

# Multimodal Rectal Cancer Management

## *Refresher*

**Claus Rödel**

Department of Radiotherapy

Goethe-University Frankfurt, Germany

## **Erklärung zu möglichen Interessenskonflikten:**

### **Berater- und Gutachtertätigkeiten**

**NEIN**

### **Honorare**

**NEIN**

### **Forschungsfinanzierung**

*Deutsche Krebshilfe*

### **Eigentümerinteressen (Patent, Urheberrecht, Verkaufslizenz)**

**NEIN**

### **Geschäftsanteile, Aktien, Fonds**

**NEIN**

# *Where do we come from?*

T1-3 Nany

5 x 5 Gy +  
immediate  
surgery

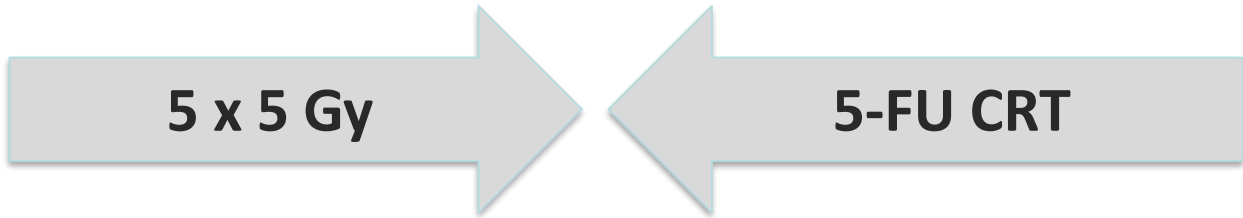
T3/4  
or cN+

5-FU ChemoRT +  
delayed surgery

# What have we learned?

Trial	Randomisation	Local control	DFS	OS
Swedish Trial	5x5 Gy + S vs S alone	✓	✓	✓
Dutch Trial	5x5 Gy + S vs S alone	✓	=	=
British Trial	5x5 Gy + S vs S alone	✓	✓	=
German Trial	Preop CRT vs postop CRT	✓	=	=
French Trial	Preop CRT vs preop RT	✓	=	=
EORTC Trial	Preop CRT vs preop RT	✓	=	=

*Fokesson et al., J Clin Oncol 2005; van Gijn et al., Lancet Oncol 2011; Sebag-Montefiore et al., Lancet 2009; Sauer et al., N Engl J Med 2004; Gerard et al., J Clin Oncol 2006; Bosset et al., Lancet Oncol 2014*



**Polish Trial**  
n=312

**Inclusion (DRE)**  
Low T3-4 Nany

**Primary Endpoint**  
Sphincter Preservation  
(15% difference)

**Trans-Tasman**  
n=326

**Inclusion**  
(ERUS; MRI)  
T3 Nany

**Primary Endpoint**  
Local Recurrences  
(10% difference at 3y)

*Buiko et al., Br J Surg 2006; Ngan SY et al., J Clin Oncol 2012*

<b>Trans-Tasman</b>	<b>5x5 Gy</b>	<b>CRT</b>	<b>P</b>
Acute Tox (Grade 3-4, %)	2	28	<.001
pCR (%)	1	15	<.001
Sphincter Preservation (%)	63	69	0.22
<b>Local Recurrences (3y, %)</b>	7.5	4.4	0.24
Overall Survival (5y, %)	74	70	0.62
Late Tox (Grade 3-4, %)	5.8	8.2	0.53

....similar results: Polish trial

Ngan SY et al., J Clin Oncol 2012

**5 x 5 Gy**

**5-FU CRT**

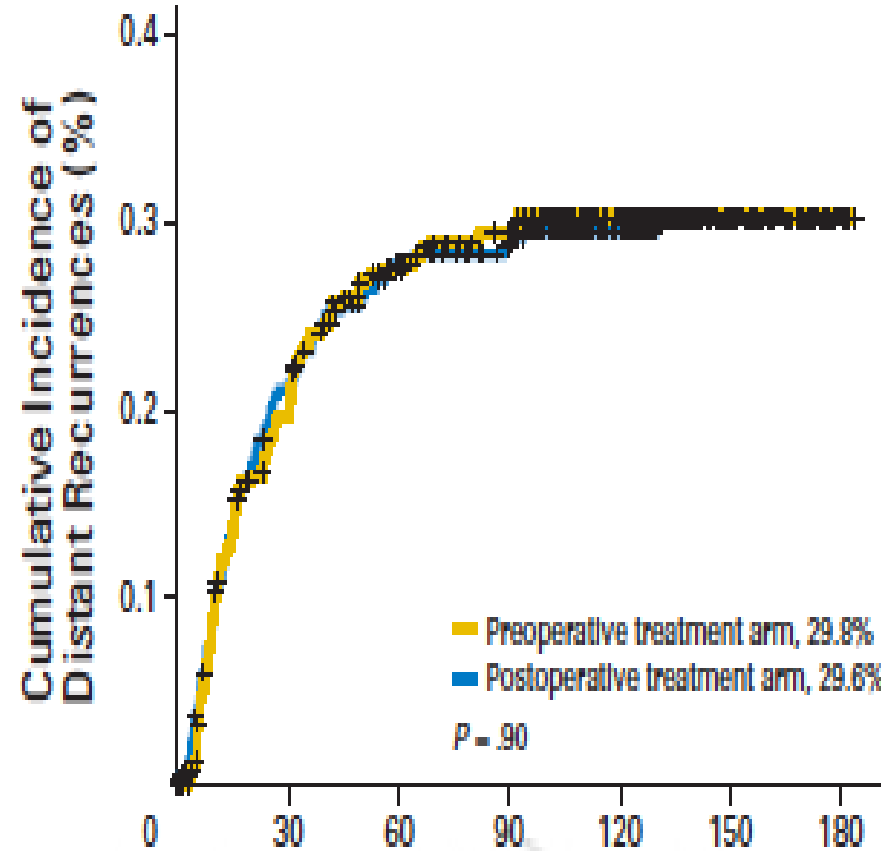
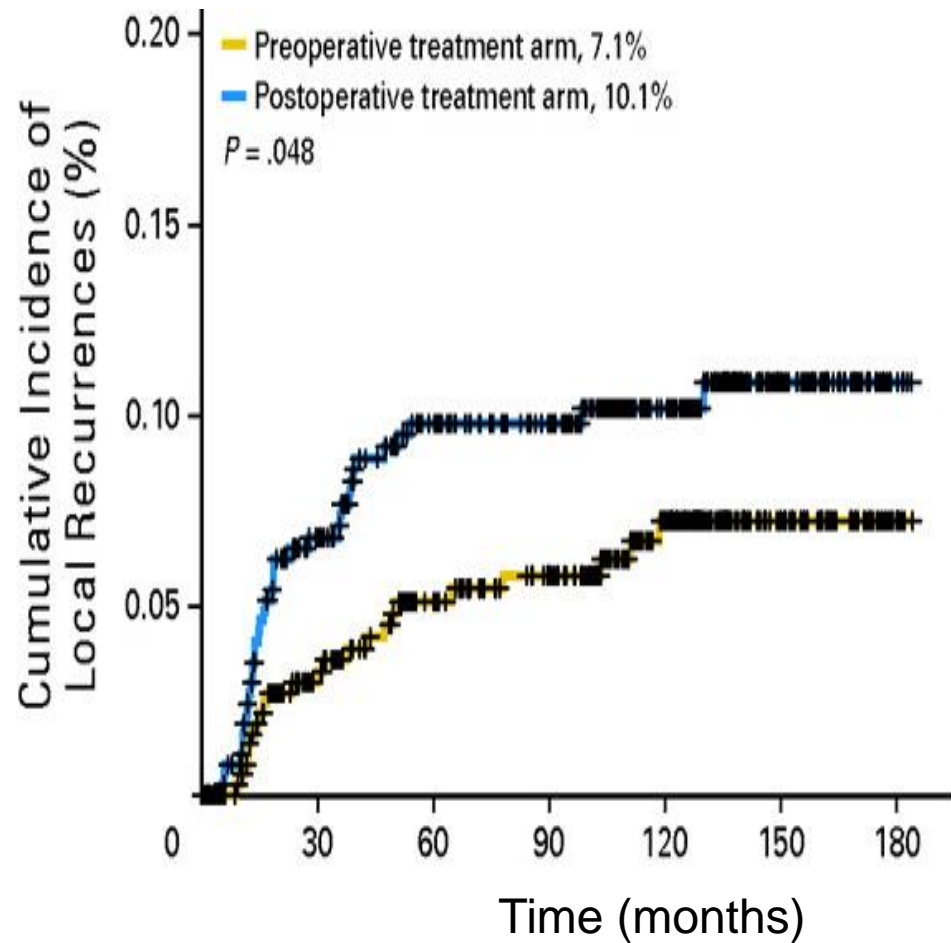
- Less acute tox
- Patient convenience
- Lower cost

- Better downsizing
- Ability to safely combine with chemo

*„The lines were drawn, alliances formed, and we sat at different dinner tables at the ASCO GI Cancers Symposium“*

*Bruce D. Minsky, Editorial, J Clin Oncol 2012*

# CAO/ARO/AIO-94: 10-year results





# *Where do we stand?*



## **De-escalating strategies:**

- Selected RT: TN-, MRI-criteria
- Selected Surgery: Response-adapted LE/NOM/W&W



## **Escalating strategies:**

- Combination chemotherapy
- Total neoadjuvant Treatment (TNT)
- Targeted agents/Immunotherapy

