Gastrointestinale Tumoren

Post ASCO 2023

Ralf Hofheinz, Mannheim Cancer Center, Universitätsmedizin Mannheim

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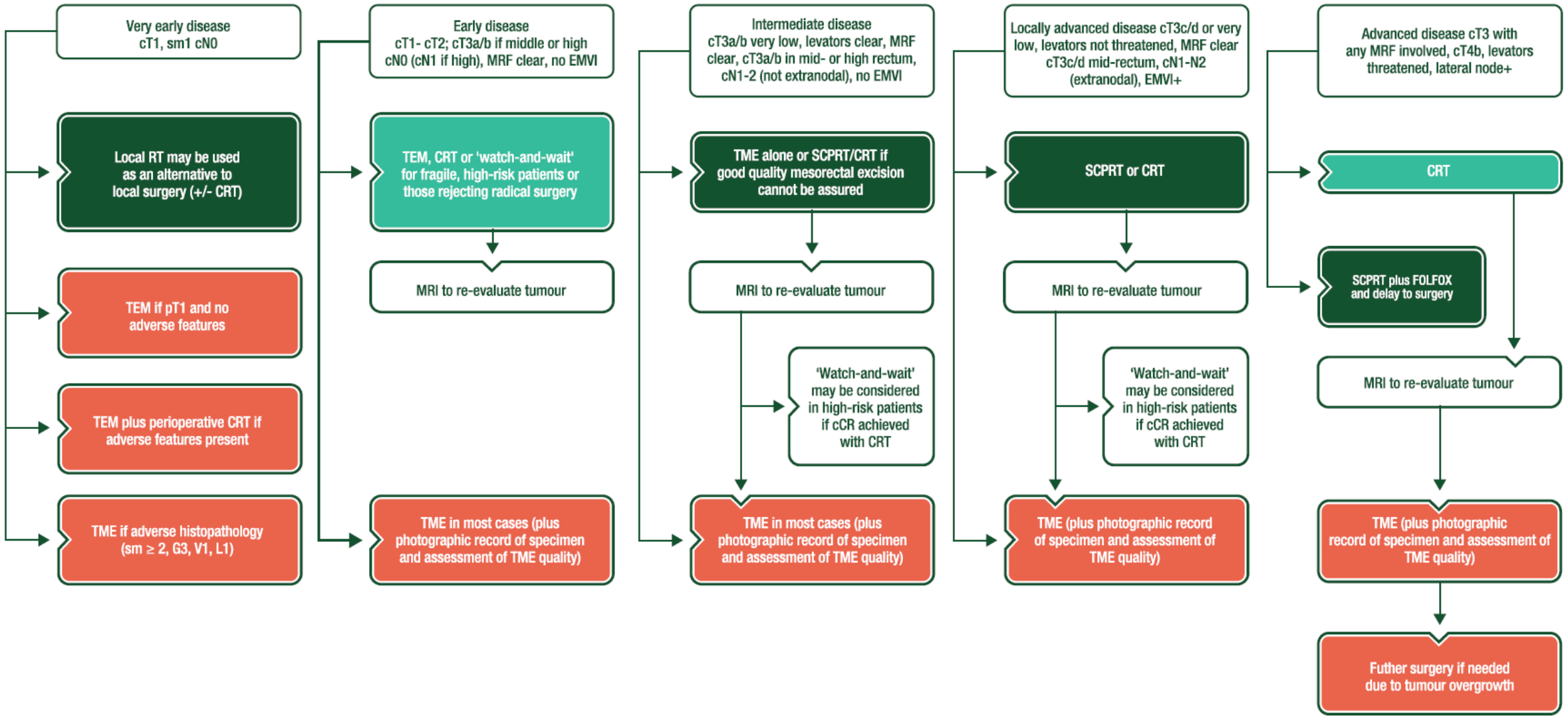
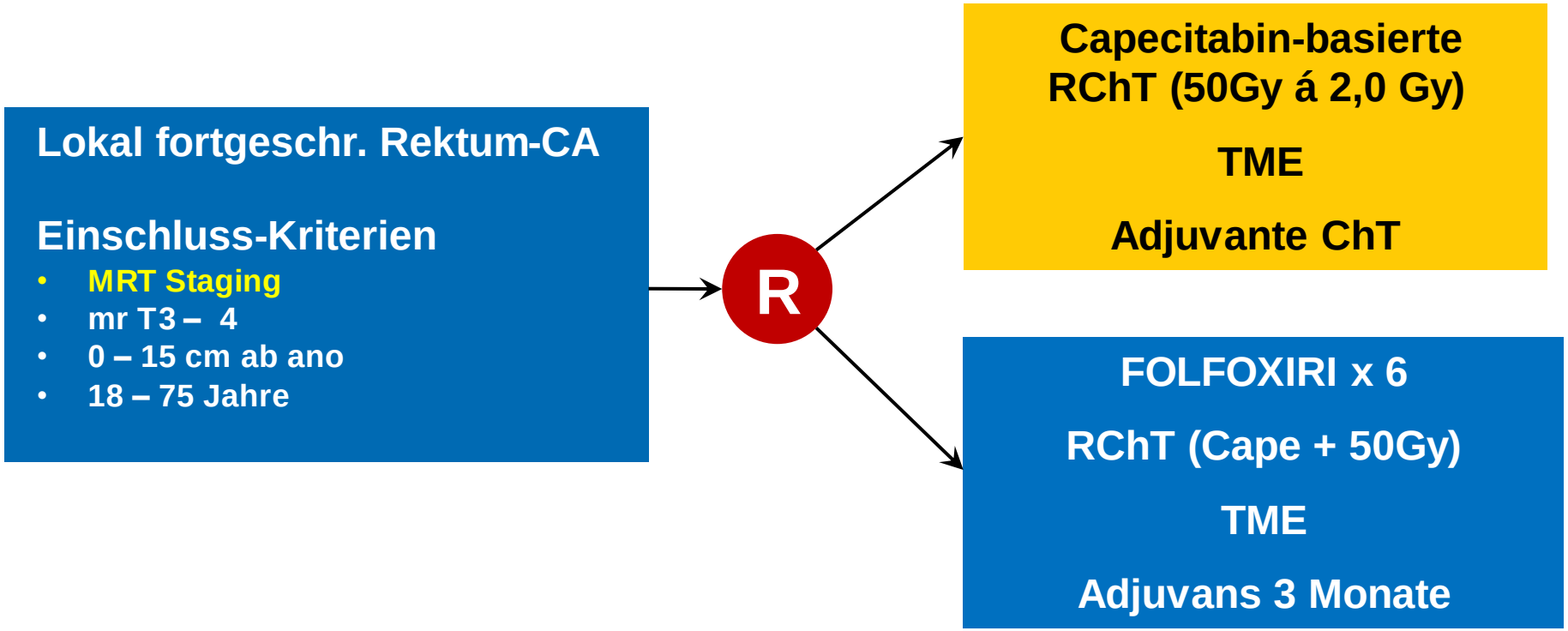
ESMO clinical practice guidelines - Rektumkarzinom

Glynne-Jones R Ann Oncol 2017 (suppl. IV)



TNT versus Standard-RChT

***PRODIGE-23*: Conroy et al. Lancet Oncol 2021; 22: 702–15**



Primärer Endpunkt: 3-Jahres Disease-free survival

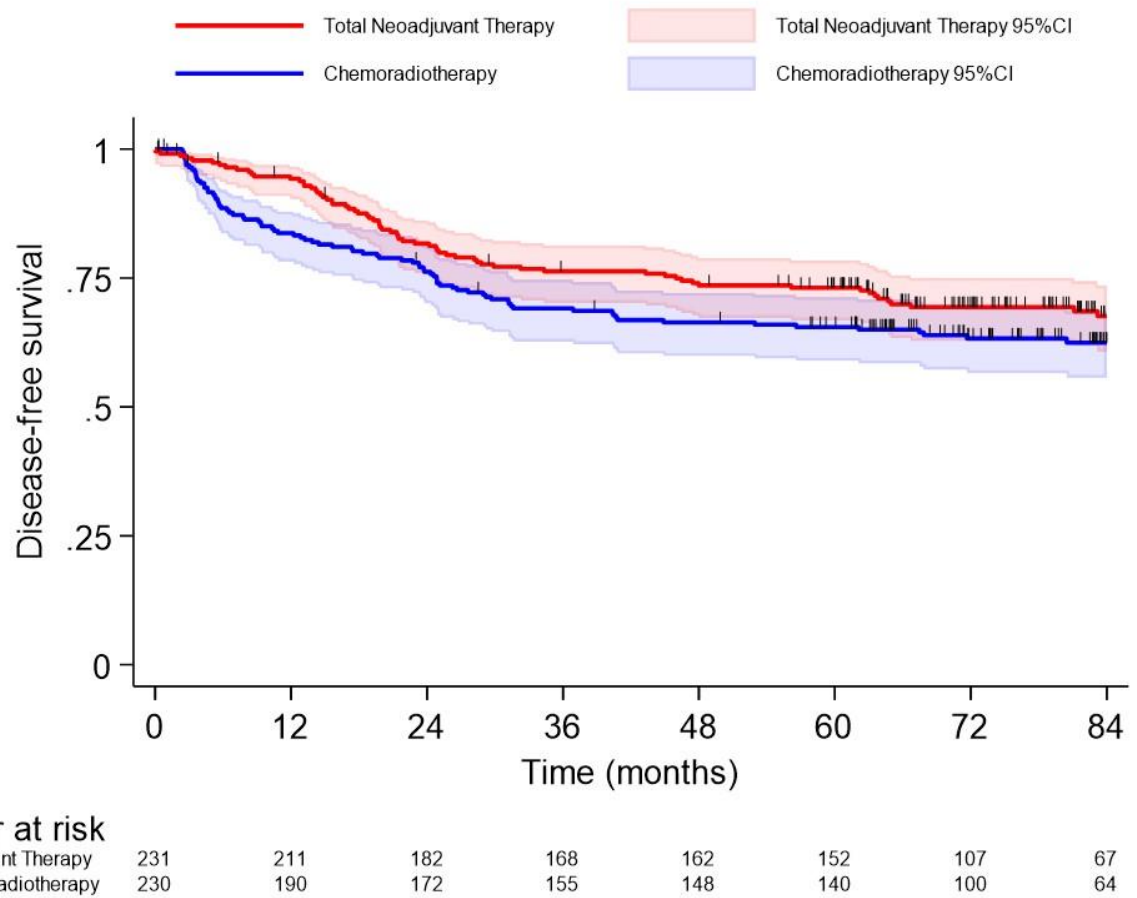
(n = 461 Patienten)

Cumulative incidence of rectal cancer recurrences

Results	TNT	SoC
Local		
At 5 years	4.7% [95%CI: 2.5-8.5]	6.4% [95%CI: 3.8-10.8]
At 7 years	5.3% [95%CI: 2.9-9.3]	8.1% [95%CI: 4.9-13.3]
Metastatic*		
At 5 years	18.4% [95%CI: 13.8-24.2]	26.6% [95%CI: 21.2-33.0]
At 7 years	20.7% [95%CI: 15.6-27.0]	27.7% [95%CI: 22.2-34.2]
Alive with metastases	19/44 (43%)	21/60 (35%)

*38% of the patients with metastatic disease were still alive at the time of the cut-off analysis

Disease-Free Survival



155 events

7-yr DFS rate:

- 67.6% [95%CI: 60.7-73.6] TNT arm
- 62.5% [95%CI: 55.6-68.6] SoC arm

5-yr DFS rate:

- 73.1% [95%CI: 66.8-78.4] TNT arm
- 65.5% [95%CI: 58.9-71.3] SoC arm

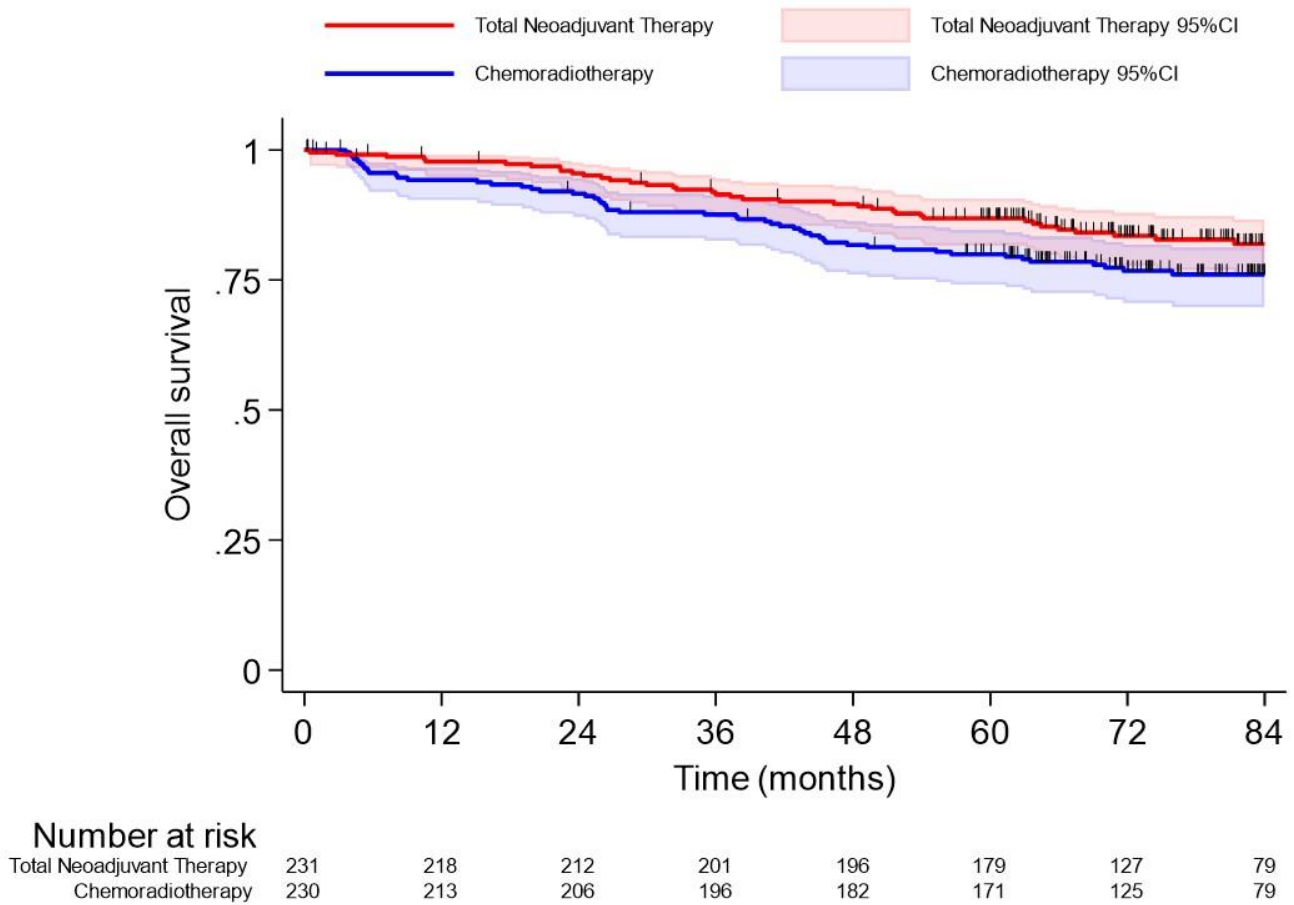
RMST (7-yr), months:

5.73 [0.05-11.41] DFS benefit for TNT arm

p=0.048

PRESENTED BY: T Conroy, MD

Overall Survival



98 events.

7-yr OS:

- 81.9% [95%CI: 75.8-86.7] TNT arm
- 76.1% [95%CI: 69.8-81.3] SoC arm

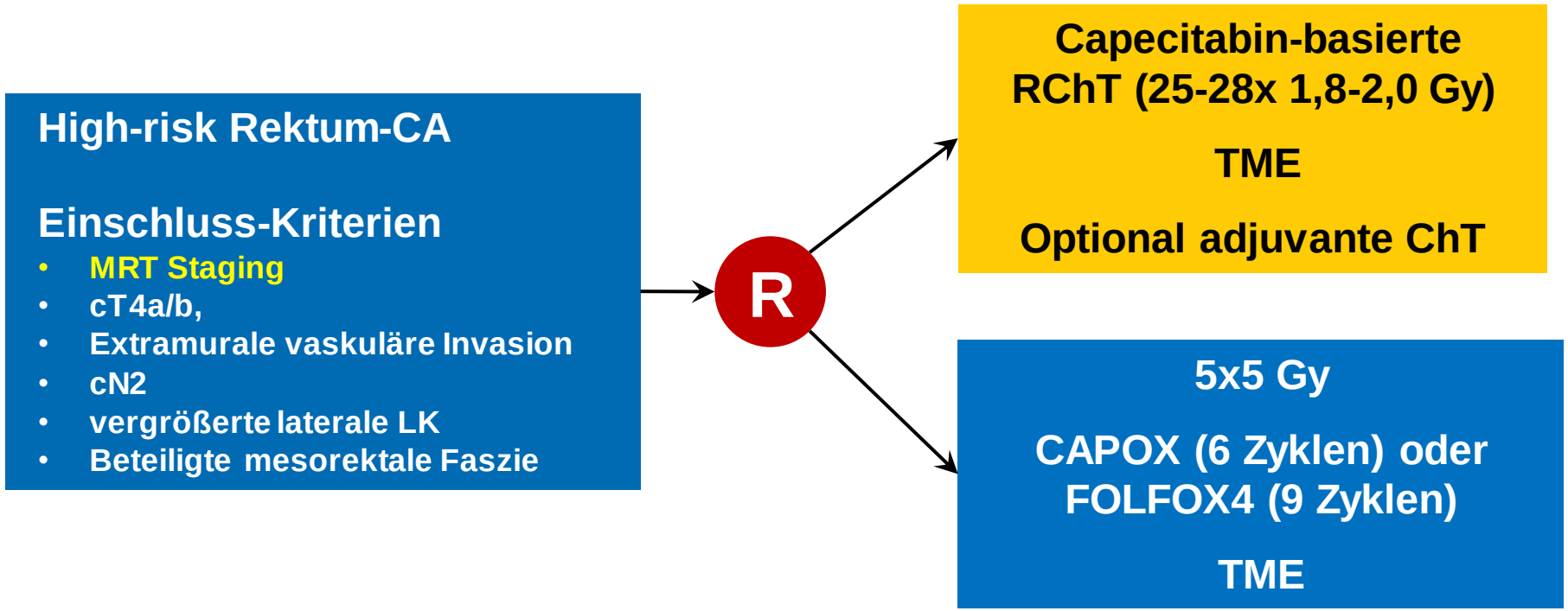
5-yr OS:

- 86.9% [95%CI: 81.6-90.7] TNT arm
- 80.0% [95%CI: 74.1-84.6] SoC arm

RMST (7-yr), months:
4.37 [0.35-8.38] benefit for TNT arm
p=0.033

TNT versus Standard-RChT

***RAPIDO*: Bahadoer et al. Lancet Oncol 2021 Jan;22(1):29-42**

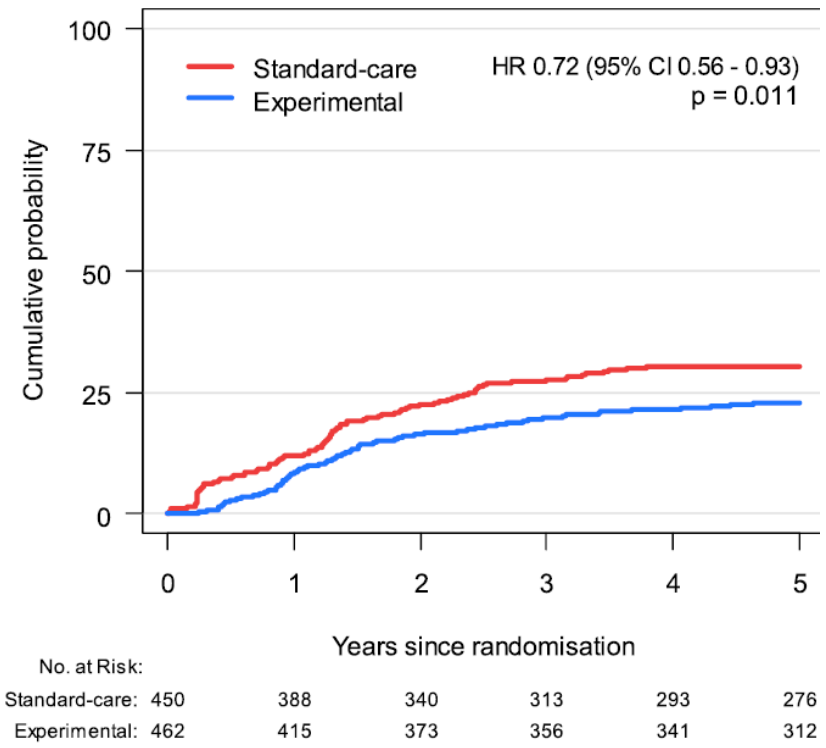


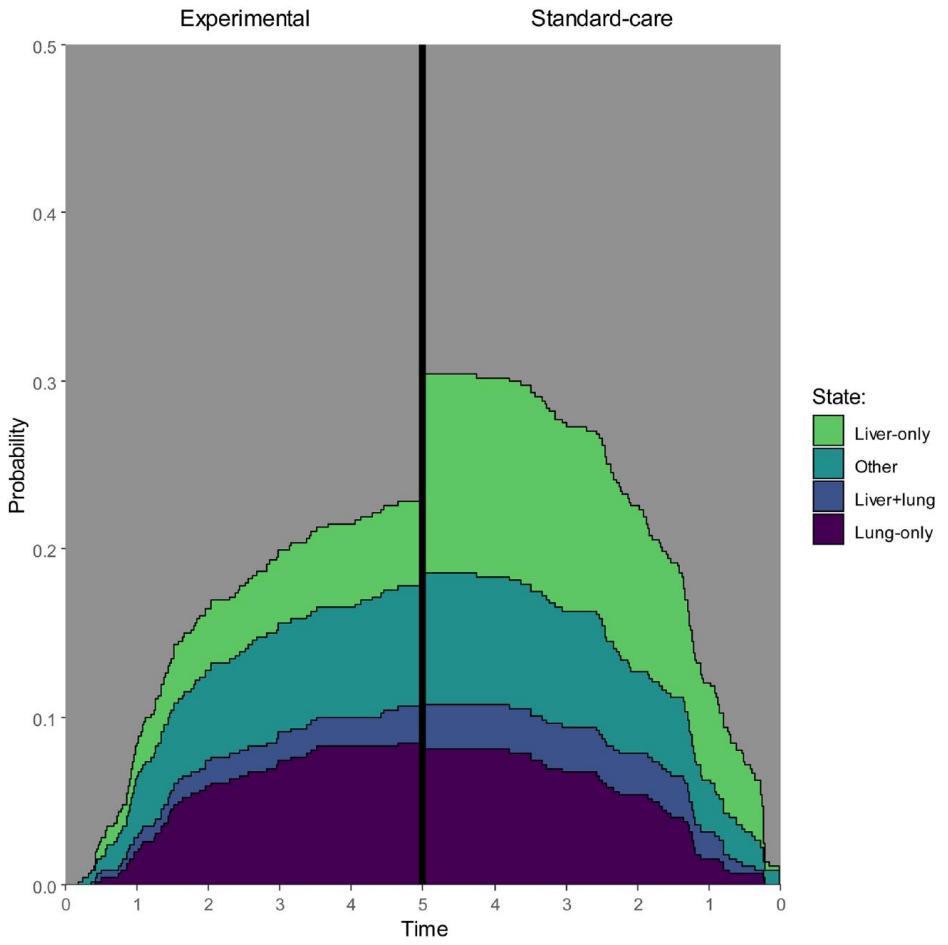
Primärer Endpunkt: Krankheitsbedingtes Therapieversagen

(n = 920 Patienten)

RAPIDO: Fernmetastasen nach > 5 Jahren FU

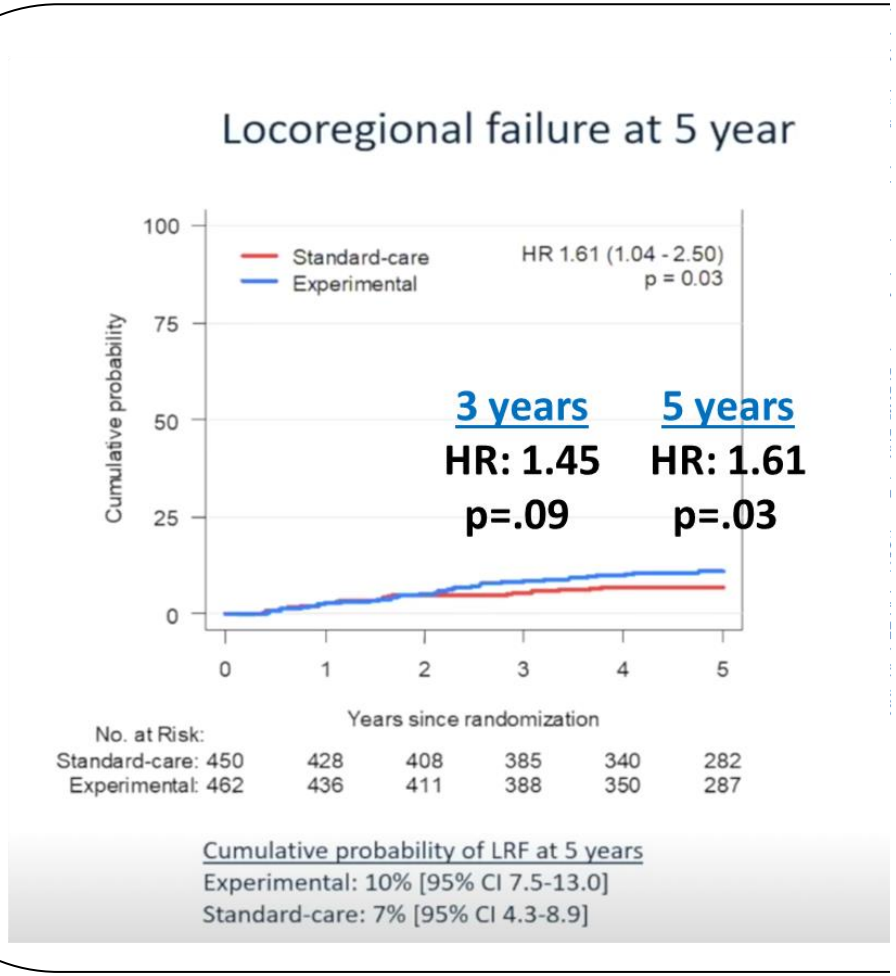
Bahadoer et al., Eur J Cancer 2023





RAPIDO: Endpunkte nach 5.4 Jahren

Bahadoer RR et al., ESSO 2022, abstract # 40-0649.



