5-10% of rectal cancers are MSI-H/dMMR
- MSI-H/dMMR cancers are often resistant to cytotoxic therapy
- Single arm prospective study of dMMR stage II & III rectal cancer



- Primary endpoint: Overall response
- Complete Clinical Response
  - Visual disappearance of rectal primary on endoscopy
  - Normal digital rectal exam
  - Pelvic MRI: lack of signal at DWI with scar on T2WI
    each target lymph node <0.5cm

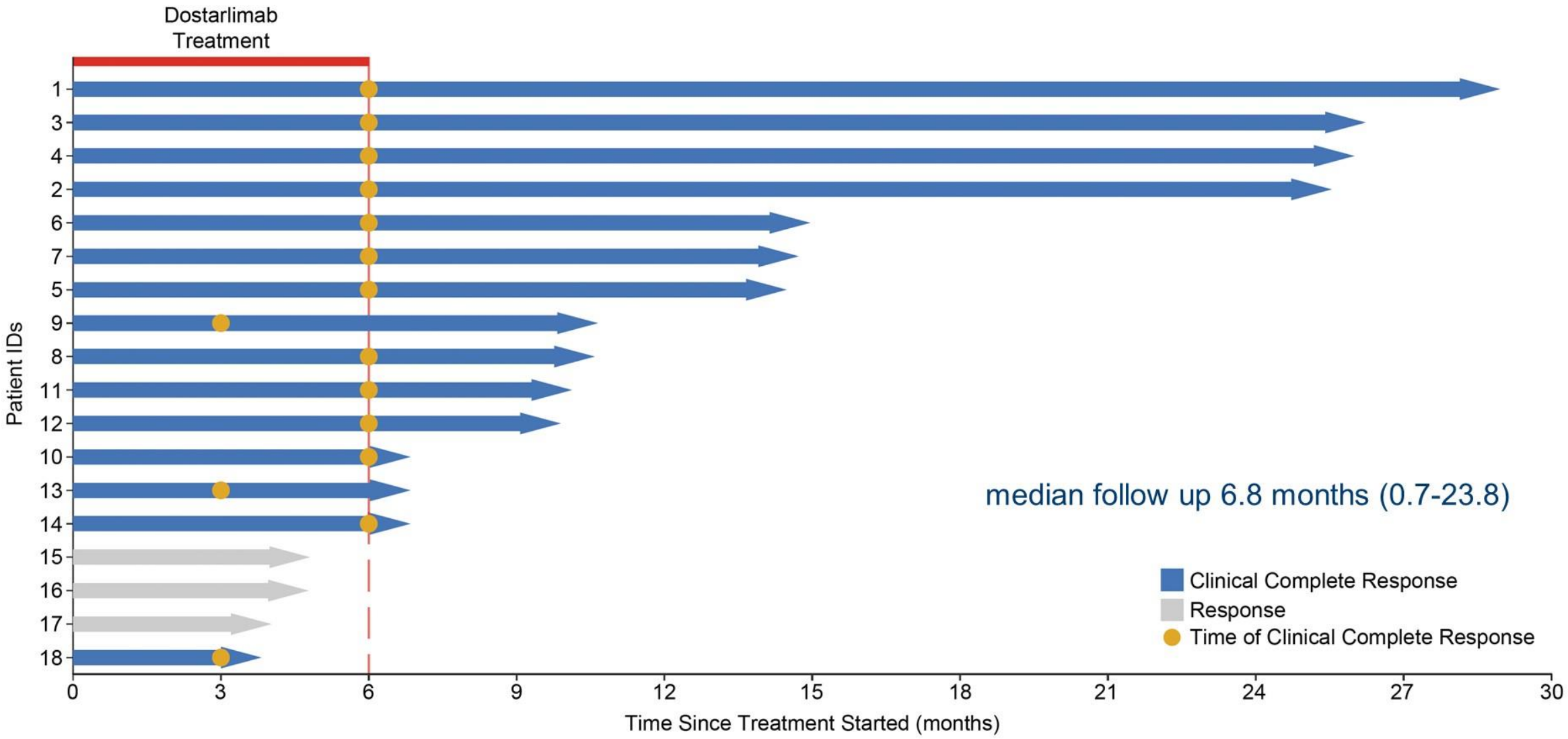
Cercek et al NEJM 2022

Individual responses to PD-1 blockade with dostarlimab

Patients who completed 6-months of dostarlimab

ID	Age	Stage T	Stage N	FU (months)	Digital rectal exam response	Endoscopic best response	Rectal MRI best response	Overall response 100%
1	38	T4	N+	23.8	CR	CR	CR	**cCR**
2	30	T3	N+	20.5	CR	CR	CR	**cCR**
3	61	T1/2	N+	20.6	CR	CR	CR	**cCR**
4	28	T4	N+	20.5	CR	CR	CR	**cCR**
5	53	T1/2	N+	9.1	CR	CR	CR	**cCR**
6	77	T1/2	N+	11.0	CR	CR	CR	**cCR**
7	77	T1/2	N+	8.7	CR	CR	CR	**cCR**
8	55	T3	N+	5.0	CR	CR	CR	**cCR**
9	68	T3	N+	4.9	CR	CR	CR	**cCR**
10	78	T3	N-	1.7	CR	CR	CR	**cCR**
11	55	T3	N+	4.7	CR	CR	CR	**cCR**
12	27	T3	N+	4.4	CR	CR	CR	**cCR**
13	26	T3	N+	0.8	CR	CR	CR	**cCR**
14	43	T3	N+	0.7	CR	CR	CR	**cCR**

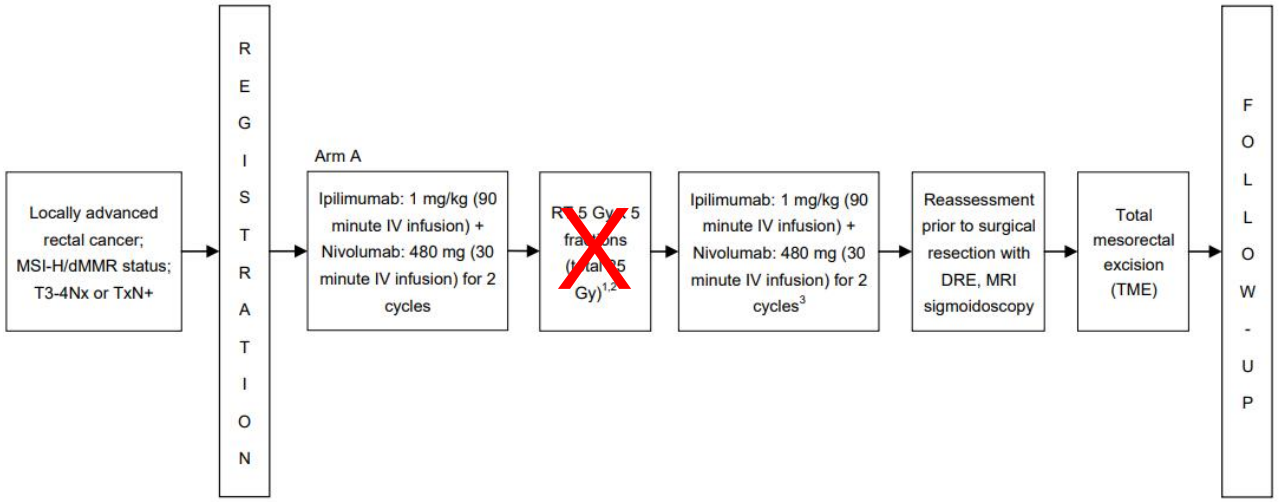
Duration of response



Permission from Cercek ASCO 2022

IMMUNOTHERAPY IN MSI-H/dMMR RECTAL CANCER NEOADJUVANT SETTING: CONCLUSIONS

- Phenomenal responses to single agent immunotherapy in the neoadjuvant setting which prevent radiation therapy and surgery in this small cohort of patients
- No Grade 3/4 AEs seen
- Consider enrolling these patients in clinical trials:
  - NOM-ERA: A Phase II Study of Neoadjuvant Nivolumab plus Ipilimumab and Short-Course Radiation in MSI-H/dMMR Locally Advanced Rectal Adenocarcinoma



1. Please see Section 5.2 for details of radiation therapy.
2. Radiation to start at least 2 weeks but no longer than 6 weeks after completion of cycle 2 of nivolumab/ipilimumab.
3. Cycle 3 of nivolumab/ipilimumab to start within 2-6 weeks of completion of radiation therapy.

THE NEW STANDARDS FOR RECTAL CANCER IN 2023

- Individualizing management approaches for each patient to minimize adverse effects/complications
  - Omission of chemotherapy and radiation therapy and surgery in select patients
    - Immunotherapy for dMMR/MSI-H
  - Omission of surgery in select patients
    - Non-operative management for patients with complete clinical response to neoadjuvant therapy
  - Omission of radiation therapy in select patients
    - Candidates for sphincter-preserving surgery with good response to chemotherapy
- Reducing the development of metastatic disease

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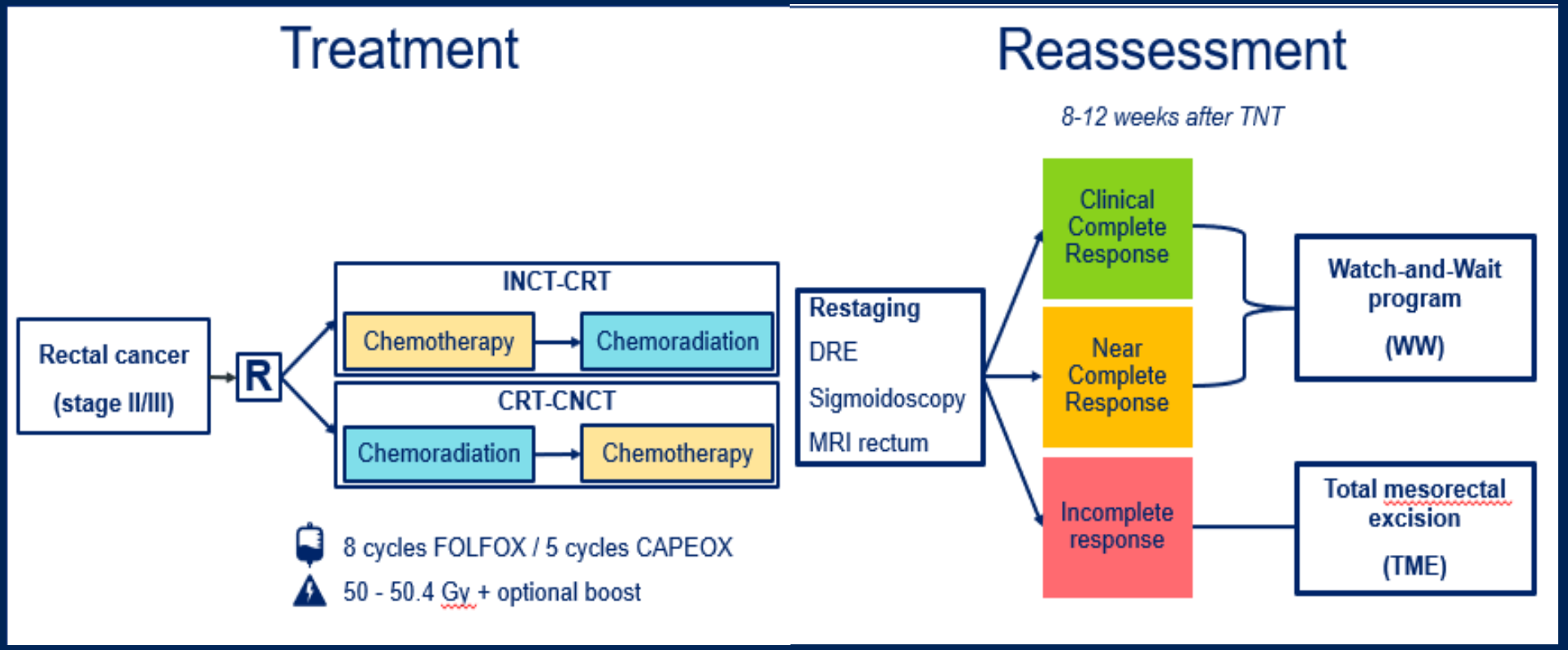
A. Long course chemoradiation
B. Short course radiation
C. FOLFOX
D. FOLFIRINOX

