Dana-Farber Cancer Institute | BWH BRIGHAM AND WOMEN'S HOSPITAL

DANA-FARBER/BRIGHAM AND WOMEN'S CANCER CENTER

Overview of the Management of Stage II-III Rectal Cancer

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FDA Oncologic Drugs Advisory Committee
February 9, 2023

Outline

- Background on Rectal Cancer
- Current Treatment Paradigms
- Non-Operative Management
- Future Research

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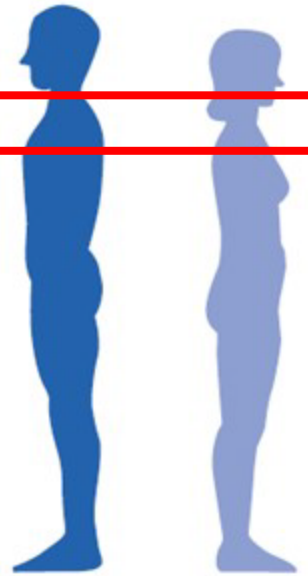
Estimated New Cancer Cases in the US in 2023

Siegel, RL. *CA: Cancer J Clin* 2023; 73: 17-48.

Male				Female			
Prostate		288,300	29%	Breast		297,790	31%
Lung & bronchus		117,550	12%	Lung & bronchus		120,790	13%
Colon & rectum	**27,440**	81,860	8%	Colon & rectum	**18,610**	71,160	8%
Urinary bladder		62,420	6%	Uterine corpus		66,200	7%
Melanoma of the skin		58,120	6%	Melanoma of the skin		39,490	4%
Kidney & renal pelvis		52,360	5%	Non-Hodgkin lymphoma		35,670	4%
Non-Hodgkin lymphoma		44,880	4%	Thyroid		31,180	3%
Oral cavity & pharynx		39,290	4%	Pancreas		30,920	3%
Leukemia		35,670	4%	Kidney & renal pelvis		29,440	3%
Pancreas		33,130	3%	Leukemia		23,940	3%
All sites		**1,010,310**		**All sites**		**948,000**	



Total estimated new cases of rectal cancer in 2023: 46,050

Microsatellite instability-high (MSI-H) accounts for 2-3% of all rectal cancer.[1-5]

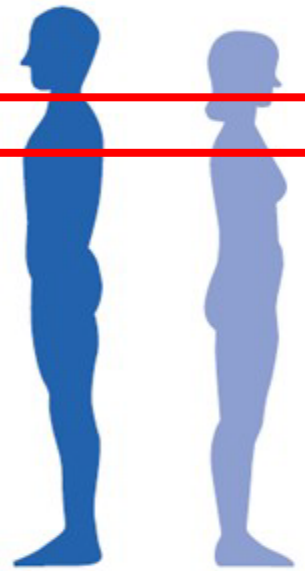
- ***Almost all are due to Lynch Syndrome***
- ***MSI-H seen in up to 10% of young-onset rectal cancers[6]***

Dana-Farber Cancer Institute

[1] Marabelli M, et al. *Dig Liver Dis* 2020; 52: 1503-11.
[2] Oh CR, et al. *Clin Colorectal Cancer* 2018; 17(4): e679-85.
[3] Samowitz WS, et al. *Cancer Causes Control* 2009; 20: 1763-68.
[4] Nilbert M, et al. *Eur J Cancer* 1999; 35(6): 942-45.
[5] Ishikubo T, et al. *Cancer Lett* 2004; 216: 55-62.
[6] Gryfe R, et al. *N Engl J Med* 2000; 342: 69-77.

Estimated Cancer Deaths in the US in 2023

Male			Female		
Lung & bronchus	67,160	21%	Lung & bronchus	59,910	21%
Prostate	34,700	11%	Breast	43,170	15%
Colon & rectum	28,470	9%	Colon & rectum	24,080	8%
Pancreas	26,620	8%	Pancreas	23,930	8%
Liver & intrahepatic bile duct	19,000	6%	Ovary	13,270	5%
Leukemia	13,900	4%	Uterine corpus	13,030	5%
Esophagus	12,920	4%	Liver & intrahepatic bile duct	10,380	4%
Urinary bladder	12,160	4%	Leukemia	9,810	3%
Non-Hodgkin lymphoma	11,780	4%	Non-Hodgkin lymphoma	8,400	3%
Brain & other nervous system	11,020	3%	Brain & other nervous system	7,970	3%
All sites	**322,080**		**All sites**	**287,740**	



Siegel, RL. *CA: Cancer J Clin* 2023; 73: 17-48.

AJCC TNM Staging Classification 8th Ed. (2017)

T	**Primary Tumor**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*: intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosae)
T1	Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)
T2	Tumor invades the muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues
T4	Tumor invades* the visceral peritoneum or invades or adheres** to adjacent organ or structure
T4a	Tumor invades* through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum)
T4b	Tumor directly invades* or adheres** to adjacent organs or structures

N	**Regional Lymph Nodes**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One to three regional lymph nodes are positive (tumor in lymph nodes measuring ≥0.2 mm), or any number of tumor deposits are present and all identifiable lymph nodes are negative
N1a	One regional lymph node is positive
N1b	Two or three regional lymph nodes are positive
N1c	No regional lymph nodes are positive, but there are tumor deposits in the subserosa, mesentery, or nonperitonealized pericolic, or perirectal/mesorectal tissues
N2	Four or more regional lymph nodes are positive
N2a	Four to six regional lymph nodes are positive
N2b	Seven or more regional lymph nodes are positive

M	**Distant Metastasis**
M0	No distant metastasis by imaging, etc.; no evidence of tumor in distant sites or organs. (This category is not assigned by pathologists)
M1	Metastasis to one or more distant sites or organs or peritoneal metastasis is identified
M1a	Metastasis to one site or organ is identified without peritoneal metastasis
M1b	Metastasis to two or more sites or organs is identified without peritoneal metastasis
M1c	Metastasis to the peritoneal surface is identified alone or with other site or organ metastases

Staging Studies

- MRI pelvis
  - Determine T and N stage, circumferential resection margin (CRM) status
  - Endorectal ultrasound if MRI contraindicated
- CT chest, abdomen
  - Determine M stage
- CEA tumor marker
- Mismatch repair (MMR) testing
- Multidisciplinary team evaluation
  - Medical oncology
  - Radiation oncology
  - Colorectal surgery
  - Radiologist

	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1, T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage IIIA	T1-T2	N1/N1c	M0
	T1	N2a	M0
Stage IIIB	T3-T4a	N1/N1c	M0
	T2-T3	N2a	M0
	T1-T2	N2b	M0
Stage IIIC	T4a	N2a	M0
	T3-T4a	N2b	M0
	T4b	N1-N2	M0
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b
Stage IVC	Any T	Any N	M1c

NCCN National Comprehensive Cancer Network®

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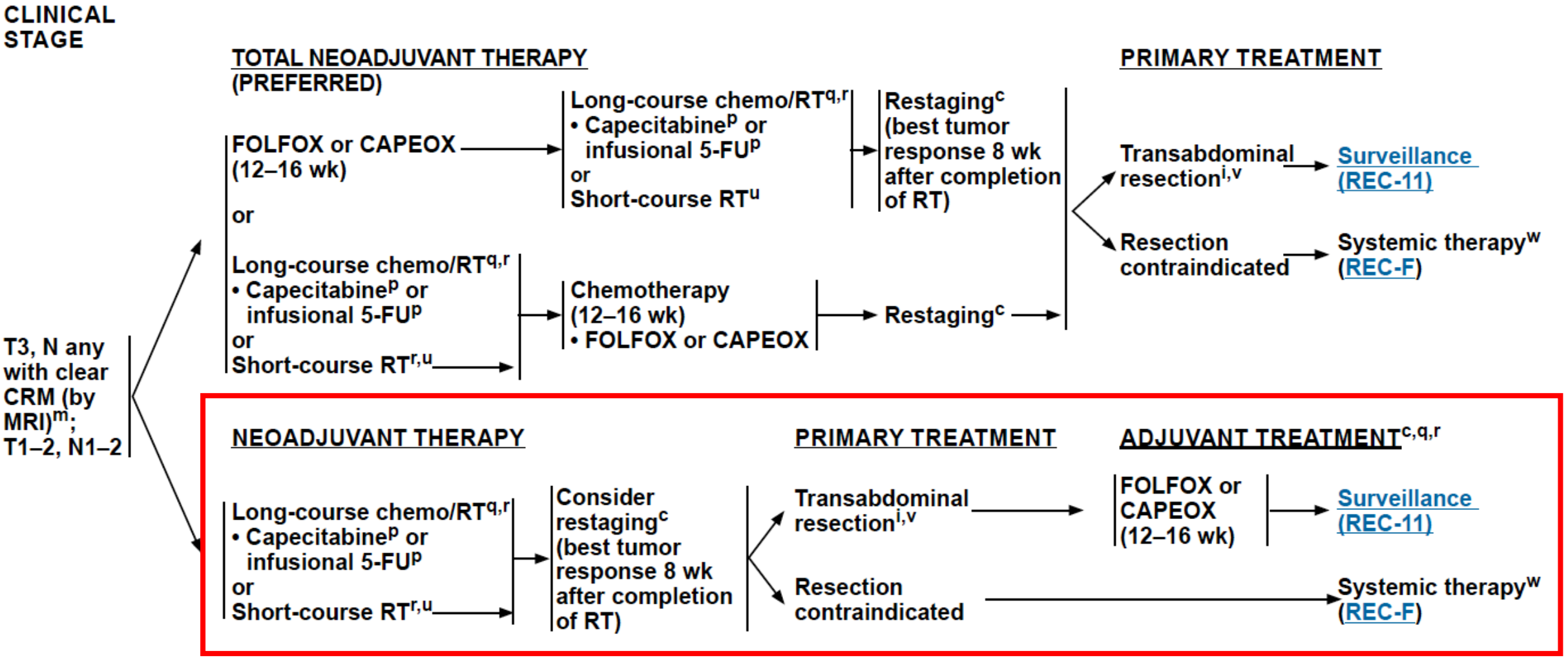
- Background on Rectal Cancer
- ***Current Treatment Paradigms***
- Non-Operative Management
- Future Research