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OPEN

Locoregional failure during and after short-course radiotherapy followed by chemotherapy and surgery compared to long-course chemoradiotherapy and surgery – A five-year follow-up of the RAPIDO trial.

Esmée A. Dijkstra, MD, Assoc prof. Per J. Nilsson[π], Prof. Geke A.P. Hospers[π], Renu R. Bahadoer, MD, Elma Meershoek-Klein Kranenbarg, MSc, Annet G.H. Roodvoets MSc, Prof. Hein Putter, Assoc prof. Åke Berglund, Prof. Andrés Cervantes, Rogier M.P.H. Crolla, MD, Mathijs P. Hendriks, MD, Jaume Capdevila, MD, Assist prof. Ibrahim Edhemovic, Prof. Corrie A.M. Marijnen[π], Prof. Cornelis J.H. van de Velde[π], Prof. Bengt Glimelius[π*], Boudewijn van Etten, MD, PhD[π*], and collaborative investigators.

[π] PI of the RAPIDO trial

[*]Shared last authorship

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PRODIGE-23 versus RAPIDO

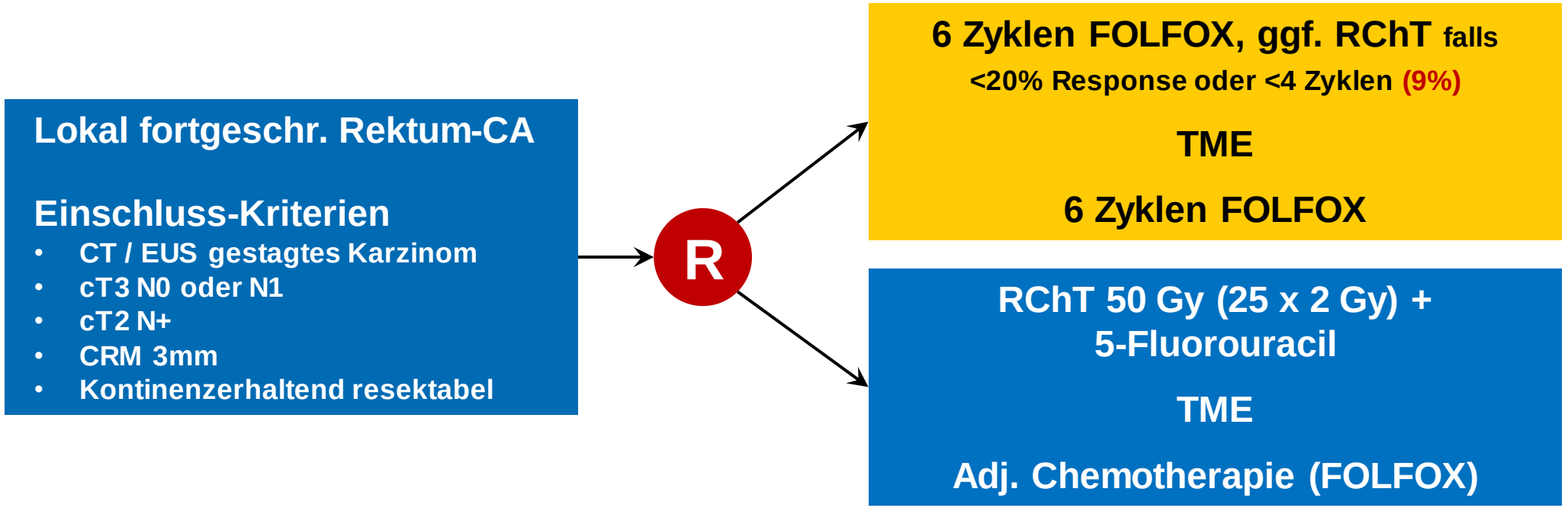
Conroy et al. Lancet Oncol 2021; 22: 702–15
Bahadoer et al. Lancet Oncol 2021 Jan;22(1):29-42

MRI T stage*		
T2	3/225 (1%)	2/225 (1%)
T3	182/225 (81%)	188/225 (84%)
T3a	17/225 (8%)	17/225 (8%)
T3b	77/225 (34%)	92/225 (41%)
T3c	73/225 (32%)	64/225 (28%)
T3d	15/225 (7%)	15/225 (7%)
T4	40/225 (18%)	35/225 (16%)
T4a	3/225 (1%)	4/225 (2%)
T4b	37/225 (16%)	31/225 (14%)
Missing	6	5
cN at inclusion*		
0†	24 (10%)	22 (10%)
1	148 (64%)	155 (67%)
2	59 (26%)	53 (23%)
Enlarged lateral nodes	23 (10%)	24 (10%)
Predicted radial mesorectal margin,* mm		
≤1	48 (21%)	54 (23%)
>1	137 (59%)	141 (61%)

Clinical T stage*†		
cT2	14 (3%)	14 (3%)
cT3	301 (65%)	299 (66%)
cT4	147 (32%)	137 (30%)
Clinical N stage*†		
cN0	42 (9%)	35 (8%)
cN1	118 (26%)	120 (27%)
cN2	302 (65%)	295 (66%)
Other high-risk criteria†		
Enlarged lateral nodes	66 (14%)	69 (15%)
Extramural vascular invasion positive	148 (32%)	125 (28%)
Mesorectal fascia positive	285 (62%)	271 (60%)

Neoadjuvante Chemo statt RChT?

***PROSPECT*: Schrag D et al., ASCO 2023; Plenary Session**

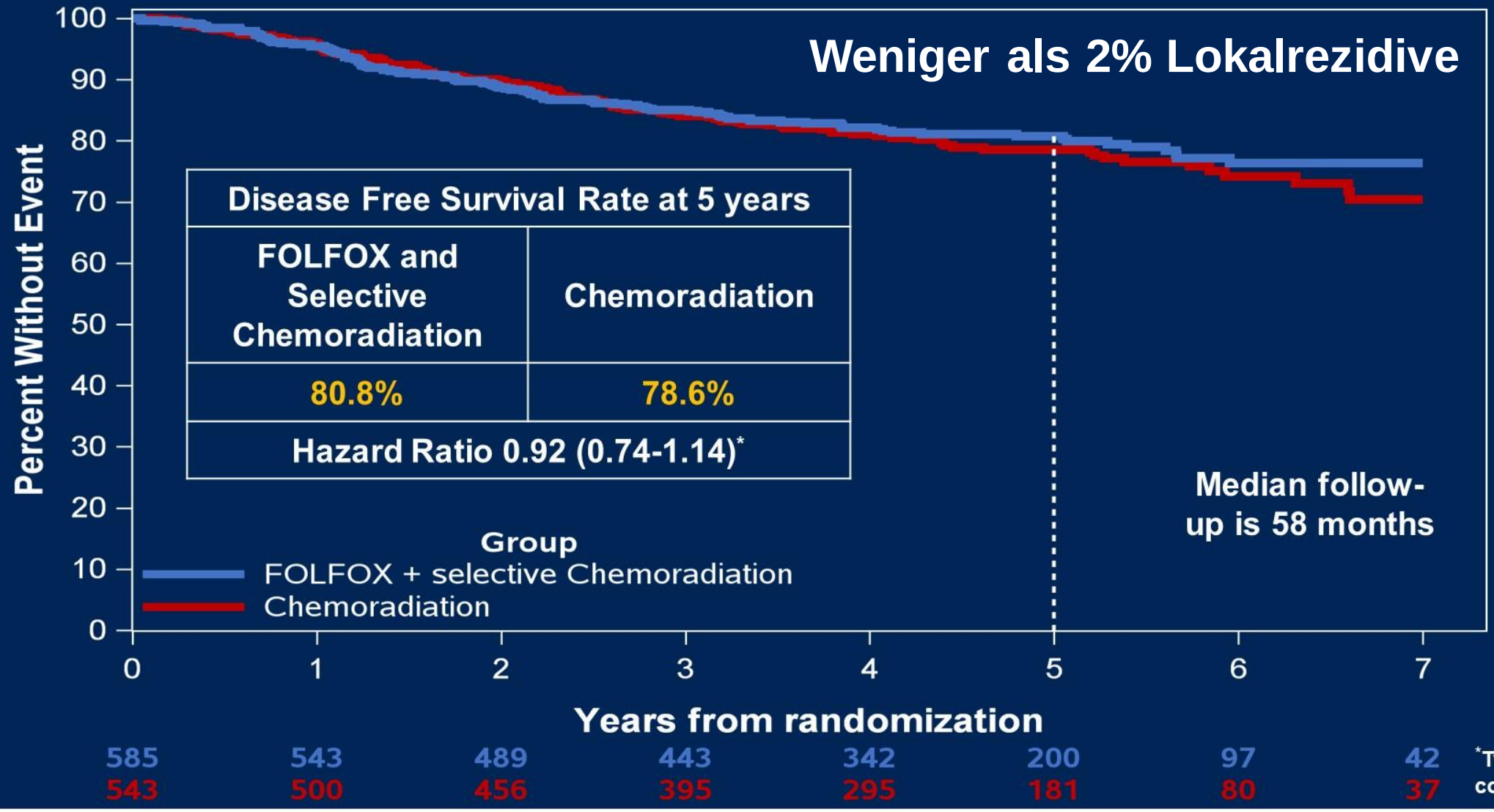


Primärer Endpunkt: Non-inferiority bzgl. Lokalrezidiv → DFS

Characteristics of PROSPECT Participants

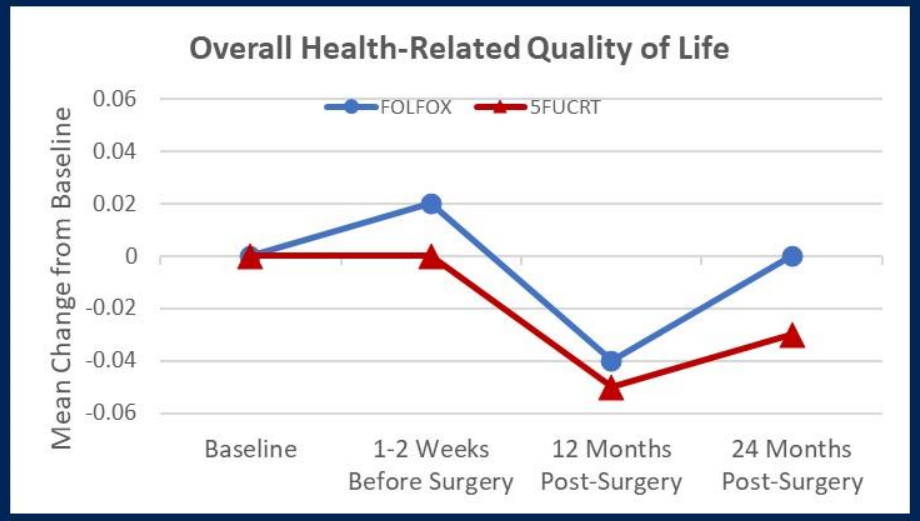
Recruitment: 264 Centers	FOLFOX and Selective Chemoradiation	Chemoradiation
N	585	543
Age Mean (SD)	57 (11)	57(11)
Sex		
Female	37%	32%
Male	63%	68%
Tumor location from the anal verge in cm (SD)	8 (3)	8 (3)
Baseline Staging Performed with MRI	84%	84%
Clinical Stage at Baseline		
cT2N+	11%	7%
cT3N-	39%	37%
cT3N+	50%	56%

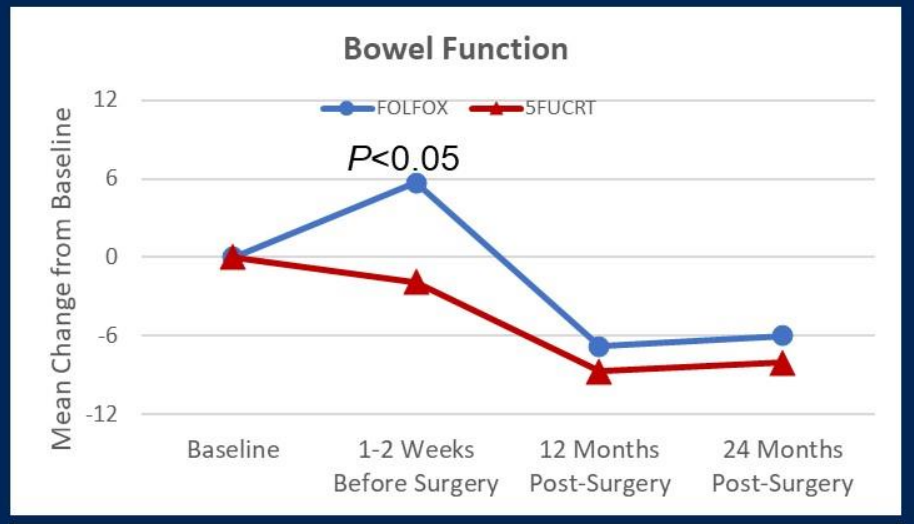
PROSPECT: Disease Free Survival

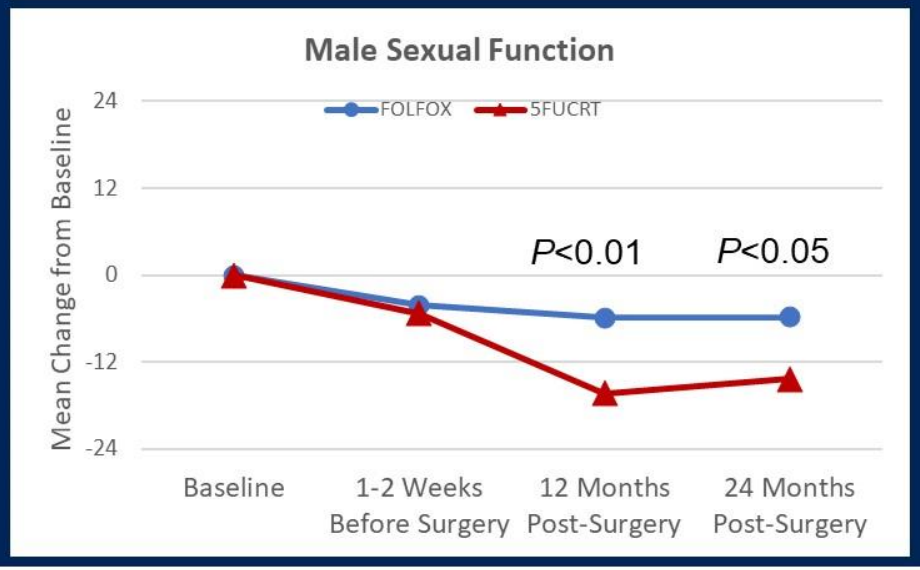


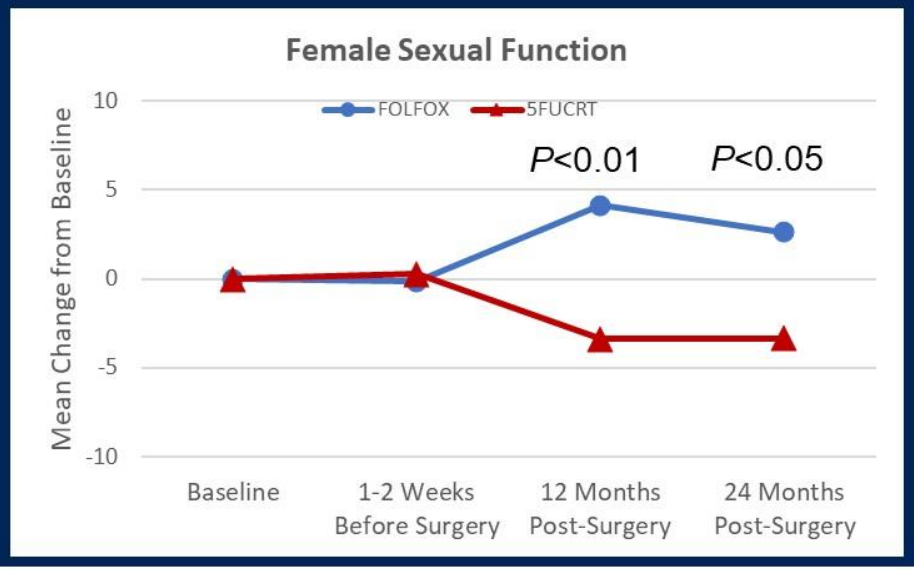
PRESENTED BY: Deb Schrag MD MPH FASCO

PROSPECT: Quality of Life Evaluation









Quality of Life: Trend, but no significant difference between groups

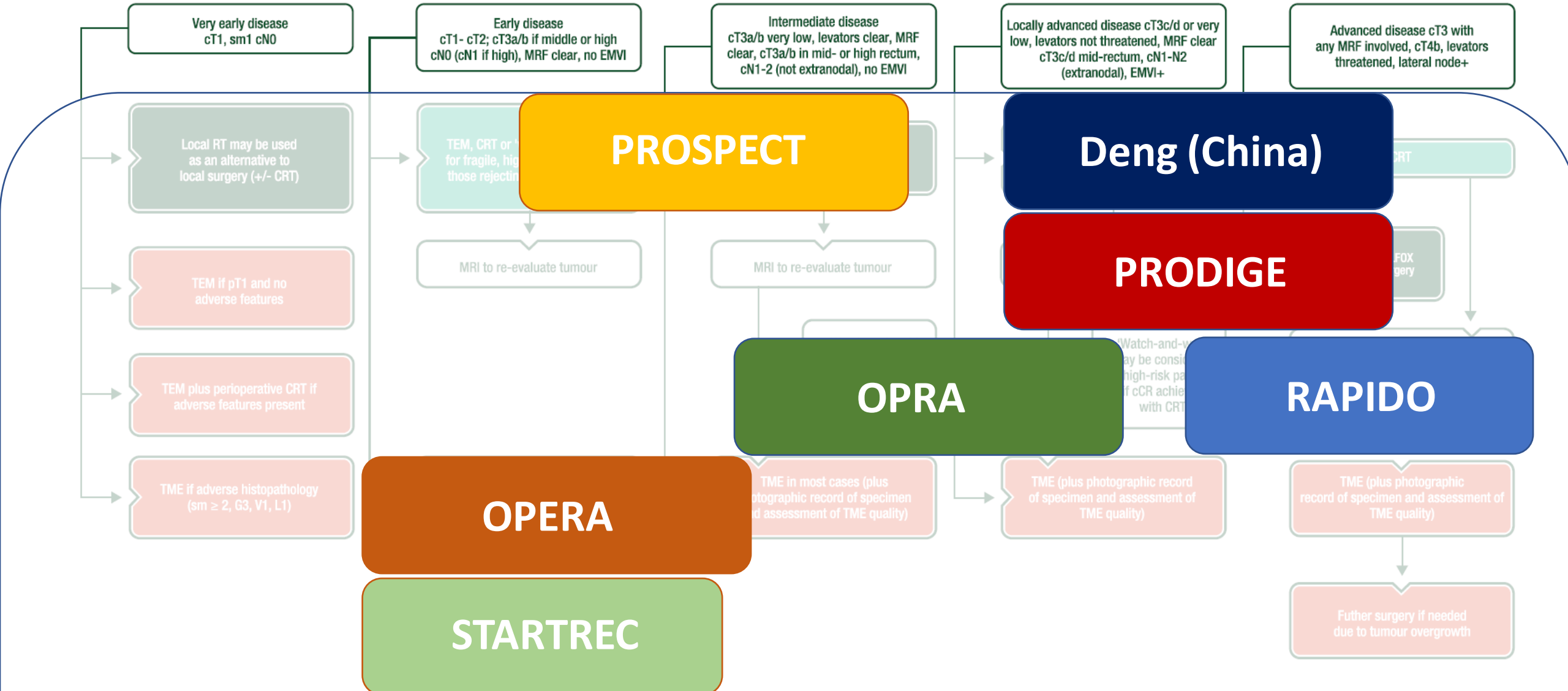
Bowel function and sexual function favor FOLFOX group

N-373

Positive values represent improvement compared to baseline

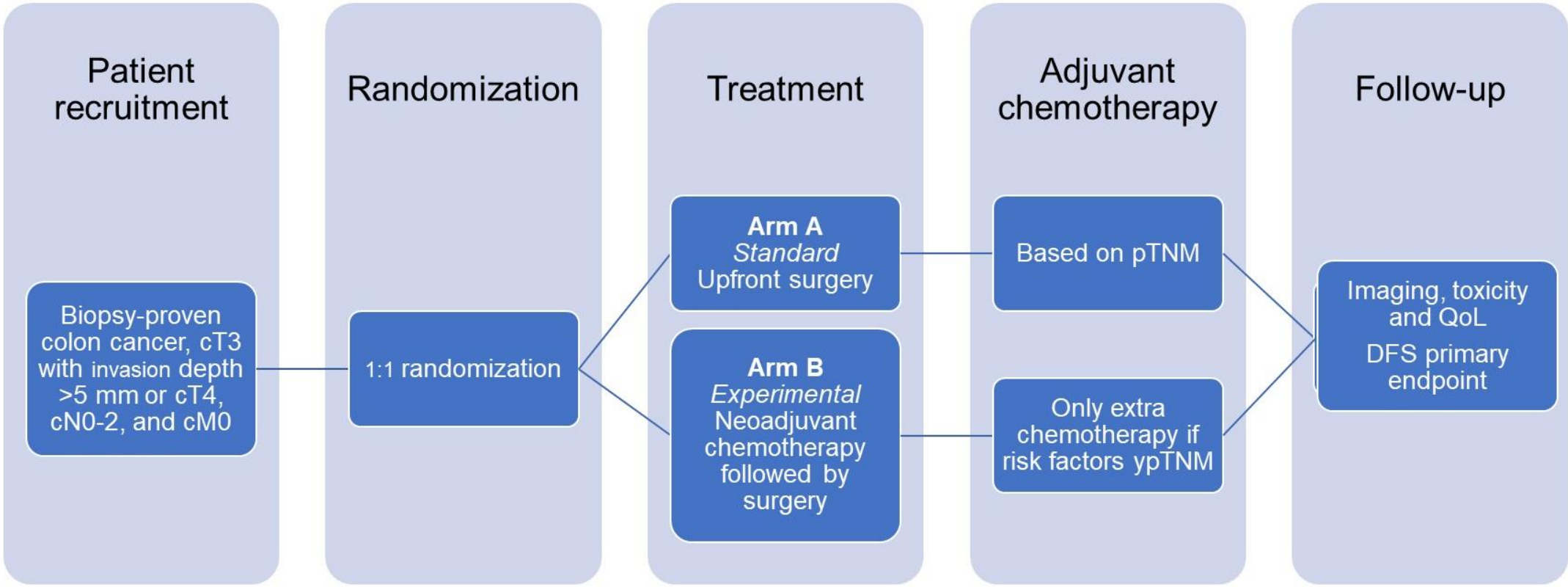
ESMO clinical practice guidelines - Rektumkarzinom