OMITTING SURGERY FOR SELECT PATIENTS

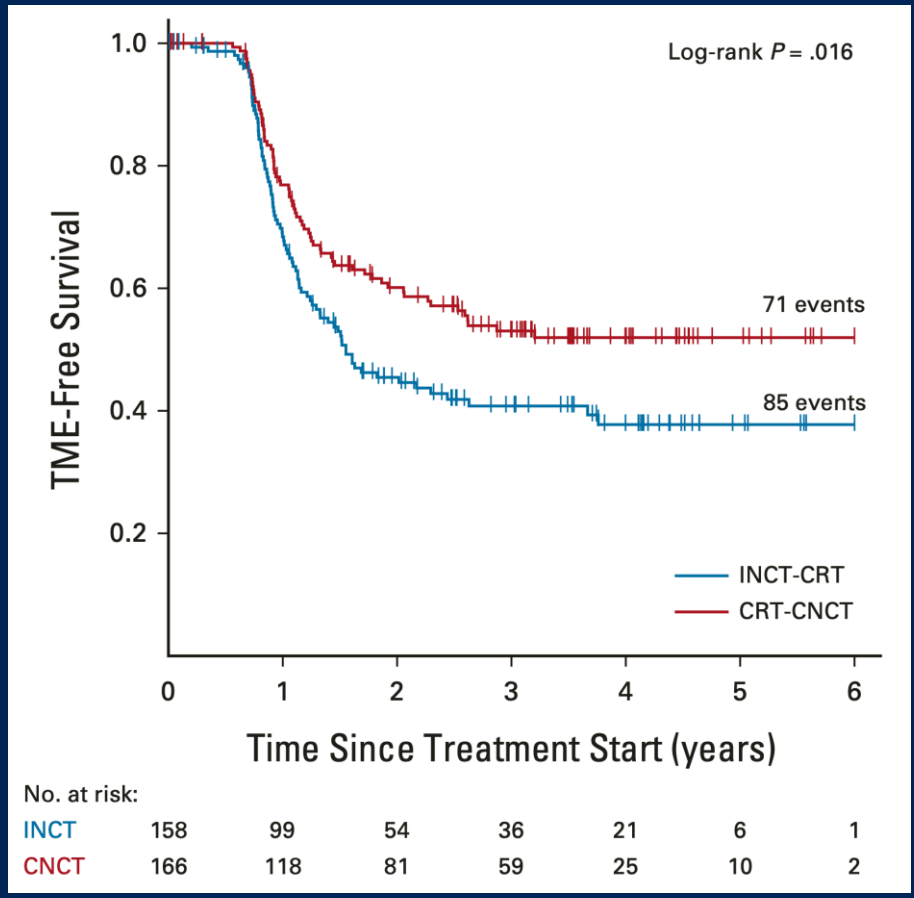
Organ Preservation in Rectal Adenocarcinoma (OPRA) Trial



Floris S Verheij, Dana M Omer, Hannah Williams, James T Buckley, Sabrina T Lin, Li-Xuan Qin, Hannah M Thompson, Jonathan B Yuval, Marc J Gollub, Abraham J Wu, Leonard B Saltz, Julio Garcia-Aguilar, on behalf of the OPRA Consortium.

OPRA Trial – Initial Results at 3 Years

- No difference in DFS between treatment strategies.
- Both similar to historical controls.
- **Higher rates of organ preservation in CRT-CNCT.**



Garcia-Aguilar, JCO 2022

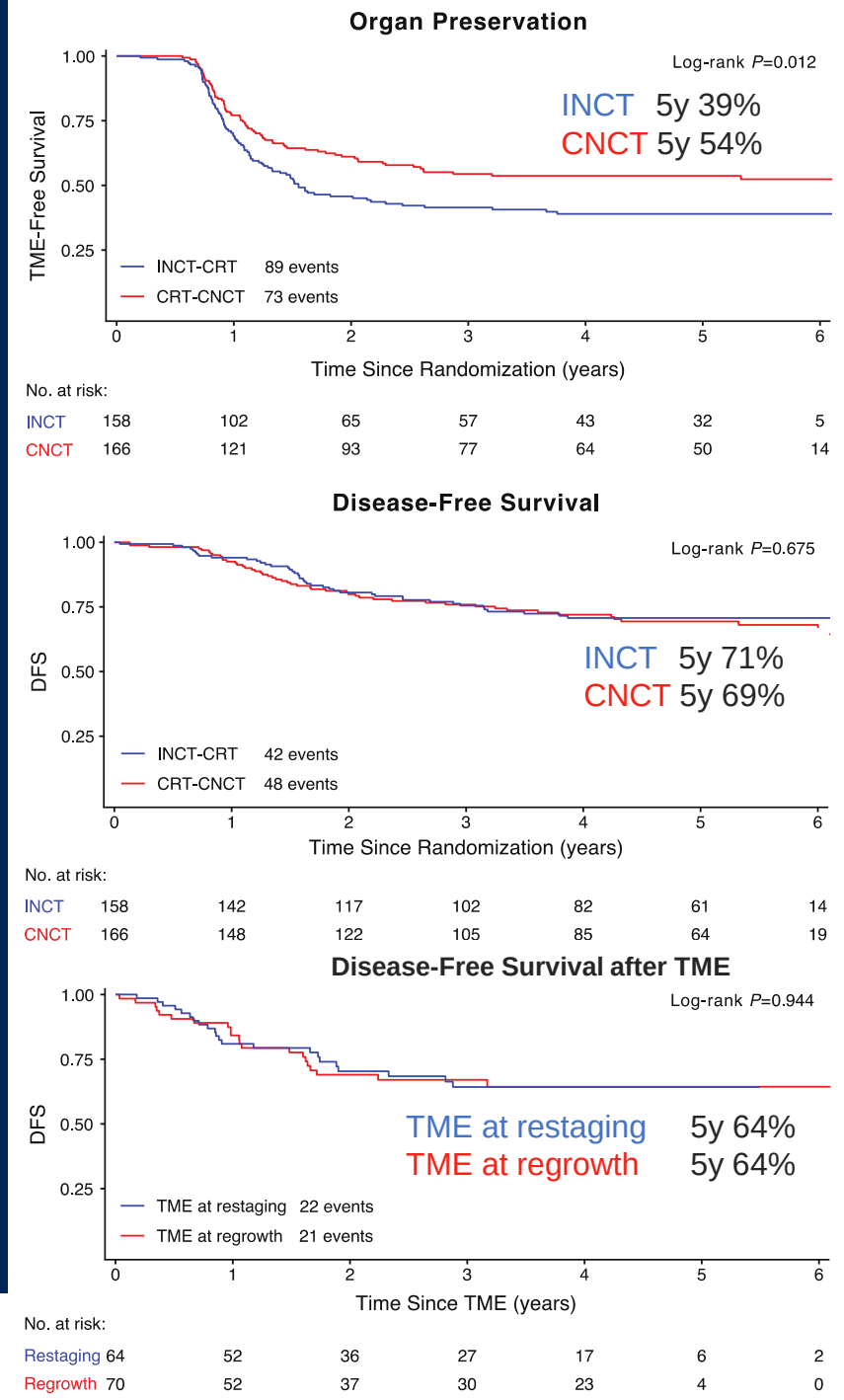
Unanswered Questions from 2022

- Do patients who develop regrowth and require salvage TME do worse than those treated with upfront TME (i.e., do we miss the window for cure)?
  - Compare 5-year DFS between TME after restaging and TME after tumor regrowth.
- Updated (5-year) organ preservation (TME-free survival) between INCT-CRT and CRT-CNCT.
- What is the timing of Regrowth (i.e., when can we stop surveillance)?

Results

Median follow-up 5.1 years

- 225/304 (74%) were offered WW:
  - 105/146 (72%) of INCT-CRT patients.
  - 120/158 (76%) of CRT-CNCT patients.
- 81 (36%) developed a regrowth:
  - 46/105 (44%) of INCT-CRT patients.
  - 35/120 (29%) of CRT-CNCT patients.
- 76 (94%) of regrowths occurred within 2 years and 80 (99%) occurred within 3 years after restaging.



PRESENTED BY: Jeremy C. Jones, MD

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Take Home Points

- Nearly half of rectal cancer patients preserve their rectum at 5 years, higher rates of organ preservation in patients treated with CRT-CNCT.

- The majority of tumor regrowths occur in the first 2 years, suggesting that a close follow-up in this period is critical.

- Salvage TME for tumor regrowth offers similar outcomes to immediate TME.