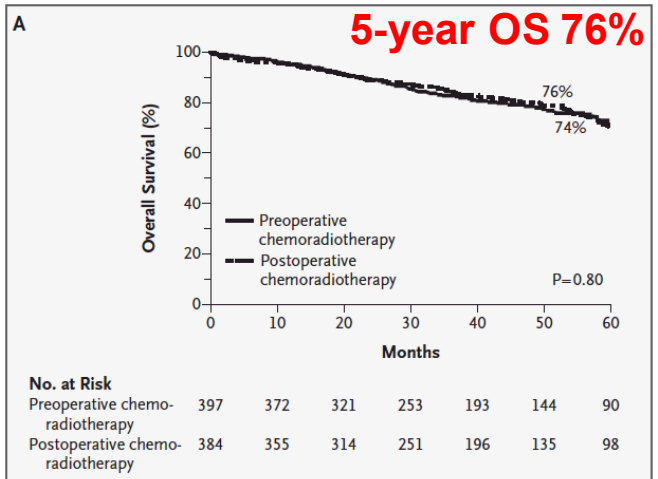
NCCN Guidelines for Rectal Cancer (v4.2022)



The Historical Standard of Care (SOC): German Rectal Cancer Study Group Trial

PRIMARY ENDPOINT

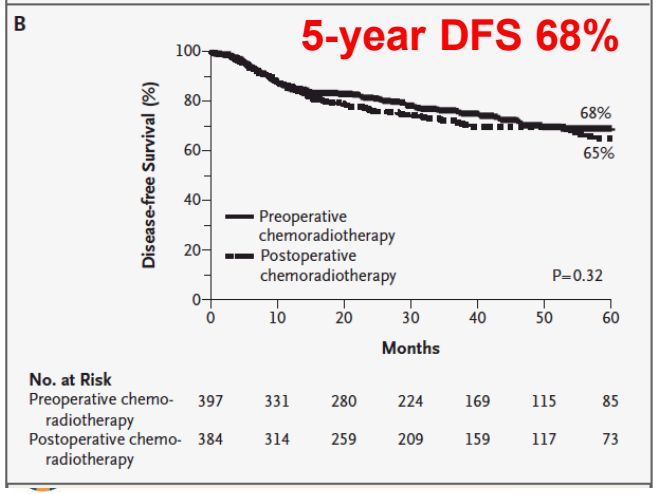
5-year OS 76%



No. at Risk

Preoperative chemoradiotherapy	397	372	321	253	193	144	90
Postoperative chemoradiotherapy	384	355	314	251	196	135	98

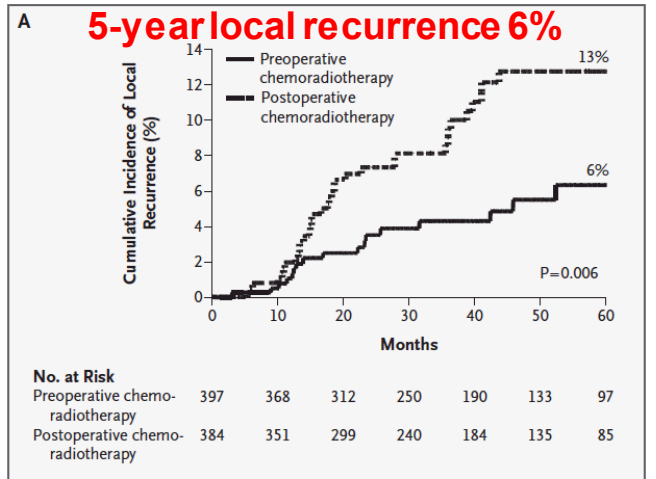
5-year DFS 68%



No. at Risk

Preoperative chemoradiotherapy	397	331	280	224	169	115	85
Postoperative chemoradiotherapy	384	314	259	209	159	117	73

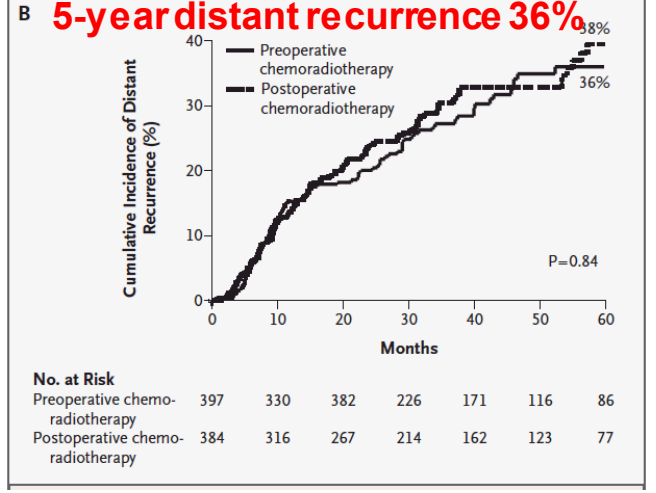
5-year local recurrence 6%



No. at Risk

Preoperative chemoradiotherapy	397	368	312	250	190	133	97
Postoperative chemoradiotherapy	384	351	299	240	184	135	85

5-year distant recurrence 36%



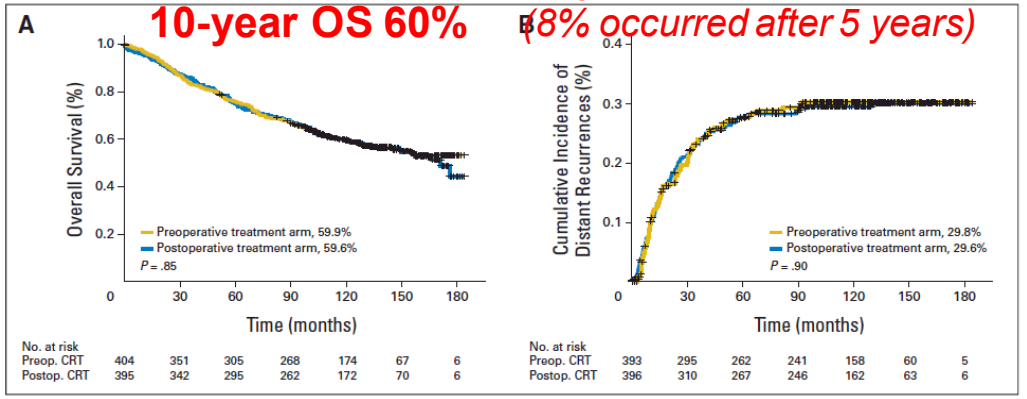
No. at Risk

Preoperative chemoradiotherapy	397	330	382	226	171	116	86
Postoperative chemoradiotherapy	384	316	267	214	162	123	77

Sauer R, et al. *N Engl J Med* 2004: 351: 1731-40.

10-year DFS 68%
10-year OS 60%

10-year distant recurrence 30% *(8% occurred after 5 years)*



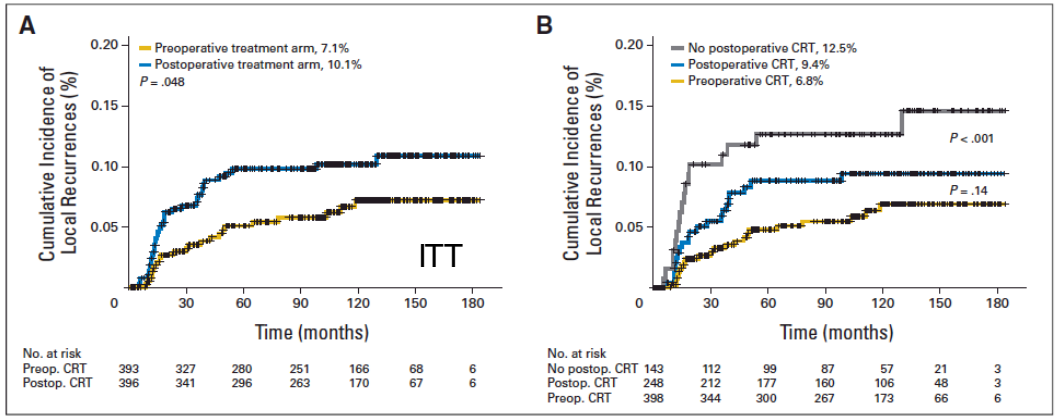
No. at risk

Preop. CRT	404	351	305	268	174	67	6
Postop. CRT	395	342	295	262	172	70	6

No. at risk

Preop. CRT	393	295	262	241	158	60	5
Postop. CRT	396	310	267	246	162	63	6

10-year local recurrence 7% *(12% occurred after 5 years)*



No. at risk

Preop. CRT	393	327	280	251	166	68	6
Postop. CRT	396	341	296	263	170	67	6

No. at risk

No postop. CRT	143	112	99	87	57	21	3
Postop. CRT	248	212	177	160	106	48	3
Preop. CRT	398	344	300	267	173	66	6

Sauer R, et al. *J Clin Oncol* 2012.

