

# THE ROLE OF SHORT-COURSE AND LONG-COURSE RADIATION THERAPY IN THE TOTAL NEOADJUVANT THERAPY FOR LOCALLY ADVANCED RECTAL ADENOCARCINOMA

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# Neoadjuvant treatment

Short course radiation therapy (SCRT)

Long course Chemoradiation (LCCRT)

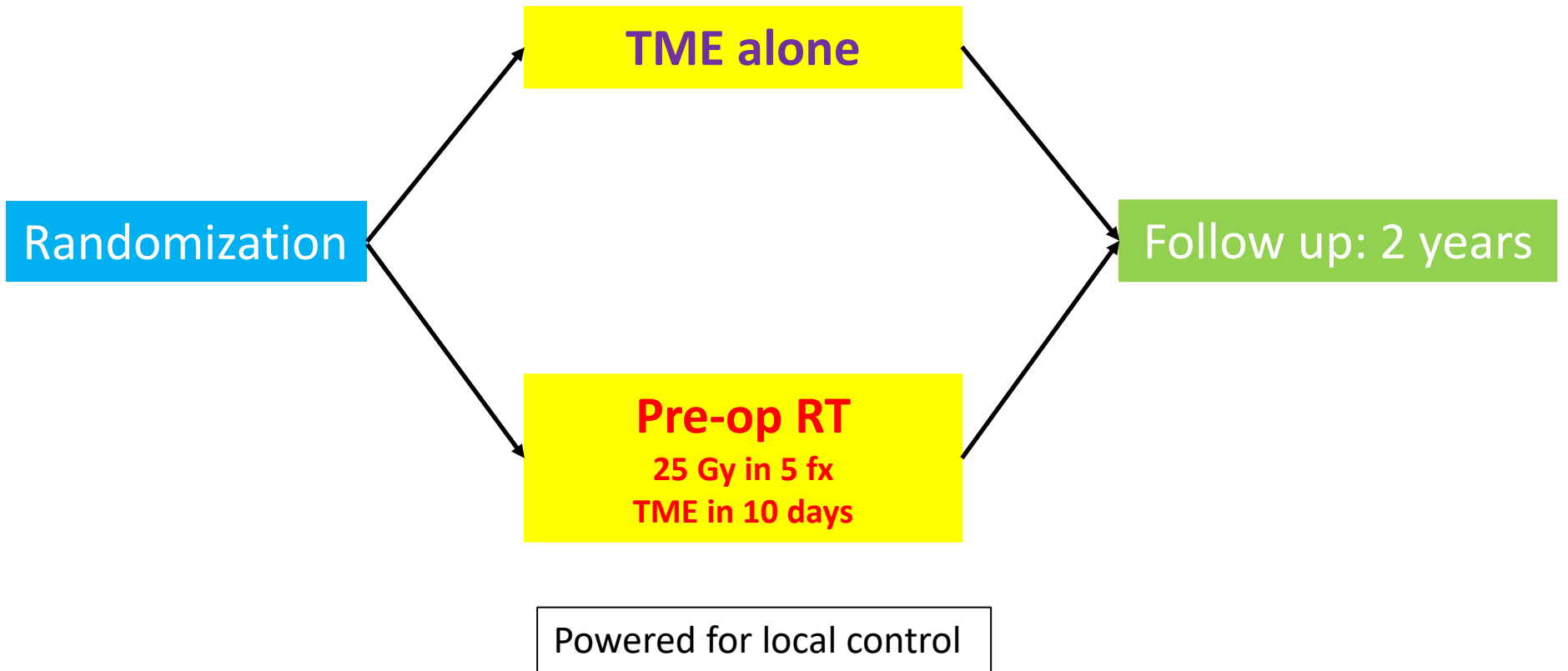
Total Neoadjuvant therapy with  
induction chemotherapy followed by LCCRT

Total Neoadjuvant therapy with  
LCCRT or SCRT followed by consolidative chemotherapy

# Short course radiation therapy

## Dutch Rectal Cancer Trial

1861 patients  
-Resectable  
-Inferior margin < 15 cm  
From anal verge  
-Below S1/S2  
-No metastatic disease



# Short course radiation therapy

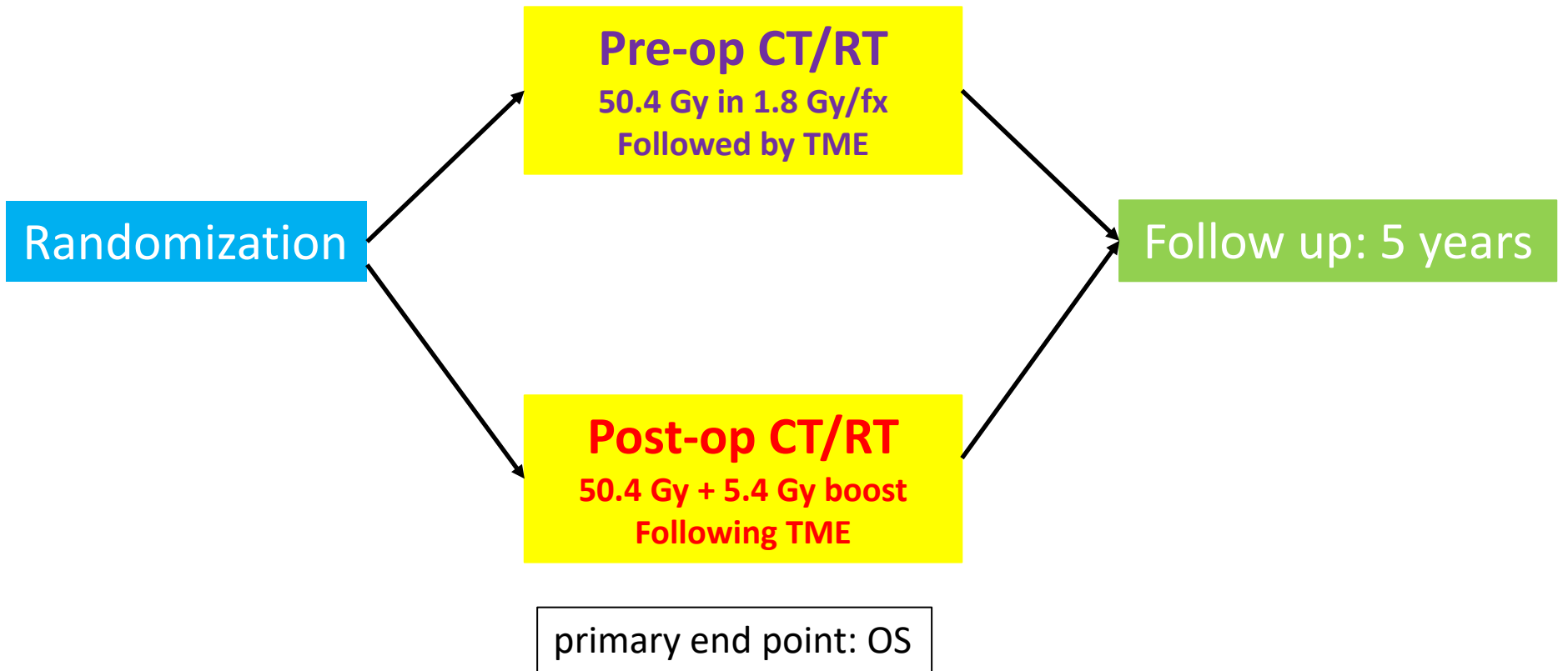
## Dutch Rectal Cancer Trial

2-year results	TME alone (%)	Preop-RT + TME (%)	P value
LR	8.2	5.3	<0.001
OS	81.8	82	0.084
10-year results	TME alone (%)	Preop-RT + TME (%)	P value
LR	11	5	<0.001
OS	49	48	NS

# Chemoradiation

## German Rectal Cancer Trial

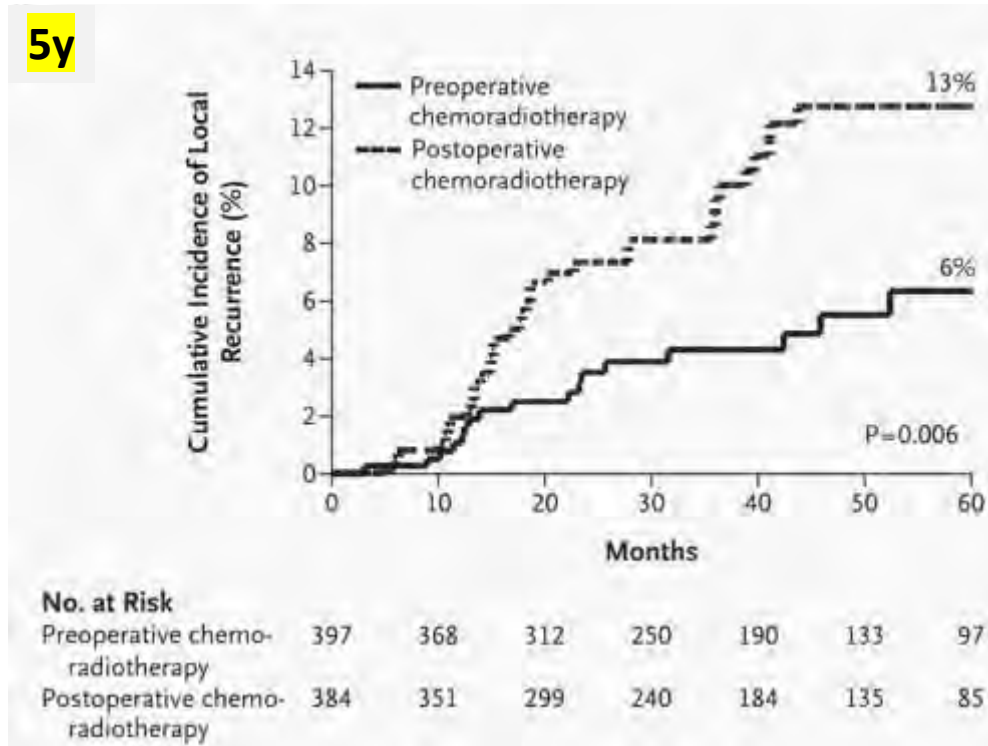
823 patients  
- Resectable  
- < 75 years old  
- No metastasis  
- Endoscopic ultrasound  
or MRI staging



