

Session: Considerations for TNT in Localized Rectal Cancer

Neoadjuvant chemotherapy for rectal cancer

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AGENDA

- What is TNT and how did we get here
- Does neoadjuvant chemo improve ...cancer outcomes?
- Does neoadjuvant chemo improve... patient outcomes beyond survival?

And more to come this morning:

Risk and response adapted neoadjuvant radiation therapy

Risk and response adapted surgical approaches and monitoring

Mismatch repair deficient cancer [hint: immunotherapy]

What are the goals of rectal cancer treatment?

CURE

Prevent local recurrence
Prevent distant metastasis

AVOID HARM

Preserve sphincters
Preserve bowel function
Preserve sexual function

Total Neoadjuvant Therapy

Chemoradiation

Long course RT with
cape 825-850 mg/m² BID

Or?

Short course RT, no drug



Chemotherapy

FOLFOX x 8

Or

Cape* Ox x 5



Total Mesorectal Excision

TME via LAR or APR

Or?

Watch + Wait

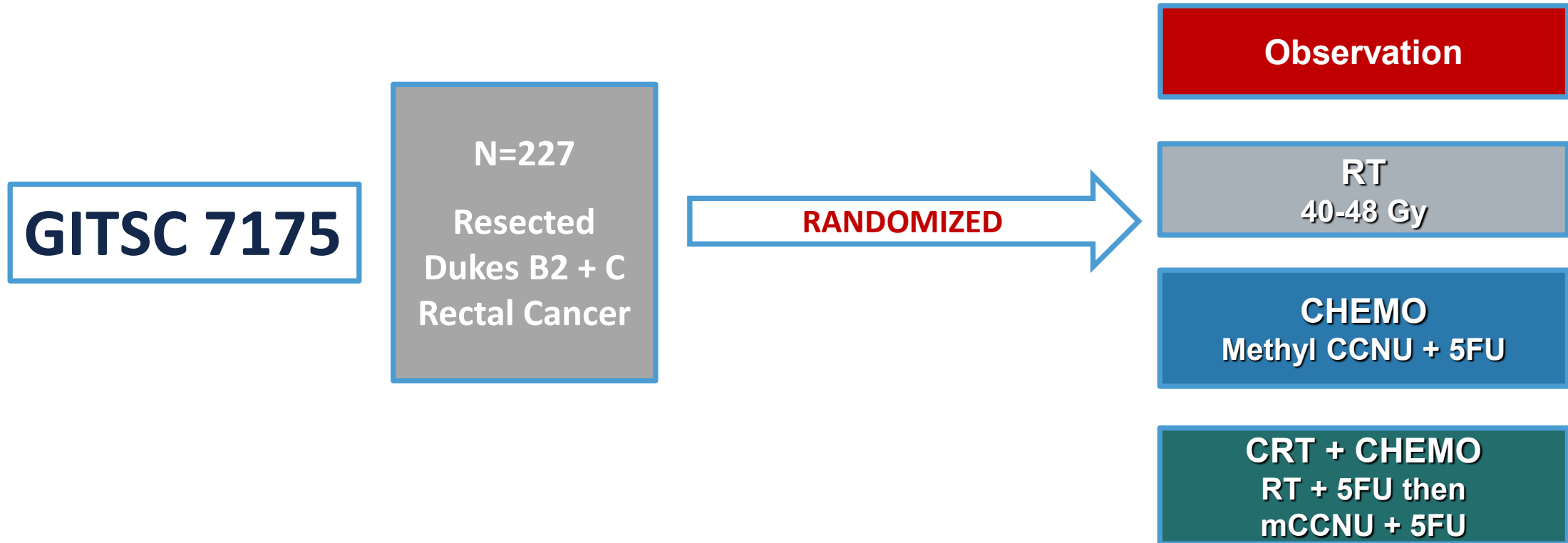


CURE!

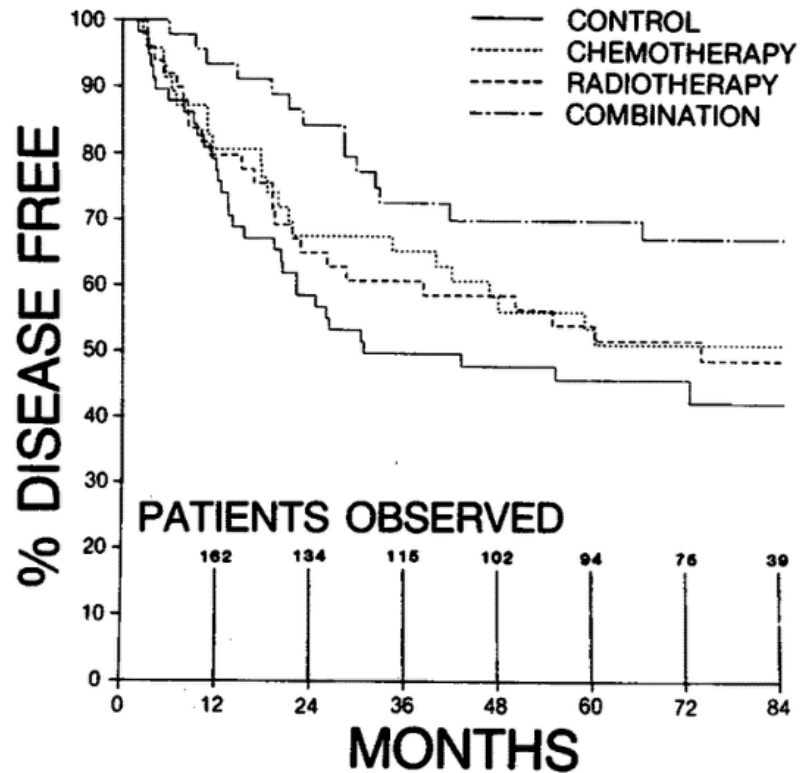


[*note: dosing of cape is 1000 mg/m² BID]

How did we get here?



