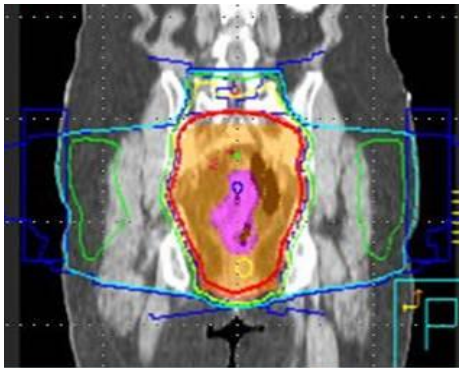
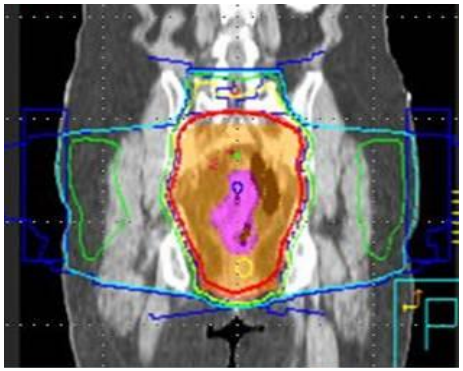


German Rectal Cancer Study Group

- CAO/ARO/AIO-94 Randomisierte Phase III *(N Engl J Med 2004)*
- CAO/ARO/AIO-03 Phase I/II *(J Clin Oncol 2003 und 2007)*
- CAO/ARO/AIO-04 Phase III *(Lancet Oncol 2012 und 2015)*

- CAO/ARO/AIO-12 Randomisierte Phase II (*J Clin Oncol 2019*)
- CAO/ARO/AIO-0214 Phase II (laufend)
- CAO/ARO/AIO-16 Phase II (laufend)
- **ACO/ARO/AIO-18.1 u.2. Randomisierte Phase III (Start 2020)**



German Rectal Cancer Study Group

- CAO/ARO/AIO-94 Randomisierte Phase III *(N Engl J Med 2004)*
- CAO/ARO/AIO-03 Phase I/II *(J Clin Oncol 2003 und 2007)*
- **CAO/ARO/AIO-04 Phase III: Update**

- CAO/ARO/AIO-12 Randomisierte Phase II *(J Clin Oncol 2019)*
- CAO/ARO/AIO-0214 Phase II (laufend)
- CAO/ARO/AIO-16 Phase II (laufend)
- ACO/ARO/AIO-18.1 u.2. Randomisierte Phase III (Mitte 2019)

CAO/ARO/AIO-04

According to CAO/ARO/AIO-94:

RT 50.4 Gy + 5-FU
1000 mg/m² d 1-5 + 29-33

5-FU
500 mg/m² d 1-5, q29
4 Cycles (4 Months)

T
M
E

Experimental Arm of CAO/ARO/AIO-04

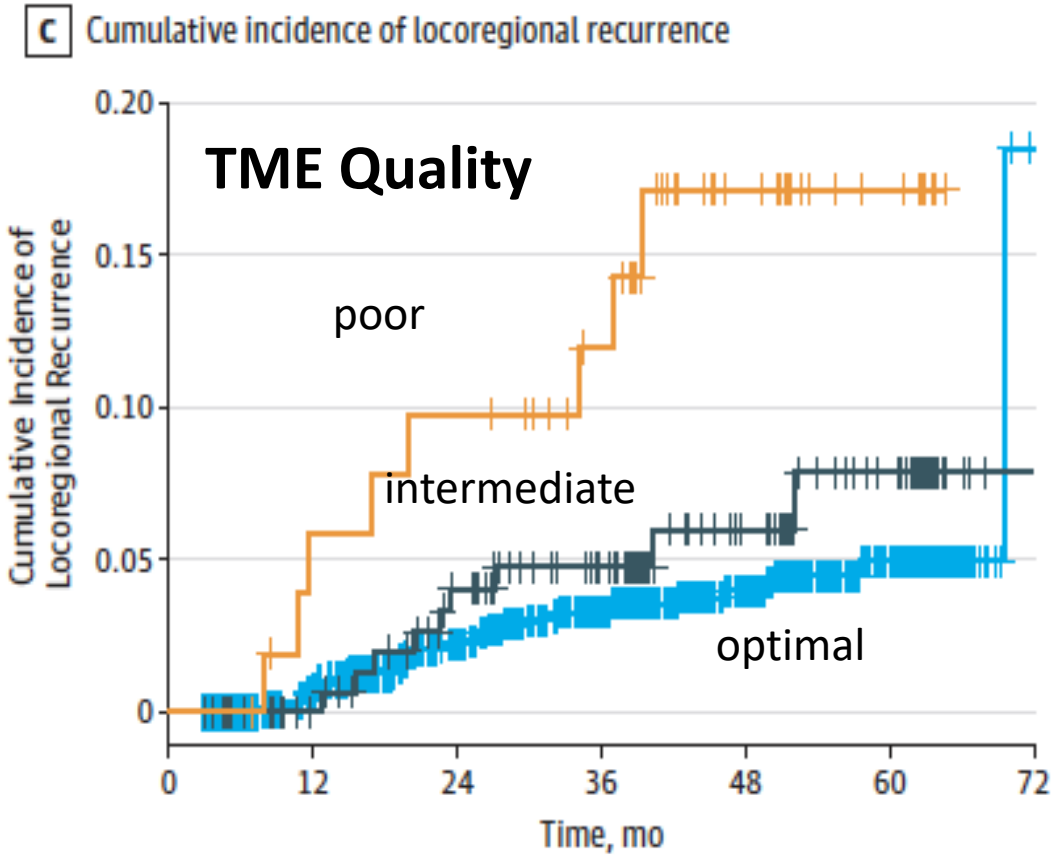
RT 50.4 Gy + 5-FU/OX
Ox: 50 mg/m² d 1, 8, 22, 29
5-FU: 250 mg/m² d 1-14+22-35

mFOLFOX6
Oxaliplatin: 100 mg/m² d1,q15
Folinsäure: 400 mg/m² d1
5-FU: 2400 mg/m² d1-2
8 Cycles (4 Months)

