

Adjuvante Therapie Colon-Ca

Claus-Henning Köhne

Universitätsklinik Onkologie und Hämatologie

Oldenburg

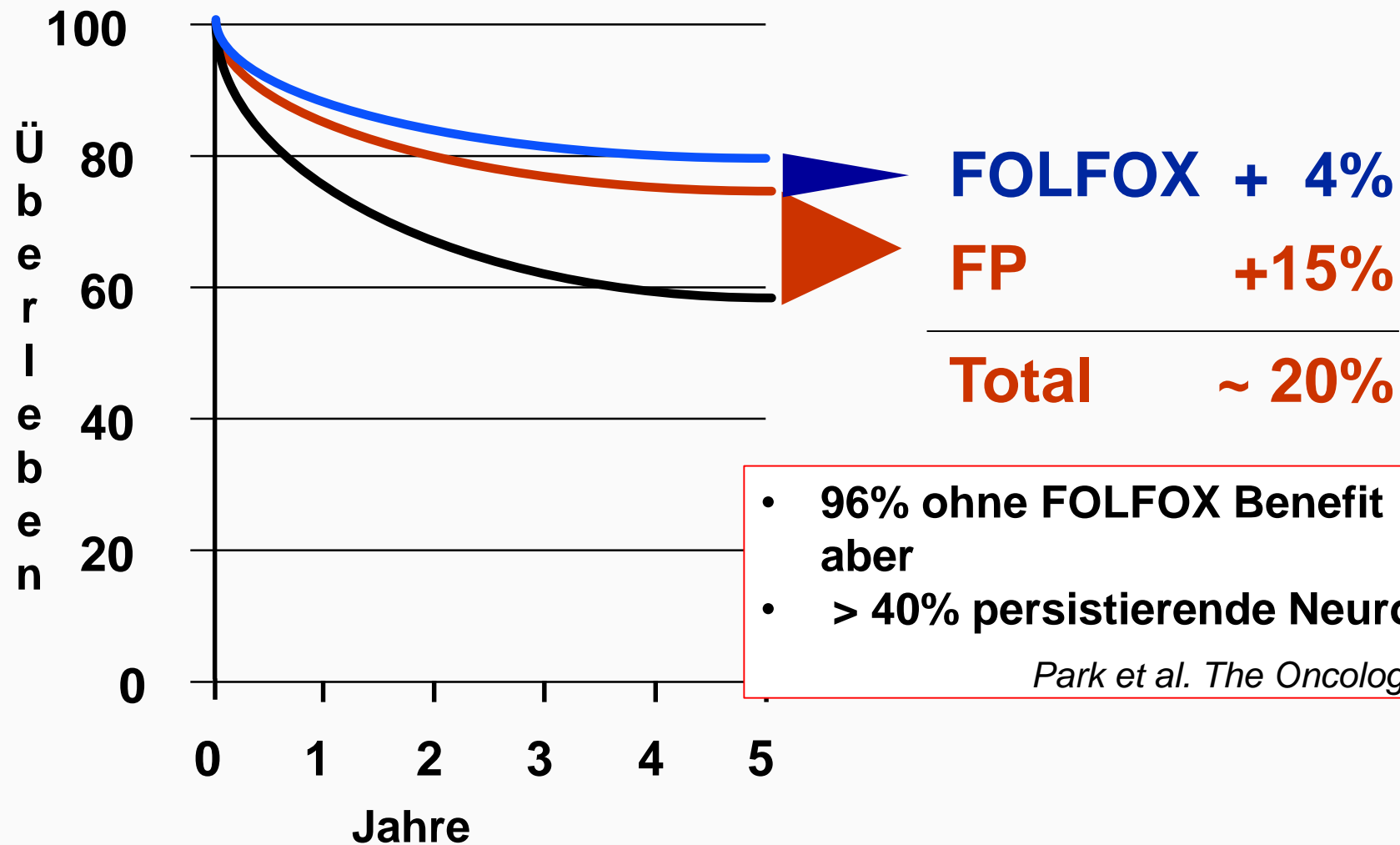


CONFLICT OF INTEREST

Claus-Henning Köhne

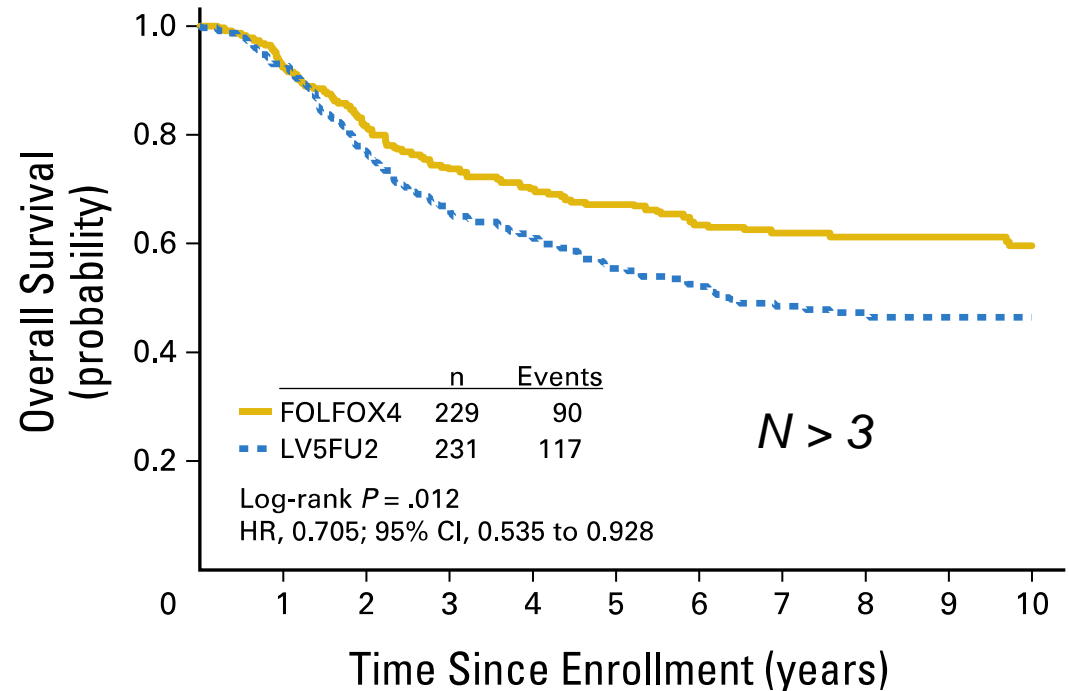
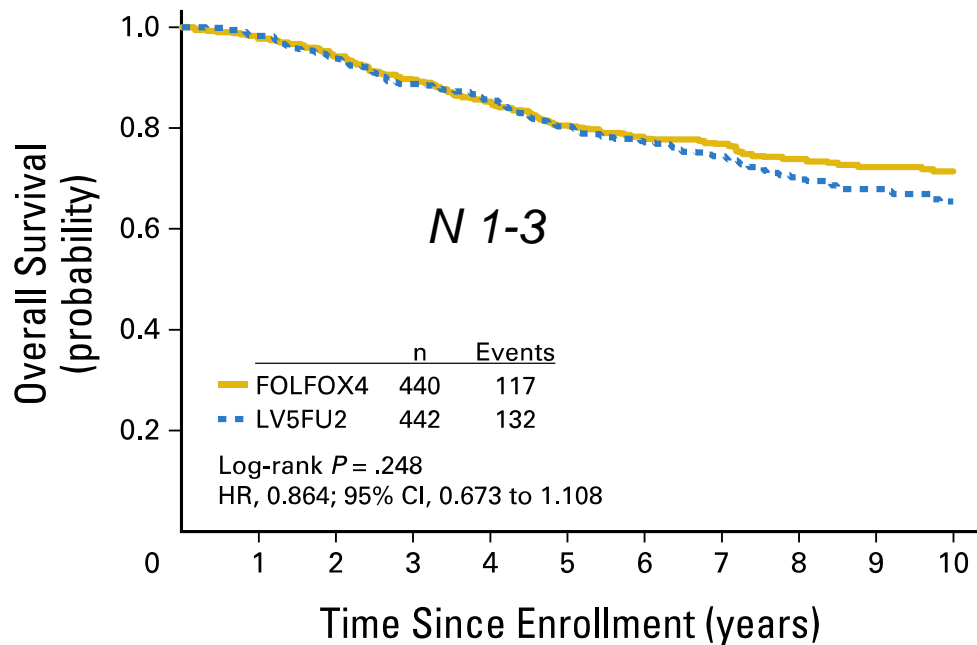
- **Personal financial interests (Vortragshonorare)**
- Lilly, Merck Kg Darmstadt, Servier, BMS
- **Institutional financial interests**
- Pfizer, Novartis, Roche, MerckKG Darmstadt, Servier, BMS, Astra Zeneca, Lilly
- **Non-financial interests**
- Berater EMA,
Wilsede Schule for Onkologie / Hämatologie / Paliativmedizin

