ACO/ARO/AIO-18.1

Short-course radiotherapy versus **chemoradiotherapy**, followed by **consolidation chemotherapy**, and selective **organ preservation** for MRI-defined intermediate and high-risk rectal cancer patients

A randomized phase III trial of the

German Rectal Cancer Study Group

Deutsche Krebshilfe
HELFEN. FORSCHEN. INFORMIEREN.

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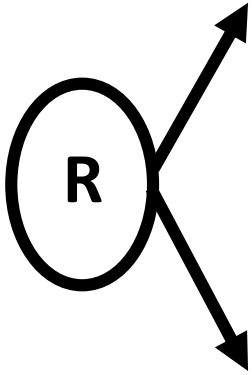
Study Design

MRI criteria: Intermediate/High-risk

- Any cT3 if low rectal (0 - < 6 cm)
- cT3c/d mid rectal (≥ 6 - 12 cm)
- cT4
- T_{any} middle/low third of rectum with clear MRI criteria for N+
- mrCRM+ (≤1mm)
- EMVI+



*Control arm (according to **RAPIDO**)*

TNT: 5x5 Gy – Consolidation CT– Surgery or **W&W**

TNT: 5-FU/OX-RT – Consolidation CT – Surgery or **W&W**

*Investigational arm (according to **CAO/ARO/AIO-12 and -16, OPRA**)*

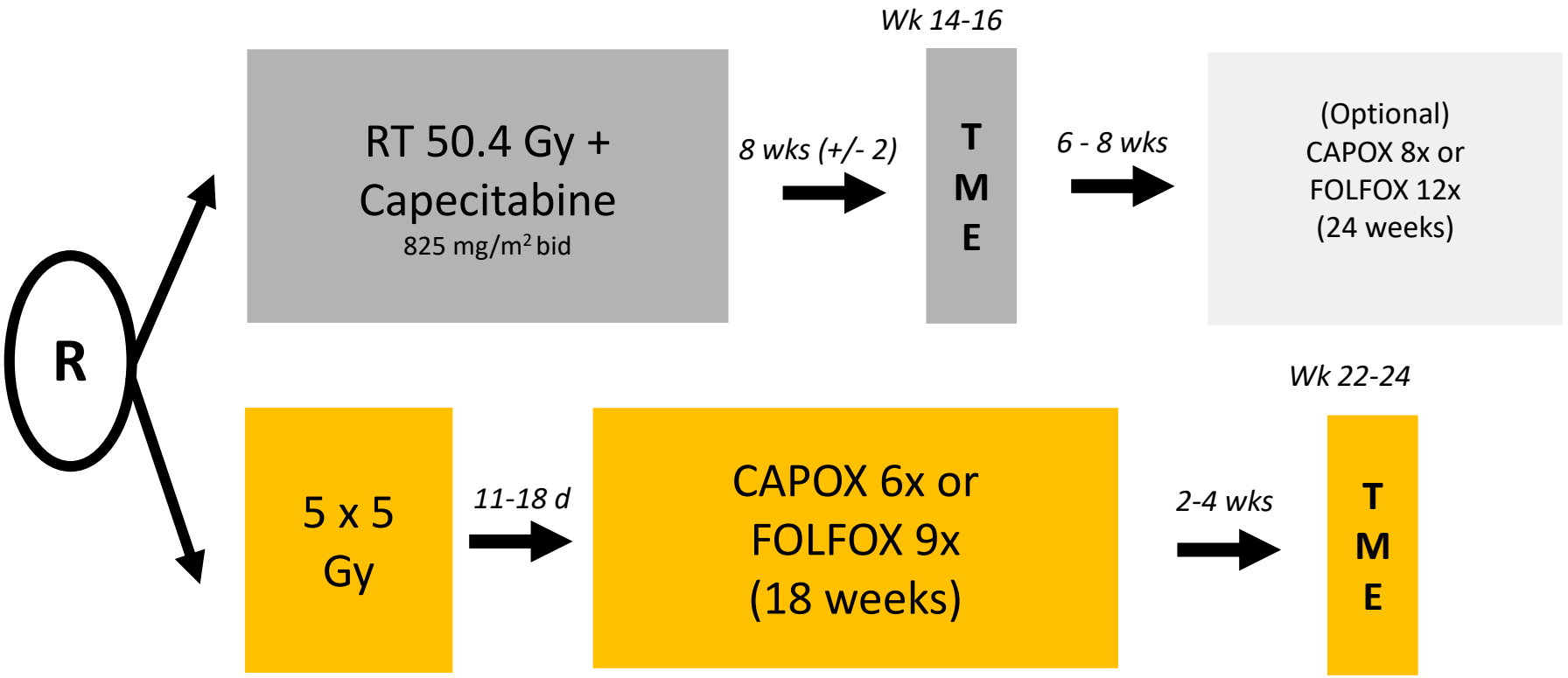
Konsentierte Stellungnahme der AIO, der ACO und der ARO zur **neoadjuvanten** Therapie beim Rektumkarzinom **(TNT)**

