EVIDENCE AND PRACTICE CHANGING TREATMENTS IN GI TUMORS

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Conflict of interests: none declared

:: Agenda

- TNT strategies
- Organ-preserving strategies
- New perspectives

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- Organ-preserving strategies
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:: Introduction

Total Neoadjuvant Therapy strategies

Not conclusive evidence	Enhanced concomitant chemoradiotherapy Addition of concomitant oxaliplatin, bevacizumab,...	ACCORD12/PRODIGE 2, STAR-01
Experimental - Initially resectable advanced rectal cancer (cT3 or cT1-3N+)	• Neoadjuvant chemotherapy: Neoadjuvant Chemotherapy → Surgery	FOWARC trial, ...
Initially non-resectable high-risk rectal cancer (cT3-4 CME <1 mm on MRI)	• Induction chemotherapy Induction Chemotherapy → Chemoradiotherapy → Surgery • Consolidation chemotherapy: Chemoradiotherapy → Consolidation Chemotherapy → Surgery Short-course → Consolidation Chemotherapy → Surgery	PRODIGE 23 study GRECCAR 4 trial GCR-3 trial CAO/ARO/AIO-12, ... RAPIDO trial Polish II study CAO/ARO/AIO-12, ...

mod. from Ominelli J, et al, Clin colorectal cancer, 2021

:: PROSPECT trial

- 1194 rectal ca pts T2-3N+, T3N0 randomized to:

RCHT 50.4 Gy + fluoripirimidine + Adj mFOLFOX6 x 8 suggested	mFOLFOX6 x 6 + Adj mFOLFOX6 x 6 for R+ pts suggested

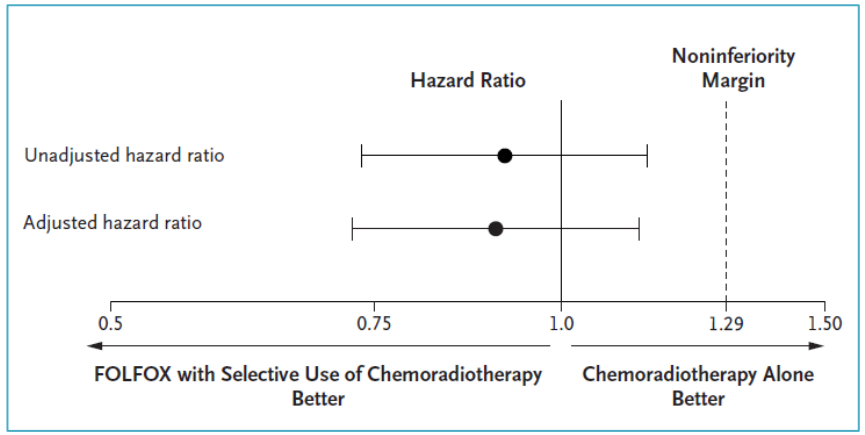
I end-point: DFS (non inferiority)

II end-point: OS, local recurrence, R0 resection, pCR, toxicity

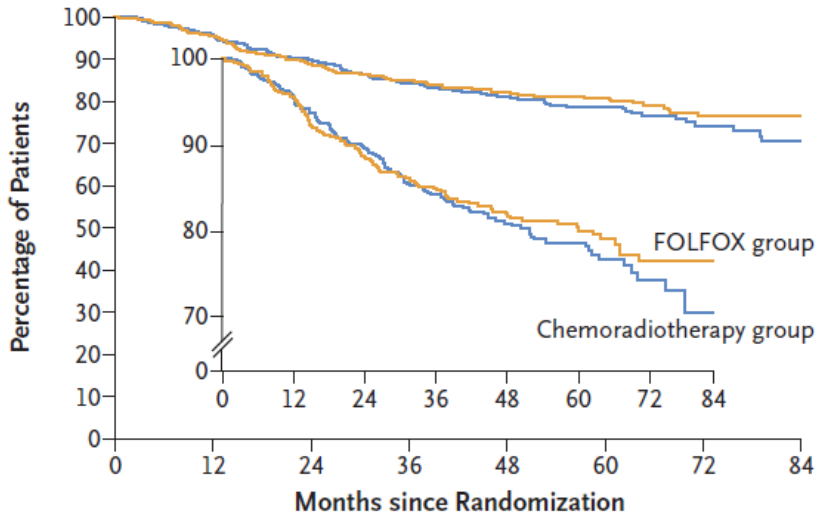
Patients who were unable to complete at least five cycles of FOLFOX were given chemoradiotherapy (with the use of the procedures used in the chemoradiotherapy group; see below). Patients whose primary tumor had decreased in size by at least 20% as determined by the surgeon on the basis of restaging imaging, proctoscopy, and physical examination proceeded to surgery, and those whose primary tumor had decreased in size by less than 20% received chemoradiotherapy.

Schrag D, et al. NEJM 2023

:: PROSPECT trial



5-year DFS: 78.6% versus 80.8%



No. at Risk								
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)	—

Schrag D, et al. NEJM 2023

:: PROSPECT trial

5-year OS: 90.2% versus 89.5% (HR 1.04)
5-year local recurrence: 1.6% versus 1.8% (HR 1.18)
R0 rate: 91.2% versus 90.4%
pCR: 24.3% versus 21.9%

Adherence to treatment in the FOLFOX group (585 pts):

- 53 (9.1%) pts received RCHT

Adhrence to treatment in the RCHT group (543 pts): 94.8%

Toxicity	RCHT	mFOLFOX6
Any grade ≥3	22.8%	41%

Schrag D, et al. NEJM 2023

The New York Times

Rectal Cancer Patients Could Be Spared t

A large "de-es
people annua

Allison Rosen, MS @ARo... · 04 giu 23
Best talk of the day goes to @debschrag talking about the most updated data in the **PROSPECT** study for **rectal** cancer patients! Pay close attention to the female sexual function!

@ASCO @OncoAlert #ASCO23 #crcsm #ayacsm @fireflyann

Matthias Gaduschnigg ... · 05 giu 23
(1/n)

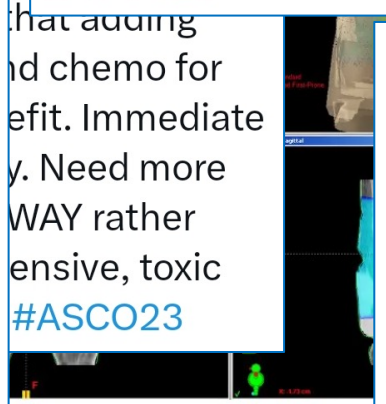
PROSPECT – important study of high quality & relevance for **rectal** cancer pts
nejm.org/doi/full/10.10...