Adjuvante Chemotherapie im Stadium III Colon-Ca



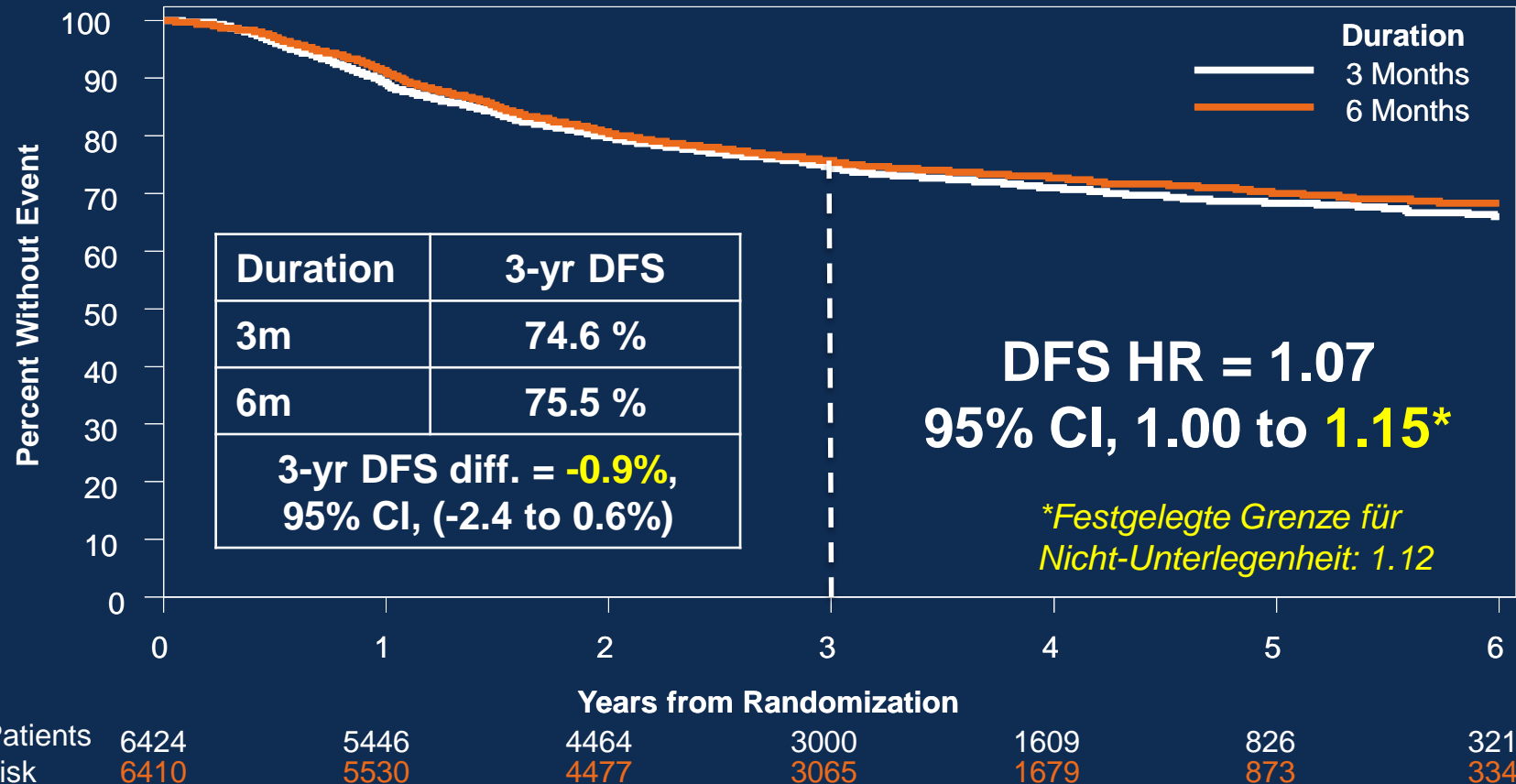
Adjuvante Therapie mit 5FU/Oxaliplatin in Colon Cancer MOSAIC Studie Stadium III pT3-4 N+ 10 Jahre Follow-up

6 Monate LV5FU2 oder FOLFOX4



Dauer der adjuvanten Therapie im Stadium III Colon-Ca

IDEA Studie 3 vs 6 Monate FOLFOX

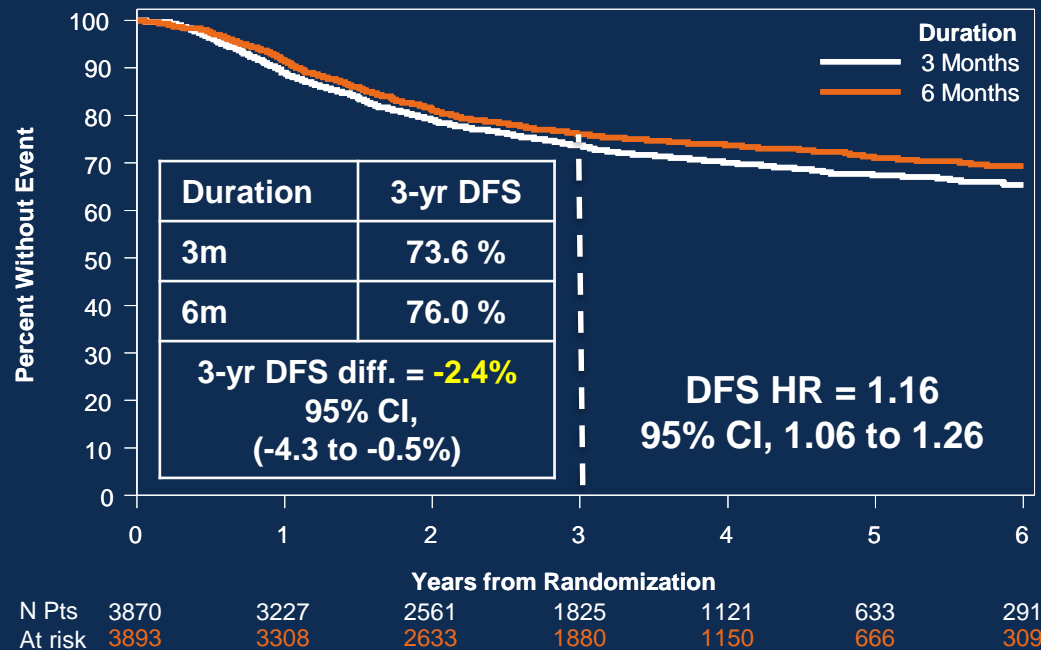


Presented by: Qian Shi, PhD on behalf of IDEA collaborators

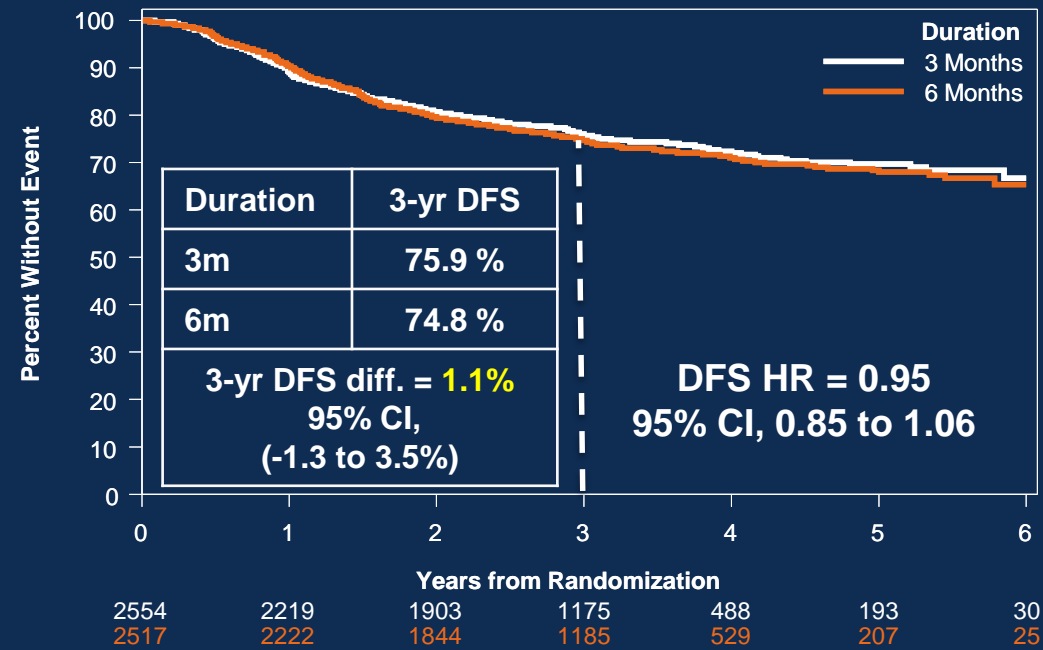
Dauer der adjuvanten Therapie im Stadium III Colon-Ca IDEA Studie 3 vs 6 Monate FOLFOX