Glynne-Jones R Ann Oncol 2017 (suppl. IV)

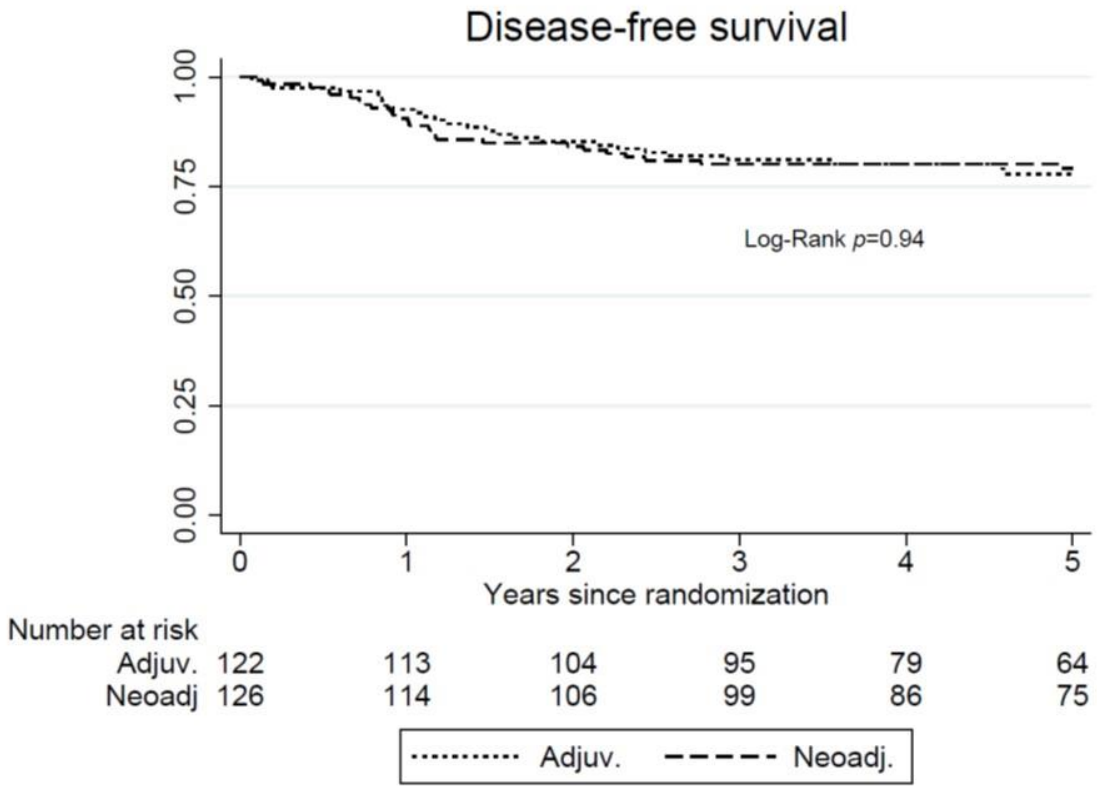


NeoCOL Studie: Design

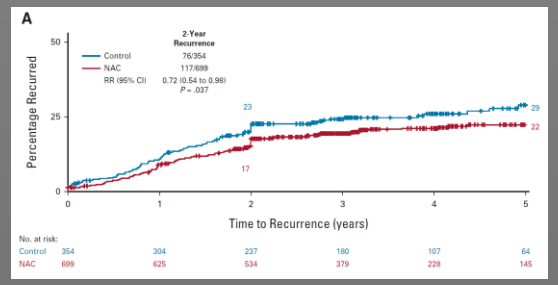
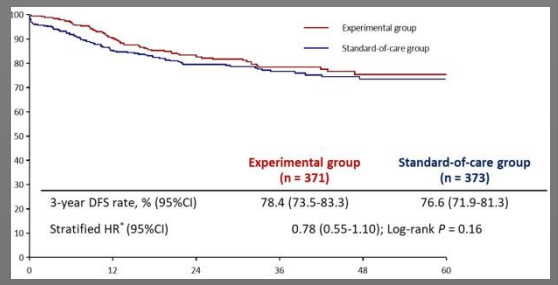
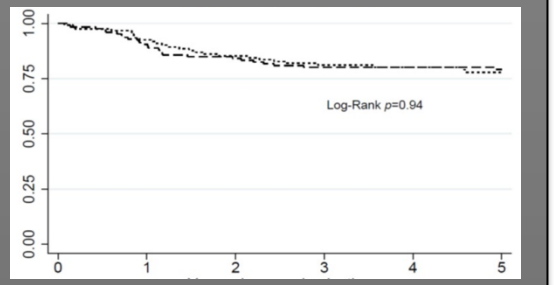
Jensen L H et al., ASCO 2023; oral session



Efficacy outcomes - Disease-free survival (DFS)

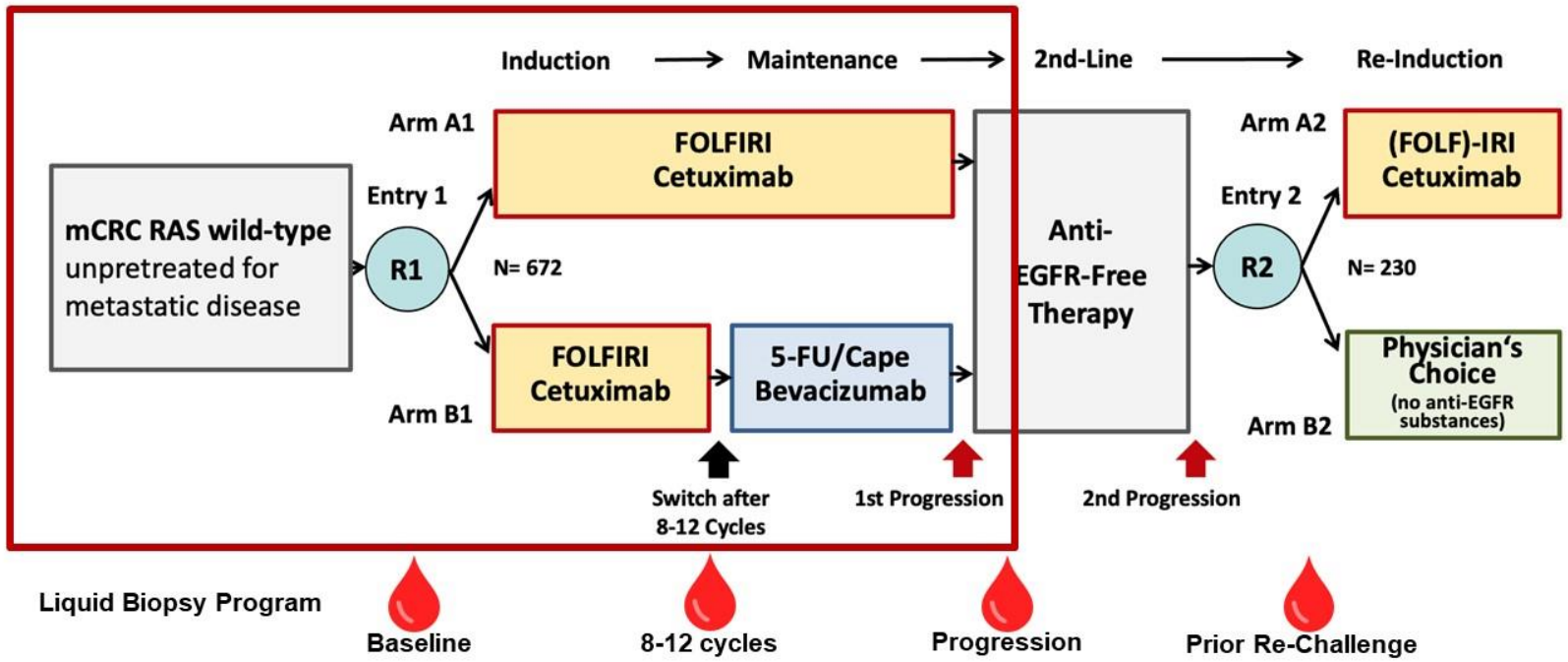


FOXTROT / OPTICAL / NeoCOL: Was wissen wir ?

	FOXTROT	OPTICAL	NeoCOL
N	1053	738	248
< T gestaged		5 %	4 %
Induktion	8 Wochen	12 Wochen	8 – 9 Wochen
Surgical morbidity	Leakage +3% (Surgery)	12/13% *overall* Clavien Dindo	Ileus/Leakage +5-6% (Surgery)
DFS	HR 0,72 (p=0,04)	HR 0,78 (p=0,16)	idem
			
	MSI kein Benefit (DFS)	MSI kein Benefit (TRG)	

FIRE-4: Study Design

AIO KRK-0114



130 Centres in Germany and Austria

Primary Endpoint:

Overall Survival (OS) after randomisation 2

Secondary endpoint:

Progression-free survival (PFS) in 1st-line, ORR, toxicity

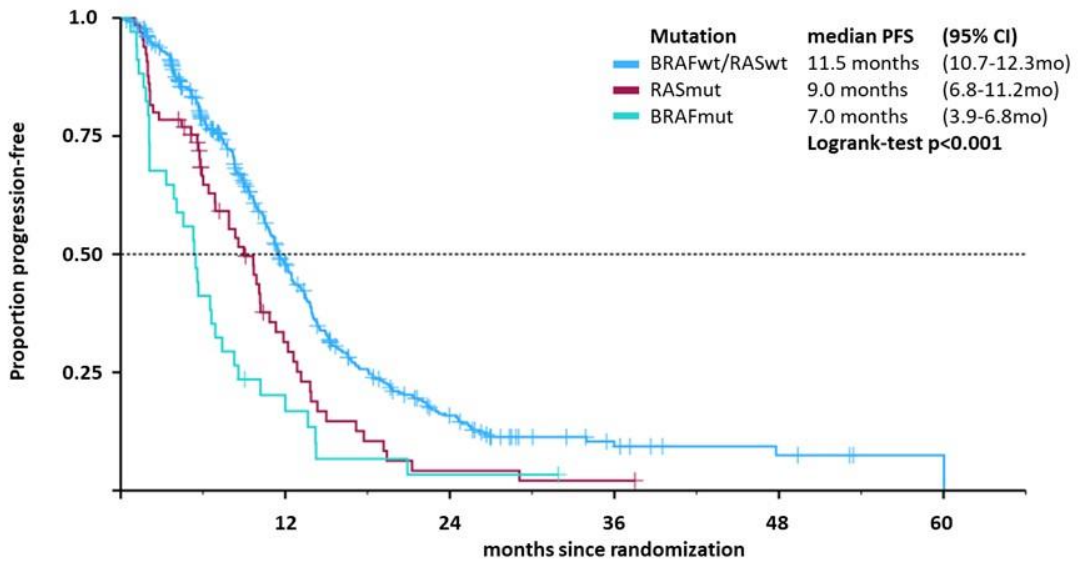
FOLFIRI: Irinotecan 180 mg/m², folinic acid 400 mg/m², 5-FU 500 mg/m² bolus, 5-FU 2,400 mg/m²
Cetuximab: Cetuximab 400mg/m² loading dose followed by 250mg/m² weekly

Stratification factors:
ECOG PS: 0 vs. 1
Leukocytes <8,000/µl vs. ≥8,000/µl
Single organ vs. muliple organ metastasis
Primary tumor sidedness: right vs. left

PRESENTED BY: Prof. Sebastian Stintzing, M.D. – Charité – Universitaetsmedizin Berlin

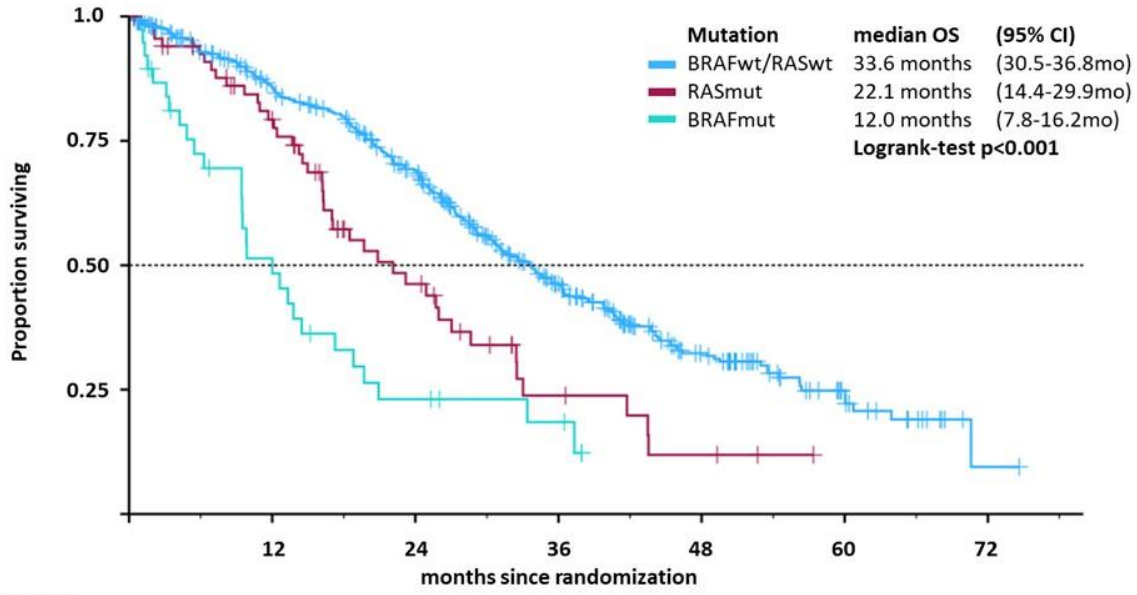
FIRE-4: Effect of baseline liquid biopsy result on survival

Progression-free survival (PFS)



Patients at risk						
BRAFwt/RASwt:	432	152	37	9	4	1
RASmut:	70	15	2	1		
BRAFmut:	38	6	1			

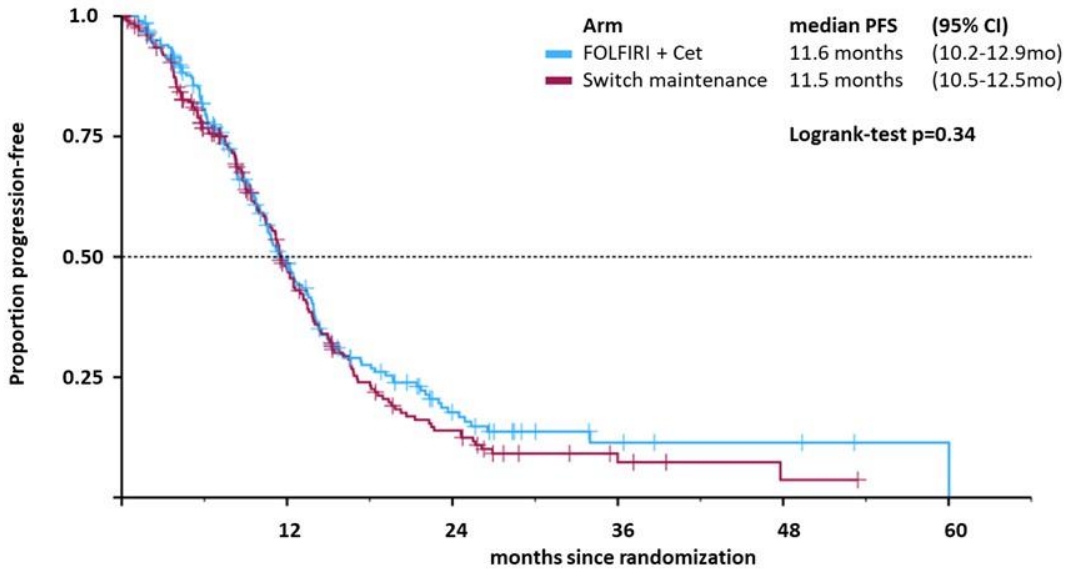
Overall survival (OS)



Patients at risk							
BRAFwt/RASwt:	432	333	246	131	59	19	1
RASmut:	70	47	21	7	3		
BRAFmut:	38	17	7	4			

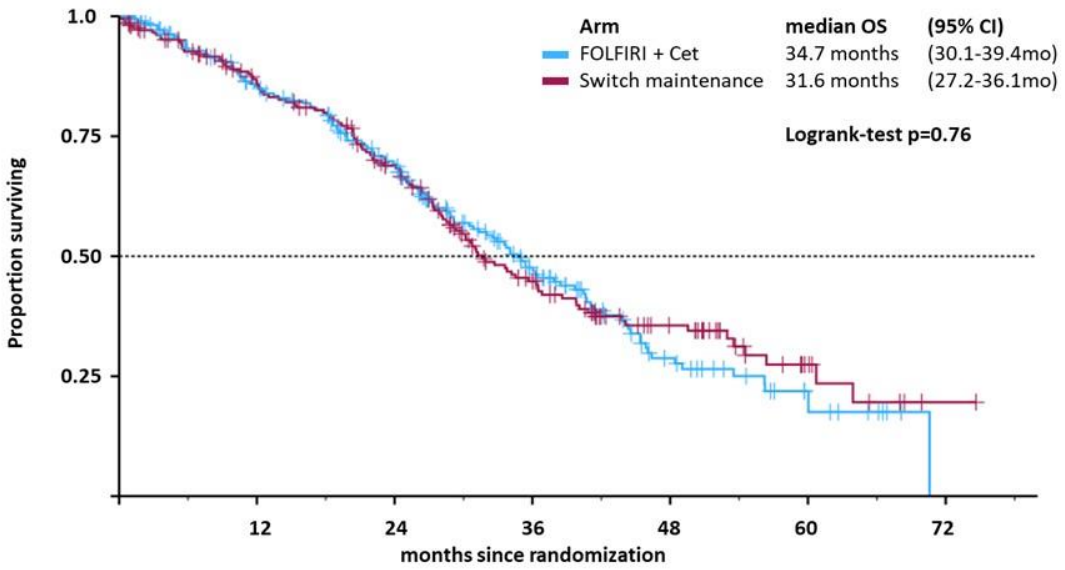
FIRE-4: Effect of treatment arm on survival
RAS/BRAF wild-type population (n=432)

Progression-free survival (PFS)



Patients at risk							
FOLFIRI + Cet:	221	77	18	5	3	0	
Switch Maintenance:	211	75	19	4	1	0	

Overall survival (OS)



Patients at risk							
FOLFIRI + Cet:	221	171	126	66	26	8	0
Switch Maintenance:	211	161	120	64	33	9	1

FIRE-4: Impact of emerging RAS mutations on survival

	Liquid Biopsy Baseline → Follow Up	PFS months (95%CI)	OS months (95%CI)
Arm A	RASwt → RASwt (n=112) RASwt→ RAS mutant (n= 27)	10.4 (8.3 - 11.6) 15.1 (11.9-19.1) P*= 0.04	36.0 (28.7-41.0) 35.4 (32.5-44.1) P*=0.73
Arm B	RASwt → RASwt (n= 142) RASwt→ RAS mutant (n= 19)	12.5 (11.2-13.6) 13.8 (8.5 - 16.8) P*= 0.47	31.1 (28.5-36.4) 28.0 (20.6-39.8) P*=0.08
All	RASwt→ RASwt (n= 254) RASwt→ RAS mutant (n= 46)	11.4 (10.5-12.5) 13.9 (11.9-16.6) P*= 0.31	32.7 (29.1-36.4) 33.6 (27.2-40.0) P*= 0.22

Arm A Continuous Cetuximab administration: **19.4%**
Arm B Switch 5FU Bevacizumab maintenance: **11.8%** **p= 0.049**

- **Emerging RAS mutations**:
  - were associated with a significantly longer median Cetuximab exposure (**27.6** weeks vs. **48.3** weeks (Logrank test **P= 0.001**))
  - were associated with a longer median PFS in the Cetuximab continuation arm (**10.4** months vs. **15.1** months (Logrank test P= **0.04**))
  - did ***not*** impact median OS

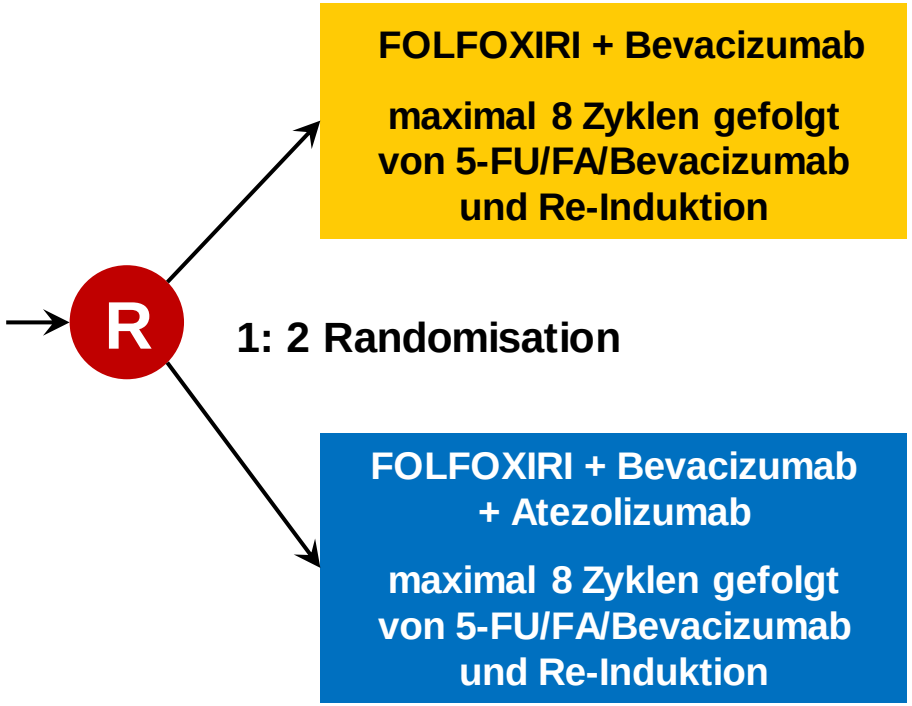
Immuntherapie auch bei mCRC mit MSS?

AtezoTribe-Studie

Antoniotti C et al., Lancet Oncol, 2022; 23; 876–87

1st line-Therapie

- Patienten konnten eingeschlossen werden unabhängig vom MSI-, BRAF- und RAS-Status
- Irresektabiität von Metastasen
- 2 : 1 Randomisation
- Strata: ECOG 0 vs 1/2, Zentrum, “sidedness”, adjuvante Therapie



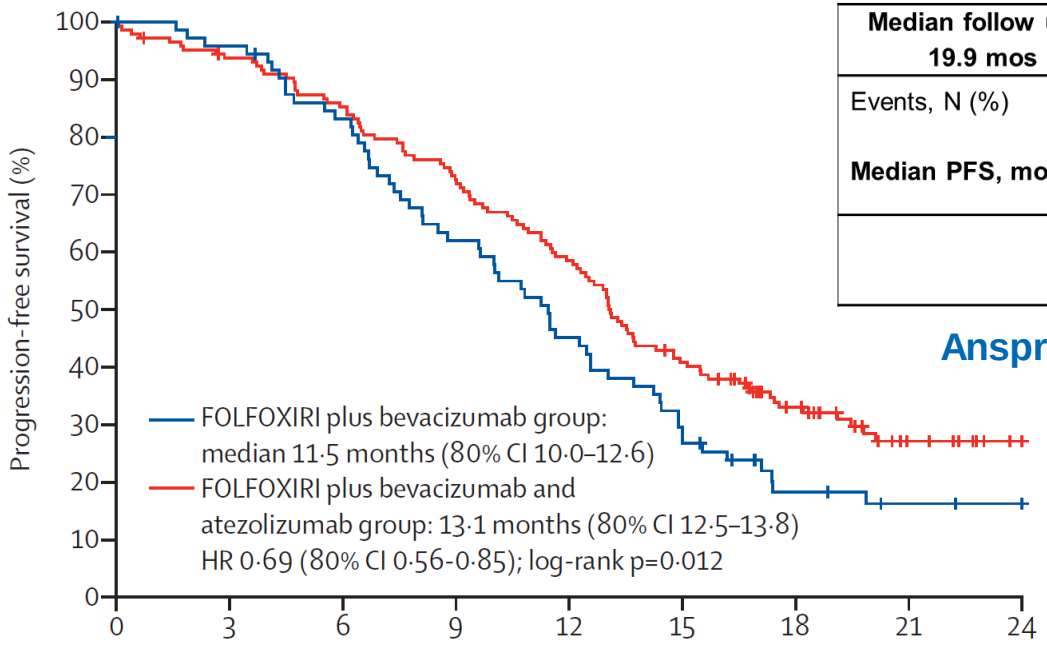
Primärer Endpunkt **Progression-free survival**

Statistik: PFS im Standardam 12 Monate: Ziel: HR 0,66 (Power 85%, α-Fehler 10%) → **129 PFS-Ereignisse**

Immuntherapie auch bei mCRC mit MSS?