HOWEVER, misleading & dangerous interpretation of @nytimes „brutal effects of RT"

nytimes.com
Rectal Cancer Patients Could Be Spared the Effects of Radiation

Nadia Laurent, MD, FA... · 04 giu 23
PROSPECT definitely moves the field forward for **rectal** cancer - just remember those that don't get 20% response to FOLFOX, have T4 or N2 tumors or need APR still need radiation
#ASCO23

that adding
nd chemo for
efit. Immediate
y. Need more
WAY rather
ensive, toxic
#ASCO23



s of a radiotherapy treatment plan for targ
color-coded from red (high) to blue (low),
ected area. Antonia Reeve/Science Source

This site is intended for healthcare professionals
Medscape
News > Medscape Medical News > Conference News > ASCO 2023

mitting Radiation in ectal Cancer: 'Less Is ore'

m Davenport
e 04, 2023

ICAGO — Many patients with locally vanced rectal cancer can skip radiotherapy to the pelvic area, and instead be treated with ery, say he

atz, MD
18,9K

Gilad Gal @GI_RadOnc · 08 giu 23
In risposta a @GI_RadOnc
Many of the patients included in the trial had "low-risk" **rectal** tumors and several guidelines were actually already considering these for primary surgery without any pre-OP treatment.
bit.ly/3OWpjDk
Both arms in **PROSPECT** are overtreatment for these patients.

Unfortunately, several newspapers reported the PROSPECT trial using provocative and misleading headlines, describing the effects of radiation as "brutal". Such inflammatory use of language not only goes beyond the evidence generated by the PROSPECT trial but also risks unnecessarily alarming a large group of patients with rectal cancer for whom radiation therapy will still form an important part of their cancer treatment with proven beneficial effects on survival and quality-of-life.

On behalf of the European radiation oncology community and our patients, ESTRO therefore urges a return to responsible communication presenting scientific facts in a balanced manner with headlines that inform rather than alarm.

Pierfrancesco Franco, Chair, ESTRO Lower GI Focus Group

Emmanouil Fokas, Course Director, ESTRO Lower GI Course

Anna Kirby, ESTRO President

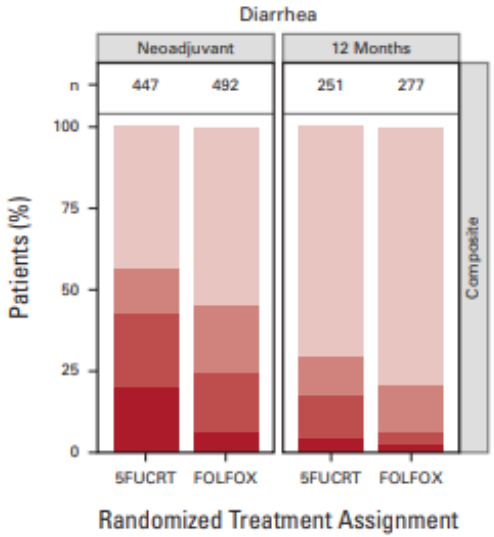
Matthias Guckenberger, ESTRO President-Elect

