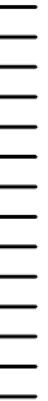


**The total neoadjuvant approach:  
when and where to add chemotherapy in  
rectal cancer**



## Advantages

Better chemotherapy compliance

Lower metastatic rates; better DFS

Earlier ileostomy reversal

Increase response rates that can:

- enhance R0 resection rate

- optimize adaptive strategies

- help pt selection for W&W

# TNT in rectal cancer: advantages

*Ludmir et al. Cancer 2017; Petrelli et al. Ann Surg 2020;  
Glynn-Jones et al. Ann Oncol 2017; Conroy et al. ASCO 2020;  
Garcia-Aguilar et al. ASCO 2020; Bahadoer et al. ASCO 2020*

Advantages	Disadvantages/uncertainties
Better chemotherapy compliance	Potential overtreatment in some pts
Lower metastatic rates; better DFS	Unclear which pts benefit (biology)
Earlier ileostomy reversal	Unclear how much chemo is needed
Increase response rates that can:	Unclear how long before restaging
-enhance R0 resection rate	Unclear inclusion criteria (TNM)
-optimize adaptive strategies	Unclear RT dose/schedule
-help pt selection for W&W	Unclear if TNT improves OS

## TNT in rectal cancer: advantages and uncertainties

*Ludmir et al. Cancer 2017; Petrelli et al. Ann Surg 2020;  
Glynn-Jones et al. Ann Oncol 2017; Conroy et al. ASCO 2020;  
Garcia-Aguilar et al. ASCO 2020; Bahadoer et al. ASCO 2020*

Trial (phase)	N	Control arm	Experimental arm	pCR (or cCR)	3-year DFS	Primary endpoint
GCR-3 (II)	108	CAPOX CRT	4x CAPOX → CAPOX CRT	14% vs 13%	70% vs 68%	pCR
EXPERT-C (II)	165	4xCAPOX → CAP CRT	4xCAPOX-Cet → CAP-Cet CRT	11% vs 17%	n.a.	pCR/cCR
KCSG-CO14-03 (II)	110	CAP CRT	CAP CRT → 2xCAPOX	6% vs 14%	n.a.	Downstaging
CAO/ARO/AIO-12 (II)	306	3xFOLFOX6 → /OX CRT	5-FU/OX CRT → 3xFOLFOX6	21% vs 28%	n.a.	pCR
OPRA (II)	324	8xFOLFOX6 → 5-FU/OX CRT	5-FU/OX CRT → 8xFOLFOX6	43% vs 59%	n.a.	DFS
GEMCAD1402 (II)	180	6xFOLFOX6 → CAP CRT	6xFOLFOX6+Aflib → CAP CRT	14% vs 23%	n.a.	DFS
Polish-2 (III)	515	5-FU/OX CRT	SCRT → 3x FOLFOX4	12% vs 16%	52% vs 53%	R0-rate
PRODIGE (III)	461	CAP CRT	6xFOLFIRNOX → CAP CRT	12% vs 28%	69% vs 78%	DFS
RAPIDO (III)	920	CAP CRT	SCRT → 9xFOLFOX6	14% vs 28%	30% vs 24% (DrTF)	DrTF

### Trial comparison difficult due to variability in:

- Study design
- Chemo cycles/dose
- Inclusion criteria (TNM)
- Patient numbers
- Primary endpoint

## Randomized TNT trials in rectal cancer

*Fernández-Martos et al. J Clin Oncol 2010/Ann Oncol 2015, Dewdney et al. JCO 2012, Fokas et al. JCO 2019, Kim et al. IJROBP 2018, Bujko et al. Ann Oncol 2016/2019, Fernández-Martos et al. JAMA Oncol 2019, Garcia-Aguilar et al. ASCO 2020, Conroy et al. ASCO 2020, Bahadoer et al. ASCO 2020*