Konsentierte Stellungnahme der ACO, der AIO und Der ARO zum **„watch and wait“-**Konzept mit intendiertem **Organerhalt** bei Rektumkarzinom

https://www.aio-portal.de

RAPIDO

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: Surgical & pathological data

	Standard Chemoradiation	5x5 Gy + CAPOX/FOLFOX
Number	400	426
(Low) anterior resection	219 (54.8)	246 (57.8)
Abdominoperineal resection	157 (39.3)	147 (34.5)
Mesorectal plane intact (assessed by surgeon)	342 (85)	334 (78)
Postop. complications: any/CD ≥ III	189 (47)/64 (16)	215 (50)/73 (18)
Postop. death < 30d	1 (<1)	3 (<1)
R0/CRM+/R2	360/37/1 (90/9/<1)	383/37/3 (90/9/<1)
Pathological complete response	57 (14.3)	120 (28.4)

Bahadoer RR et al., ASCO 2020
Van der Valk MJM etv al., Radiother Oncol 2020

RAPIDO: Oncological Results at 3 years (I)

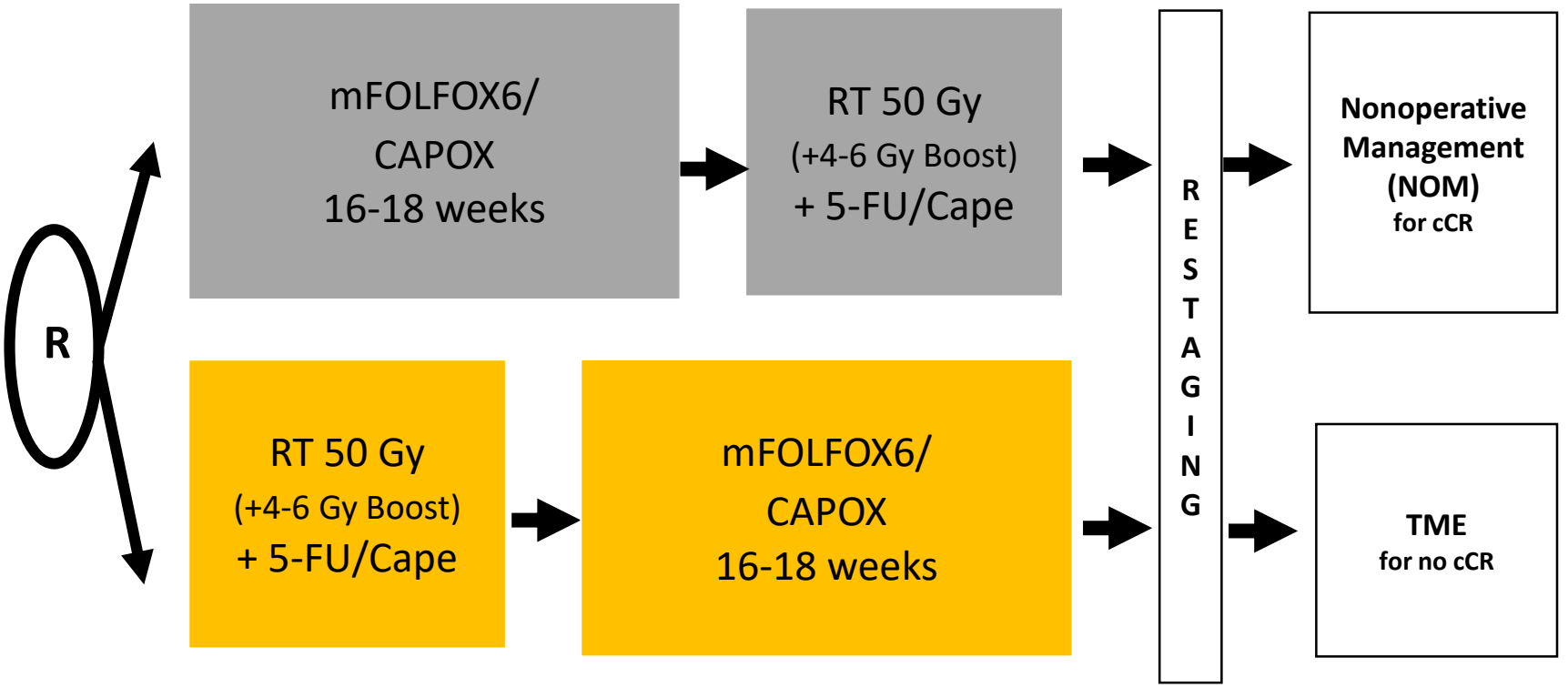
	Standard Chemoradiation	5x5 Gy + CAPOX/FOLFOX	HR (95% CI)/p