FOLFOX



CAPOX



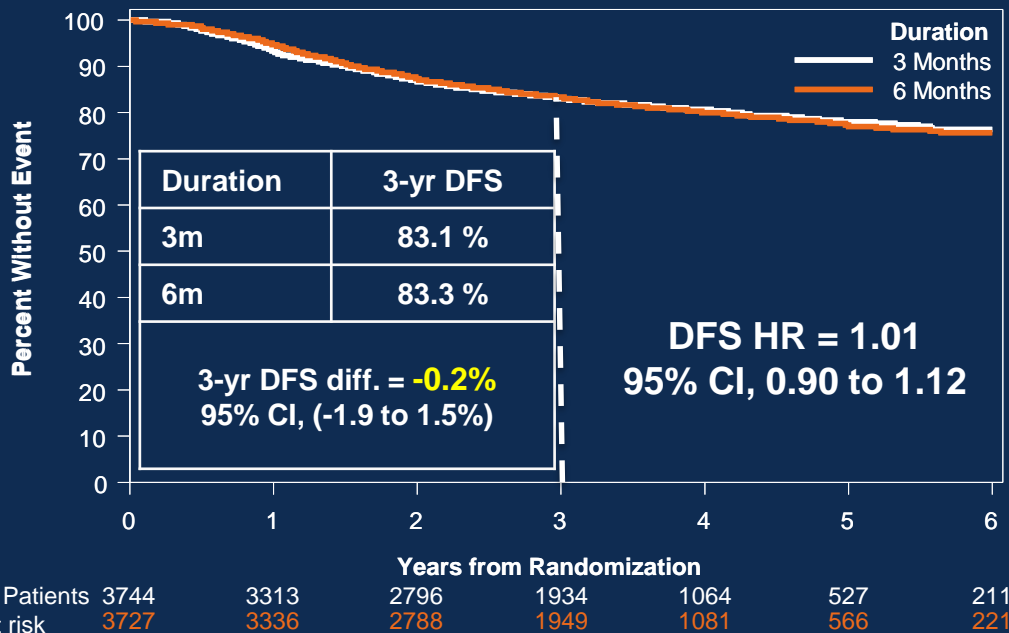
Interaction p-value = 0.0051

Presented by: Qian Shi, PhD on behalf of IDEA collaborators

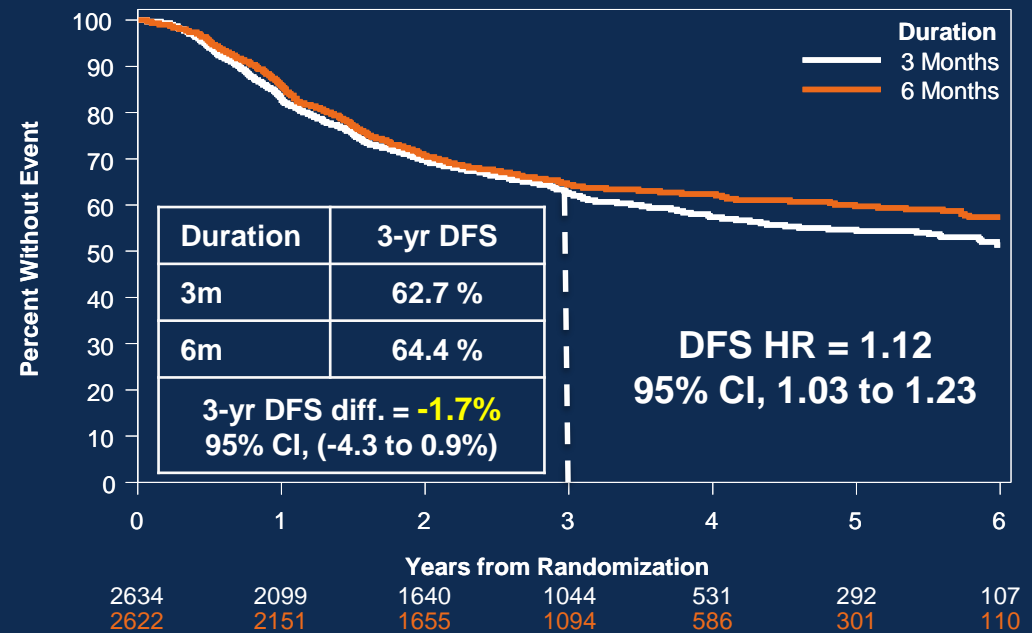
Dauer der adjuvanten Therapie im Stadium III Colon-Ca IDEA Studie 3 vs 6 Monate FOLFOX



T1-3 N1 (58.7%)



T4 or N2 (41.3%)



Interaction p-value = 0.11

Presented by: Qian Shi, PhD on behalf of IDEA collaborators

Adjuvante Therapie des Colon-Ca im UICC Stadium III

Risiko Gruppe	Niedriges Risiko (T1-3 N1) ~60%	3 Monate CAPOX oder FOLFOX	6 Monate Inf.FU/FA
	Hohes Risiko (T4 and / or N2) ~40%	6 Monate FOLFOX	3 Monate FOLFOX oder CAPEOX oder 3 Monate FOLFOX/CAPEOX + 3 Monate FU/FA

3=6 Monate

Mögliche
Alternative
weniger gut
abgesichert

3 Monate sind
6 Monate
unterlegen

ESMO Special Symposium

Wie sollten “high risk” Stadium II Colon-Ca Patienten adjuvant behandelt werden?

- Gar nicht ?
- Fluoropyrimidin?
- FOLFOX ?
- Ist MSI wichtig ?



Onkologisches Zentrum
Oldenburg



OLDENBURG

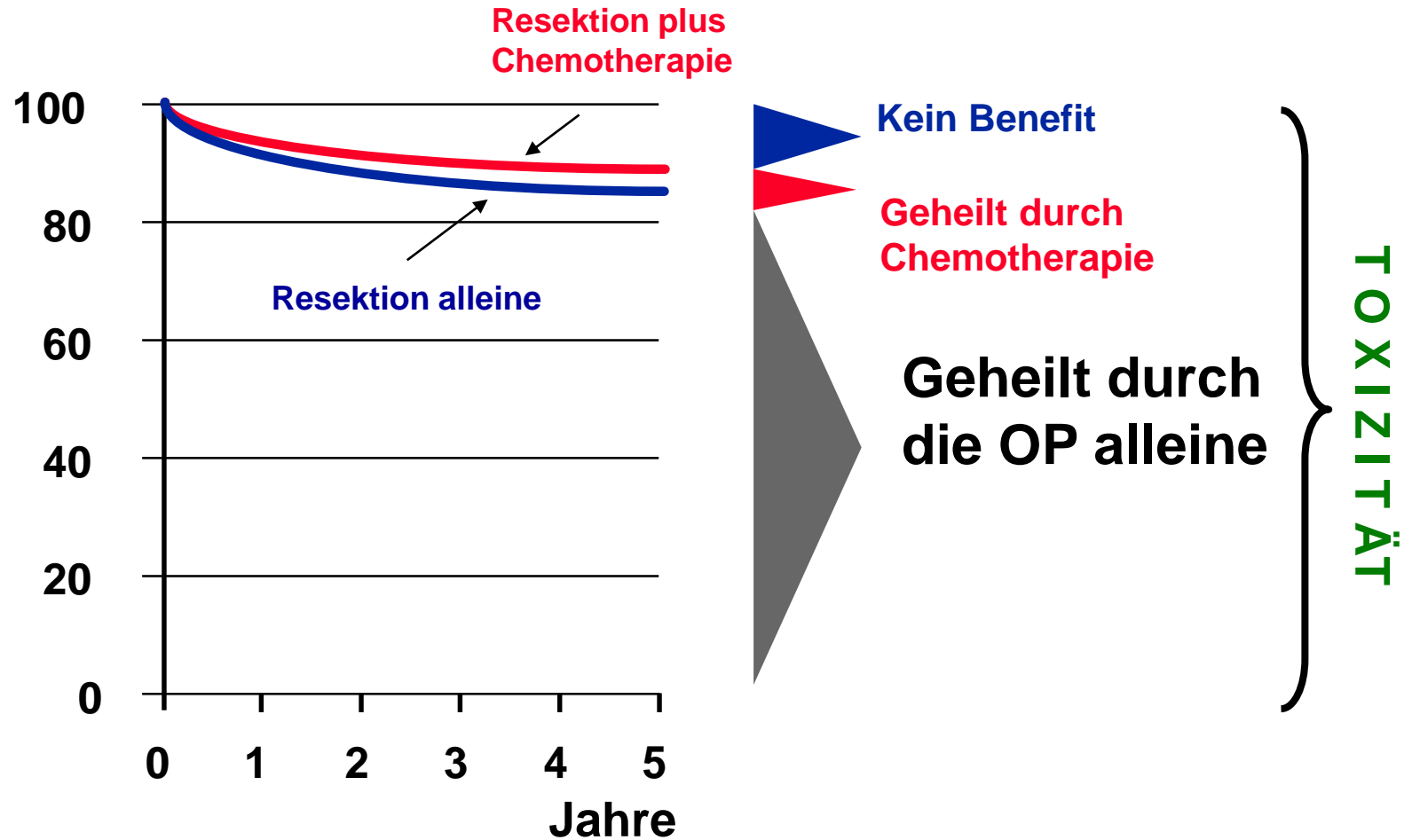


ems

european medical school
oldenburg-groningen

Patienten Gruppen im Stadium II Colon-Ca

Adjuvante Therapie

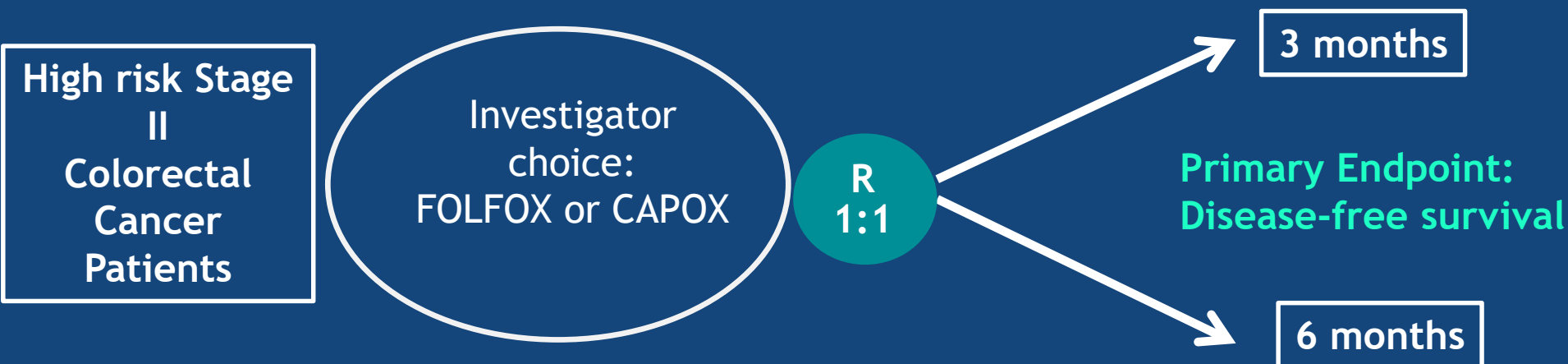


Definition of High Risk Stage II Disease

- T4
- Poorly differentiated
- Invasion (vascular/lymphatic/perineural)
- Inadequate nodal harvest (<10 SCOT, <12 TOSCA, HORG, ACHIEVE)
- Obstruction
- Perforation

Although no consensus exists on the definition of high-risk stage II colon cancer, the European Society for Medical Oncology and American Society of Clinical Oncology guidelines include T4 lesions, perforation, and number of analyzed lymph nodes fewer than 10 or 12 as high-risk characteristics.