Emergence of Total Neoadjuvant Therapy (TNT)

- Improved tolerance and completion of chemotherapy
- Higher rates of downstaging, facilitating R0 resection
- Higher rates of pathologic complete response
- Potential for non-operative management
- Minimizes length of time with ileostomy
- Addresses micrometastases with earlier use of systemic chemotherapy

Selected Phase II-III Trials of TNT vs. SOC

TRIAL	PATIENTS	TNT	SOC	MEDIAN F/U TIME (YEARS)	3-YEAR DFS (%)	3-YEAR OS (%)	PATH CR (%)	3-YEAR LOCO-REGIONAL RELAPSE (%)	3-YEAR DISTANT METASTASIS (%)
Spanish GCR-3 (n=108)[a]	T3-4 or N+, middle 1/3 or distal	Chemo→LCRT→TME	LCRT→TME→chemo	5.8	TNT: 62* SOC: 64* *P*=0.85	TNT: 75* SOC: 78* *P*=0.64	TNT: 14 SOC: 13 --	TNT: 5* SOC: 2* *P*=0.61	TNT: 23%* SOC: 21%* *P*=0.79
POLISH II (n=515)[b]	Fixed T3 or T4	SCRT→chemo→TME→(chemo)	LCRT/FLOX→TME→(chemo)	3	TNT: 53 SOC: 52 *P*=0.85	TNT: 73 SOC: 65 *P*=0.05	TNT: 16 SOC: 12 *P*=0.17	TNT: 22 SOC: 21 *P*=0.82	TNT: 30 SOC: 27 *P*=0.25
RAPIDO (n=912)[c]	T4N2,other high-risk	SCRT→chemo→TME	LCRT→TME→(chemo)	3	TNT: 24** SOC: 30** *P*=0.02	TNT: 89 SOC: 89 *P*=0.59	TNT: 28 SOC: 14 *P*<0.001	TNT: 9 SOC: 6 *P*=0.09	TNT: 20 SOC: 27 *P*=0.005
PRODIGE 23 (n=461)[d]	T3-4	FOLFIRINOX→LCRT→TME→FOLFOX	LCRT→TME→chemo	3	TNT: 76 SOC: 69 *P*=0.03	TNT: 91 SOC: 88 *P*=0.08	TNT: 28 SOC: 12 *P*<0.001	TNT: 4 SOC: 6 *P*=0.56	TNT: 17 SOC: 25 --
STELLAR (n=599)[e]	T3-4 or N+, middle 1/3 or distal	SCRT→chemo→TME→chemo	LCRT→TME→chemo	3	TNT: 65 SOC: 62 *P*=0.88***	TNT: 87 SOC: 75 *P*=0.03	TNT: 22# SOC: 12 *P*=0.002	TNT: 8 SOC: 11 *P*=0.46	TNT: 23 SOC: 25 *P*=0.48

* 5-year outcome
** Disease-related treatment failure
*** Non-inferiority
# Includes sustained cCR

[a] Gernandez-Martos C, et al. *Ann Oncol* 2015; 26: 1722-28.
[b] Bujko K, et al. *Ann Oncol* 2016; 27: 834-42.
[c] Bahadoer RR, et al. *Lancet Oncol* 2021; 22: 29-42.
[d] Conroy T, et al. *Lancet Oncol* 2021; 22: 702-15.
[e] Jin J, et al. *J Clin Oncol* 2022; 40: 1681-92.

TNT=total neoadjuvant therapy; SOC=standard of care; LCRT=long-course chemoradiation; TME=total mesorectal excision; SCRT=short-course radiation therapy; F/U=follow-up; DFS=disease-free survival; OS=overall survival; CR=complete response.

Summary of TNT Data to Date

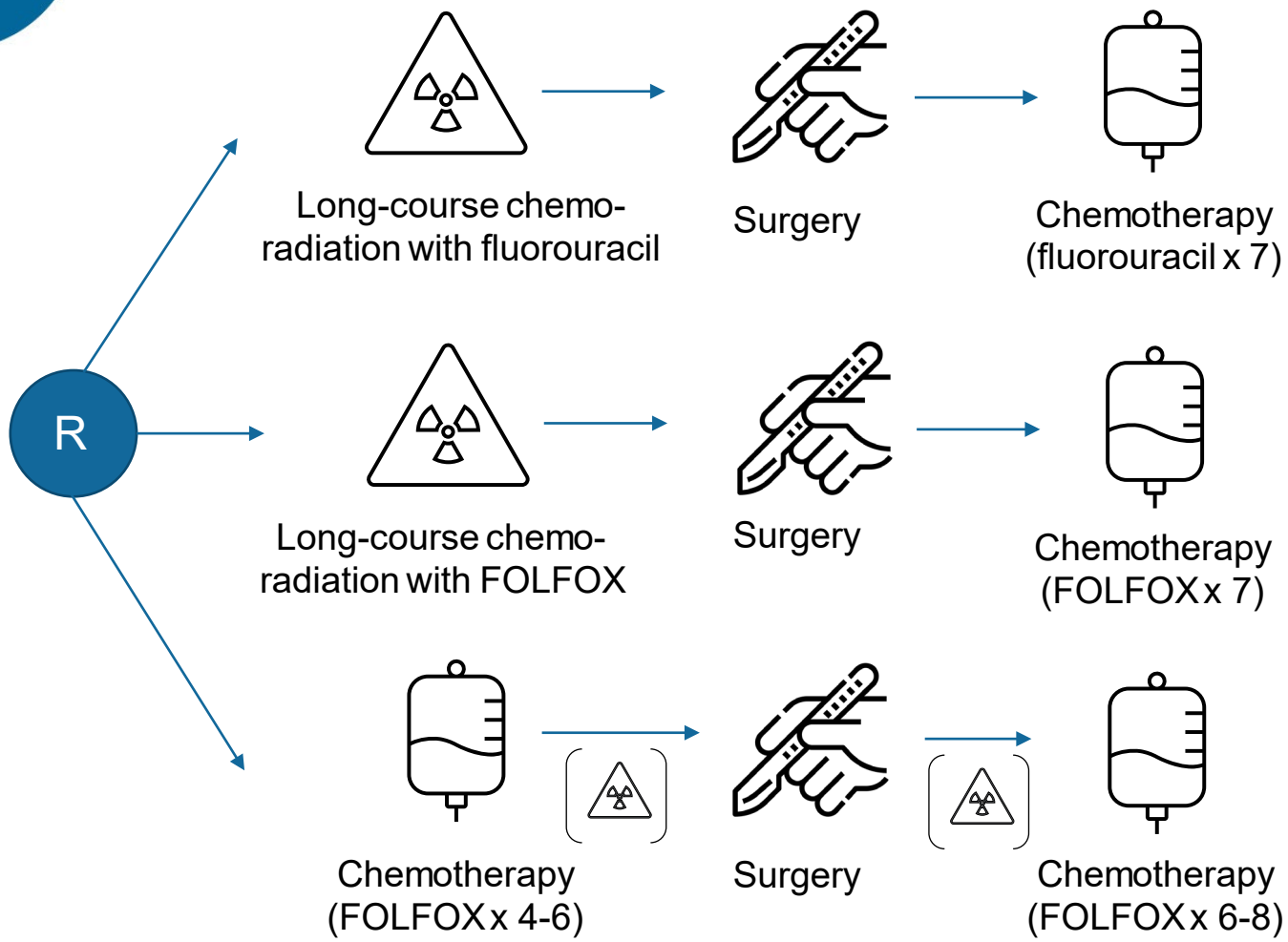
- Benefits:
  - Higher pathologic CR rates
  - Better compliance with treatment
  - Improved DFS in some studies
- Disadvantages:
  - May result in over-treatment
  - No difference in sphincter-sparing surgery and ileostomy rate
  - No OS benefit
- Insufficient data to conclude superiority over SOC
  - No difference in locoregional failure, inconclusive data on 3-year DFS
  - No long-term DFS or OS data
  - Heterogeneous populations, treatments, and endpoints included in trials
  - No known biomarkers to improve patient selection

Shi DD and Mamon HJ. *J Clin Oncol* 2020.
Kasi A, et al. *JAMA Network Open* 2020; 3(12).

Treatment for Rectal Cancer is Toxic

- Bowel dysfunction
- Urinary dysfunction
- Sexual dysfunction
- Infertility
- Permanent ostomy
- Body image issues

Can Radiation Be Eliminated?



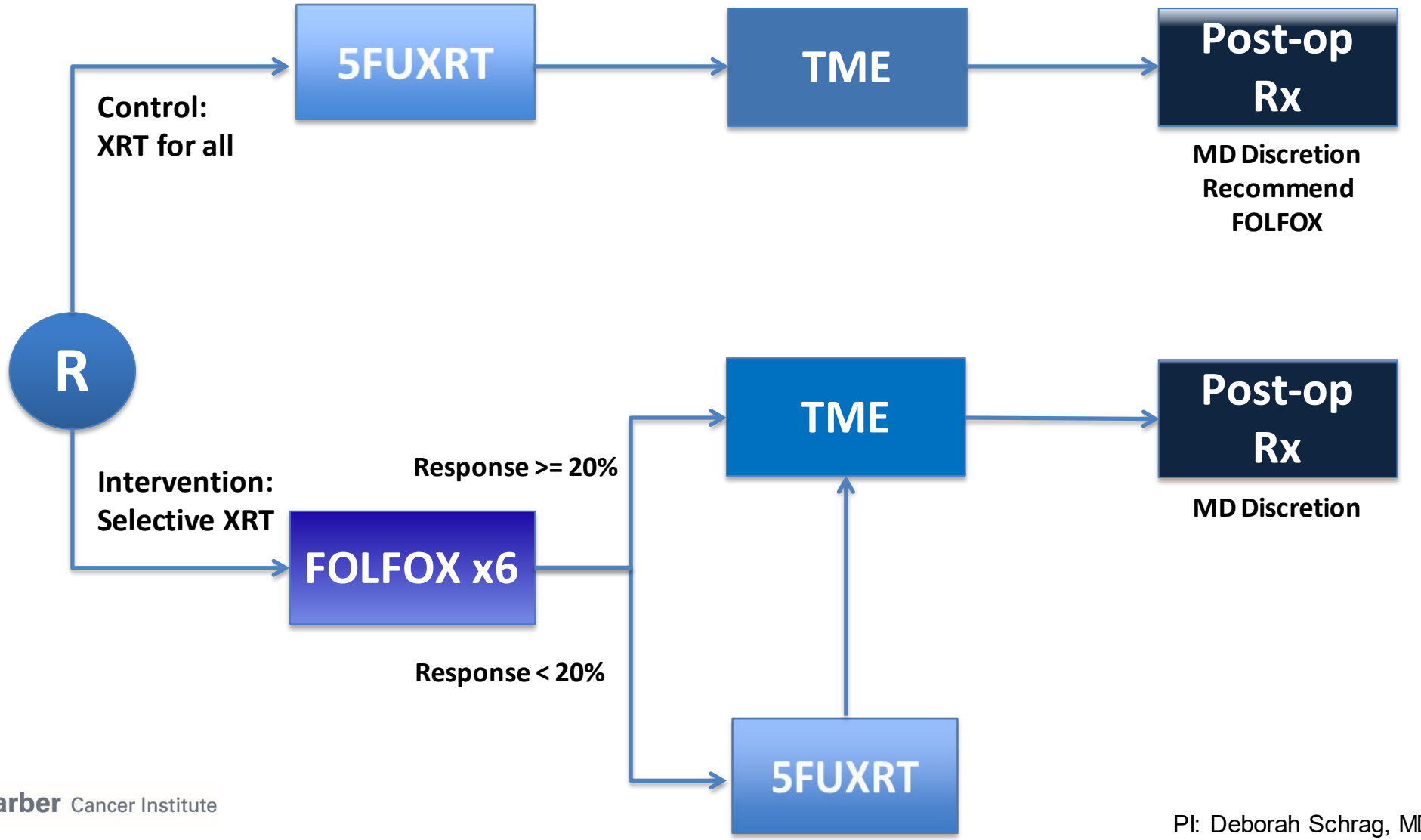
FOWARC TRIAL

FOWARC (N=495)	CHEMO	CRT	SOC	P VALUE
Eligibility criteria	T3-4 and/or N+			--
Median follow-up time	45.2 months			--
3-year DFS (%)*	73.5	77.2	72.9	0.71
Path CR rate (%)	6.5	27.5	14.0	
3-year locoregional relapse (%)	8.3	7.0	8.0	0.87
3-year OS (%)	90.7	89.1	91.3	0.97

* Primary endpoint

Deng Y, et al. *J Clin Oncol* 2019; 37: 3223-33.