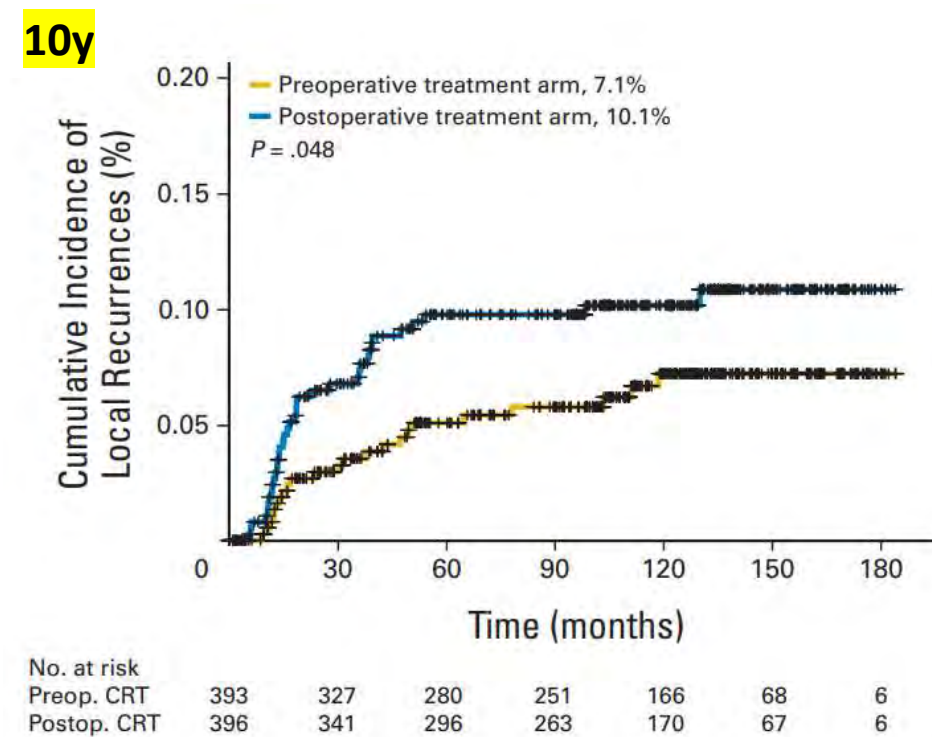
Sauer, et al., et al. NEJM 2004; 351:1731

# Chemoradiation

## German Rectal Cancer Trial



Sauer, et al., et al. NEJM 2004; 351:1731



Sauer, et al. J clin Oncol 2012; 30: 1926

# Chemoradiation

## German Rectal Cancer Trial

5 year	LR	Disease-free survival (DFS)	Distant metastases (DM)	OS
Preoperative CRT	6%	68%	36%	76%
Postoperative CRT	13%	65%	38%	74%

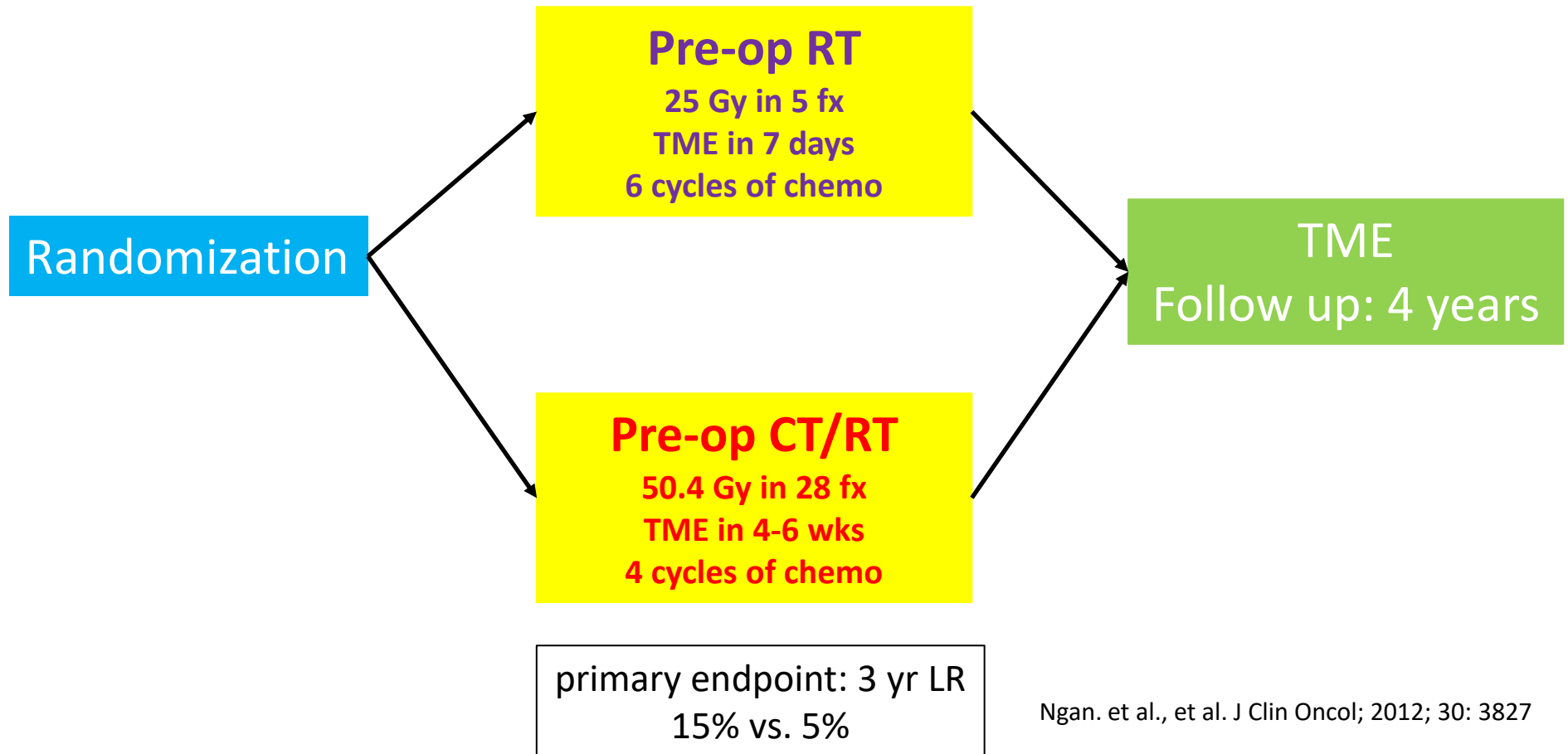
10 year	LR	DFS	DM	OS
Preoperative CRT	7.1%	68.1%	29.8%	59.6%
Postoperative CRT	10.1%	67.8%	29.6%	59.9%

Sauer, et al. NEJM 2004; 351:1731-1740  
Sauer, et al. J Clin Oncol 2012; 30:1926-1933

# Short course radiation therapy vs Long course Chemoradiation

## Australian Intergroup Trial

326 patients  
- ECOG 0-2  
- < 12 cm from verge  
- cT3 cNx cM0

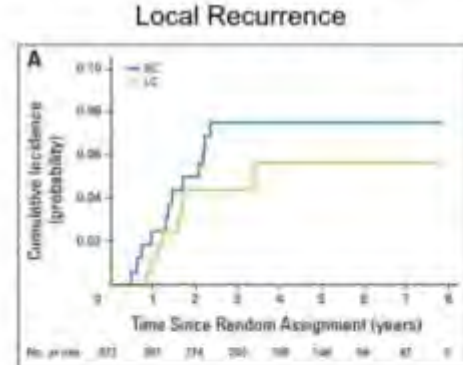


Ngan. et al., et al. J Clin Oncol; 2012; 30: 3827

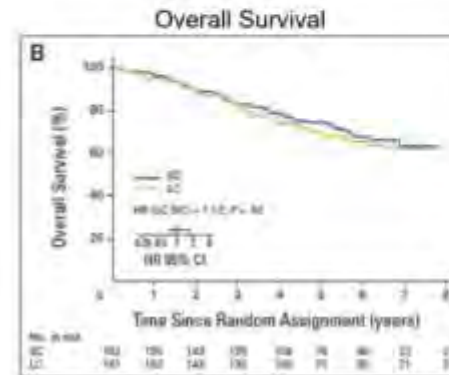


# Short course radiation therapy vs Long course Chemoradiation

## Australian Intergroup Trial



- Three-year LR rates between short-course and long-course were not statistically significantly different
- No differences in rates of distant recurrence, relapse-free survival, overall survival
- PCR 15% for long course CRT vs 1% for short course RT



Ngan, et al. J Clin Oncol. 2012;30:3827-3833

# Short course radiation therapy vs Long course Chemoradiation

## Accepted Preoperative Regimens

Short course radiation therapy	Long course Chemoradiation
5 Gy x 5	1.8 Gy x 28 or 2 Gy x 25
Delivered over 1 week/Very economical treatment	With concurrent 5 FU or capecitabine
Surgery in 1 week	Surgery in 4-8 weeks
Northern Europe	Southern Europe/US
No downstaging from the preop stage	A higher improved PCR
Very economical treatment	Sphincter preservation
Less acute toxicity	There may be improved reduction of late side effects

# Why should TNT be standard of care for high-risk locally advanced rectal cancer?

Traditional Sandwich Approach	Total Neoadjuvant Therapy
LCCRT → TME → adjuvant chemotherapy	Induction chemotherapy → LCCRT → TME
	LCCRT → consolidative chemotherapy → TME
SCRT → TME → adjuvant chemotherapy	SCRT → consolidative chemotherapy → TME
<b>Limitations with Adjuvant Therapy</b>	<b>Advantage of Total Neoadjuvant Therapy</b>
Adjuvant therapy may be delayed	Improve tolerability and compliance
Compliance may be poor	Early treatment of micrometastatic disease Improve pCR
Delivery may be suboptimal	Potential for non-operative watchful waiting