Ben Slotman, ESTRO Past-President

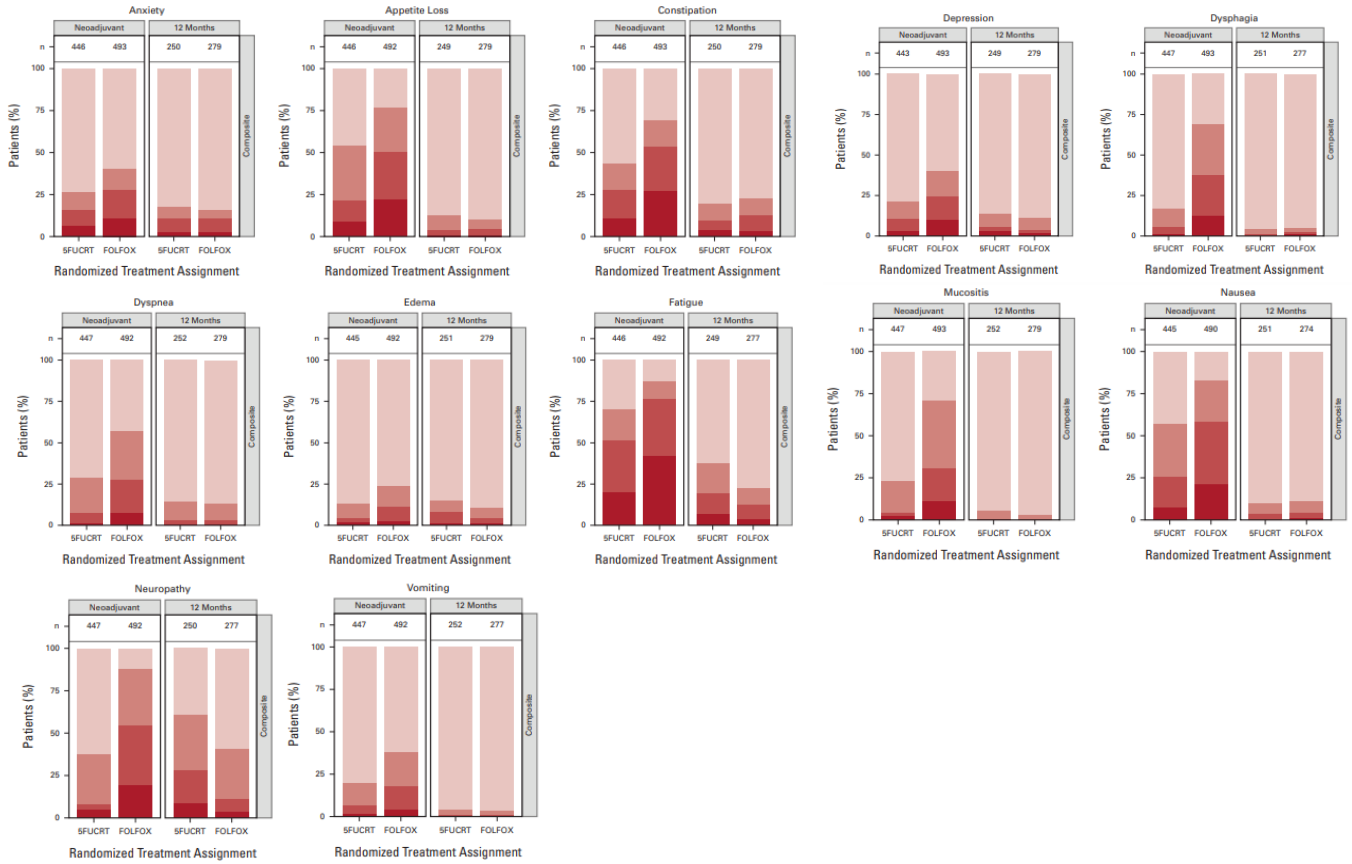
ESTRO

:: PROSPECT trial – patient-reported outcomes analysis

Favoring FOLFOX

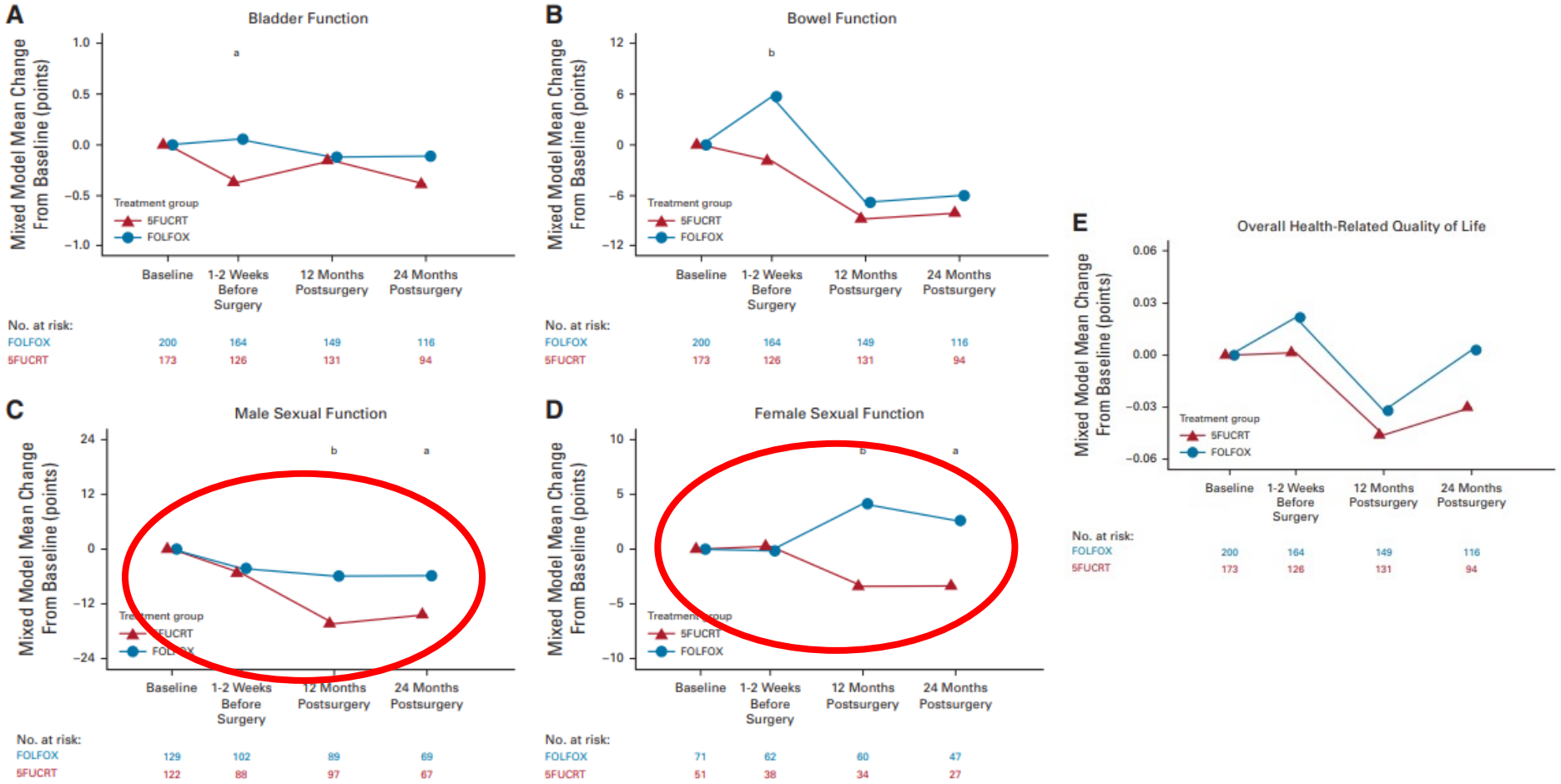


Favoring RCHT



Basch E, et al. JCO 2023

:: PROSPECT trial – patient-reported outcomes analysis



Basch E, et al. JCO 2023

:: CONVERT phase III trial – initial results

663 LARC patients **cT2N+** or **cT3-4aN0-2** randomized to:

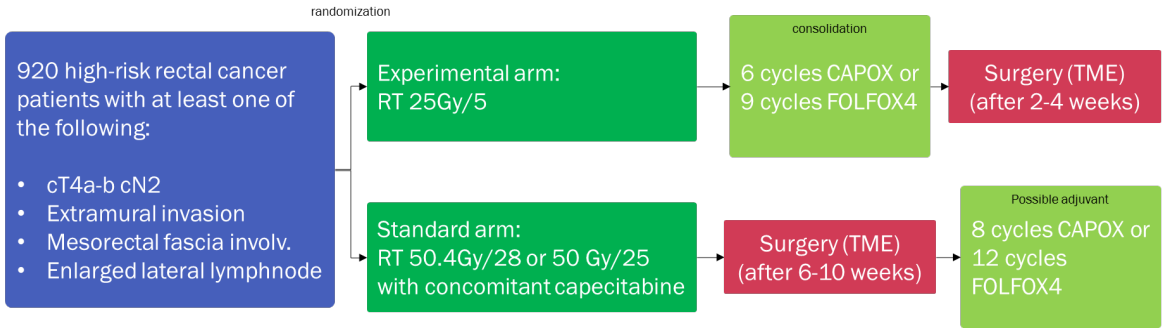
- Arm A: RCHT 50-45/25 fx IMRT + cape -> TME 6-10 w -> adj CAPOX x 6
- Arm B: CAPOX x 4 -> TME 2-4w -> adj CAPOX x 4