CAO/ARO/AIO-04: Update published results

Rödel et al. ***Lancet Oncol 2012***	**Initiale Ergebnisse: pCR, Tox, Compliance**
Rödel et al. ***Lancet Oncol 2015***	**Primärer Endpunkt: DFS verbessert!!**
Fokas et al. ***J Nat Cancer Inst 2017***	**TRG als Surrogat-Endpunkt**
Fokas et al. ***Ann Oncol 2018***	**NAR Score als Surrogat-Endpunkt**
Von der Grün et al. ***Radiother Oncol 2018***	**Lymphknotenbefall bei ypT0-2**
Kitz et al. ***JAMA Surg 2018***	**Chirurgische Qualität (TME)**
Hofheinz et al. ***Ann Oncol 2018***	**Altersabhängigkeit**
Diefenhardt et al. ***Int J Cancer 2019***	**Leukozytose als prädiktiver Marker**
Diefenhardt et al. ***JAMA Oncol 2019***	**Geschlecht, Toxizität und onkologische Ergebnisse**
Diefenhardt et al. ***2020, submitted***	**Therapie-Compliance und onkologische Ergebnisse**
Kosmala et al. ***2020 submitted***	**Patient reported outcomes**

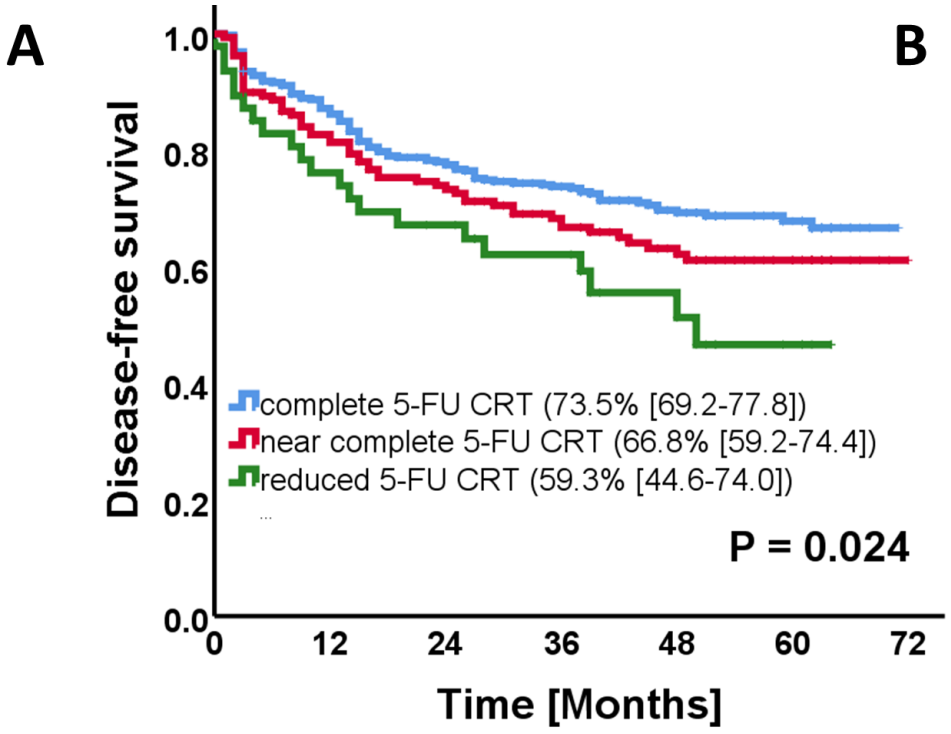
CAO/ARO/AIO-04: TME-Qualität



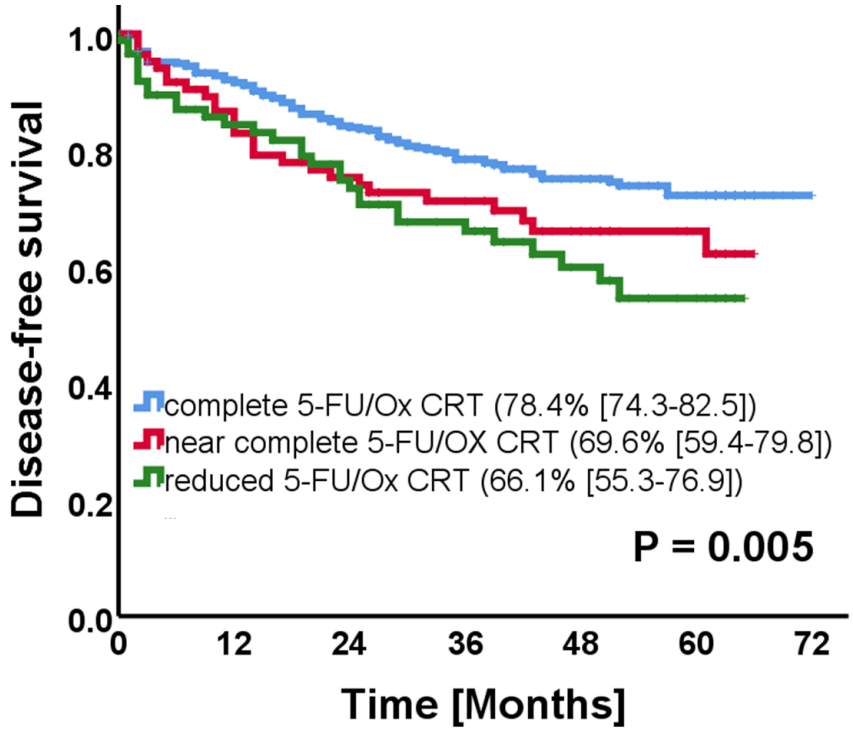
No. at risk							
Mesorectal	930	864	790	669	428	193	1
Intramesorectal	169	154	138	112	68	40	1
Muscularis propria	53	48	46	38	18	7	0

Kitz et al., JAMA Surg 2018

CAO/ARO/AIO-04: Compliance to CRT



N risk:							
	419	349	302	248	156	67	0
	159	122	107	87	61	38	0
	47	33	28	22	11	5	0