# Treatment Paradigms with TNT

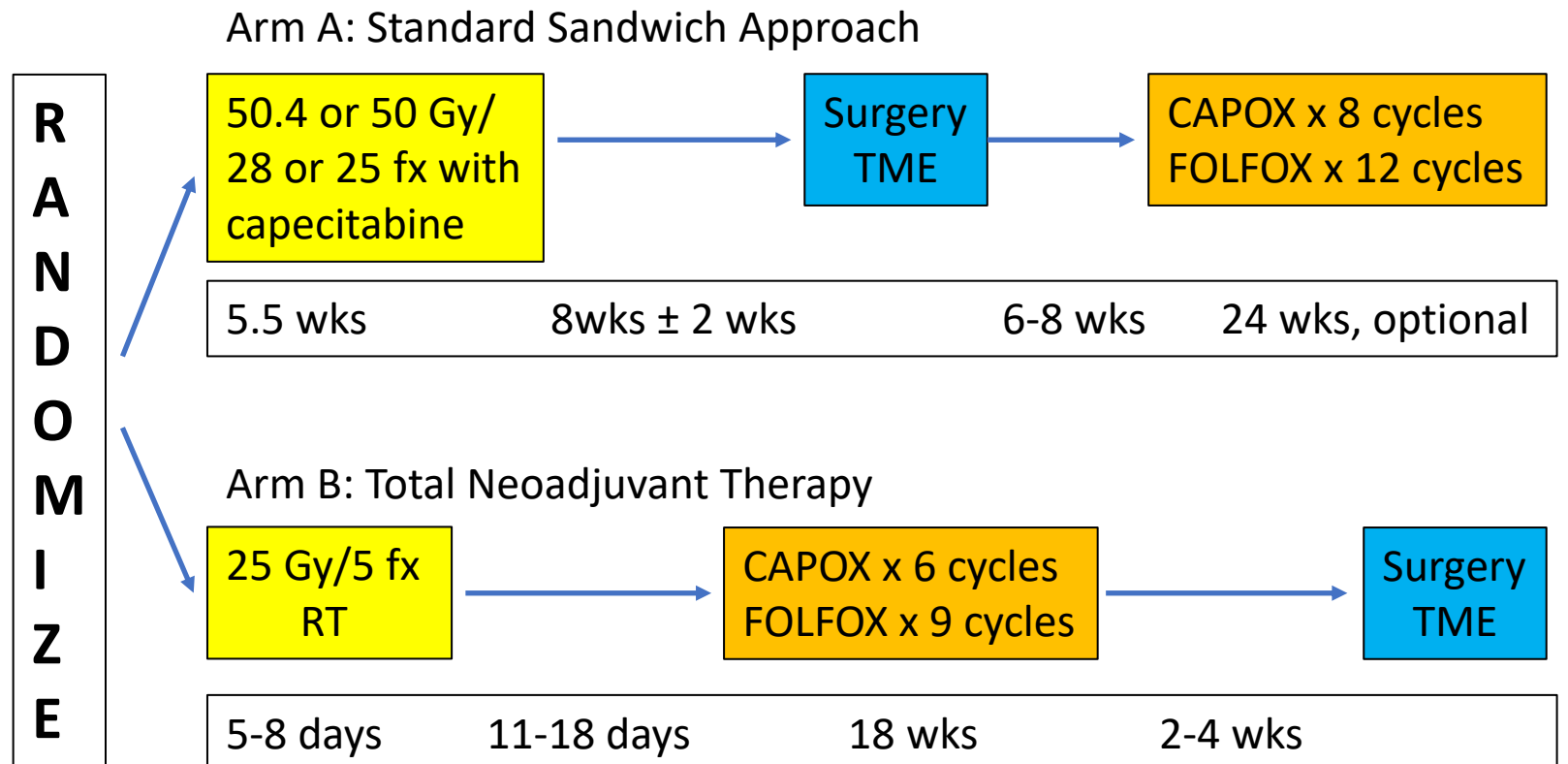
## Two landmark trials

- **RAPIDO Trial**
- CRT vs TNT (SCRT-consolidation CT)
- **PRODIGE 23 Trial**
- CRT vs TNT (induction CT-LCCRT)

# CRT vs TNT (SCRT-consolidation CT)

## RAPIDO Trial

- N=912
- MRI with high-risk features ( $\geq 1$  of the following)
  - T4
  - N2
  - EMVI +
  - Involved mesorectal fascia
  - Enlarged lateral LNs
- Primary endpoint: Disease-related treatment failure



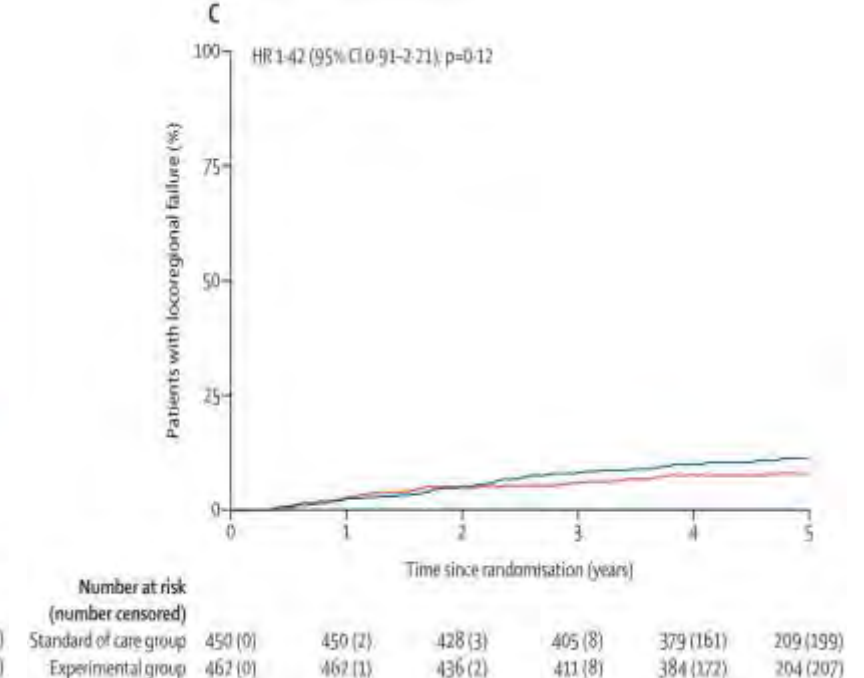
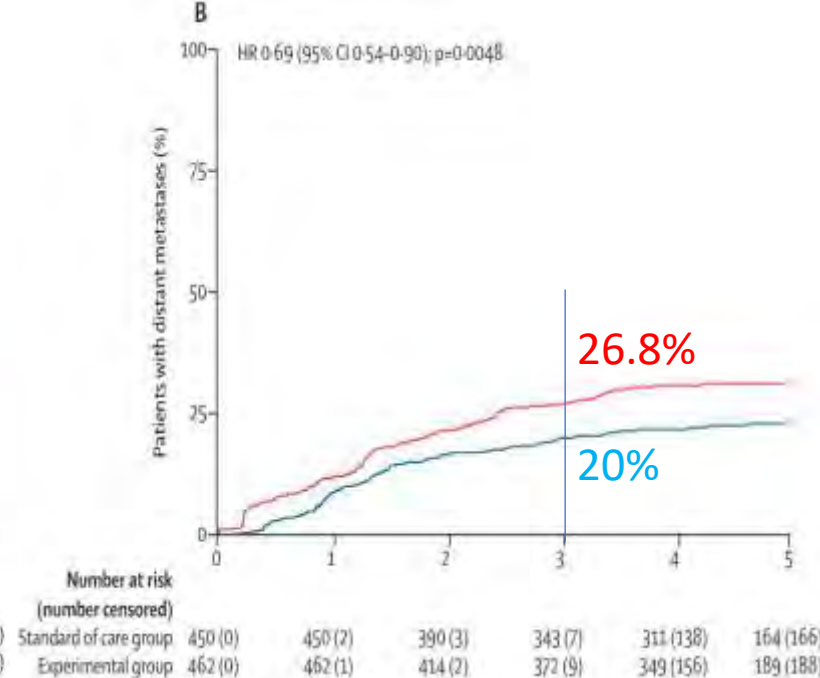
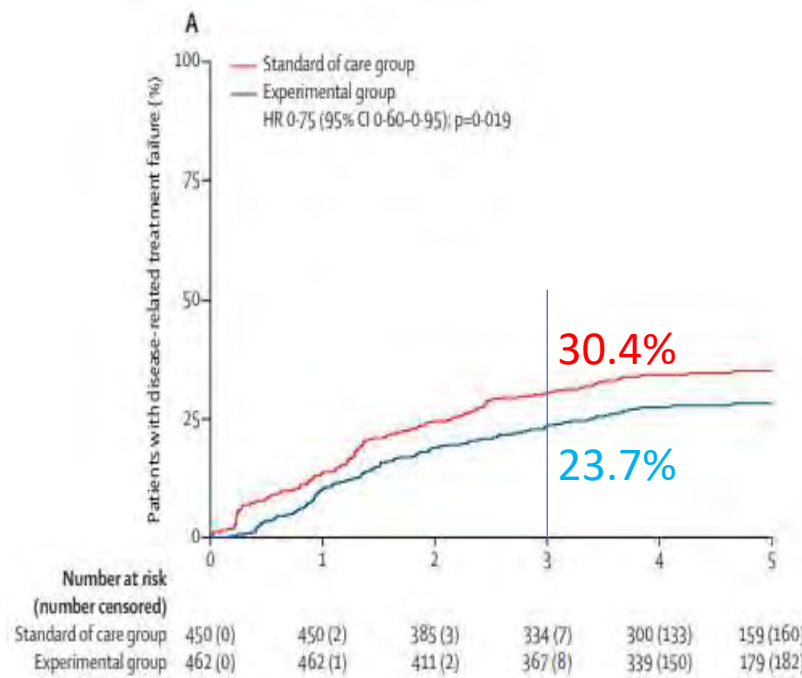
# CRT vs TNT (SCRT-consolidation CT)

## RAPIDO Trial

disease-related treatment failure

Distant metastases

Locoregional failure



— Standard of care group  
— Experimental group

# CRT vs TNT (SCRT-consolidation CT)

## RAPIDO Trial

	Experimental group	Standard of care group	p value
<b>Patients with a resection within 6 months after the end of preoperative treatment</b>			
<b>Residual tumour classification</b>			
R0 >1 mm	382/423 (90%)	360/398 (90%)	0.87*
R1 ≤1 mm	38/423 (9%)	37/398 (9%)	..
R2	3/423 (1%)	1/398 (<1%)	..
<b>Pathological complete response</b>			
Yes	120/423 (28%)	57/398 (14%)	<0.0001*
No	303/423 (72%)	341/398 (86%)	..

**Table 2: Number of surgeries with curative intent, disease-related treatment failures, and pathological outcomes**

# CRT vs TNT (SCRT-consolidation CT)

## RAPIDO Trial

Surgical procedures. Surgical procedures in patients undergoing standard surgery with curative intention. Data are presented as n (%) or median (IQR). \*Irresectable tumour or distant metastasis detected at surgery.

	Experimental arm (n = 426)		Standard arm (n = 400)		p
Type of approach					
Laparoscopic	178	(42%)	182	(46%)	0.310
Laparoscopic converted to open	42	(10%)	29	(7%)	
Open	206	(48%)	189	(47%)	
Type of resection	3	(<1%)	2	(<1%)	0.562
No resection*	22	(5%)	12	(3%)	
Hartmann procedure	147	(34%)	157	(39%)	
Abdominoperineal resection	246	(58%)	219	(55%)	
(Low) Anterior resection of which without stoma	25	(10%)	27	(12%)	
Other type of resection	9	(2%)	10	(3%)	
Duration of surgery					0.607
in minutes (median, IQR)	245 (198–330)		245 (185–324)		
missing	n = 27		n = 21		
Blood loss					0.007
in ml (median, IQR)	300 (150–650)		250 (100–500)		
missing	n = 83		n = 89		
Mesorectal plain as assessed by surgeon					0.032
Intact	334	(78%)	342	85%	
Breached	40	(9%)	23	6%	
Missing	52	(12%)	35	9%	



# CRT vs TNT-consolidation CT

## RAPIDO Trial

Surgical complications. Surgical complications within 30 days of surgery were reported, and graded according to the Clavien-Dindo classification. Data are displayed as n (%) or median (IQR). \*Highest grade reported per patient. \*\*Postoperative death <30 days or in-hospital death.