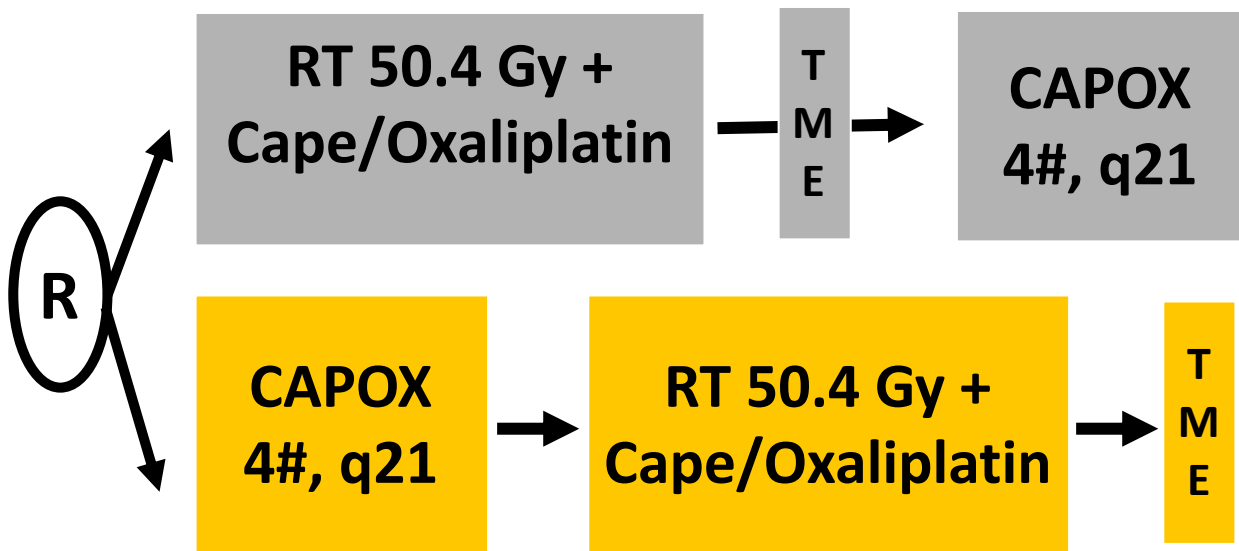
Trial (phase)	N	Control arm	Experimental arm	pCR (or cCR)	3-year DFS	Primary endpoint
GCR-3 (II)	108	CAPOX CRT	4x CAPOX → CAPOX CRT	14% vs 13%	70% vs 68%	pCR
EXPERT-C (II)	165	4xCAPOX → CAP CRT	4xCAPOX-Cet → CAP-Cet CRT	11% vs 17%	n.a.	pCR/cCR
KCSG-CO14-03 (II)	110	CAP CRT	CAP CRT → 2xCAPOX	6% vs 14%	n.a.	Downstaging
CAO/ARO/AIO-12 (II)	306	3xFOLFOX6 → /OX CRT	5-FU/OX CRT → 3xFOLFOX6	21% vs 28%	n.a.	pCR
OPRA (II)	324	8xFOLFOX6 → 5-FU/OX CRT	5-FU/OX CRT → 8xFOLFOX6	43% vs 59%	n.a.	DFS
GEMCAD1402 (II)	180	6xFOLFOX6 → CAP CRT	6xFOLFOX6+Aflib → CAP CRT	14% vs 23%	n.a.	DFS
Polish-2 (III)	515	5-FU/OX CRT	SCRT → 3x FOLFOX4	12% vs 16%	52% vs 53%	R0-rate
PRODIGE (III)	461	CAP CRT	6xFOLFIRNOX → CAP CRT	12% vs 28%	69% vs 78%	DFS
RAPIDO (III)	920	CAP CRT	SCRT → 9xFOLFOX6	14% vs 28%	30% vs 24% (DrTF)	DrTF

**Trial comparison difficult due to variability in:**

- Study design
- Chemo cycles/dose
- Inclusion criteria (TNM)
- Patient numbers
- Primary endpoint

## Randomized TNT trials in rectal cancer

*Fernández-Martos et al. J Clin Oncol 2010/Ann Oncol 2015, Dewdney et al. JCO 2012, Fokas et al. JCO 2019, Kim et al. IJROBP 2018, Bujko et al. Ann Oncol 2016/2019, Fernández-Martos et al. JAMA Oncol 2019, Garcia-Aguilar et al. ASCO 2020, Conroy et al. ASCO 2020, Bahadoer et al. ASCO 2020*