DrTF* (primary endpoint)	**30.4 %**	**23.7 %**	**0.75 (0.60-0.96) p=0.019**
Distant M1	26.8%	20.0%	0.69 (0.54-0.90) p=0.005
Locoreg. failure	6.0%	8.7%	1.45 (0.93-2.26) p=0.09
OS	88.8%	89.1%	0.92 (0.67-1.25) p=0.59
Overall health/QoL/LARS	n.s.	n.s.	n.s.

* Defined as distant M1; locoregional failure, new primary colorectal cancer, treatment related death

Bahadoer RR et al., ASCO 2020

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: Baseline Characteristics

	Induction chemo - Chemoradiation	Chemoradiation - Consolidation chemo
Number	148	158
Age (mean, SD)	58 (11)	57 (11)
Gender M/F	95/53	96/62
cT1-2	11 (7)	21 (13)
cT3	114 (77)	121 (77)
cT4	23 (16)	16 (10)
cN0	45 (30)	45 (28)
cN+	103 (70)	113 (72)

Garcia-Aguilar J et al., ASCO 2020

OPRA: Oncological Results at 3 years (median F/u: 2.3 y)

	Inductionchemo - Chemoradiation	Chemoradiation - Consolidation chemo	p
DFS	77 %	78 %	0.63
M1-free Survival	82%	84%	0.83
TME-free Survival	**43%**	**59%**	0.007