# *Where do we stand?*



## De-escalating strategies:

- **Selected RT: TN-, MRI-criteria**
- Selected Surgery: Response-adapted LE/NOM/W&W



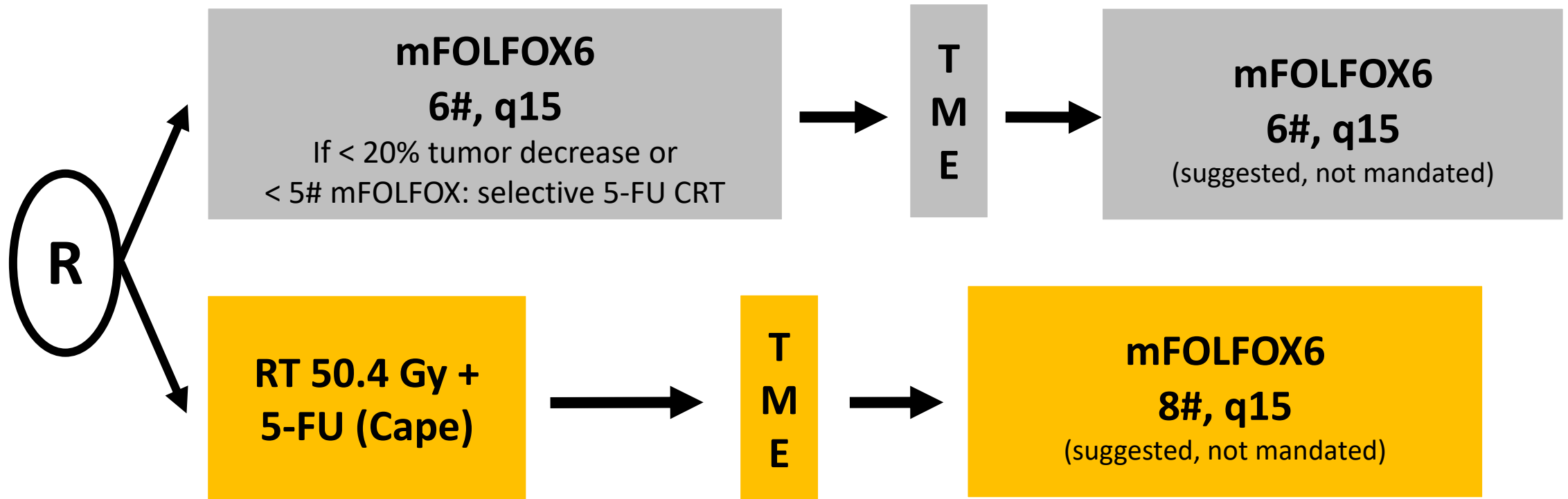
## Escalating strategies:

- Combination chemotherapy
- Total neoadjuvant Treatment (TNT)
- Targeted agents/Immunotherapy

# PROSPECT noninferior phase II/III trial

**Inclusion:** cT2N1, cT3N0, cT3N1; > 3 mm to MRF; sphincter-sparing surgery possible

**Exclusion:** T4, N2;  $\leq 3$  mm to MRF; APR required



**Primary endpoint (phase III):** DFS = disease recurrence or death from any cause

Noninferiority: HR < 1.29 corresponding to a 5% absolute reduction in 5y-DFS

# Patients and Tumor characteristics (per protocol analysis\*)

	mFOLFOX 6	5-FU CRT
Number	585	543
Age (median, range, years)	57 (19-91)	57 (25-84)
Sex (M/F, %)	63/37	68/32
cT2N1 (%)	11	7
cT3N0 (%)	40	36.5
cT3N1 (%)	49	56.5
Distance from AV in cm (median, range)	8 (2-25)	8 (2-18)
</= 5 cm (%)	14	17
> 5 – </= 10 cm (%)	64	63
> 10 cm (%)	22	20

\* All patients who received any dose of protocol-specified treatment: n=1128; n=1194 were randomized

# Tox, Compliance of Neoadjuvant Tx, Surgical & Pathological data

	mFOLFOX 6	5-FU CRT
Number	585	543
Time randomization to TME (median)	19.0 weeks	15.6 weeks
Tox CTC Grade 3-4 of preop. Tx (%)	41	22.8
Compliance	95% received at least 5 #; 9.1% received CRT	95% received full dose RT
Unterwent surgery	535 (91%)	510 (94%)
R0	99%	97%
Pathological complete response (%)	21.9	24.3
ypN0	75%	77%
APR/LAR	2.4%/97.6%	2.0%/98%

## Type, Tox of Postop Tx

	<b>mFOLFOX 6</b> n=535	<b>5-FU CRT</b> n=510
No adjuvant Tx	97 (18%)	87 (17%)
Adjuvant FOLFOX/CAPOX	355 (66%)	341 (66%)
Adjuvant 5-FU/Cape	77 (14%)	64 (13%)
Other	6 (1%)	18 (4%)
Tox CTC Grade 3-4 of any postop Tx	112 (25.6%)	165 (32.4%)
Overall treatment time (randomization to last postop Tx, weeks)	35.5 (IQR: 33-39)	37 (IQR: 34-40)

## DFS, OS and local recurrence

<i>Median F/U = 58 months</i>	<b>mFOLFOX 6</b>	<b>5-FU CRT</b>	<b>HR/p</b>
<b>5y-DFS (primary endpoint)</b>	<b>80.8%</b>	<b>78.6 %</b>	<b>0.92</b> <b>(90.2% CI: 0.74-1.14)</b> <b>NI p=0.0051</b>
5y-OS	89.5%	90.2%	
5y-local recurrence incidence rate	1.8%	1.6%	

# Patient-Reported Outcomes in the PROSPECT Trial

N= 940/1128 contributed PRO-CTCAE data (493 FOLFOX; 447 5FU-CRT).

## ***During neoadjuvant treatment:***

- Lower rates of diarrhea and better overall bowel function with FOLFOX
- Lower rates of anxiety, appetite loss, constipation, depression, dysphagia, dyspnea, edema, fatigue, mucositis, nausea, neuropathy, and vomiting with 5FU-CRT

## ***At 12 months after surgery*** (297 FOLFOX /252 5FU-CRT completed PRO-CTCAE):

- HRQL did not differ
- Lower rates of fatigue, neuropathy, better sexual function with FOLFOX
- Bladder function did not differ



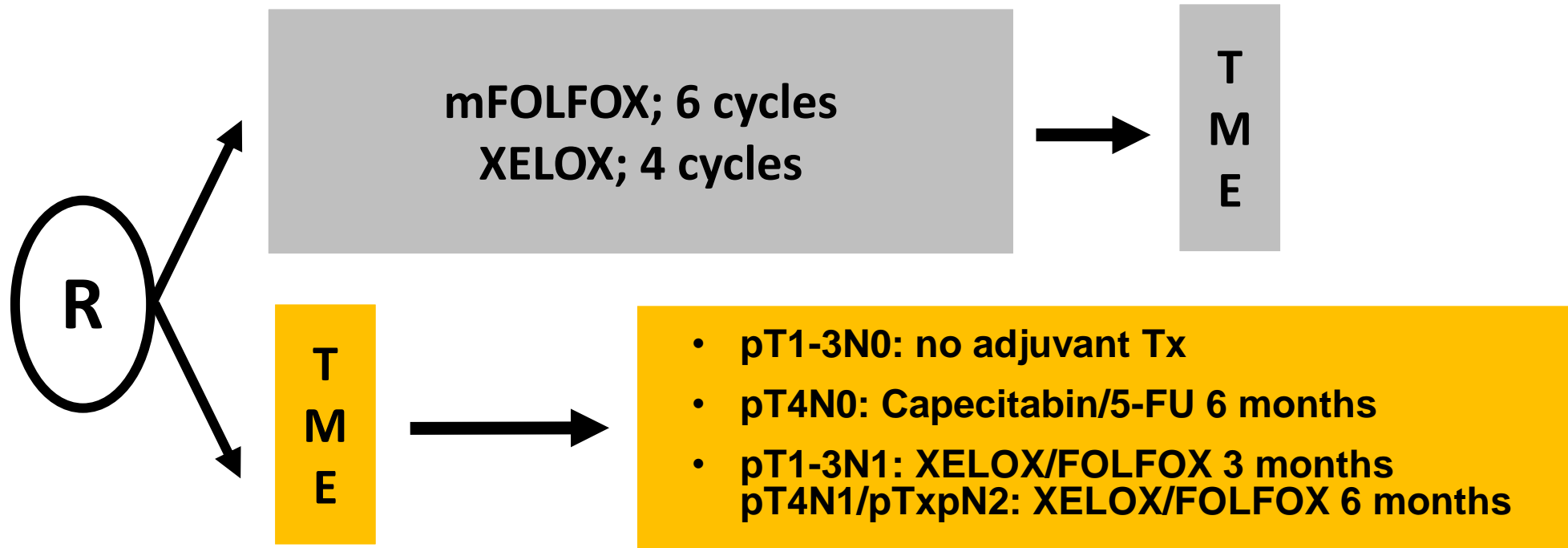
# ESMO risk classification rectal cancer