PROSPECT N1048:
Phase II/III Trial of Selective Preoperative Radiation



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International Watch and Wait Database (IWWD)

- International multi-center observational registry study
- Heterogeneous study population (cT1-4 N0-2)
- Non-uniform staging and response assessment methods
- Variable treatment strategies

IWWD (N=880)	
Eligibility criteria	Avoided TME and had cCR
Median follow-up time	3.3 years
2-year tumor regrowth rate (%)*	25.2
5-year disease-specific survival (%)	93.8
3-year distant metastases (%)	8.1
5-year OS (%)	84.7
Timepoint of response assessment (from treatment start)	Not available

* Primary endpoint

- 64% diagnosed within 1 year
- 88% within 2 years
- 18% also had distant metastases
- 78% received TME, 22% local excision

- 11% diagnosed within 1 year
- 54% within 2 years
- 75% within 3 years

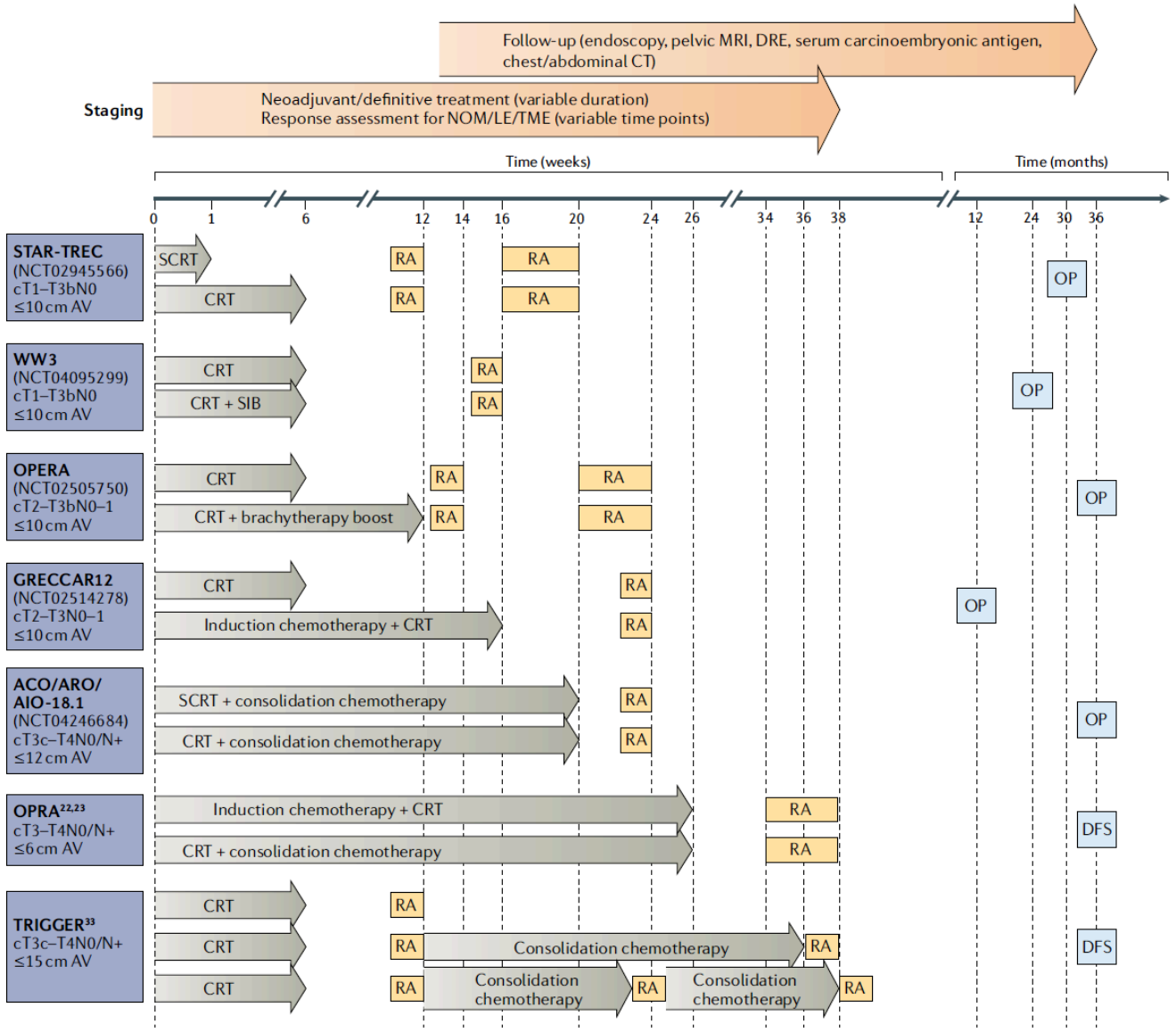
van der Valk MJM, et al. *Lancet* 2018; 391: 2537-45.

Selected Randomized Trials of NOM (T3-4 N0-2)

Study details[a,b]	Disease stage and other clinical features	Treatment schedule	RA time point	Primary end point
ACO/ARO/AIO-18.1, phase III (NCT04246684) $n=702$	cT3c–T4N0–2, ≤12 cm AV	SCRT followed by consolidation FOLFOX and TME surgery (or NOM for patients with a cCR) vs CRT followed by consolidation FOLFOX and TME (or NOM for patients with a cCR)	24 weeks after treatment start	3-year organ preservation
OPRA[22,23], phase II $n=300$	cT3–T4N0–2, ≤6 cm AV	Induction mFOLFOX6 followed by CRT and surgery or NOM vs CRT followed by consolidation mFOLFOX6 and surgery or NOM	34–38 weeks after treatment start	3-year DFS
TRIGGER[33], phase II/III $n=90$	cT3c–T4N0–2, ≤15 cm AV	CRT followed by surgery and adjuvant CAPOX or FOLFOX vs CRT followed by either NOM (mrTRG I–II) or CAPOX or FOLFOX (mrTRG III–IV) and restaging with subsequent NOM or surgery (depending on mrTRG at restaging)	12, 24 and 36–38 weeks after treatment start	Recruitment rate (phase II); 3-year DFS (phase III)
Brazilian[c], phase III (NCT02052921) $n=150$	cT3–T4N0–2, ≤10 cm AV	CRT followed by watch-and-wait vs 5-FU-containing CRT followed by TME after a cCR at 12 weeks post-CRT	12 weeks after treatment start	3-year DFS
TESS, phase II, (NCT03840239) $n=168$	cT3–4aN0–2, ≤5 cm AV	Induction CAPOX followed by CRT vs CRT (NOM for patients with a cCR; LE or TEM for patients with a PR; TME for patients with a poor response)	20–24 weeks after treatment start	Sphincter preservation (absence of a stoma) at 18 months

Fokas E, et al. *Nature Rev Clin Oncol* 2021; 18: 805-16.

Variability in Endpoints and Time of Response Assessment



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OPRA[22,23], phase II $n=300$	cT3–T4N0–2, ≤6 cm AV	Induction mFOLFOX6 followed by CRT and surgery or NOM vs CRT followed by consolidation mFOLFOX6 and surgery or NOM	34–38 weeks after treatment start	3-year DFS
TRIGGER[33], phase II/III $n=90$	cT3c–T4N0–2, ≤15 cm AV	CRT followed by surgery and adjuvant CAPOX or FOLFOX vs CRT followed by either NOM (mrTRG I–II) or CAPOX or FOLFOX (mrTRG III–IV) and restaging with subsequent NOM or surgery (depending on mrTRG at restaging)	12, 24 and 36–38 weeks after treatment start	Recruitment rate (phase II); 3-year DFS (phase III)
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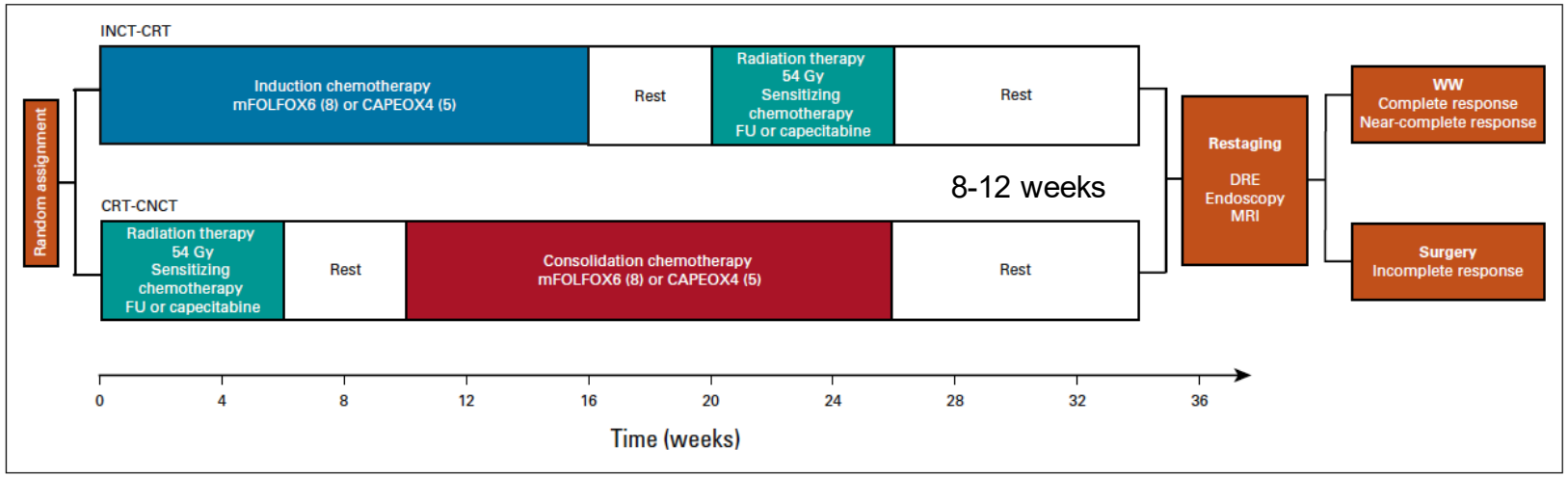
OPRA Phase II Randomized Trial