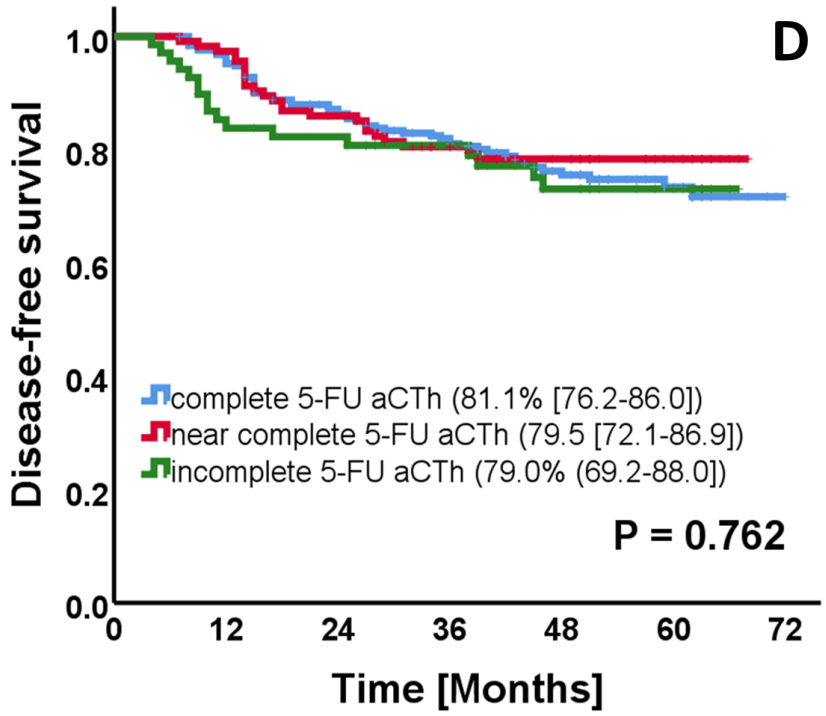


N risk:							
	434	382	327	268	164	78	0
	85	66	58	46	30	16	0
	88	63	53	42	26	10	0

Diefenhard et al., 2020 submitted

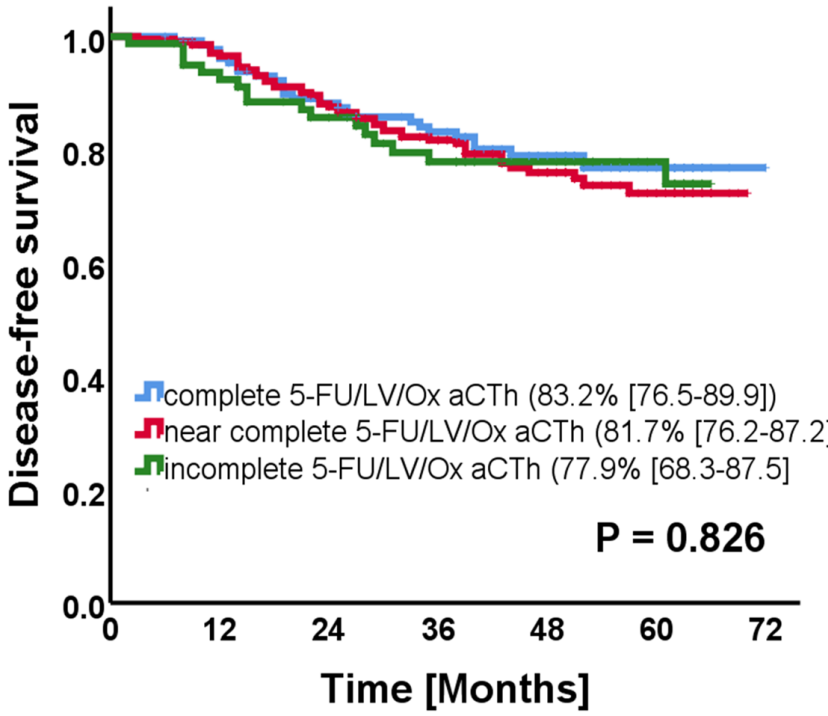
CAO/ARO/AIO-04: Compliance to CRT

C



N risk:							
	253	241	208	173	109	48	0
	117	111	97	79	54	25	0
	69	56	53	46	33	19	0

D



N risk:							
	134	124	110	94	60	23	0
	205	195	173	140	85	45	0
	80	73	60	47	34	19	0