- I end-point: 3-y locoregional failure-free surv (non-inferiority)
- II end-point: 3-y DFS, pCR, TRG, R0 rate

	RCHT	CHT	P
pCR	13.8%	11%	0.33
TRG 0-1	**36.8%**	**23.2%**	**<0.001**
R0	99.6%	99.6%	0.99
Postoperative complications	25.7%	18.8%	0.05
Neoadj deaths	0	2	-
G3 toxicity	12.3%	8.3%	0.11

Mei WJ E, et al. Ann Surg 2023

:: RAPIDO trial – 5 year follow-up



Secondary analysis of RAPIDO trial

Study end-point: Locoregional relapse (LRR) analysis after R0/R1 resection

5-y DMFS: 77% versus 69.6% (p=0.011). No OS differences

LRR after R0 or R1 resection: EXPERIMENTAL versus STANDARD: 10.2% versus 6.1%; **p=0.027**
LRR after R0: EXP versus SND: 7.2% verus 3.9%; **p=0.049**
LRR after R1: EXP versus SND: 39% versus 20.5%; p=0.06

<u>Possible interpretation?</u>

- EXP patients had more often LRR after 3DCRT, and EXP patients were treated significantly more with 3DCRT than SND (p=0.029). In fact, no differences were seen in IMRT patients

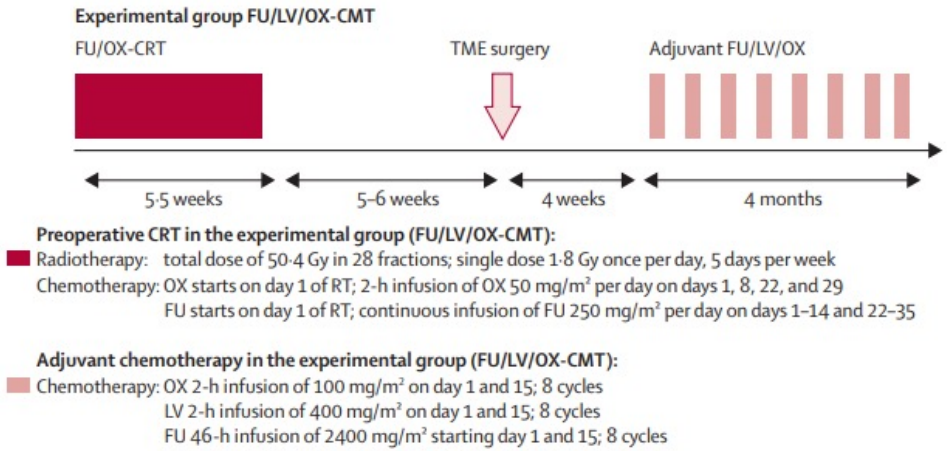
<u>Additional comments?</u>

- Need to refine TNT treatment with early response assessment to avoid the weakest TNT parts (i.e. CHT)

Dijkstra EA, et al. Ann Surg 2023

:: post-hoc analysis: CAO/ARO/AIO-12 versus CAO/ARO/AIO-04

CAO/ARO/AIO-04 (2012)
607 pts



CAO/ARO/AIO-12 (2019)
306 pts

Arm A: induc. FOLFOX x 3 + RCHT -> TME
Arm B: RCHT + consol. FOLFOX x 3 -> TME

IMRT: 50.4 Gy/28 fx + FU/OX (from CAO/ARO/AIO-04)

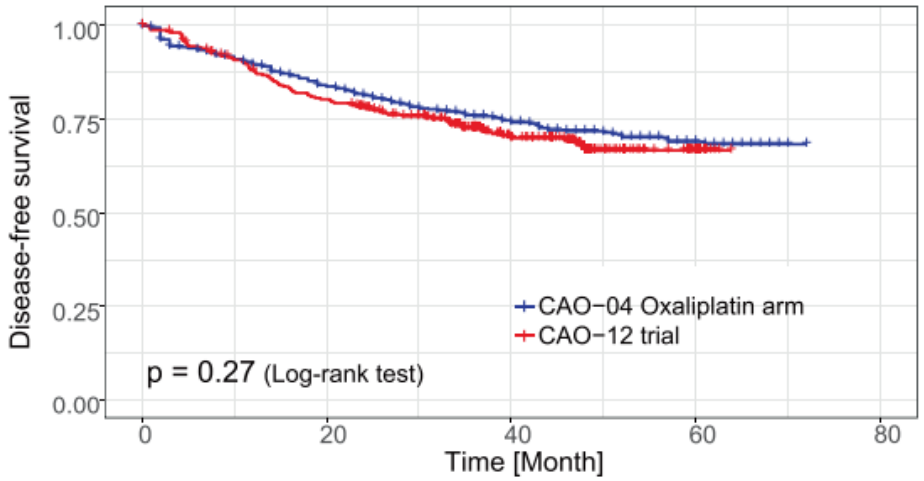
913 patients cT3N0 - cT3-4 cN1-2
I end-point: TRG

Diefenhardt M, et al. Radiother Oncol 2023

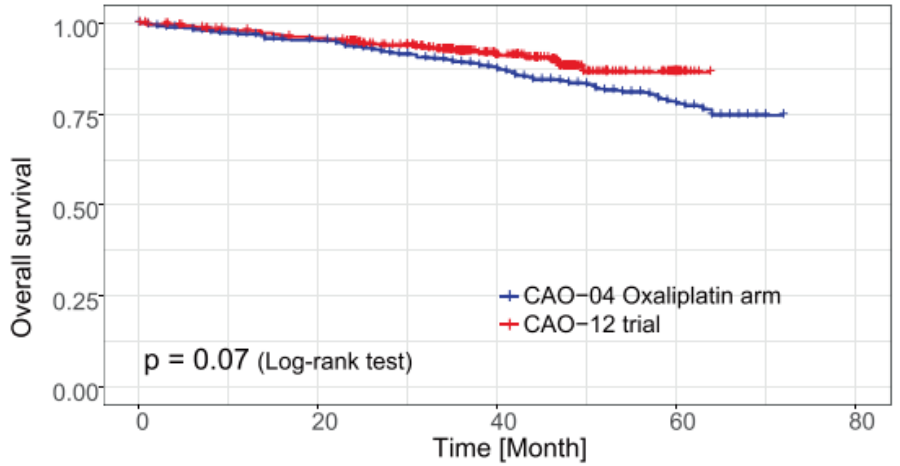
:: post-hoc analysis: CAO/ARO/AIO-12 versus CAO/ARO/AIO-04