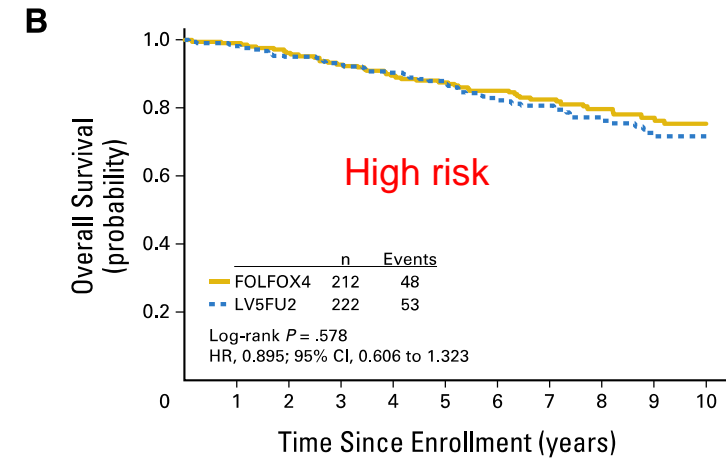
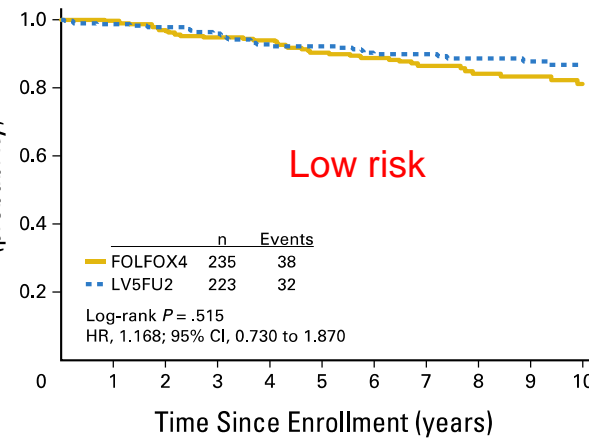
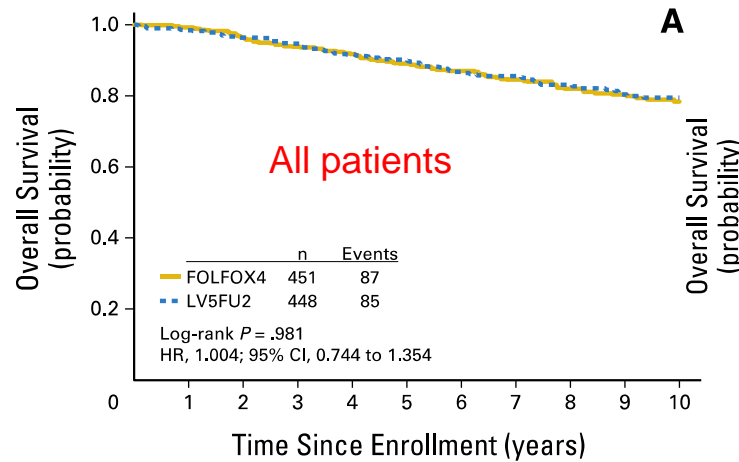
Study Schema To evaluate the *non-inferiority* of 3m vs 6m



Prospective analysis of *four* concurrently conducted phase III randomized trials

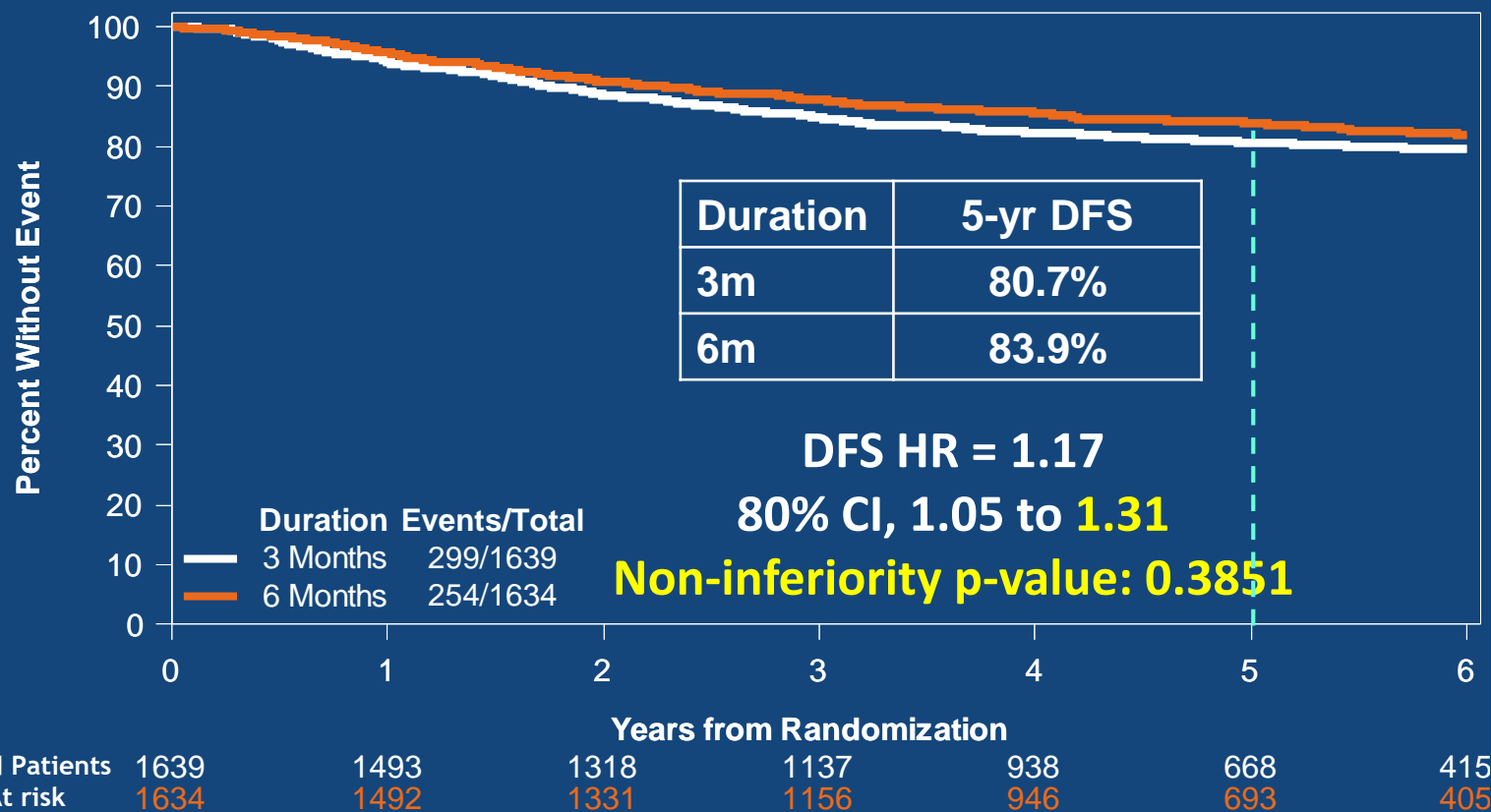
Trial	Regimen(s)	HR stage II Colorectal Cancer Patients	Enrolling Country
TOSCA	CAPOX or FOLFOX4	1268	Italy
SCOT	CAPOX or mFOLFOX6	1078*	UK, Denmark, Spain, Australia, Sweden
HORG	CAPOX or FOLFOX4	413	Greece
ACHIEVE2	CAPOX or mFOLFOX6	514	Japan

Updated MOSAIK Data Low Risk & High Risk Stage II FOLFOX vs. FU/LV



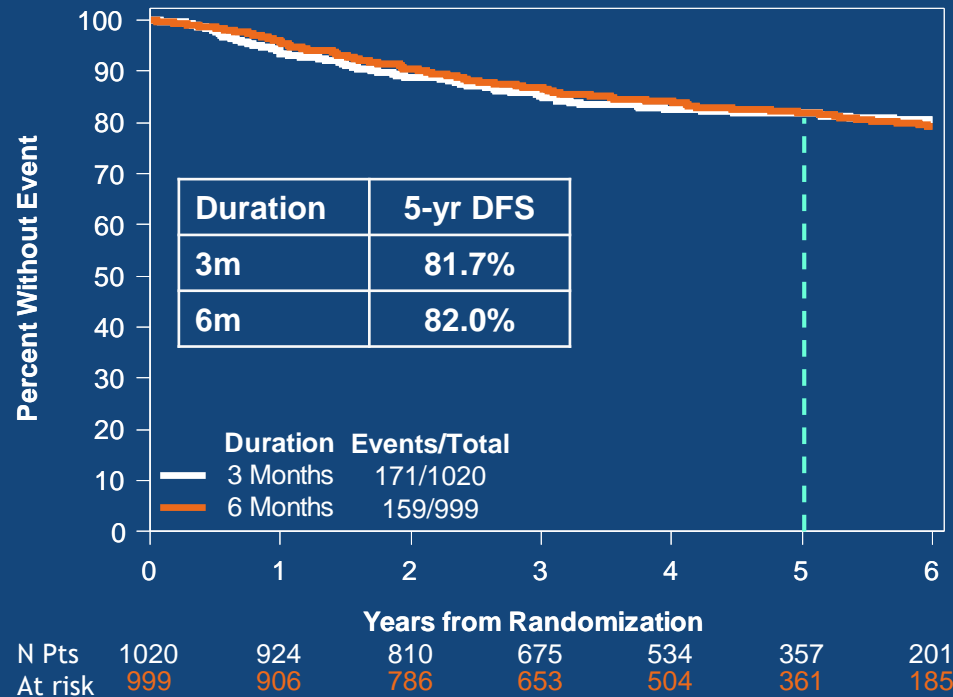
		5 y DFS		6y OS	
	N Pat	HR	P-value	HR	P-value
high risk	569	0.72 0.51-1.01	.062	0.91 0.66-.97	.648
low risk	330	1.36 0.76-2.45	1.01	1.36 0.67-2.5	.399

Results: Primary DFS Analysis (mITT)