Early (good)	Intermediate	Locally Advanced („Bad“)	Advanced („Ugly“)
<p>cT1-cT2cN0/1; cT3a/b (middle/high), cN0, MRF clear, no EMVI</p>	<p>cT3a/b very low, levators clear, MRF clear; cT3a/b (middle or high); cN1-2, no EMVI</p>	<p>cT3c/d; very low, levators threatened, MRF-; cT3c/d middle; cT4aN0 cN1-N2 (extranodal); EMVI+</p>	<p>cT3 with MRF+, any cT4a/b, lateral node+</p>

# ACO/ARO/AIO-18.2 phase 3 trial

## Inclusion:

0-6 cm: T1-2N+, mrCRM-/EMVI-; 6-12 cm: T1-2N+; T3a/bN0, mrCRM-/EMVI-;  
12-16cm: T1-2N+; T3-4NX



## Primary endpoint

DFS: **78%** (standard TME) to **85%** at 3y (neoadjuvant FOLFOX)

HR 0.65; power 90%, two-sided p>5%, n=818

# *Where do we stand?*



## De-escalating strategies:

- Selected RT: TN-, MRI-criteria
- **Selected Surgery: Response-adapted LE/NOM/W&W**



## Escalating strategies:

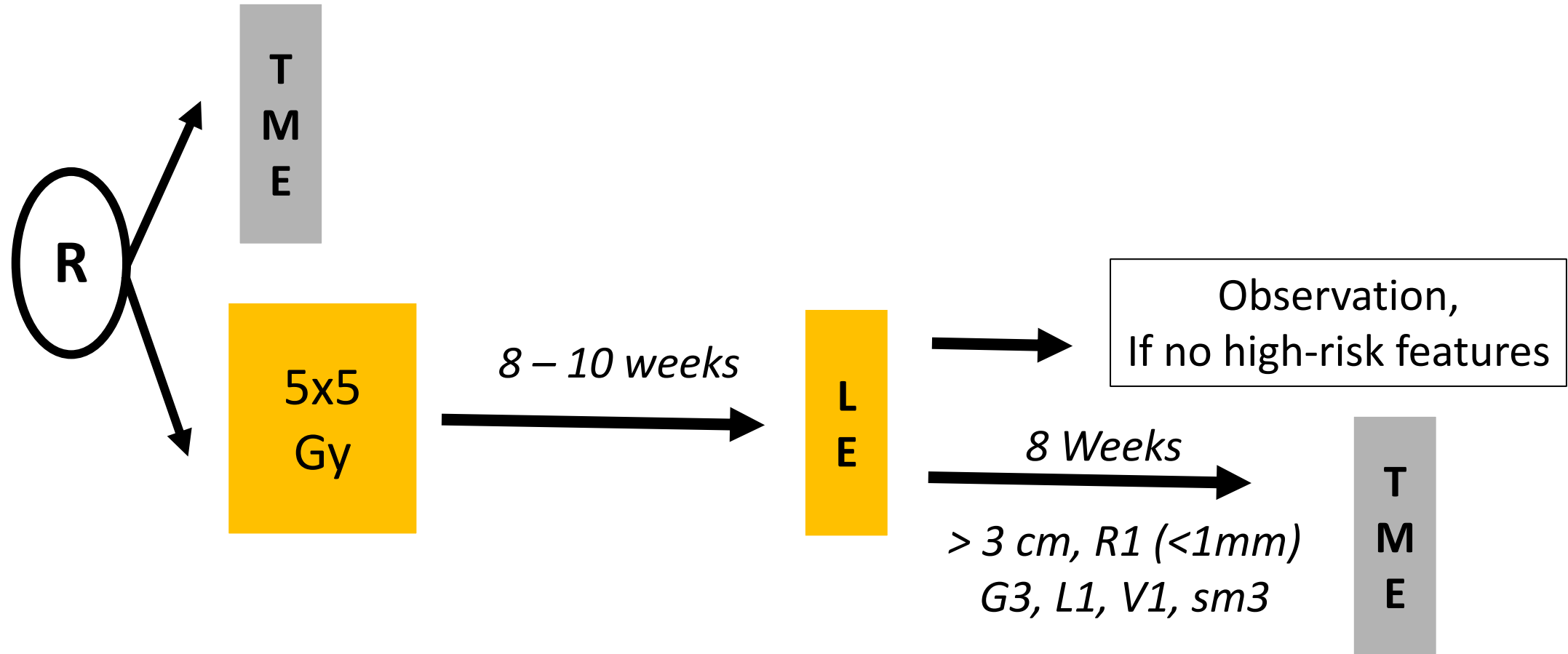
- Combination chemotherapy
- Total neoadjuvant Treatment (TNT)
- Targeted agents/Immunotherapy

# Strategies for Organ Preservation with 5x5Gy, CRT, TNT

<b>• <i>Standard-RT/CRT + Limited Surgery (LE)/W&amp;W</i></b>			
GRECCAR 2	III	Distal cT2-3	CRT followed by LE vs TME
TREC	II	cT1-2N0	5x5Gy + LE vs TME
STAR-TREC	II	cT1-3bN0	TME vs CRT + LE/W&W vs 5x5Gy + LE/W&W
<b>• <i>Increased RT-Dose followed by selected W&amp;W</i></b>			
DANISH	II	cT2-3N0-1	CRT 60 Gy (SIB) + 5 Gy Brachy
MORPHEUS	III	cT2-T3aN0	CRT (45Gy) + Boost 9 Gy EBRT vs 30 Gy (Brachy)
OPERA	III	cT2-T3aN0-1	CRT (45Gy) + Boost 9 Gy EBRT vs 90 Gy (CBX)
<b>• <i>„TNT“ followed by selected W&amp;W</i></b>			
NORMAL-R	II	Stage I/II/III	5x5Gy + consol. FOLFOX
OPRA	II	Stage II/III	Induction-/consolidation FOLFOX + CRT
ACO/ARO/AIO-18.1	III	Stage II/III	5x5Gy + consol. FOLFOX vs CRT+ consol. FOLFOX

# TREC (randomized feasibility study)

cT1-2, max diameter 3 cm, cN0M0



Primary endpoint: cumulative recruitment at 12, 18, 24 months

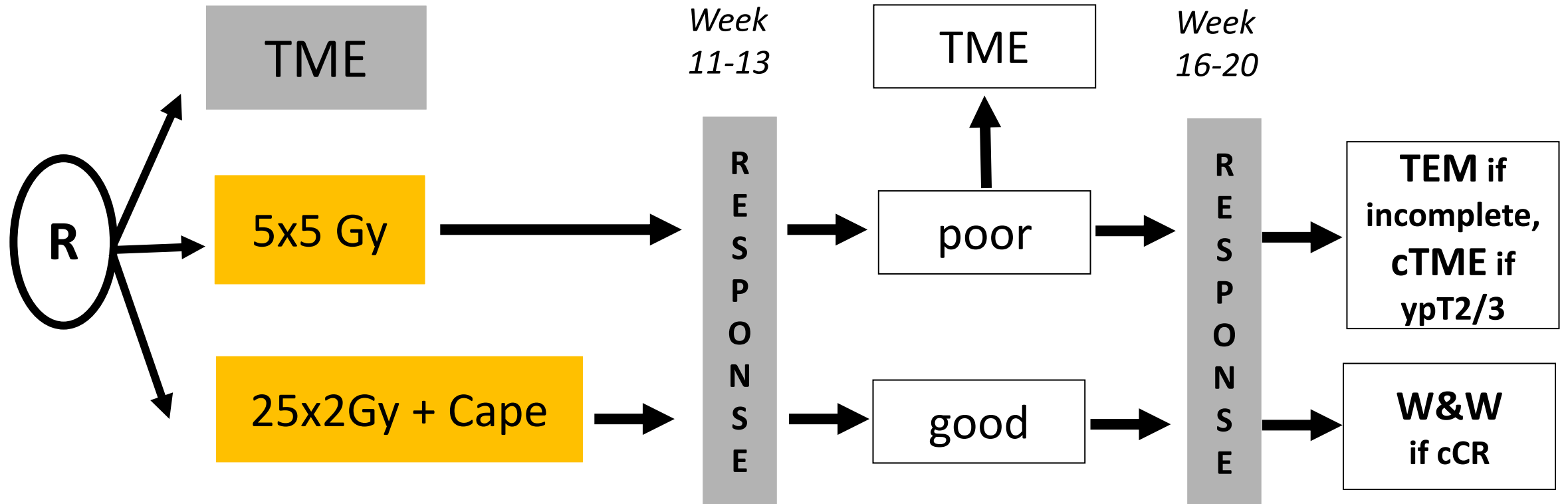
# TREC

	TME	5x5 Gy + TEM	P-value
Number of pts	28	27	
High-risk features	24 (86%)	16 (59%)	.03
Converted to TME	n.a.	8 (30%)	-
SAE	11 (39%)	4 (15%)	.04
Organ preservation	n.a.	19 (70%)	-
DFS at 3 years	85%	76%	.12
Local recurrence	0%	3 (11%)	n.g.
QoL/functional outcome		↑	

*Bach SP et al., Lancet Gastroenterol Hepatol 2021*

# STAR-TREC

Inclusion: cT1-3b N0M0, < 4 cm



Primary endpoint (PE): sufficient recruitment to sustain phase 3 (with local control as PE)