Characteristics	No.	CAO-04 trial experimental arm n = 607	CAO-12 Entire cohort n = 306	P-value	CAO-12 Arm A n = 156	P-value [vs CAO-04]	CAO-12 Arm B n = 150	P-value [vs CAO-04]
pCR								
yes	170	105 (17.3 %)	65 (21.2 %)		27 (17.3 %)		38 (25.3 %)	
no	724	483 (79.6 %)	241 (78.8 %)	0.221	129 (82.7 %)	0.899	112 (74.7 %)	0.039

Disease-free survival



Overall survival



No differences in local and distant relapse

Diefenhardt M, et al. Radiother Oncol 2023

:: post-hoc analysis: CAO/ARO/AIO-12 versus CAO/ARO/AIO-04

Characteristics	No.	CAO-04 trial experimental arm n = 607	CAO-12 Entire cohort n = 306	P-value
Age				
median age		63.54 years	61.1 years	0.046**
0	698	479 (78.9 %)	219 (71.6 %)	
1	196	115 (18.9 %)	81 (26.5 %)	
2	6	6 (1.0 %)	0 (0 %)	0.007*
missing	13	7 (1.2 %)	6 (1.9 %)	
cT				
cT2	32	22 (3.6 %)	10 (3.3 %)	
cT3	794	543 (89.5 %)	251 (82.0 %)	
cT4	86	41 (6.8 %)	45 (14.7 %)	< 0.001*
missing	1	1 (0.1 %)	0 (0 %)	
cN				
cN0	175	145 (23.9 %)	30 (9.8 %)	
cN+	714	447 (73.6 %)	267 (87.3 %)	< 0.001*
missing	24	15 (2.5 %)	9 (2.9 %)	

Diefenhardt M, et al. Radiother Oncol 2023

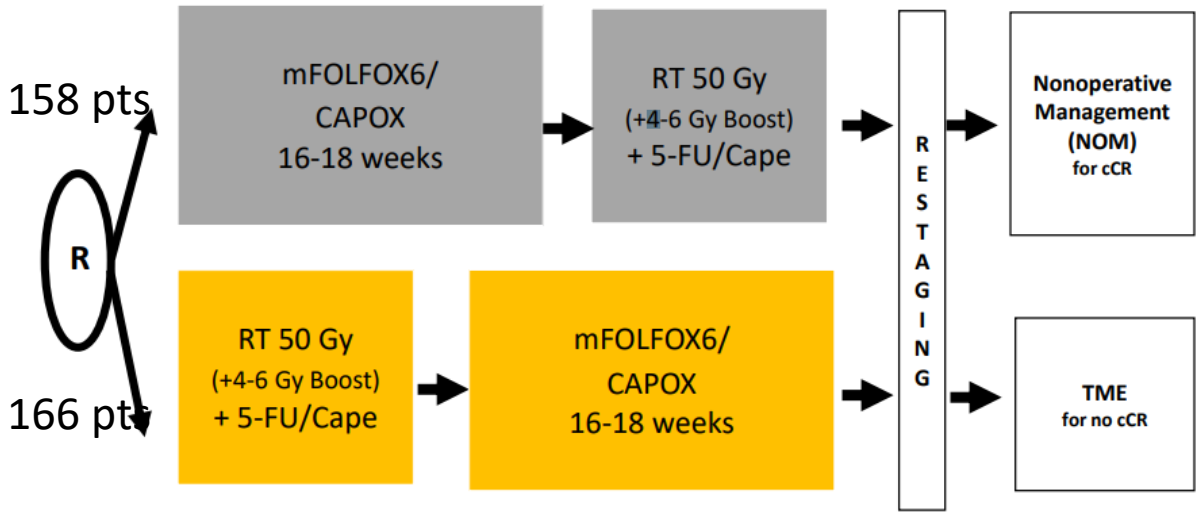
:: Agenda

- TNT strategies
- Organ-preserving strategies
- New perspectives

:: OPRA trial – long term results

OPRA (Organ preservation in Rectal Adenocarcinoma-Trial)

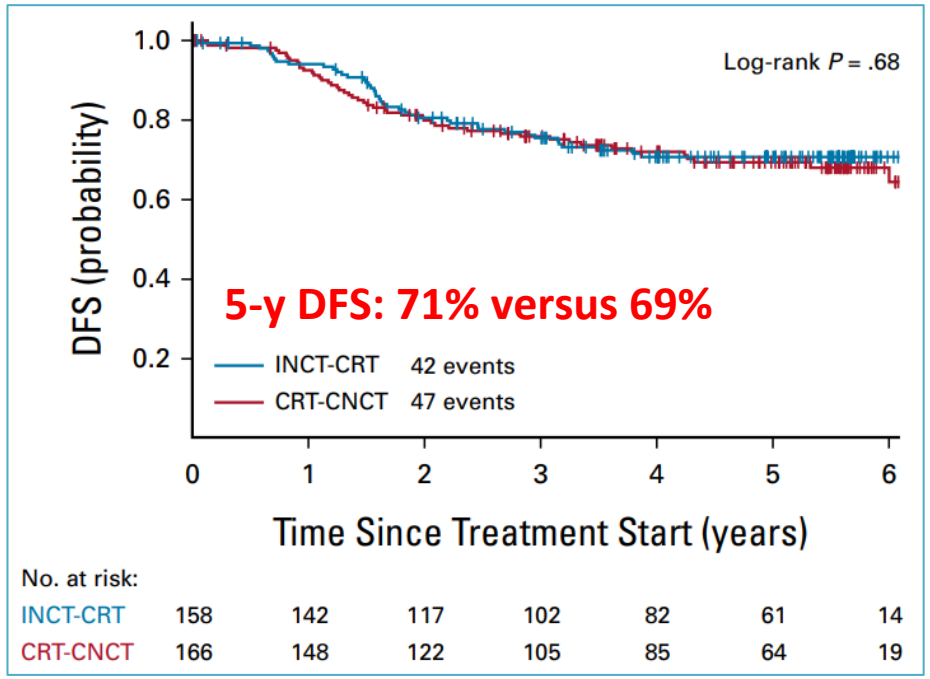
UICC stage II and III, distal RC (requiring APR or coloanal anastomosis)