## GCR-3 phase II trial

low T3, T4, T3N+, CRM<2mm

Primary endpoint: pCR

*Fernández-Martos et al. J Clin Oncol 2010*

*Fernández-Martos et al. Ann Oncol 2015*

	<b>CRT</b>	<b>CT/CRT</b>	<b>p</b>
<b>pCR</b>	<b>13%</b>	<b>14%</b>	<b>n.s.</b>
<b>Acute toxicity grade 3-4</b>	<b>54%</b>	<b>19%</b>	<b>0.004</b>
<b>5-year DFS</b>	<b>64%</b>	<b>62%</b>	<b>0.85</b>

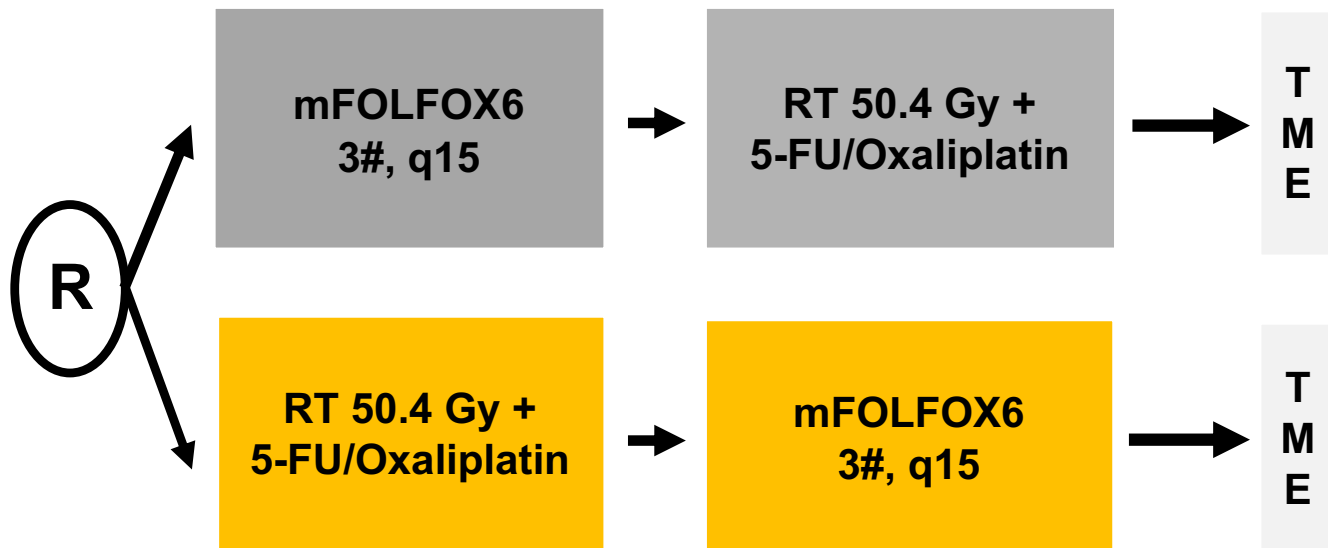
## **GCR-3 phase II trial**

**low T3, T4, T3N+, CRM<2mm**

**Primary endpoint: pCR**

*Fernández-Martos et al. J Clin Oncol 2010*

*Fernández-Martos et al. Ann Oncol 2015*



## CAO/ARO/AIO-12 phase II trial

low T3, T3c/d mid rectal, T4, N+

Primary endpoint: pCR

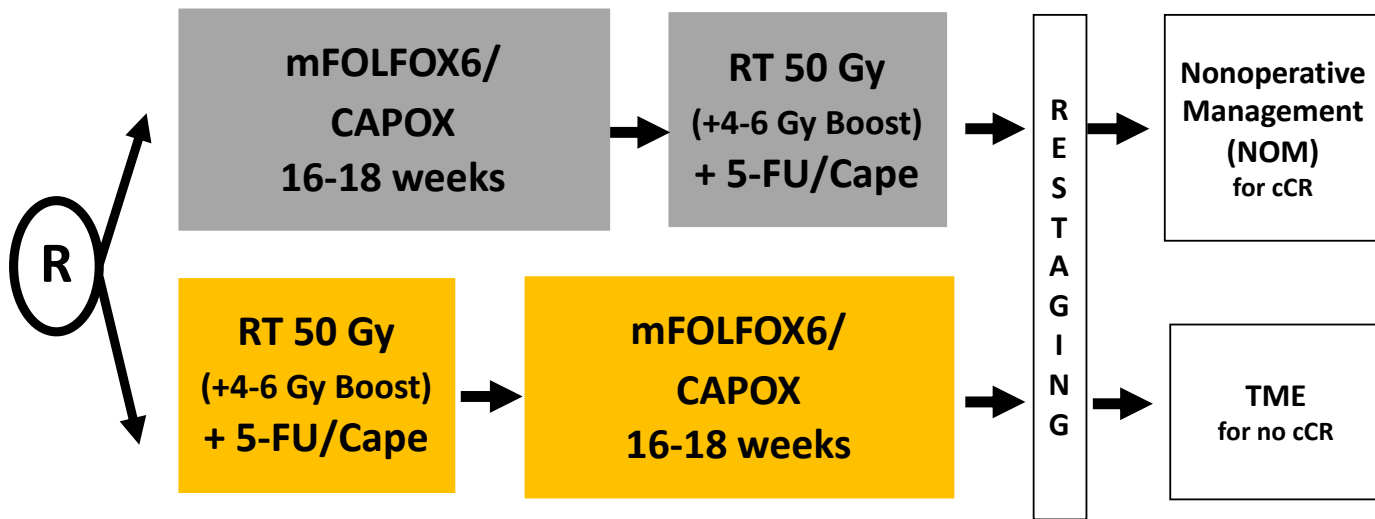


	CT/CRT/S	CRT/CT/S
<b>Abdominoperineal resection</b>	<b>28%</b>	<b>23%</b>
<b>R0-resection</b>	<b>92%</b>	<b>90%</b>
<b>pCR* (ITT analysis)</b>	<b>17% (P=0.210)</b>	<b>25% (P=0.0002)</b>
<b>pCR + cCR</b>	<b>21%</b>	<b>28%</b>
<b>Grade 3-4 Tox CRT/CT</b>	<b>37% / 22%</b>	<b>27%/ 22%</b>
<b>Postoperative morbidity Grade 3-5</b>	<b>17%</b>	<b>16%</b>