	Experimental arm (n = 426)	Standard arm (n = 400)	p
Patients with 1 or more surgical complication ≥CD grade III	63 (15%)	55 (14%)	0.670
Intra-abdominal infection	21 (5%)	18 (5%)	
Wound complications	13 (3%)	17 (4%)	
Ileus	17 (4%)	7 (2%)	
Anastomotic leakage (out of n patients with a primary anastomosis)	14 (3%) 246	9 (2%) 219	
Stoma related problems (out of n patients with a stoma)	3 (1%) 400	8 (2%) 372	
Other surgical complication	11 (3%)	7 (2%)	

# CRT vs TNT (SCRT-consolidation CT)

## RAPIDO Trial

### Preop chemotherapy

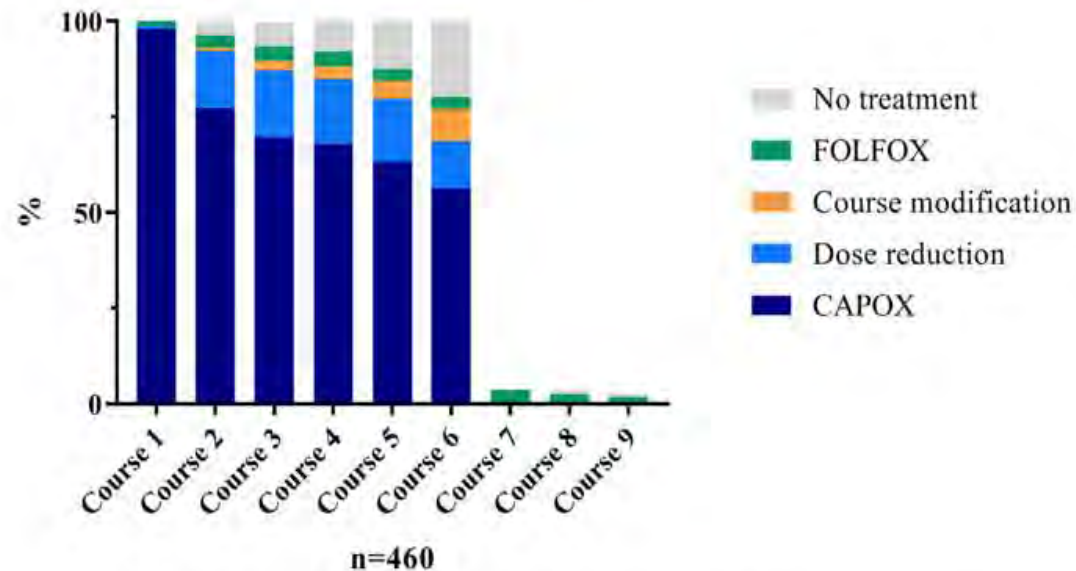


Fig. 2. Compliance in experimental arm. Proportion of patients treated with chemotherapy per course.

### Postop chemotherapy

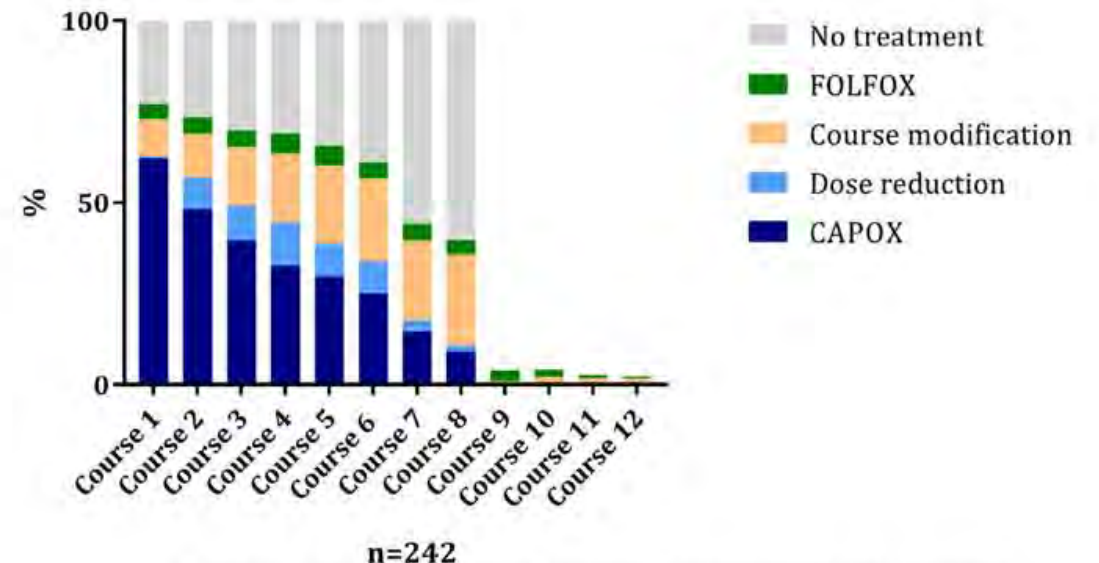


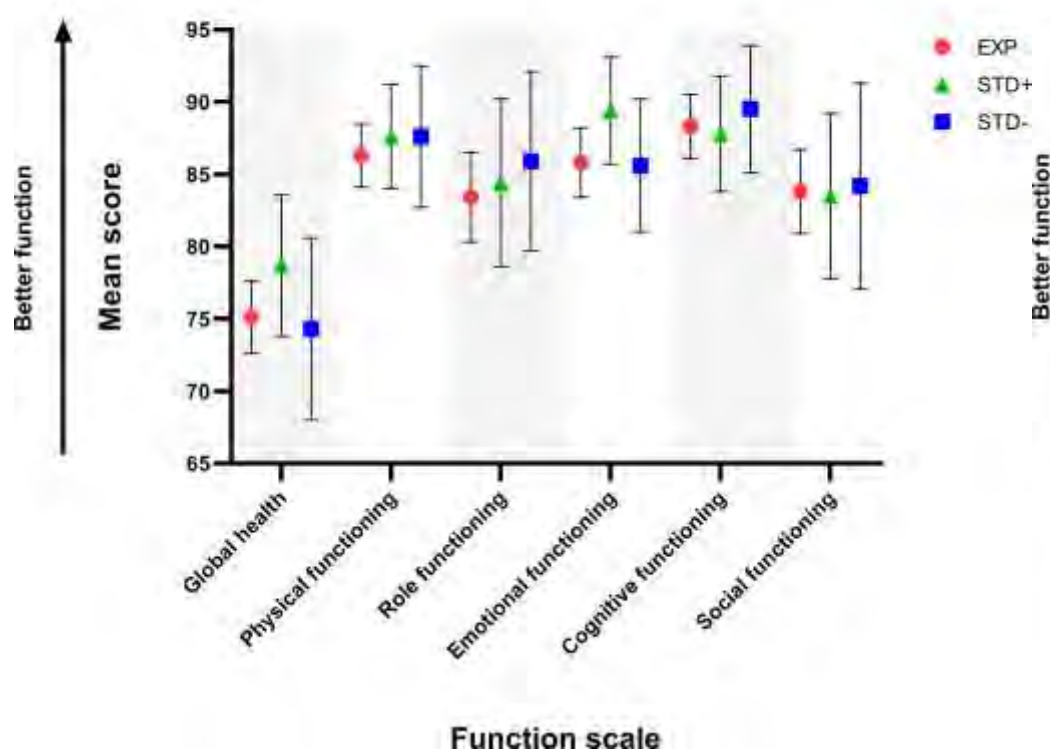
Fig. 3. Compliance in experimental arm. (A) Proportion of patients treated with capacitabine per week during chemotherapy. (B) Proportion of patients with a policy for postoperative chemotherapy receiving treatment.

## Chemotherapy Compliance

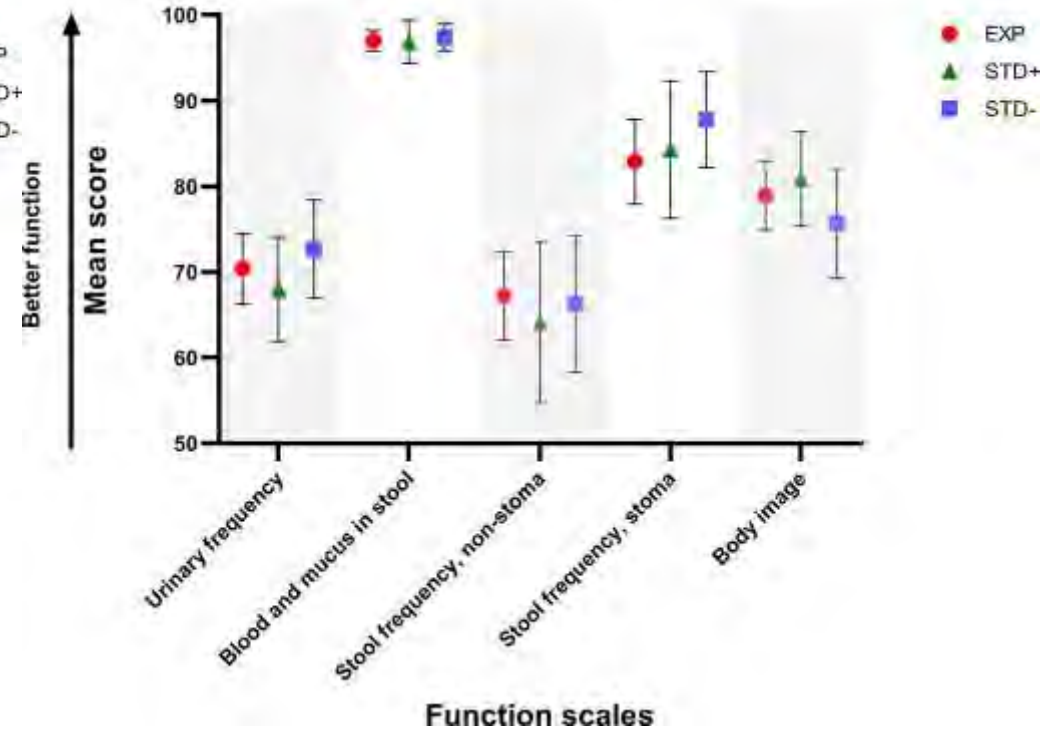
# CRT vs TNT (SCRT-consolidation CT)