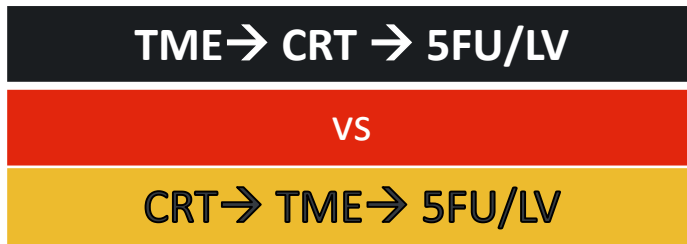
GITSC 7175: adjuvant therapy improves DFS



Best outcomes with all three modalities

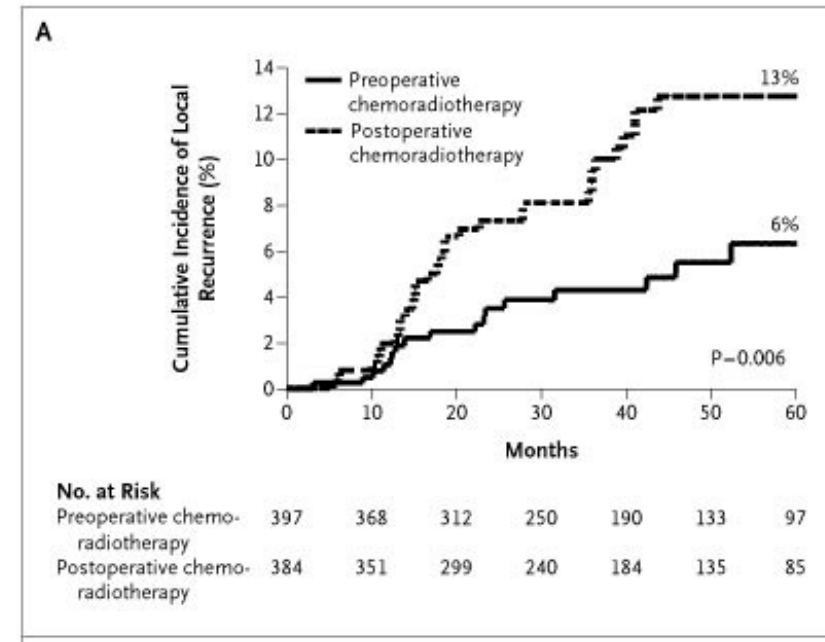
..but unacceptably low rates of cure!

Towards TNT: moving chemoradiotherapy upfront with the German Rectal Cancer Trial



N=421

- No difference OS [76 vs 74%]
- No difference in distant mets
- BETTER local outcomes



BETTER LONG-TERM FUNCTION

Sphincter preservation: 19% → 39%

Long-term GI effects: 15% → 9%

Long-term any severe: 24% → 14%

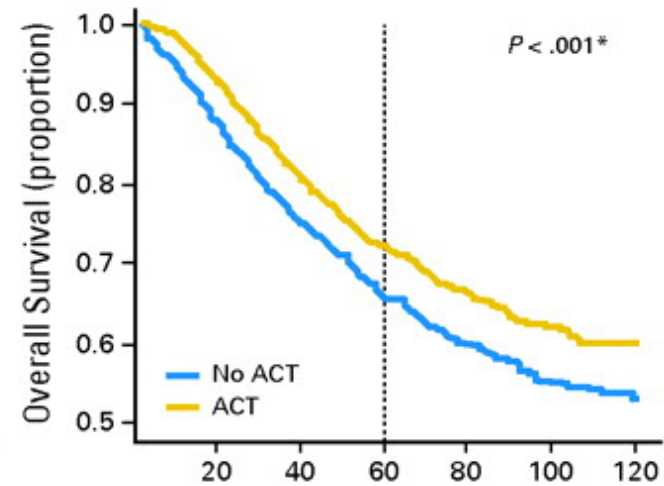
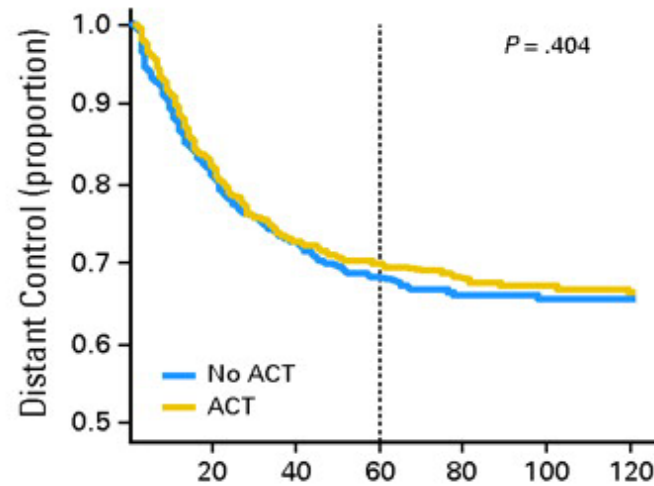
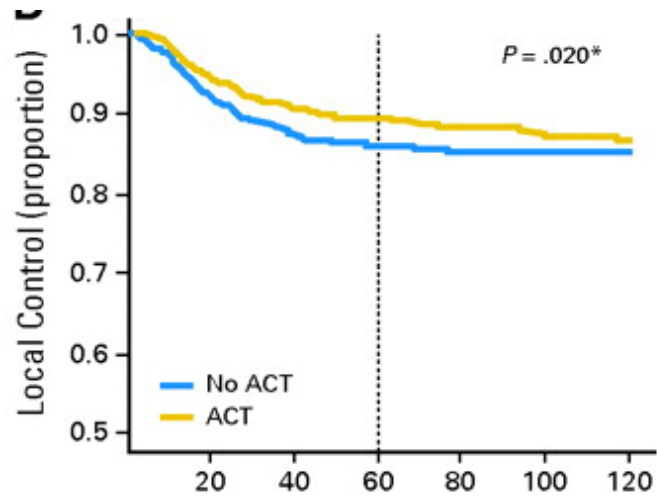
Why move chemotherapy up front?