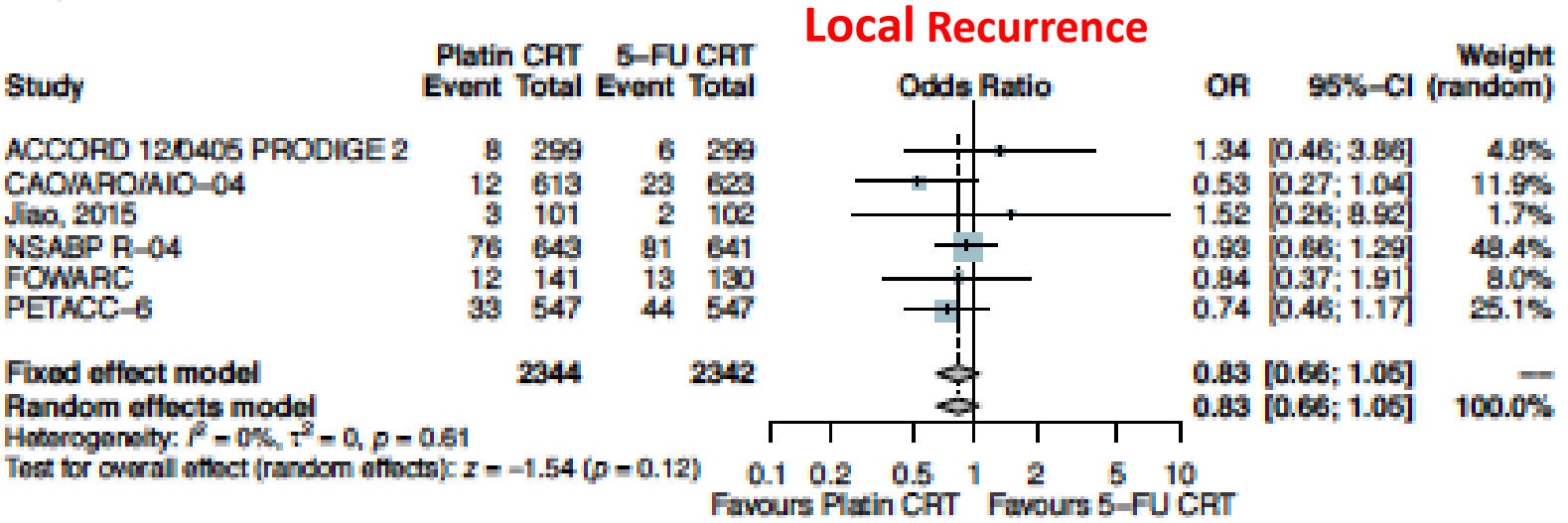
Diefenhard et al., 2020 submitted

Disease-free Survival

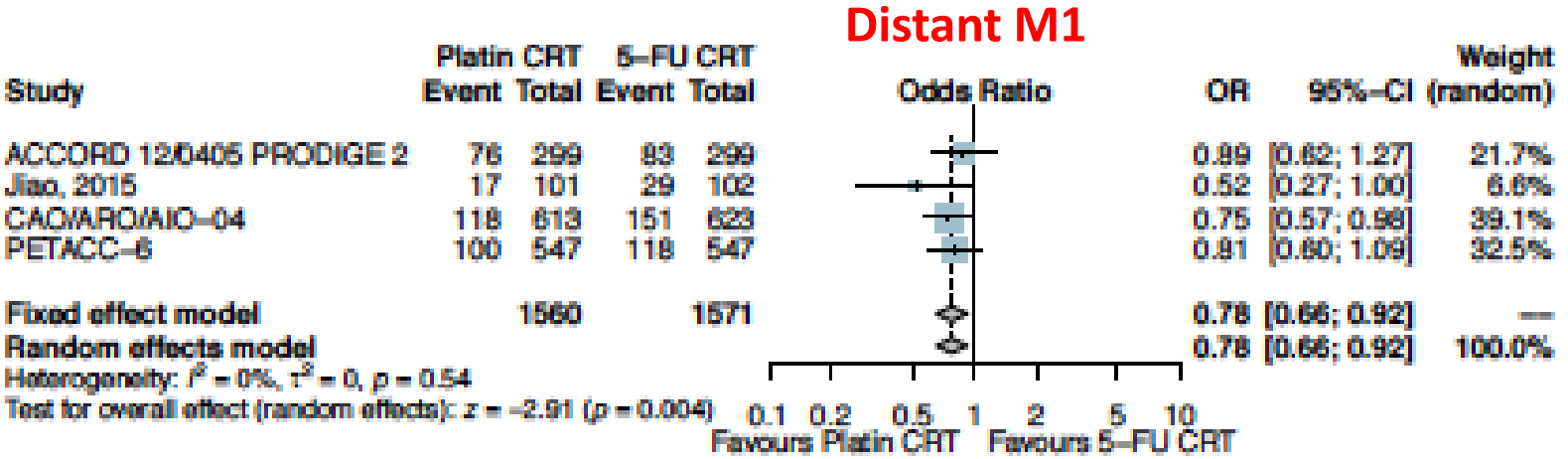
Rectal Cancer Stage II/III Neoadjuvant oxaliplatin-CRT	n	Absolute Difference	HR	P-value
ACCORD 12	584	**4.3% (5y)**	0.86	0.25
NSAPB R-04	1284	**5% (5y)**	0.91	0.34
STAR-01	739	**3.6% (3y)**	0.89	0.37
CAO/ARO/AIO-04	1236	**4.7% (3y)**	0.79	0.03
Chinese	206	**10.6% (3y)**	n.g.	0.08
PETACC-6	1094	*Full paper pending*		
FORWARC	475	*Follow-up continues*		

Colon Cancer Stage II/III	n	Absolute Difference	HR	P-value
MOSAIC	2246	**5% (3y)**	0.77	.002
NSABP C-07	2407	**4% (3y)**	0.80	.003