# Strategies for Organ Preservation with 5x5Gy, CRT, TNT

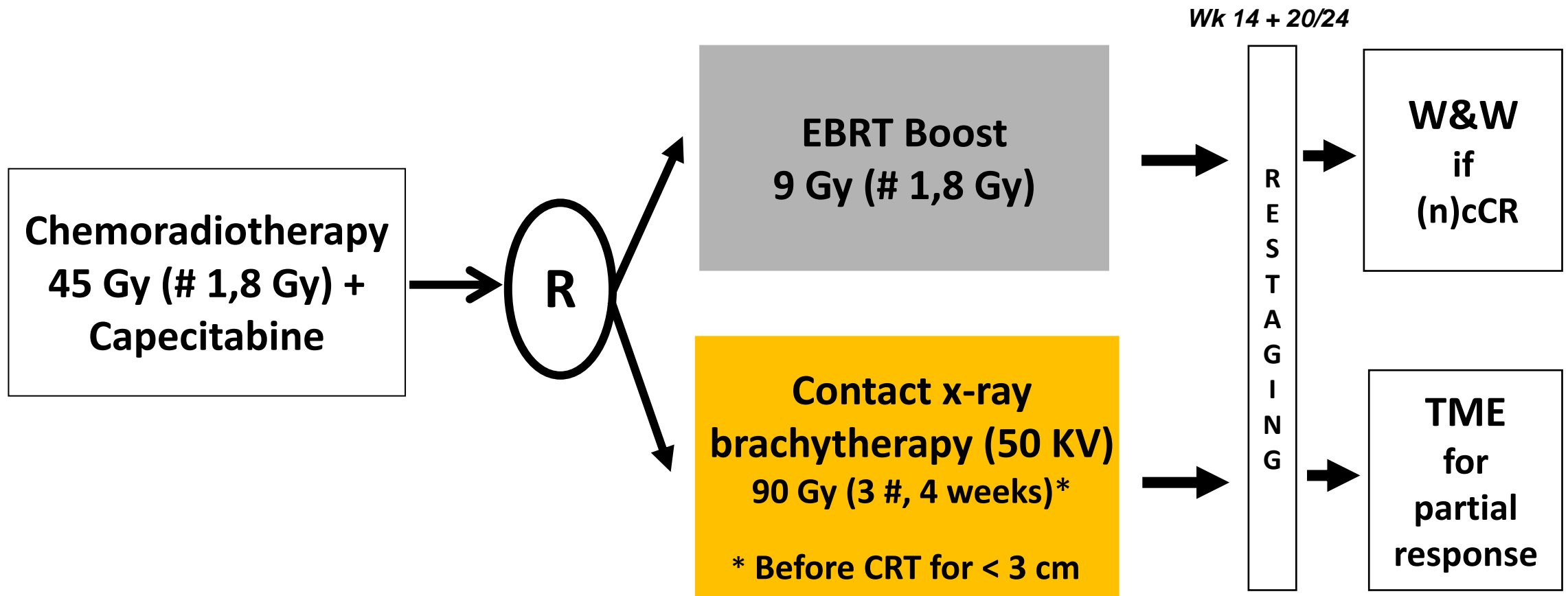
<b>• <i>Standard-RT/CRT + Limited Surgery (LE)/W&amp;W</i></b>			
GRECCAR 2	III	Distal cT2-3	CRT followed by LE vs TME
TREC	II	cT1-2N0	5x5Gy + LE vs TME
STAR-TREC	II	cT1-3bN0	TME vs CRT + LE/W&W vs 5x5Gy + LE/W&W
<b>• <i>Increased RT-Dose followed by selected W&amp;W</i></b>			
DANISH	II	cT2-3N0-1	CRT 60 Gy (SIB) + 5 Gy Brachy
MORPHEUS	III	cT2-T3aN0	CRT (45Gy) + Boost 9 Gy EBRT vs 30 Gy (Brachy)
OPERA	III	cT2-T3aN0-1	CRT (45Gy) + Boost 9 Gy EBRT vs 90 Gy (CBX)
<b>• <i>„TNT“ followed by selected W&amp;W</i></b>			
NORMAL-R	II	Stage I/II/III	5x5Gy + consol. FOLFOX
OPRA	II	Stage II/III	Induction-/consolidation FOLFOX + CRT
ACO/ARO/AIO-18.1	III	Stage II/III	5x5Gy + consol. FOLFOX vs CRT+ consol. FOLFOX



# OPERA (Organ Preservation for Early Rectal Adenocarcinoma)

**cT2-T3b N0-1 (<8mm) M0, low-mid rectal cancer, < 5cm in diameter, < 50% circumference, G1-2**

Primary endpoint: Rate of organ preservation at 3 years (20% vs 40%; alpha 5%, power 92.5%; n=214)



# OPERA

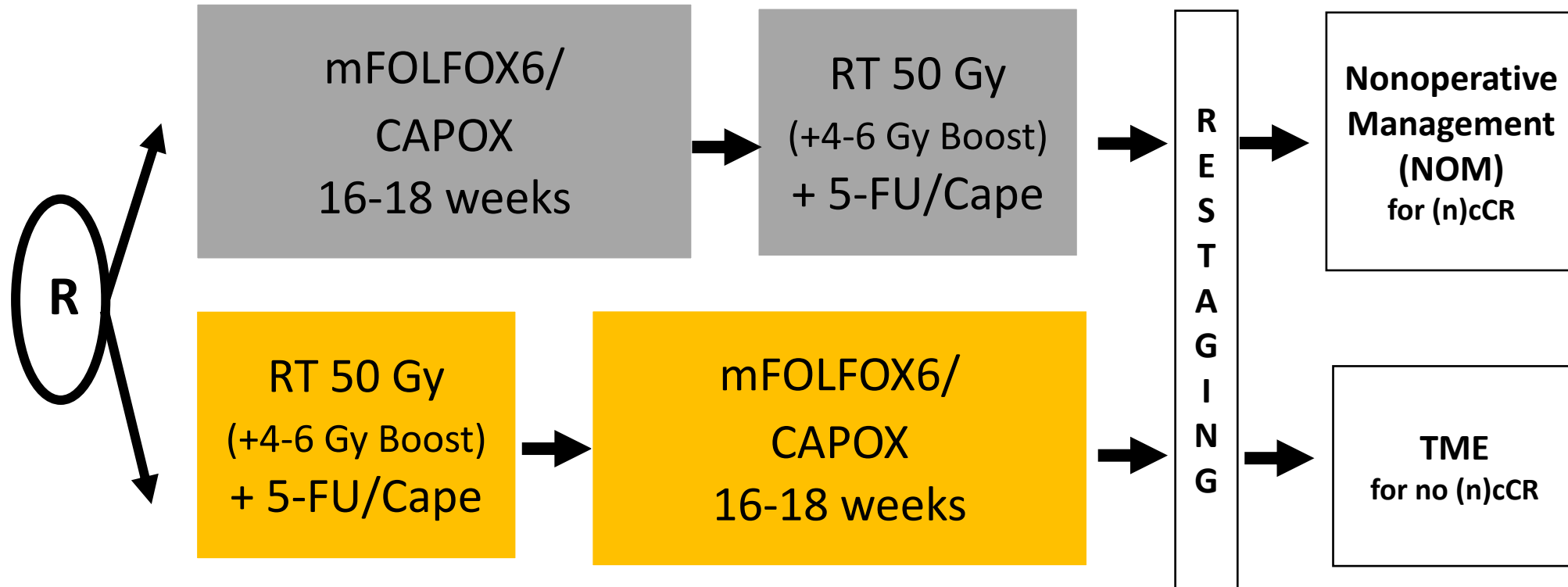
cT2-T3b N0-1 M0 Median F/u: 38 months	<b>CRT+EBRT</b> N=69	<b>CRT+Brachy</b> N=72	<b>p</b>
cCR/near cCR (as assessed week 24)	46%/17%	68%/24%	<.0001
TME/LE for residual tumor or local regrowth	26/20	13/7	
<b>Organ preservation at 3y (all)</b>	<b>59%</b>	<b>81%</b>	<b>.0026</b>
<b>Tumors &lt; 3 cm/&gt;3cm</b>	<b>63%/55%</b>	<b>97%/68%</b>	<b>.012/0.1</b>
TME-free OS at 3y	57%	79%	.0026
LARS > 30 (for pts w/o TME)	21%	17%	
Late tox (grade 1-2 rectal bleeding)	12%	63%	<.0001

# Strategies for Organ Preservation with 5x5Gy, CRT, TNT

<b>• <i>Standard-RT/CRT + Limited Surgery (LE)/W&amp;W</i></b>			
GRECCAR 2	III	Distal cT2-3	CRT followed by LE vs TME
TREC	II	cT1-2N0	5x5Gy + LE vs TME
STAR-TREC	II	cT1-3bN0	TME vs CRT + LE/W&W vs 5x5Gy + LE/W&W
<b>• <i>Increased RT-Dose followed by selected W&amp;W</i></b>			
DANISH	II	cT2-3N0-1	CRT 60 Gy (SIB) + 5 Gy Brachy
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<b>• <i>„TNT“ followed by selected W&amp;W</i></b>			
NORMAL-R	II	Stage I/II/III	5x5Gy + consol. FOLFOX
OPRA	II	Stage II/III	Induction-/consolidation FOLFOX + CRT
ACO/ARO/AIO-18.1	III	Stage II/III	5x5Gy + consol. FOLFOX vs CRT+ consol. FOLFOX

