Multimodal Rectal Cancer Management

Refresher

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Erklärung zu möglichen Interessenskonflikten:

Berater- und Gutachtertätigkeiten

NEIN

Honorare

NEIN

Forschungsfinanzierung

Deutsche Krebshilfe

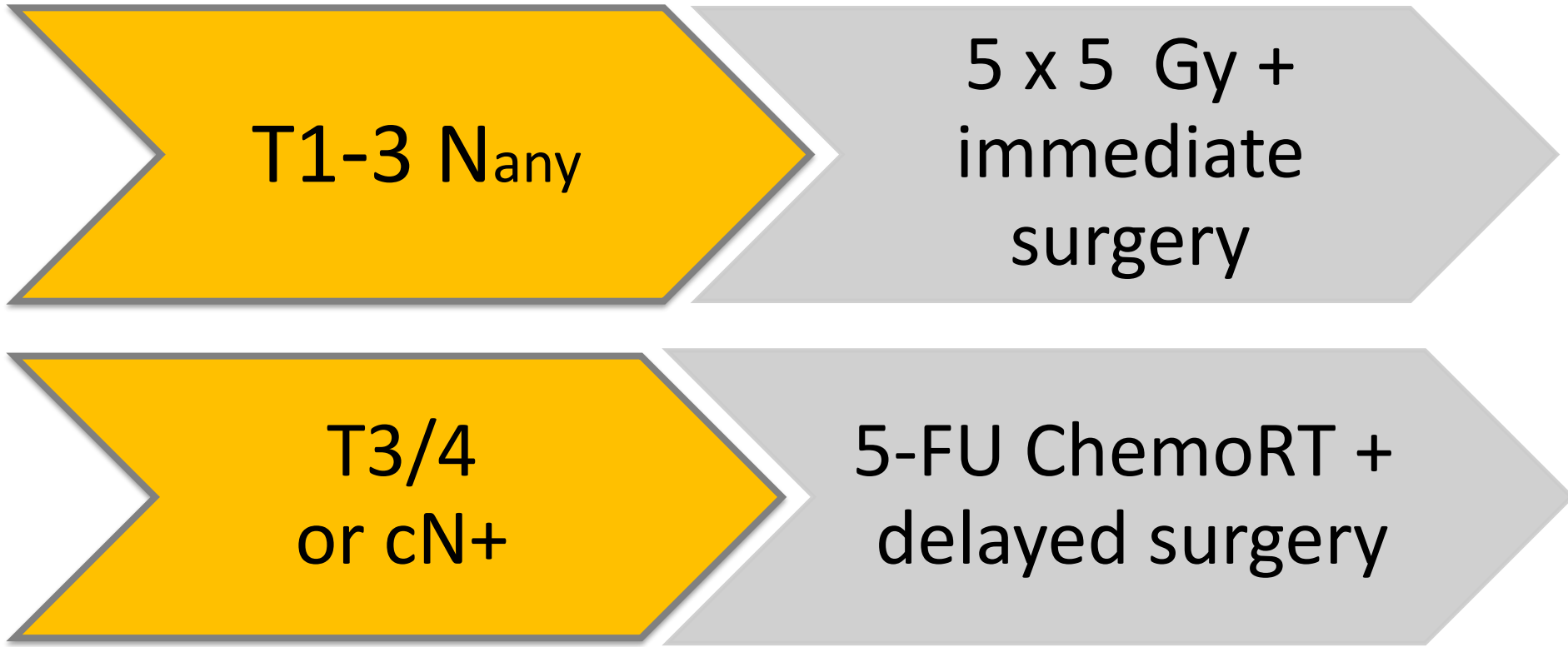
Eigentümerinteressen (Patent, Urheberrecht, Verkaufslizenz)

NEIN

Geschäftsanteile, Aktien, Fonds

NEIN

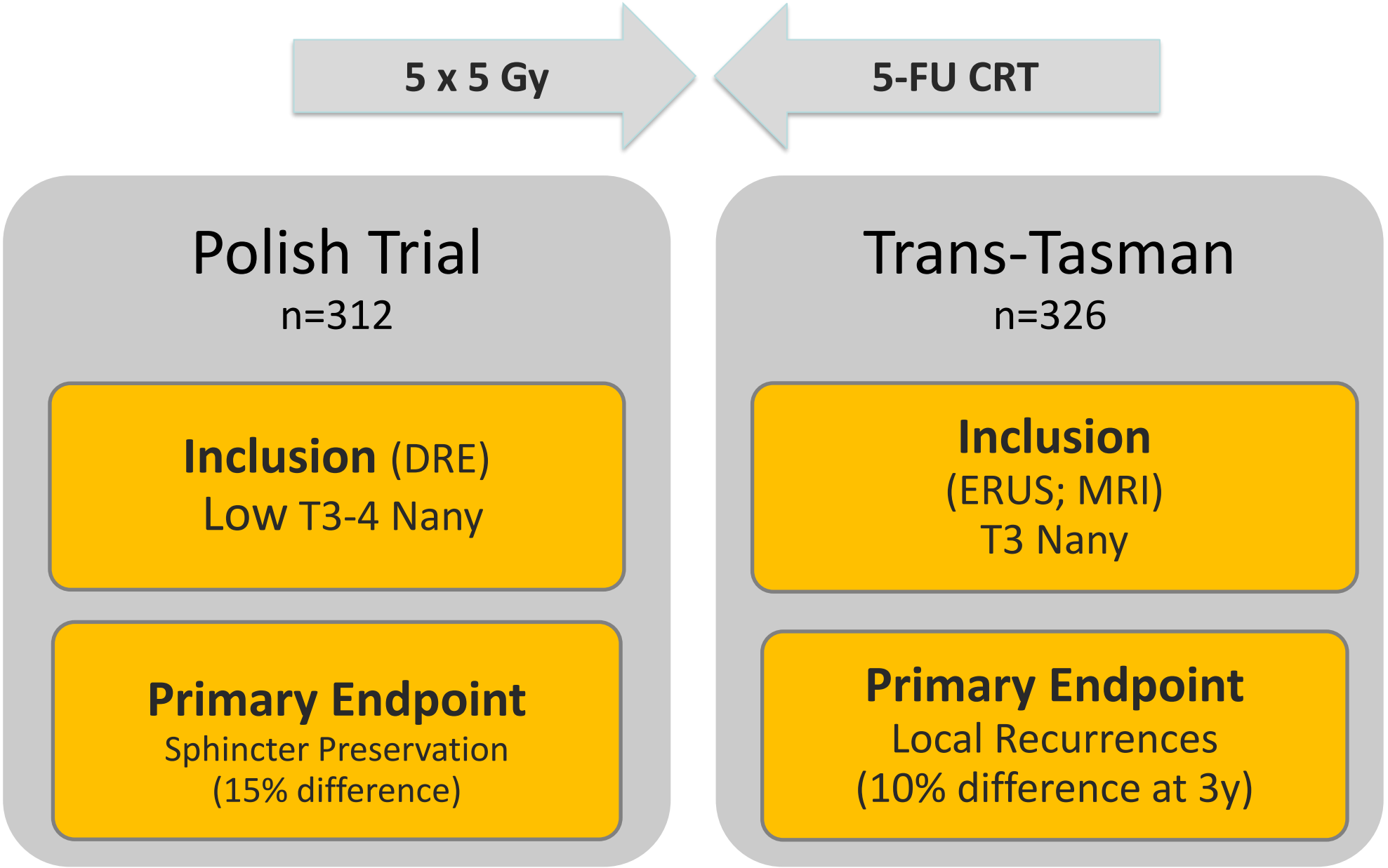
Where do we come from?



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

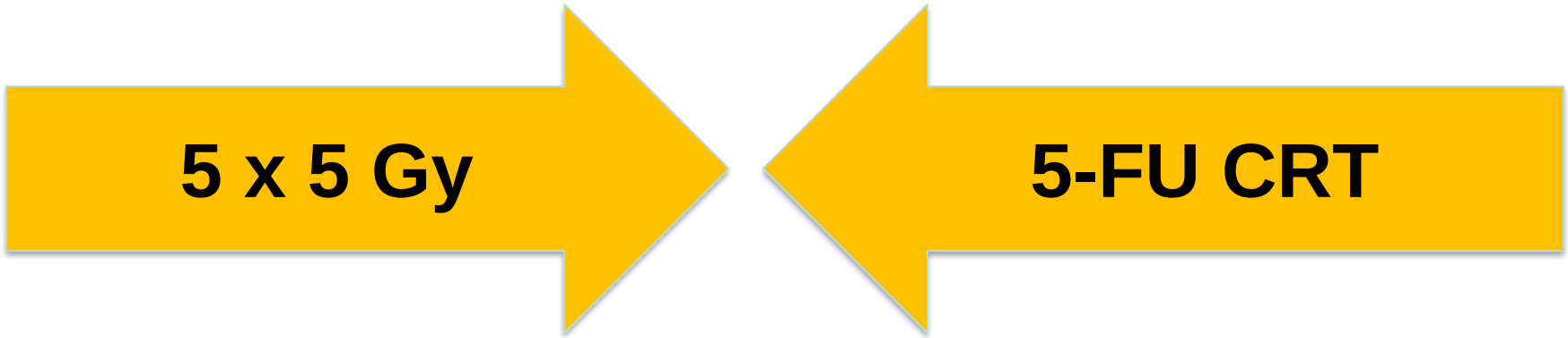


Buiko et al., Br J Surg 2006; Ngan SY et al., J Clin Oncol 2012

Trans-Tasman	5x5 Gy	CRT	P
Acute Tox (Grade 3-4, %)	2	28	<.001
pCR (%)	1	15	<.001
Sphincter Preservation (%)	63	69	0.22
Local Recurrences (3y, %)	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