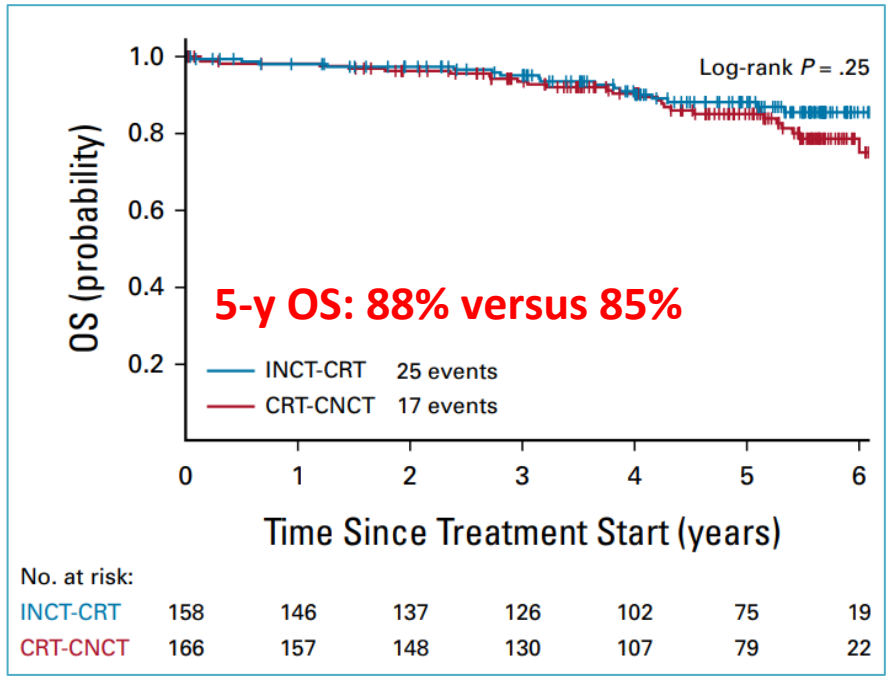


Primary Endpoint: **3y-DFS:** 85% compared to historical 75%; 80% Power, alpha=0.05, n=222
Secondary Endpoint: **3y-NOM** rate: 20% to 35%, n=333

Verheij FS, et al. JCO 2023

:: OPRA trial – long term results





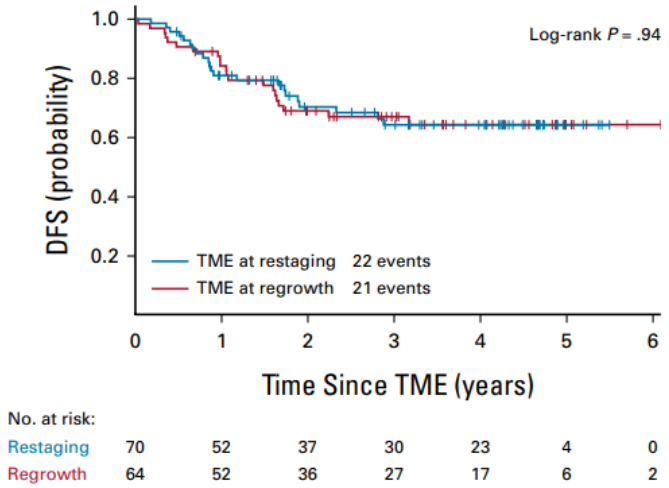
5-y LRFS: 94% versus 90%
5-y DMFS: 80% versus 78%

Verheij FS, et al. JCO 2023

:: OPRA trial – long term results

	Induction	Consolidation	p
Watch & wait	72%	76%	
cCR	51%	58%	
ncCR	45%	39%	
Tumor regrowth	44%	29%	
5-y organ preservation (ITT)	**39%**	**54%**	**0.012**

Tumor regrowth occurred in 81 (36%) of WW patients.
94% occurred within 2 year
99% occurred within 3 years



- R0 resection and sphincter-preserving surgery were similar between TME and WW patients

WW patients requiring TME after tumor regrowth have equivalent survival to patients recommended to undergo TME after TNT for incomplete response

Verheij FS, et al. JCO 2023

:: OPRA trial – secondary analysis

- Does treatment sequence and/or its completion influence toxicity and clinical outcomes?

Compliance to chemotherapy, RT dose, and G3-4 toxicity were not associated with TME-free survival or DFS in the multivariable analysis.

	Induction	Consolidation	p
Tox G≥3	41%	34%	0.3
Tox G5	1.2%	1.8%	n.s.

TME-free survival	
Organ preservation	**Consolidation: HR 0.68 95%CI 0.50-0.94; p=0.02**
cN status	**cN+: HR 1.75 95%CI 1.18-2.58; p=0.005**