## CAO/ARO/AIO-12 phase II trial

low T3, T3c/d mid rectal, T4, N+

Primary endpoint: pCR



## OPRA phase II trial

UICC stage II and III, lower rectal third

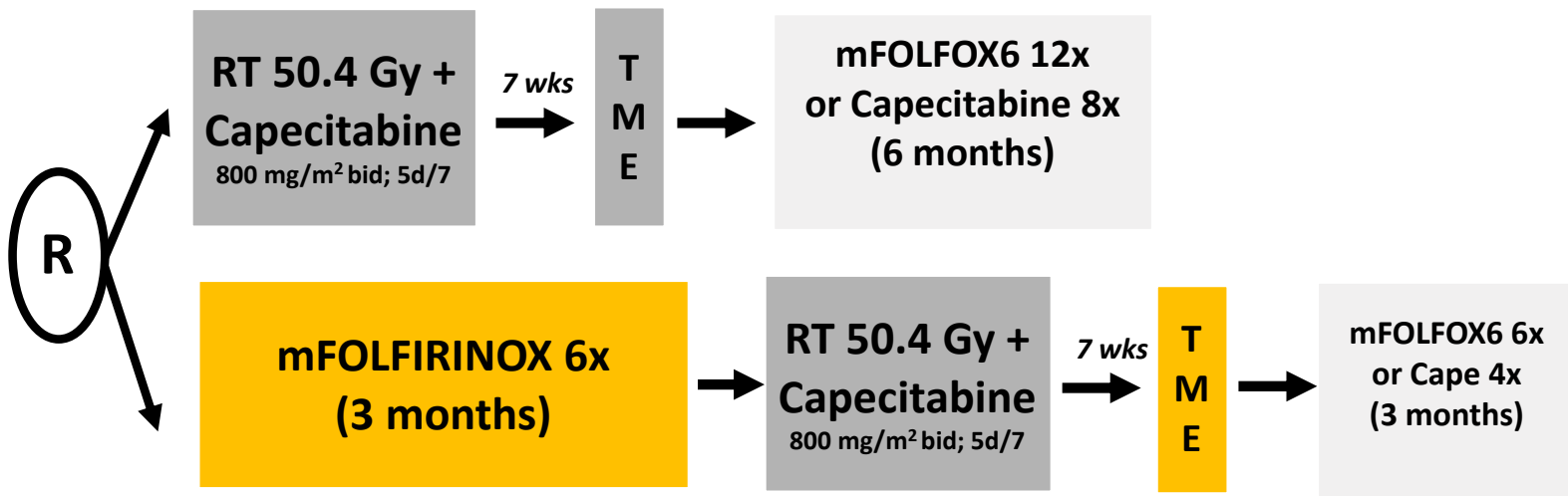
Primary endpoint: DFS

	CT/CRT	CRT/CT	p
<b>DFS</b>	<b>77%</b>	<b>78%</b>	<b>0.90</b>
<b>M1-free Survival</b>	<b>82%</b>	<b>84%</b>	<b>0.83</b>
<b>TME-free Survival</b>	<b>43%</b>	<b>59%</b>	<b>0.007</b>
<b>Overall <math>\geq</math> grade 3 toxicity</b>	<b>49%</b>	<b>45%</b>	<b>0.63</b>

## OPRA phase II trial

UICC stage II and III, lower rectal third

Primary endpoint: DFS