Garcia-Aguilar J et al., ASCO 2020

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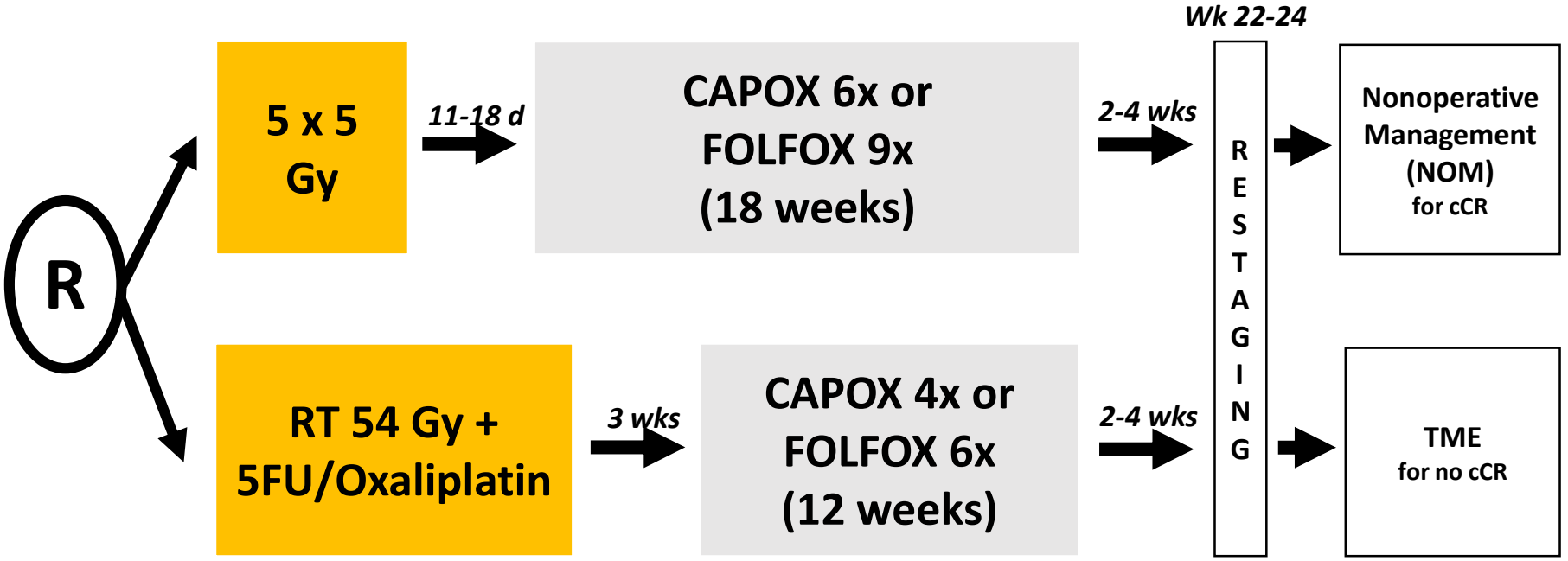

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Treatment - Control Arm

- **IMRT** 5 x 5 Gy with differential PTV concepts based on risk factors (sphincter; upper border)

- **Consolidation chemotherapy:**
  mFOLFOX (9 cycles) every 2 weeks
  - Folinic Acid: 400 mg/m², 2h-civ
  - Oxaliplatin: 85 mg/m², 2h-civ
  - 5-FU: 2400 mg/m², 46h-civ civ

- **Alternative: CAPOX (6 cycles) every 3 weeks**
  - Capecitabine: 1000 mg/m² bid d1-14 every 3 weeks
  - Oxaliplatin: 130 mg/m² d1 every 3 weeks

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Treatment - Experimental Arm

- **IMRT** 25 x 1,8 Gy with differential PTV concepts based on risk factors (sphincter; upper border) and 5 x 1,8 Gy Boost (Total dose: **45 Gy + 9 Gy**)

- **Concurrent chemotherapy:**
  - 5-FU: 250 mg/m², civ d1-14, d22-35 of RT
  - Oxaliplatin: 50 mg/m², d1, 8, 22, 29 of RT

- **Consolidation chemotherapy:**
  mFOLFOX (6 cycles) every 2 weeks
  or CAPOX (4 cycles) every 3 weeks