1) Adjuvant chemotherapy is only marginally effective

Effect of Adjuvant Chemotherapy on Oncologic Outcomes

Valentini pooled analysis

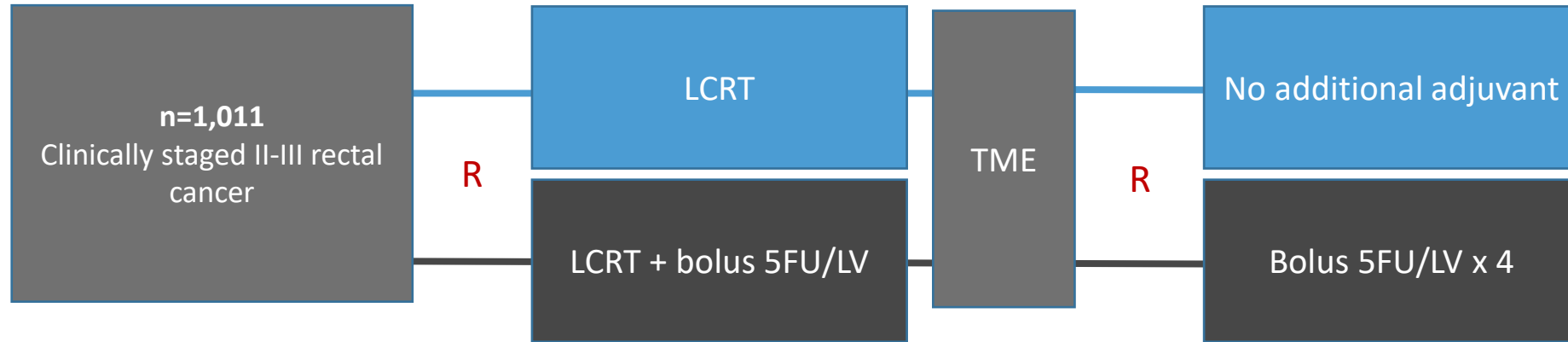
Adjuvant?	Local Control			Distant Control			Overall Survival		
	5 Years	10 Years	P	5 Years	10 Years	P	5 Years	10 Years	P
No Chemo N=1,209	85.9	84.9	0.02	68.3	65.5	0.4	66.1	53.1	<0.01
Chemo N=1,572	89.2	86.6		70.0	66.3		72.3	60.4	



Why move chemotherapy up front?

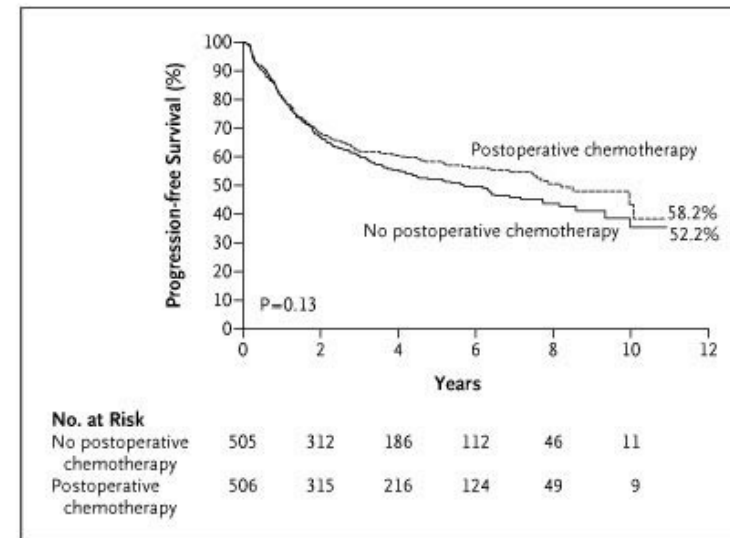
- 1) Adjuvant chemotherapy is only marginally effective
- 2) Adjuvant chemotherapy adherence is poor

Postoperative chemotherapy delivery is poor: EORTC 2291



CHEMO RECEIPT IN ADJ CHEMO ARM

- 66% completed 4 cycles
- 27% received NONE



5 year outcomes

OS HR 0.85, 0.68-1.04
DFS HR 0.87, 0.72-1.04

Why move chemotherapy up front?