## PRODIGE23 phase III trial

cT3 „at risk of local recurrence“, cT4, <15 cm from anal verge

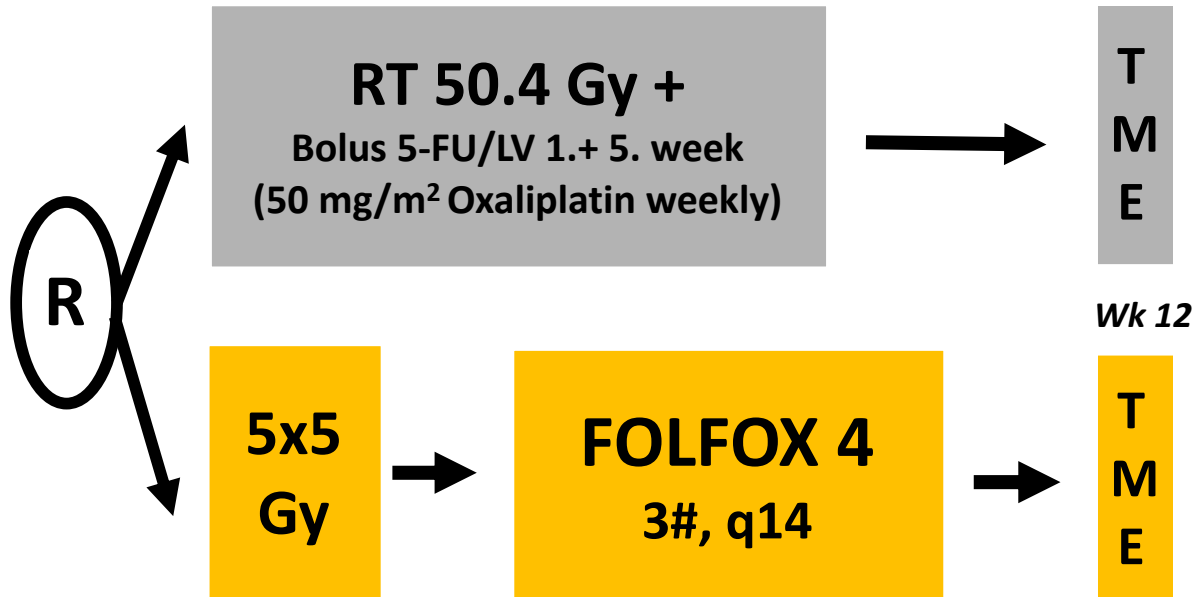
Primary endpoint: DFS

Median F/u= 46.5 months	CRT	CT/CRT	HR/p
<b>DFS (primary endpoint)</b>	<b>68.5 %</b>	<b>75.7 %</b>	<b>0.69 , 0.034</b>
<b>Distant M1-free survival</b>	<b>71.7%</b>	<b>78.8%</b>	<b>0.64, 0.017</b>
<b>pCR</b>	<b>12.1%</b>	<b>27.8%</b>	<b>&lt;0.001</b>
<b>G-CSF use due to <math>\geq</math> grade 3 neutropenia after IC</b>	<b>-</b>	<b>27%</b>	<b>-</b>
<b>Overall local relapse</b>	<b>„No difference 4.8% vs 7%“</b>		
<b>OS</b>	<b>not available</b>		
<b>Health-related QoL</b>	<b>Overall trend in favor for TNT</b>		