Evidence from Meta-Analysis

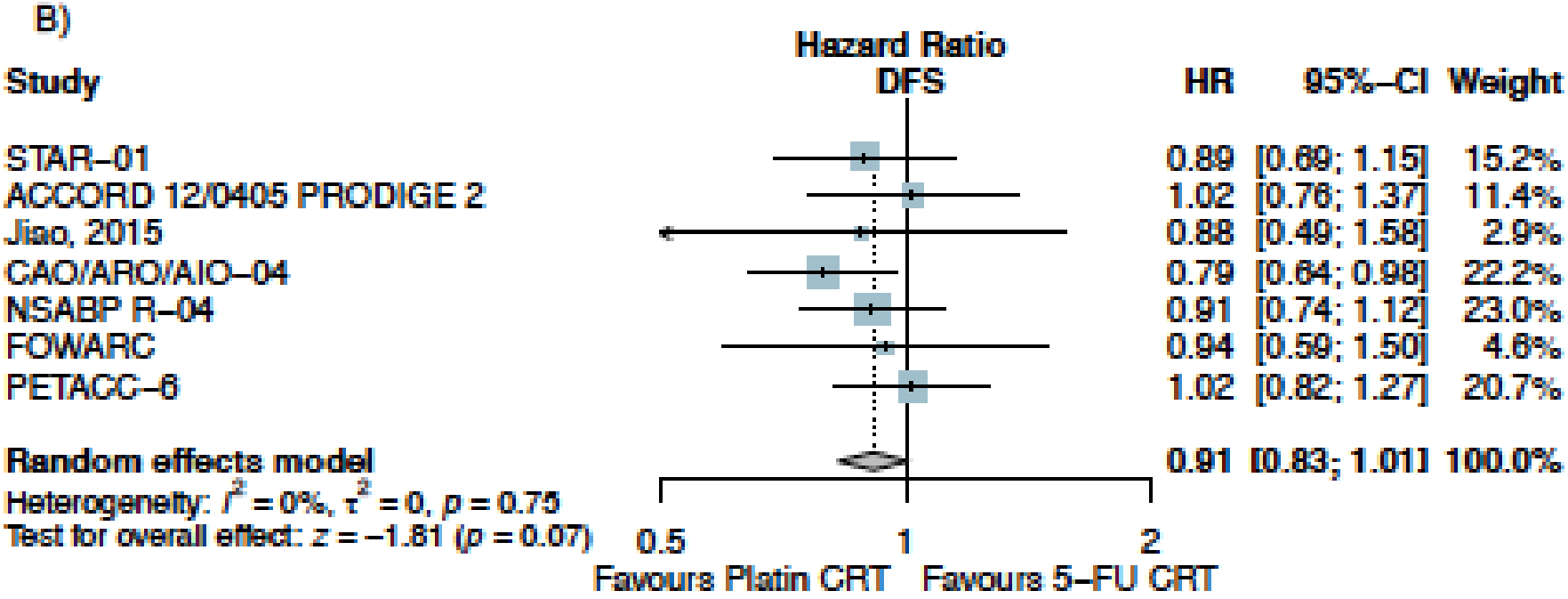


B)

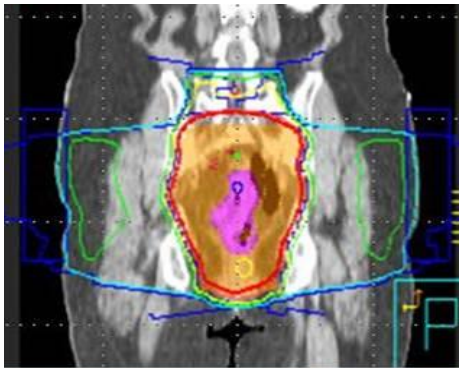


Hüttner, M. et al., 2019 submitted

Evidence from Meta-Analysis: DFS



Hüttner, M. et al., 2019 submitted



German Rectal Cancer Study Group

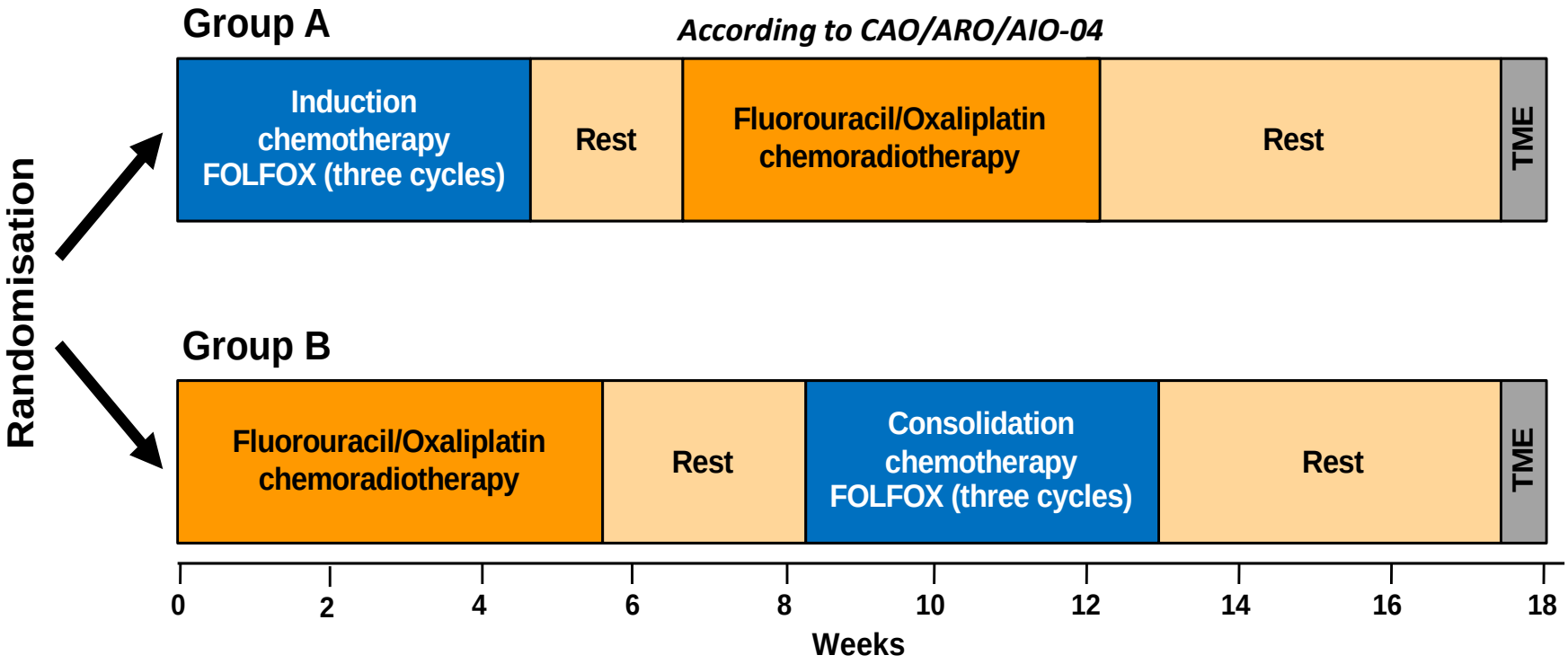
- CAO/ARO/AIO-94 Randomisierte Phase III *(N Engl J Med 2004)*
- CAO/ARO/AIO-03 Phase I/II *(J Clin Oncol 2003 und 2007)*
- CAO/ARO/AIO-04 Phase III: Update

- **CAO/ARO/AIO-12 Randomisierte Phase II *(J Clin Oncol 2019*)**
- CAO/ARO/AIO-0214 Phase II (laufend)
- CAO/ARO/AIO-16 Phase II (laufend)
- ACO/ARO/AIO-18.1 u.2. Randomisierte Phase III (Mitte 2019)