# 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

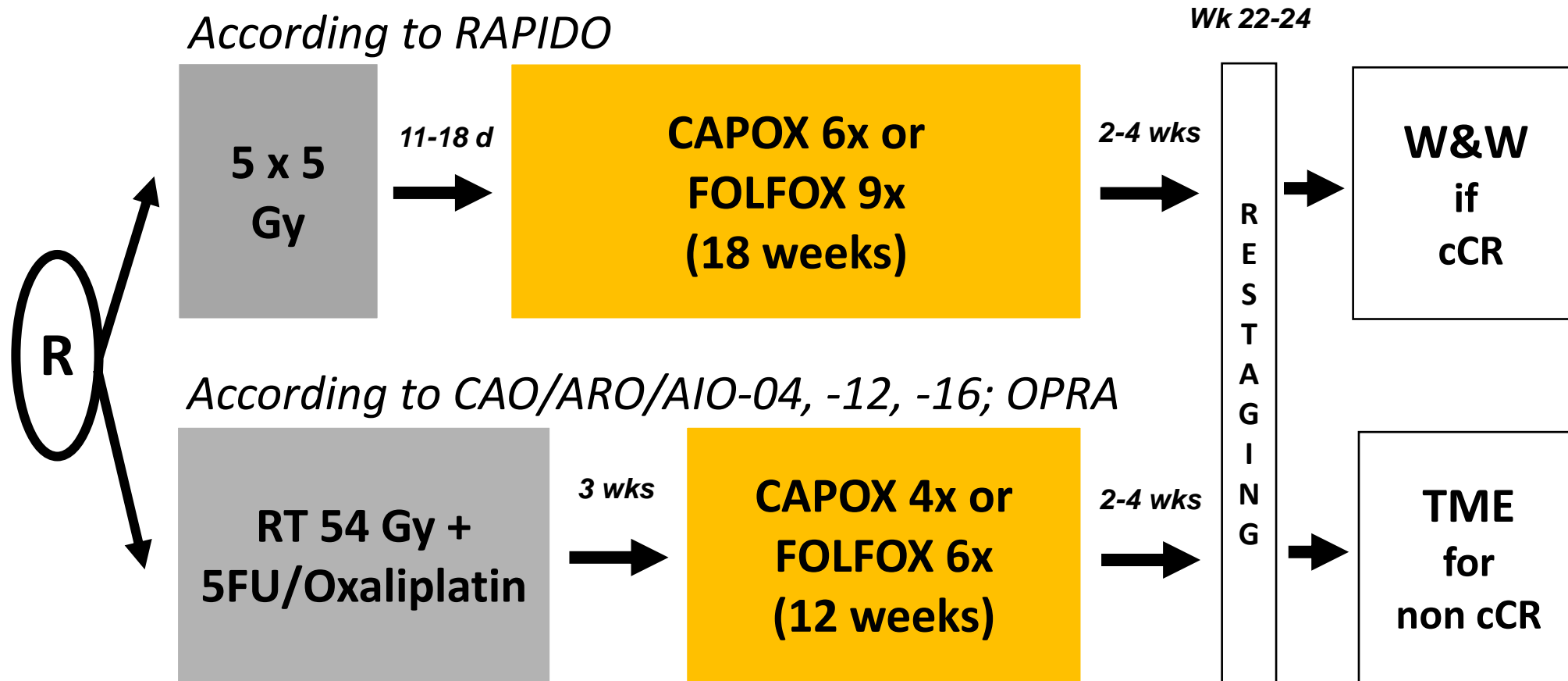
# OPRA: Oncologic Results (median F/u: 3 years)

	<b>Inductionchemo - Chemoradiation N=158</b>	<b>Chemoradiation - Consolidation chemo N=166</b>	<b>p</b>
<b>3y-DFS</b>	<b>76 %</b>	<b>76 %</b>	<b>0.63</b>
W&W at restaging	105 (71%)	120 (76%)	
Developed local regrowth	42/105 (40%)	33/120 (27%)	
<b>3y-TME-free survival</b>	<b>41%</b>	<b>53%</b>	<b>0.01</b>

# ACO/ARO/AIO-18.1 randomized phase III trial



Inclusion criteria: cT3<sub>any</sub> if low rectal third, cT3<sub>c/d</sub>, N+, cT4 if mid rectal cancer



Primary endpoint: **Organ preservation** at 3 years (30% to 40%; sample size: 702)

# *Where do we stand?*



## De-escalating strategies:

- Selected RT: TN-, MRI-criteria
- Selected Surgery: Response-adapted LE/NOM/W&W

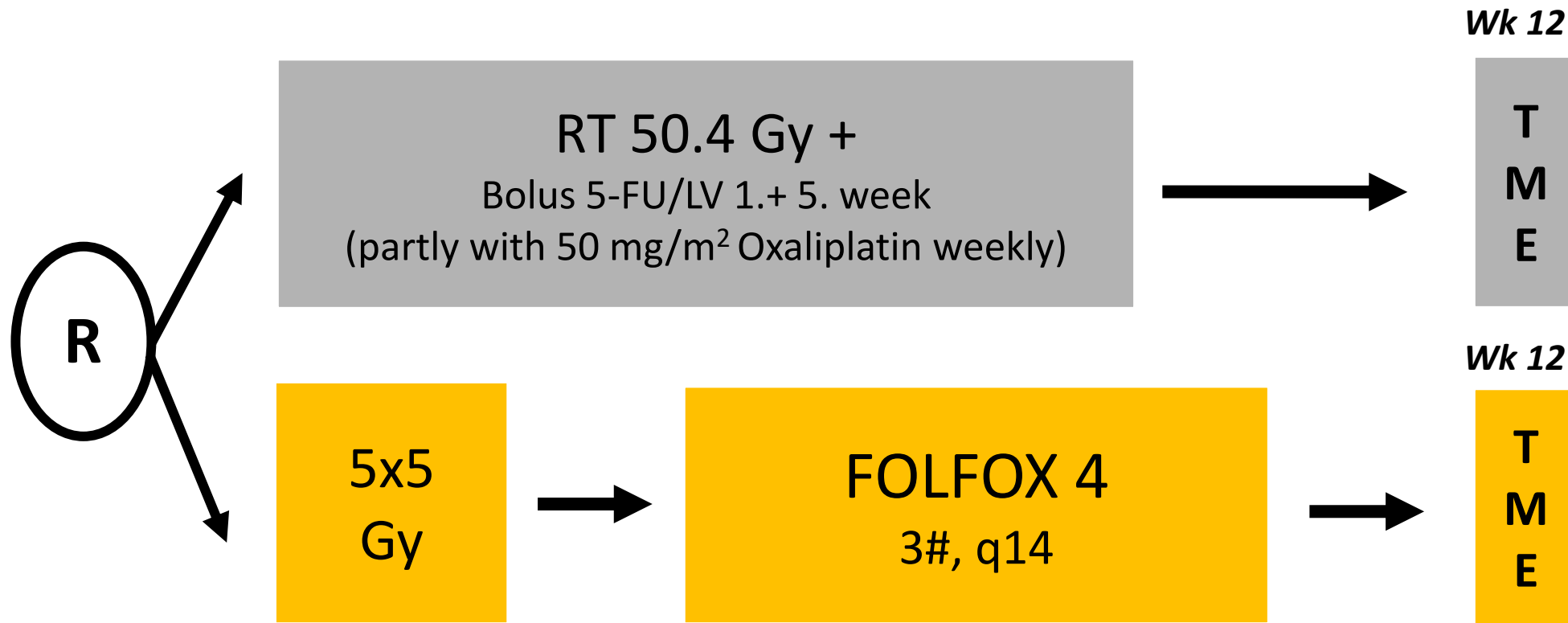


## Escalating strategies:

- Combination chemotherapy
- **Total neoadjuvant Treatment (TNT)**
- Targeted agents/Immunotherapy