## RAPIDO Trial

QLQ-C30 function scales at 36 months

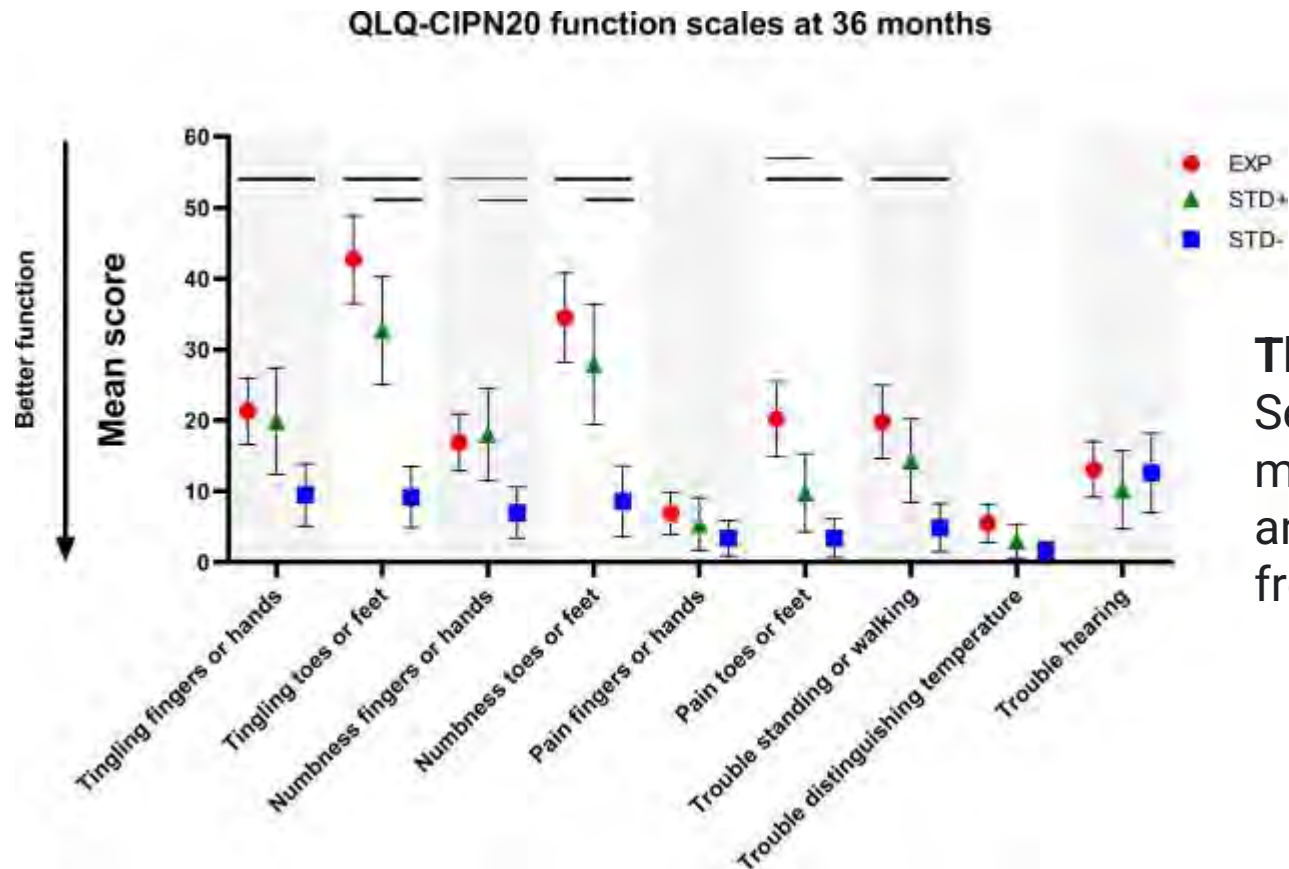


QLQ-CR29 function scales at 36 months



# CRT vs TNT (SCRT-consolidation CT)

## RAPIDO Trial



### The EORTC QLQ-CIPN20:

Sensory raw scale scores range from 1 to 36, motor raw scale scores range from 1 to 32, and autonomic raw scale scores range from 1 to 12 for men and 1–8 for women

# CRT vs TNT (SCRT-consolidation CT)

## RAPIDO Trial

- TNT doubled pCR rate from 14 to 28%
- TNT lowered disease-related treatment failure from 30.4% to 23.9%
- TNT lowered distant metastases rate from 26.8% to 20%.
- 3-year overall survival 89% in both treatment arms.
- No differences in surgery, postoperative complications and QOL in both treatment arms

# A five-year follow-up of the RAPIDO trial

- 460 SCRT + chemo and 446 LCCRT
- median follow-up = 5.6 years
- LRR after an R0/R1 resection was detected more often (44/431 (10%) with TNT/SCRT vs. 26/428 (6%) with LCCRT;  $p=0.027$ ), with more often a breached mesorectum (9/44 (21%) vs. 1/26 (4);  $p=0.048$ ).
- Overall survival after LRF was comparable (HR 0.76 (95%CI 0.46-1.26);  $p=0.29$ ).
- Conclusion The TNT/SCRT was associated with an increased risk of LRR whereas the reduction in disease-related treatment failure and distant metastases remained after 5 years.

# CRT vs TNT (induction CT-LCCRT)

## PRODIGE 23 Trial

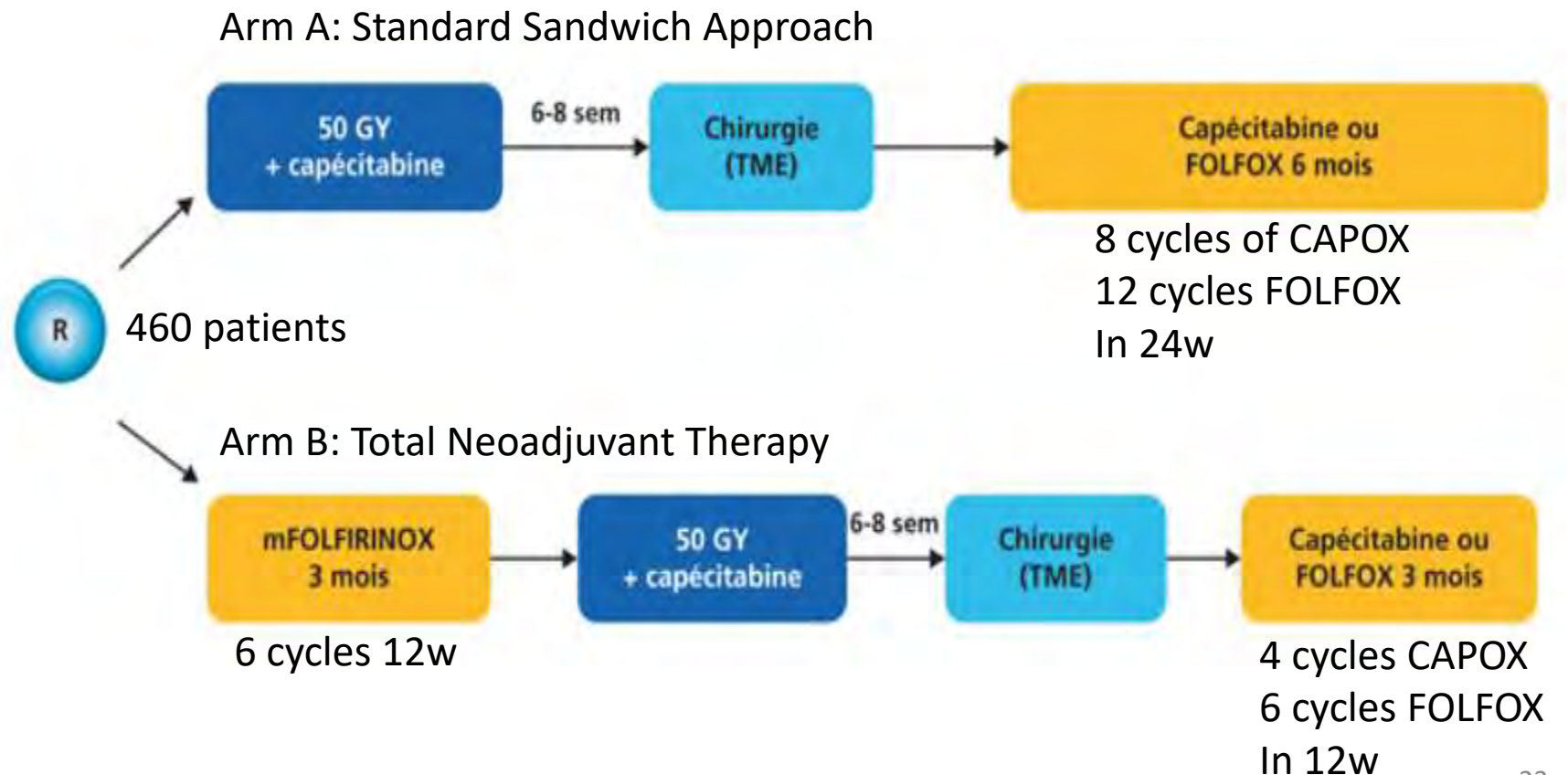
460+ patients

### Inclusion criteria:

Patients aged from 18 to 75 years  
WHO performance status 0 or 1  
Histologically confirmed rectal ADK  
<15 cm from the anal verge  
cT3 at risk of local recurrence or cT4  
Staged with MRI  
(+ endorectal ultrasound if mrT3)  
Adequate hematologic/blood chemistry levels  
Patient information and written informed consent

### Primary Endpoint:

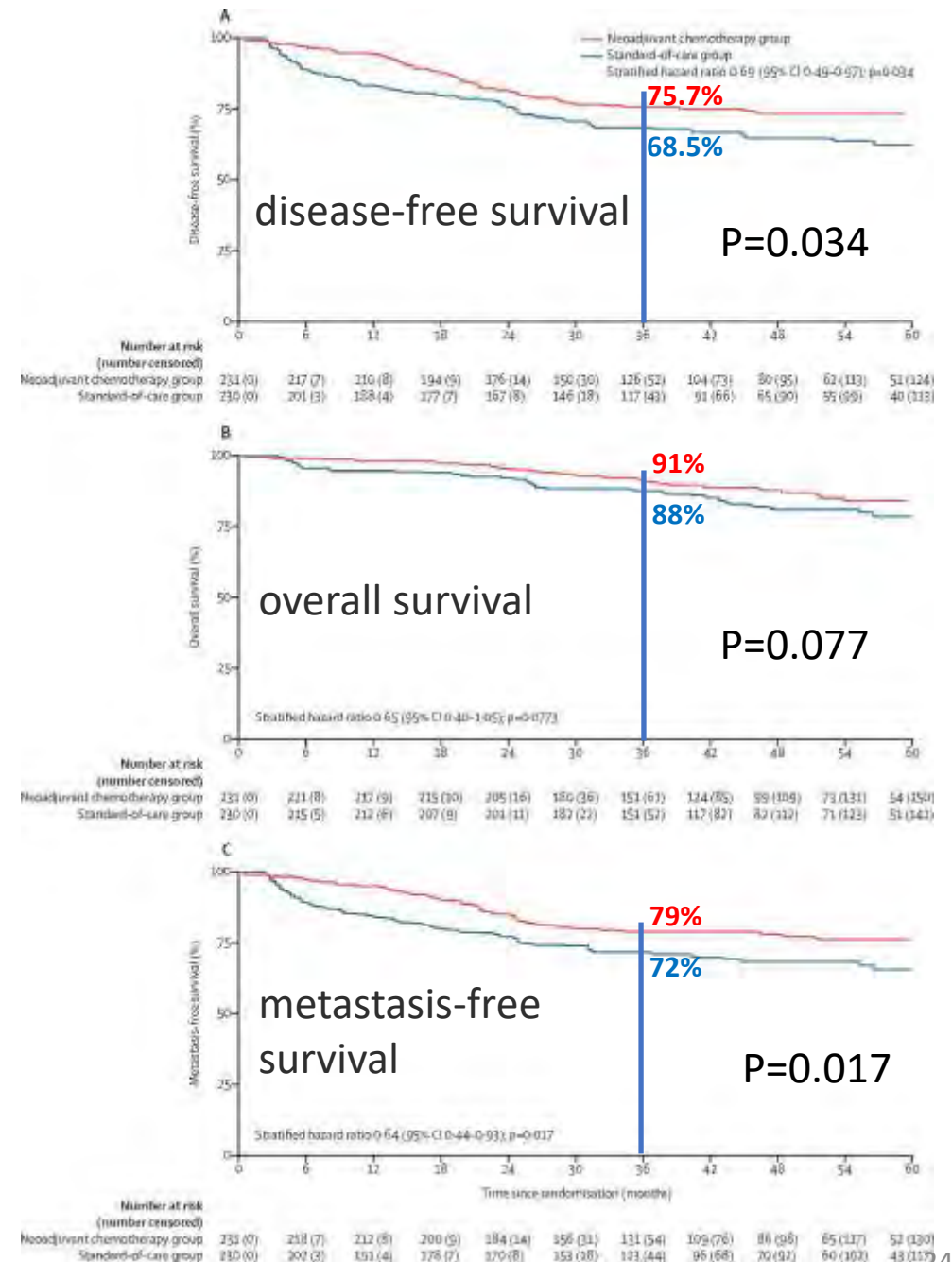
Disease free survival  
Median follow-up : 46.5 months  
136 DFS events occurred