Comparison to historical control 3-year DFS of 75%

OPRA (N=324)	CNCT	INCT
Eligibility criteria	T3-4 and/or N+, ≤6 cm	
Median follow-up time	3 years	
3-year DFS (%)*	76	76
Local recurrence-free survival (%)**	94	94
Distant metastasis-free survival (%)	82	84
3-year OS (%)	(>90)	(>90)
Timepoint of response assessment (from treatment start)	34-38 weeks	
Clinical CR (%)	76	74
Tumor regrowth (%)	28	40
3-year organ preservation rate (%)	53	41
3-year TME-free survival (%)	60	47

→ *Negative study*

Outcomes comparable to TNT trials

First benchmark data from prospective RCT on clinical CR (cCR) and organ preservation rates with TNT

* Primary endpoint: Time from random assignment to locoregional failure, distant metastasis, new invasive colorectal primary cancer, or death.

** Locoregional failure: Unresectable rectal primary after TNT, R2 resection, or recurrence in primary tumor bed after R0-R1 resection.

Garcia-Aguilar J, et al. *J Clin Oncol* 2022.

MSKCC Regression Schema* & Surveillance Strategy

	Complete Response	Near Complete Response	Incomplete Response
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	Only dark T2 signal, no intermediate T2 signal	Mostly dark T2 signal, some remaining intermediate signal	More intermediate than dark T2 signal, no T2 scar
	AND	AND/OR	AND/OR
	No visible lymph nodes	Partial regression of lymph nodes	No regression of lymph nodes
MRI-DW	No visible tumor on B800-B1000 signal	Significant regression of signal on B800-B1000	Insignificant regression of signal on B800-B1000
	AND/OR	AND/OR	AND/OR
	Lack of or low signal on ADC map Uniform, linear signal in wall above tumor is ok	Minimal or low residual signal on ADC map	Obvious low signal on ADC map

** Assessed at 8-12 weeks post-TNT*

Smith JJ, et al. *BMC Cancer* 2015; 15: 767.

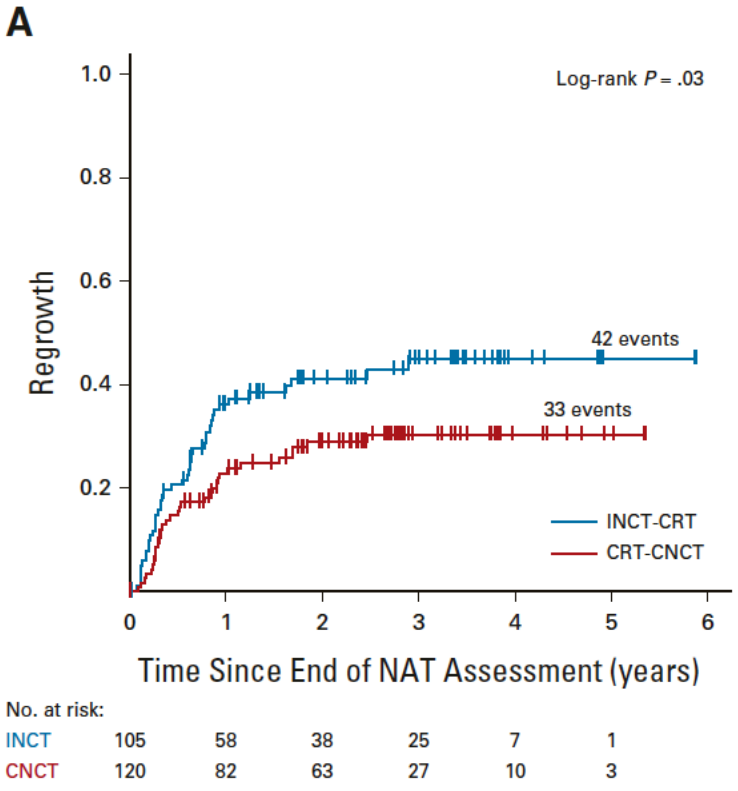
	Y 1	Y 2	Y 3-5	>Y 5
Endoscopy	q 4 mo	q 4 mo	q 6 mo	q 12 mo
DRE	q 4 mo	q 4 mo	q 6 mo	q 12 mo
MRI	q 6 mo	q 6 mo	q 12 mo	NA
CT imaging	q 12 mo	q 12 mo	q 12 mo	q 12 mo
CEA	q 4 mo	q 4 mo	q 6-12 mo	q 12 mo

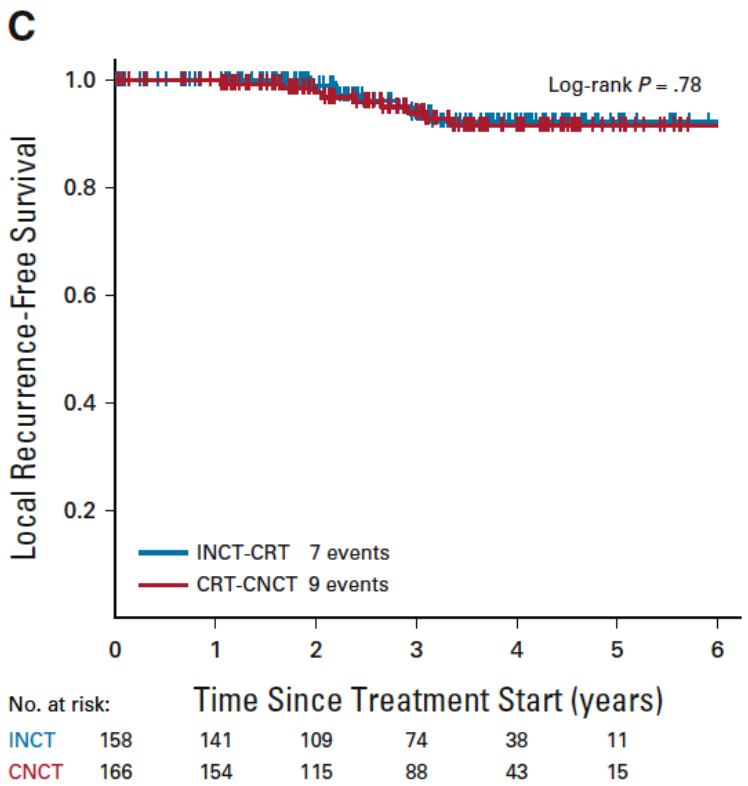
Smith JJ, et al. *JAMA Surg* 2020; 155(7): 657-8.

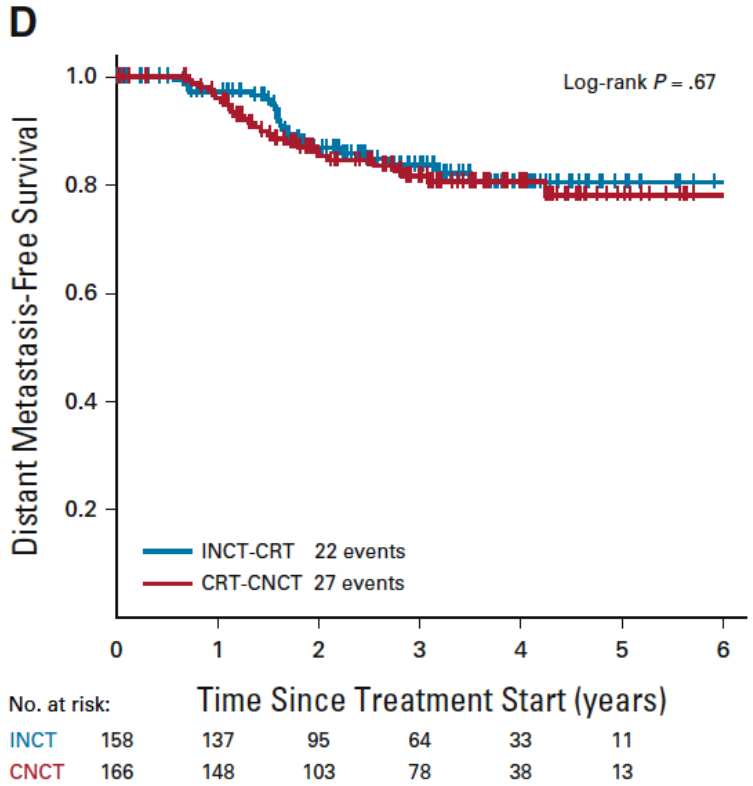
Dana-Farber Cancer Institute

OPRA: Tumor Regrowth and Recurrence Rates

Majority of tumor regrowths and local recurrences occurred within 2-3 years of completing TNT.