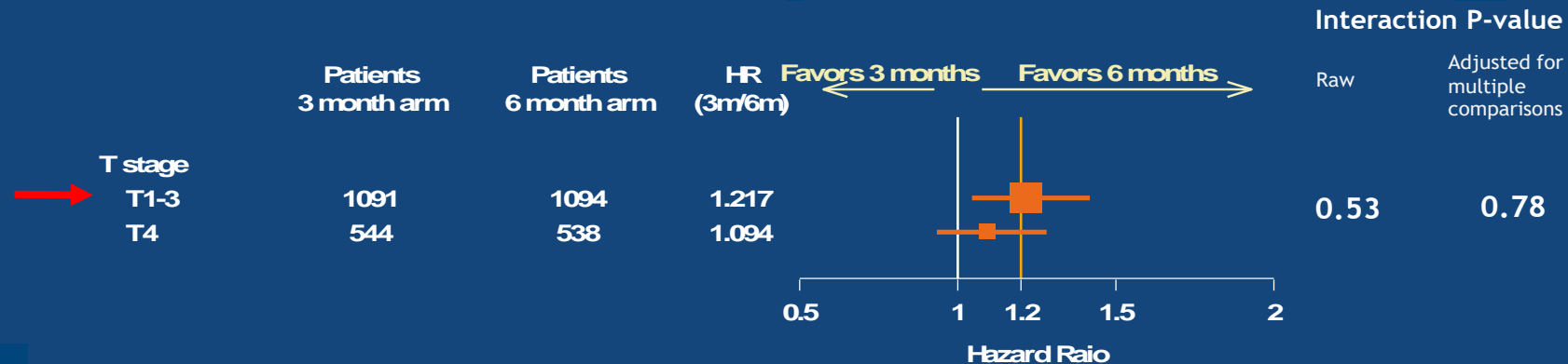
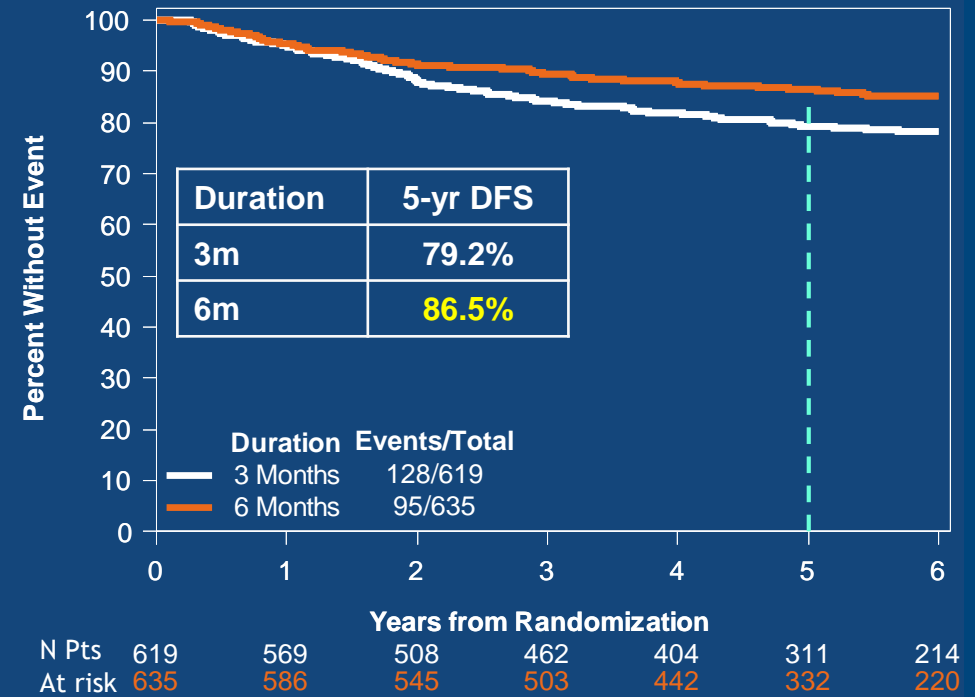


Results: DFS Comparison by Regimen

CAPOX



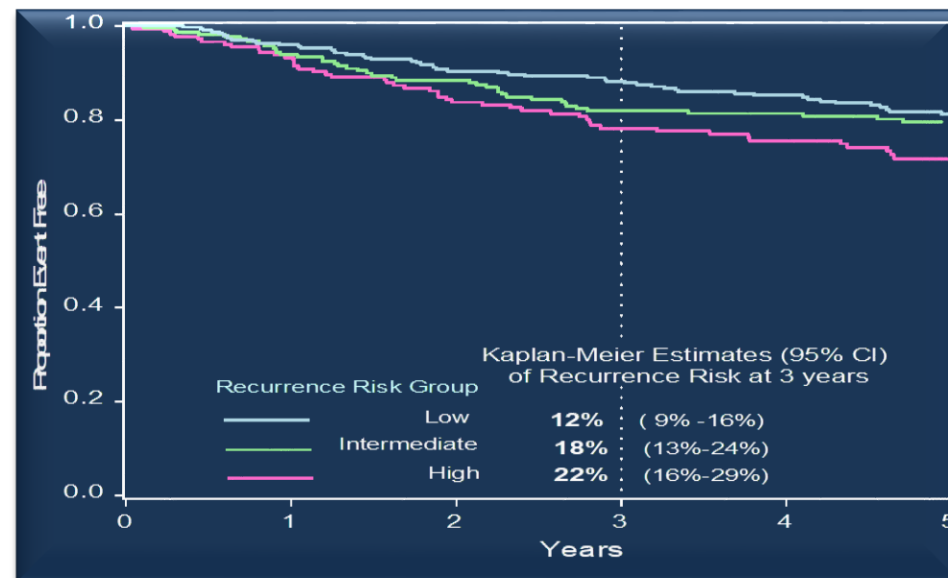
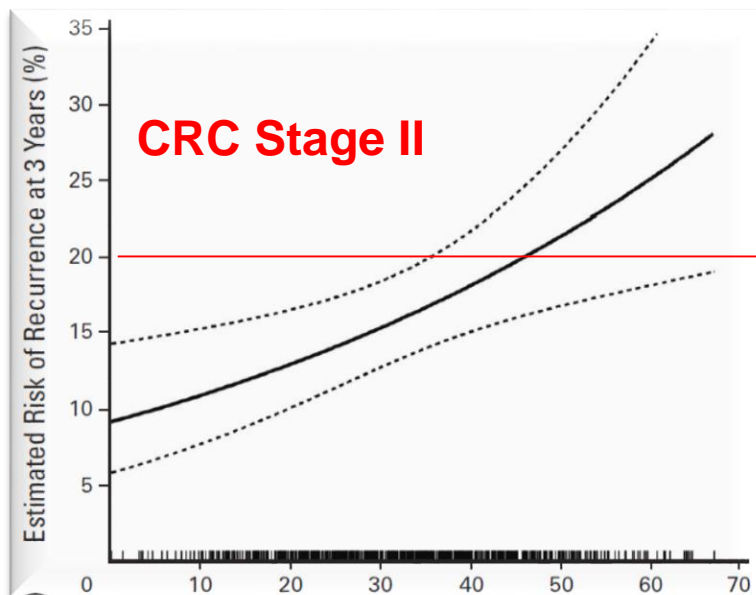
FOLFOX



Stadium II Colon-Ca

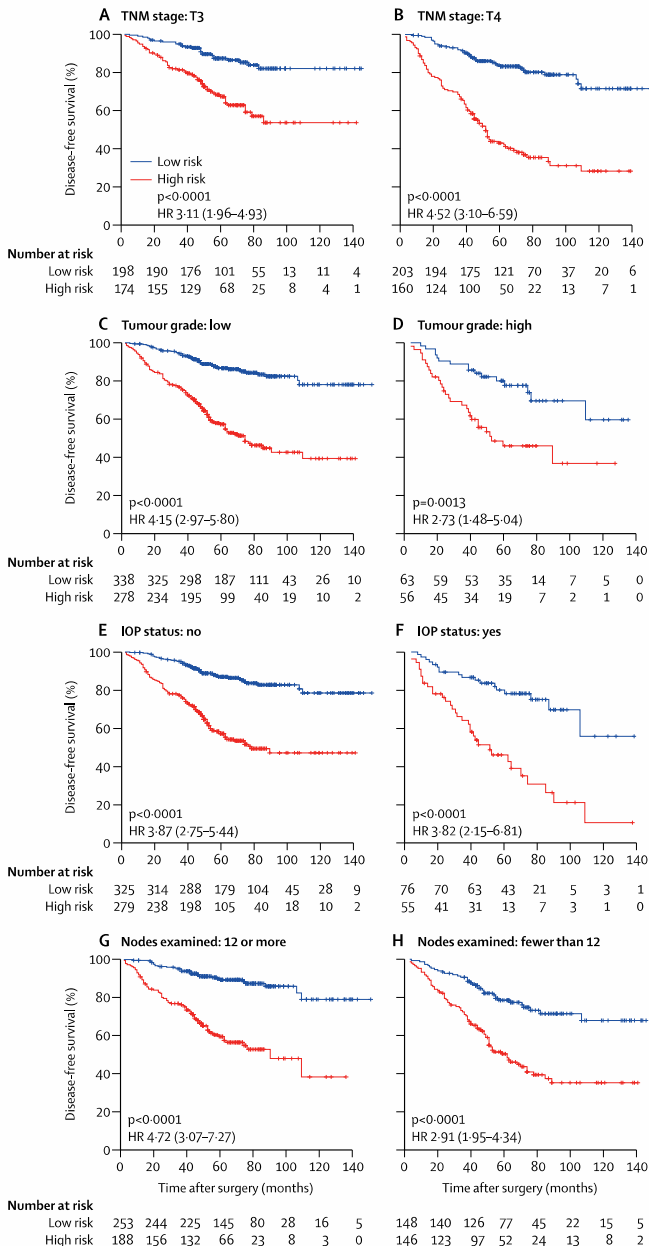
**Gibt es eine bessere
Definition eines
„high risk“ Patienten?**

Gen-Expression Assays (OncoType Dx)