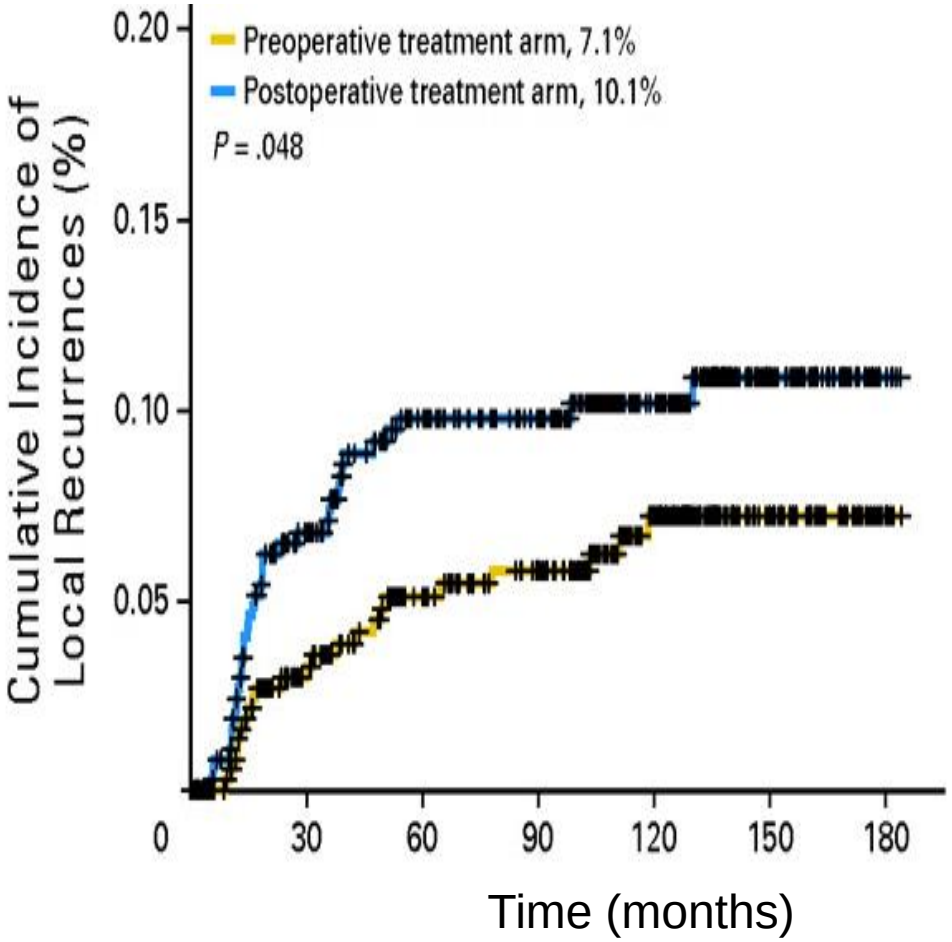
- Less acute tox
- Patient convenience
- Lower cost

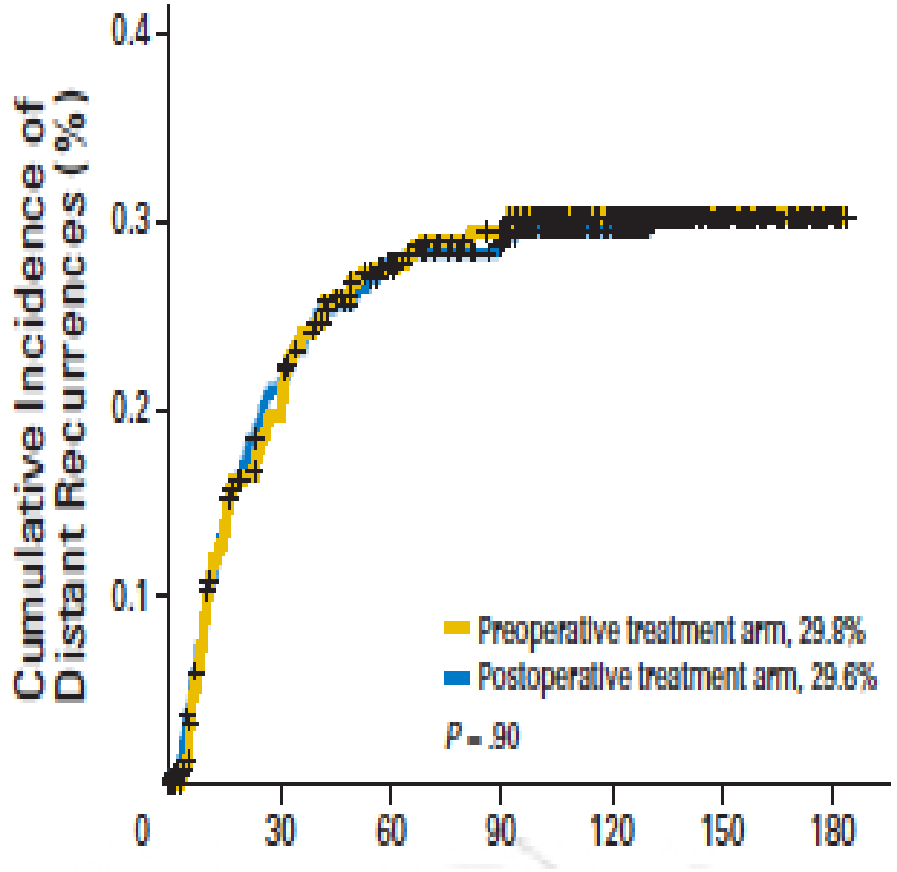
- Better downsizing
- Ability to safely combine with chemo

„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

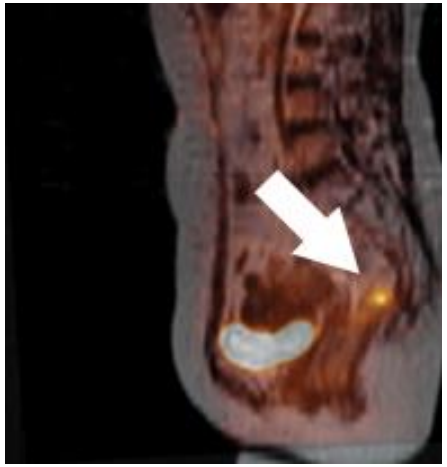
CAO/ARO/AIO-94: 10-year results





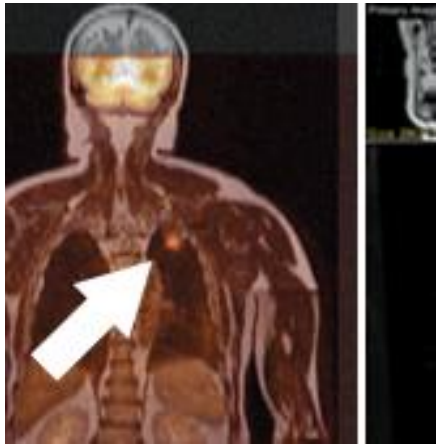
Sauer R. et al., J Clin Oncol 2012

Where do we stand?



De-escalating strategies:

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



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

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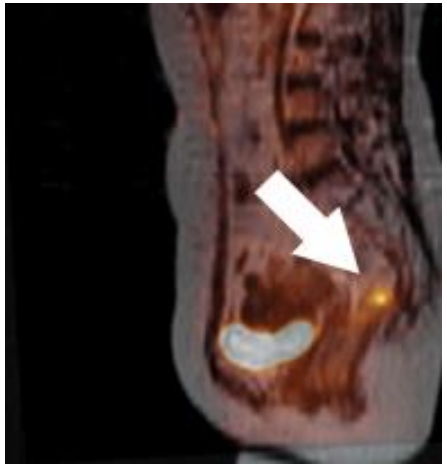

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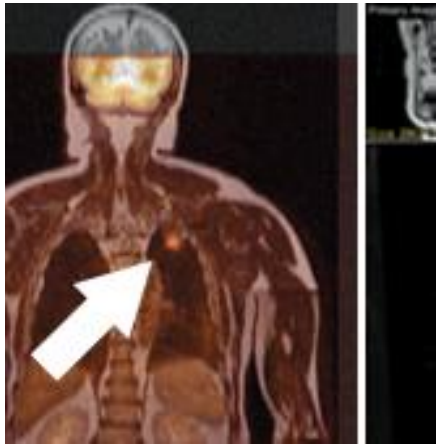