# POLISH II – Trial

Inclusion: Fixed T3 or T4 („nonresectable“) rectal cancer



Primary endpoint: R0 resection rate (75% > 85%), 540 pts. required



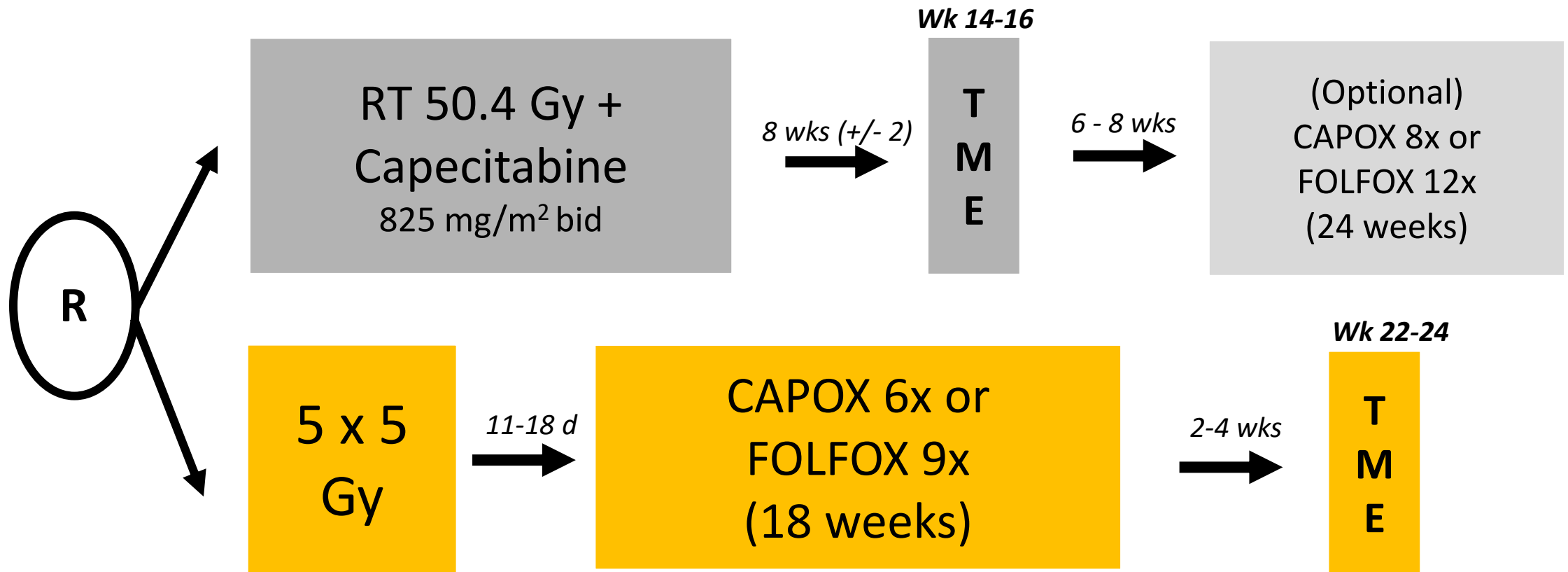
# Polish Trial II

	50.4 Gy 5-FU/(Ox)	5x5 Gy FOLFOX	P-value
Number of pts	254	261	
<b>R0 resection (%)</b>	<b>71</b>	<b>77</b>	<b>.07</b>
pCR (%)	12	16	.21
Acute tox grade 1+2/ 3+4 / 5 (%)	50 / 21 / 3	60/ 23 / 1	.006
Postop complication (%)	25	29	.18
Local Failure @ 8y (%)	32	35	.60
Distant Metastases @ 3y (%)	34	36	.54
Overall Survival @ 8y (%)	49	49	.65

# RAPIDO

Inclusion: MRI-defined high-risk ( $\geq 1$  of the following):

T4a/b; Mesorectal fascia +; N2 or enlarged lateral N+; EMVI+



Primary Endpoint: **3y-DrTF**: 30% to 22.5% (80% Power, alpha=0.05), n=842

## RAPIDO: Tox, Compliance, Surgical & Pathological data

	Standard Chemoradiation	5x5 Gy + CAPOX/FOLFOX
Number	450	462
Tox CTC Grade 3-4 of preop. Tx (%)	<b>25</b>	<b>48</b>
Compliance CRT/RT (%)	93	100
Compliance Cht (at least 75% of planned dose, %)	Adjuvant 58	84
Pathological complete response (%)	<b>14.3</b>	<b>28.4</b>
R0/CRM+/R2 (%)	90/9/<1	90/9/<1
Postop. complications: any/CD ≥ III (%)	47/16	50/18
Mesorectal plane intact (%) (assessed by surgeon)	<b>85</b>	<b>78</b>

## RAPIDO: Results at 3 years (median F/U: 4.6 years)

	Standard Chemoradiation	5x5 Gy + CAPOX/FOLFOX	HR (95% CI)/p
<b>DrTF* (primary endpoint)</b> * M1; locoregional failure; new CRC; treatment-related death	<b>30.4 %</b>	<b>23.7 %</b>	<b>0.75 (0.60-0.96)</b> <b>p=0.019</b>
Distant M1	26.8%	20.0%	0.69 (0.54-0.90) p=0.005
Locoreg. failure	6.0%	8.3%	1.42 (0.91-2.21) p=0.12
OS	88.8%	89.1%	0.92 (0.67-1.25) p=0.59
LARS score/ QLQ-C30/-CR29	No significant	differences	

## RAPIDO: Results at 5 years (median F/U: 5.6 years)

	Standard Chemoradiation	5x5 Gy + CAPOX/FOLFOX	HR (95% CI)/p
<b>DrTF* (primary endpoint)</b> * M1; locoregional failure; new CRC; treatment-related death	<b>34.0 %</b>	<b>27.8 %</b>	<b>0.79 (0.63-1.00)</b> <b>p=0.048</b>
Distant M1	30.4%	23.0%	0.73 (0.57-0.93) p=0.011
Locoreg. failure	8.1%	11.7%	p=0.07
Locoregional recurrence After RO/1 resection	6.1%	10.2%	p=0.027
OS	80.2%	81.7%	0.91 (0.70-1.19) p=0.50

# Should all patients receive „RAPIDO“ like TNT?

***RAPIDO: DrTF and M1 benefit!***

(ACO/ARO/AIO Consensus to generally recommend TNT)

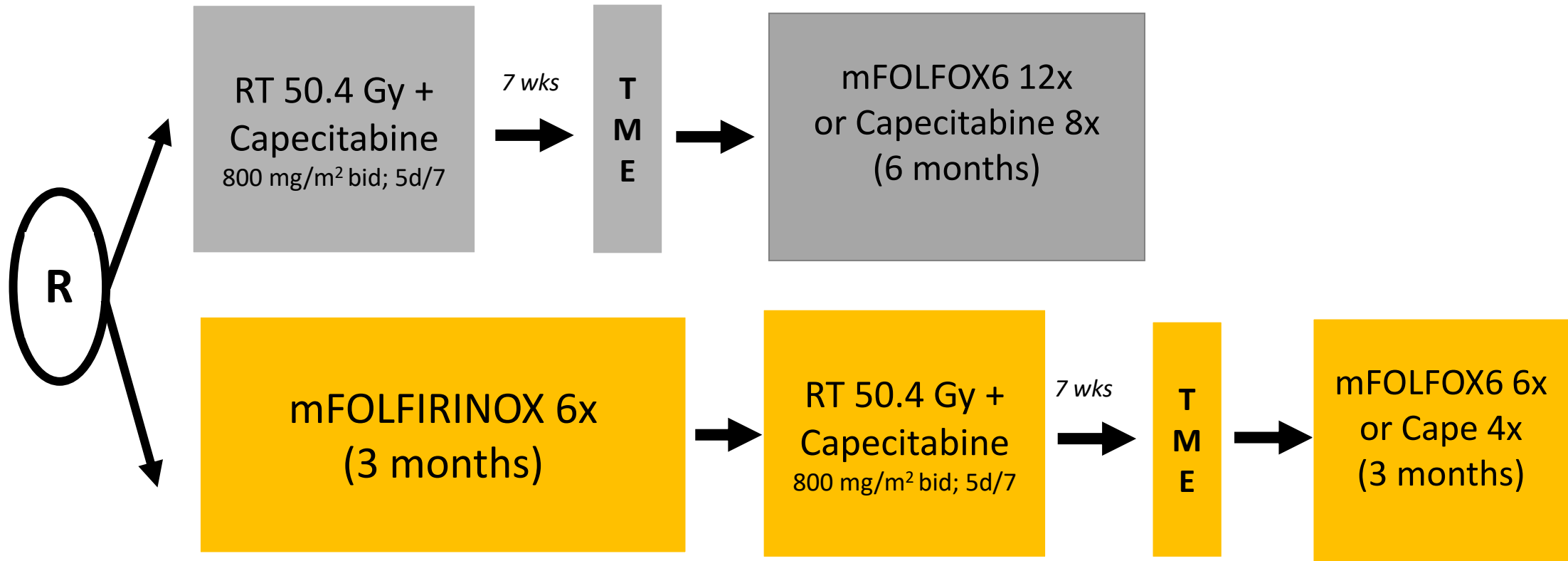
***But***

- **POLISH II:** negative, **STELLAR:** non-inferiority
- Evidence primarily for T4; CRM+; N2, lat. N+, EMVI
- Tox from combination chemotherapy (elderly, frail?)
- Some concern: early progression in non-responders, TME-quality, local control.

# PRODIGE 23

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

Age: 18-75 y, WHO PS 0-1



Primary Endpoint: **3y-DFS**: 75% to 85% (90% Power, alpha=0.05), n=460

## PRODIGE 23: Results at 3 years

Median F/u= 46.5 months	CRT	mFOLFIRINOX + CRT	HR/p
<b>DFS (primary endpoint)</b>	<b>68.5 %</b>	<b>75.7 %</b>	<b>0.69 , p=0.034</b>
Distant M1-free survival	71.7%	78.8%	0.64 p=0.017
Overall local relapse	„No difference 4.8% vs 7%“		
OS	Not given; „54% with relapse alive at time of analysis“		

*Conroy T et al., Lancet Oncol 2021*  
**update ASCO 2023 with OS benefit of 7% at 5 years**