## PRODIGE23 phase III trial

cT3 „at risk of local recurrence“, cT4, <15 cm from anal verge

Primary endpoint: DFS



## Polish-2 phase III trial

fixed T3 or T4 („nonresectable“)

Primary endpoint: R0-rate

*Bujko et al. Ann Oncol 2016*

*Bujko et al. Ann Oncol 2019*

	CRT	SCRT/CT	P
<b>R0-rate</b>	<b>71%</b>	<b>77%</b>	<b>0.07</b>
<b>pCR</b>	<b>12%</b>	<b>16%</b>	<b>0.21</b>
<b>Toxicity grade 1-2/ 3-4 / 5</b>	<b>50 / 21 / 3%</b>	<b>60/ 23 / 1%</b>	<b>0.006</b>
<b>8-year DFS</b>	<b>41%</b>	<b>43%</b>	<b>0.65</b>
<b>8-year OS</b>	<b>49%</b>	<b>49%</b>	<b>0.38</b>

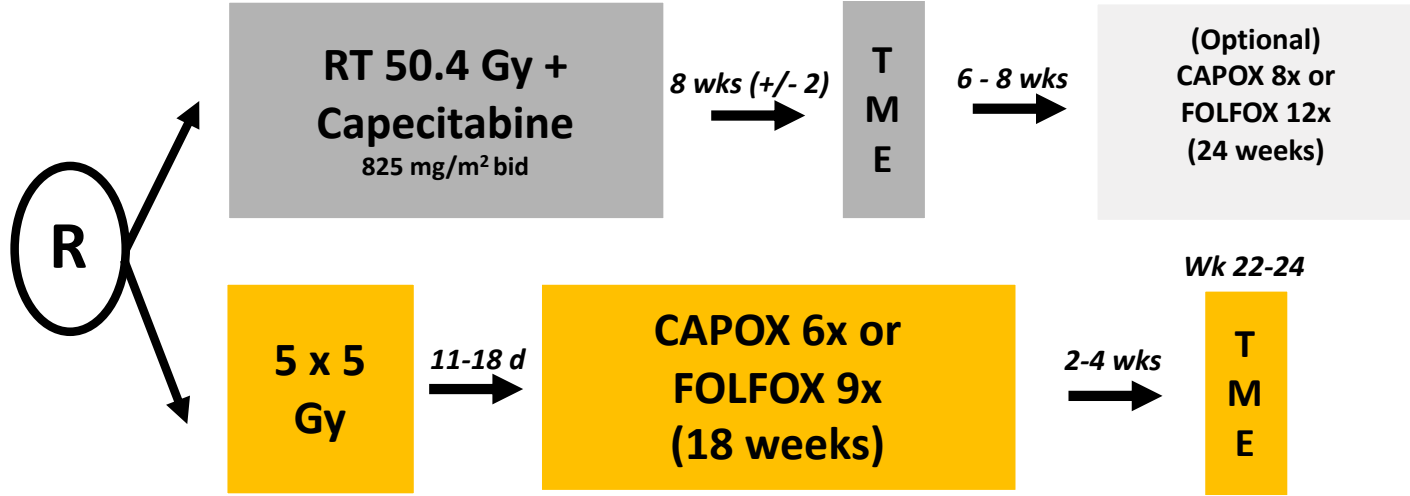
## Polish-2 phase III trial

fixed T3 or T4 („nonresectable“)