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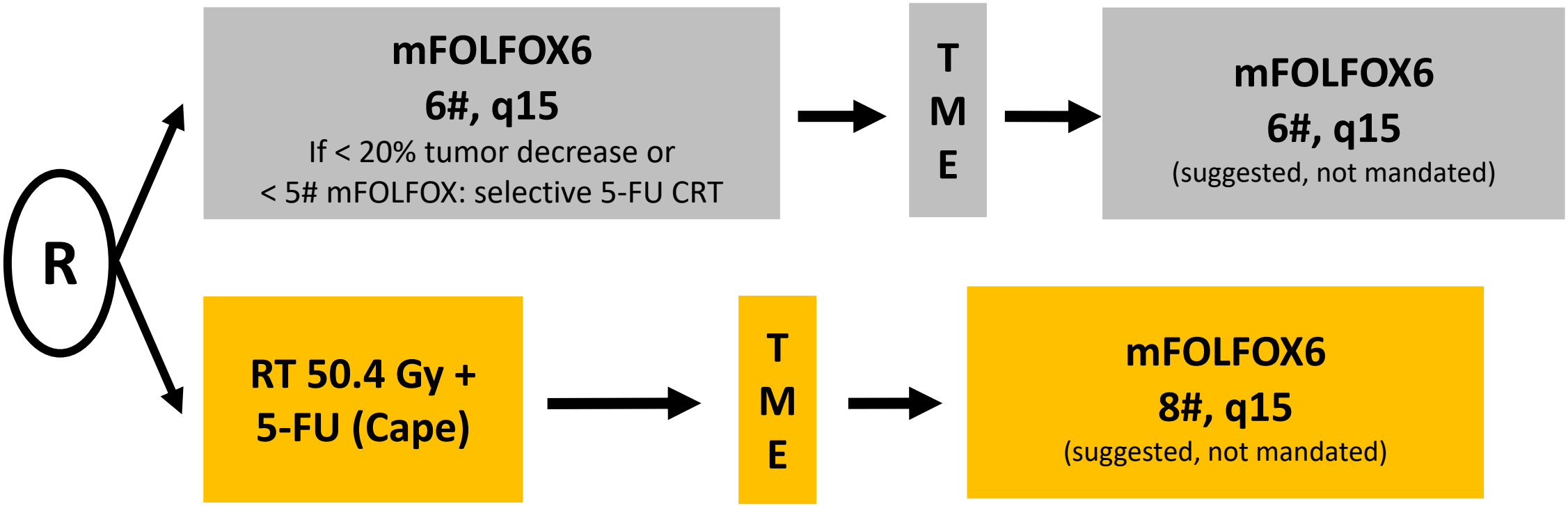
PROSPECT noninferior phase II/III trial

Inclusion: cT2N1, cT3N0, cT3N1; > 3 mm to MRF; sphincter-sparing surgery possible
Exclusion: T4, N2; ≦ 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

Schrag D et al., N Engl J Med 2023

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 (%) cT3N0 (%) cT3N1 (%)	11 40 49	7 36.5 56.5
Distance from AV in cm (median, range)	8 (2-25)	8 (2-18)
</= 5 cm (%) > 5 – </= 10 cm (%) > 10 cm (%)	14 64 22	17 63 20

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

Schrag D et al., N Engl J Med 2023

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%

Schrag D et al., N Engl J Med 2023

Type, Tox of Postop Tx

	mFOLFOX 6 n=535	**5-FU CRT** n=510
No adjuvant Tx	97 (18%)	87 (17%)
Adjuvant FOLFOX/CAPOX Adjuvant 5-FU/Cape Other	355 (66%) 77 (14%) 6 (1%)	341 (66%) 64 (13%) 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)

Schrag D et al., N Engl J Med 2023

DFS, OS and local recurrence

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

Schrag D et al., N Engl J Med 2023ç

Patient-Reported Outcomes in the PROSPECT Trial

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

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

Basch E et al., J Clin Oncol 2023

ESMO risk classification rectal cancer

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

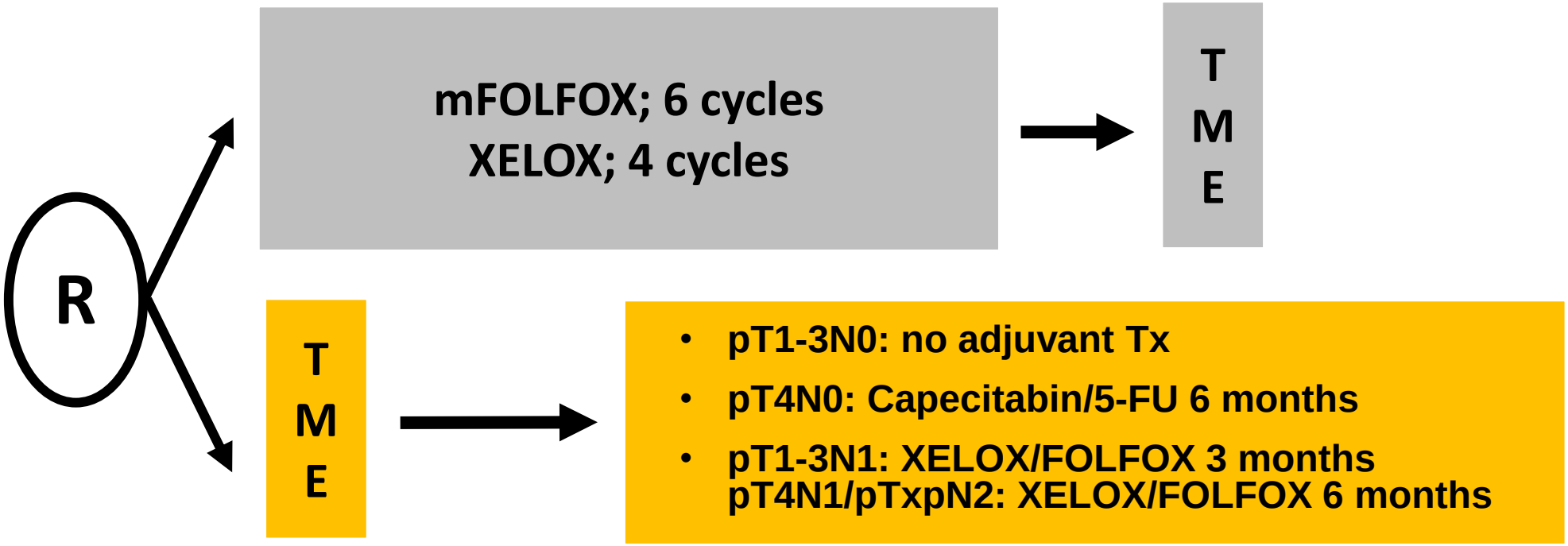
Glynne-Jones et al., Ann Oncol 2017

ACO/ARO/AIO-18.2 phase 3 trial

Deutsche Krebshilfe
HELFEN. FORSCHEN. INFORMIEREN.

Inclusion:

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

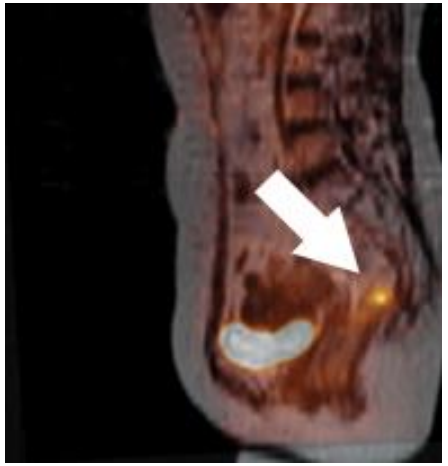


Primary endpoint

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:

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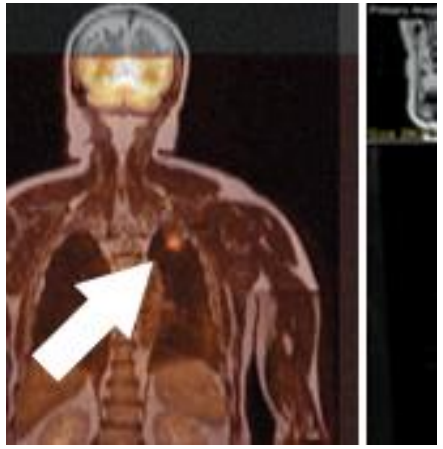


Escalating strategies:

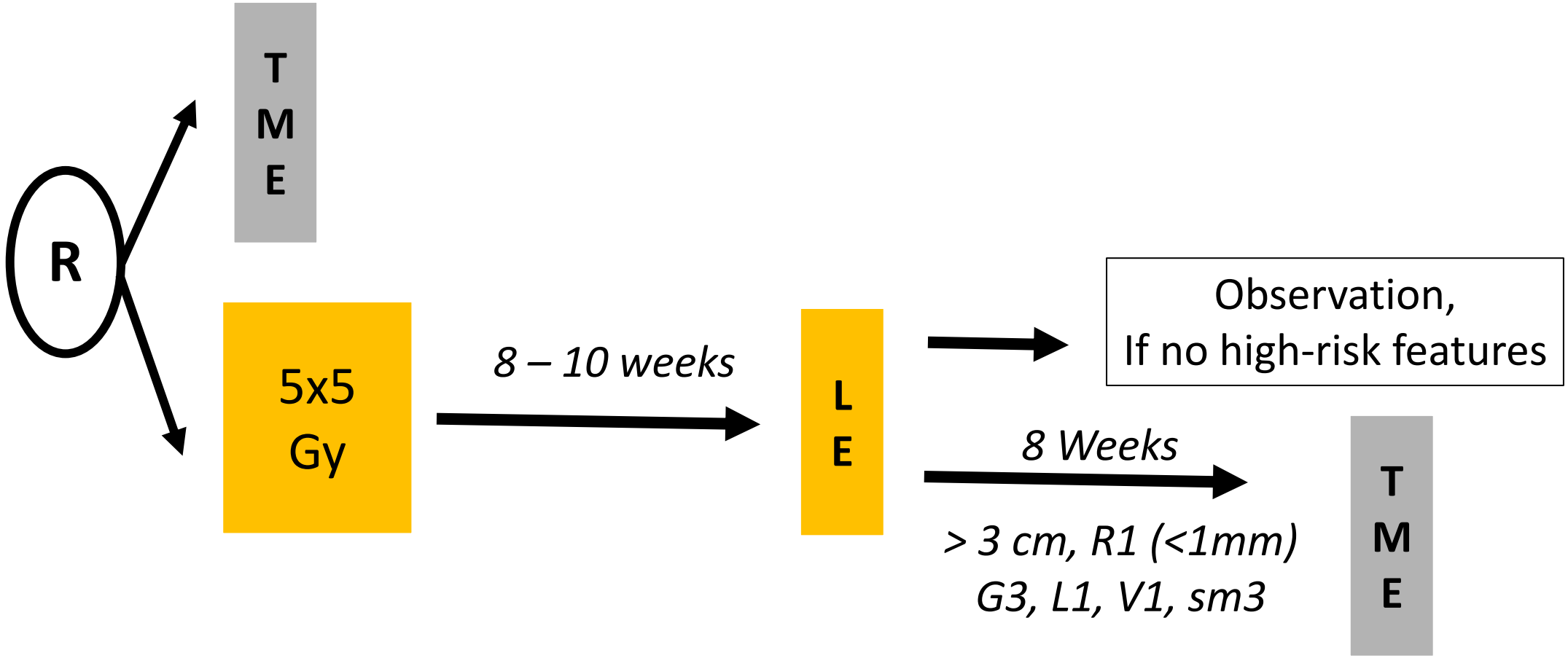
- Combination chemotherapy
- Total neoadjuvant Treatment (TNT)
- Targeted agents/Immunotherapy

Strategies for Organ Preservation with 5x5Gy, CRT, TNT

• ***Standard-RT/CRT + Limited Surgery (LE)/W&W***			
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
• ***Increased RT-Dose followed by selected W&W***			
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)**
• ***„TNT" followed by selected W&W***			
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

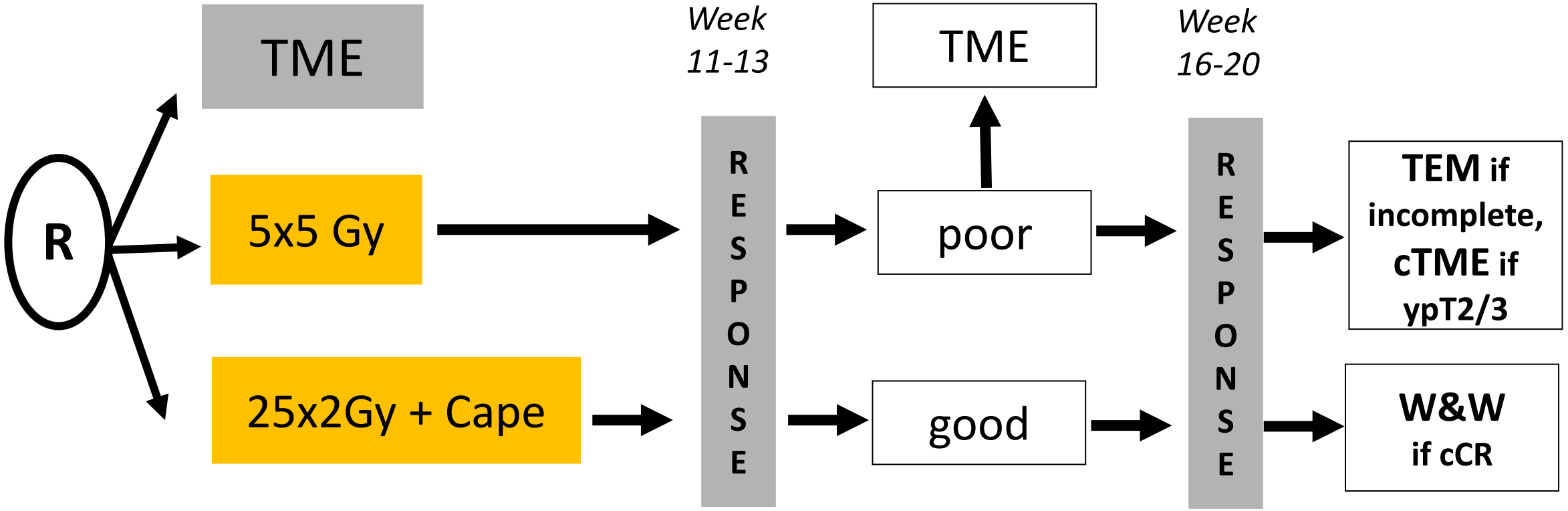
TREC

	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

• ***Standard-RT/CRT + Limited Surgery (LE)/W&W***			
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TREC	II	cT1-2N0	**5x5Gy** + LE *vs* TME
STAR-TREC	II	cT1-3bN0	TME *vs* **CRT** + LE/W&W *vs* **5x5Gy** + LE/W&W
• ***Increased RT-Dose followed by selected W&W***			
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OPERA	III	cT2-T3aN0-1	CRT (45Gy) + Boost 9 Gy EBRT vs 90 Gy **(CBX)**
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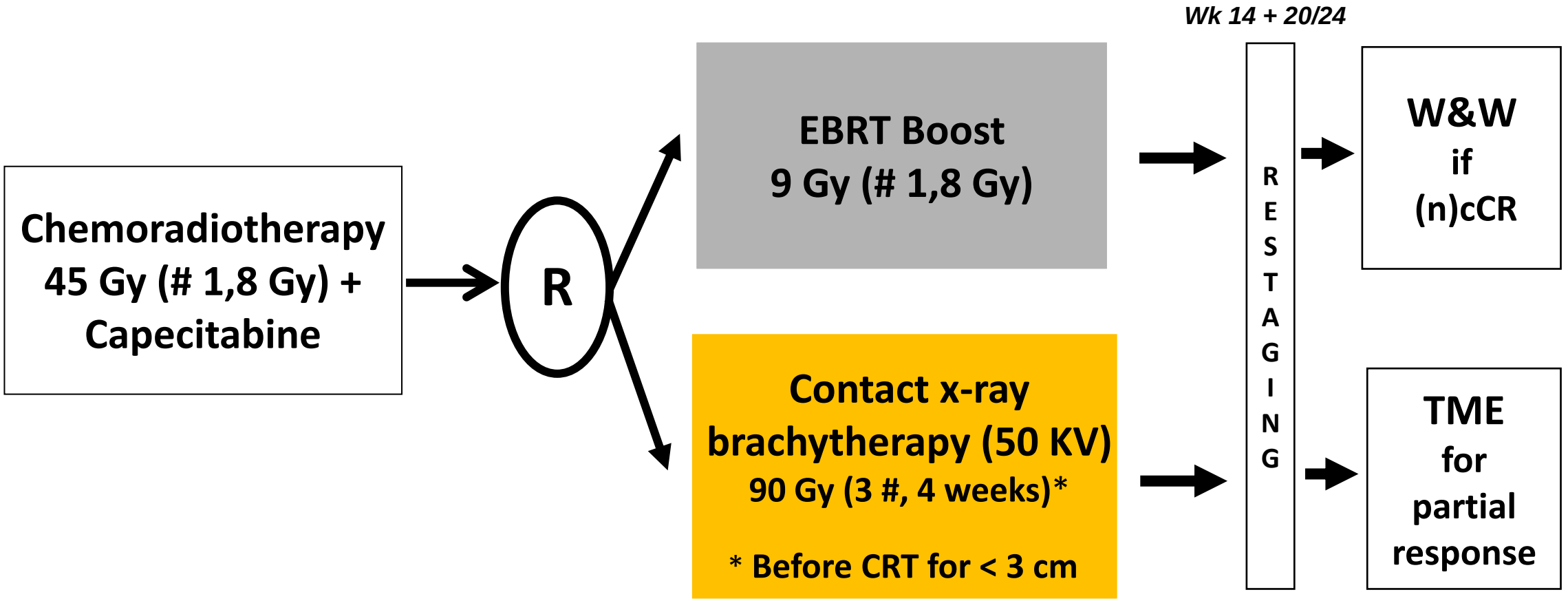
ACO/ARO/AIO-18.1	III	Stage II/III	**5x5Gy** + consol. FOLFOX *vs* **CRT**+ consol. FOLFOX

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	**CRT+EBRT** **N=69**	**CRT+Brachy** **N=72**	**p**
cCR/near cCR (as assessed week 24)	46%/17%	68%/24%	<.0001
TME/LE for residual tumor or local regrowth	26/20	13/7	
Organ preservation at 3y (all) **Tumors < 3 cm/>3cm**	**59%** **63%/55%**	**81%** **97%/68%**	**.0026** **.012/0.1**
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