# CRT vs TNT (induction CT-LCCRT)

## PRODIGE 23 Trial

Figure 2. Kaplan-Meier estimates of disease-free survival (A), overall survival (B), and metastasis-free survival (C) in the intention-to-treat population, according to treatment group

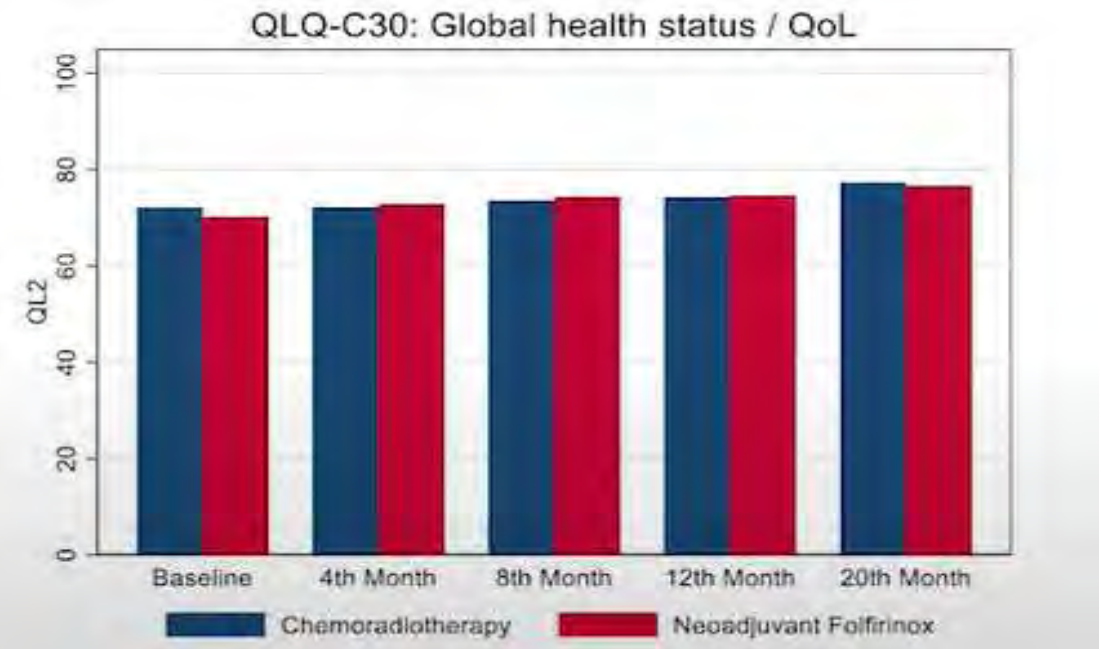




# CRT vs TNT (induction CT-LCCRT)

## PRODIGE 23 Trial

	Control arm, %	Experimental arm, %	HR and p values
3yr DFS	68.5	75.7	0.69 (0.49-0.097), P=0.034
3 yr MFS	71.7	78.8	0.64 (0.44-0.93), P<0.02
Primary tumor resection rate	93.5	92.2	Ns
Type of resection - Low anterior or intersphincteric - Abdominoperineal TME, complete mesorectum	85.1 14	85.9 14.1	Ns
Postoperative mortality	2.8	0	P=0.03
Overall morbidity	31.2	29.3	Ns
Median hospital stay, days	12	11	Ns
Median n <sup>o</sup> of postop RBCs	0	0	Ns
ypTON0	12.1	27.8	P<0.001
R0/ R1-R2	94.4/5.6	95.3/4.7	Ns



No statistical differences in baseline HRQOL between arms

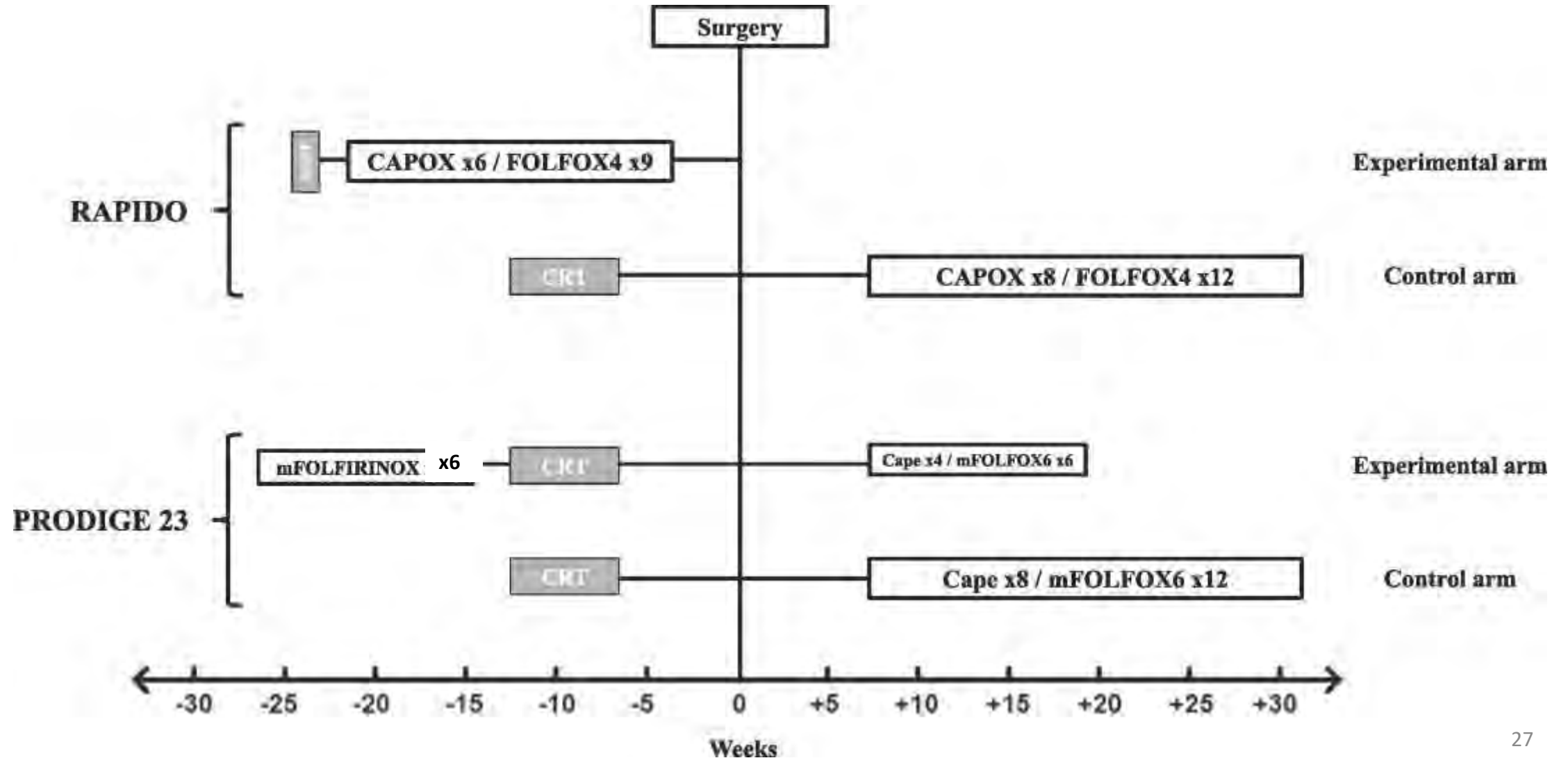
Overall global Health status of QOL measured by QLQ-C30 improved over time in both arms.

# CRT vs TNT (induction CT-LCCRT)

## PRODIGE 23 Trial

- mFOLFIRINOX is a safe regimen with manageable toxicities
- TNT with mFOLFIRINOX significantly increases
  - Probability of pCR
  - DFS and metastasis-free survival
- QOL scores are not significantly different between two arms
- TNT with mFOLFIRINOX should be an option of care for initial management of locally advanced rectal cancer.