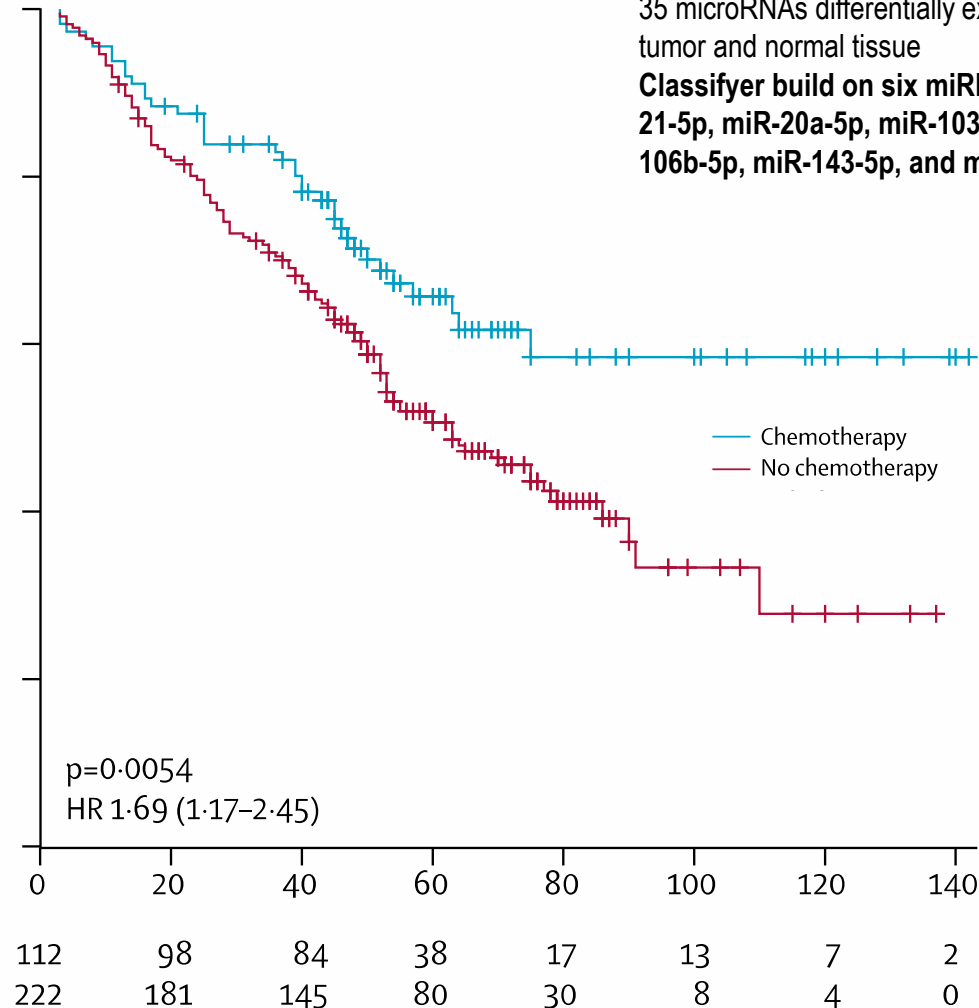


	Recurrences/Patients		Statistics		RR & 95% CI	
	Chemotherapy	None	(O-E)	Var.	(chemotherapy:none)	
By chemotherapy benefit group:						
Low benefit	24 of 153 (15.7%)	42 of 140 (30.0%)	-12.8	16.2	0.45 (0.28 to 0.74)	
Intermediate benefit	15 of 245 (6.1%)	33 of 267 (12.4%)	-8.2	12.0	0.51 (0.29 to 0.89)	
High benefit	30 of 327 (9.2%)	33 of 304 (10.9%)	-2.7	15.7	0.84 (0.51 to 1.38)	
■ Subtotal:	69 of 725 (9.5%)	108 of 711 (15.2%)	-23.8	44.0	0.58 (0.43 to 0.78)	
					2P = .0003	
					Chemotherapy better	None better

Prognostic and predictive value of a microRNA signature in stage II colon cancer: a microRNA expression analysis

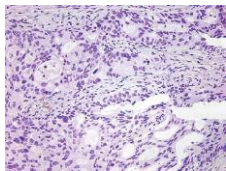


miRNA-defined high risk

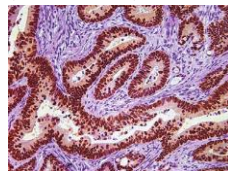


Zhang et al. Lancet Oncol 2013

A Specimen without CDX2 Nuclear Expression

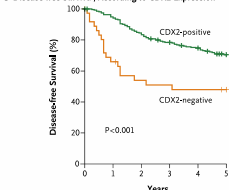


B Specimen with CDX2 Nuclear Expression



Prognostic and predictive value of CDX2 in stage II colon cancer

C Disease-free Survival, According to CDX2 Expression

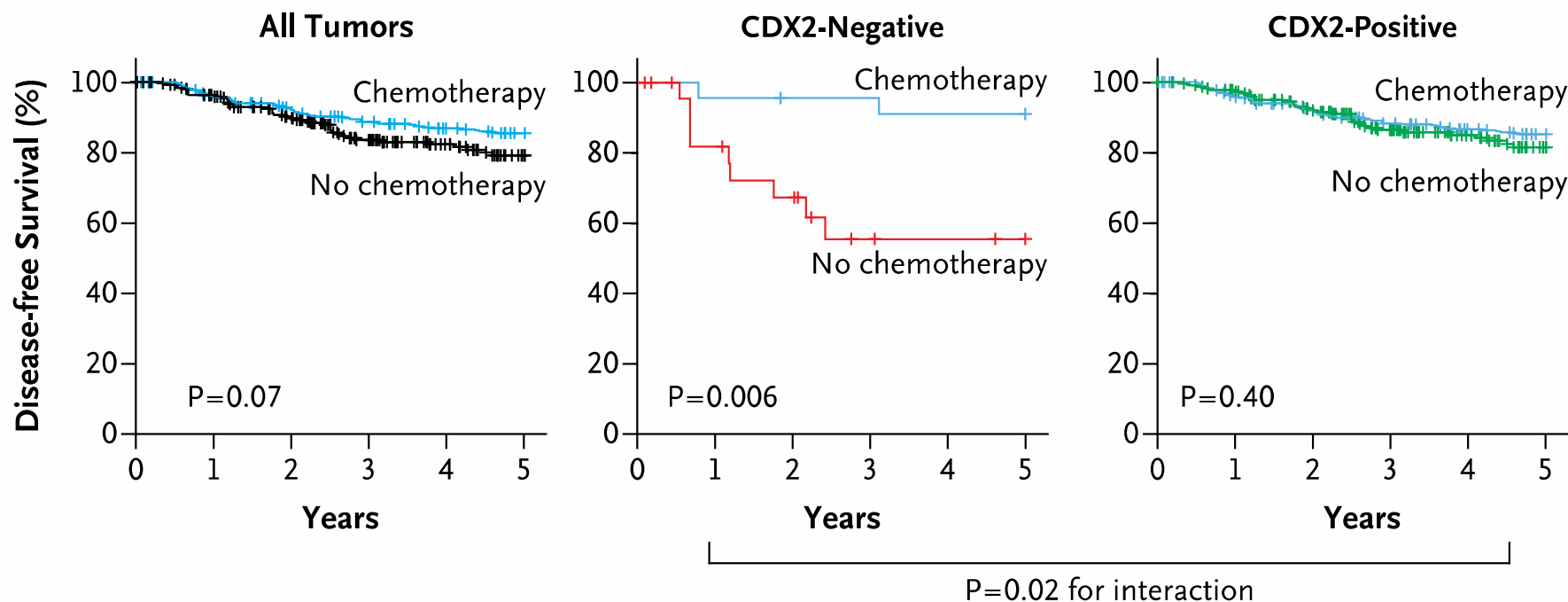


No. at Risk
CDX2-positive 276 258 225 199 182 150
CDX2-negative 38 23 18 17 16 15

D Multivariate Analysis

Subgroup	Hazard Ratio (95% CI)	P Value
CDX2-negative	2.42 (1.36–4.29)	0.003
Tumor stage, according to increase in stage	2.71 (1.92–3.84)	<0.001
Tumor grade, according to increase in grade	0.79 (0.61–1.03)	0.08
Age, modeled as a continuous variable	1.00 (0.99–1.02)	0.68
Male vs. female sex	0.91 (0.61–1.35)	0.63