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OMITTING RADIATION FOR SELECT PATIENTS

RATIONALE FOR PROSPECT

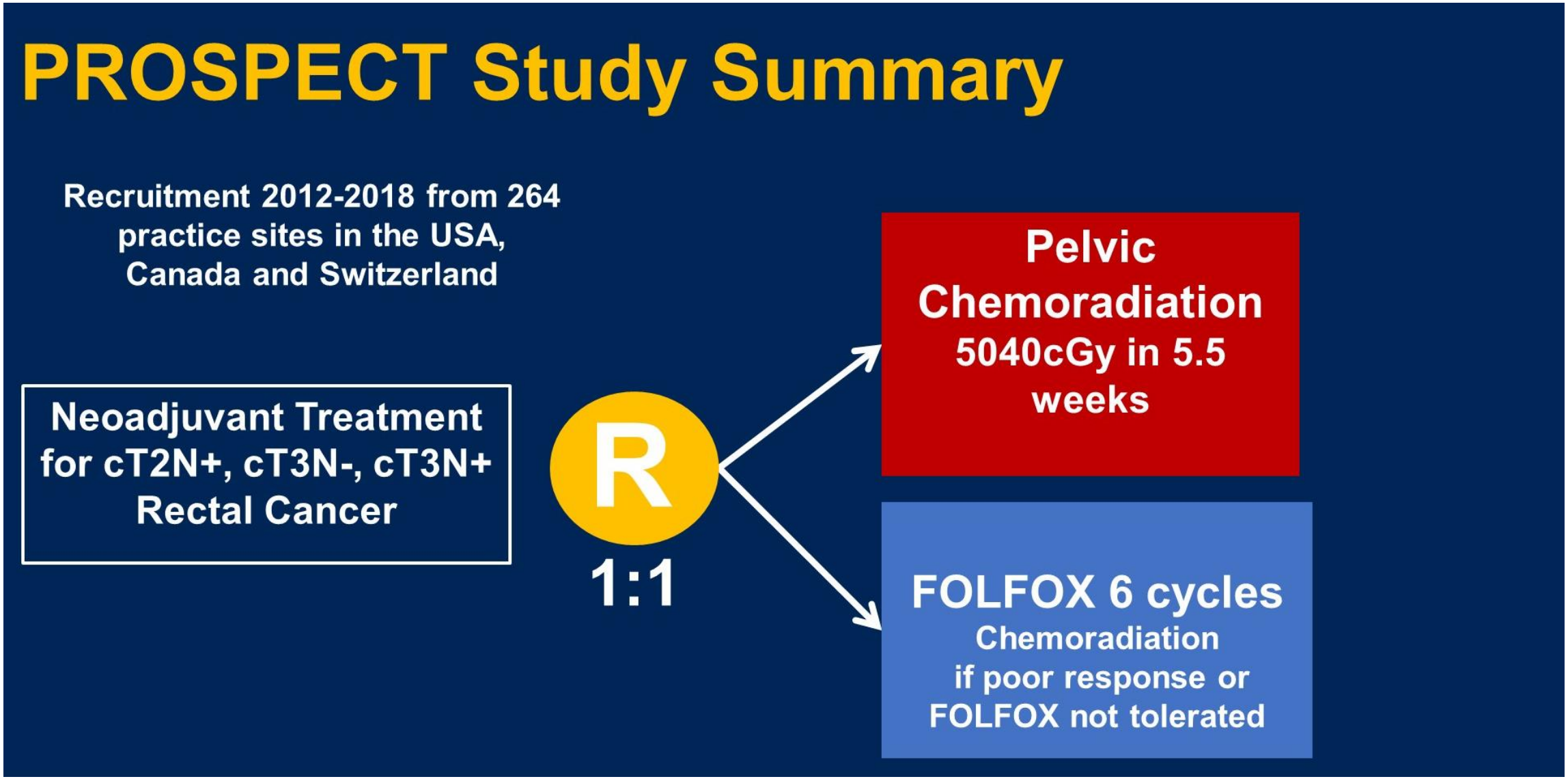
Adverse effects from radiation:

- Impaired bowel, bladder and sexual function
- Pelvic fracture and secondary malignancies
- Impaired bone marrow reserve
- Infertility and premature menopause

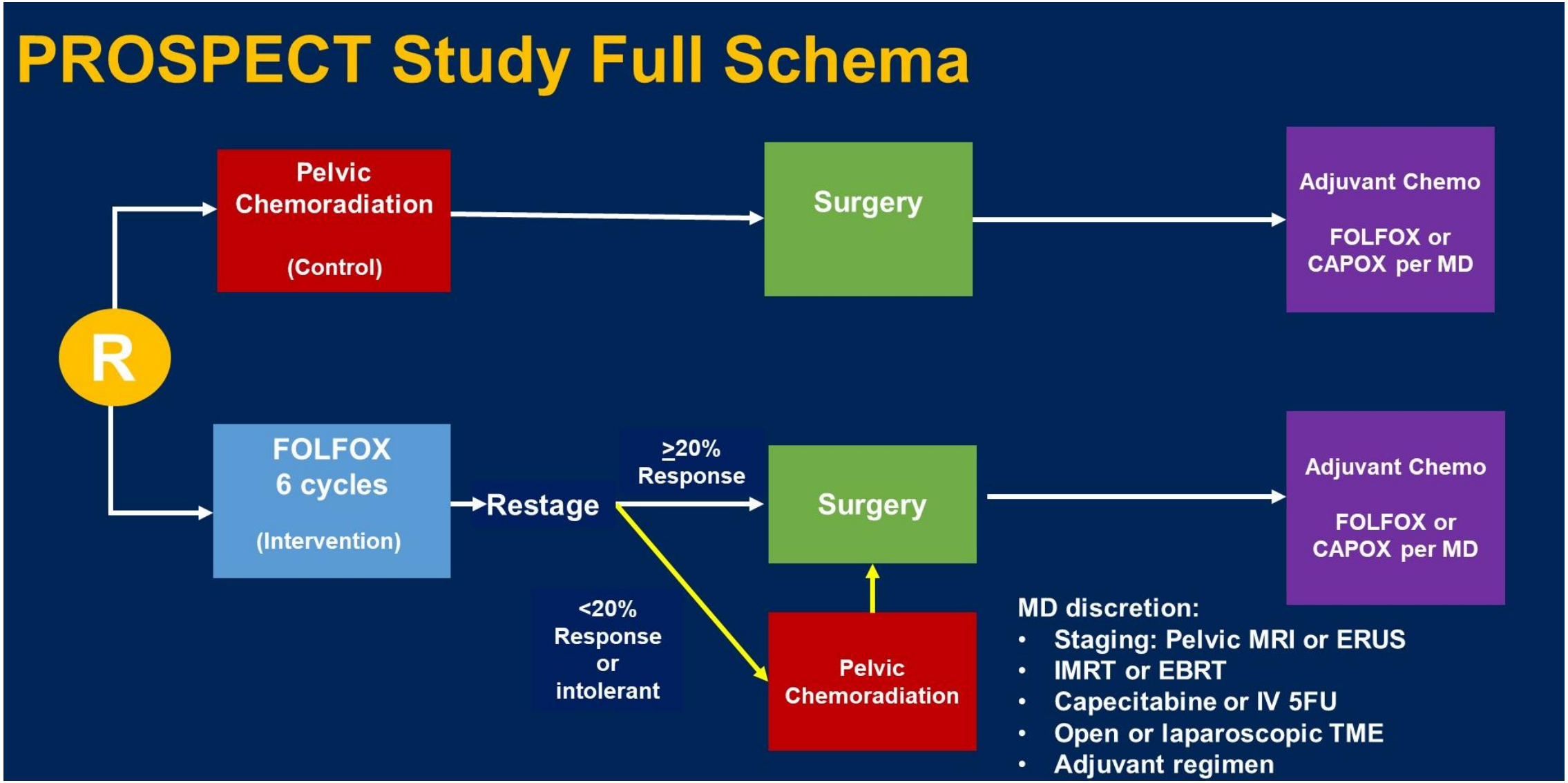
Advances in management:

- Systemic therapy with FOLFOX
- Total mesorectal excision is the standard
- Better screening (fewer T4s)
- Improved imaging with MRI

PROSPECT Study Summary



Schrag ASCO 2023



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PROSPECT Main Eligibility Criteria

Inclusion:

- Clinical Stage T2N+, T3N-, T3N+
- Chemoradiation is indicated
- Candidate for sphincter-sparing surgery

Exclusion:

- Tumor requiring an APR
- cT4 tumor
- ≥ 4 pelvic lymph nodes ≥ 1cm in short axis

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PROSPECT OUTCOMES

	FOLFOX with selective radiation	Standard of care	HR
Survival outcomes			
DFS at 5 years*	80.8%	78.6	0.92
Recurrence free at 5 years	98.2%	98.4%	1.18
OS at 5 years	89.5%	90.2%	1.04
Surgical outcomes			
Path CR	22%	24%	
R0 resection	99%	97%	
LAR	98%	98%	