- 1) Adjuvant chemotherapy is only marginally effective
- 2) Adjuvant chemotherapy adherence is poor
- 3) Neoadjuvant chemotherapy improves downstaging

Neoadjuvant chemotherapy downstages the primary

Royal Marsden High Risk Phase 2

CapeOx x 4 → CRT → TME → Cape x 4

- N= 105
- 19% T4, 37% N2, 43% levator, 47% CRM
- 88% R0, 89% TME
- **20% pCR**
- **6/105 local recurrence**

MSKCC neoadj chemo only Phase 2

FOLFOX-bev x 4, FOLFOX x 2 → CRT if progressing → TME → completion chemo

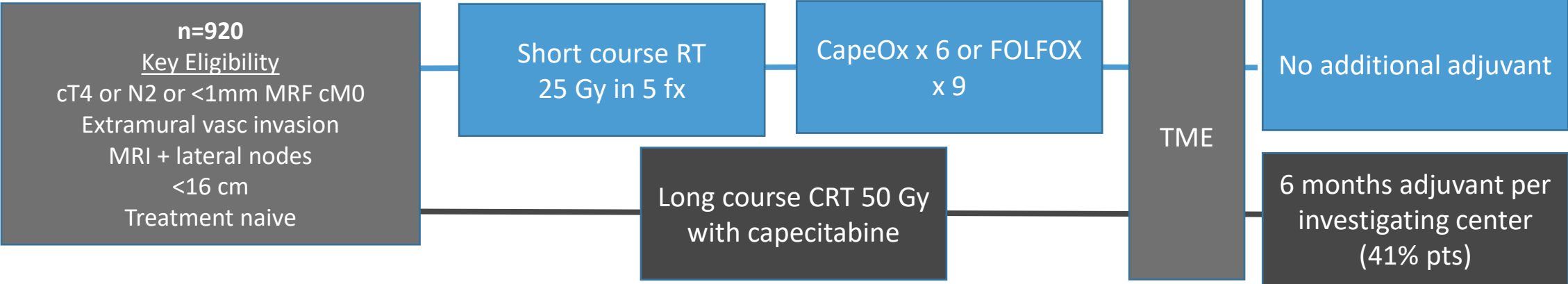
- N= 32
- cT3, N0 or up to 4 nodes , 5-12 cm
- **94% completed neoadj chemotherapy, 6% needed RT**
- **pCR 25%, 4 year DFS 84%**

Why move chemotherapy up front?

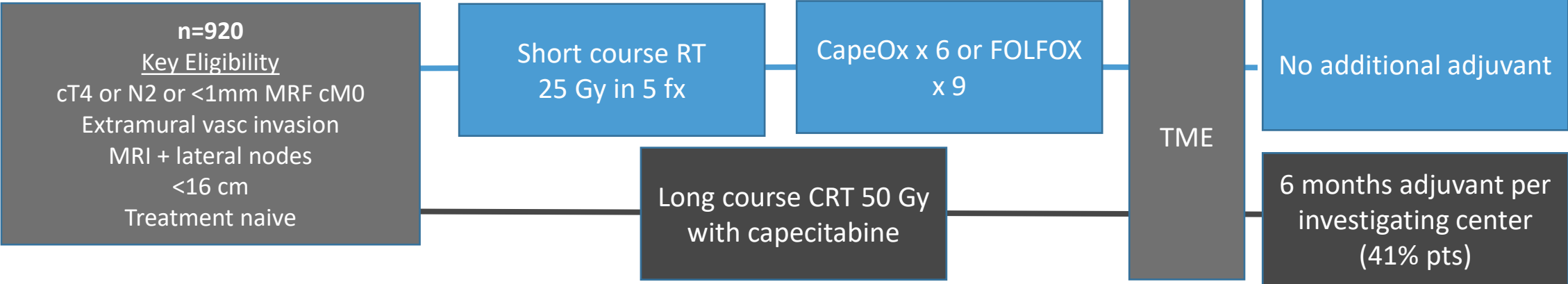
- 1) Adjuvant chemotherapy is only marginally effective
- 2) Adjuvant chemotherapy adherence is poor
- 3) Neoadjuvant chemotherapy improves downstaging

Can earlier, more consistent chemotherapy delivery decrease distant met rate and help cure more people?