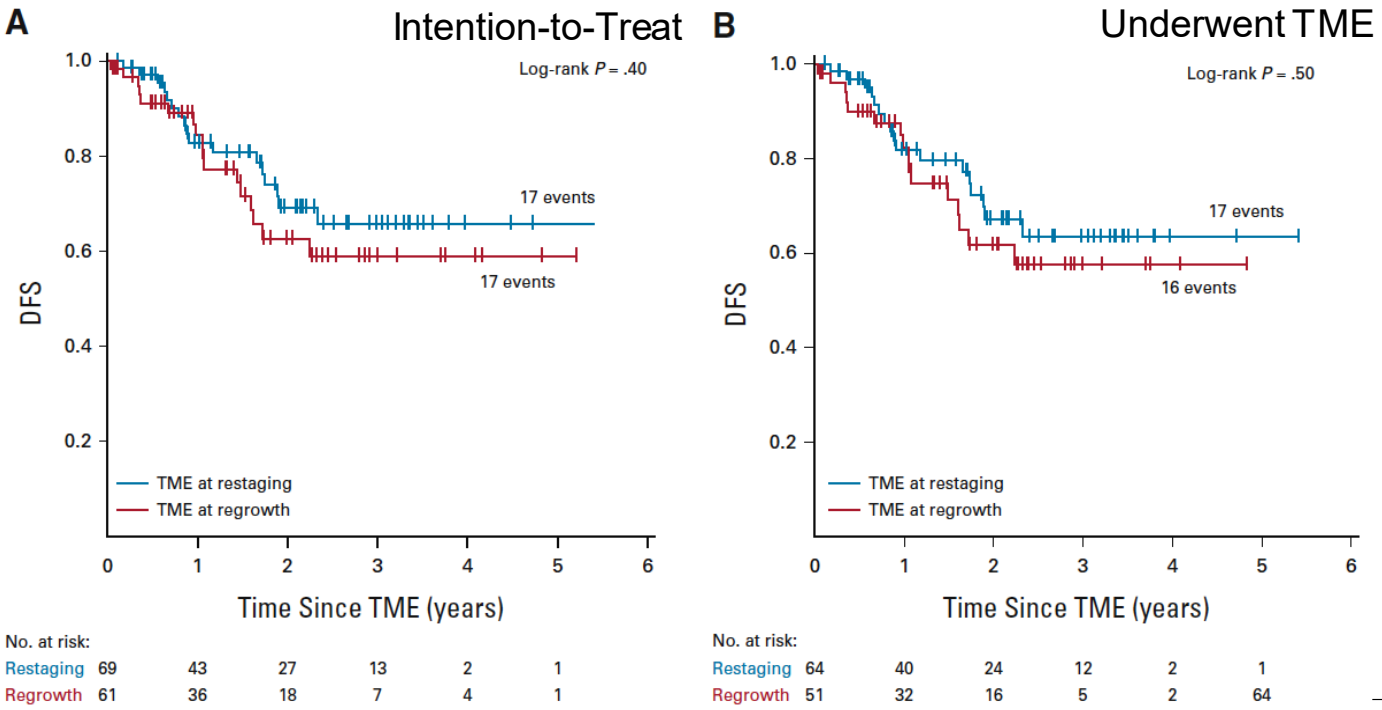






Garcia-Aguilar J, et al. *J Clin Oncol* 2022.

OPRA: DFS for TME after Restaging vs. Tumor Regrowth



	Actual TME Timing (n = 133)			
	TME Recommended at Restaging (n = 71)		TME Recommended After Local Regrowth (n = 62)	
Recurrence Type	INCT-CRT (n = 38), No. (%)	CRT-CNCT (n = 33), No. (%)	INCT-CRT (n = 35), No. (%)	CRT-CNCT (n = 27), No. (%)
Local recurrence, n = 16	3 (7.9)	4 (12.1)	4 (11.4)	5 (18.5)
Distant recurrence, n = 32	7 (18.4)	8 (24.2)	6 (17.1)	5 (18.5)
Both distant and local recurrence, n = 9[a]	0	3 (9)	3 (8.6)	3 (11.1)
TME Type				
APR, n = 67	16 (42.1)	16 (48.5)	20 (57.1)	15 (55.6)
LAR, n = 66	22 (57.9)	17 (51.2)	15 (42.9)	12 (44.4)

Garcia-Aguilar J, et al. *J Clin Oncol* 2022.

Dossa F, et al. *Lancet Gastroenterol Hepatol* 2017; 2: 501-13.

Outcomes of W&W Compared to Patients Undergoing Surgery with Pathologic CR

A Non-regrowth recurrence for patients treated by W&W *vs* surgery with pCR

	W&W		Surgery with pCR		Weight (%)	Risk ratio IV, random (95% CI)
	Events	Total	Events	Total		
Araujo et al (2015)[39]	7	42	7	69	56·8	1·64 (0·62–4·35)
Smith et al (2012)[58]	3	32	3	57	22·8	1·78 (0·38–8·31)
Gossedge et al (2012)[43]	1	15	1	13	7·6	0·87 (0·06–12·52)
Smith et al (2015)[60]	1	18	1	30	7·4	1·67 (0·11–25·03)
Maas et al (2011)[50]	0	21	1	20	5·5	0·33 (0·01–7·75)
Total	**12**	**128**	**13**	**189**	**100·0**	**1·46 (0·70–3·05)**

Heterogeneity: τ^2=0·00; χ^2=1·12, DF=4 (p=0·89); I^2=0%

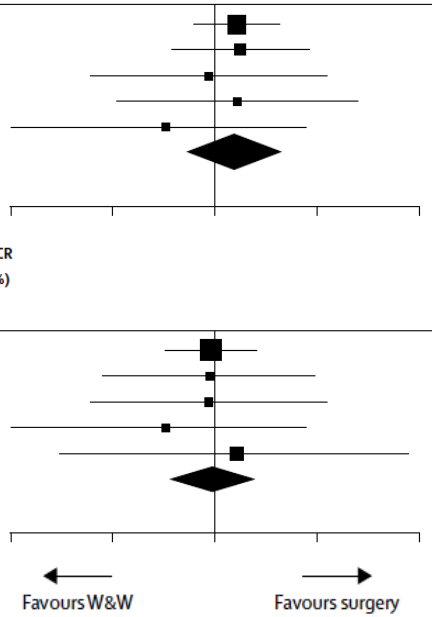
Test for overall effect: Z=1·01, p=0·31

B Cancer-specific mortality for patients treated by W&W *vs* surgery with pCR

	W&W		Surgery with pCR		Weight (%)	Risk ratio IV, random (95% CI)
	Events	Total	Events	Total		
Araujo et al (2015)[39]	5	42	9	69	66·2	0·91 (0·33–2·54)
Smith et al (2012)[58]	1	32	2	57	12·4	0·89 (0·08–9·44)
Gossedge et al (2012)[43]	1	15	1	13	9·7	0·87 (0·06–12·52)
Maas et al (2011)[50]	0	21	1	20	7·0	0·33 (0·01–7·77)
Smith et al (2015)[60]	0	18	0	30	4·6	1·63 (0·03–78·76)
Total	**7**	**128**	**13**	**189**	**100·0**	**0·87 (0·38–1·99)**

Heterogeneity: τ^2=0·00; χ^2=0·47, DF=4 (p=0·98); I^2=0%

Test for overall effect: Z=0·34, p=0·74



A Disease-free survival for patients treated by surgery with pCR *vs* W&W

	W&W		Surgery with pCR		Weight (%)	HR IV, random (95% CI)
	Events	Total	Events	Total		
Araujo et al (2015)[39]	23	42	22	69	77·4	0·47 (0·26–0·84)
Smith et al (2012)[58]	N/A	32	N/A	57	10·1	0·29 (0·06–1·43)
Maas et al (2011)[50]	1	21	4	20	5·5	1·39 (0·15–12·41)
Smith et al (2015)[60]	2	18	2	30	6·9	0·42 (0·06–2·98)
Total		**113**		**176**	**100·0**	**0·47 (0·28–0·78)**

Heterogeneity: τ^2=0·00; χ^2=1·31, DF=3 (p=0·73); I^2=0%

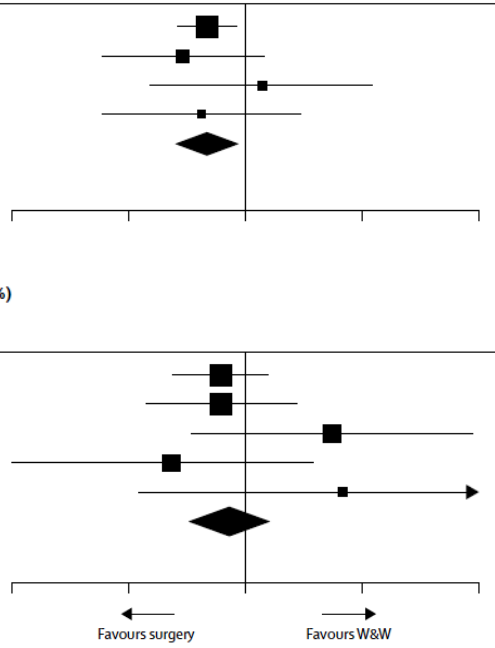
Test for overall effect: Z=2·89, p=0·004

B Overall survival for patients treated by surgery with pCR *vs* W&W

	W&W		Surgery with pCR		Weight (%)	HR IV, random (95% CI)
	Events	Total	Events	Total		
Araujo et al (2015)[39]	8	42	10	69	59·6	0·62 (0·24–1·58)
Smith et al (2012)[58]	N/A	32	N/A	57	23·5	0·61 (0·14–2·74)
Maas et al (2011)[50]	0	21	2	20	6·9	5·50 (0·34–88·03)
Gossedge et al (2012)[43]	1	15	1	13	6·8	0·23 (0·01–3·81)
Smith et al (2015)[60]	0	18	1	30	3·3	6·89 (0·12–395·98)
Total		**128**		**189**	**100·0**	**0·73 (0·35–1·51)**

Heterogeneity: τ^2=0·01; χ^2=4·03, DF=4 (p=0·40); I^2=1%

Test for overall effect: Z=0·85, p=0·40



Patients with sustained cCR should have equivalent overall survival to those undergoing surgery with pCR.