Total neoadjuvant Treatment (TNT) sequence:

CAO/ARO/AIO-12

MRI-defined intermediate/high-risk rectal cancer



Fokas et al., J Clin Oncol 2019

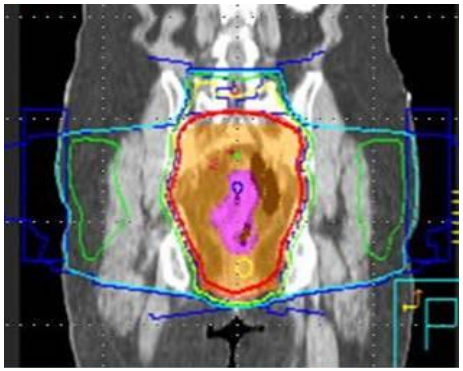
Total neoadjuvant Treatment (TNT) sequence: CAO/ARO/AIO-12

MRI-defined intermediate/high-risk rectal cancer

Main results	CT/CRT/S (n=156)	CRT/CT/S (n=150)
Full dose RT/concurrent 5-FU/OX	91%/76%	97%/93%
Completed 3 cycles of FOLFOX	92%	85%
pCR*	17% (P=0.210)	25% (P=0.0002)
Clavien-Dindo classification		
None	54%	66%
Grade 1-2	25%	18%
Grade 3-5	17%	16%

**Statistical calculation: each group versus 15% expected after standard CRT*

Fokas et al., J Clin Oncol 2019



German Rectal Cancer Study Group

- CAO/ARO/AIO-94 Randomisierte Phase III *(N Engl J Med 2004)*
- CAO/ARO/AIO-03 Phase I/II *(J Clin Oncol 2003 und 2007)*
- CAO/ARO/AIO-04 Phase III: Update

- CAO/ARO/AIO-12 Randomisierte Phase II *(J Clin Oncol 2019)*
- CAO/ARO/AIO-0214 Phase II (laufend)
- **CAO/ARO/AIO-16 Phase II (laufend)**
- ACO/ARO/AIO-18.1 u.2. Randomisierte Phase III (Mitte 2019)

CAO/ARO/AIO-16

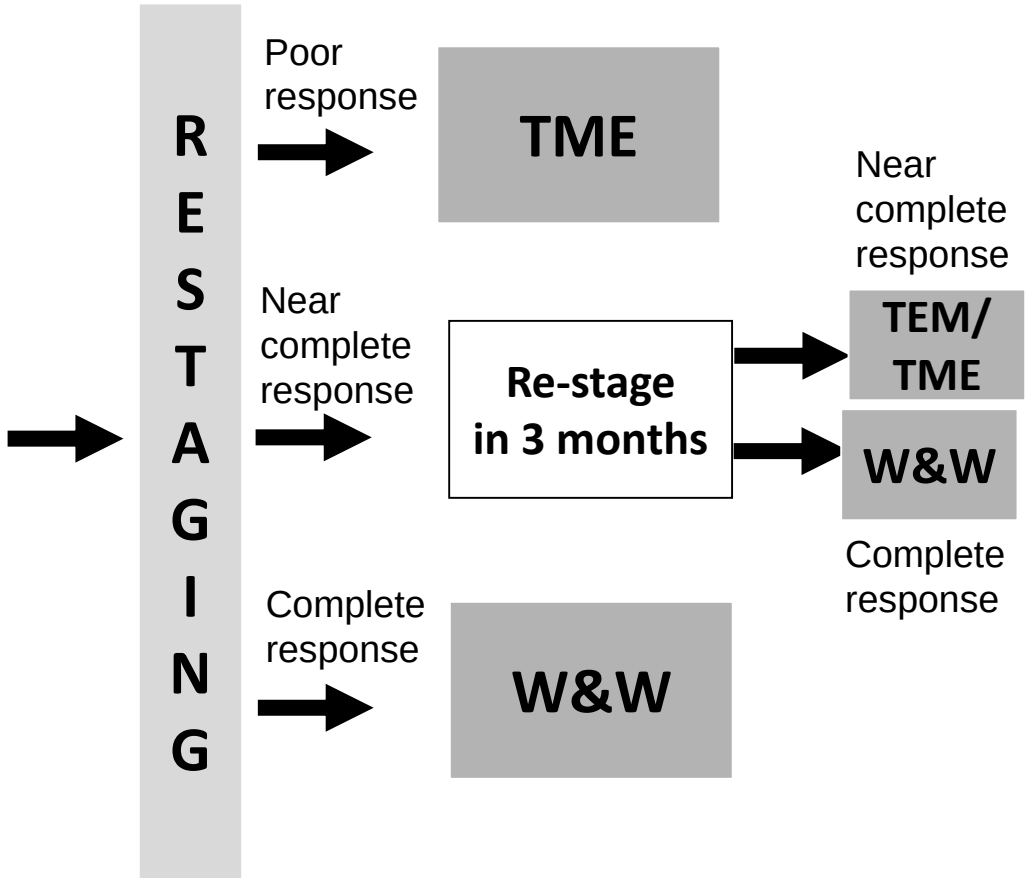
(Phase II, Tübingen, Erlangen, Würzburg, FFM)