RAPIDO Trial: upfront chemo may offer better oncologic outcomes

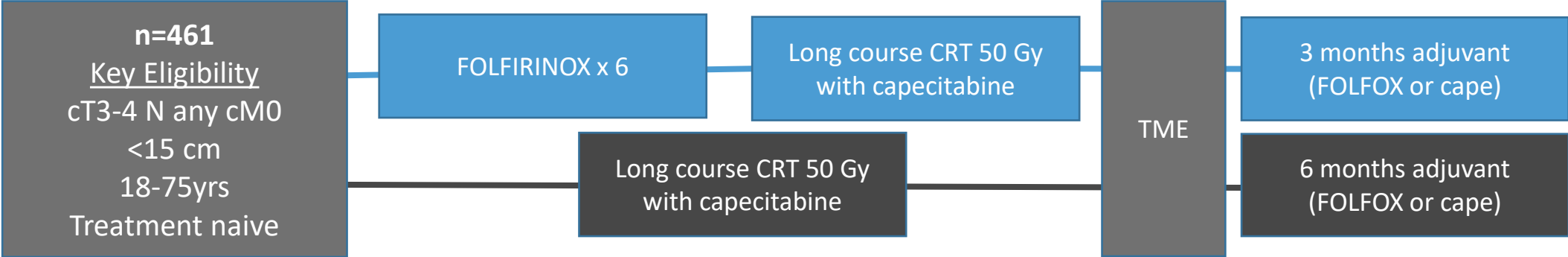


RAPIDO Trial: upfront chemo may offer better oncologic outcomes

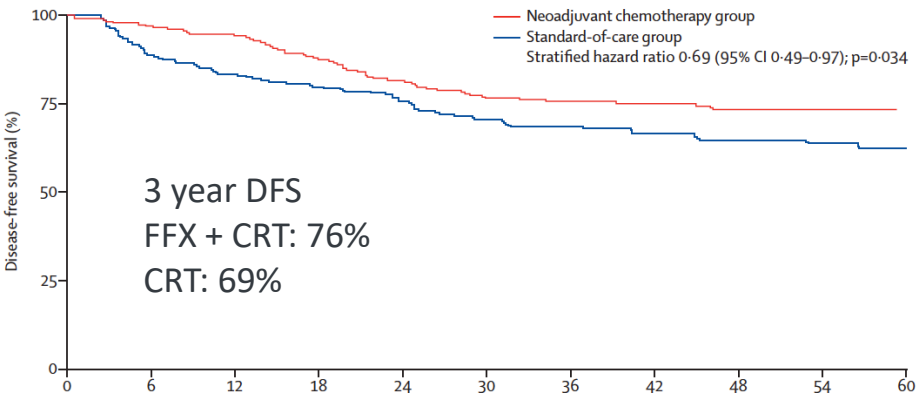
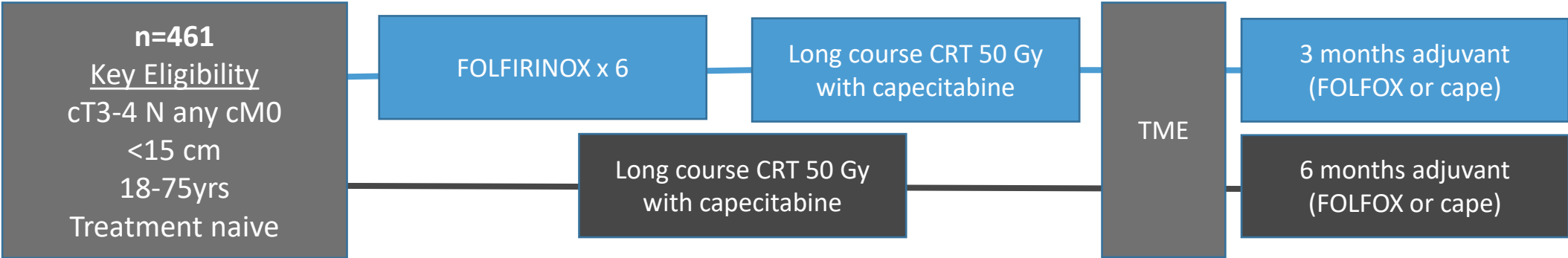


5 year Outcomes	SC + FOLFOX	Long Course CRT	
*Disease related treatment failure	28%	34%	HR 0.79, 0.63-1.00
Distant Mets	23%	30%	HR 0.73, 0.57-0.93
Local failure	12%	8%	0.07
Overall Survival	82%	80%	HR 0.91, 0.70-1.19
pCR	28%	14%	p<0.0001

UNICANCER-PRODIGE 23: Escalating chemotherapy



UNICANCER-PRODIGE 23: Escalating chemotherapy



Outcome	FFX + CRT	CRT	
DFS at 3 years	76%	69%	HR 0.69, .49-.97
OS at 3 years	91%	88%	HR 0.65, .4-1.05
Distant Met Free at 3 years	79%	72%	HR 0.64, .44-.93
Local Recur. At 3 years	4%	6%	HR 0.78, .34-1.8
pCR	28%	12%	p<0.0001

Does neoadj chemotherapy persevere function?

- **Not in the setting of trimodality therapy**
- pCR rates are improved by TNT
- No difference between rates of APR

Example Trials	APR Rate
Prodigie 23	
- LC CRT	14%
- FFX-CRT	14%
RAPIDO	
- LC CRT	40%
- SC RT--FOLFOX	35%
CAO/ARO/AIO-04	
- CRT with 5FU	24%
- CRT with ox + 5FU	25%

Bahadoer, et al Lancet Oncol 2021; 22: 29-42

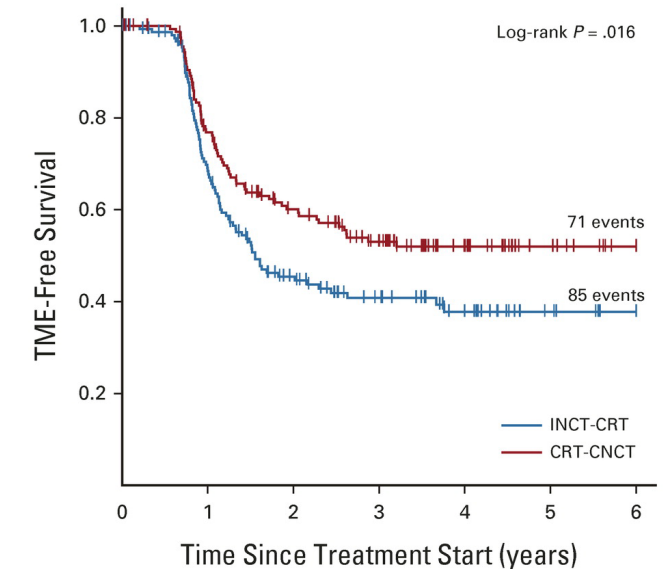
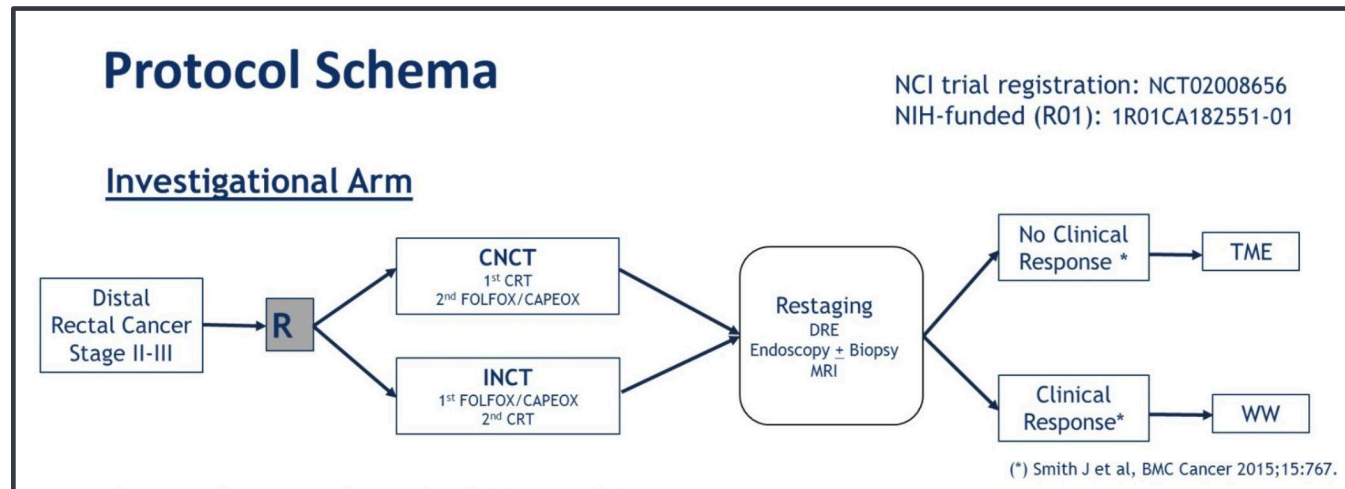
Conroy T, et al. Lancet Oncol 2021; 22(5):702-715