Outcomes of Patients with Clinical CR Undergoing W&W vs. Surgery

C Non-regrowth recurrence for patients treated by W&W *vs* surgery with cCR

	W&W		Surgery with cCR		Weight (%)	Risk ratio IV, random (95% CI)
	Events	Total	Events	Total		
Seshadri et al (2013)[12]	3	23	2	10	53·1	0·65 (0·13–3·32)
Li et al (2015)[48]	1	30	6	92	32·7	0·51 (0·06–4·08)
Lai et al (2016)[11]	0	18	1	26	14·2	0·49 (0·02–11·43)
Total	**4**	**71**	**9**	**128**	**100·0**	**0·58 (0·18–1·90)**

Heterogeneity: τ^2=0·00; χ^2=0·04, DF=2 (p=0·98); I^2=0%

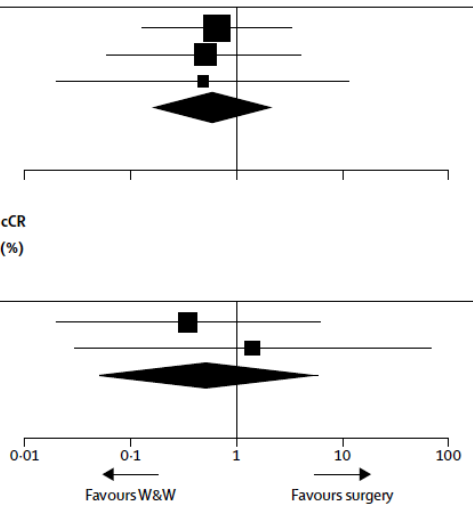
Test for overall effect: Z=0·90, p=0·37

D Cancer-specific mortality for patients treated by W&W *vs* surgery with cCR

	W&W		Surgery with cCR		Weight (%)	Risk ratio IV, random (95% CI)
	Events	Total	Events	Total		
Li et al (2015)[48]	0	30	4	92	64·2	0·35 (0·02–6·26)
Lai et al (2016)[11]	0	18	0	26	35·8	1·42 (0·03–68·46)
Total	**0**	**48**	**4**	**118**	**100·0**	**0·58 (0·06–5·84)**

Heterogeneity: τ^2=0·00; χ^2=0·33, DF=1 (p=0·57); I^2=0%

Test for overall effect: Z=0·47, p=0·64



C Disease-free survival for patients treated by surgery with cCR *vs* W&W

	W&W		Surgery with cCR		Weight (%)	HR IV, random (95% CI)
	Events	Total	Events	Total		
Li et al (2015)[48]	3	30	10	92	65·6	0·65 (0·18–2·36)
Lai et al (2016)[11]	2	18	3	26	34·4	0·43 (0·07–2·56)
Total	**5**	**48**	**13**	**118**	**100·0**	**0·56 (0·20–1·60)**

Heterogeneity: τ^2=0·00; χ^2=0·13, DF=1 (p=0·71); I^2=0%

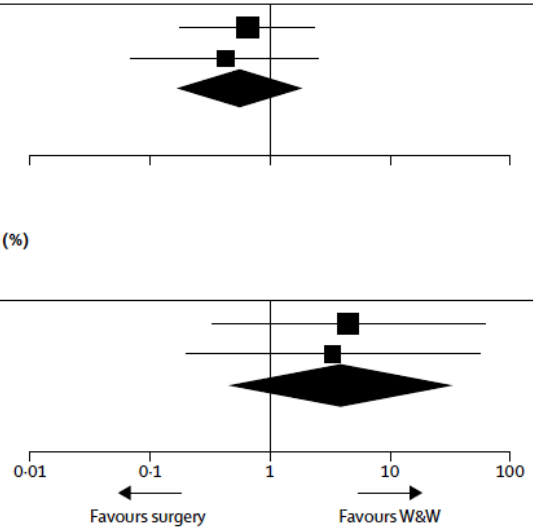
Test for overall effect: Z=1·08, p=0·28

D Overall survival for patients treated by surgery with cCR *vs* W&W

	W&W		Surgery with cCR		Weight (%)	HR IV, random (95% CI)
	Events	Total	Events	Total		
Li et al (2015)[48]	0	30	3	92	53·5	4·50 (0·33–62·28)
Lai et al (2016)[11]	2	18	3	26	46·5	3·33 (0·20–55·69)
Total	**2**	**48**	**6**	**118**	**100·0**	**3·91 (0·57–26·72)**

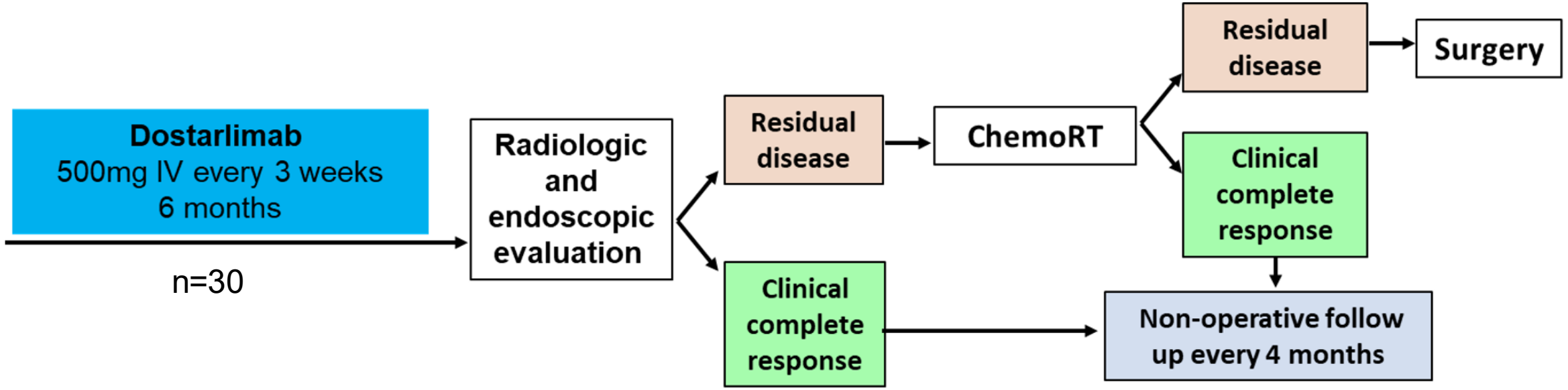
Heterogeneity: τ^2=0·00; χ^2=0·02, DF=1 (p=0·88); I^2=0%

Test for overall effect: Z=1·39, p=0·16



Dossa F, et al. *Lancet Gastroenterol Hepatol* 2017; 2: 501-13.

Dostarlimab for MSI-H Stage II-III Rectal Cancer



- Primary endpoint
  - Overall response rate at 6 months per MSKCC regression criteria
  - pCR or cCR rate at 12 months
- Secondary endpoint
  - Safety and tolerability

Cercek A, et al. *N Engl J Med* 2022.

Dostarlimab Led to a 100% Clinical CR Rate

ID	Age	Stage T	Stage N	FU (months)	Digital rectal exam response	Endoscopic best response	Rectal MRI best response	Overall response
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**

Median follow up:
6.8 months
(0.7-23.8)

Cercek A, et al. *N Engl J Med* 2022.

Dostarlimab Phase II Trial: Limitations

Short follow up

Single institution study with extensive expertise in non-operative management

Small sample size

ID	Age	Stage T	Stage N	FU (months)	Digital rectal exam response	Endoscopic best response	Rectal MRI best response	Overall response
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**

Lack of other endpoints

International Consensus Recommendations (1)

Box 1 | **Definitions of clinical end points for organ preservation strategies in rectal cancer**

Organ preservation

- Rectum intact, owing to no radical total mesorectal excision (TME), no locoregional regrowth unless amenable to limited, curative (R0) salvage surgery by local excision (LE) and no permanent stoma (including a never reversed protective stoma, or a stoma owing to toxicities and/or poor functional outcomes).

Clinical complete response (cCR)[a]

- Digital rectal examination (DRE) and rectoscopy: no palpable tumour material present, no residual tumour material or only a small residual erythematous ulcer or scar.
- MRI[b]: substantial downsizing with no observable residual tumour material, or residual fibrosis only (with limited signal on diffusion-weighted imaging), sometimes associated with residual wall thickening owing to oedema, no suspicious lymph nodes.
- Endoscopic biopsy: not mandatory to define cCR, biopsy should not be performed, especially if the DRE, rectoscopy and MRI criteria for cCR are all fulfilled.

Near cCR (ncCR)

- DRE and rectoscopy: the presence of small and smooth regular irregularities including residual ulcer, or small mucosal nodules or minor mucosal abnormalities, with mild persisting erythema of the scar.
- MRI: obvious downstaging with residual fibrosis but heterogeneous or irregular aspects and signal or regression of lymph nodes with no malignant enhancement features, but with a size of >5 mm.
- Endoscopic biopsy[c]: not mandatory to define ncCR.

Poor response

- The presence of a palpable tumour mass and visible macroscopic tumour and/or lack of regression of involved lymph nodes (patients who do not fulfill the criteria for either a cCR or ncCR).

Locoregional regrowth

- Detection of a tumour involving either the bowel wall, mesorectum and/or pelvic organs that occurs after an initial cCR and watch-and-wait strategy.

Local regrowth

- Detection of a tumour involving the bowel wall only that occurs after an initial cCR and watch-and-wait strategy.

Locoregional recurrence

- Detection of a tumour involving either the bowel wall, mesorectum and/or pelvic organs that occurs after LE or TME.

Local recurrence

- Detection of a tumour involving the bowel wall only that occurs after LE or TME.

TME-free disease-free survival (DFS)[d]

- Time from randomization to one of the following events: radical TME owing to an incomplete response at restaging, any locoregional regrowth after initial cCR requiring salvage TME, any locoregional recurrence after LE or non-salvageable regrowth (a regrowth that cannot be removed with an R0 resection), the development of distant metastases or death (from all causes), whichever occurs first.

Organ preservation-adapted DFS[e]

- Time from randomization to one of the following events: no resection of primary tumour owing to local disease progression or the patient being unfit for surgery; nonradical resection of the primary tumour (R2 resection); locoregional recurrence after R0/1 resection of the primary tumour; nonsalvageable local regrowth (no operation or only R2 salvage resection possible) in patients undergoing nonoperative management; any distant metastatic disease before, at or after surgery or nonoperative management; the occurrence of a second primary colorectal cancer, a second primary other cancer, treatment-related death, death from the same cancer, death from another type of cancer or non-cancer-related death.

[a]All criteria, including DRE, rectoscopy and MRI, should be fulfilled to define a cCR. [b]Gadolinium contrast medium is no longer compulsory for MRI conducted with the intention of defining a cCR. [c]In contrast to the study by Martens et al.[5], in which biopsy sampling was suggested for patients with a ncCR (showing dysplastic changes), the panel did not recommend mandatory biopsy sampling to define ncCR in the present Consensus Statement owing to the risks of a false-negative result and a lack of added diagnostic value. [d]Consensus was not reached for the definition of TME-free DFS that was provided separately by the primary investigator of the OPRA trial (author J.G.-A.). [e]If a salvage operation for the local regrowth is performed with curative intent (R0/1), it should not count as an event. If, however, no operation, or only an R2 resection is possible, and/or disease recurrence occurs after salvage surgery, this should count as an event.