Verheij FS, et al. Int J Radiat Oncol Phys 2024

:: OPRA trial – secondary analysis

- IND/CONS chemo schemes: FOLFOX x 8 or CAPOX x 5

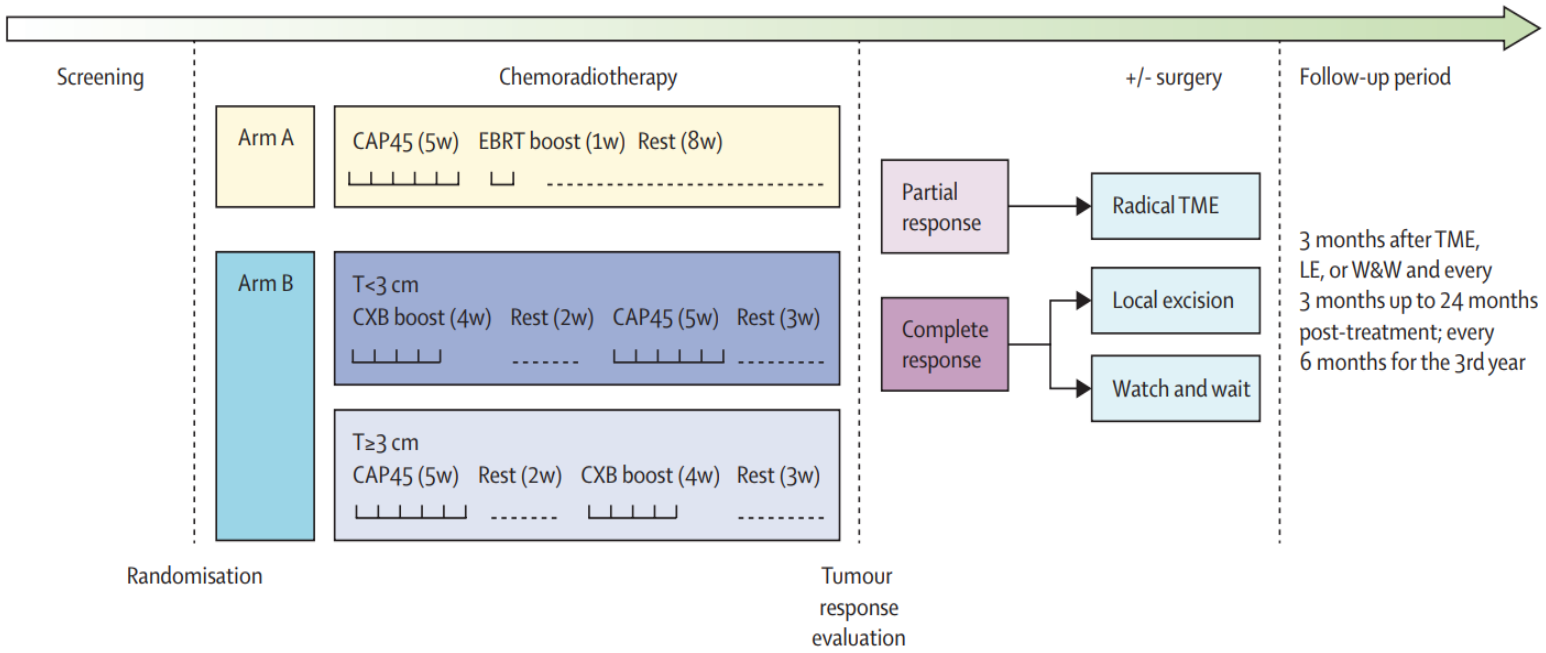
Compliance to treatment analysis

	Induction	Consolidation	
CHT start	**99%**	**94%**	**0.04**
FOLFOX completion	86%	83%	
CAPOX completion	74%	77%	
RT start	**93%**	**98%**	**0.03**
Dead before RT start	3%	0%	
No RT	7%	2%	
RT dose >45 Gy	97%	98%	

Verheij FS, et al. Int J Radiat Oncol Phys 2024

:: OPERA trial

- 148 pts randomized to EBRT boost (5x1.8Gy; total dose 54 Gy) or contact BRT boost (3x30Gy)

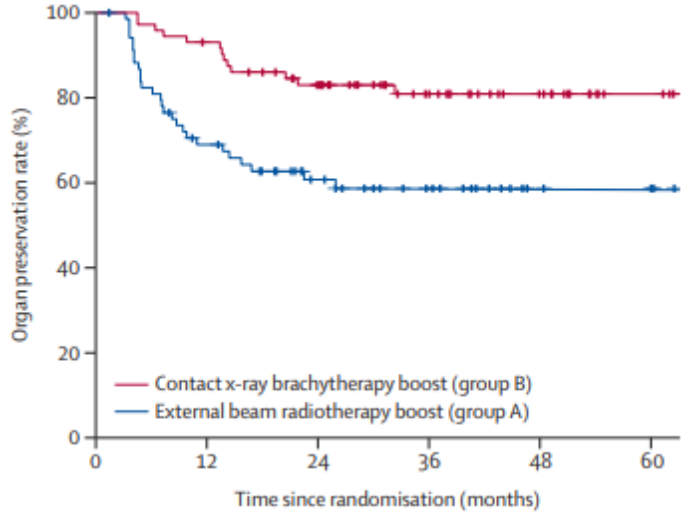


cT2/3a-b cN0-1
I end-point: 3-y organ preservation (OP)
II end-point: cCR, survival, toxicity
Post-hoc: local regrowth, distant relapse

Gerard JP, et al. Lancet Gastro Hepat 2023

:: OPERA trial

- Median FU 38.2 months



	EBRT	CXB	p
OP	59%	81%	HR 0·36, 95% CI 0·19–0·70; **p=0·0026**
OP T<3 cm	63%	97%	HR 0·07, 95% CI 0·01–0·57; **p=0·012**
OP T>3 cm	55%	68%	HR 0·54, 95% CI 0·26–1·10; p=0·11
cCR week 14	39%	47%	
cCR + ncCR week 14	58%	81%	**0.0006**

Gerard JP, et al. Lancet Gastro Hepat 2023

:: OPERA trial

- No grade 4-5 tox

	EBRT	CXB	P
Acute grade 3	4%	5%	n.s.
Late rectal bleeding grade 2	12%	63%	<0.0001

Study limitations:

- Unpowered analysis for T>3 cm (no significant correlation)
- Rigid rectoscopy was regularly performed for response assessment in CXB group (especially for T<3 cm) but not regularly for EBRT group
- No defined consensus for ncCR patients

Gerard JP, et al. Lancet Gastro Hepat 2023

:: OPERA trial – 36 months update

- Is organ preservation or surgical outcome compromised by dose escalation?

- Surgery in 66 pts: local excision in 27 (20%) and TME in 39 (29%)

	TME	APER	Anterior resection	
Arm A (EBRT)	26 (39%)	10 (38.5%)	16 (61.5%)	
Arm B (CXB)	13 (19%)	7 (53.8%)	6 (46.2%)	
p	HR 0.38, p=0.00419	>0.05		

No differences in surgical complication rate and outcomes (staging, R-status)

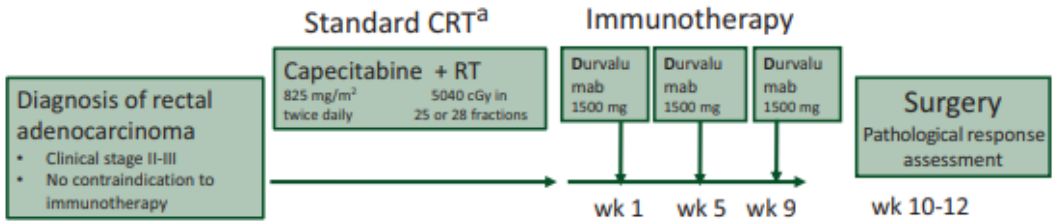
Myint AS, et al. Colorectal Dis 2023

:: Agenda

- TNT strategies
- Organ-preserving strategies
- New perspectives

:: PANDORA trial

- Phase II study on 60 recal ca pts T3-4 N1-2



- I end-point: pCR
- II end-points: adverse events, DFS

Median surg time	pCR	Median FU	Local relapse	Distant relapse
12.7 weeks	34.5%	22.2 mo	3.6%	11%