Garcia-Aguilar et al. Lancet Oncol 2015; 15: 957-66

Rodel C, et al. Lancet Oncol 2012; 13: 679-87

Kasi A, et al. JAMA Netw Open 2020; 3(12): e203009

What is the best order of chemotherapy + RT?



5 year Outcomes	Chemo First	Chemo Second	
DFS	72%	71%	$P=0.60$
Distant met free survival	82%	79%	$P=0.66$
Overall survival	88%	88%	$P=0.73$
TME-free survival	39%	54%	$P=0.01$

How does neoadjuvant chemotherapy help?

CURE

Prevent local recurrence
Prevent distant metastasis

- improve path CR
- Decrease distant mets and improves DFS
- ? Small differences in OS vs outback chemo

How does neoadjuvant chemotherapy help?

AVOID HARM

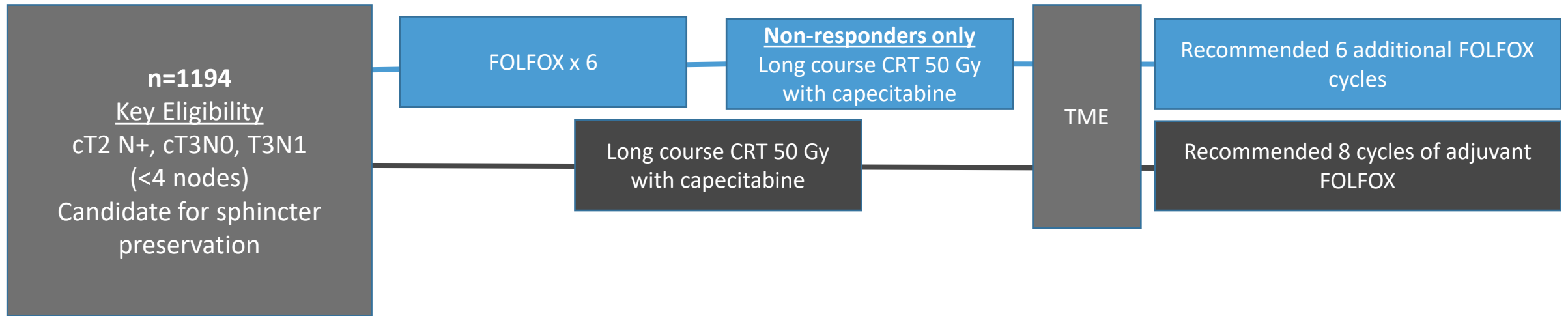
**Preserve sphincters
Preserve bowel function
Preserve sexual function**



Not on its own

Can we take advantage of chemotherapy effect on the primary to selectively avoid RT and surgery which cause these long-term complications?

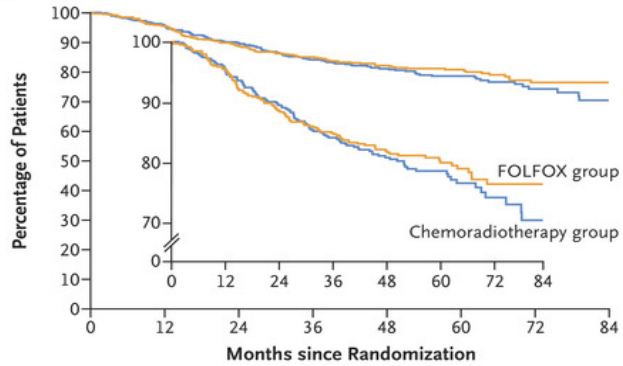
SELECTIVE RT for low/ intermediate risk rectal cancers PROSPECT TRIAL: N1048



Treatment Adherence

- 95% FOLFOX group received at least 5 neoadj cycles
- 9% of neoadj FOLFOX group received neoadjuvant RT
- 1% of neoadj FOLFOX group received adjuvant RT
- Adjuvant chemotherapy receipt:
 - 80% neoadj chemo group received adjuvant FOLFOX
 - 78% neoadj CRT group received adjuvant FOLFOX/CapeOx