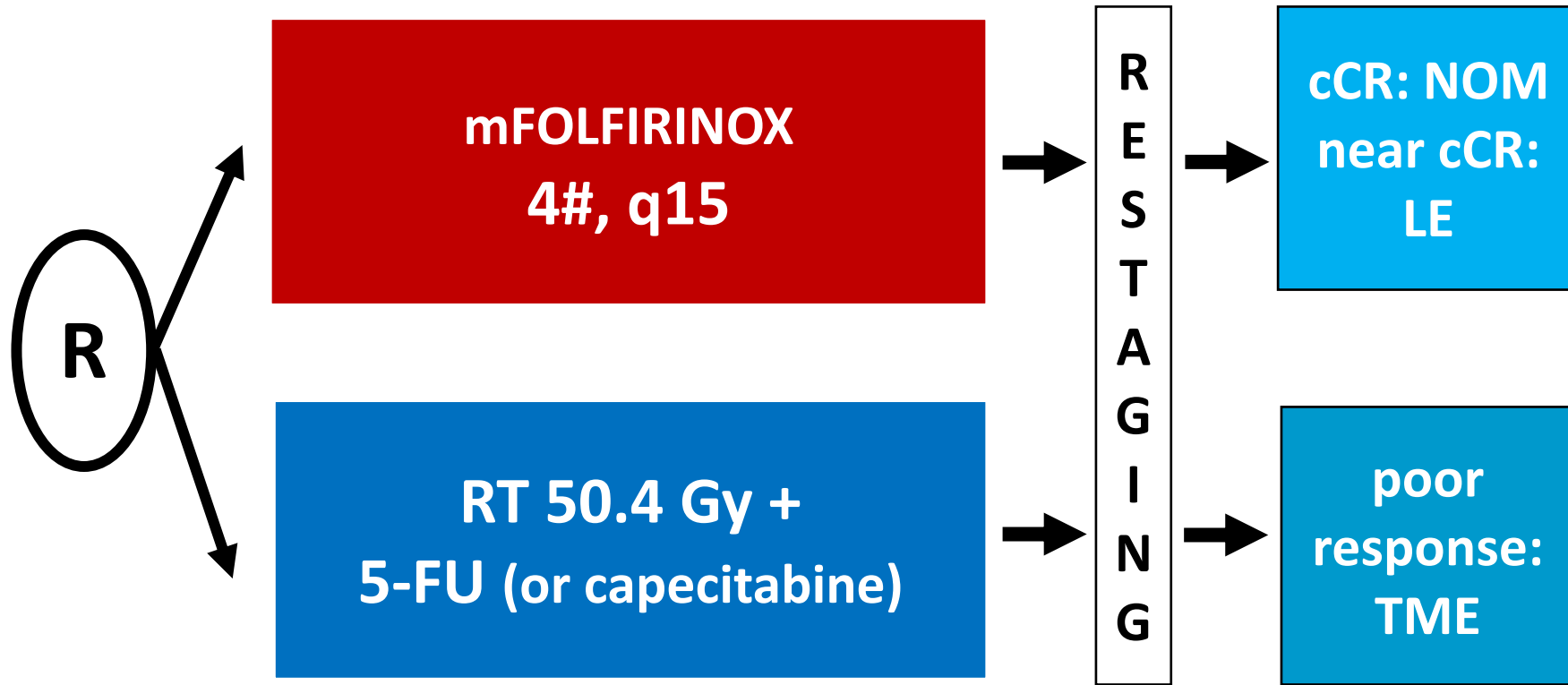


***Where do we go from here?***

***Ongoing studies***

# GRECCAR12 phase III trial

cT2-T3N0-1, ( $\leq 3$  lymph nodes,  $\leq 8$ mm), Tumour size  $\leq 4$  cm,  $\leq 10$  cm AV,



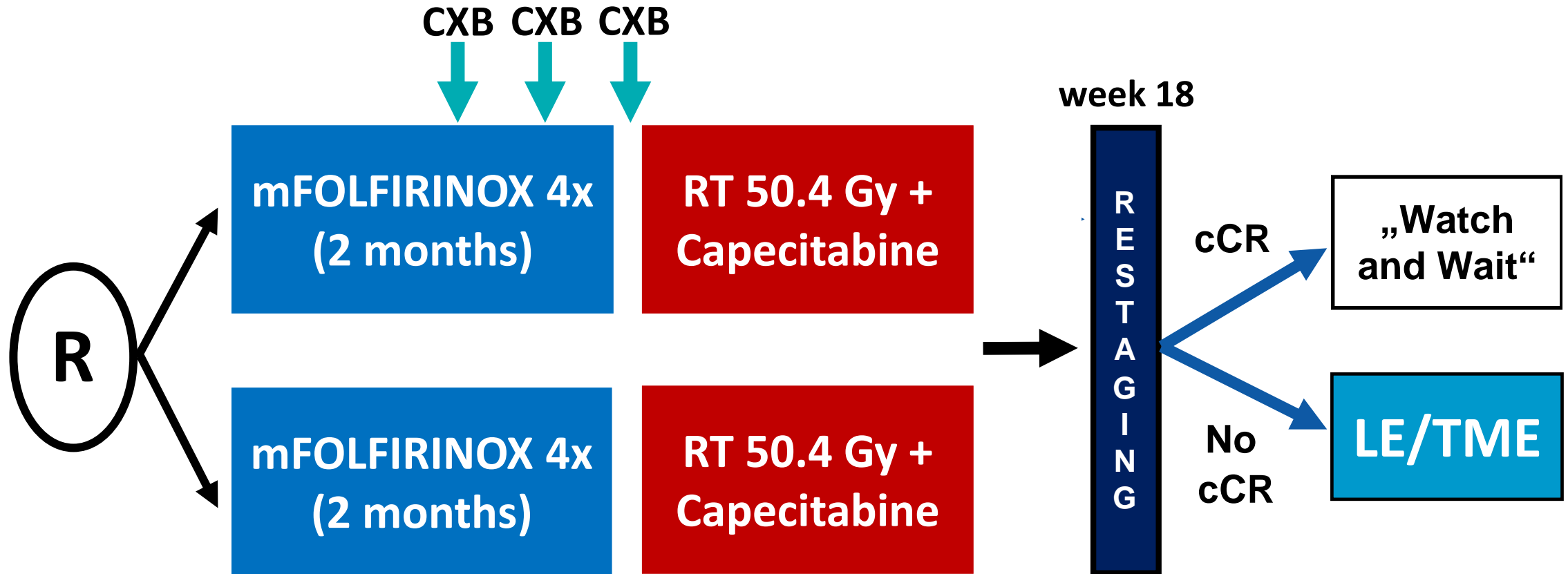
**Primary endpoint:** 12-month organ preservation, N=218

**NCT02514278**

cCR: clinical complete response

# TRESOR randomized phase III trial

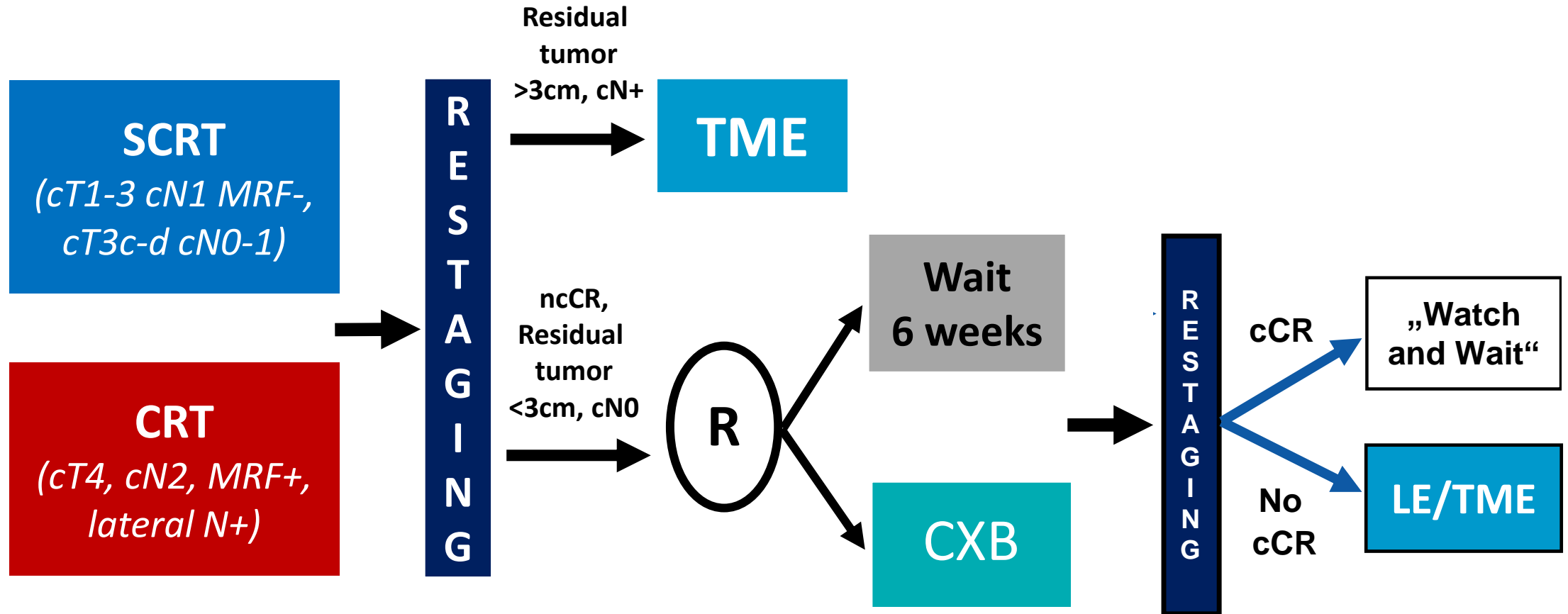
cT2-T3 >3.5cm, N0-N1



**Primary endpoint: 3-year TME-free survival; n=200**

\*CXB: contact brachytherapy with Papillon (3 x 30 Gy *prescribed to tumor surface*)