# Study design of RAPIDO and PRODIGE 23

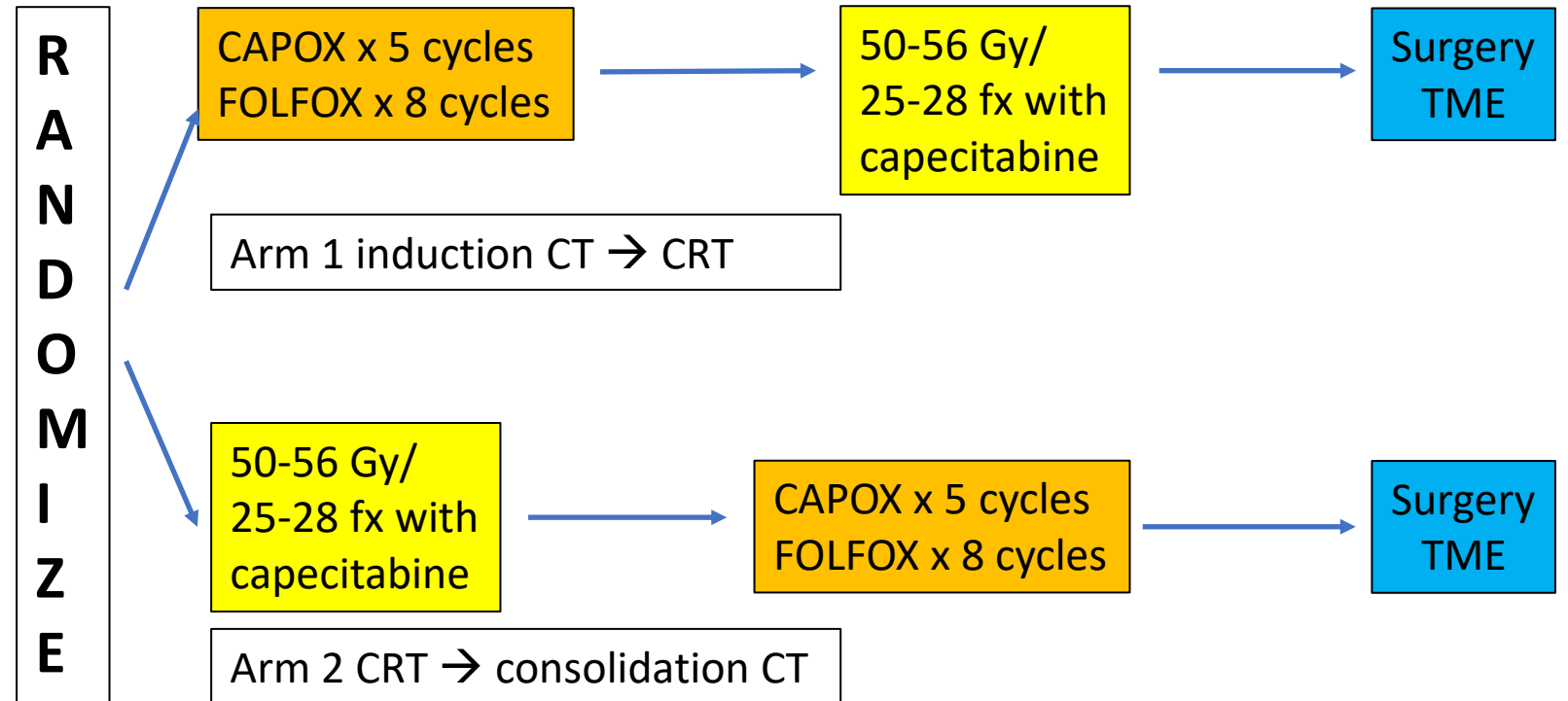


# TNT-induction CT vs. TNT-consolidation CT

## OPRA Trial

MRI clinical stage II (T3-4, N0) or stage III (any T, N1-2) biopsy proven rectal adenocarcinoma staged. 324 patients were accrued.

The primary end point was DFS, defined as the interval from random assignment to the first occurrence of locoregional failure, distant metastasis, a new invasive colorectal primary cancer, or death from any cause.

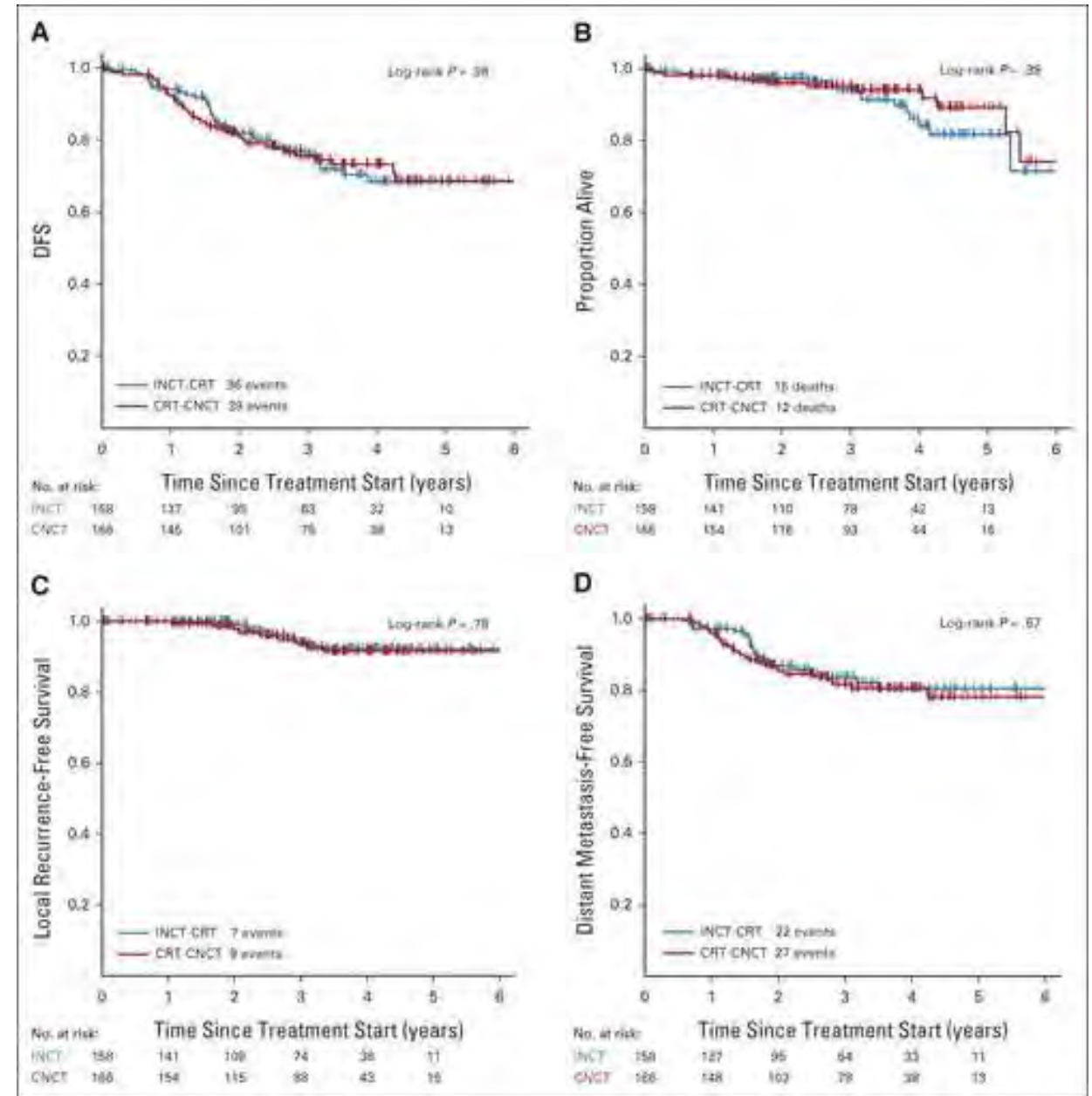


# TNT-induction CT vs. TNT-consolidation CT

## OPRA Trial

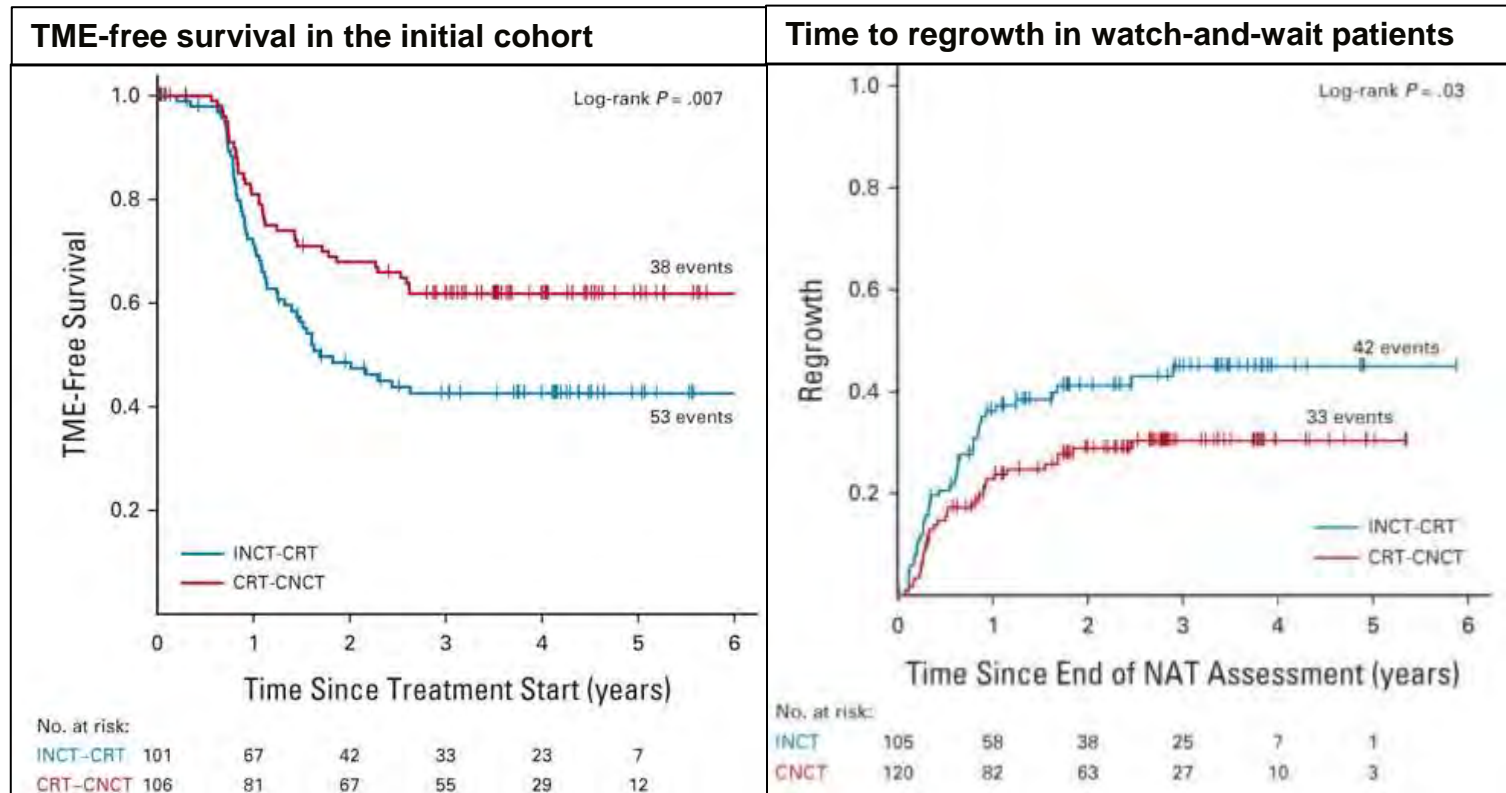
**FIG 2.** Kaplan-Meier estimates of (A) DFS, (B) overall survival, (C) local recurrence-free survival, and (D) distant metastasis-free survival in the intention-to-treat population by study group.

Garcia Aguilar: J Clin Oncol, 2022.2546-2556



# TNT-induction CT vs. TNT-consolidation CT

## OPRA Trial



# TNT-induction CT vs. TNT-consolidation CT

## OPRA Trial

Three-year DFS was 76% for both INCT-CRT group and CRT-CNCT group.