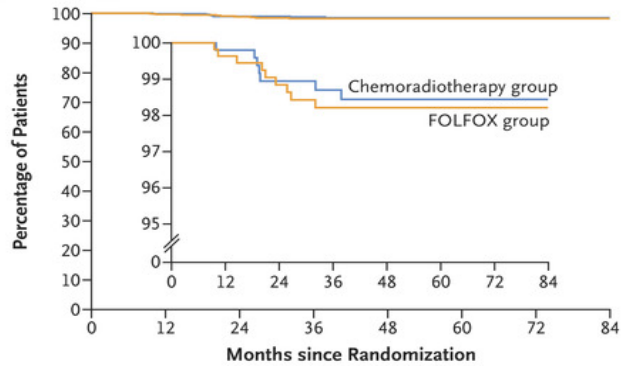
B Disease-free Survival



No. at Risk									
		0	12	24	36	48	60	72	84
FOLFOX group	585	543	489	443	342	200	97	42	
Chemoradiotherapy group	543	500	456	395	295	181	80	37	

Group	No. of Events/ Total No.	Hazard Ratio (90.2% CI)	5-Year Estimate percent	Stratified P Value for NI
FOLFOX group	114/585	0.92 (0.74–1.14)	80.8 (77.9–83.7)	0.005
Chemoradiotherapy group	113/543	Reference	78.6 (75.4–81.8)	—

D Freedom from Local Recurrence



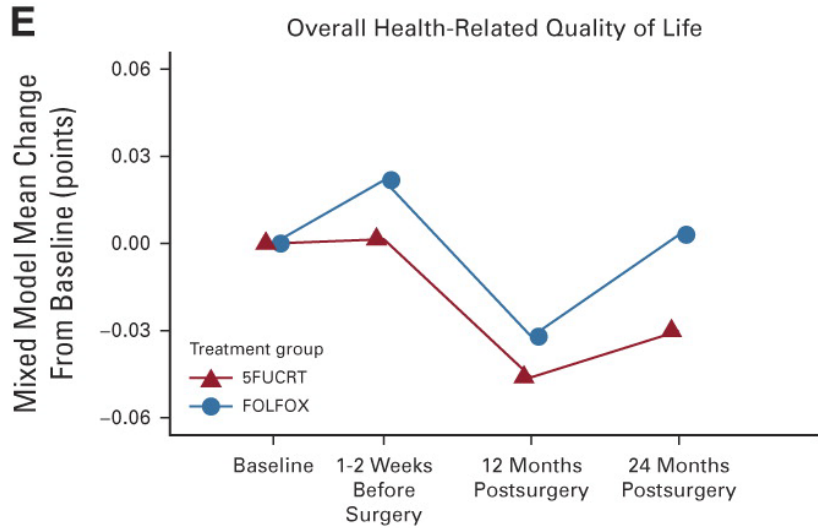
No. at Risk									
		0	12	24	36	48	60	72	84
FOLFOX group	585	542	483	438	339	195	95	39	
Chemoradiotherapy group	543	499	455	389	289	175	78	36	

Group	No. of Events/ Total No.	Hazard Ratio (95% CI)	5-Year Estimate percent
FOLFOX group	9/585	1.18 (0.44–3.16)	98.2 (97.1–99.4)
Chemoradiotherapy group	7/543	Reference	98.4 (97.3–99.6)

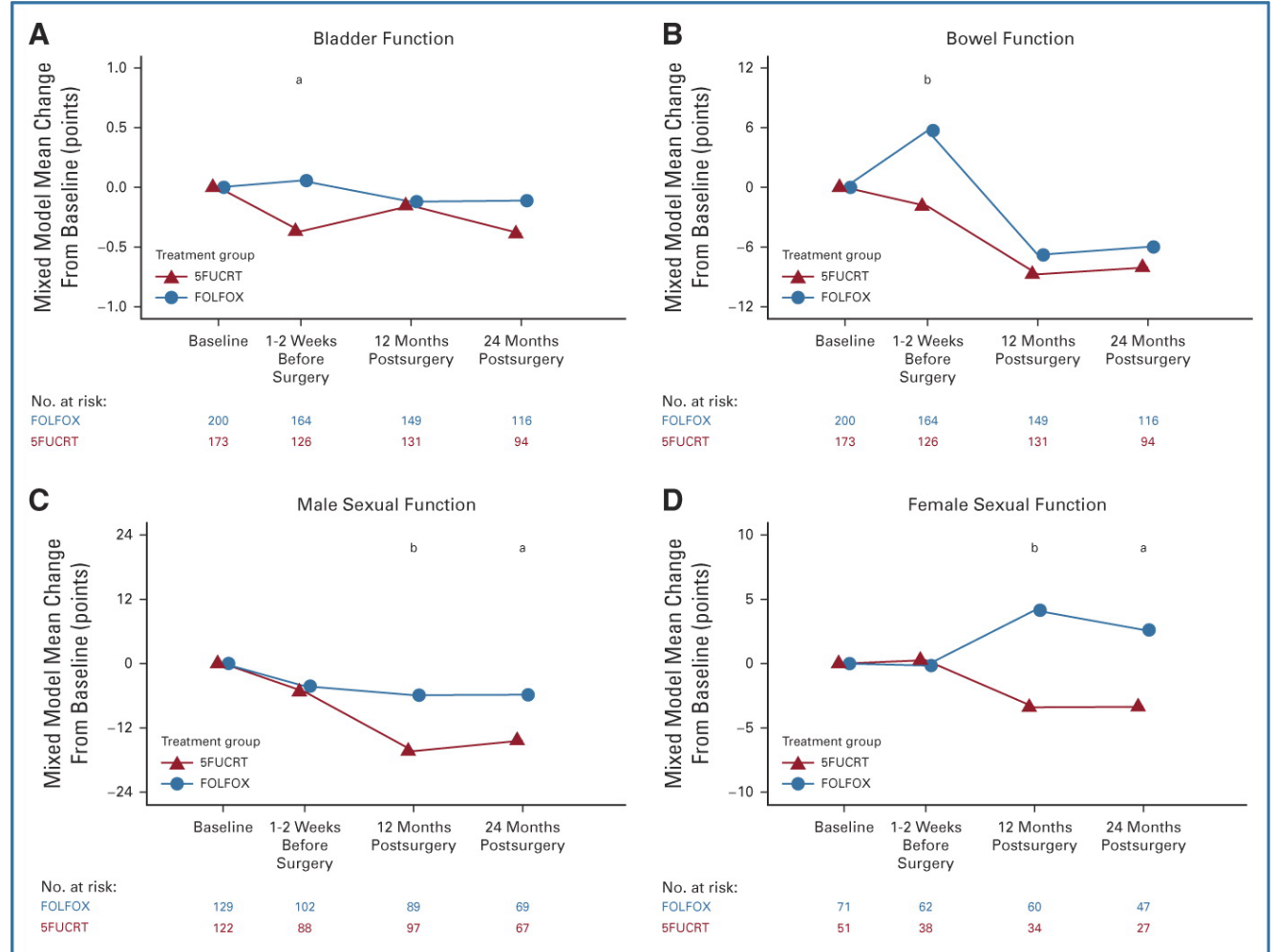
PROSPECT: Neoadj FOLFOX with selective RT is NON-INFERIOR to neoadjuvant LCRT