	Grade 1/2	Grade 3
Gastrointestinal toxicity		
Anorexia	1 (1.8)	
Diarrhea	2 (3.6)	1 (1.8)
Mucorrhea	1 (1.8)	
Nausea	1 (1.8)	
Pancolitis		1 (1.8)
General toxicity		
Asthenia	7 (12.7)	
AST/ALT increase	1 (1.8)	1 (1.8)
Cardiac toxicity	1 (1.8)	
Chest pain	1 (1.8)	
Dysgeusia	1 (1.8)	
Erythema	1 (1.8)	
Fever	1 (1.8)	
Hyperthyroidism	1 (1.8)	
Hypothyroidism	5 (9.1)	
Hot flushes	1 (1.8)	
Lipase/amylase increase	5 (9.1)	1 (1.8)
Pneumonitis	1 (1.8)	
Pruritus	1 (1.8)	
Sarcoidosis-like reaction	1 (1.8)	
Skin toxicity	2 (3.6)	
Stomatitis	1 (1.8)	
Weight loss	1 (1.8)	

Grassi E et al., ESMO 2023

PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

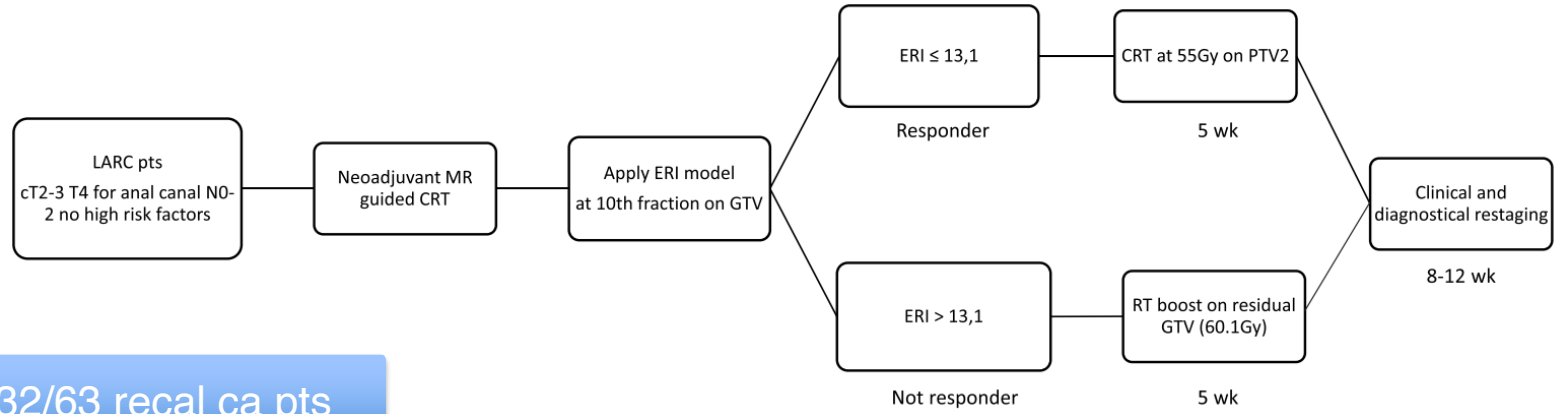
Andrea Cercek, M.D., Melissa Lumish, M.D., Jenna Sinopoli, N.P., Jill Weiss, B.A., Jinru Shia, M.D., Michelle Lamendola-Essel, D.H.Sc., Imane H. El Dika, M.D., Neil Segal, M.D., Marina Shcherba, M.D., Ryan Sugarman, M.D., Ph.D., Zsofia Stadler, M.D., Rona Yaeger, M.D., et al.

NEJM 2022

Methods: We initiated a prospective phase 2 study in which single-agent dostarlimab, an anti-PD-1 monoclonal antibody, was administered every 3 weeks for 6 months in patients with mismatch repair-deficient stage II or III rectal adenocarcinoma. This treatment was to be followed by standard chemoradiotherapy and surgery. Patients who had a clinical complete response after completion of dostarlimab therapy would proceed without chemoradiotherapy and surgery. The primary end points are sustained clinical complete response 12 months after completion of dostarlimab therapy or pathological complete response after completion of dostarlimab therapy with or without chemoradiotherapy and overall response to neoadjuvant dostarlimab therapy with or without chemoradiotherapy.

Results: A total of 12 patients have completed treatment with dostarlimab and have undergone at least 6 months of follow-up. All 12 patients (100%; 95% confidence interval, 74 to 100) had a clinical complete response, with no evidence of tumor on magnetic resonance imaging, ^{18}F-fluorodeoxyglucose-positron-emission tomography, endoscopic evaluation, digital rectal examination, or biopsy. At the time of this report, no patients had received chemoradiotherapy or undergone surgery, and no cases of progression or recurrence had been reported during follow-up (range, 6 to 25 months). No adverse events of grade 3 or higher have been reported.

:: THUNDER 2 phase II trial (NCT04815694)



Interim analysis of 32/63 recal ca pts

ERI* response:
16 (50%) Responders
16 (50%) Non-responders 50%

Toxicity	G1	G2	G3	P
No boost	11 (34.5%)	3 (9.4%)	1 (3.2%)	0.54
Boost	11 (34.5%)	4 (12.5%)	0	

$$ERI_{TCP} = -ln\left[\left(1-\left(\frac{V_{ther}}{V_{pre}}\right)\right)^{V_{pre}}\right]$$

*Cusumano D et al., RedJournal 2022

Chiloiro G et al., Radiat Oncol 2023

:: Conclusions

- New evidence from TNT studies confirm the favourable outcome of IND/CONS chemo in high-risk RC
- Consolidation chemo might improve better organ preservation
- New evidence of chemo alone as non-inferior neoadjuvant treatment (but also higher toxicity) -> importance of QoL assessment
- RT dose intensification as the 3° arm of neoadj strategies
- How much chemo is required?

- Ready for a tailored approach in locally advanced RC in 2024?

Thanks for your attention!

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