AtezoTribe-Studie: PFS verbessert

Antoniotti C et al., Lancet Oncol, 2022; 23; 876–87



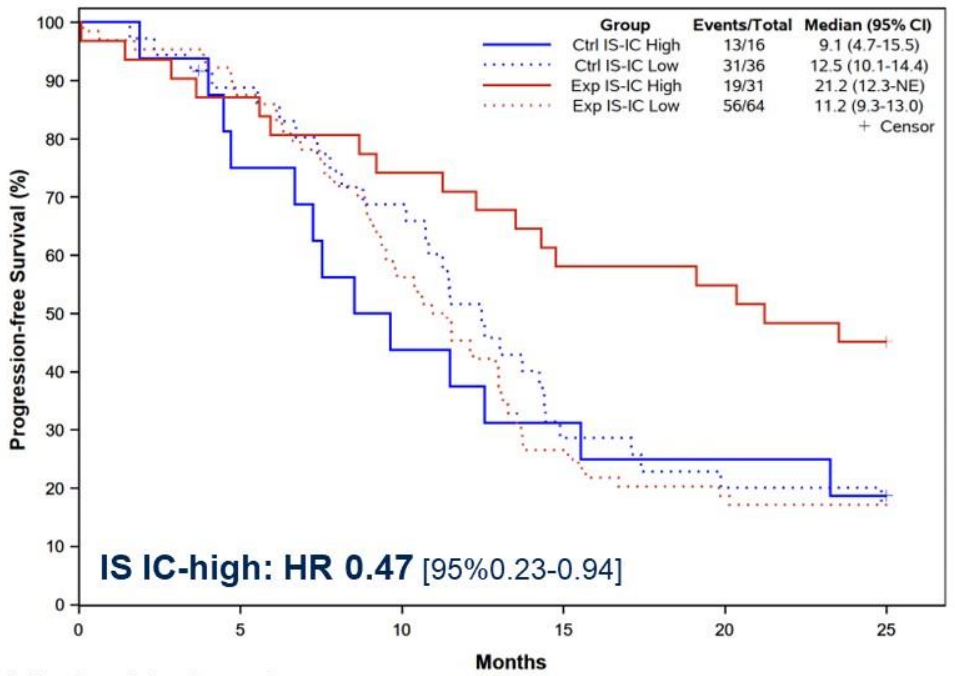
Median follow up = 19.9 mos	FOLFOXIRI/Bev N = 73	FOLFOXIRI/Bev/Atezo N = 145
Events, N (%)	60 (82%)	99 (68%)
Median PFS, mos	**11.5**	**13.1**
	HR = 0.69 [80% CI: 0.56-0.85] p=0.012	

Ansprech- & Resektionsraten vergleichbar

HR PFS (MSS): 0,78 [95% CI: 0,62–0,97]
HR PFS (MSI): 0,11 [95% CI: 0,04–0,35]

Outcomes according to Immunoscore IC and arm – pMMR cohort

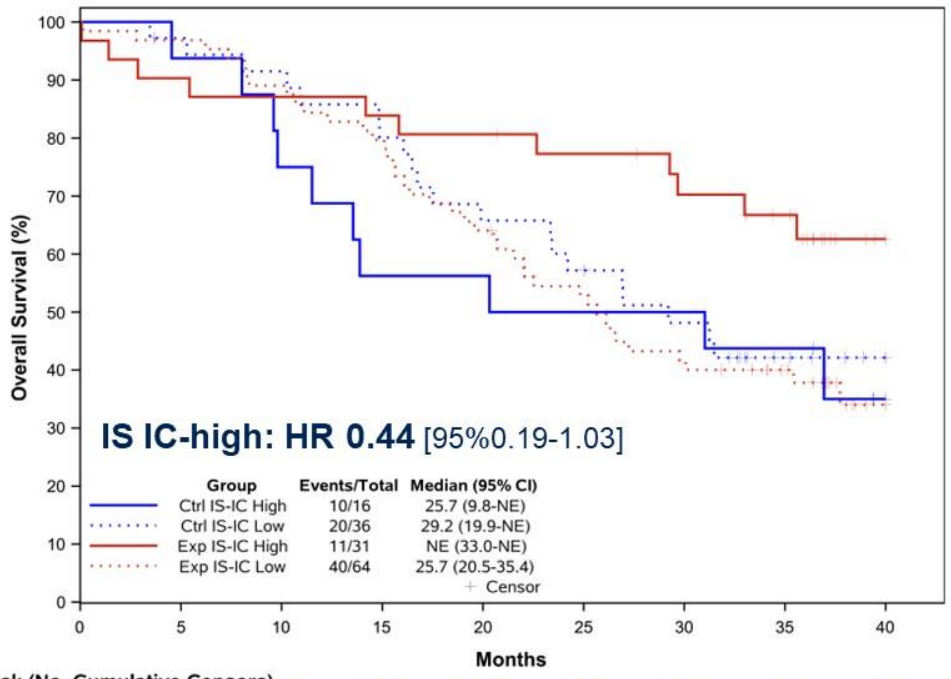
Progression-Free Survival



No. at Risk (No. Cumulative Censors)

Ctrl IS-IC High	16 (0)	12 (0)	7 (0)	5 (0)	4 (0)	3 (0)
Ctrl IS-IC Low	36 (0)	31 (1)	24 (1)	10 (1)	7 (1)	6 (1)
Exp IS-IC High	31 (0)	27 (0)	23 (0)	18 (0)	17 (0)	14 (0)
Exp IS-IC Low	64 (0)	56 (0)	36 (0)	17 (0)	12 (0)	11 (0)

Overall Survival



No. at Risk (No. Cumulative Censors)

Ctrl IS-IC High	16 (0)	15 (0)	12 (0)	9 (0)	9 (0)	8 (0)	8 (0)	6 (1)	2 (4)
Ctrl IS-IC Low	36 (0)	34 (1)	32 (1)	28 (1)	23 (1)	20 (1)	16 (2)	8 (8)	4 (12)
Exp IS-IC High	31 (0)	28 (0)	27 (0)	26 (0)	25 (0)	23 (1)	20 (2)	17 (4)	5 (15)
Exp IS-IC Low	64 (0)	62 (0)	57 (0)	51 (0)	41 (0)	33 (1)	26 (1)	19 (7)	4 (20)

LEAP-017 Study Design

Key Eligibility Criteria

- Unresectable and metastatic CRC that progressed on OR after OR could not tolerate standard treatment
- Not MSI-H/dMMR by local testing
- ECOG 0-1

R
1:1
N = 434

Pembrolizumab 400 mg IV Q6W[a]
+
Lenvatinib 20 mg PO QD[a]

Standard of Care (Investigator Choice)
Regorafenib 160 mg QD[b] Q4W
or
Trifluridine/tipiracil 35 mg/m^2 Q4W[c]

Stratification factor

- Presence or absence of liver metastases

Primary endpoint: OS
Key secondary endpoints: PFS, ORR per RECIST, v1.1 by BICR

[a]Treatment with pembrolizumab continued until progression, up to 2 years, and with lenvatinib for >25 cycles until disease progression or treatment discontinuation; [b]On D1-21, no dose on d22-28 with cycle 1 dose escalation from 80 mg QD permitted as per local guidelines; [c]BID on d1-5 and d8-12, no doses on d6-7 or d13-28. Data cut-off February 20, 2023.

Baseline Characteristics (ITT)

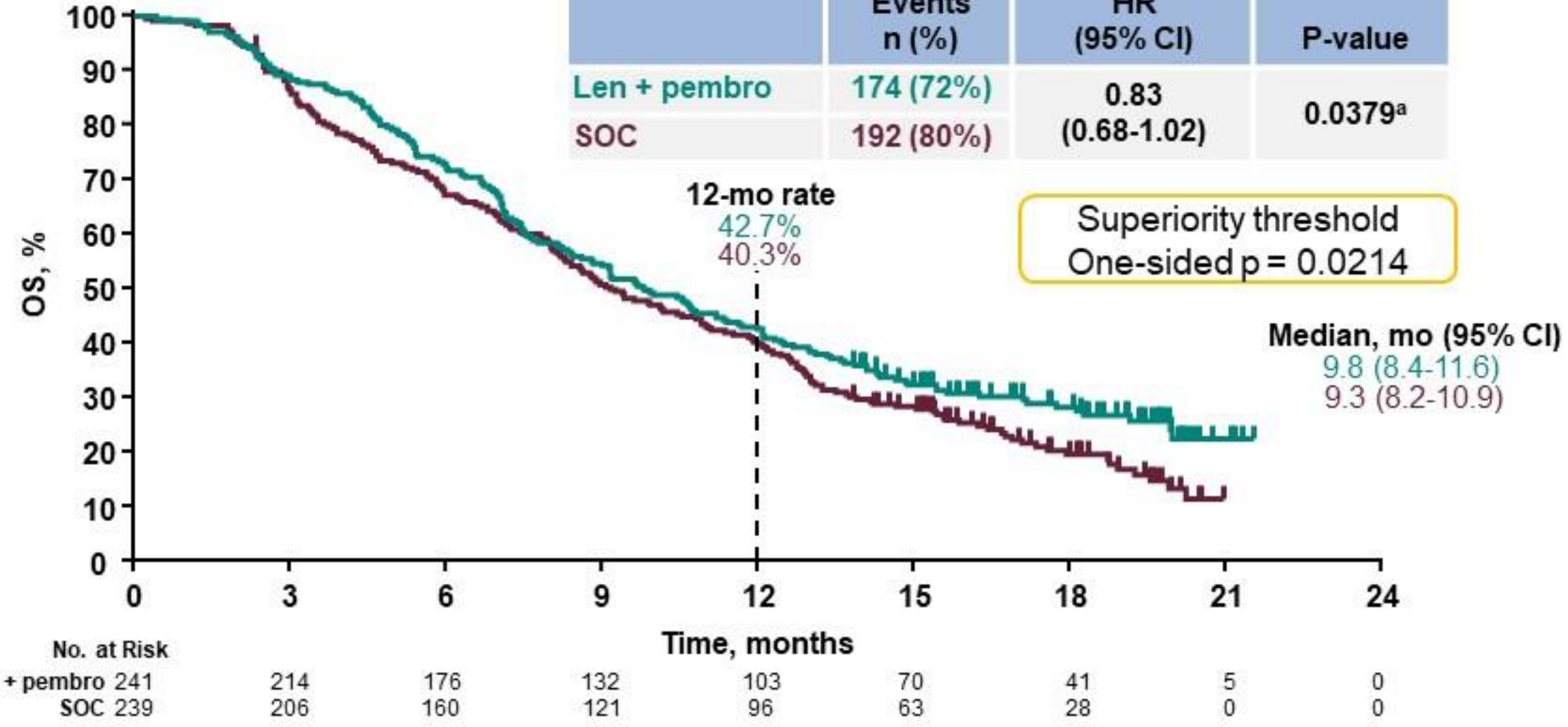
Characteristics, n (%)	Lenvatinib + Pembrolizumab N = 241	SOC N = 239
Age, median (range), years	58 (23-87)	58 (21-84)
≥ 65 years	79 (32.8)	76 (31.8)
Male	136 (56.4)	142 (59.4)
ECOG PS 0	129 (53.5)	132 (55.2)
White	152 (63.1)	152 (63.6)
Region		
Asia	77 (32.0)	77 (32.2)
Western Europe/NA	90 (37.3)	83 (34.7)
Rest of World	74 (30.7)	79 (33.1)
Primary tumor site		
Left	176 (73.0)	177 (74.1)
Right	64 (26.6)	58 (24.3)
Other/missing	1 (0.4)	4 (1.7)
Presence of liver metastases		
Yes	168 (69.7)	168 (70.3)
No	73 (30.3)	71 (29.7)
Prior anti-VEGF therapy, yes	203 (84.2)	207 (86.6)

Characteristics, n (%)	Lenvatinib + Pembrolizumab N = 241	SOC N = 239
Lines of prior systemic therapy		
1	10 (4.1)	5 (2.1)
2	126 (52.3)	120 (50.2)
≥3	105 (43.6)	114 (47.7)
PD-L1 status[a]		
CPS ≥1	85 (35.3)	96 (40.2)
CPS <1	126 (52.3)	113 (47.3)
Missing	30 (12.4)	30 (12.6)
Non-MSI-H/pMMR		
pMMR only	127 (52.7)	130 (54.4)
Non-MSI-H only	72 (29.9)	73 (30.5)
pMMR and Non-MSI-H	42 (17.4)	36 (15.1)
BRAF/RAS mutant status[b]		
BRAF/RAS wildtype	217 (90.0)/99 (41.1)	212 (88.7)/111 (46.4)
RAS mutant	139 (57.7)	128 (53.6)
BRAF mutant	5 (2.1)	13 (5.4)
Chemotherapy choice[c]		
Trifluridine/tipiracil	122 (50.6)	116 (48.5)
Regorafenib	119 (49.4)	123 (51.5)

NA, North America; [a]PD-L1 status was centrally assessed; [b]22 (9.1%) and 14 (5.9%) had BRAF/RAS unknown or missing status in the lenvatinib + pembrolizumab and SOC arms; [c]Investigator choice before randomization; Data cut-off February 20, 2023.

Overall Survival (FA)

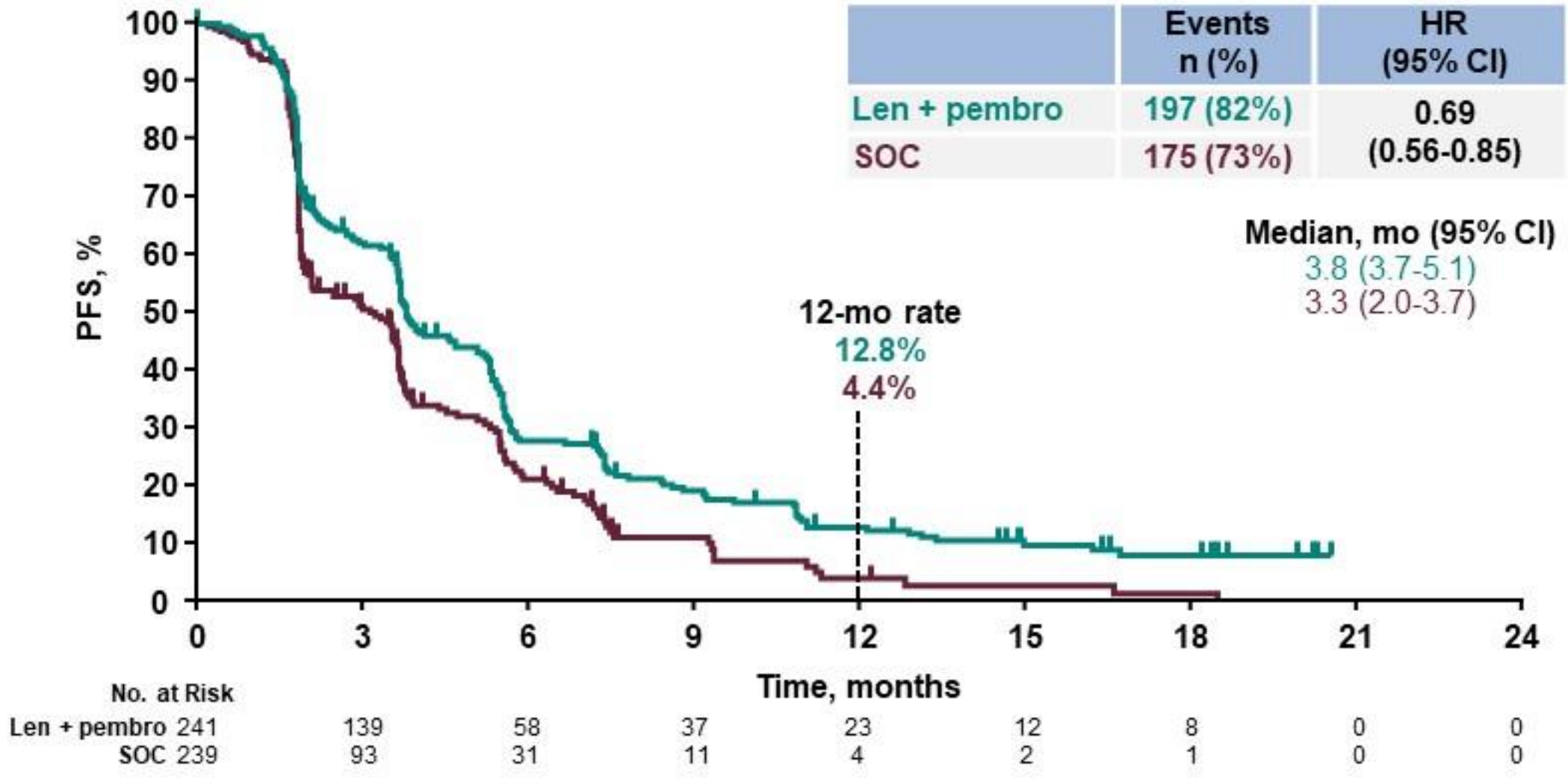
	Events n (%)	HR (95% CI)	P-value
Len + pembro	174 (72%)	0.83 (0.68-1.02)	0.0379[a]
SOC	192 (80%)		



No. at Risk								
Len + pembro	241	214	176	132	103	70	41	5	0
SOC	239	206	160	121	96	63	28	0	0

[a]OS did not meet pre-specified superiority threshold of one-sided p = 0.0214; Data cut-off February 20, 2023.

Progression-free Survival (FA) RECIST v1.1, BICR



	Events n (%)	HR (95% CI)
Len + pembro	197 (82%)	0.69 (0.56-0.85)
SOC	175 (73%)	

Median, mo (95% CI)
3.8 (3.7-5.1)
3.3 (2.0-3.7)

[a]PFS was not tested at IA; HR (95% CI) for len + pembro vs SOC was 0.71 (0.57-0.87) with median duration of study follow-up of 11.6 months (range, 7.0-15.4) (Data cut-off July 21, 2022) at IA and 18.6 months (range, 14.0-22.5) at FA. Data cut-off February 20, 2023.

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MARGIT MANNHEIMER ARBEITSGRUPPE FÜR GASTROINTESTINALE TUMOREN

UNIVERSITÄT HEIDELBERG ZUKUNFT SEIT 1386

Oberer GI Trakt

Ösophagogastrale Adenokarzinome Immuntherapie (n = 3)

Pankreaskarzinom: neoadjuvant & palliativ 1st line (n = 2)

Gallenwege: KEYNOTE 966 & HER2-gezielte Therapien (n = 3)

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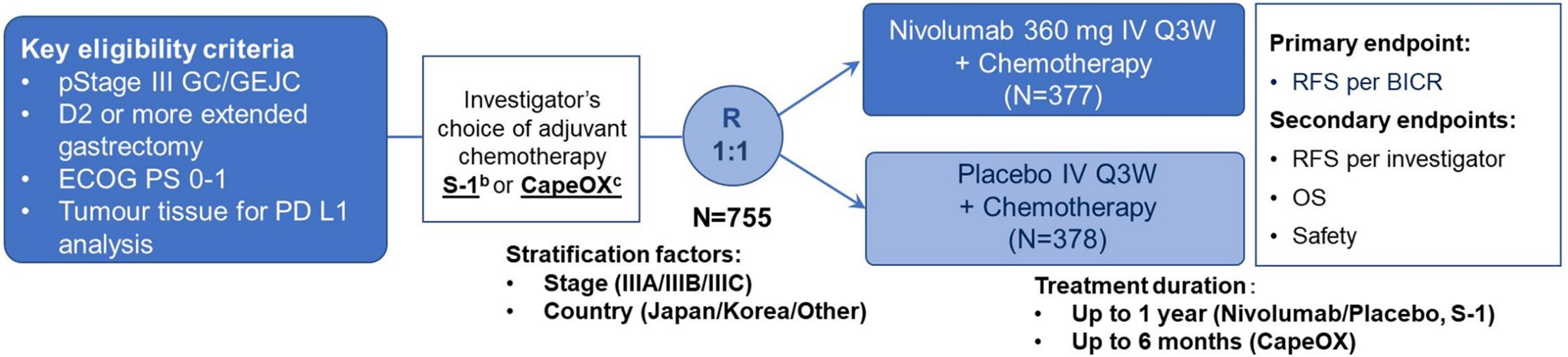
Additive Immuntherapie nach Resektion
ATTRACTION 5 Studie (Asien 100%, Adeno 100%)

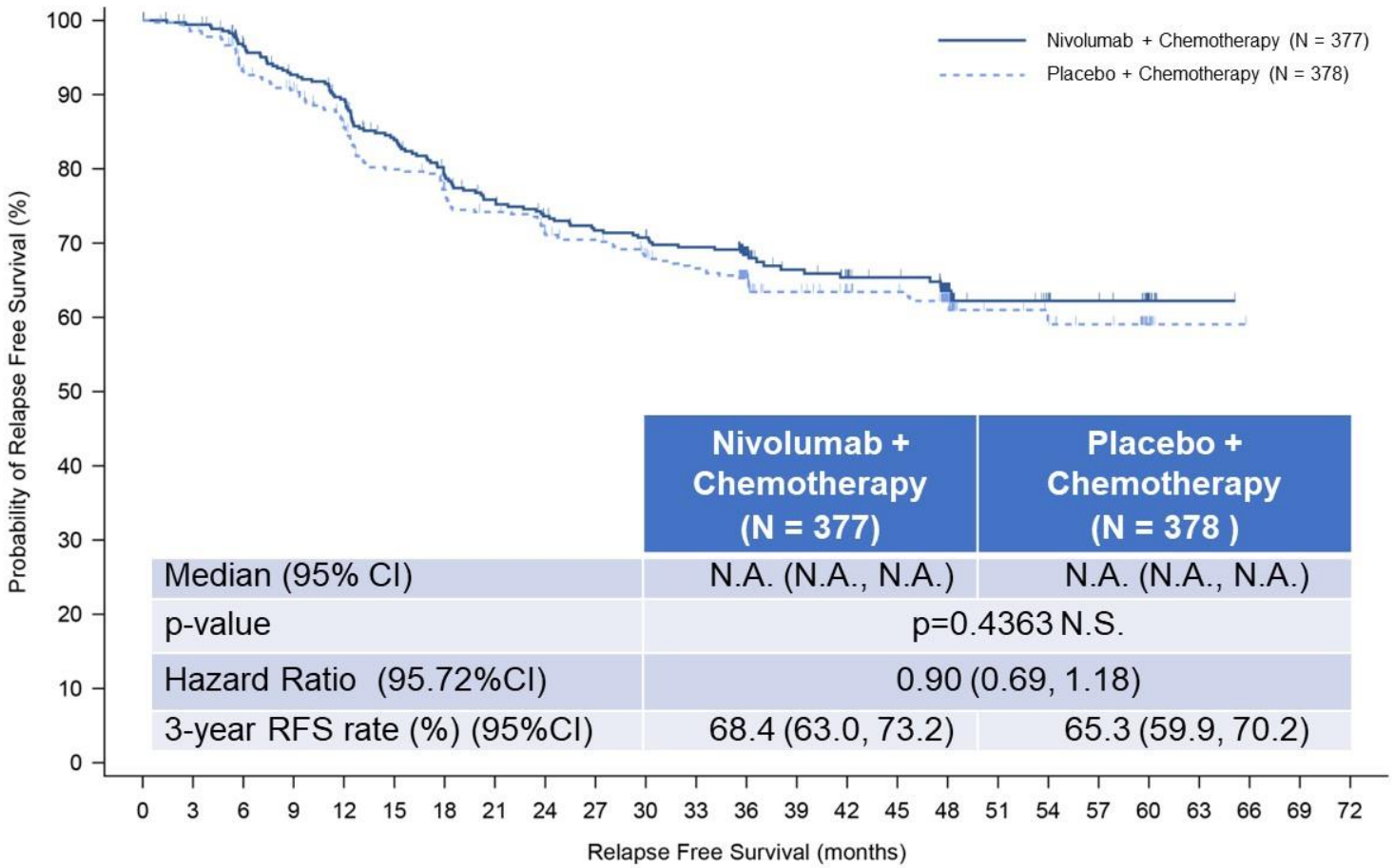


- Planned sample size: 700 patients (assuming HR=0.67; 3-year RFS, 71% vs 60%)
- Patients were randomized from February 2017 to August 2019
- All data are based on a clinical data cutoff of August 2022, at which point the minimum follow-up after the last patient randomized was 36 months

[a]ClinicalTrials.gov number, NCT03006705; [b]**S-1 therapy:** S-1 40 mg/m^2/dose orally twice daily (day1-28) , Q6W; [c]**CapeOX therapy:** Oxaliplatin 130 mg/m^2 IV once daily (day1), and Capecitabine 1000 mg/m^2/dose orally twice daily (day1-14), Q3W.