Primary endpoint: R0-rate

*Bujko et al. Ann Oncol 2016*

*Bujko et al. Ann Oncol 2019*



## RAPIDO phase III trial

cT4 or MRF+ or N2 or lateral N+ or EMVI+

Primary endpoint: DrTF

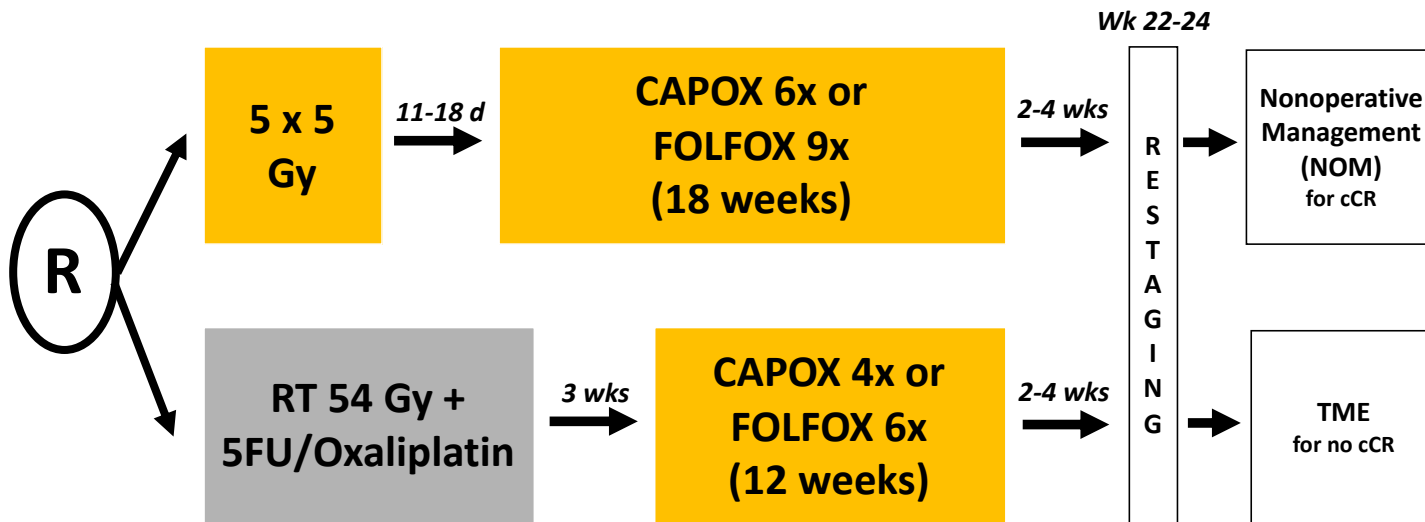


	CRT	SCRT/CT	HR/p
DrTF*	30.4 %	23.7 %	0.75/ p=0.019
Distant M1	26.8%	20.0%	0.69/ p=0.005
Locoreg. failure	6.0%	8.7%	1.45/ p=0.09
OS	88.8%	89.1%	0.92/ p=0.59
Overall $\geq$ grade 3 toxicity	25%	48%	p<0.05
Overall health/QoL/LARS	n.s.	n.s.	n.s.

## RAPIDO phase III trial

cT4 or MRF+ or N2 or lateral N+ or EMVI+

Primary endpoint: DrTF



## ACO/ARO/AIO-18 phase III trial

Any cT3 if low rectal third, cT3c/d, N+, T4 mid rectal third

Primary endpoint: 3-year organ preservation rate

PI: C. Rödel

- n=702
- 80 centers
- NCT04246684

# Conclusion

- If TNT, then which TNT sequence?

CRT/CT if the aim is to ↑ cCR rates to enable organ preservation (CAO/ARO/AIO-12 & OPRA)

- Is TNT the new standard for all pts with locally-advanced rectal cancer?

DFS benefit for high-risk (“ugly”) (RAPIDO; PRODIGE23); DFS benefit for “bad” (PRODIGE23); consider QoL, elderly/frail & patient’s preference; understand biology

- Which RT modality (SCRT vs CRT) as part of TNT for organ preservation?

ACO/ARO/AIO-18 phase III trial will address this question

Advantages	Disadvantages/uncertainties
Better chemotherapy compliance	Potential overtreatment in some pts
Lower metastatic rates; better DFS	Unclear which pts benefit (biology)
Earlier ileostomy reversal	Unclear how much chemo is needed
Increase response rates that can:	Unclear how long before restaging
-enhance R0 resection rate	Unclear inclusion criteria (TNM)
-optimize adaptive strategies	Unclear RT dose/schedule
-help pt selection for W&W	Unclear if TNT improves OS