Gerard JP et al., Lancet Gastroenterol Hepatol 2023

Strategies for Organ Preservation with 5x5Gy, CRT, TNT

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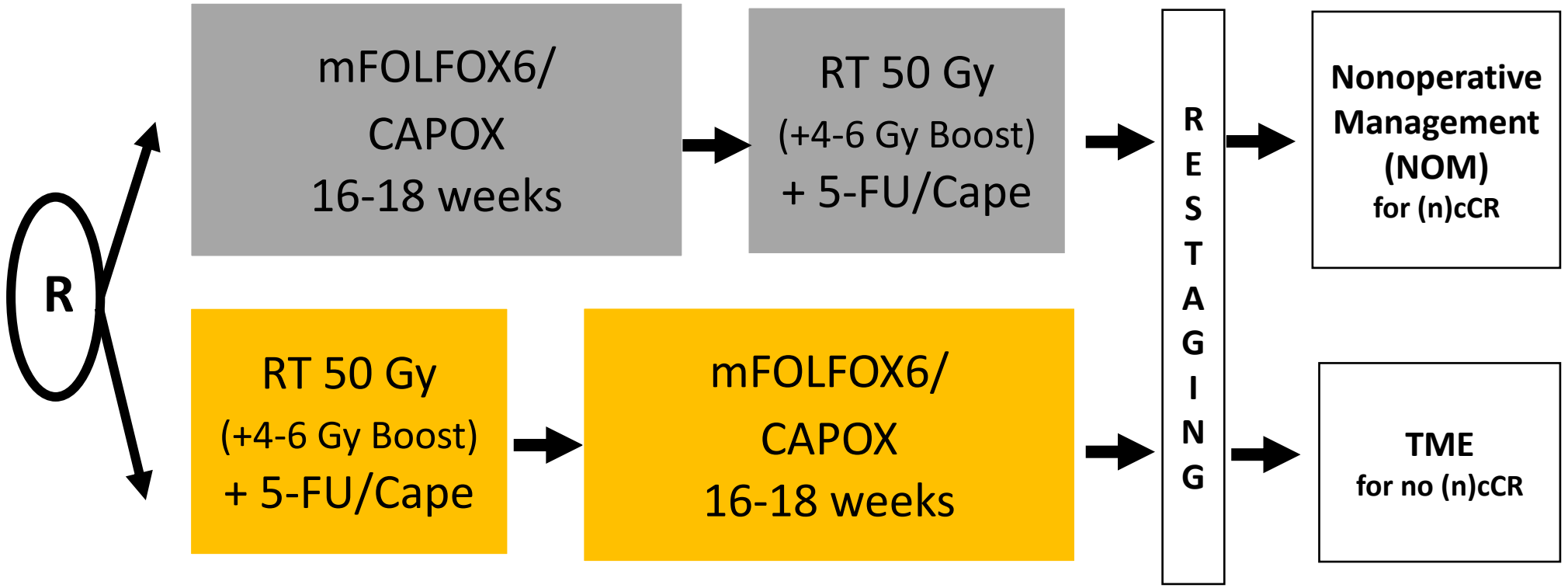
OPRA (Organ preservation in Rectal Adenocarcinoma-Trial)

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

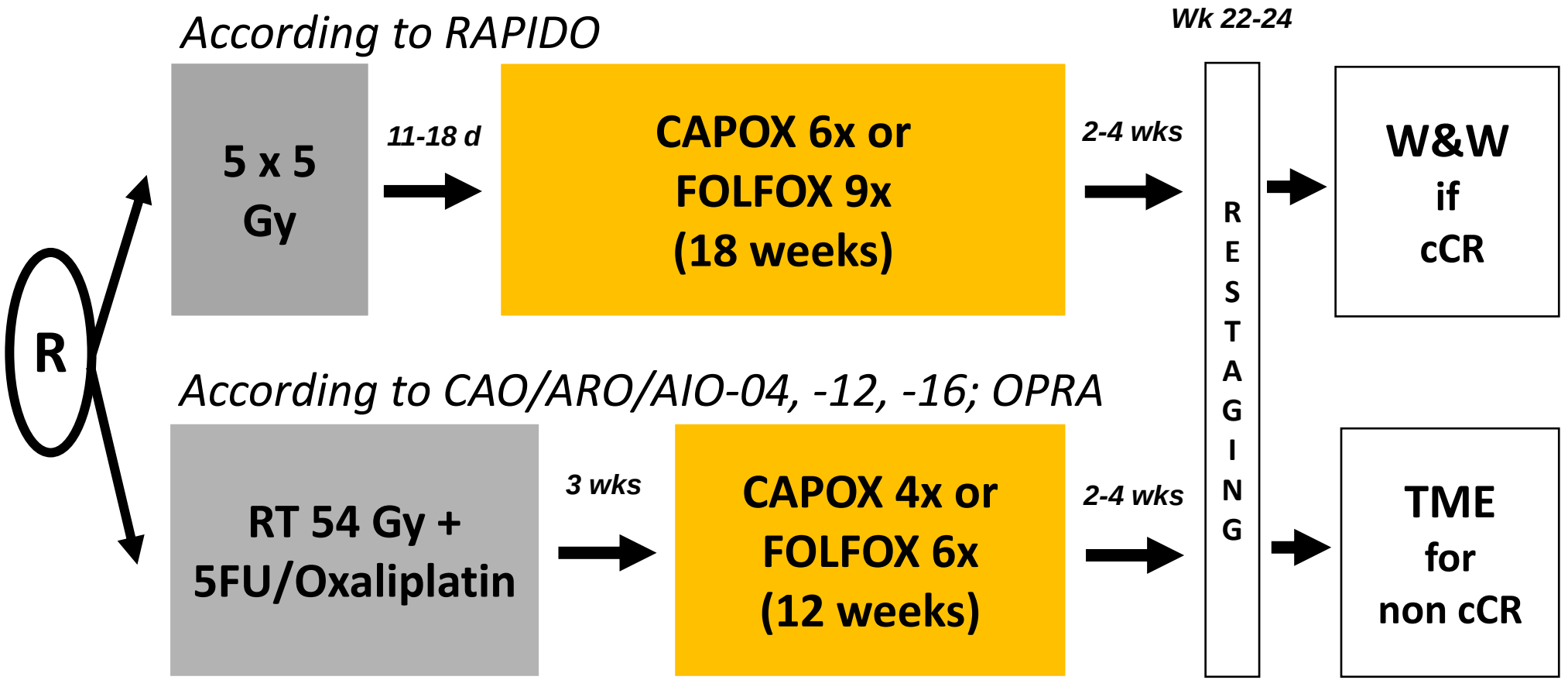
OPRA: Oncologic Results (median F/u: 3 years)

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

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

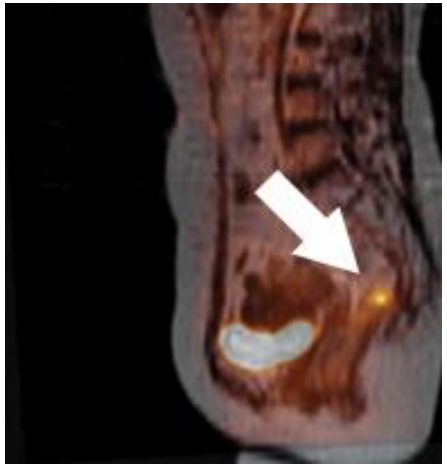
ACO/ARO/AIO-18.1 randomized phase III trial

Inclusion criteria: $cT3_{any}$ if low rectal third, $cT3_{c/d}$, N+, cT4 if mid rectal cancer



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

Where do we stand?



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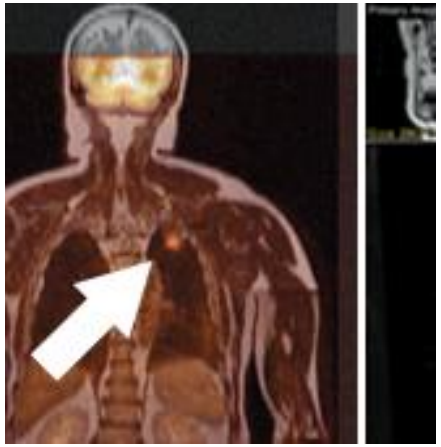

Escalating strategies:

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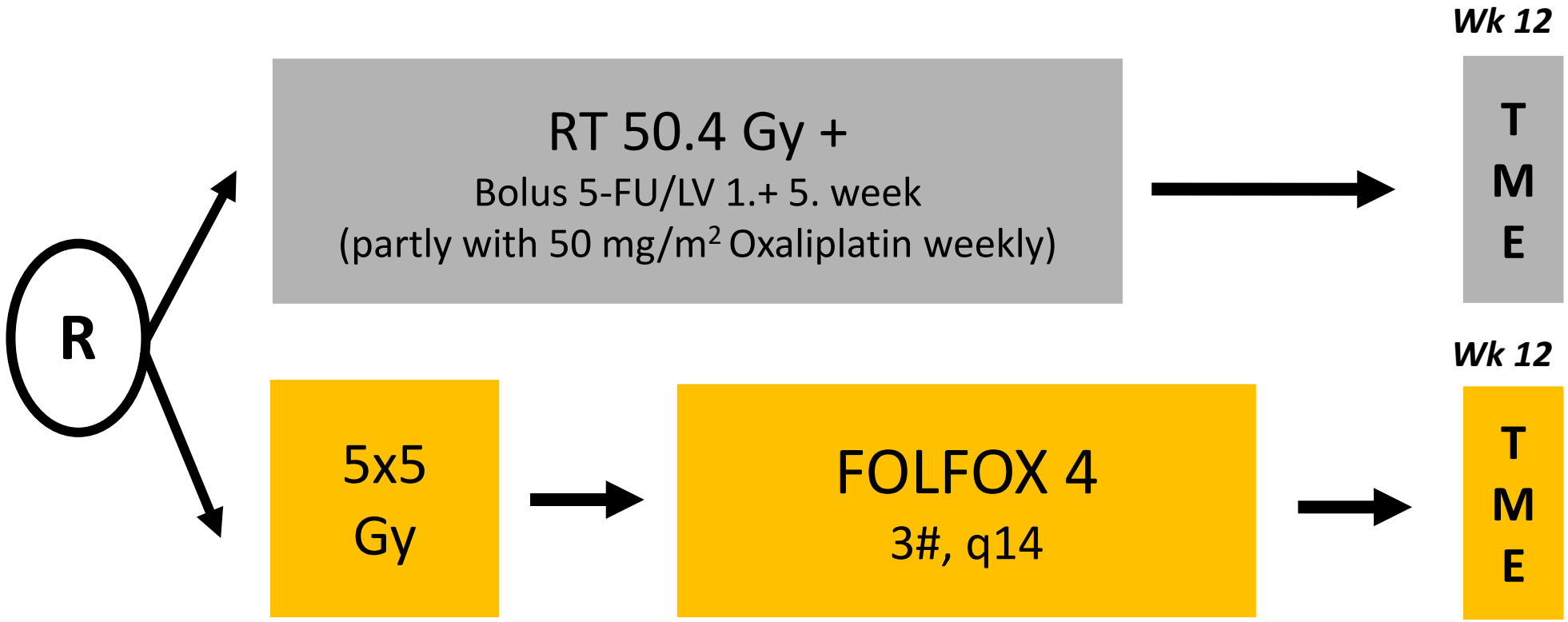
POLISH II – Trial

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



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

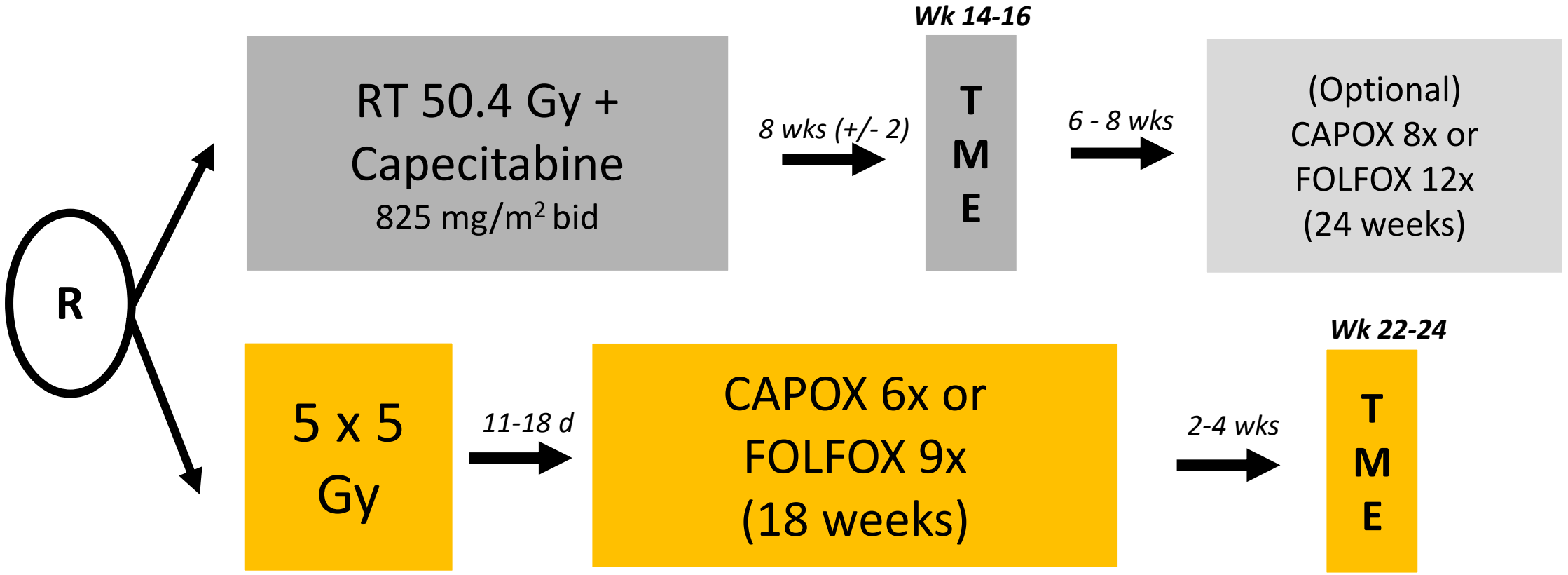
Polish Trial II

	50.4 Gy 5-FU/(Ox)	5x5 Gy FOLFOX	P-value
Number of pts	254	261	
R0 resection (%)	**71**	**77**	**.07**
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

Bujko et al., Ann Oncol 2017; Ciseł B et al., Ann Oncol 2019

RAPIDO

Inclusion: MRI-defined high-risk (≥ 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 (%)	**25**	**48**
Compliance CRT/RT (%)	93	100
Compliance Cht (at least 75% of planned dose, %)	Adjuvant 58	84
Pathological complete response (%)	**14.3**	**28.4**
R0/CRM+/R2 (%)	90/9/<1	90/9/<1
Postop. complications: any/CD ≥ III (%)	47/16	50/18
Mesorectal plane intact (%) (assessed by surgeon)	**85**	**78**

Van der Valk MJM et al., Radiother Oncol 2020; Bahadoer RR et al., Lancet Oncol 2021

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

	Standard Chemoradiation	5x5 Gy + CAPOX/FOLFOX	HR (95% CI)/p
DrTF* (primary endpoint) * M1; locoregional failure; new CRC; treatment-related death	**30.4 %**	**23.7 %**	**0.75 (0.60-0.96)** **p=0.019**
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	

Bahadoer RR et al., Lancet Oncol 2021; Dijkstra EA et al. Radiother Oncol 2022

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

	Standard Chemoradiation	5x5 Gy + CAPOX/FOLFOX	HR (95% CI)/p
DrTF* (primary endpoint) * M1; locoregional failure; new CRC; treatment-related death	**34.0 %**	**27.8 %**	**0.79 (0.63-1.00)** **p=0.048**
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

Dijkstra EA et al., Ann Surg 2023

Should all patients receive „RAPIDO“ like TNT?

RAPIDO: DrTF and M1 benefit!

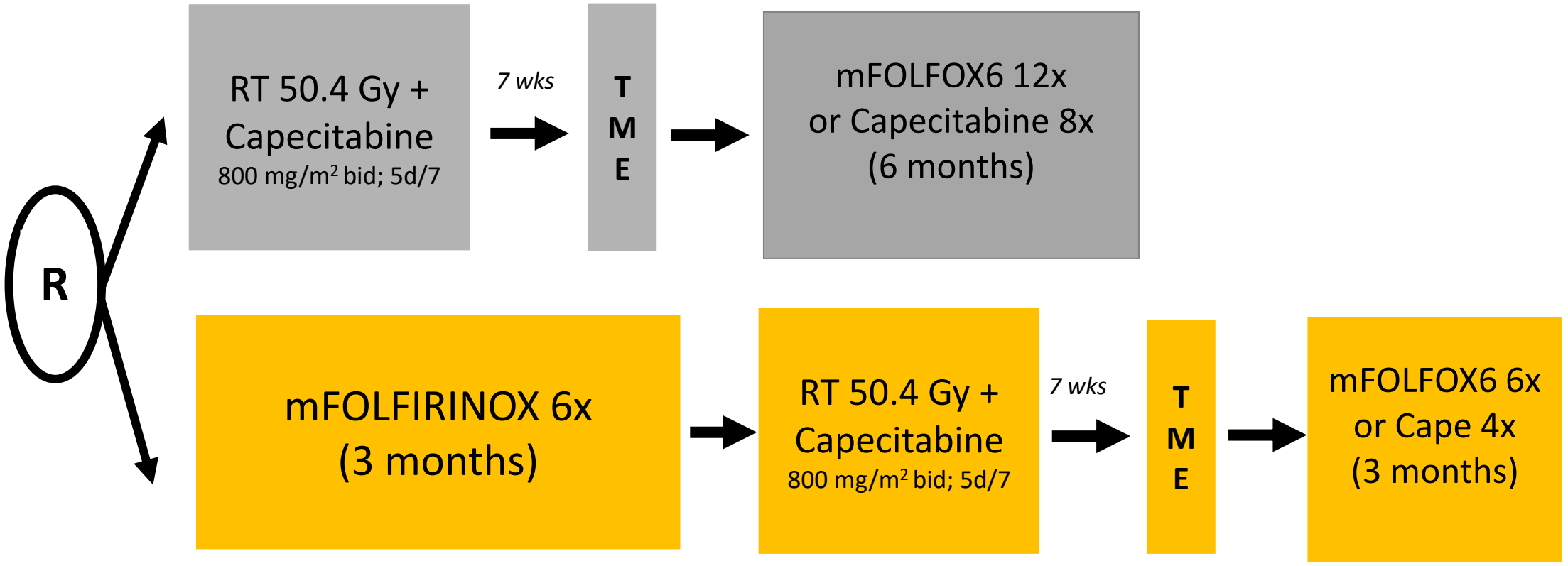
(ACO/ARO/AIO Consensus to generally recommend TNT)