Abbreviations: BICR, blinded independent central review; CapeOX, capecitabine/oxaliplatin; GC, gastric cancer; GEJC, gastroesophageal junction cancer; IV, intravenous; Q3W, every 3 weeks; Q6W, every 6 weeks; S-1, tegafur/gimeracil/oteracil; BICR, blinded independent central review

Primary endpoint: RFS per BICR



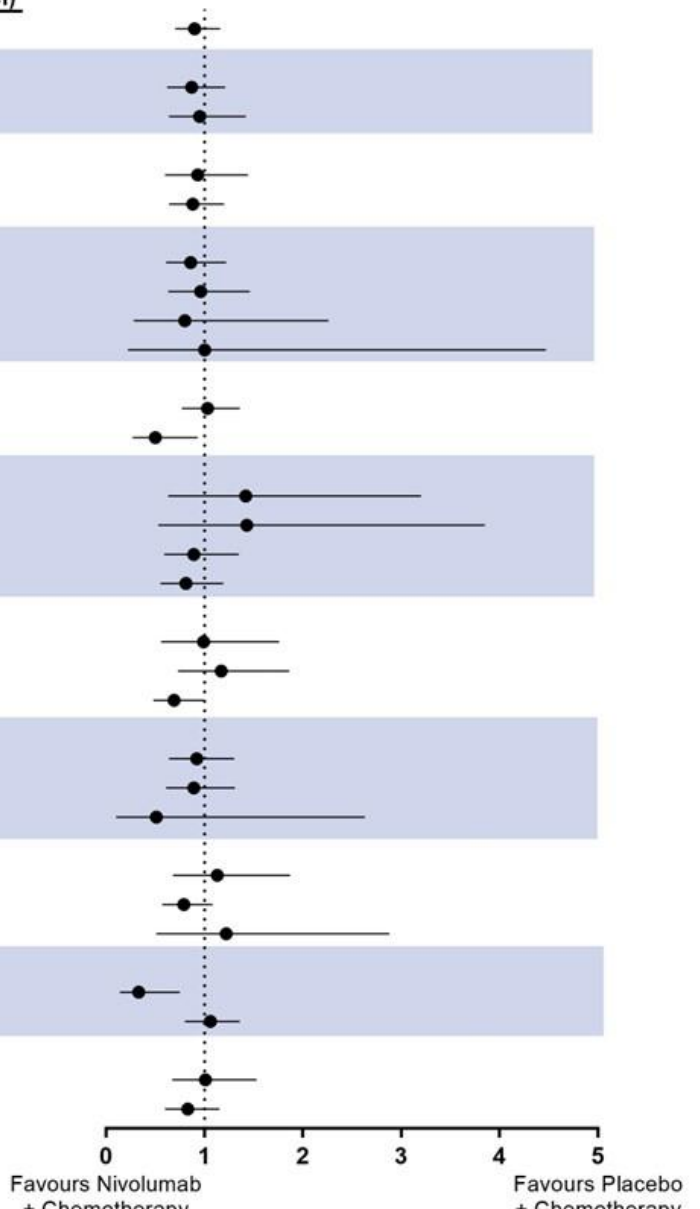
	Nivolumab + Chemotherapy (N = 377)	Placebo + Chemotherapy (N = 378)
Median (95% CI)	N.A. (N.A., N.A.)	N.A. (N.A., N.A.)
p-value	p=0.4363 N.S.	
Hazard Ratio (95.72%CI)	0.90 (0.69, 1.18)	
3-year RFS rate (%) (95%CI)	68.4 (63.0, 73.2)	65.3 (59.9, 70.2)

At Risk

Nivolumab + Chemotherapy	377	349	326	310	297	273	255	241	231	223	219	214	162	127	120	114	58	33	28	24	9	1	0	0	0
Placebo + Chemotherapy	378	353	324	311	288	267	254	242	228	223	212	204	148	118	110	107	57	33	30	26	10	1	0	0	0

RFS per BICR in subgroups

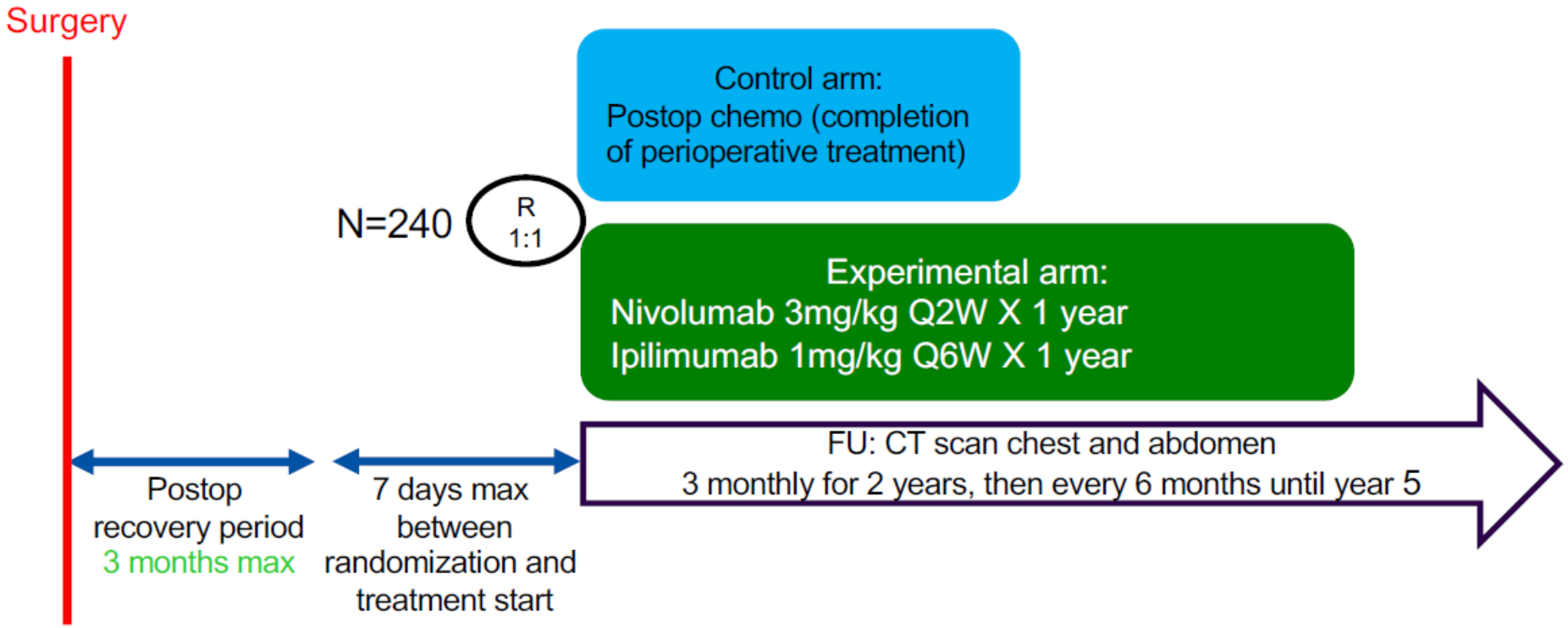
	Nivolumab + Chemotherapy No. of events	Placebo + Chemotherapy No. of events	Unstratified HR (95%CI)
Overall	113/377	124/378	0.90 (0.70-1.16)
Age			
<65 years	63/212	78/222	0.87 (0.62-1.21)
≥65years	50/165	46/156	0.95 (0.64-1.42)
Sex			
Female	39/110	43/115	0.93 (0.60-1.44)
Male	74/267	81/263	0.88 (0.64-1.20)
Country			
Japan	60/182	67/183	0.86 (0.61-1.22)
Korea	44/157	44/155	0.96 (0.63-1.46)
Taiwan	6/23	9/24	0.80 (0.28-2.26)
China	3/15	4/16	1.00 (0.22-4.47)
ECOG PS			
0	98/299	95/294	1.03 (0.77-1.36)
1	15/78	29/84	0.50 (0.27-0.93)
Primary sites			
GEJ	10/21	14/31	1.42 (0.63-3.20)
Gastric fundus	9/26	7/25	1.43 (0.53-3.85)
Gastric corpus	44/161	46/154	0.89 (0.59-1.35)
Gastric antrum and pylorus	50/169	57/168	0.81 (0.55-1.19)
Pathological stage			
IIIA	23/110	24/111	0.99 (0.56-1.76)
IIIB	37/127	33/129	1.17 (0.73-1.86)
IIIC	53/140	67/138	0.69 (0.48-0.99)
Type of surgery			
Total gastrectomy	61/164	64/164	0.92 (0.64-1.30)
Distal gastrectomy	50/204	55/199	0.89 (0.61-1.31)
Others	2/9	5/15	0.51 (0.10-2.63)
Histology			
Intestinal type	31/134	29/140	1.13 (0.68-1.87)
Diffuse type	71/213	83/209	0.79 (0.57-1.08)
Others	11/30	10/26	1.22 (0.51-2.88)
Tumor cell PD-L1 expression			
≥1%	9/52	15/34	0.33 (0.14-0.75)
<1%	103/309	106/333	1.06 (0.81-1.40)
Chemotherapy regimen			
S-1	46/132	45/135	1.01 (0.67-1.53)
CapeOX	67/245	79/243	0.83 (0.60-1.15)



Additive Immuntherapie nach Resektion

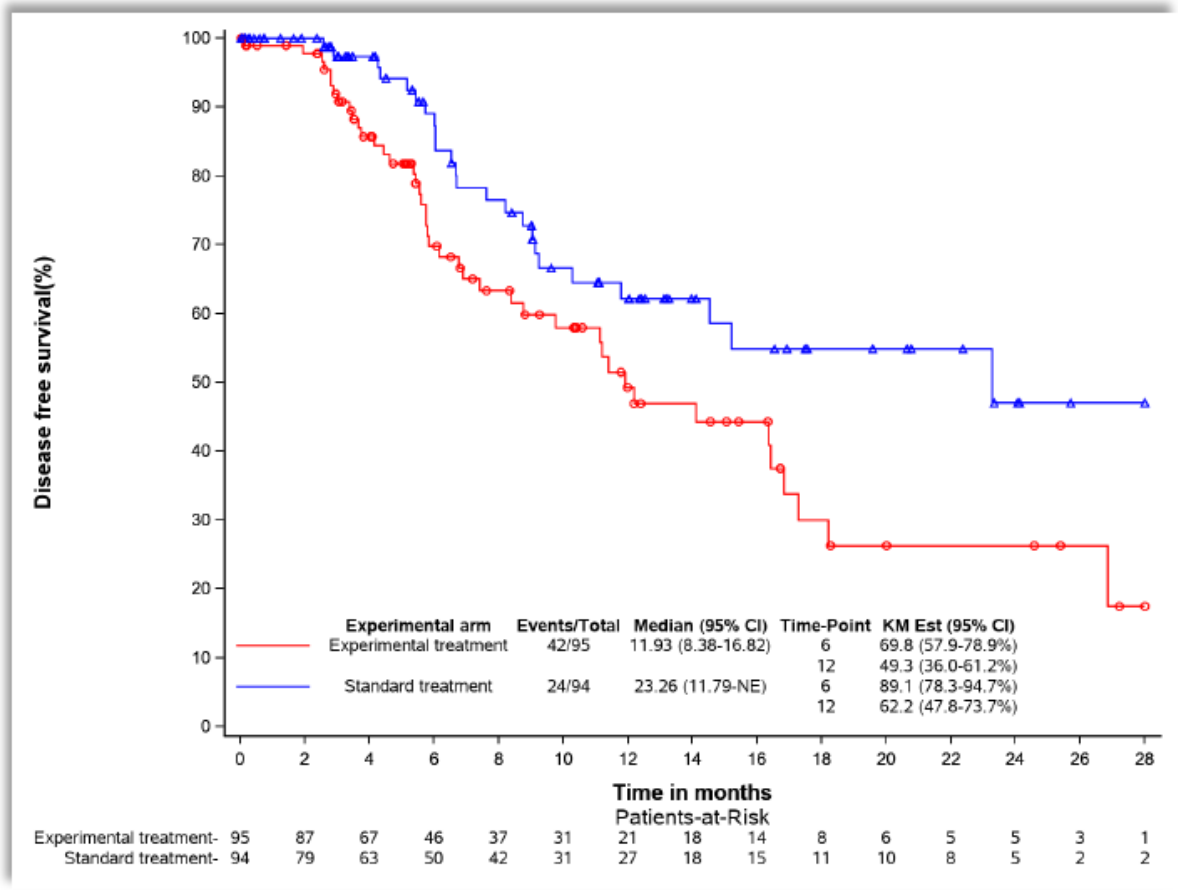
VESTIGE Studie für Hochrisiko EGA

- Gastric or EGJ adenocarcinoma stage Ib-IV
- Completed pre-operative chemotherapy with a fluoropyrimidine/platin-containing regimen followed by surgery within 12 weeks prior to randomization
- Recovered from surgery
- ypN1-3 status according to current (8th) version of TNM classification system AND/OR
- R0 or R1 resection according to current (8th) version of TNM



Additive Immuntherapie nach Resektion

VESTIGE Studie: Disease-free survival



	CT am	Nivo/Ipi arm
Median DFS(m) (95% CI)	23.26 (11.79 – NE)	11.93 (8.36- 16.82)
12m DFS % (95% CI)	62.2 (47.8-73.7)	49.3 36.0- 61.2)

	Event/Total	Hazard Ratio (95% CI)[Cox]	P-value
Nivo/Ipi arm	42/95	1.80 (1.09-2.98)	0.0195*
CT arm	24/94	Reference	

[Cox]Cox model; *Logrank test

Study design

This is a randomised, open-label, phase 2 trial

Key eligibility criteria

- Histologically confirmed cT3-4aN+M0 gastric/GEJ adenocarcinoma
- ECOG PS 0-1
- Resectable

Stratification factors

- **Tumour location** (gastric vs GEJ)
- Lauren's classification (diffuse vs intestinal/mixed)

R 1:1

n = 54

Toripalimab 240 mg + SOX[1]/XELOX [2] q3w 3 cycles
↓
Surgery
↓
Toripalimab 240 mg + SOX/XELOX q3w 5 cycles
↓
Toripalimab 240 mg for 6 months

n = 54

SOX/XELOX q3w 3 cycles
↓
Surgery
↓
SOX/XELOX q3w 5 cycles

Primärer Endpunkt : TRG

[1]S-1, 40-60 mg twice a day for 2 weeks followed by a rest of 1 week and oxaliplatin 130 mg/m2, day 1, every 3 weeks; [2]Capecitabine 1000 mg/m2 twice a day for 2 weeks followed by a rest of 1 week and oxaliplatin 130 mg/m2, day 1, every 3 weeks

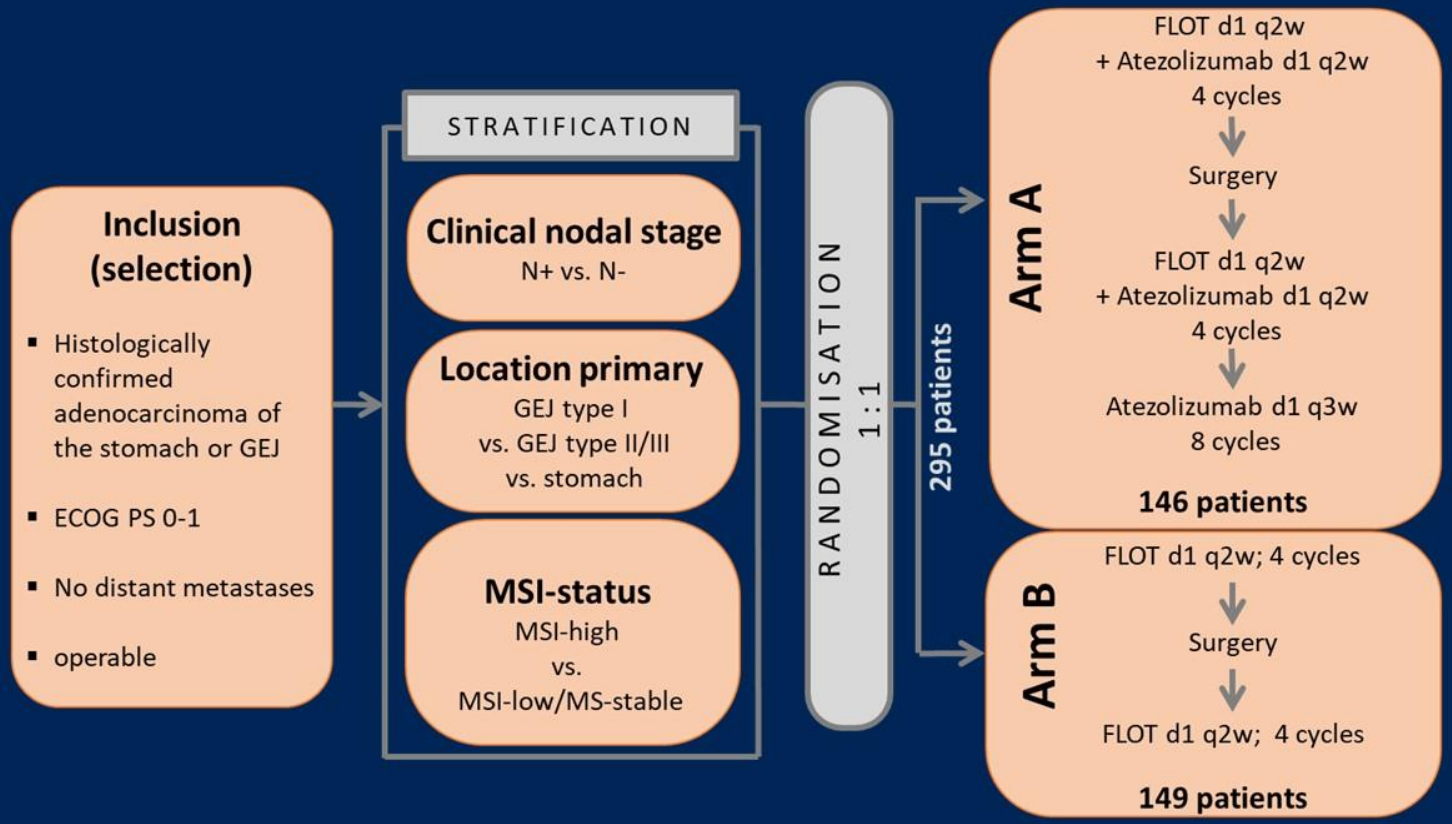
Pathological outcomes-tumor regression grade

	Toripalimab + chemotherapy (n = 54)	Chemotherapy (n = 54)	P value
TRG			
TRG 0 (ypT0N0M0)	**12 (22%)**	**4 (7%)**	0.03
TRG 1	12 (22%)	7 (13%)	
TRG 2	16 (30%)	29 (54%)	
TRG 3	11 (20%)	12 (22%)	
Combined TRG 0-1	**24 (44%)**	**11 (20%)**	0.01
No surgery	3 (6%)	2 (4%)	

Primary endpoint

Study Flow Chart

DANTE is an investigator-initiated phase-II trial with the potential to transition into a phase-III trial



PRESENTED BY:
Prof. Dr. Salah-Eddin Al-Batran
IKF Institut für Klinische Krebsforschung am Krankenhaus Nordwest

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Pathological regression (local assessment)

Pathological Regression **FLOT + Atezolizumab (arm A) vs. FLOT (arm B)**	Becker Classification			
	TRG1a[1]		TRG1a/b[2]	
	A	B	A	B
All patients (N= 295; 146|149)	35 (24%)	23 (15%)	71 (49%)	58 (39%)
PD-L1 CPS ≥1 (N=170; 82|88)	20 (24%)	13 (15%)	42 (51%)	40 (46%)
PD-L1 CPS ≥5 (N=81; 40|41)	11 (28%)	8 (20%)	22 (55%)	18 (44%)
PD-L1 CPS ≥10 (N=53; 27|26)	9 (33%)	3 (12%)	18 (67%)	10 (39%)
MSI high (N=23; 8|15)	5 (63%)	4 (27%)	6 (75%)	7 (47%)

[1]pathological complete regression acc. to Becker
[2]pathological subtotal regression acc. to Becker

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Merck Provides Update on Phase 3 KEYNOTE-585 Trial in Locally Advanced Resectable Gastric and Gastroesophageal Junction (GEJ) Adenocarcinoma

6/20/2023

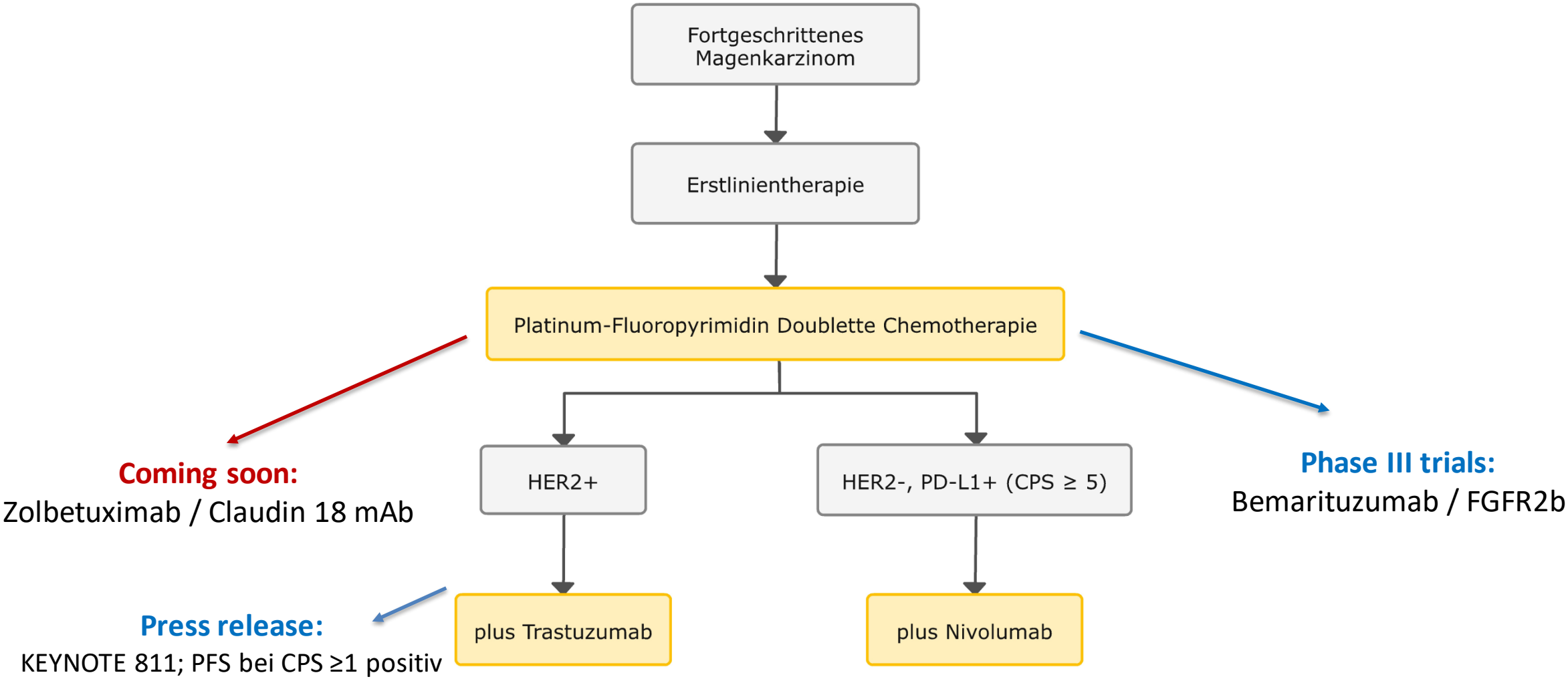
RAHWAY, N.J.--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside of the United States and Canada, today announced topline results from the Phase 3 KEYNOTE-585 trial, investigating KEYTRUDA, Merck's anti-PD-1 therapy, in combination with chemotherapy as neoadjuvant treatment, followed by adjuvant treatment with KEYTRUDA plus chemotherapy, then KEYTRUDA monotherapy in patients with locally advanced resectable gastric and gastroesophageal junction (GEJ) adenocarcinoma. At a pre-specified interim analysis conducted by an independent Data Monitoring Committee, the study met one of its primary endpoints of pathological complete response (pCR) rate and demonstrated a statistically significant improvement in pCR rates compared with chemotherapy alone. For the primary endpoint of event-free survival (EFS), there was an improvement in the KEYTRUDA arm; however, results did not meet statistical significance per the pre-specified statistical analysis plan. The endpoint of overall survival (OS) was not formally tested since superiority was not reached for EFS. The safety profile of KEYTRUDA in this trial was consistent with that observed in previously reported studies. Results will be presented at an upcoming medical meeting.