Non-inferiority margin was met

9% in experimental arm received radiation

- <20% response
- Poor tolerance of FOLFOX

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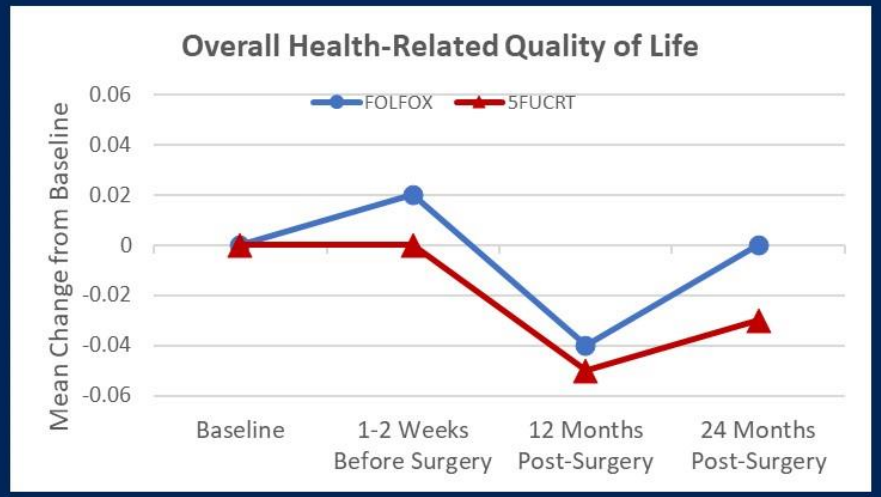
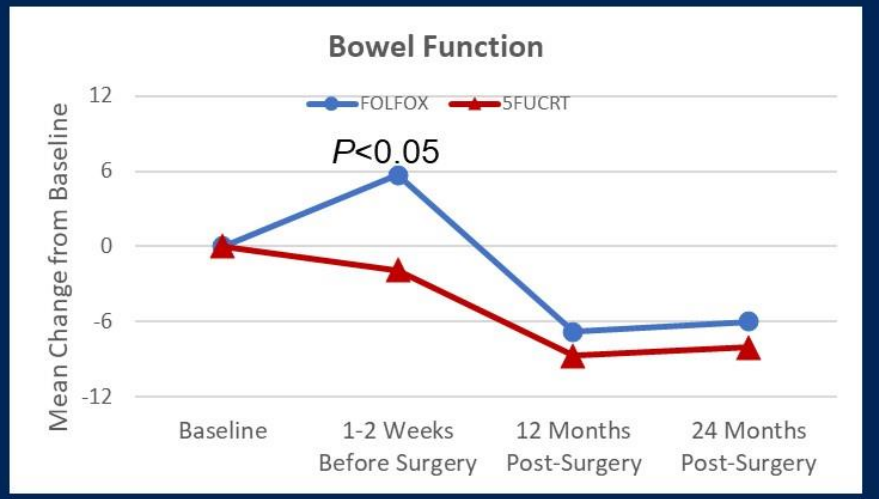
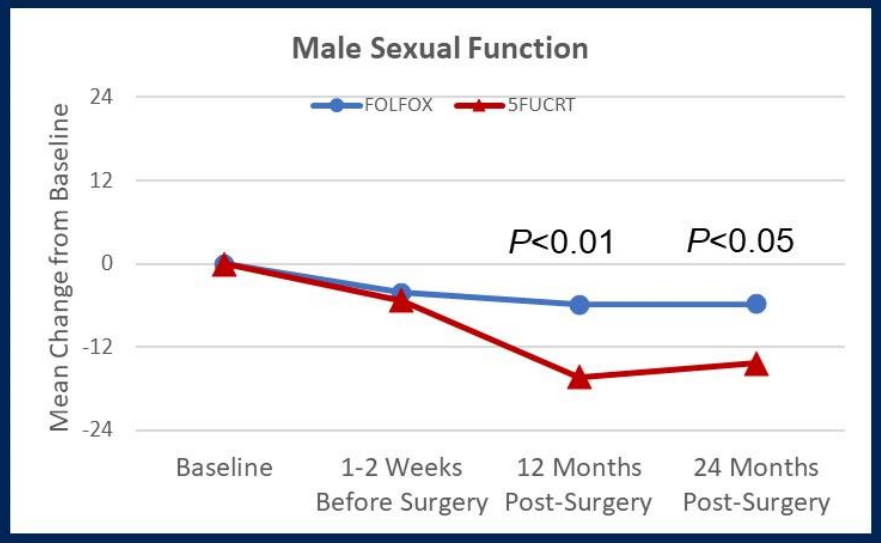
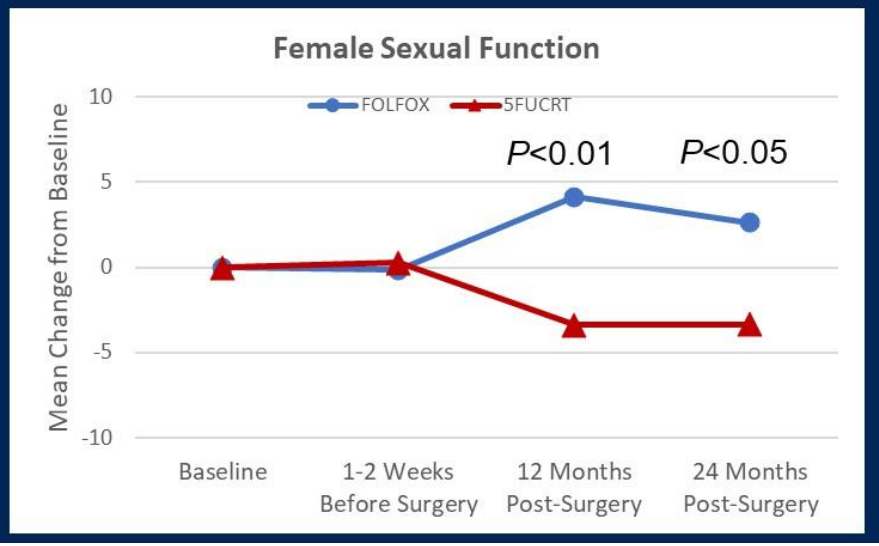
PROSPECT: Quality of Life Evaluation









Quality of Life: Trend, but no significant difference between groups

Bowel function and sexual function favor FOLFOX group

N-373

Positive values represent improvement compared to baseline

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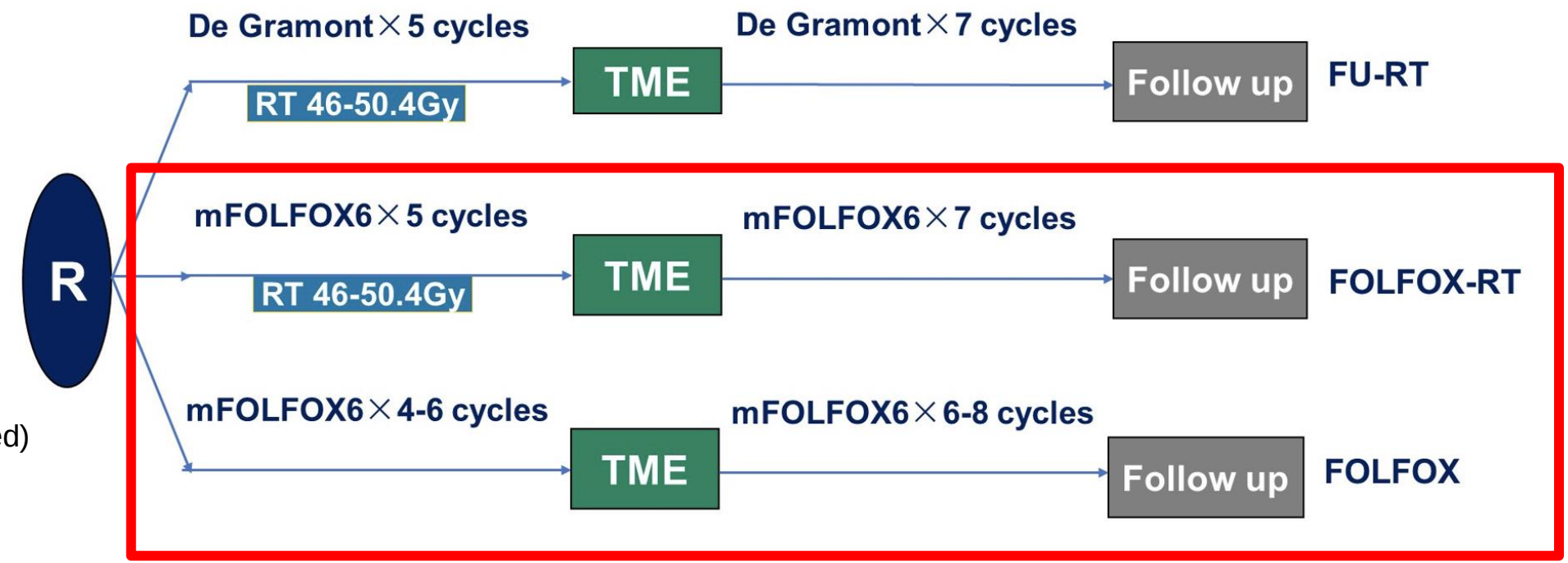
PROSPECT TRIAL CONCLUSIONS

- Neoadjuvant FOLFOX with selective omission of radiation (for patients with > 20% response) is a safe and effective management approach
  - Does not compromise DFS or OS
  - Does not compromise surgical outcomes
  - Associated with improved sexual and bowel function

FOWARC STUDY DESIGN

Inclusion criteria

- 18-75 years
- ECOG 0-1
- Rectal adenoca
- <12 cm from anal verge
- Stage II-III
  - By MRI + CT (EUS accepted)
- Estimated to be resectable



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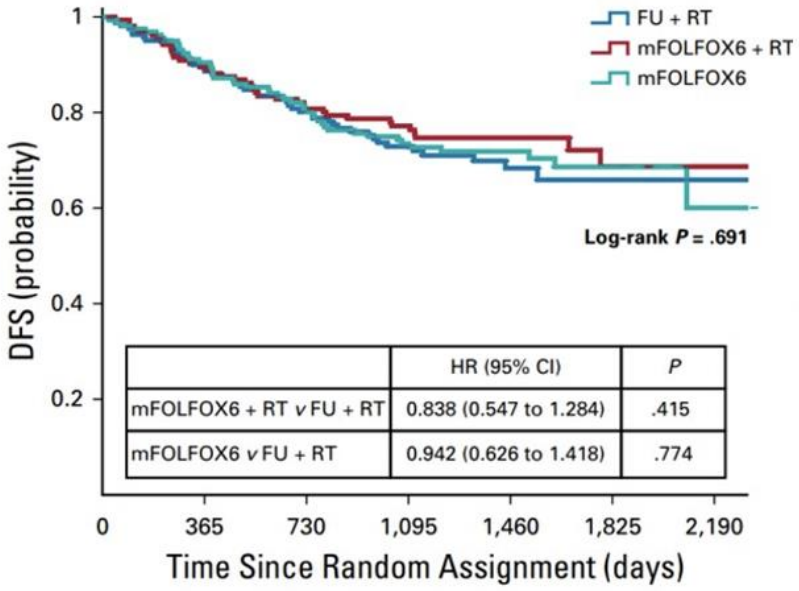
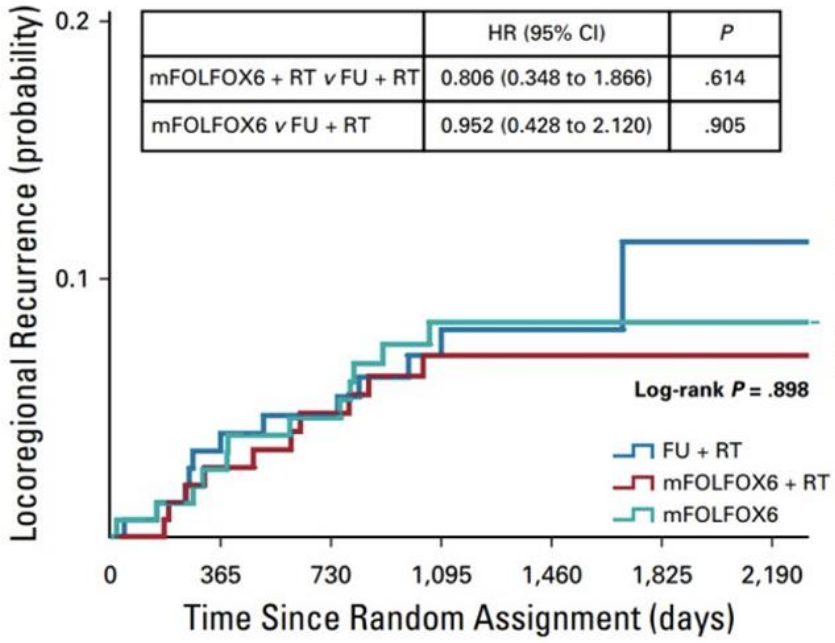
DFS, LRS & OS AT 3 YEARS COMPARABLE