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
DFS (primary endpoint)	**68.5 %**	**75.7 %**	**0.69 , p=0.034**
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

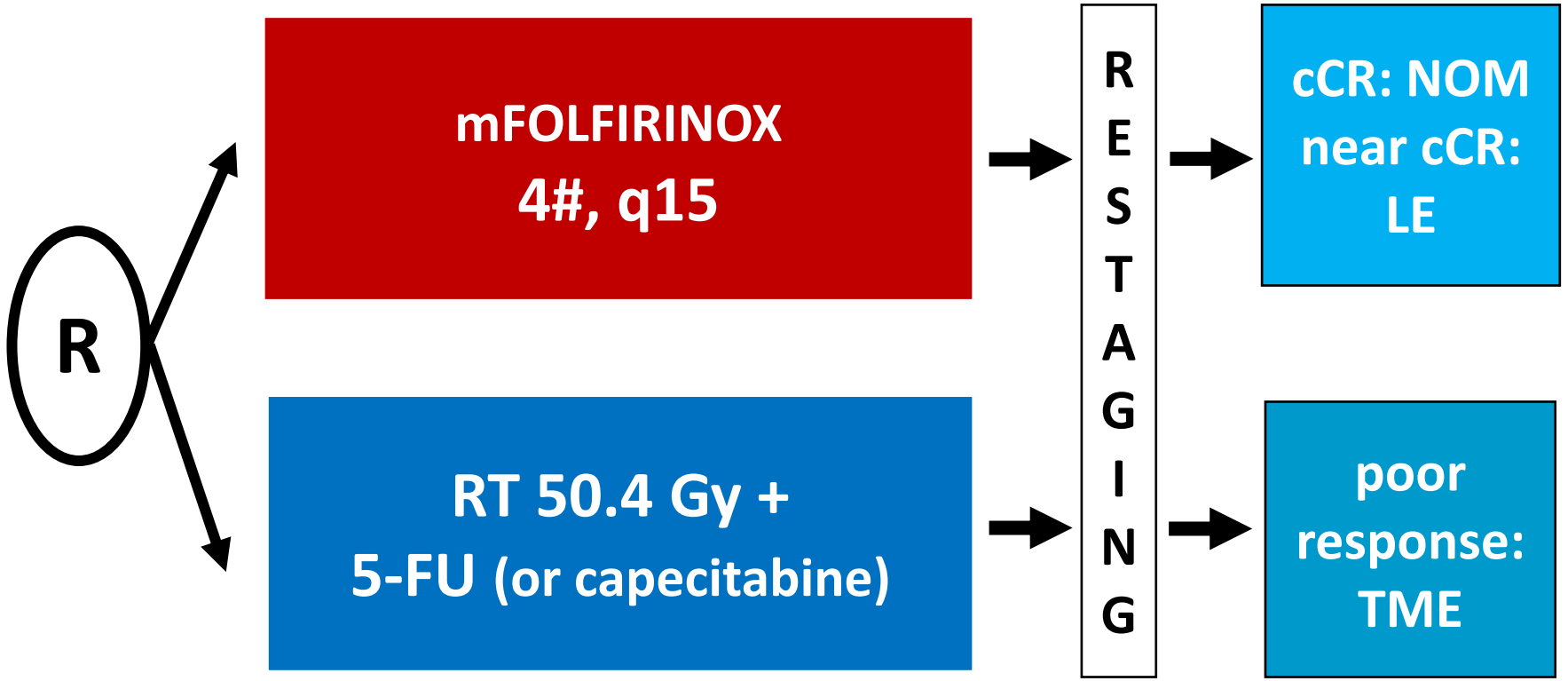
update ASCO 2023 with OS benefit of 7% at 5 years

Where do we go from here?