"While a statistically significant improvement in pathological complete response was observed in this study, we are disappointed that the KEYTRUDA regimen did not significantly improve event-free survival, a result that

Imfinzi plus chemotherapy significantly improved pathologic complete response in gastric and gastroesophageal junction cancers in MATTERHORN Phase III trial

Immuntherapie perioperativ bei AEG: Was wissen wir ?

	Matterhorn *Press release*	KEYNOTE 585 *Press release*	DANTE *ASCO 2022*	Yuan *ASCO 2023*
N	≈ 900	≈ 800	295	108
Backbone	FLOT	FP / Cisplatin (FLOT)	FLOT	SOX / XELOX
pCR	Sign. besser	Sign. besser	Sign. besser	Sign. besser
DFS	Nicht berichtet	Verfehlt	Nicht berichtet	Nicht berichtet
Besonderheiten	Endpunkt für allcomers	Endpunkt für allcomers	pCR 24 vs 15% (allcomers) Größter Benefit ab CPS 10	pCR 24 vs 9% (allcomers)

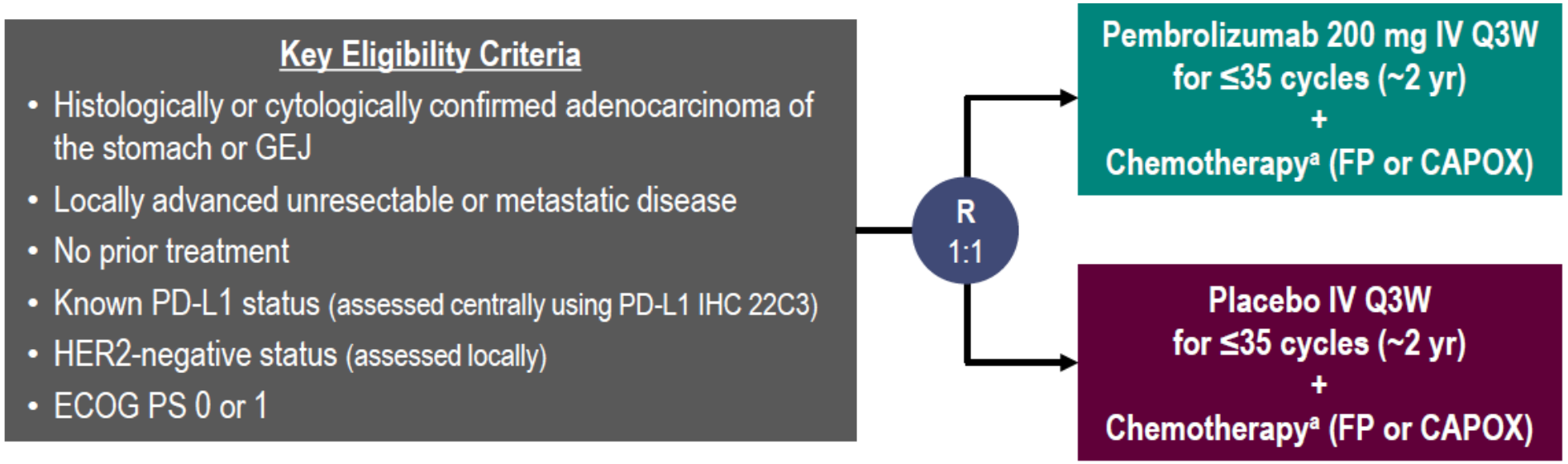


Metastasierte ösophagogastrale Adenokarzinome - Onkopedia

(Lordick et al. 2022)

Keynote 859: Chemotherapie +/- Pembrolizumab

Ösophagogastrales Adenokarzinome; CPS allcomer



Stratification Factors

- Geographic region (Europe/Israel/North America/ Australia vs Asia vs rest of world)
- PD-L1 CPS (<1 vs ≥1)
- Choice of chemotherapy[a] (FP vs CAPOX)

- **Primary End Point:** OS
- **Secondary End Points:** PFS,[b] ORR,[b] DOR,[b] and safety

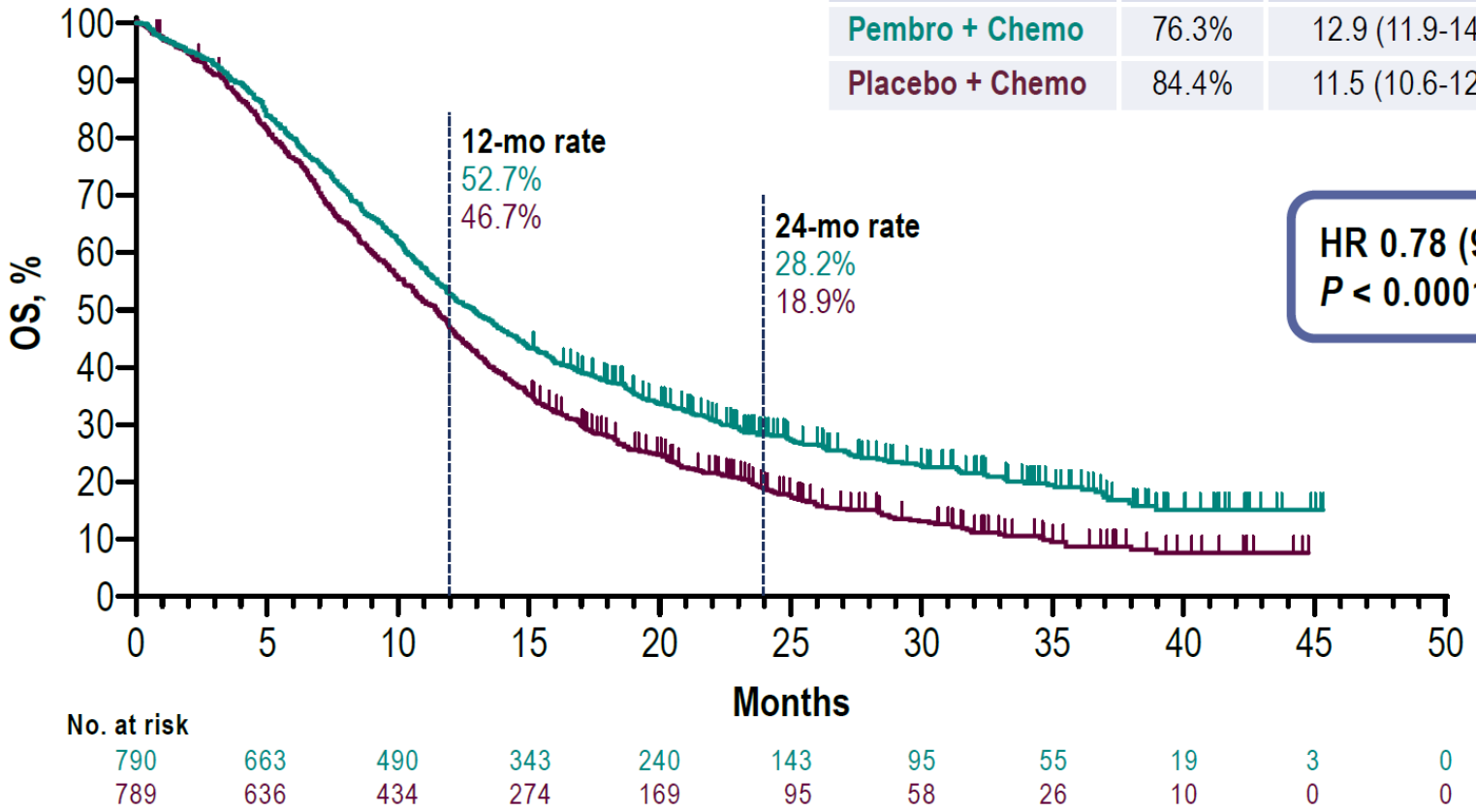
Rha S Y et al, ESMO virtual plenary 2023

Keynote 859: Chemotherapie +/- Pembrolizumab

Überleben; CPS allcomer

OS, ITT Population

	Pts w/ Event	Median, mo (95% CI)
Pembro + Chemo	76.3%	12.9 (11.9-14.0)
Placebo + Chemo	84.4%	11.5 (10.6-12.1)

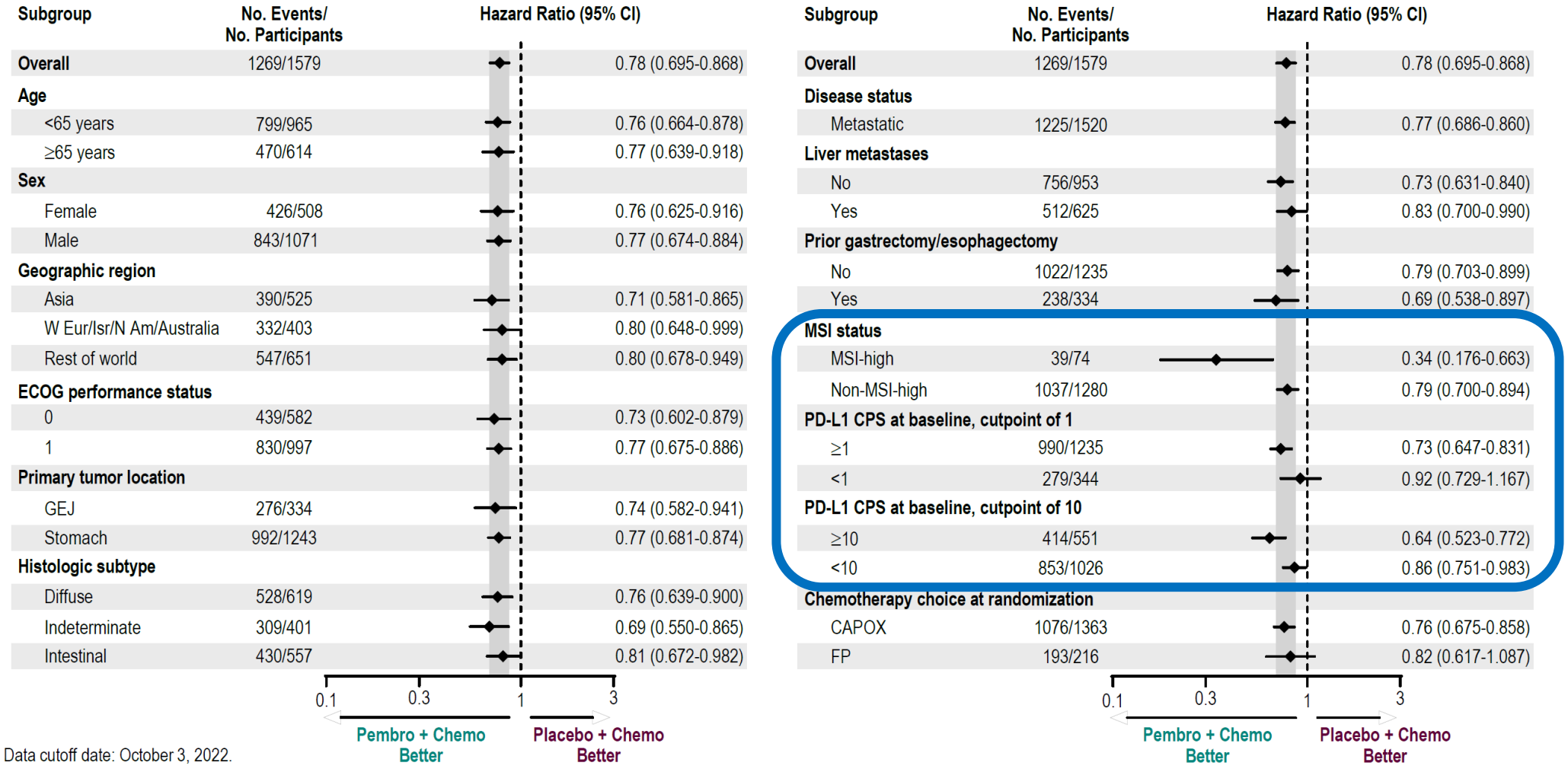


HR 0.78 (95% CI, 0.70-0.87)
P < 0.0001

Rha S Y et al, ESMO virtual plenary 2023

Keynote 859: Chemotherapie +/- Pembrolizumab

Überleben – Forest Plot



Data cutoff date: October 3, 2022.

Rha S Y et al, ESMO virtualy plenary 2023

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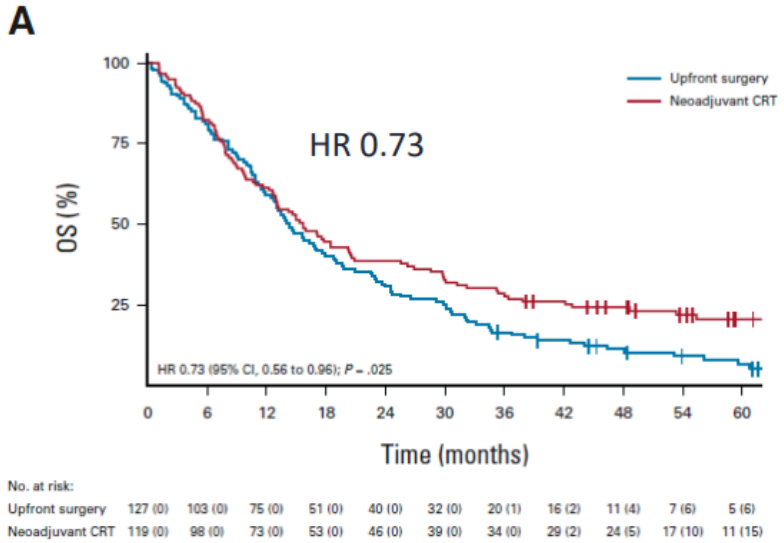
Gallenwege: KEYNOTE 966 & HER2-gezielte Therapien (n = 3)

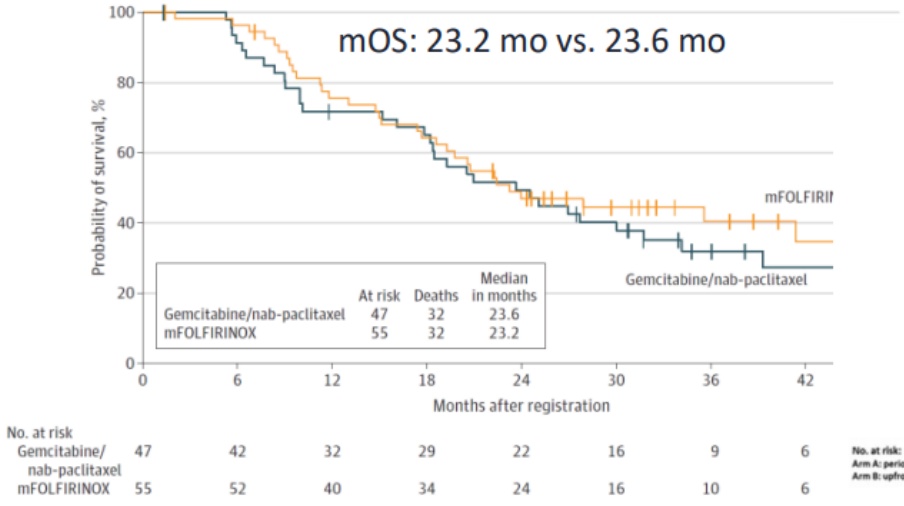
Pankreaskarzinom: Präoperative Therapie bei resektablem Befund

PREOPANC



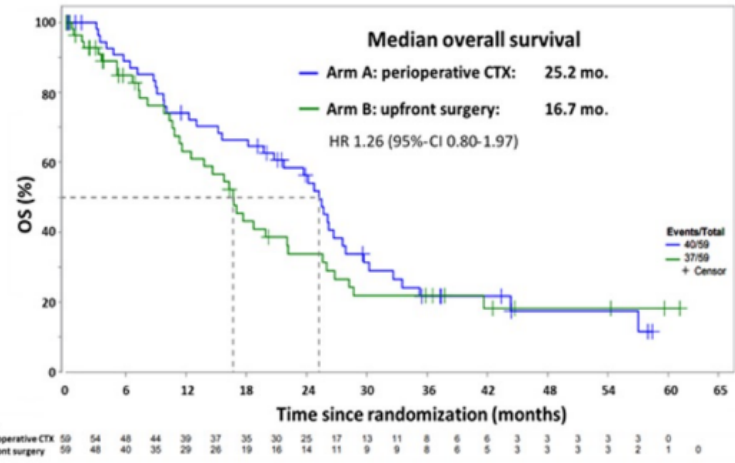
Versteijne, JCO 2022

SWOG 1505



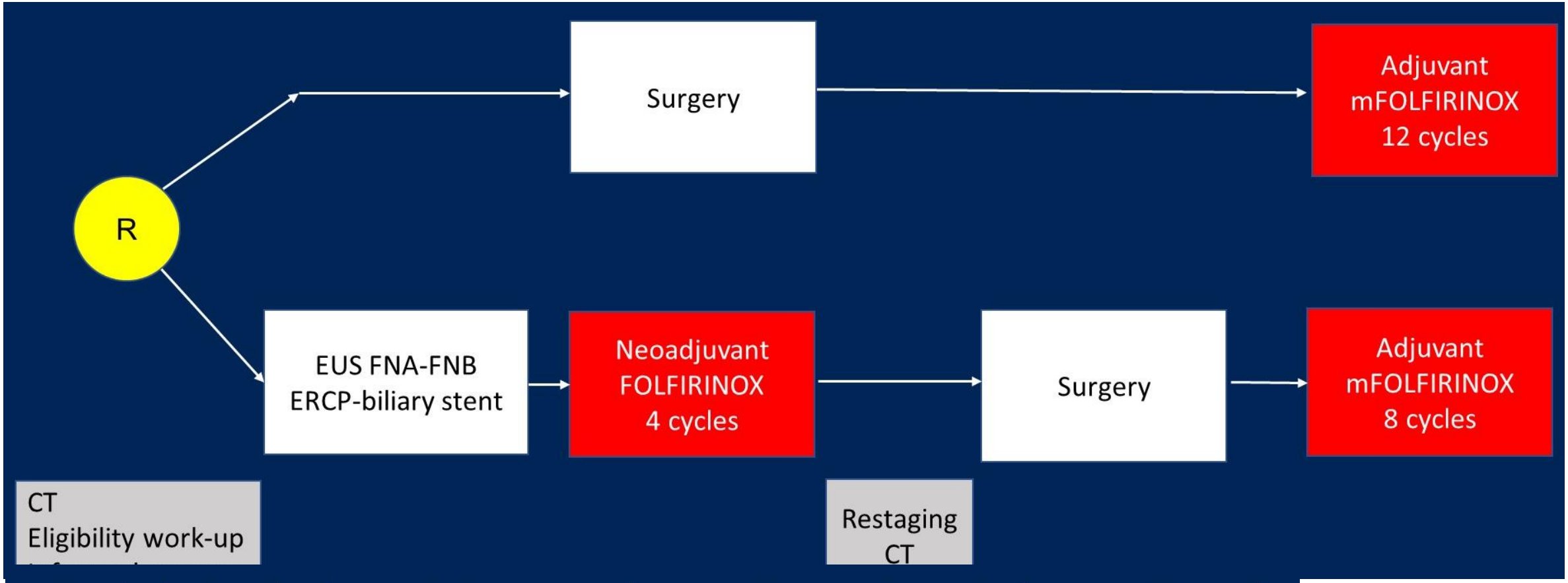
Sohal et al., JAMA Oncol 2021

NEONAX



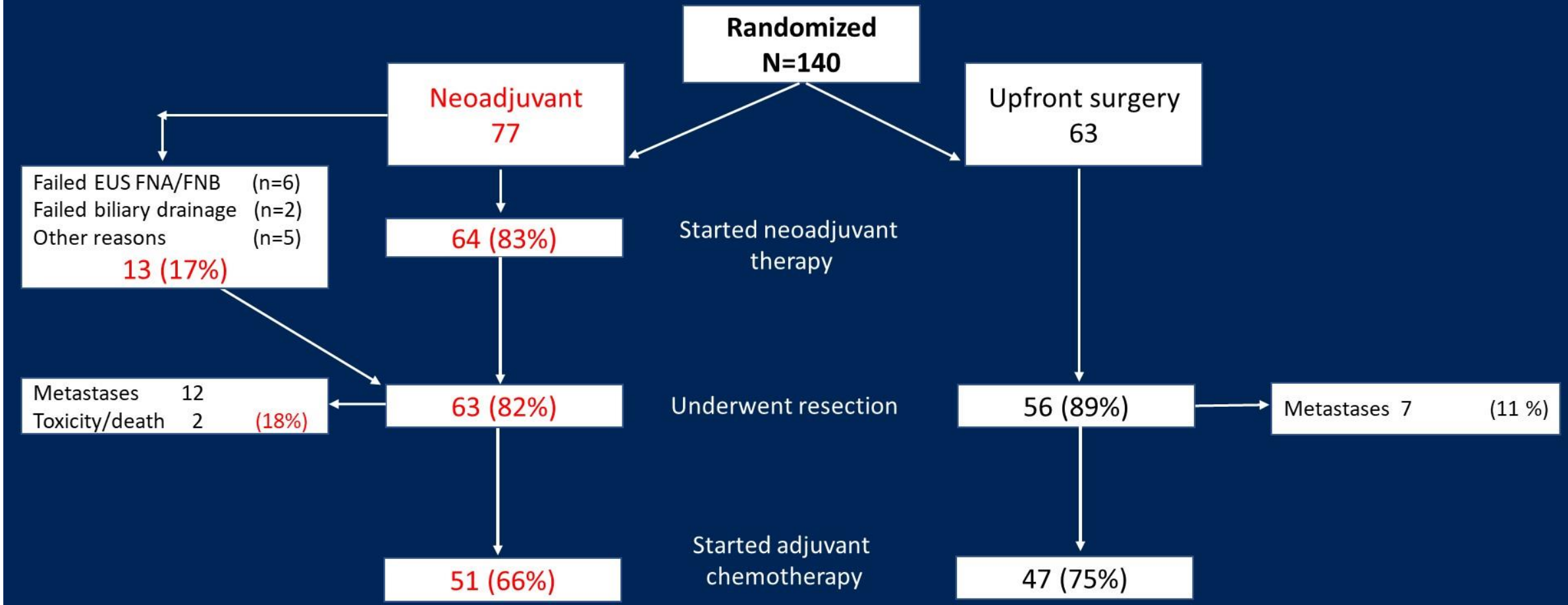
Seufferlein et al., Annals Oncology 2022

Pankreaskarzinom: NORPACT Studie



- Study designed to have 80 % power to detect an increase in survival rate at 18 months from 50% to 70 % with neoadjuvant therapy (significance level 0.15)
- Sample size 140

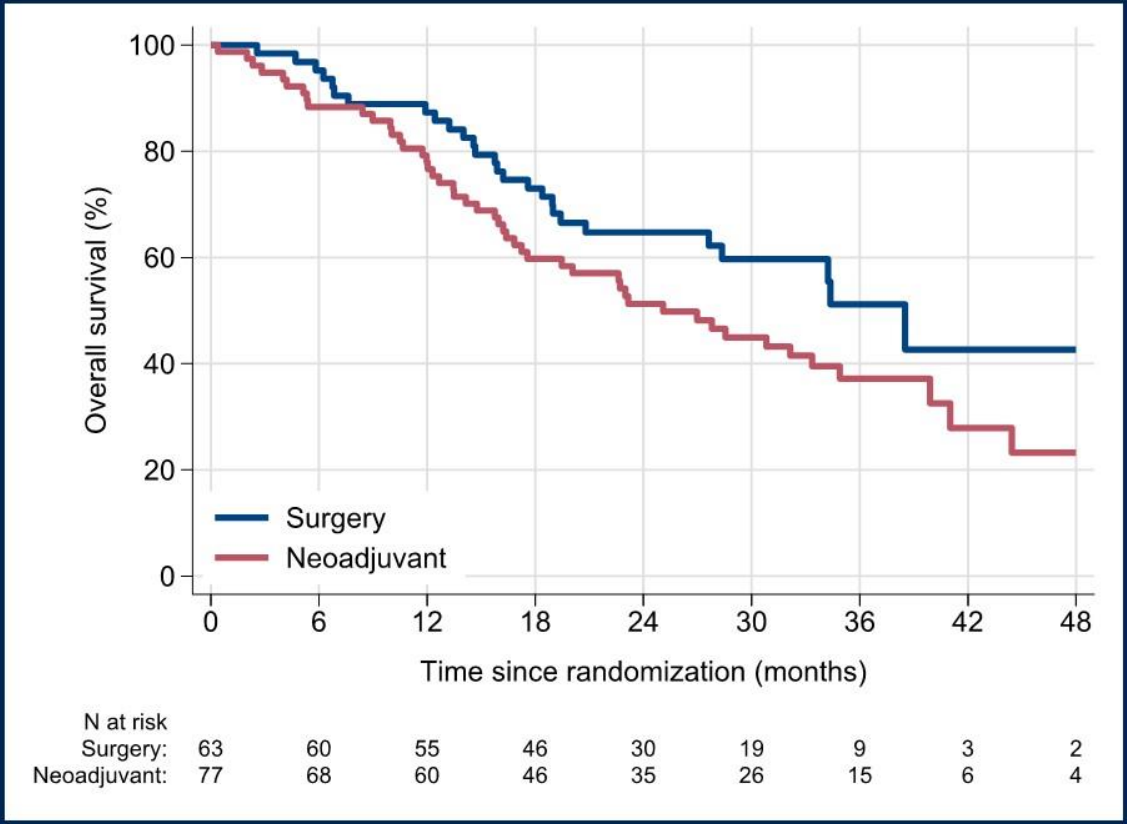
Flow chart



Histopathology

	Neoadjuvant group (n=63)	Upfront surgery (n=56)	p-value
Intention-to-treat			
R0	56%	39%	0.076
N0	29%	14%	0.060
Per-protocol	(n=46)	(n=49)	
R0	59%	33%	0.011
N0	37%	10%	0.002