Organ preservation

TNT According to ***CAO/ARO/AIO-12***

RT 50.4 Gy + 5-FU/Oxaliplatin

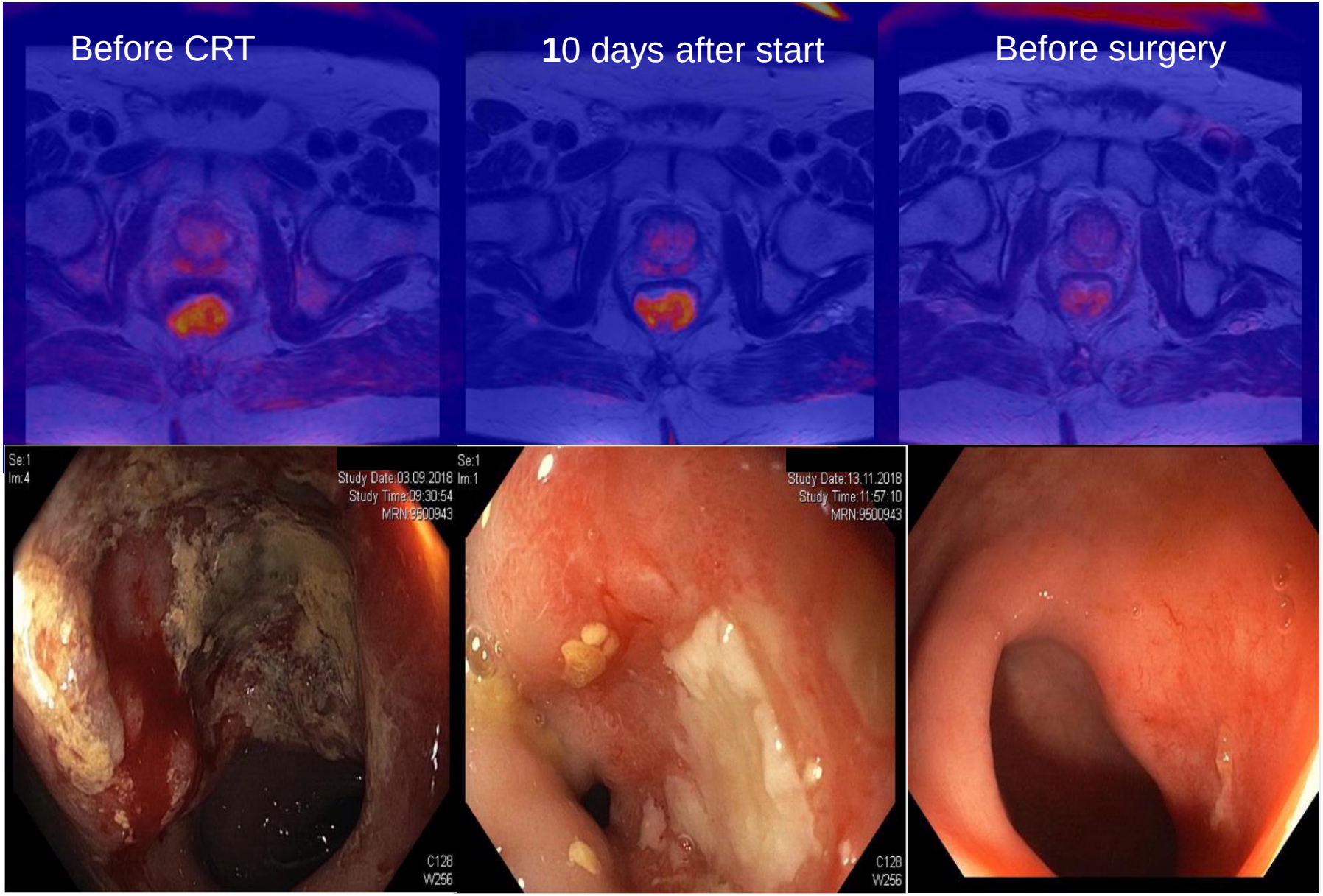
mFOLFOX6 3#, q15



Primary endpoint: cCR (n=89),
3y loco-regional control

d 106

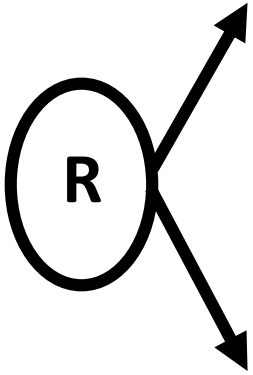
Monitoring tumor response



ACO/ARO/AIO-18.1

MRI criteria: Intermediate/High-risk

- Any cT3 if low rectal (0-6 cm)
- cT3c/d mid rectal (> 6-12 cm)
- any T3 with clear cN+
- cT4
- mrCRM+ (<1 mm)
- EMVI+



Control arm

According to current S3 guidelines:

CAP/5-FU-RT – Surgery (or selected W&W) – optional adjuvant Chemo

TNT: 5-FU/OX-RT – FOLFOX (3 cycles) – Surgery (or selected W&W)

Investigational arm

Preferred arm of CAO/ARO/AIO-12
Currently tested in CAO/ARO/AIO-16 for W&W approach

ACO/ARO/AIO-18.1.

Inclusion Criteria

Intermediate/High-risk based on MRI criteria:

- Any cT3 if low rectal (0-6 cm)
- cT3c/d mid rectal (<6-12 cm)
- any T3 with clear cN+
- cT4
- mrCRM+ (<2mm)
- EMVI+

- ERUS if MRI is not definitive to exclude T1/T2 in low, T3a/b in mid RC
- CT abdomen/chest to exclude M1
- Age > 18, no upper age limit
- ECOG 0-1
- Adequate hem, hep, renal function

ACO/ARO/AIO-18.1.

Control Arm

- **IMRT** 28 x 1.8 Gy with differential PTV concepts based on risk factors (sphincter; upper border)

- **Concurrent chemotherapy:**
  - 225 mg/sqm 5-FU civ d1-38 of RT
  - 825 mg/sqm bid Capecitabine d1-38 of RT

- **Interval** completion of CRT to Surgery: 6-8 weeks

- **Adjuvant** chemotherapy after R0 resection: optional (according to S3 guidelines)

ACO/ARO/AIO-18.1.

Control Arm

- **Adjuvant** chemotherapy: Recommendations

ypTNM stage	< 70 years	≥70 years
0/I/II (low risk)	No adjuvant treatment (or Capecitabine, 5 cycles)	No adjuvant treatment (or Capecitabine, (5 cycles)
II high risk (V1, L1, G3, T4, ...)	Capecitabine, 5 cycles	Capecitabine, 5 cycles
III	XELOX (5 cycles) FOLFOX4 (8 cycles) mFOLFOX6 (8 cycles)	Capecitabine, 5 cycles

ACO/ARO/AIO-18.1.