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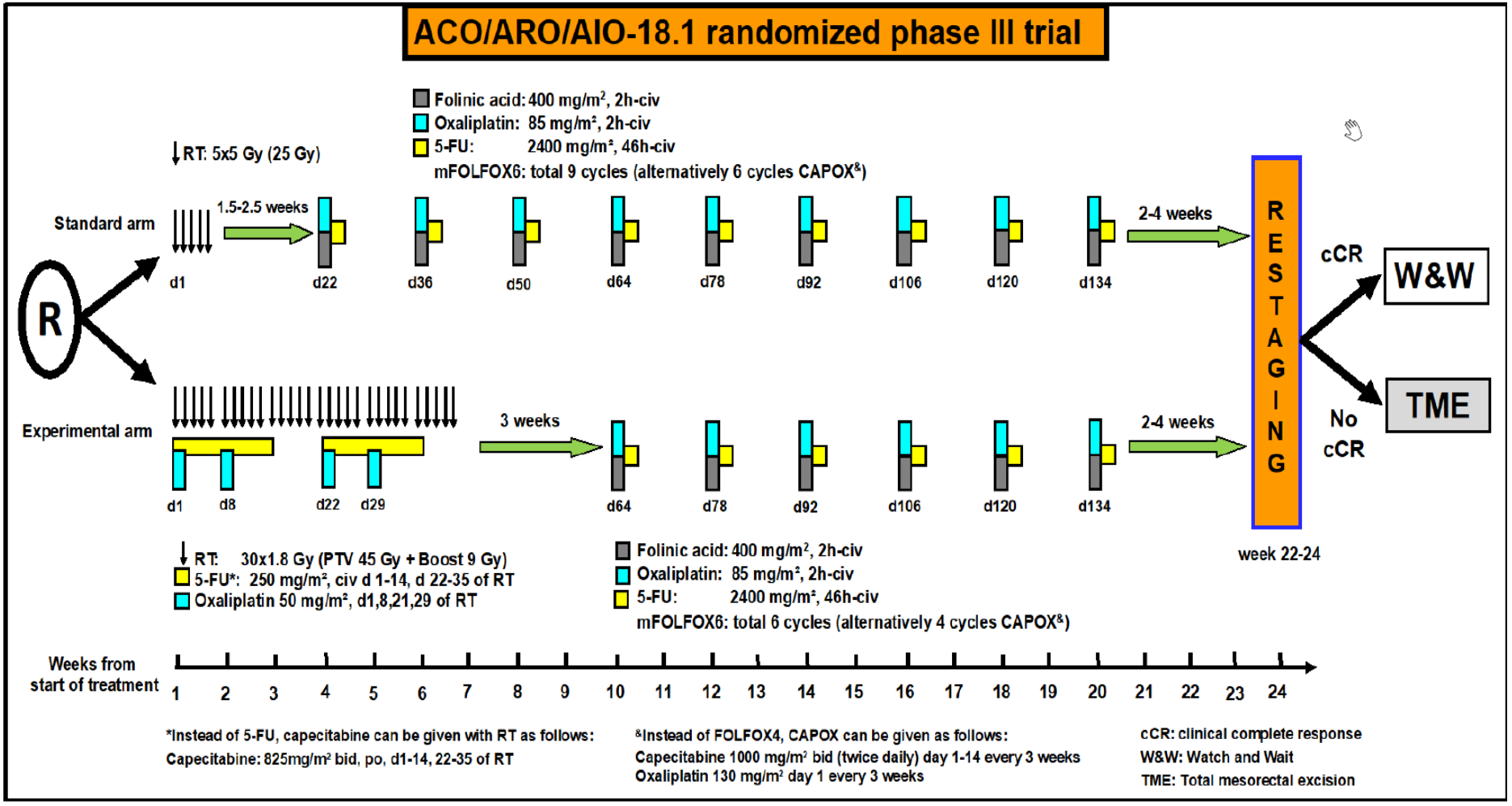
Study Schedule



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Primary Endpoint: Organ Preservation

Survival with rectum intact, no major surgery, no stoma

The primary endpoint will not be reached if any of the following occurs:

- Death
- any major surgery other than local excision (R0) performed after randomization, during TNT, at re-staging scheduled 22-24 weeks after start of TNT due to clinical non-cCR, or for any locoregional regrowth after initial cCR requiring salvage-TME
- any locoregional regrowth not amenable to salvage surgery
- any stoma (non-re-converted protective stoma within 6 months after completion of TNT, or any stoma needed for toxicity or poor function), whichever occurs first.