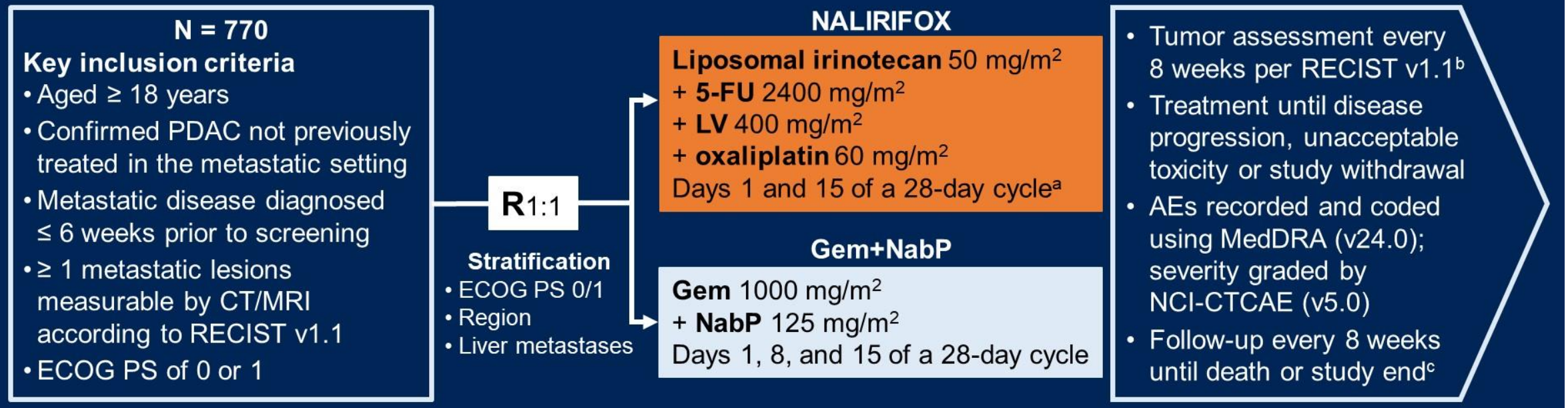
Overall survival - Intention-to-treat



Median overall survival
25.1 months (neoadjuvant)
38.5 months (upfront surgery)
HR 1.52 (95% CI, 0.94-2.46), p=0.096

Proportion alive at 18 months
60% vs 73%, p=0.1

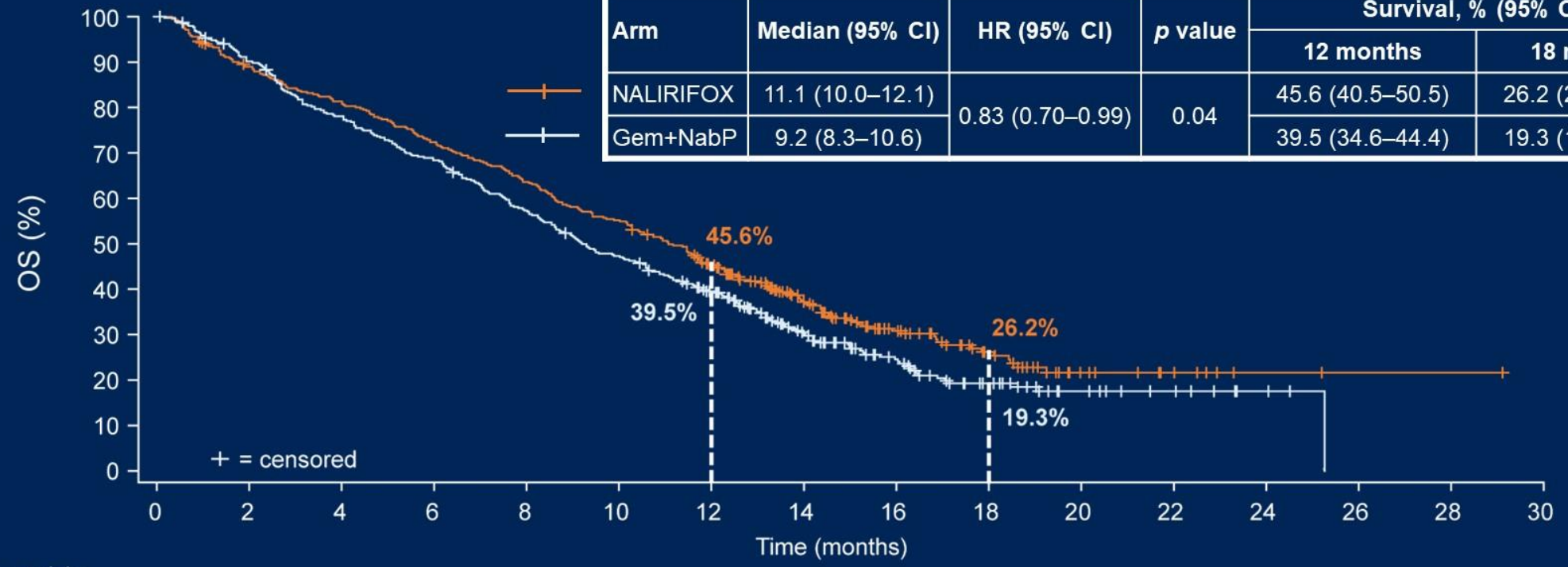
NAPOLI 3: Study design



[a]Administered sequentially as a continuous infusion over 46 hours on days 1 and 15 of a 28-day cycle (dose delays and oxaliplatin discontinuation were permitted). [b]Until progressive disease. [c]The study was completed once all patients had discontinued the study treatment and at least 543 OS events had occurred in randomized patients.
5-FU, 5-fluorouracil; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; Gem, gemcitabine; LV, leucovorin; MedDRA, Medical Dictionary for Regulatory Activities; MRI, magnetic resonance imaging; NabP, nab-paclitaxel; NALIRIFOX, liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PDAC, pancreatic ductal adenocarcinoma; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors.

NAPOLI 3: OS (ITT population)

Arm	Median (95% CI)	HR (95% CI)	*p* value	Survival, % (95% CI)	
				12 months	18 months
NALIRIFOX	11.1 (10.0–12.1)	0.83 (0.70–0.99)	0.04	45.6 (40.5–50.5)	26.2 (20.9–31.7)
Gem+NabP	9.2 (8.3–10.6)			39.5 (34.6–44.4)	19.3 (14.8–24.2)



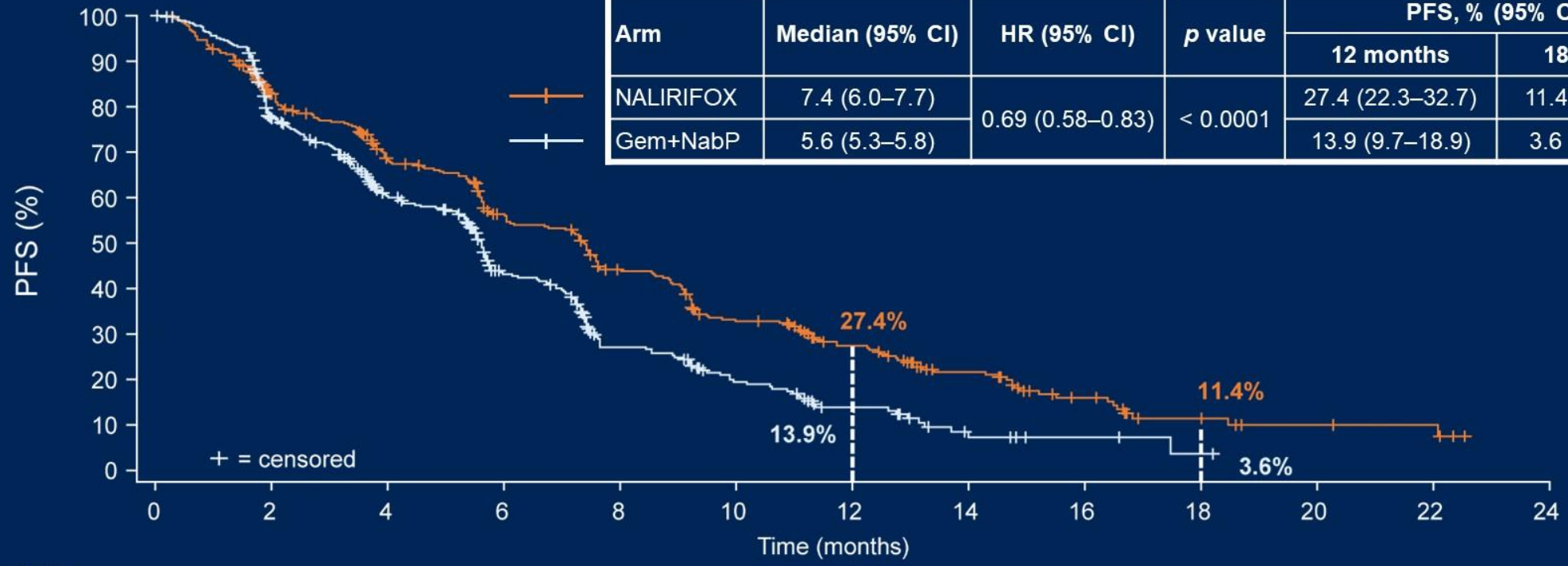
No. at risk:

NALIRIFOX	383	337	308	274	241	209	162	98	59	32	13	7	2	1	1	0
Gem+NabP	387	345	298	261	218	179	140	80	50	28	15	10	3	0	0	0

Hazard ratio and 95% CI based on a Cox proportional hazards regression model, stratified by ECOG PS (0 vs 1), region (North America vs ROW), liver metastases (yes vs no) per IRT. P boundary for efficacy claim *p* value < 0.048.
CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; Gem, gemcitabine; HR, hazard ratio; IRT, interactive response technology; ITT, intention-to-treat; NabP, nab-paclitaxel; NALIRIFOX, liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin; OS, overall survival; ROW, rest of world.

NAPOLI 3: PFS per investigator (ITT population)

Arm	Median (95% CI)	HR (95% CI)	*p* value	PFS, % (95% CI)	
				12 months	18 months
NALIRIFOX	7.4 (6.0–7.7)	0.69 (0.58–0.83)	< 0.0001	27.4 (22.3–32.7)	11.4 (7.1–16.9)
Gem+NabP	5.6 (5.3–5.8)			13.9 (9.7–18.9)	3.6 (0.5–12.3)



No. at risk:

NALIRIFOX	383	271	210	164	122	87	61	39	20	9	5	4	0
Gem+NabP	387	267	182	112	60	38	19	6	3	1	0	0	0

Hazard ratio and 95% CI based on a Cox proportional hazards regression model, stratified by ECOG PS (0 vs 1), region (North America vs ROW), liver metastases (yes vs no) per IRT. P boundary for efficacy claim *p* value < 0.048.
CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; Gem, gemcitabine; HR, hazard ratio; IRT, interactive response technology; ITT, intention-to-treat; NabP, nab-paclitaxel; NALIRIFOX, liposomal irinotecan + 5-fluorouracil/leucovorin + oxaliplatin; PFS, progression-free survival; ROW, rest of world.

However…does NALIRIFOX represent a substantial advance over FOLFIRINOX?

	NALIRIFOX (n=370)	FOLFIRINOX (n=171) *From PRODIGE/ACCORD ph III trial*
Median OS	**11.2 months**	**11.1 months**
OS at 12 months	45.6%	48.4%
OS at 18 months	26.2%	18.6%
Median PFS	7.4 months	6.4 months
ORR	41.8%	31.6 %
Grade 3/4 AEs	Neutropenia 23.8% / F&N 2.4% Diarrhea 20.3%, PSN (3.2 + 3.5% + 0.3%)	Neutropenia 45.7% / F&N 5.4% Diarrhea 12.7%, PSN 9.0%

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Oberer GI Trakt

Ösophagogastrale Adenokarzinome Immuntherapie (n = 3)

Pankreaskarzinom: neoadjuvant & palliativ 1st line (n = 2)

Gallenwege: KEYNOTE 966 & HER2-gezielte Therapien (n = 3)

KEYNOTE-966 Study Design
Randomized, Double-Blind, Phase 3 Trial

Key Eligibility Criteria

- Histologically confirmed extrahepatic or intrahepatic cholangiocarcinoma or gallbladder cancer
- Unresectable locally advanced or metastatic disease measurable per RECIST v1.1 by investigator review
- No prior systemic therapy[a]
- ECOG PS 0 or 1
- Life expectancy >3 months

R
1:1

Pembrolizumab 200 mg IV Q3W (maximum, 35 cycles)
+
Gemcitabine 1000 mg/m^2 IV on days 1 and 8 Q3W (no maximum)
+
Cisplatin 25 mg/m^2 IV on days 1 and 8 Q3W (maximum, 8 cycles)

Placebo IV Q3W for (maximum, 35 cycles)
+
Gemcitabine 1000 mg/m^2 IV on days 1 and 8 Q3W (no maximum)
+
Cisplatin 25 mg/m^2 IV on days 1 and 8 Q3W (maximum, 8 cycles)

Stratification Factors

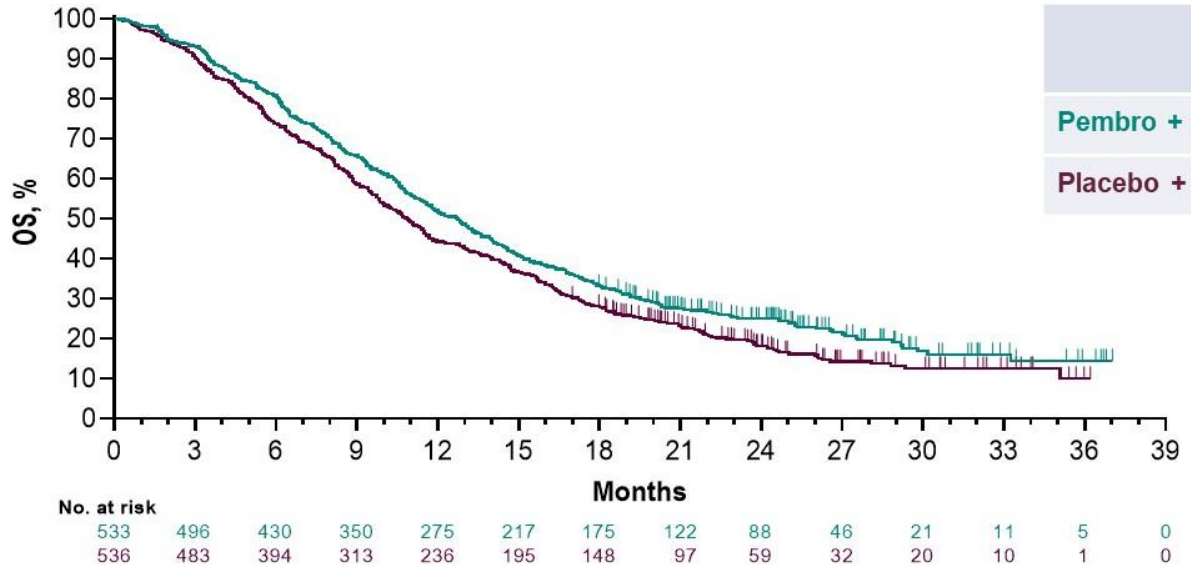
- Geographic region (Asia vs not Asia)
- Disease stage (locally advanced vs metastatic)
- Site of origin (extrahepatic vs gallbladder vs intrahepatic)

- **Primary End Point:** OS
- **Secondary End Points:** PFS, ORR, and DOR assessed per RECIST v1.1 by blinded, independent central review and safety
- **Prespecified Exploratory End Points:** PRO end points

Treatment was continued until disease progression, unacceptable toxicity, investigator decision, or, for pembrolizumab and cisplatin, the maximum number of cycles was reached.
[a]Neoadjuvant or adjuvant chemotherapy was permitted if it was completed ≥6 months before the diagnosis of unresectable or metastatic disease.
ClinicalTrials.gov identifier: NCT04003636.

Background

- In KEYNOTE-966, adding the PD-1 inhibitor pembrolizumab to gem/cis provided a statistically significant, clinically meaningful improvement in OS to patients as first-line therapy for biliary tract cancer (BTC)[1]



	Pts w/ Event	Median (95% CI), mo
Pembro + Gem/Cis	78%	12.7 (11.5-13.6)
Placebo + Gem/Cis	83%	10.9 (9.9-11.6)

HR 0.83 (95% CI, 0.72-0.95)
***P* = 0.0034**

Below the signficance boundary of *P* = 0.0200

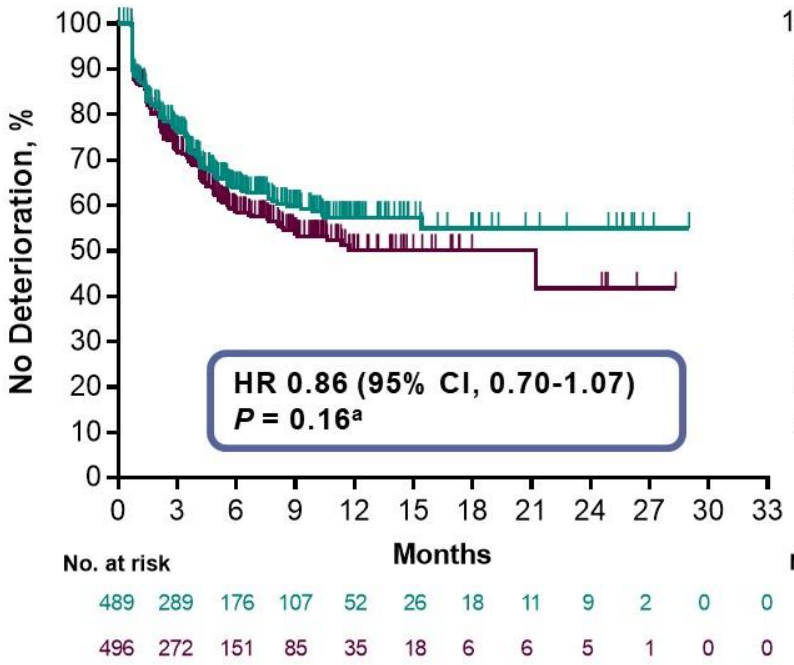
- KEYNOTE-966 showed similar safety profiles between the pembrolizumab and placebo groups[1]
  - 70% of patients treated with pembrolizumab + gem/cis had grade 3 or 4 treatment-related adverse events vs 69% for placebo + gem/cis

[1]Kelley et al. Lancet 2023; 2023;S0140-6736(23)00727-4.

EORTC QLQ-C30

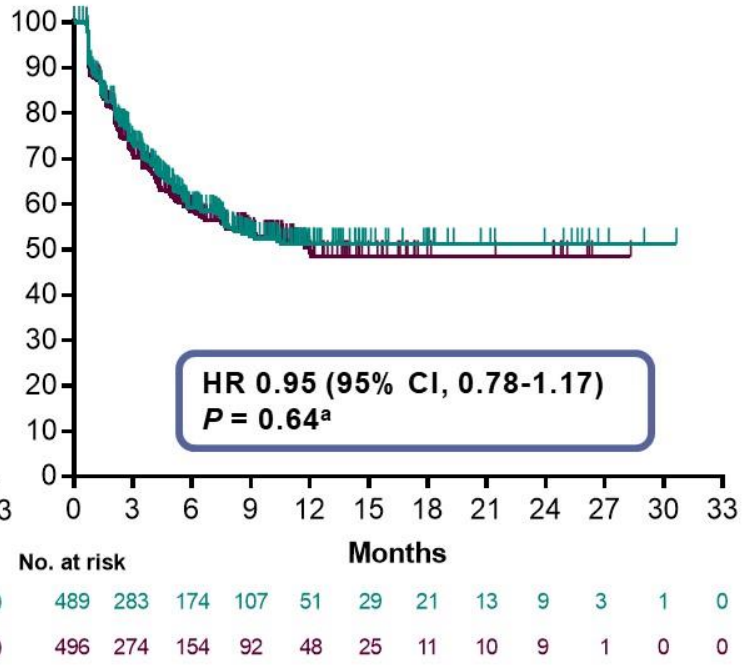
TTD Estimates in GHS/QoL, Physical Functioning and Role Functioning Domains

Global Health Status/Quality of Life



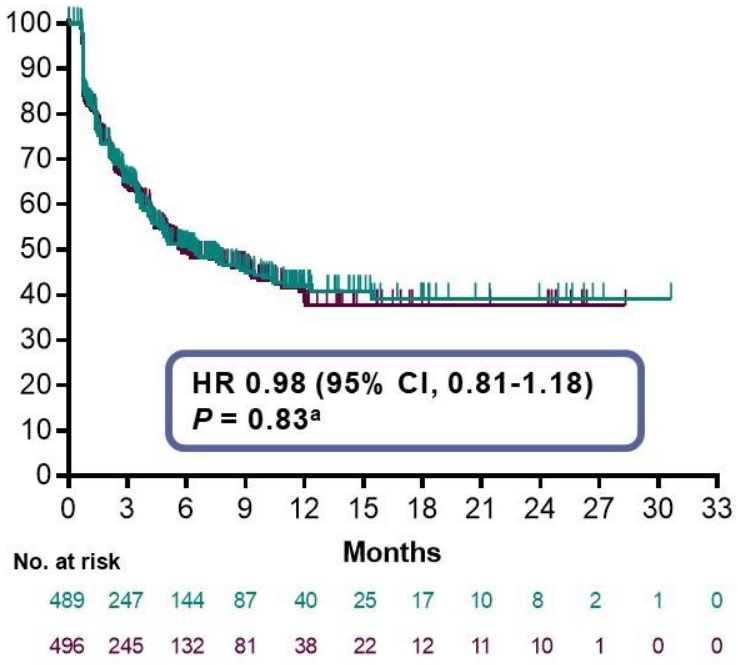
	Pts w/ Event	Median (95% CI), mo
Pembro + Gem/Cis	33%	NR (15.41, NR)
Placebo + Gem/Cis	37%	21.22 (8.31, NR)

Physical Functioning



	Pts w/ Event	Median (95% CI), mo
Pembro + Gem/Cis	37%	NR (7.69, NR)
Placebo + Gem/Cis	38%	11.99 (7.66, NR)

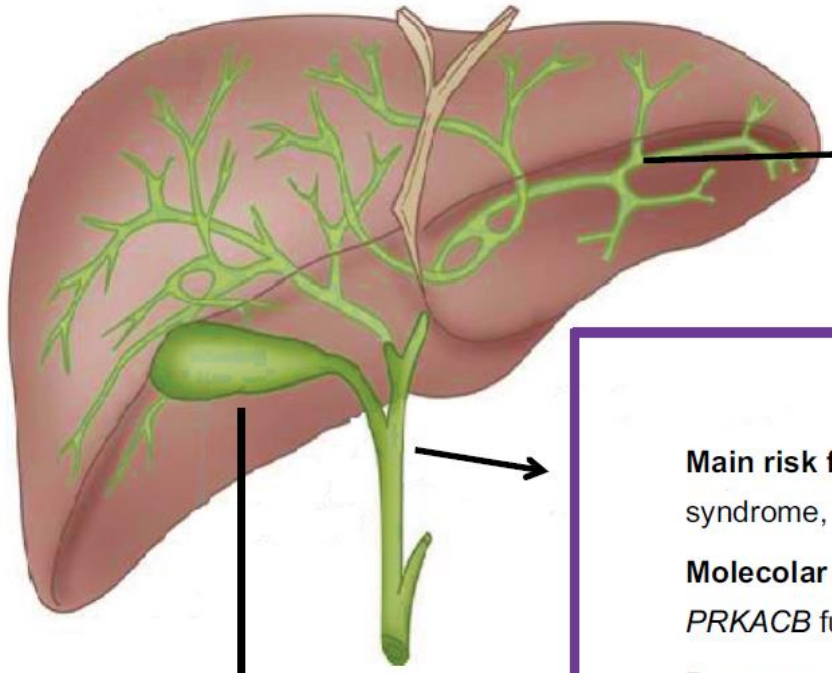
Role Functioning



	Pts w/ Event	Median (95% CI), mo
Pembro + Gem/Cis	45%	6.47 (4.63, 9.46)
Placebo + Gem/Cis	46%	5.75 (4.67, 9.30)

[a]P-values are nominal.
Data cutoff date: December 15, 2022.