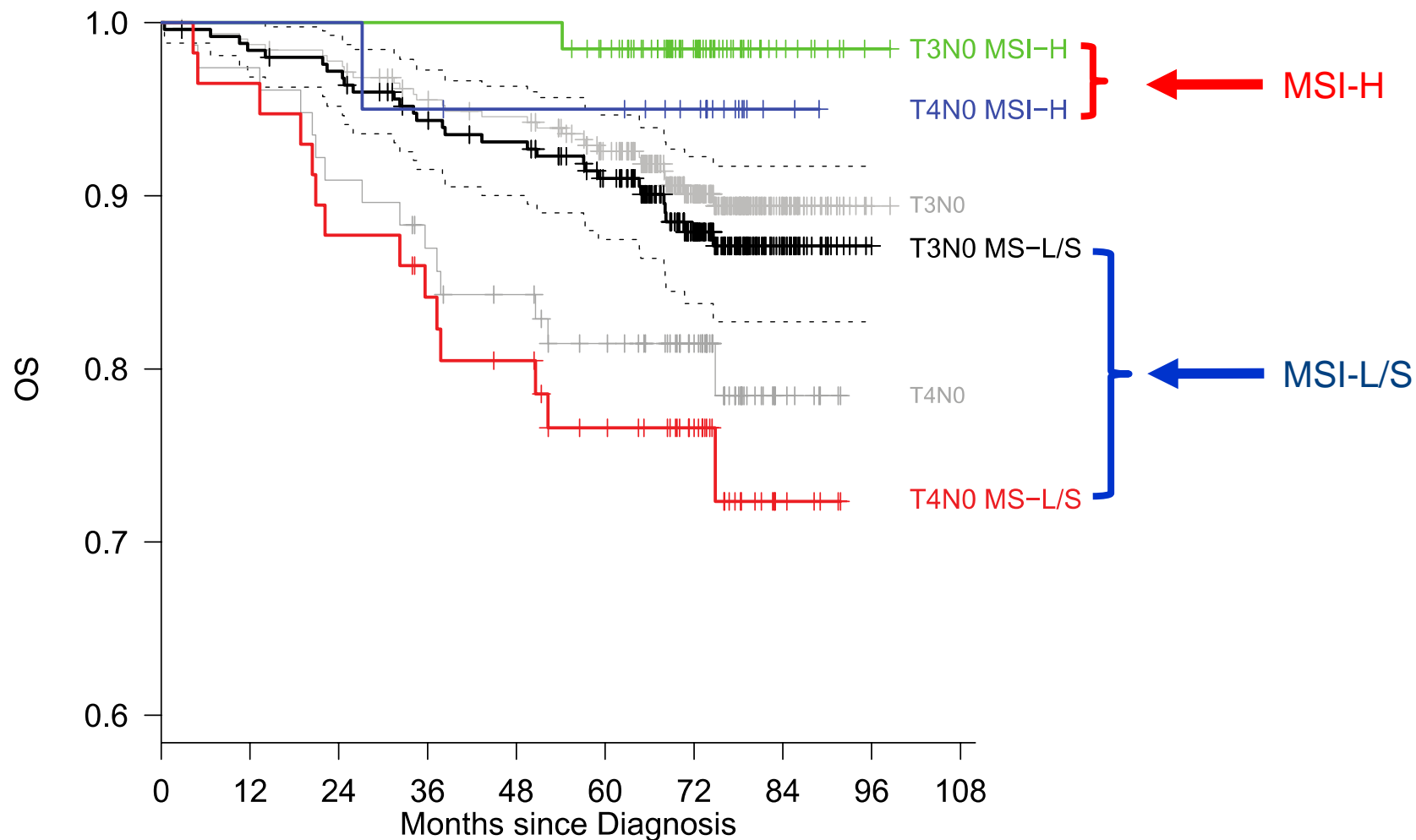
A Patients with Stage II Disease



No. at Risk

Chemotherapy	412	388	365	344	326	310	23	22	21	21	20	20	389	366	344	323	306	290
No chemotherapy	257	230	199	150	114	84	25	18	14	8	7	6	232	212	185	142	107	78

Integrated Analysis of Molecular and Clinical Prognostic Factors in Stage II Colon Cancer



At risk:								Number of events	
T3N0 MS-L/S	251	246	242	230	225	209	138	31	29
T3N0 MSI-H	66	66	66	66	66	61	35	9	1
T4N0 MS-L/S	57	55	50	46	43	37	26	5	14
T4N0 MSI-H	20	20	20	19	18	18	14	2	1

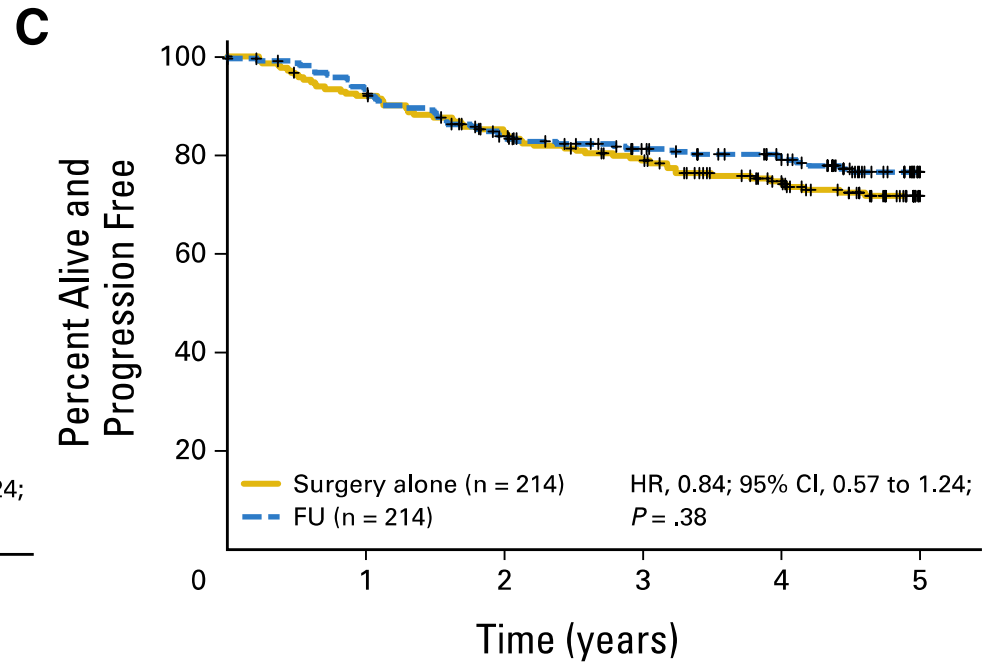
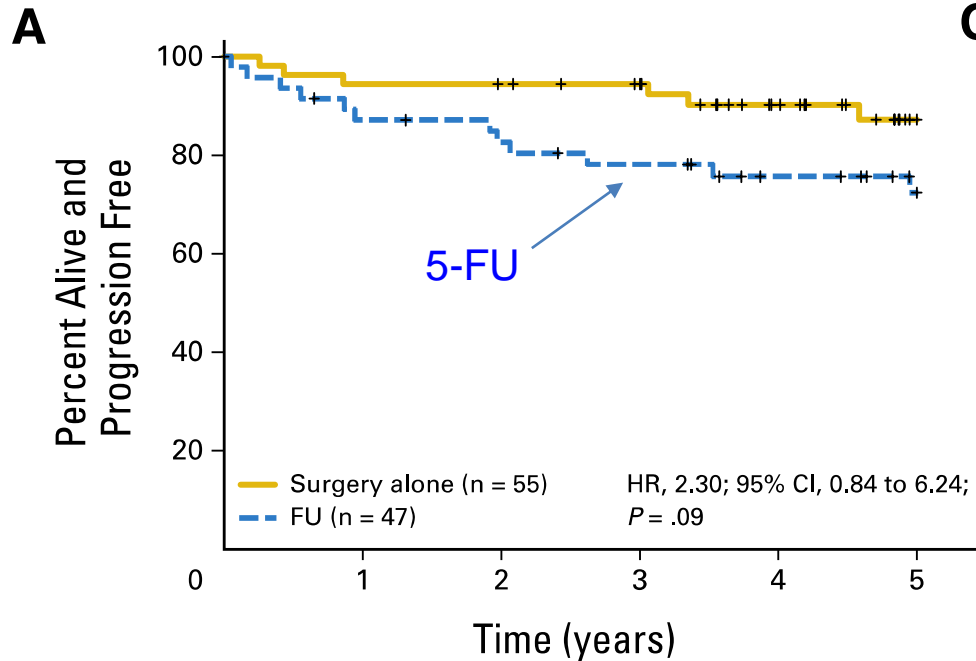
Stage II Colon Cancer

VOLUME 28 · NUMBER 20 · JULY 10 2010

JOURNAL OF CLINICAL ONCOLOGY

dMMR / MSI-H

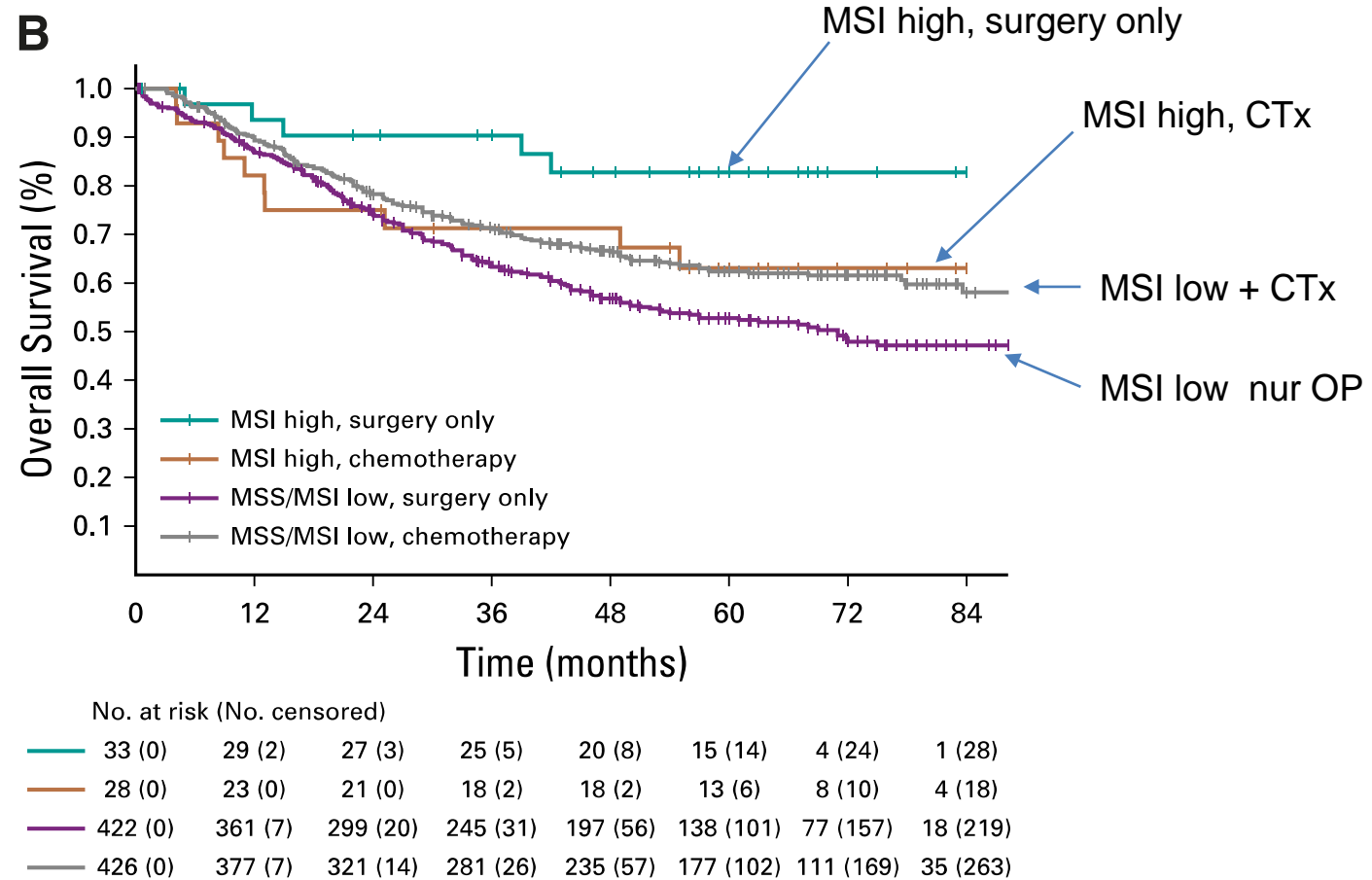
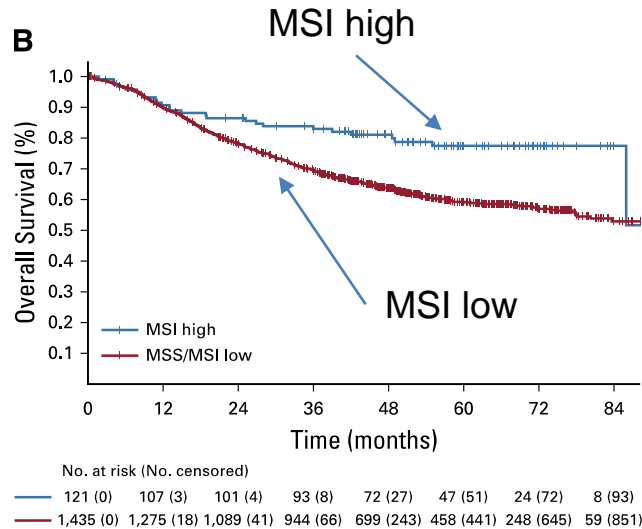
pMMR / MSS