Experimental Arm

- **IMRT** 28 x 1.8 Gy with differential PTV concepts based on risk factors (sphincter; upper border)

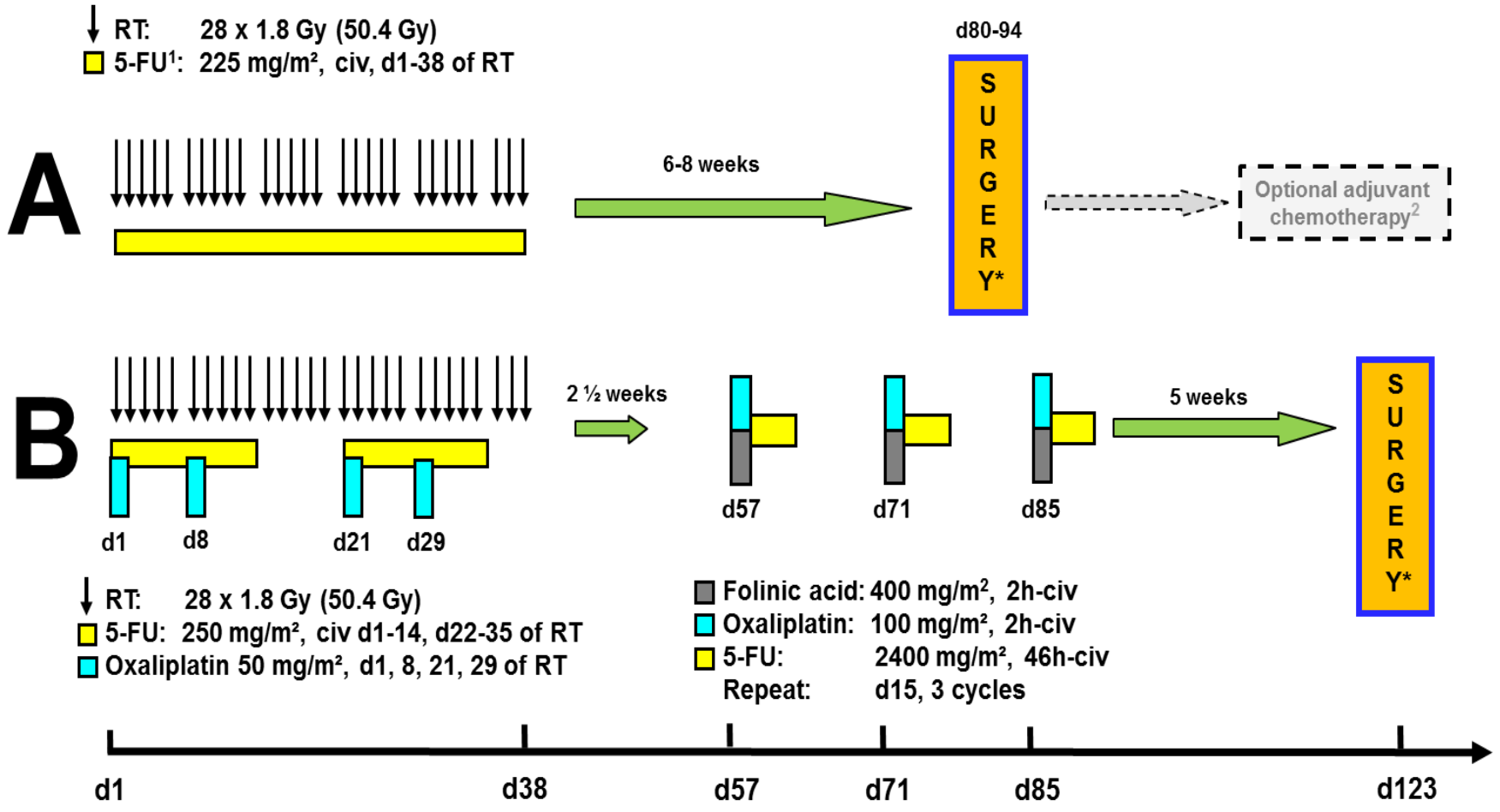
- **Concurrent chemotherapy:**
  - 250 mg/sqm 5-FU civ d1-14, d22-35 of RT
  - 50 mg/sqm Oxaliplatin d1, 8, 21, 29 of RT
- **Consolidation chemotherapy**
  - Folinic acid 400 mg/sqm, 2h-civ
  - Oxaliplatin 100 mg/sqm, 2h-civ
  - 5-FU 2400 mg/sqm, 46-civ, q d15, 3 cycles

ACO/ARO/AIO-18.1.

Experimental Arm

- **Interval completion of CT to surgery/W&W: 5 weeks (d123)**
- **No adjuvant chemotherapy**

ACO/ARO/AIO-18.1 Randomized Phase III Trial



[1]Instead of 5-FU, capecitabine can be given with RT as follows:
Capecitabine: 825 mg/m² bid, po, d1-38 of RT

[2]Optional adjuvant chemotherapy as described in trial protocol

*Optional Watch&Wait management in case of clinical complete response

Primary Endpoint: DFS

(more details: ***Fokas E. et al., Lancet Oncol 2020 in press***)

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

Primary Endpoint: DFS (continued)

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

ACO/ARO/AIO-18.1.

Sample Size

We hypothesized that the **3-year DFS** survival probabilities would improve from **70% in the control arm** to **78% in the investigational arm** (hazard ratio of 0.7). 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 **822 patients (322 events) in total.**

ACO/ARO/AIO-18.1.

Secondary Endpoints

- **Acute and late toxicity** assessment according to NCI CTCAE V.4.0
- Surgical morbidity and complications
- Rate of sphincter-sparing surgery
- Pathological TNM-staging
- R0 resection rate; negative circumferential resection rate
- Tumor regression grading according to Dworak, NAR score
- Quality of TME according to MERCURY
- **Rate of W&W with or without local regrowth**
- Cumulative incidence of local and distant recurrences
- Overall survival
- **Quality of life, functional outcome (PROMS)**
- Translational / biomarker studies (**FCI Frankfurt**)