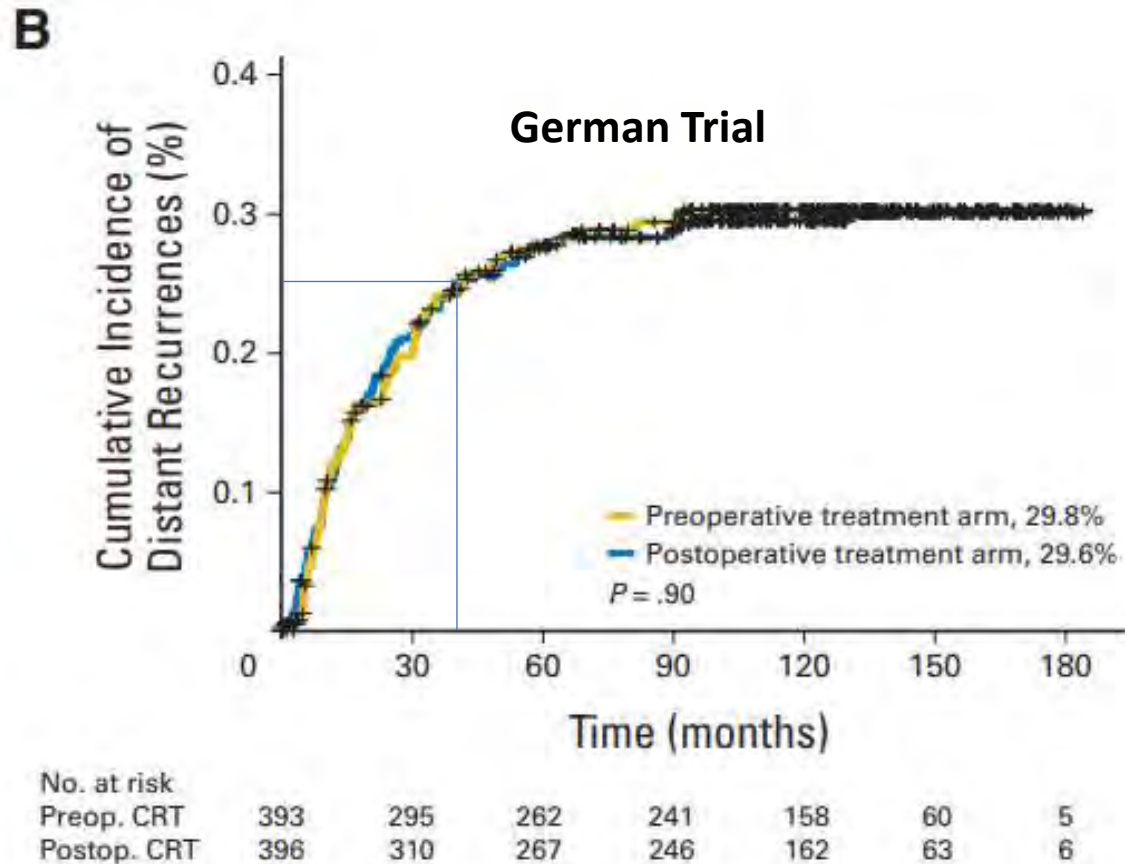
Three-year TME-free survival was 41% in the INCT-CRT group and 53% in the CRT-CNCT group.

No differences were found between groups in local recurrence-free survival, distant metastasis-free survival, or overall survival.

Patients who underwent TME after restaging and patients who underwent TME after regrowth had similar DFS rates.

Organ preservation is achievable in half of the patients with rectal cancer treated with total neoadjuvant therapy, without an apparent detriment in survival, compared with historical controls treated with chemoradiotherapy, TME, and postoperative chemotherapy.

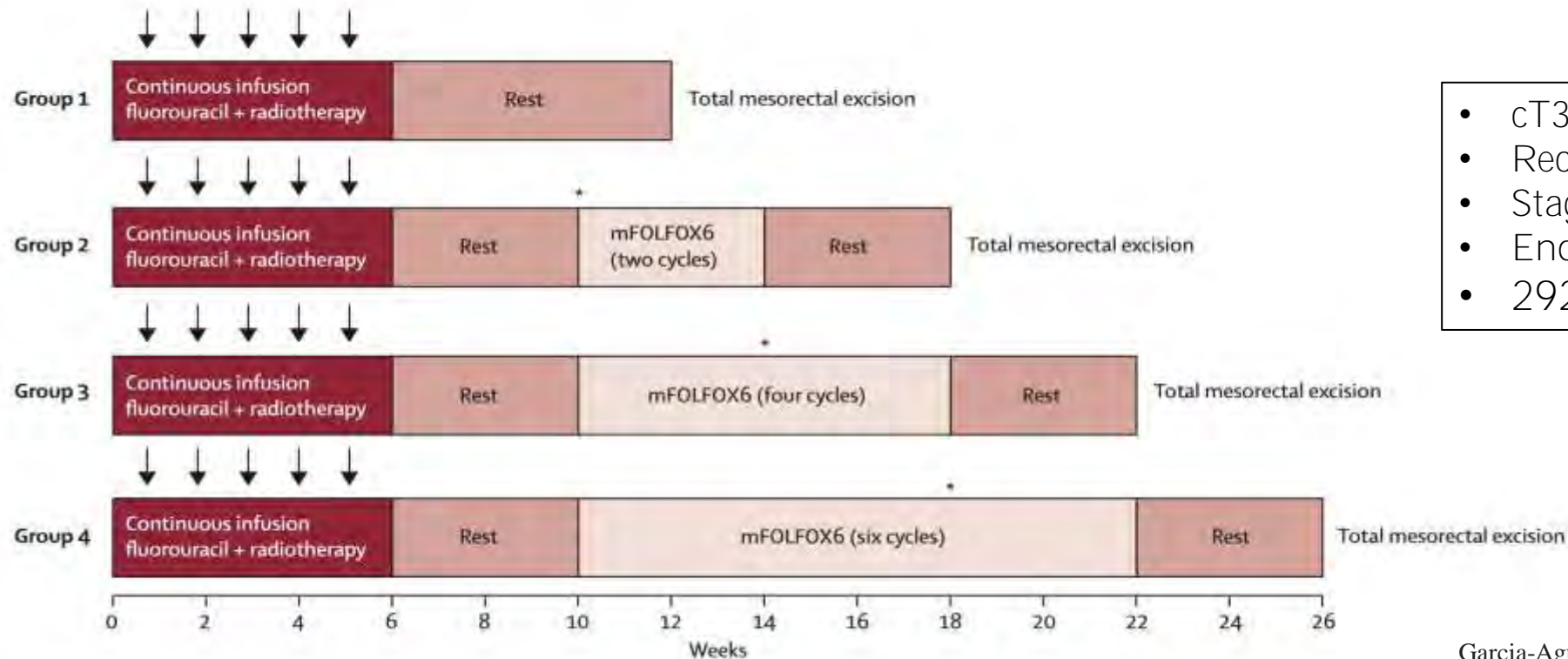
# Distant Metastases in TNT Trials



Trial	Arm	3 yr DM
RAPIDO	SCRT→FOLFOX→TME	20%
	CRT→TME→FOLFOX	27%
PRODIGE	FOLFIRINOX→CRT→TME	21%
	CRT→TME→FOLFOX	28%
OPRA	FOLFOX→CRT→TME	16%
	CRT→FOLFOX→TME	18%



# Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial



- cT3–4N0 or T(any)N1/2
- Rectal Adenocarcinoma
- Staged with MRI or Endorectal Ultrasound
- 292 pts registered

Garcia-Aguilar J, et al. *Lancet Oncol.* 2015;16(8):957.

	Group1 n=60	Group2 n=67	Group3 n=67	Group4 n=65	<i>p</i>
pCR	11(18%)	17(25%)	20(30%)	25(38%)	0.0036

# Ongoing GERMAN TNT Trial CAO/ARO/AIO-18.1

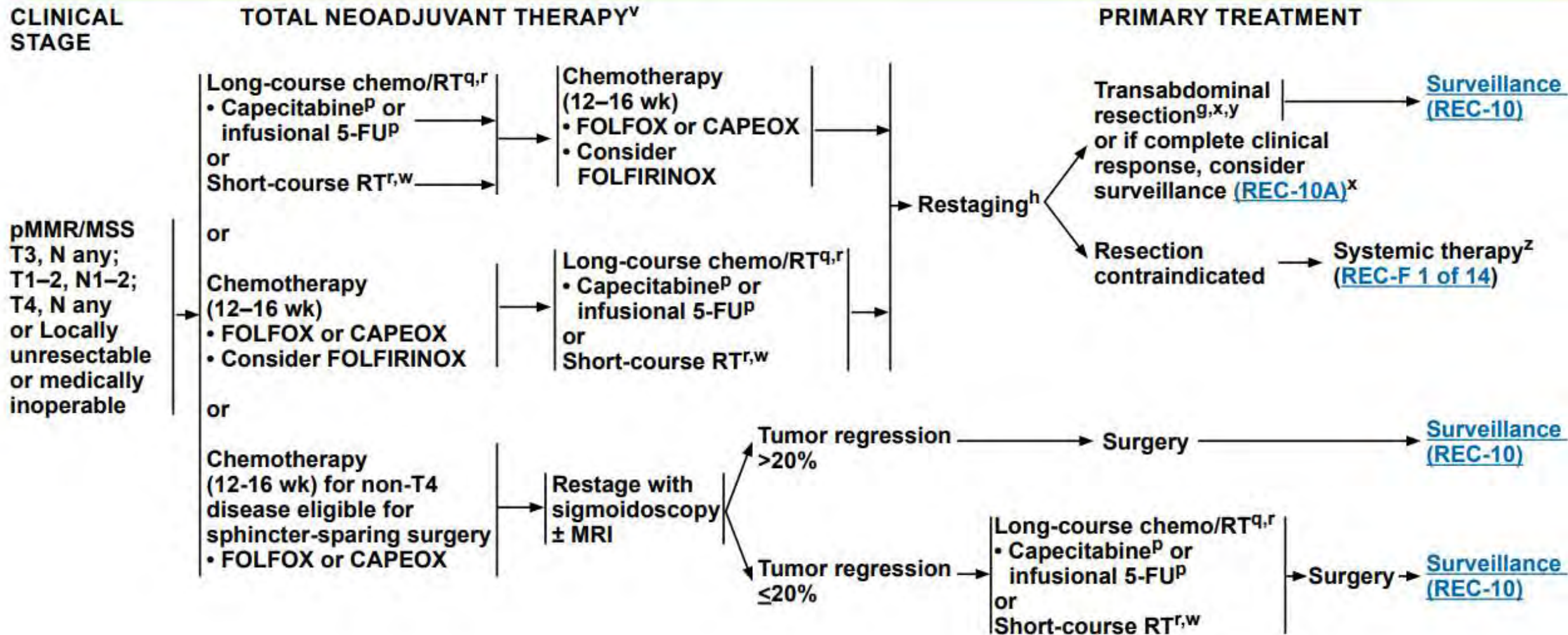


**Primary endpoint: Organ preservation at 3 years**

Hypothesis: 30% in control, 40% in experimental arm

Power 90% at two-sided significance level of 5%.

Sample size **351 patients per group**



CRM (Circumferential resection margin): measured at the closest distance of the tumor to the mesorectal fascia.  
 Clear CRM: Greatest than 1 mm from mesorectal fascia and levator muscles and not invading into the intersphincteric plane.



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