Recommended Primary End Points

- Phase I/II trials of treatment intensification to enable NOM: **cCR**
- Phase II/III trials: **Organ preservation at 30-36 months**
- Critical secondary outcomes: **Rectal function, toxicity, QoL**

Fokas E, et al. *Nature Rev Clin Oncol* 2021; 18: 805-16.

International Consensus Recommendations (2)

Box 2 | **Consensus recommendations on the optimal RA time points for cCR determination**

- Standard short-course radiotherapy (duration of 5 days) or chemoradiotherapy (CRT; duration of about 6 weeks) for patients with early-stage tumours.
  - A two-step approach is recommended, involving initial measurement at 12 weeks from the start of treatment and then, in patients with a near clinical complete response (ncCR) at initial assessment, a repeat assessment at 16–20 weeks should be used to determine cCR, as performed in the STAR-TREC trial (NCT02945566).
- CRT followed by brachytherapy (duration of 12 weeks).
  - cCR should be determined at 14 weeks after start of treatment and should be repeated at 20–24 weeks in patients with a ncCR at initial assessment, as performed in the OPERA trial (NCT02505750).
- Total neoadjuvant treatment with CRT and either induction or consolidation chemotherapy (duration of 16–20 weeks).
  - cCR should be determined at 24 weeks after start of treatment, as performed in the GRECCAR12 (NCT02514278) and ACO/ARO/AIO-18.1 (NCT04246684) trials.
- Total neoadjuvant treatment with standard short-course radiotherapy or CRT followed by prolonged consolidation chemotherapy (duration of 26–34 weeks).
  - cCR should be determined at 34–38 weeks after start of treatment, as performed in the OPRA[22] and TRIGGER trials[33].

RA, response assessment. The panel recommended that cCR should be determined from the start of treatment. Owing to variations in preoperative treatment design and duration across the different trials, recommendations regarding a time point enabling the earlier detection of patients with a poor response before the recommended time point cannot be provided because there is insufficient evidence. Nevertheless, caution is needed, especially in patients with tumours featuring certain high-risk characteristics (such as advanced cT stage[32]), and selective earlier imaging could be advocated to enable the identification of poor responders who might have disease progression during preoperative treatment in order to offer immediate surgery.

Table 2 | **Consensus follow-up methods and intervals for organ preservation strategies**

Year	Serum carcino-embryonic antigen	DRE	Endoscopy	Pelvic MRI	Chest and/or abdominal CT
1	3 months	3–4 months	3–4 months	3–4 months	6–12 months
2	3 months	3–4 months	3–4 months	3–4 months	Annually
3	3 months	6 months	6 months	6 months	Annually
4	6 months	6 months	6 months	6 months	Annually
5	6 months	6 months	6 months	6 months	Annually

First follow-up assessments typically occur at 6–8 weeks following completion of preoperative or definitive treatment. DRE, digital rectal examination.

Fokas E, et al. *Nature Rev Clin Oncol* 2021; 18: 805-16.

NCCN Guidelines for Rectal Cancer (v4.2022)

Footnote:

In those patients who achieve a complete clinical response with no evidence of residual disease on digital rectal examination, rectal MRI, and direct endoscopic evaluation, a "watch and wait," nonoperative (chemotherapy and/or RT) management approach may be considered in centers with experienced multidisciplinary teams. The degree to which risk of local and/or distant failure may be increased relative to standard surgical resection has not yet been adequately characterized. Decisions for nonoperative management should involve a careful discussion with the patient of his/her risk tolerance. Surveillance recommendations include DRE, proctoscopy every 3-4 months for 2 years, then every 6 months for a total of 5 years. MRI rectum is recommended every 6 months for at least 3 years to monitor for extraluminal local recurrence.

Outline

- Background on Rectal Cancer
- Current Treatment Paradigms
- Non-Operative Management
- ***Future Research***

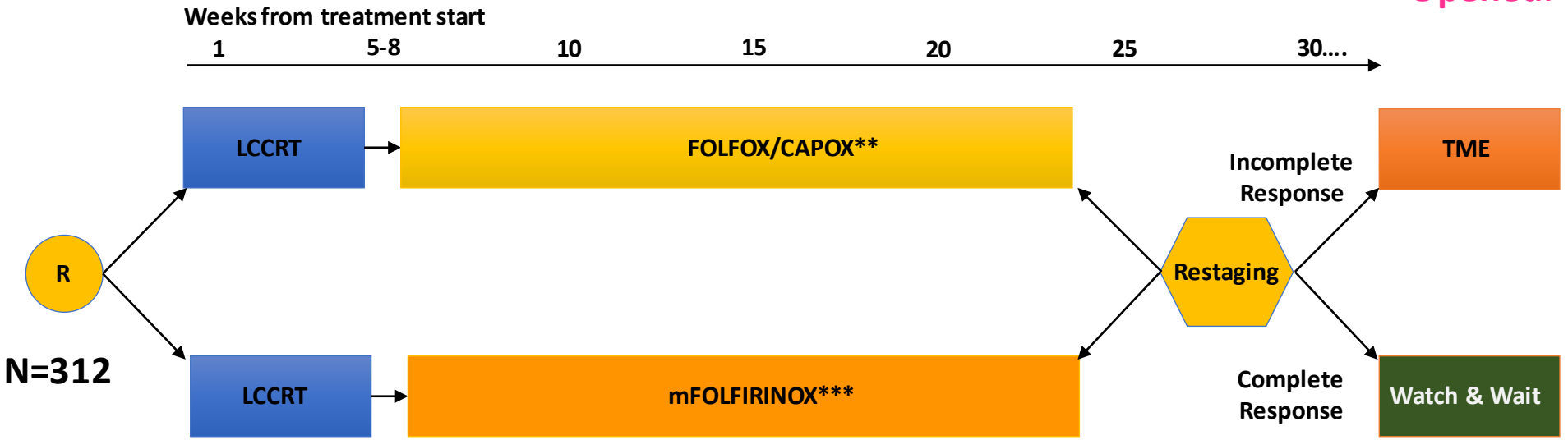
The Janus Phase II Rectal Cancer Study

Slide provided courtesy of Dr. Joshua Smith

An Alliance, NRG & SWOG Study

Opened: 9 Nov 2022!

A022104



Patients with locally advanced rectal cancer: <=12cm cT4N0, anyT, N1; T3N0 that would require APR or coloanal anastomosis

** LCRT = long-course chemoradiation (5 weeks)

***mFOLFOX6 = 8 cycles (1 cycle = 2 weeks)

****mFOLFIRINOX = 8 cycles (1 cycle = 2 weeks)

#CAPOX = 5 cycles (1 cycle = 3 weeks)

Primary Endpoint

cCR**

**Garcia-Aguilar J et al. ASCO 2020; Garcia-Aguilar *J Clin Oncol* 2022; ***T. Conroy et al. ASCO 2020 (and *Lancet Oncology* 2021)

****Smith JJ, et al. *BMC Cancer* 2015

Schema Legend: Randomization = R; LCRT = long-course chemoradiation; cCR = clinical complete response; Response determination = endoscopy, MRI and clinical exam 8-12 weeks post-completion of assigned TNT regimen; DFS = disease-free survival; OP = organ preservation; QoL = quality of life; OS = overall survival; APR – abdominoperineal resection; CAA = coloanal anastomosis

Remaining Questions for Non-Operative Management

- What are the long-term DFS and OS outcomes?
- Does non-operative management result in improved functional outcomes and quality of life?
- Are there biomarkers (e.g., ctDNA, radiomics) that can better predict pCR?
- What is the optimal surrogate endpoint for clinical trials of non-operative management?
- Is a non-operative management strategy feasible in the community setting?

Centralized Multidisciplinary Care Improves Outcomes

- European data demonstrate benefits of centralized care and centers of excellence
  - Improved outcomes with colorectal-trained, high-volume surgeon
  - Decreased perioperative morbidity
  - Decreased stoma rate
  - Improved DFS and OS, decreased local recurrence
- Consortium for Optimizing Surgical Treatment of Rectal Cancer (OSTRiCh) established in 2011 to improve quality and uniformity of rectal cancer care in U.S.
  - Significant variation in use of neoadjuvant treatment
  - Vast majority of patients treated in low- and intermediate-volume centers

Wexner SD & White CM. *Clin Colon Rectal Surg* 2020; 33:318-24.

National Accreditation Program for Rectal Cancer (NAPRC)

Standard 1	Institutional administrative commitment
Standard 2	Program scope and governance 2.1 Rectal cancer multidisciplinary care 2.2 Rectal cancer program director 2.3 Rectal cancer program coordinator 2.4 Rectal cancer MDT meetings 2.5 Rectal cancer MDT attendance
Standard 3	Facility and equipment resources (CoC accreditation)
Standard 4	Personnel and services resources (CoC accreditation)
Standard 5	Patient care: expectations and protocols 5.1 Review of diagnostic pathology 5.2 Staging before definitive treatment 5.3 Standardized staging reporting for MRI results 5.4 CEA level 5.5 Rectal cancer MDT treatment plan discussion 5.6 Treatment evaluation and recommendation summary 5.7 Definitive treatment timing 5.8 Treatment evaluation and recommendation summary 5.9 Pathology reports after surgical resection 5.10 Photographs of surgical specimens 5.11 MDT postsurgical treatment outcome discussion 5.12 Postsurgical treatment outcome discussion summary 5.13 Adjuvant therapy after surgical resection
Standard 6	Data surveillance and systems
Standard 7	Quality improvement
Standard 8	Education: professional and community outreach

https://dailynews.ascopubs.org/do/landscape-rectal-cancer-care-centralization-defining-centers-excellence-united-states

- Only 2.9% of 1315 hospitals evaluated met thresholds for adherence to 5 selected NAPRC measures
- Disparities exist in the types of centers with readiness for accreditation
  - Academic institutions
  - High-volume centers
  - Serve highly-resourced, high socioeconomic status population
- Currently 75 accredited programs
- No outcome data yet
- Concern about widening disparities in access to quality care

Antunez AG, et al. *JAMA Surg* 2019; 154(6): 516-23.

Dana-Farber Cancer Institute | BWH BRIGHAM AND WOMEN'S HOSPITAL

DANA-FARBER/BRIGHAM AND WOMEN'S CANCER CENTER

Thank You