3y-DFS



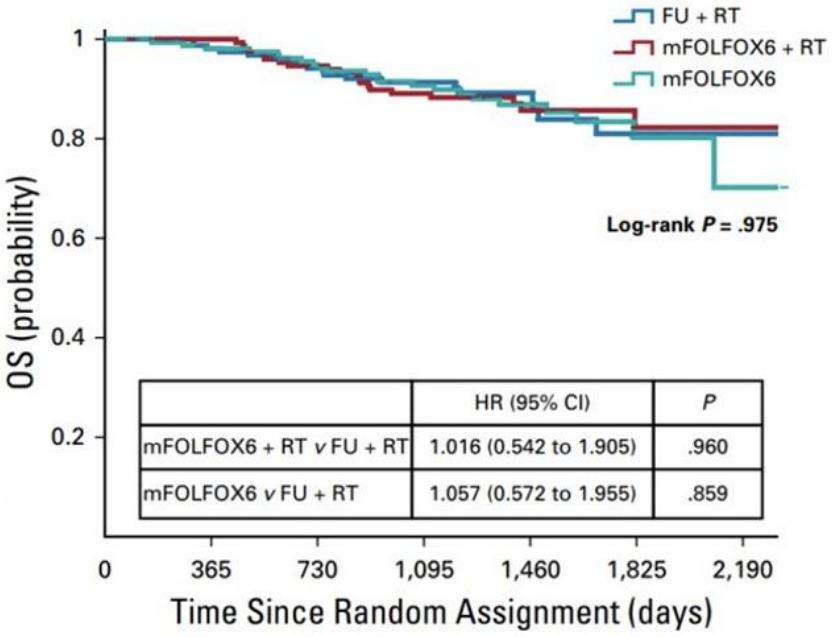
	HR (95% CI)	P
mFOLFOX6 + RT *v* FU + RT	0.838 (0.547 to 1.284)	.415
mFOLFOX6 *v* FU + RT	0.942 (0.626 to 1.418)	.774

3y-LRS



	HR (95% CI)	P
mFOLFOX6 + RT *v* FU + RT	0.806 (0.348 to 1.866)	.614
mFOLFOX6 *v* FU + RT	0.952 (0.428 to 2.120)	.905

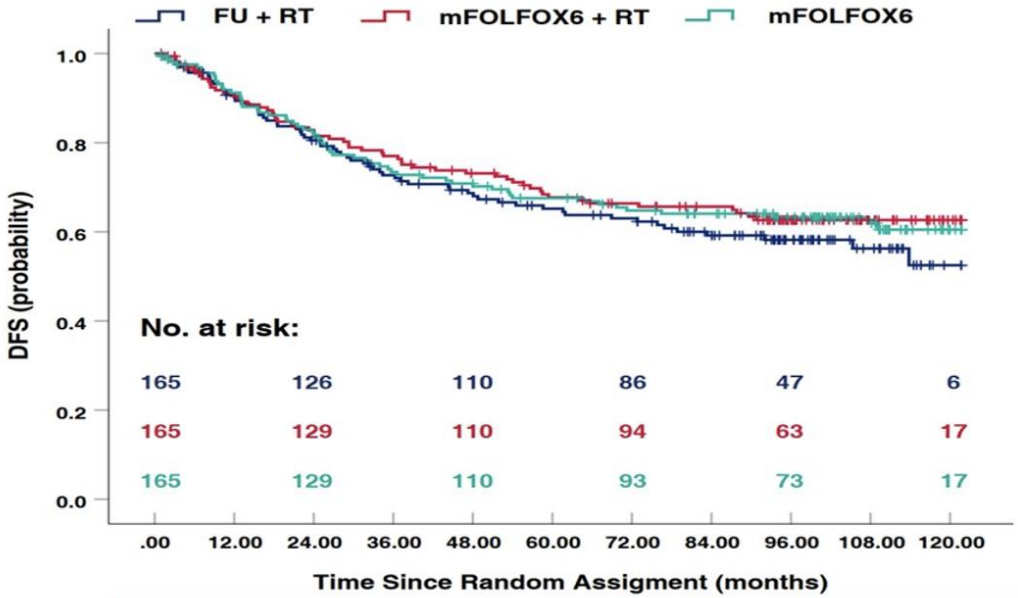
3y-OS



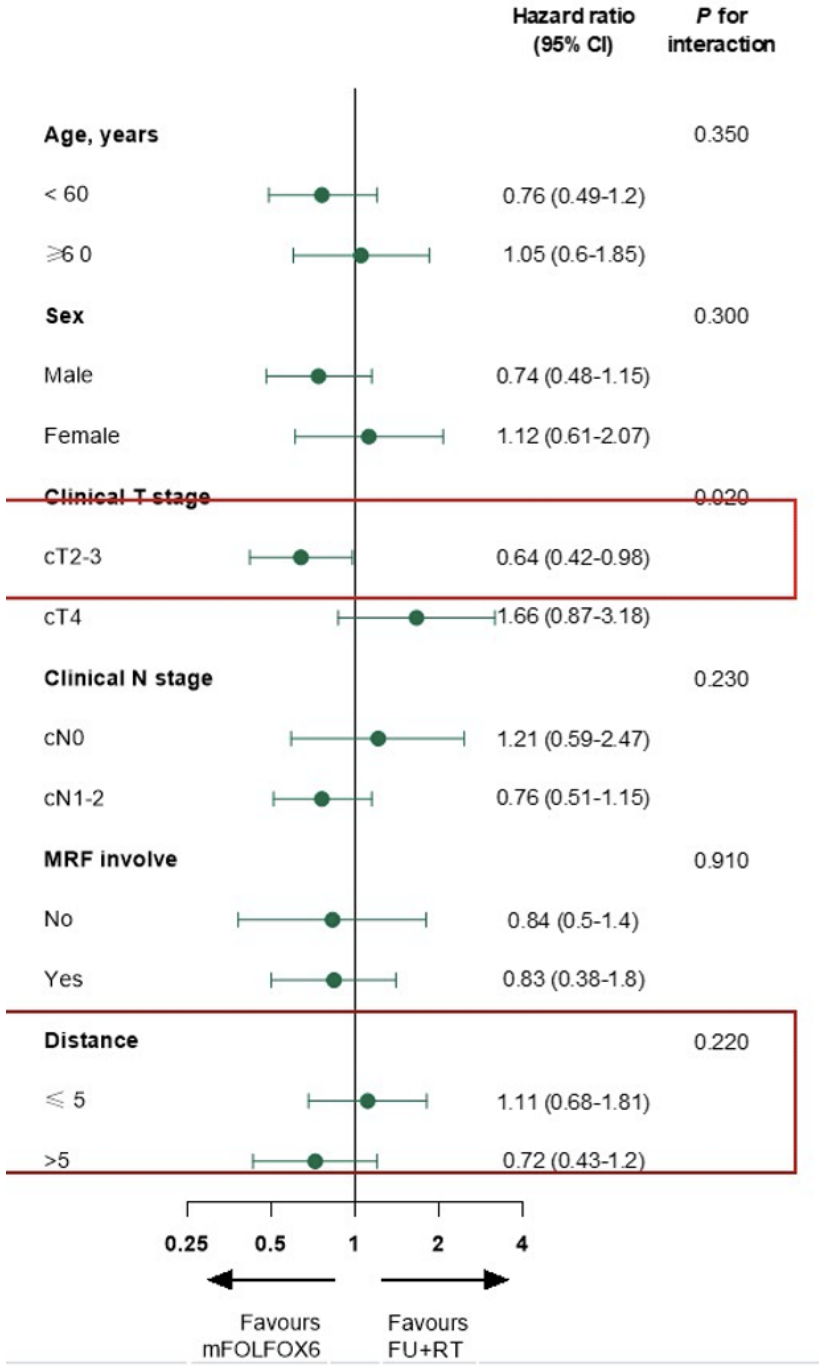
	HR (95% CI)	P
mFOLFOX6 + RT *v* FU + RT	1.016 (0.542 to 1.905)	.960
mFOLFOX6 *v* FU + RT	1.057 (0.572 to 1.955)	.859

Deng JCO 2021

FORWARC 5-YEAR DFS UPDATE



Treatment	5y-DFS	10y-DFS	HR (95% CI)
FU-RT	65.2%	52.5%	Ref
FOLFOX-RT	67.7%	62.6%	0.83 (0.58-1.19)
FOLFOX	67.5%	60.5%	0.86 (0.60-1.23)



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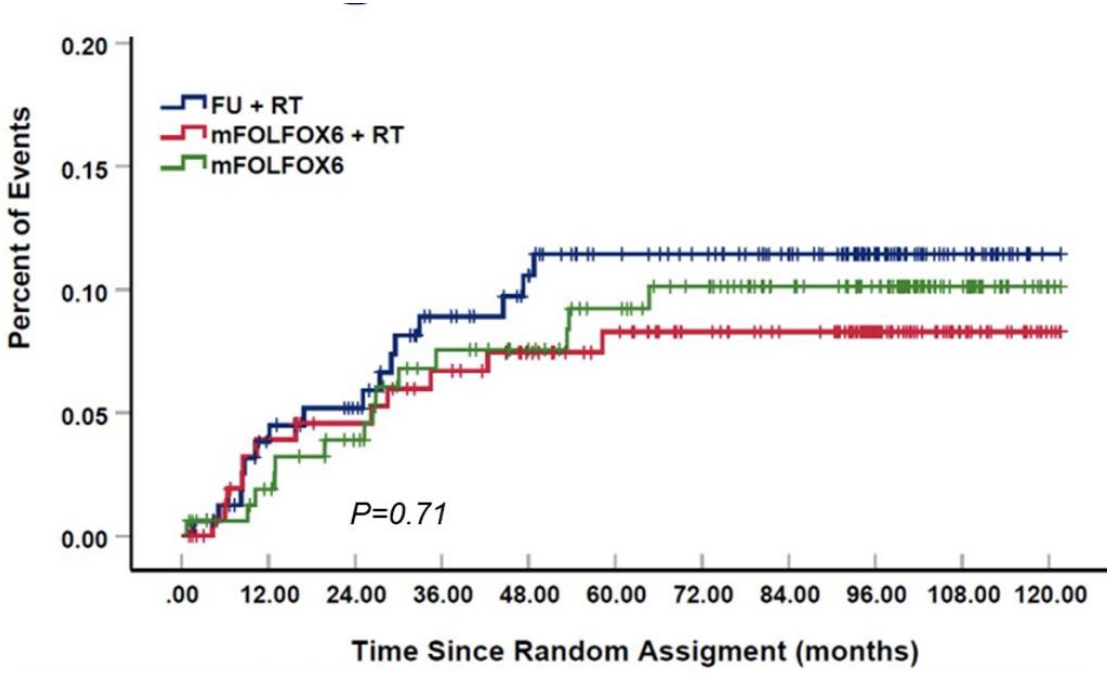
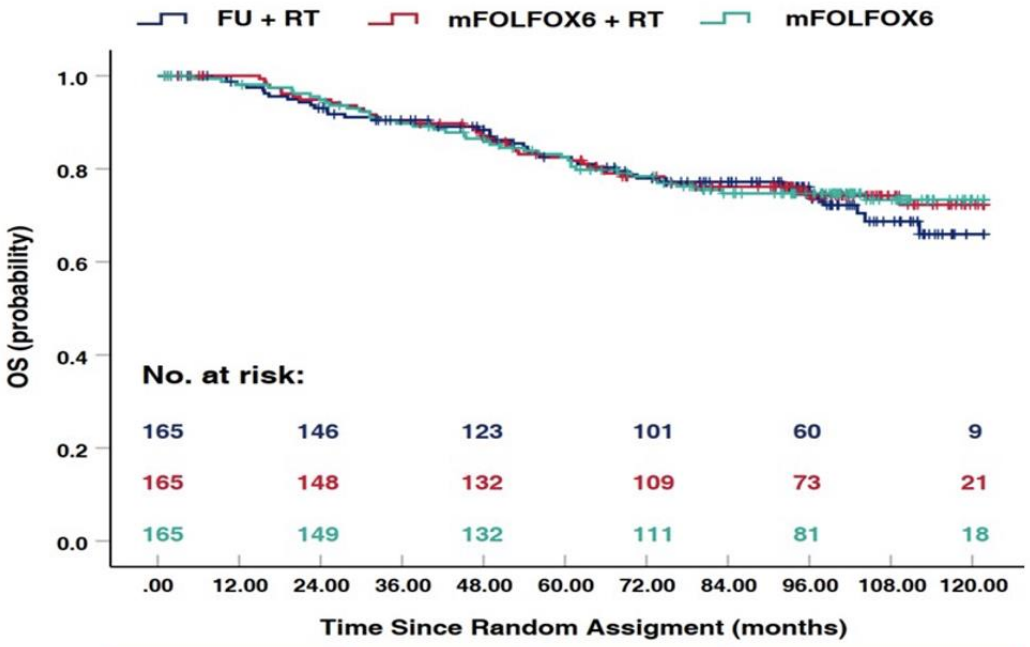
FORWARC 5-YEAR UPDATE