5 year Outcomes	FOLFOX	LCRT	HR (95% CI)
DFS	81%	79%	0.90 (0.74-1.14)
Local recurrence free	98%	98%	1.18 (0.44-3.16)
Overall survival	89%	90%	1.04 (0.74-1.44)

PROSPECT: Patient Experience Favors FOLFOX



- HRQOL better in FOLFOX + selective RT
- Sexual function better with FOLFOX
- Bowel + bladder function minimally better



How does neoadjuvant chemotherapy help?

AVOID HARM

Preserve sphincters

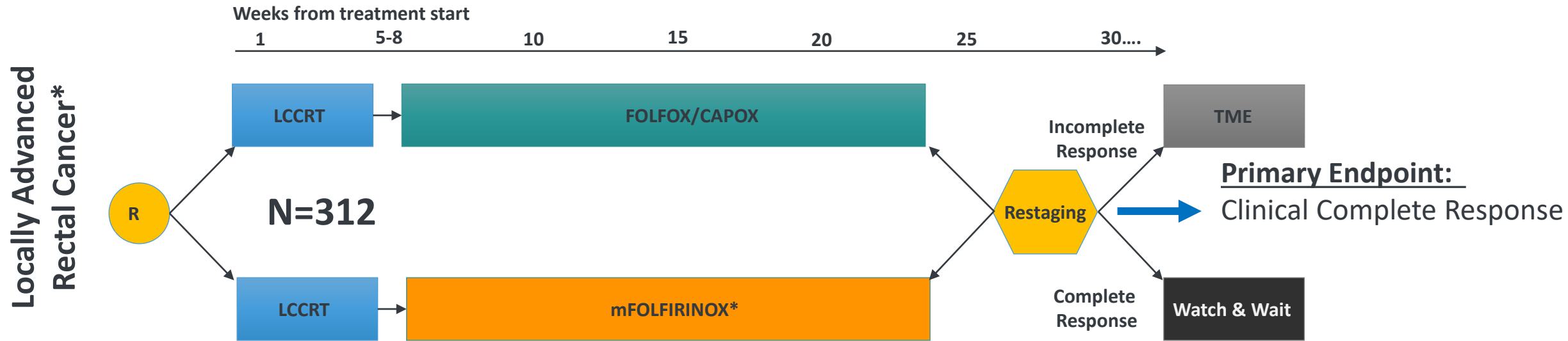
Preserve bowel function

Preserve sexual function



Selective RT: Better sexual, maybe bowel function in lower risk

SELECTIVE SURGERY AFTER TNT: A022104, JANUS TRIAL



PI:
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smithj5@mskcc.org

Schema Legend: Randomization = R; LCCRT = long-course chemoradiation; Restaging determination = endoscopy, MRI and clinical exam 8-12 weeks post-completion of assigned TNT regimen

* <=12cm, cT4N0, anyT, N+; T3N0 that would require APR or coloanal anastomosis

How does neoadjuvant chemotherapy help?

AVOID HARM

Preserve sphincters

Preserve bowel function

Preserve sexual function

- ✓ PROSPECT: Better sexual, maybe bowel function in lower risk
- ✓ NOM: sphincter preservation, better bowel function, likely better sexual function – TBD from JANUS

TNT Facilitates More Favorable Outcomes

	Local Failure	Distant failure	Permanent ostomy	GI dysfunction	Sexual dysfunction
Proctectomy	Red	Red	Red	Yellow	Yellow
TME + CRT + Chemo	Green	Yellow	Red	Red	Red
CRT + TME + Chemo	Green	Yellow	Yellow	Yellow	Red
TNT: CRT + Chemo + TME	Green	Green	Yellow	Yellow	Yellow
TNT: CRT + Chemo + NOM	Green	Green	Green	Green	Yellow
TNT: Chemo + selective CRT + TME (low-int risk only)	Green	Green	Green	Green	Green