Biliary tract cancer: Potentielle molekulare Targets



iCCA

Main risk factors: Cholangitis, obesity, diabetes, chronic hepatitis B/C, hepatolithiasis, Lynch syndrome

Molecolar mutations: *FGFR 1–3*, IDH 1/2, *BAP1*, *ARID1A* alteration, *EPHA2*

eCCA

Main risk factors: Cholangitis, Lynch syndrome, gallstones

Molecolar mutations: *PRKACA* or *PRKACB* fusion, *ELF3*, *ARID1B* mutation

Poor prognosis subtype with high immune checkpoint activity: *TP53, BRCA 1/2, PIK3CA mutation*

GBC

Main risk factors: Obesity, diabetes, chronic cholecystitis, gallstones

Molecolar mutation: *EGFR, ERBB3, PTEN, ARID2, MLL2, MLL3, TERT* promoter mutation, APOBEC signature

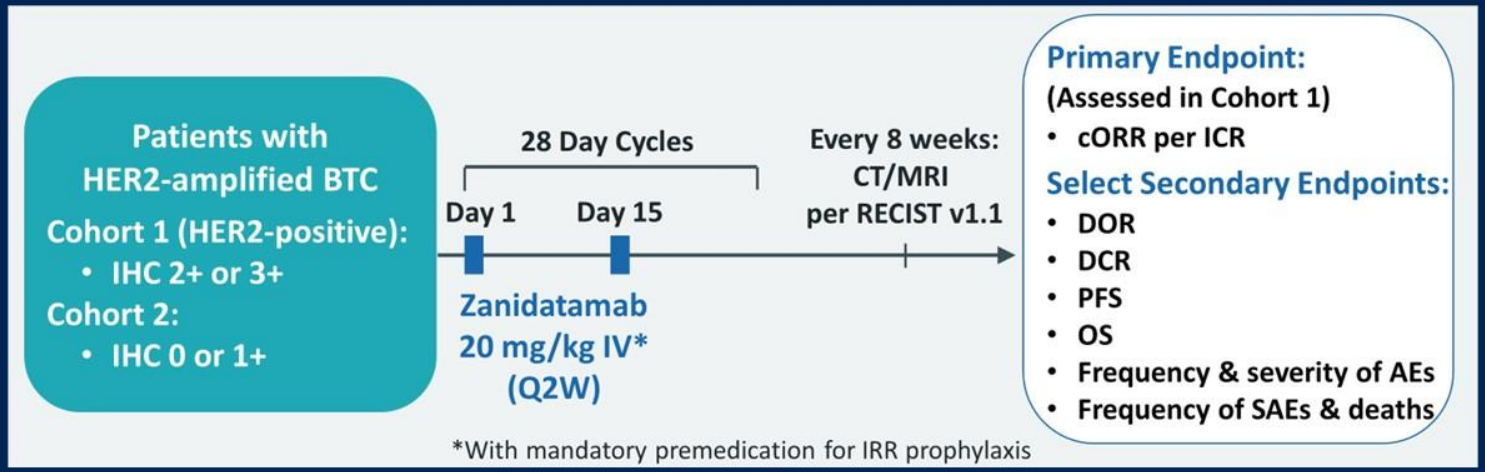
iCCA and eCCA (shared): *KRAS, SMAD4, ARID1A, GNAS*

HERIZON-BTC-01 Study Design

- Phase 2b study of zanidatamab monotherapy in patients with HER2-amplified BTC

Key Eligibility Criteria

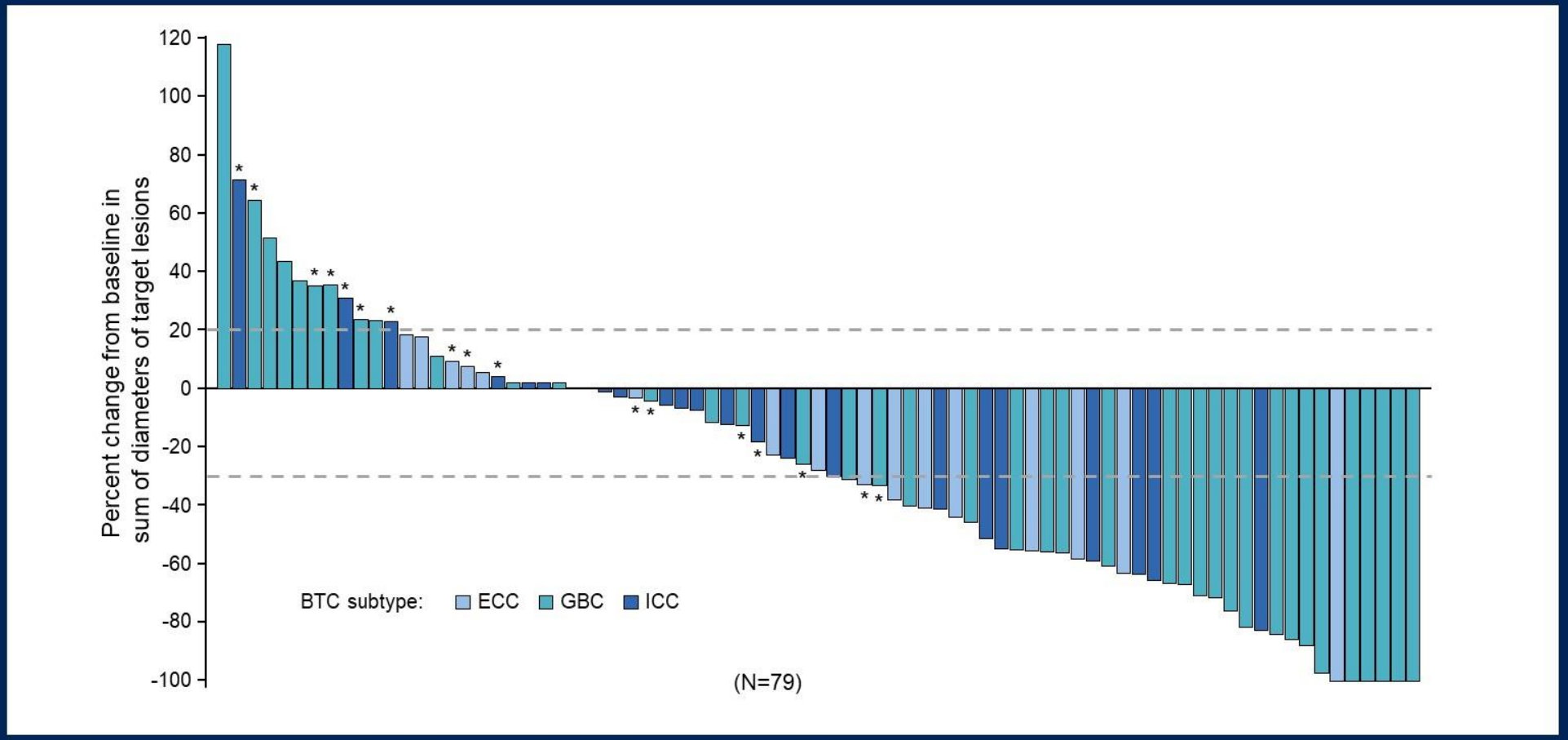
- Locally advanced or metastatic BTC[1]
- Tissue required to confirm HER2 status by central lab
- Progressed after treatment with a gemcitabine-containing regimen
- No prior HER2-targeted therapies
- ECOG PS of 0 or 1



[1] Excludes ampullary

AE = adverse event; cORR = confirmed objective response rate; CT = computed tomography scan; DCR = disease control rate; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group performance status; ICR = independent central review; IHC = immunohistochemistry; IRR = infusion-related reaction; IV = intravenous; MRI = magnetic resonance imaging; OS = overall survival; Q2W = every two weeks; RECIST= Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event.

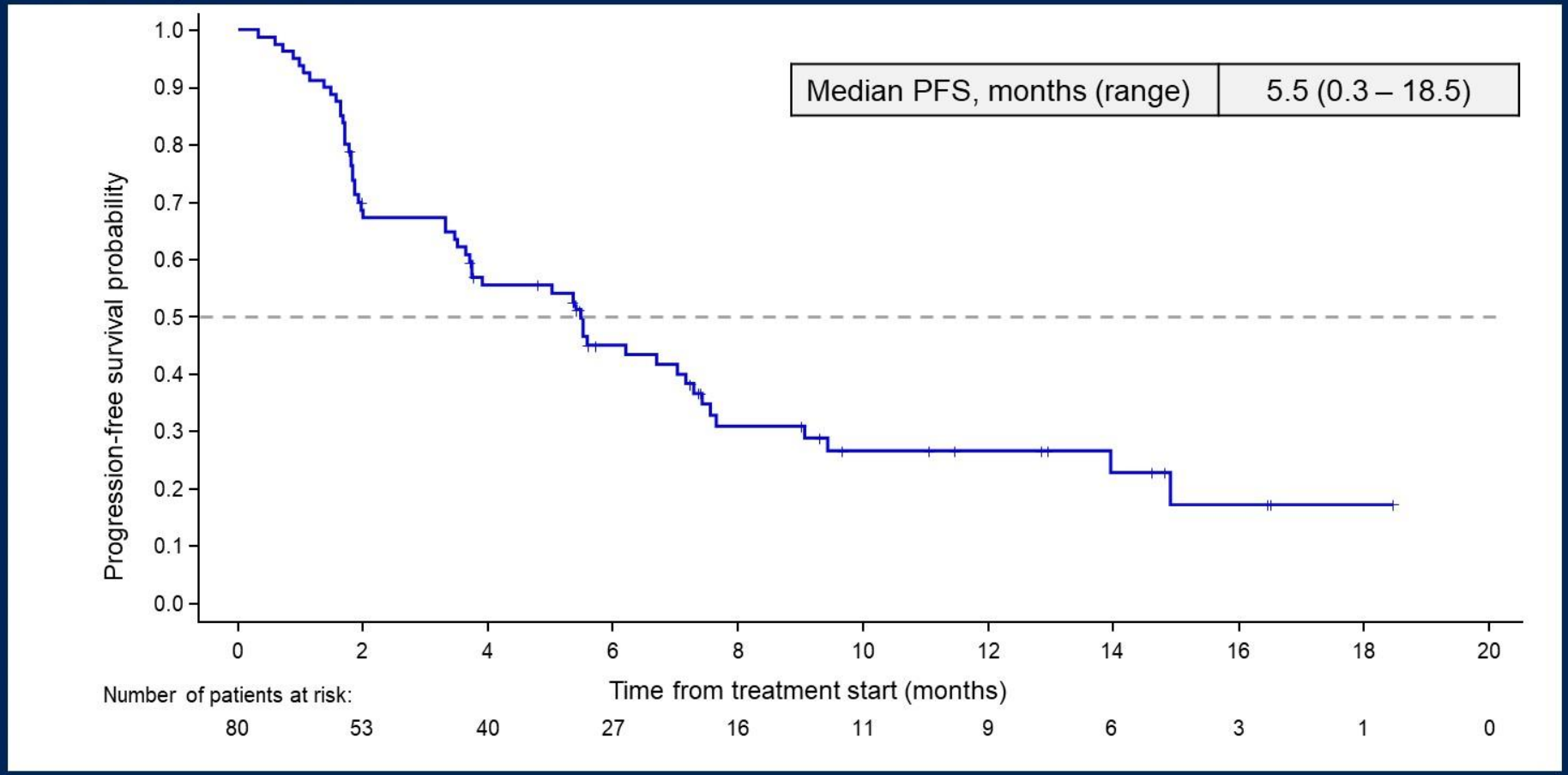
Majority of evaluable patients (68.4%) had a decrease in target lesions (Cohort 1)



* Indicates patients with IHC 2+ status; all other patients had IHC status of 3+.
Dotted lines indicate 20% increase and 30% decrease in sum of diameters of target tumors.

Progression-free Survival in Patients with HER2-positive BTC (Cohort 1)

- OS data not yet mature



Study Design

- SGNTUC-019 (NCT04579380) is an open-label phase 2 basket study evaluating antitumor activity and safety of tucatinib and trastuzumab[a] in patients with HER2-altered solid tumors

Key eligibility criteria

- HER2 overexpression, amplification, or mutation per IHC/ISH or NGS testing determined locally
- Unresectable locally advanced or metastatic cancer
- Baseline measurable disease
- Previously treated with ≥1 prior systemic treatment for locally advanced or metastatic disease
- No prior HER2-directed therapy[b]

- Cohort 1: Cervical (overexpression or amplification)
- Cohort 2: Uterine (overexpression or amplification)
- **Cohort 3: Biliary Tract (overexpression or amplification)[c]**
- Cohort 4: Urothelial (overexpression or amplification)
- Cohort 5: Nonsquamous NSCLC (overexpression or amplification)
- Cohort 6: Other solid tumors (overexpression or amplification)
- Cohort 7: Nonsquamous NSCLC (mutation)
- Cohort 8: Breast (mutation)
- Cohort 9: Other solid tumors (mutation)

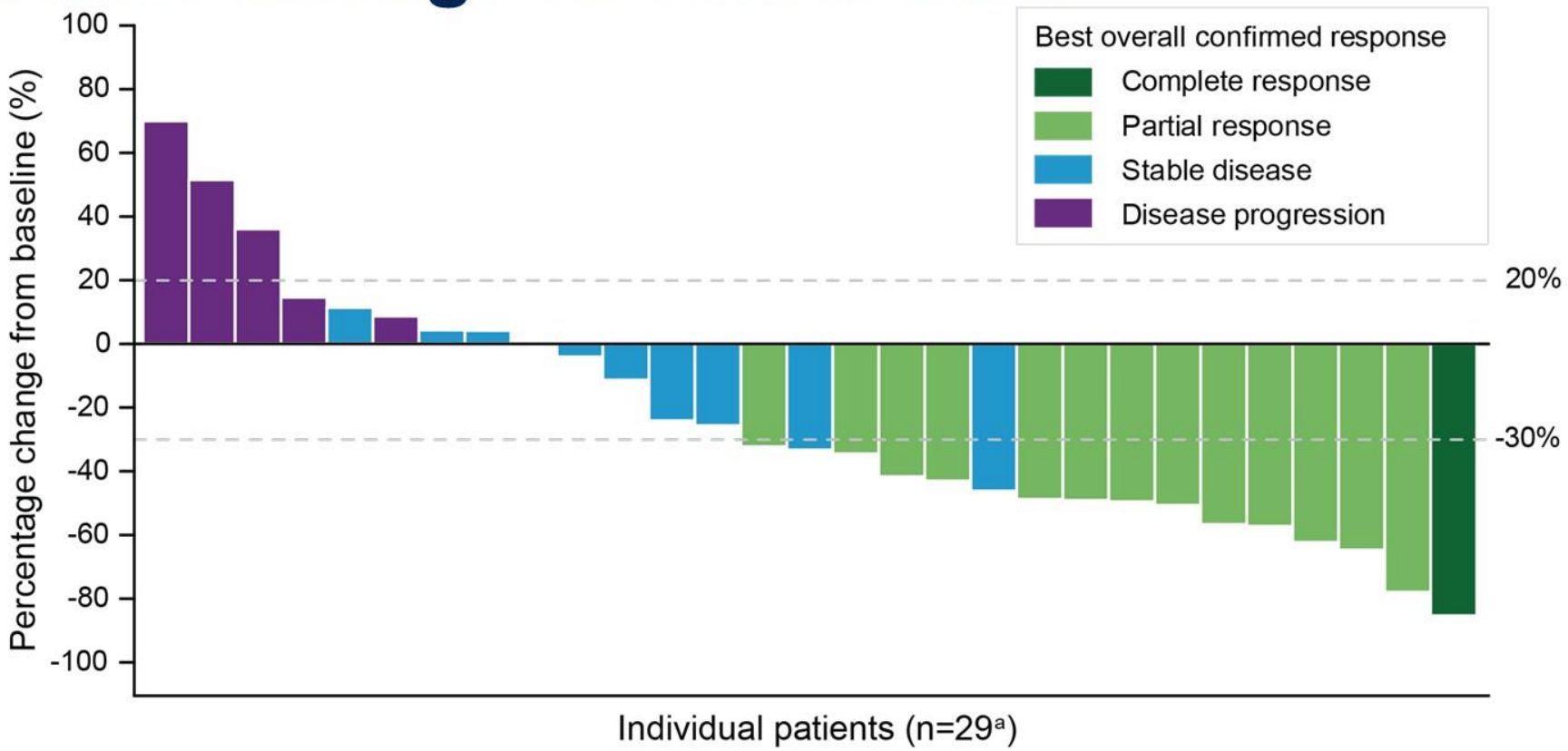
Outcomes

Primary endpoint:
Confirmed ORR per RECIST 1.1 by investigator

Secondary endpoints:
Safety, DCR, DOR, PFS, and OS

a Tucatinib dose: 300 mg PO BID; trastuzumab dose: 6 mg/kg IV Q3W (loading dose of 8 mg/kg C1D1); each treatment cycle is 21 days. b Except for patients with uterine serous carcinoma or HER2-mutated gastroesophageal cancer without HER2-overexpression or amplification. c The cohort aimed to enroll up to 30 patients, a number calculated per the 90% exact CI given a range of expected confirmed ORR of 10% to 30%.
BID, twice daily; C1D1, Day 1 of Cycle 1; DCR, disease control rate; DOR, duration of response; IHC, immunohistochemistry; ISH, in situ hybridization; IV, intravenous; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

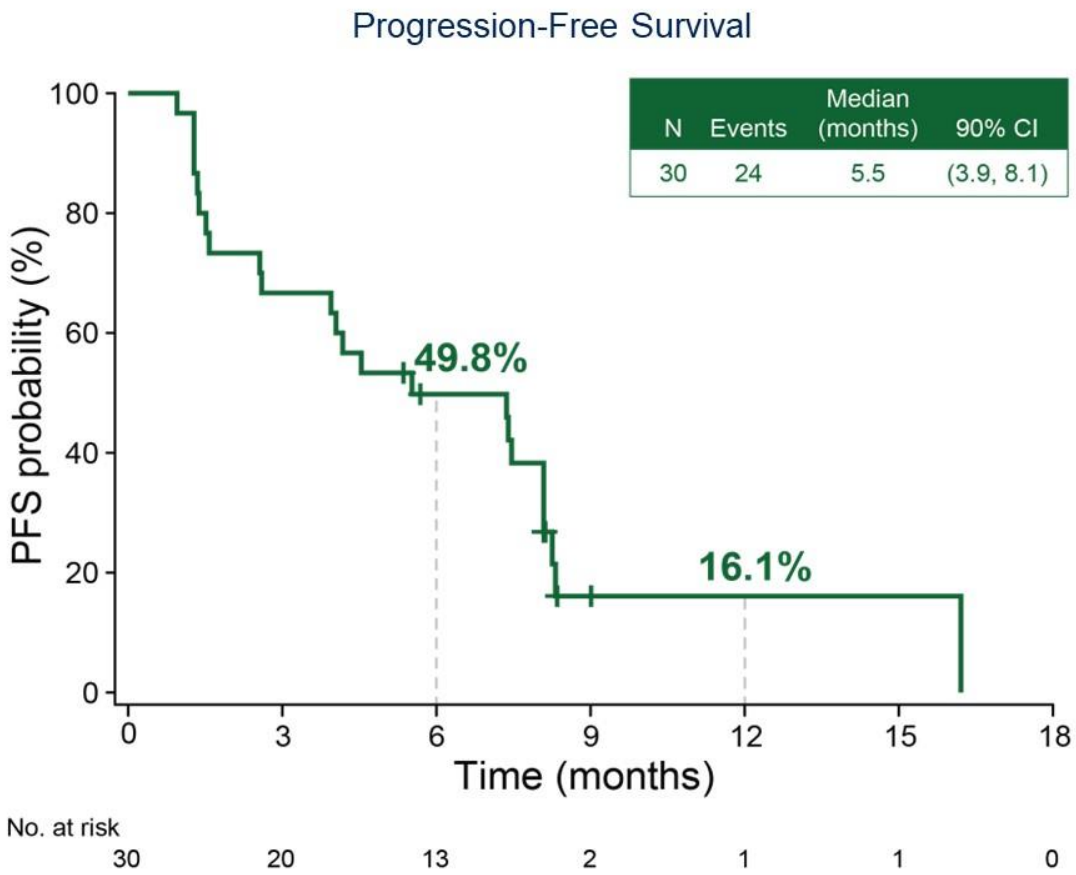
Maximum Change in Tumor Size

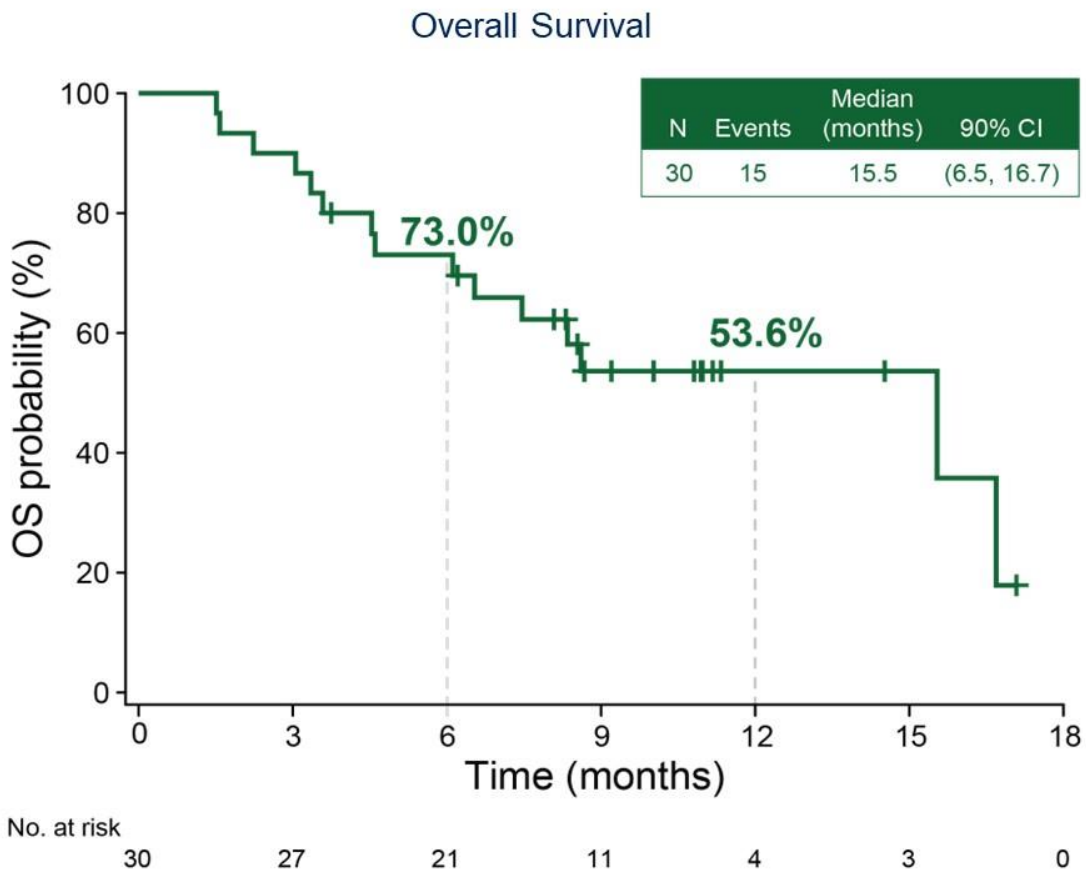


Twenty-one patients (70.0%[b]) had a reduction in tumor size
Median time to first response was 2.1 months (range, 1.2-4.3)

Data cutoff: Jan 30, 2023.
a Excludes 1 patient with no postbaseline response assessment. b Percentage was calculated with 30 as the denominator.

Progression-Free Survival and Overall Survival





Data cutoff: Jan 30, 2023.
PFS, progression-free survival; OS, overall survival.

PRESENTED BY: Yoshiaki Nakamura, MD, PhD

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Gastrointestinale Tumoren

Post ASCO 2023

Danke !

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