5-Year Local regional recurrence



Treatment	5y-LR(%)	10y-LR (%)	HR (95% CI)
FU-RT	10.8	10.8	Ref
FOLFOX-RT	8.0	8.0	0.825 (0.38-1.81)
FOLFOX	8.8	9.6	0.800 (0.37-1.75)

5-Year Overall Survival



Treatment	5y-OS	10y-OS	HR (95% CI)
FU-RT	82.5%	65.9%	Ref
FOLFOX-RT	81.8%	72.3%	0.91 (0.58-1.41)
FOLFOX	81.8%	73.4%	0.91 (0.58-1.41)

OMITTING RADIATION FOR LARC

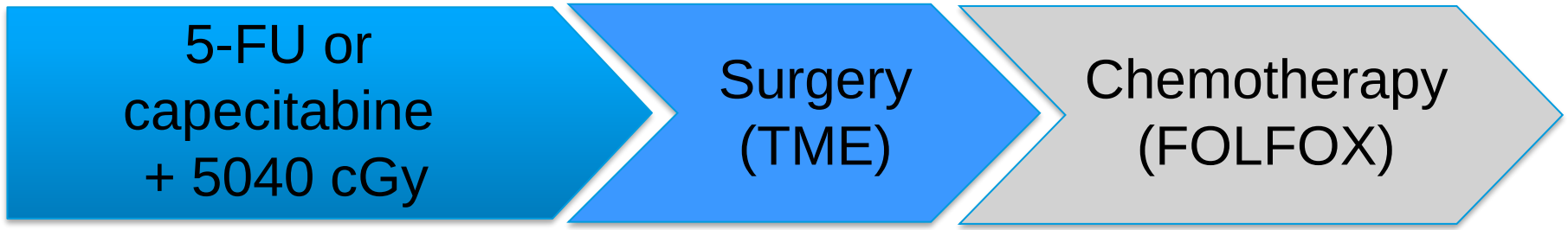
- Confirms findings from the PROSPECT study, that radiation can safely be omitted for select patients without compromising DFS, OS, or local recurrence
- Reserve for
  - Mid – high rectal tumors
  - T3 tumors

REDUCING DEVELOPMENT OF METASTATIC DISEASE

OUTCOMES IN RECTAL CANCER

	Preoperative chemoradiation with 5-FU[1]	Preoperative chemoradiation with 5-FU Capecitabine[2]
5 year OS	76%	76%
Local Relapse	6%	6%
Distant Metastasis	36%	19%

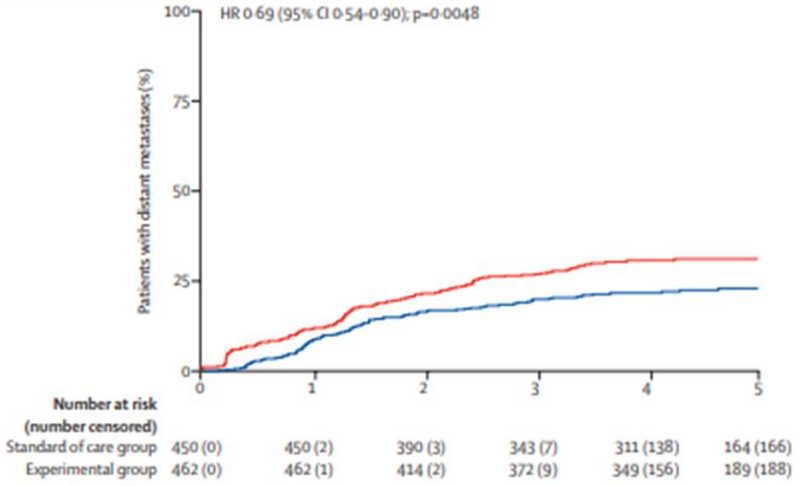
?



NEOADJUVANT THERAPY IN RECTAL CANCER REDUCES METASTASIS-FREE SURVIVAL

Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial

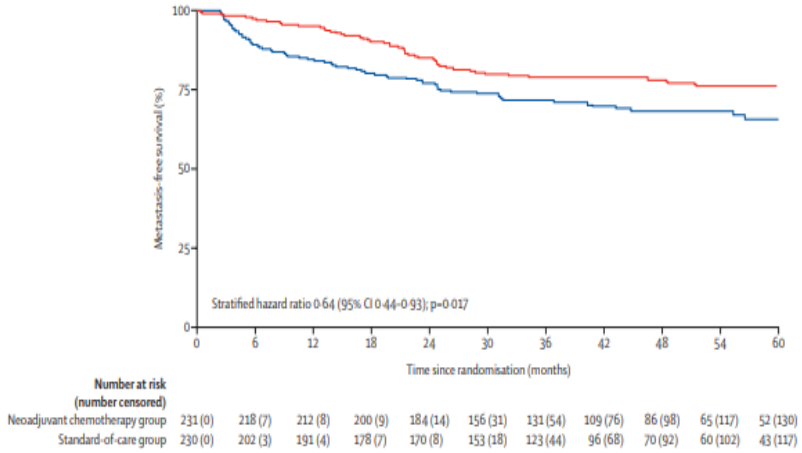
Renu R Bahadoer, Esmée A Dijkstra*, Boudewijn van Etten†, Corrie A M Marijnen†, Hein Putter, Elma Meershoek-Klein Kranenbarg, Annet G H Roodvoets, Iris D Nagtegaal, Regina G H Beets-Tan, Lennart K Blomqvist, Tone Fokstuen, Albert J ten Tije, Jaume Capdevila, Mathijs P Hendriks, Ibrahim Edhemovic, Andrés Cervantes, Per J Nilsson†‡, Bengt Glimelius†‡, Cornelis J H van de Velde†‡, Geke A P Hospers†‡, and the RAPIDO collaborative investigators§*



3-year distant metastasis rate:
20% vs. 26.8%
P = 0.0048

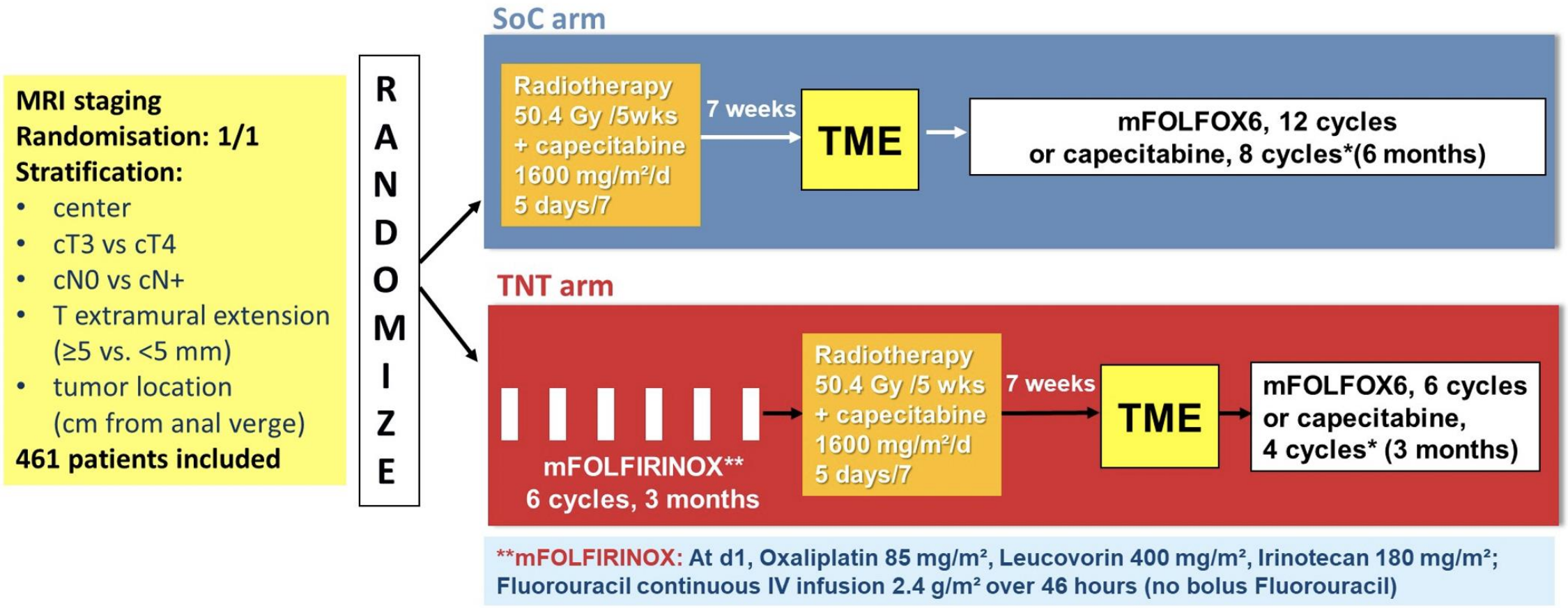
Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial

*Thierry Conroy, Jean-François Bosset, Pierre-Luc Etienne, Emmanuel Rio, Éric François, Nathalie Mesgouez-Nebout, Véronique Vendrely, Xavier Artignan, Olivier Bouché, Dany Gargot, Valérie Boige, Nathalie Bonichon-Lamichhane, Christophe Louvet, Clotilde Morand, Christelle de la Fouchardière, Najib Lamfichekh, Béata Juzyna, Claire Jouffroy-Zeller, Eric Rullier, Frédéric Marchal, Sophie Gourgou, Florence Castan, Christophe Borg, on behalf of the Unicancer Gastrointestinal Group and Partenariat de Recherche en Oncologie Digestive (PRODIGE) Group**



3-year MFS:
79% vs. 72%
P = 0.017

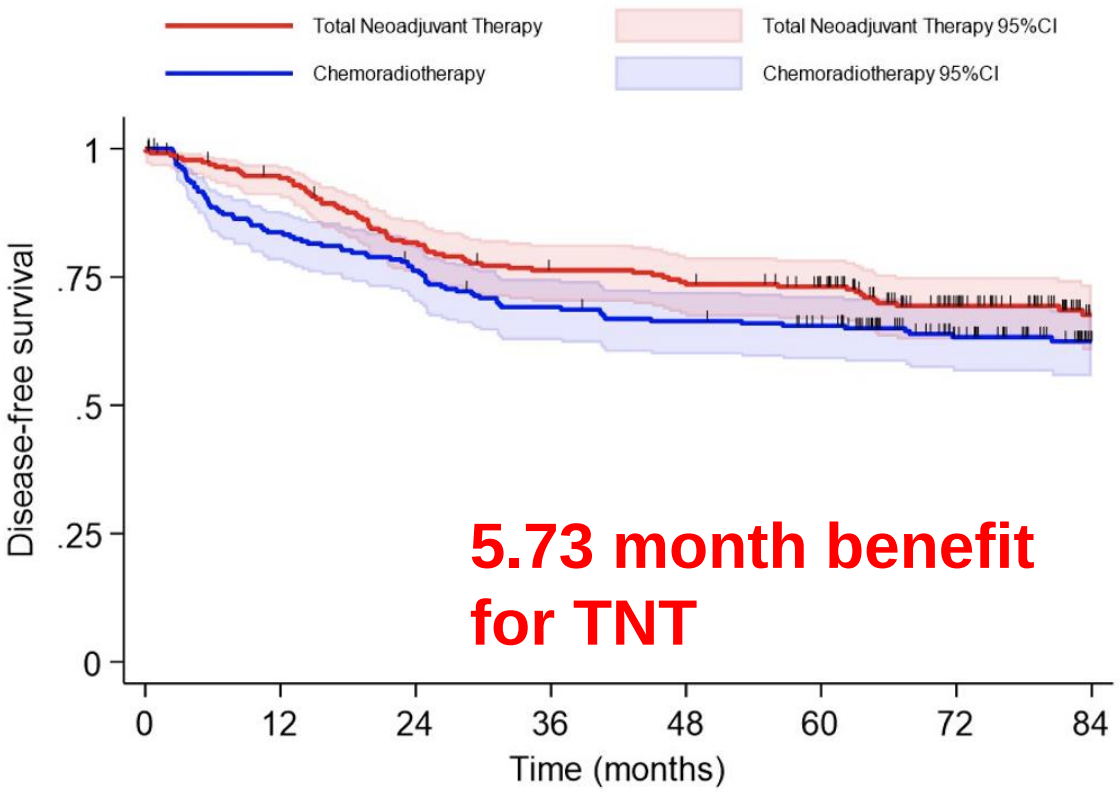
PRODIGE 23 TRIAL: ASCO 2023 UPDATE



*according to center choice throughout the study; adjuvant chemotherapy was mandatory in both arms regardless of ypTNM stage.