Sample Size

We hypothesized that the **3-year organ preservation** rate will improve from **30%** in the control arm to **40%** in the investigational arm (hazard ratio of 0.76). With a power of 90% and a two-sided type I error of 5%, the sample size required to obtain a statistically significant difference is **702 patients** (564 events) in total.

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Secondary Endpoints

- **Disease-free survival**
- Rate of clinical complete response after TNT
- Rate of immediate TME after TNT
- Cumulative incidence of locoregional regrowth after cCR
- Rate of salvage surgery (LE/TME with or without APR/stoma) after locoregional regrowth
- Cumulative incidence of local recurrence after (salvage) surgery
- Postoperative complications of (salvage) surgery
- Rate of sphincter-sparing (salvage) surgery
- Pathological TNM-staging
- R0 resection rate; negative circumferential resection rate
- Tumor regression grading according to Dworak
- Neoadjuvant rectal score
- Quality of TME according to MERCURY
- Acute and late toxicity assessment according to NCI CTCAE V.5.0)
- **Quality of life and functional outcome**
- Cumulative incidence of distant metastases
- **Overall survival**

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Secondary Endpoint: DFS

Event	DFS	Time from randomization until
No resection of primary tumor due to local progression or patient unfit for surgery	E	Date of scheduled, but not performed surgery
No resection of primary tumor due to clinical complete response (endoscopy/MRI) + patient opts for W&W management	I	_
Non-radical resection of primary tumor (R2-resection)	E	Date of surgery
Locoregional recurrence after R0/1 resection of the primary tumor	E	Date of locoregional recurrence
Local re-growth after initial complete response followed by curative salvage operation (R0/1)	I	_
Non-salvageable local regrowth in case of W&W management (no operation or R2 salvage resection)	E	Date of diagnosis of non-salvageable re-growth or date of R2 salvage surgery

Fokas E et al., Lancet Oncol 2020

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Primary Endpoint: DFS

Event	DFS	Time from randomization until
Any distant metastatic disease before, at, or after surgery or W&W management	E	Date of distant metastases
Second primary colorectal cancer	E	Date of second colorectal primary
Second primary, other cancer	E	date of second primary, other cancer
Death from same cancer	E	Date of death
Death from other cancer	E	Date of death
Non-cancer related death	E	Date of death
Lost to follow-up	C	Date last follow-up

Fokas E et al., Lancet Oncol 2020

W I S S E N A U S E R S T E R H A N D

Deutsche Krebsgesellschaft e. V. Kuno-Fischer-Straße 8 14057 Berlin

Die in der StudyBox gelistete Studie zum Organerhalt beim Rektumkarzinom **(ACO/ARO/AIO-18.1)**, die von der Deutschen Krebshilfe gefördert wird, wird durch die DKG ausdrücklich unterstützt.

Einzelne Zentren haben die Befürchtung geäußert, durch die Teilnahme an der Studie die erforderliche Zahl operativer Primärfälle beim Rektumkarzinom nicht mehr zu erreichen und damit ihr Zertifikat zu verlieren. Um hier einen Fehlanreiz zu vermeiden, wird in Abstimmung mit der Zertifizierungskommission folgendes Vorgehen umgesetzt:

Zertifizierte Darmkrebszentren, die an der ACO/ARO/AIO-18.1- Studie teilnehmen und infolge ihrer Teilnahme die Mindestvorgabe von mindestens 20 operativen Primärfällen beim Rektumkarzinom nicht erreichen, **können Studienpatienten, die sie im Datenfeld „Watch and Wait“ führen, zu den operativen Primärfällen hinzuzählen.** Dieses Vorgehen ist im Audit nachvollziehbar darzulegen.

Mit freundlichen Grüßen

ACO/ARO/AIO-18.1

- Three **innovative** aspects: TNT, adaptive treatment based on response, selective organ preservation.
- With optimized TNT „rectal cancer could become anal cancer (rather than colon cancer)“.