# OPAXX phase II trial

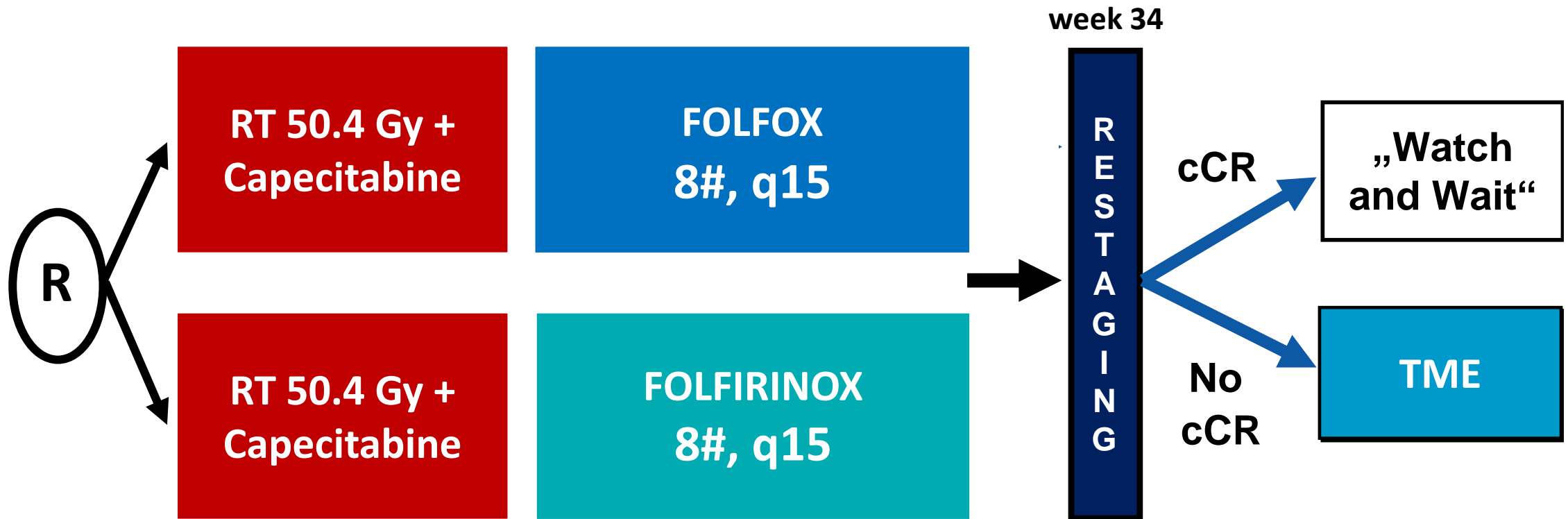


**Primary endpoint: 1-year Organ preservation; n=336 (168: SCRT; 168: CRT)**

\*CXB: contact brachytherapy with Papillon (3 x 30 Gy *prescribed to tumor surface*)

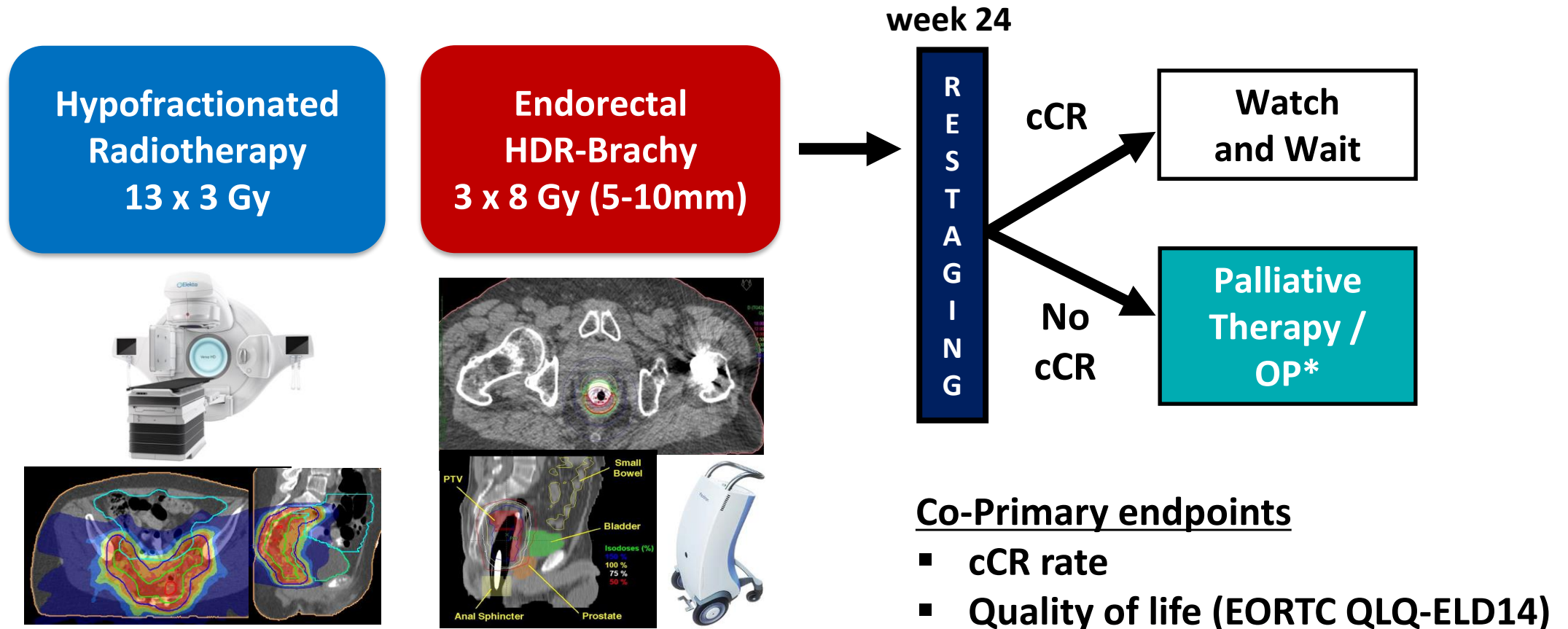
# JANUS/NRG GI010 phase II

Inclusion: cT4; N+; any T3N0 requiring APR



Primary Endpoint: **cCR**, N=312

# ACO/ARO/AIO-22 phase-II trial in elderly frail patients



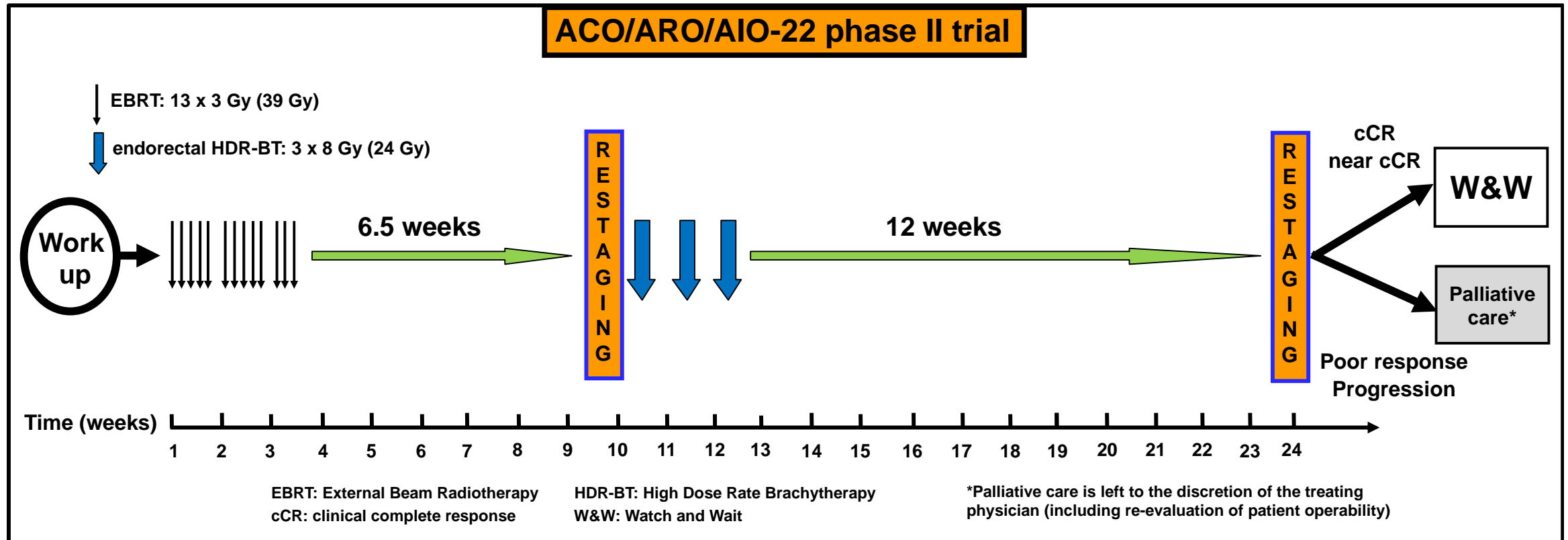
N=80; DKH Förderantrag gestellt

## ≥70 years old:

- assessed as inoperable from surgeons
- **and/or** Geriatric 8 (G8)-Frailty-Score  $\leq 14$
- **and/or** ASA PS  $\geq 3$

\*Reevaluation of operability

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