Conroy ASCO 2023

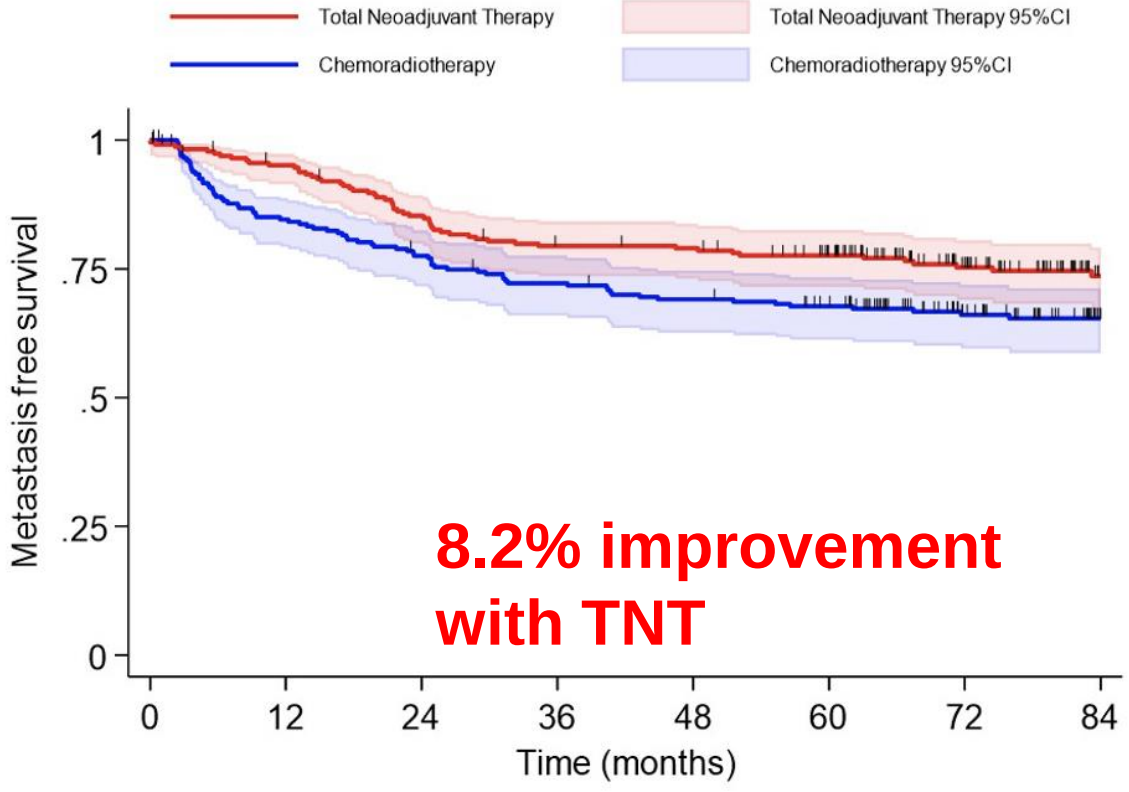
Disease-Free Survival



5.73 month benefit for TNT

	TNT	SOC	
5 yr	73.1%	65.5%	
7 yr	67.6%	62.5%	p value 0.048

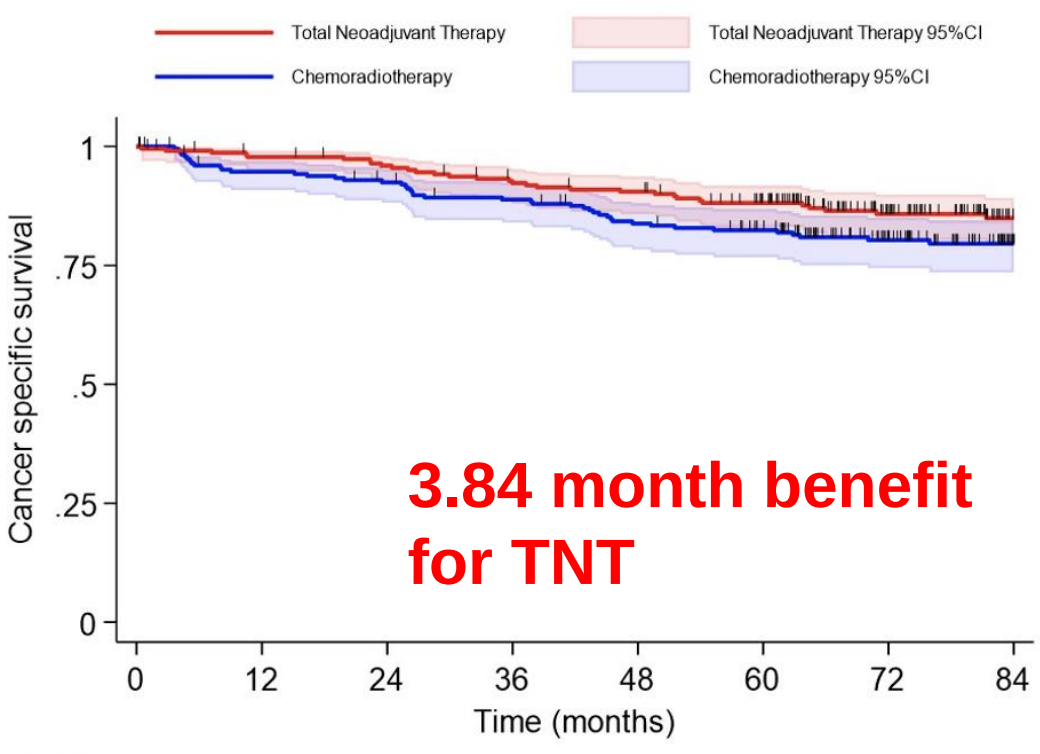
Metastasis-Free Survival



8.2% improvement with TNT

	TNT	SOC	
5 yr	77.6%	67.7%	
7 yr	73.6%	65.4%	p value 0.011

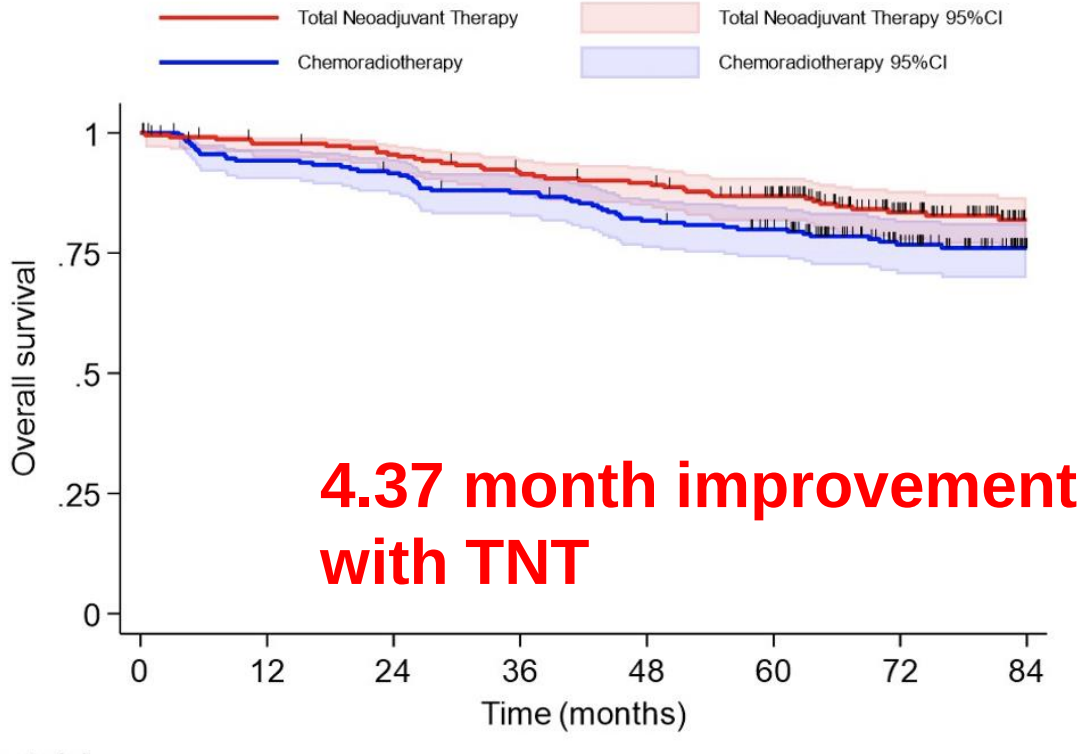
Cancer-specific Survival



3.84 month benefit for TNT

	TNT	SOC	
5 yr	88.1%	82.4%	
7 yr	84.9%	79.6%	p value 0.051

Overall Survival



4.37 month improvement with TNT

	TNT	SOC	
5 yr	86.9%	80.0%	
7 yr	81.9%	76.1%	p value 0.033

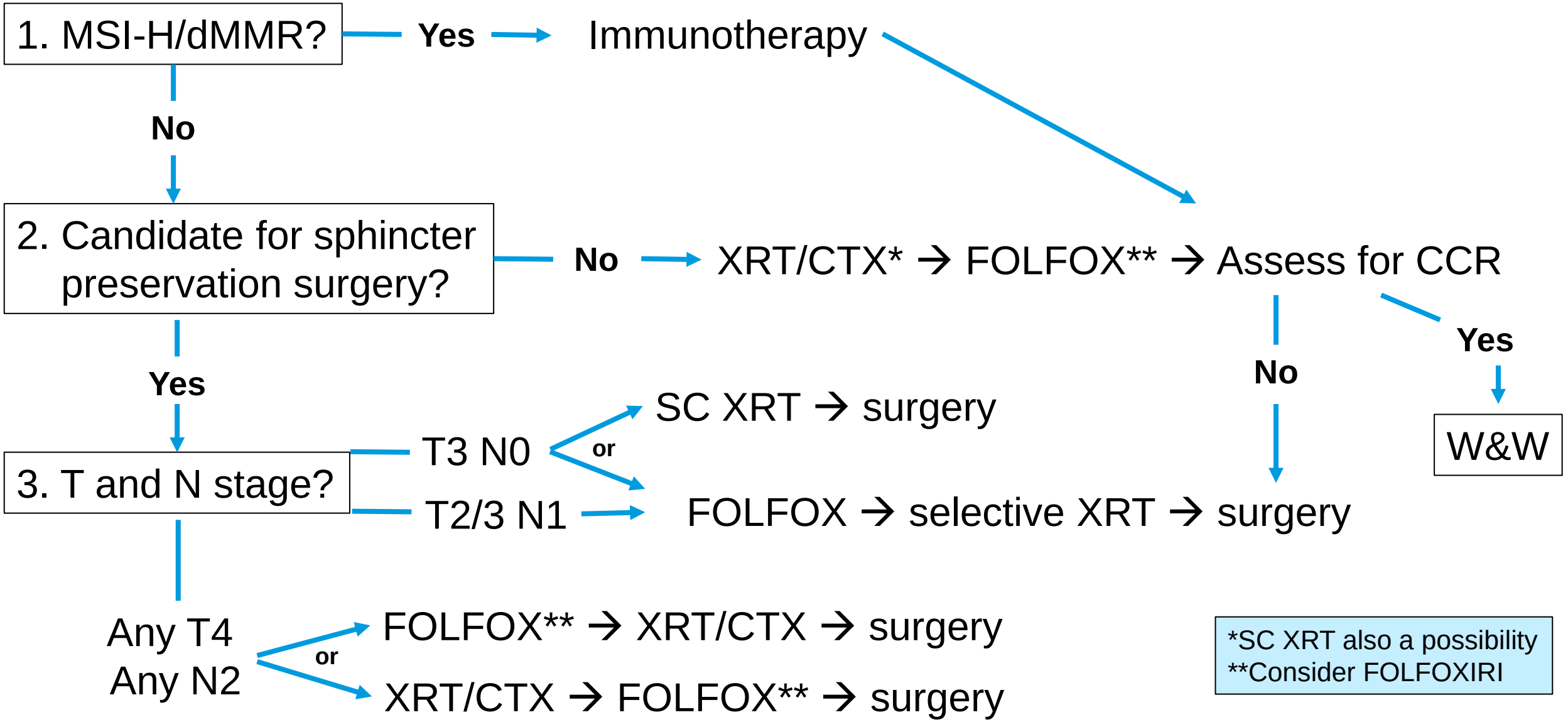
TNT FOR RECTAL CANCER

- Is the standard of care for locally advanced (T3N+, T4N0, T4N+)
- Improves DFS, MFS & OS

- Remaining questions
  - Management of T3N0
  - Does everyone need FOLFIRINOX?
  - Optimal timing of chemotherapy?
    - All neoadjuvant or perioperative?

LOCALLY ADVANCED RECTAL CANCER: PUTTING IT ALL TOGETHER

LOCALLY ADVANCED RECTAL CANCER MANAGEMENT

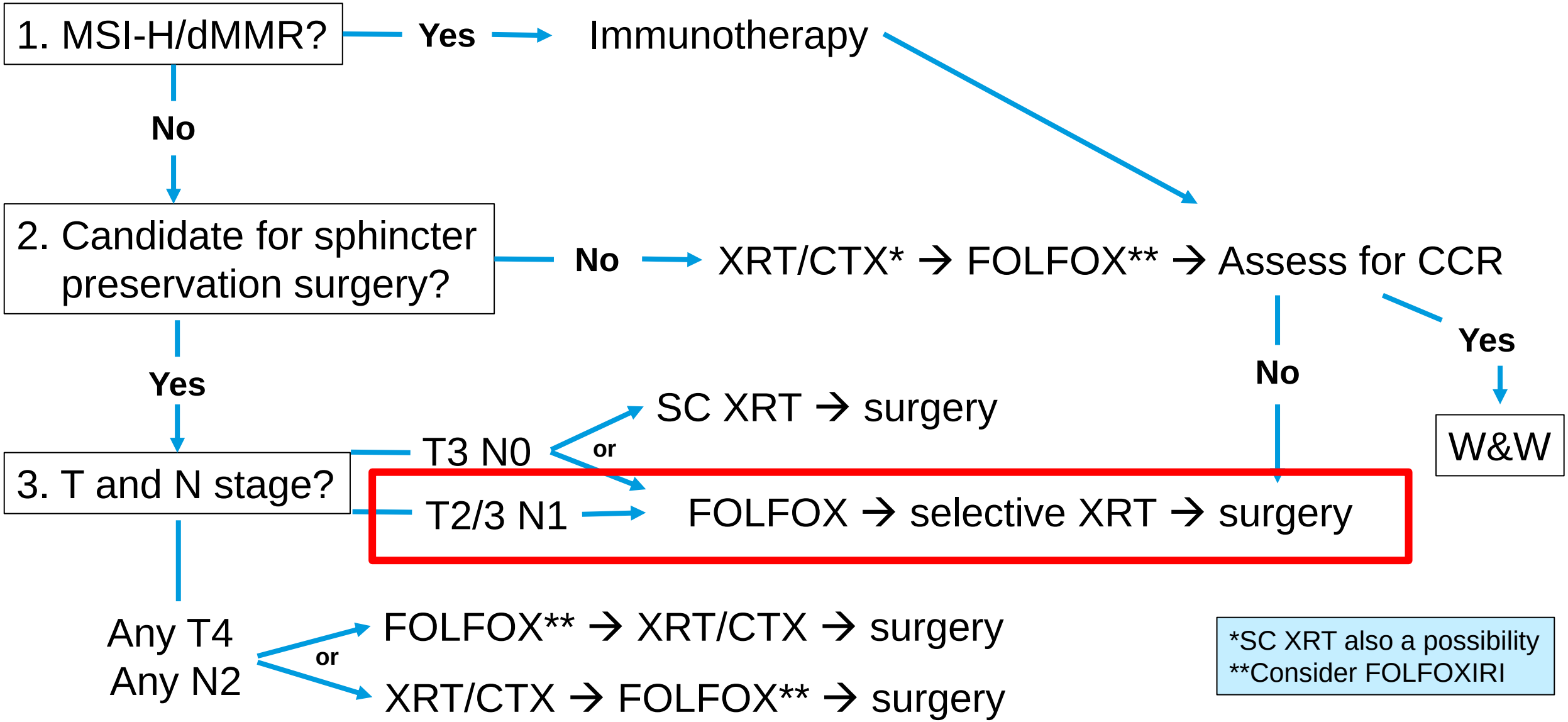


CASE 1

61 yo male presented to ED with 2-month history of increased frequency of bowel movements (10-12/day), pain with defecation, 20-pound weight loss. CT A/P: thickening of the distal rectum with no evidence of metastatic disease. Colonoscopy: mass 6 cm from anal verge. Biopsy: moderately differentiated adenocarcinoma. CT chest negative. Pelvic MRI: T3N1 lesion. **Tumor has normal expression of MMR proteins**. Next best step in management?

A. Long course chemoradiation
B. Short course radiation
C. FOLFOX
D. FOLFIRINOX

LOCALLY ADVANCED RECTAL CANCER MANAGEMENT



USE OF ctDNA IN LOCALLY ADVANCED RECTAL CANCER

- Ongoing studies will help determine whether ctDNA after resection will guide treatment and improve outcomes
- Not recommended for routine use at this time
- However, if it is used, use only to guide escalation of therapy
  - Example: if ctDNA+, give adjuvant therapy
- At this time false negativity rate is approx. 50%, and using to de-escalate therapy may miss a window of opportunity for cure

QUESTIONS & DISCUSSION