Ongoing studies

GRECCAR12 phase III trial

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

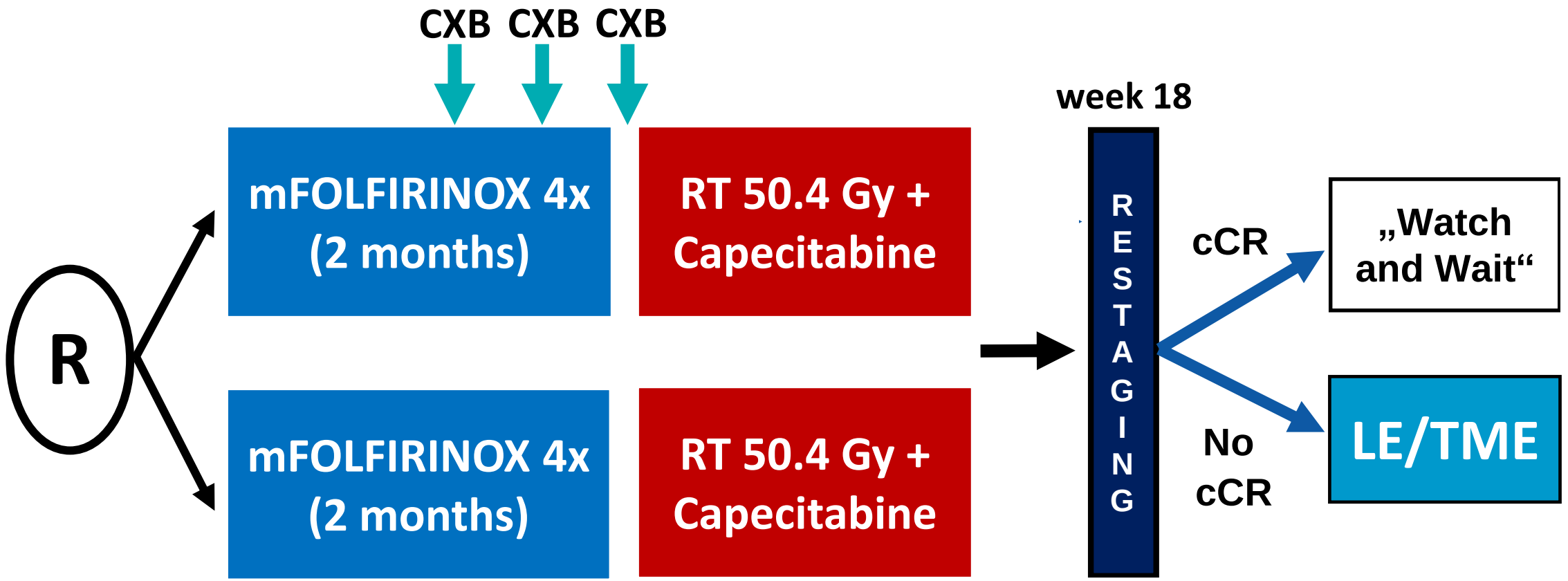


Primary endpoint: 12-month organ preservation, N=218

NCT02514278 cCR: clinical complete response

TRESOR randomized phase III trial

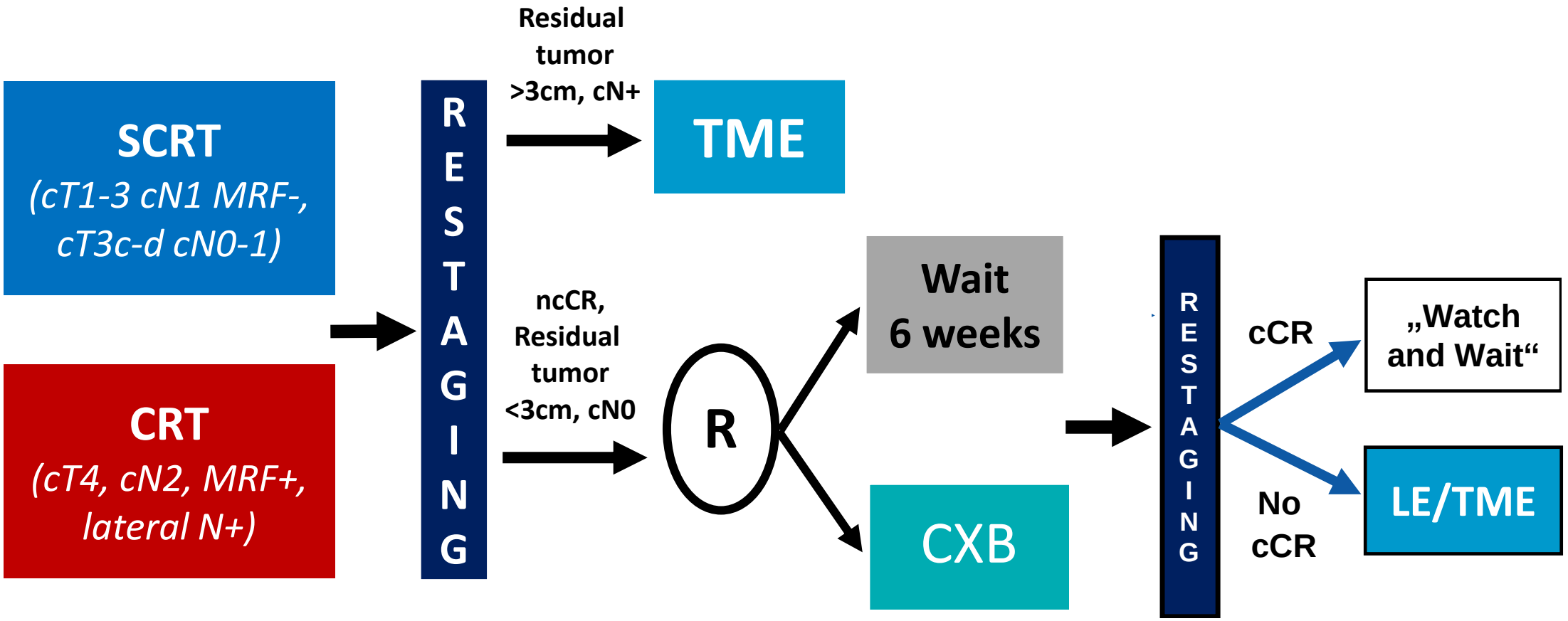
cT2-T3 >3.5cm, N0-N1



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



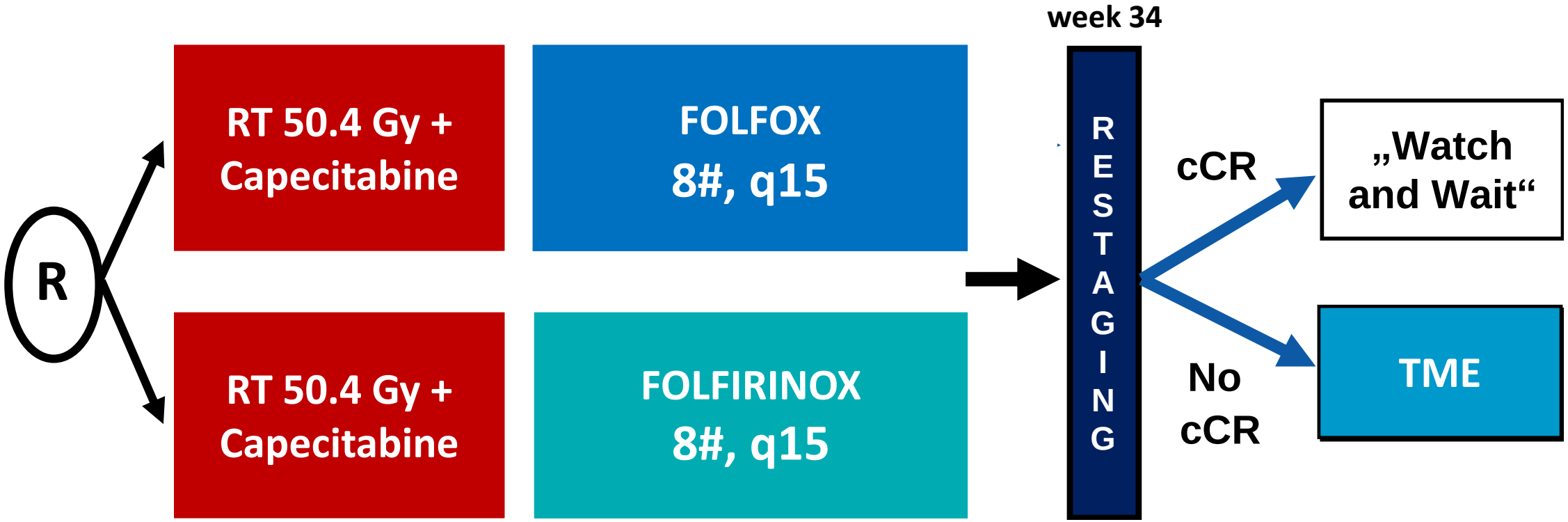
Primary endpoint: 1-year Organ preservation; n=336 (168: SCRT; 168: CRT)

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

Dutch trial register: NL75896.031.20

JANUS/NRG GI010 phase II

Inclusion: cT4; N+; any T3N0 requiring APR

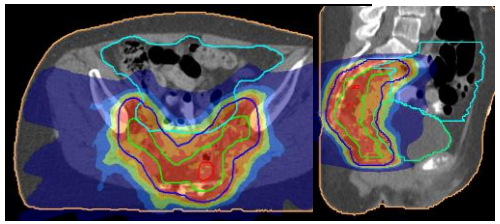


Primary Endpoint: **cCR,** N=312

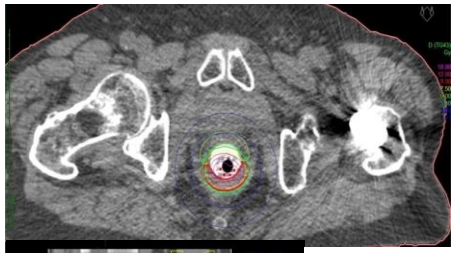
NCT05610163

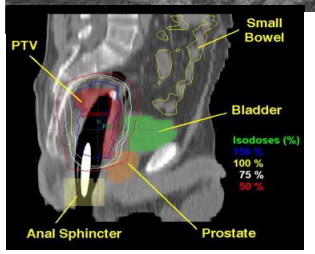
ACO/ARO/AIO-22 phase-II trial in elderly frail patients

Hypofractionated Radiotherapy 13 x 3 Gy



Endorectal HDR-Brachy 3 x 8 Gy (5-10mm)





week 24

RESTAGING

cCR → Watch and Wait

No cCR → Palliative Therapy / OP*

Co-Primary endpoints

- **cCR rate**
- **Quality of life (EORTC QLQ-ELD14)**

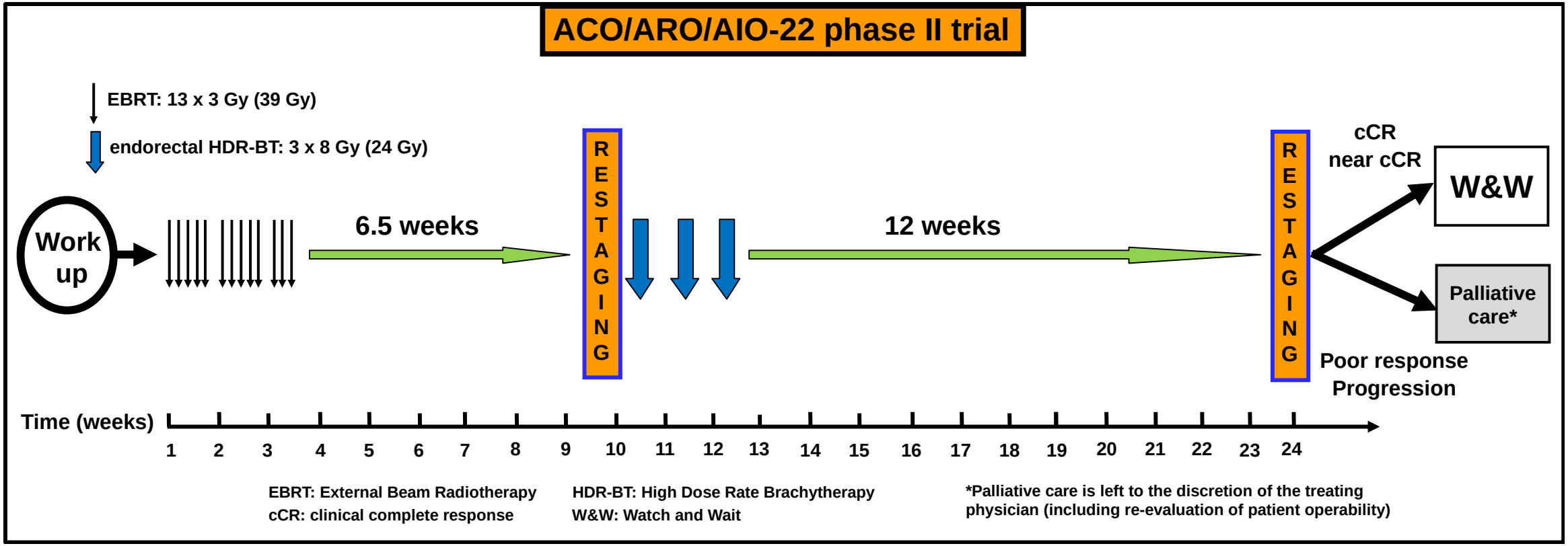
N=80; DKH Förderantrag gestellt

≥70 years old:

- assessed as inoperable from surgeons
- ***and/or*** Geriatric 8 (G8)-Frailty-Score ≤ 14
- ***and/or*** ASA PS ≥ 3

*Reevaluation of operability

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



N=80; DKH Förderantrag gestellt

*Reevaluation of operability

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