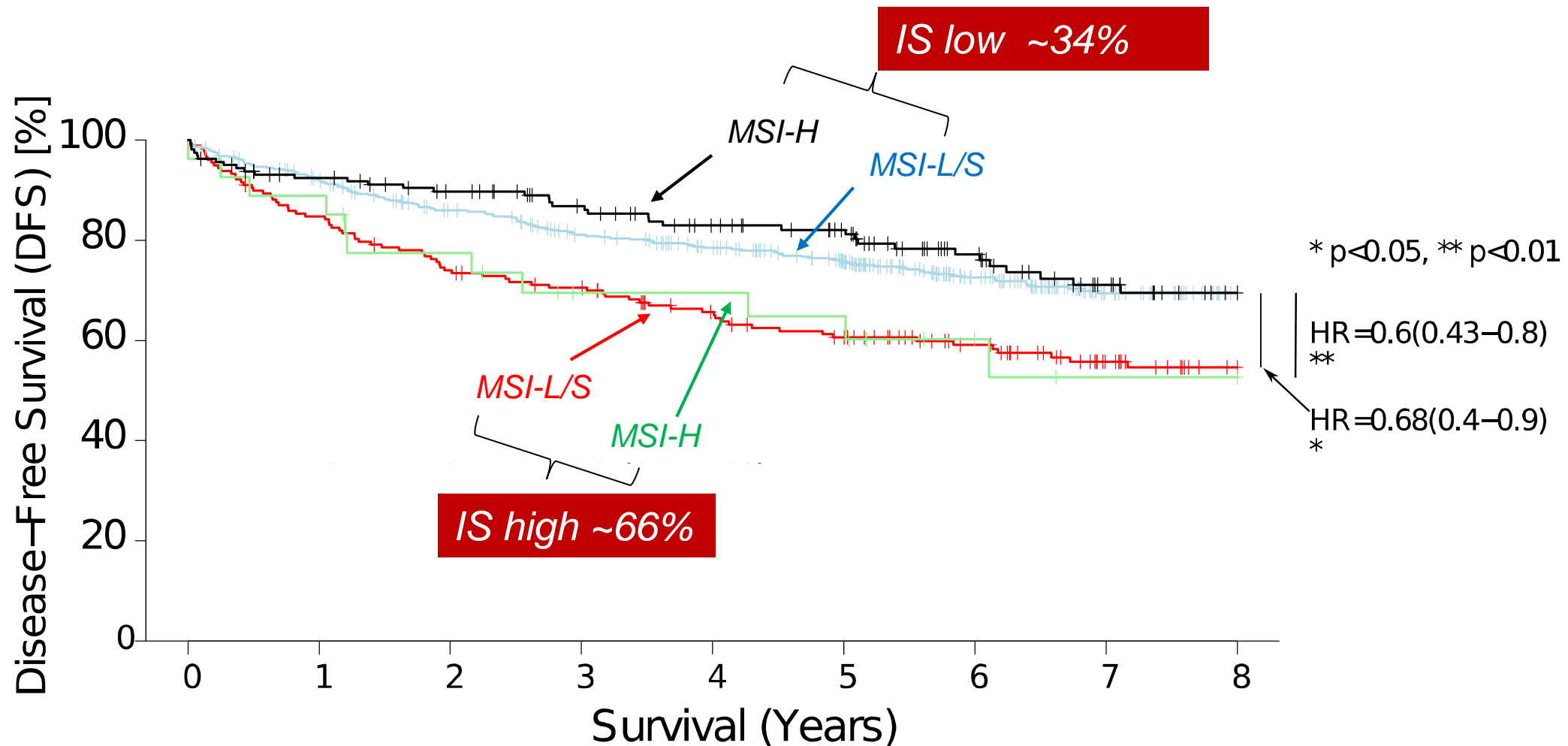
Chemotherapy in patients with dMMR / MSI-high tumor is detrimental

Sargent D J et al. JCO 2010;28:3219

Individual Patient Data Meta-Analysis of the Value of Microsatellite Instability As a Biomarker in Gastric Cancer



Immunoscore and MSI in Stage II Colon Cancer



- IS-Low/MSS 75/178 (21.17%)
- IS-Low/MSI-H 11/27 (3.21%)
- IS-High/MSS 126/474 (56.36%)
- IS-High/MSI-H 37/162 (19.26%)

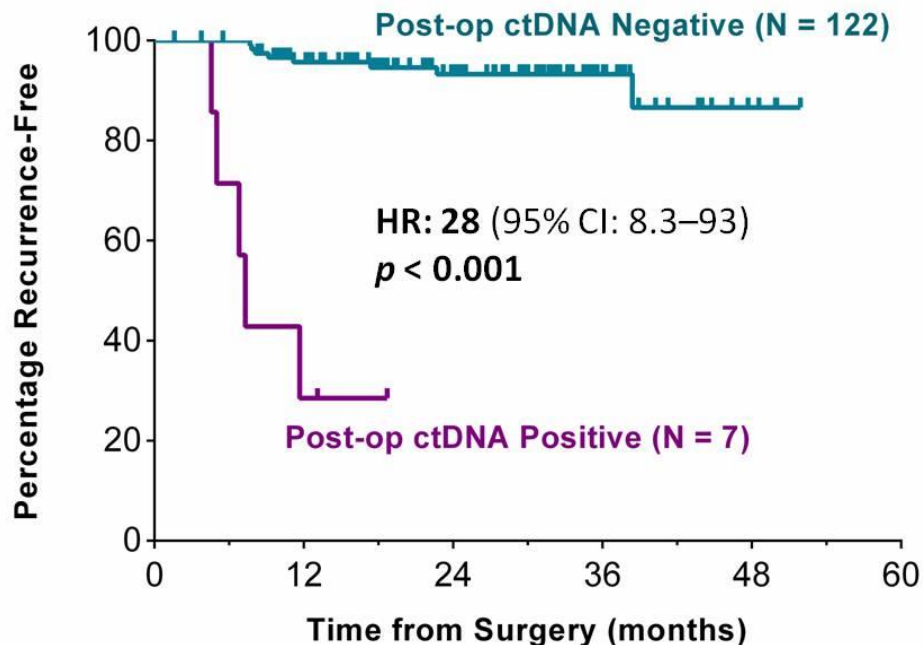
Pages et al. Lancet 2018

Liquid biopsy Stadium II Colon Cancer

Recurrence-Free Survival

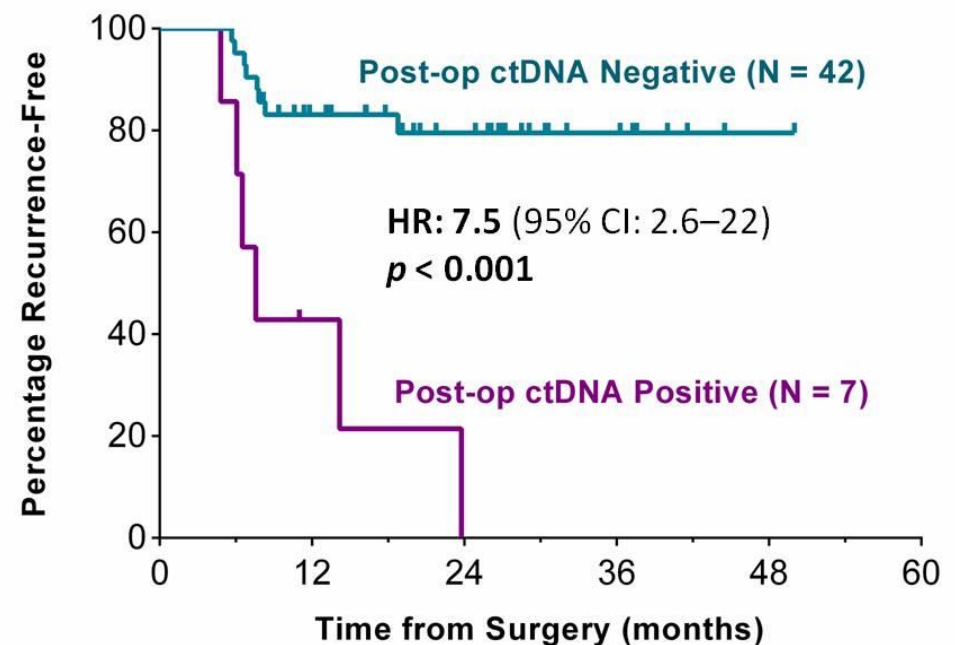
Clinical Low-Risk

(dMMR or pMMR + no poor prognostic features)



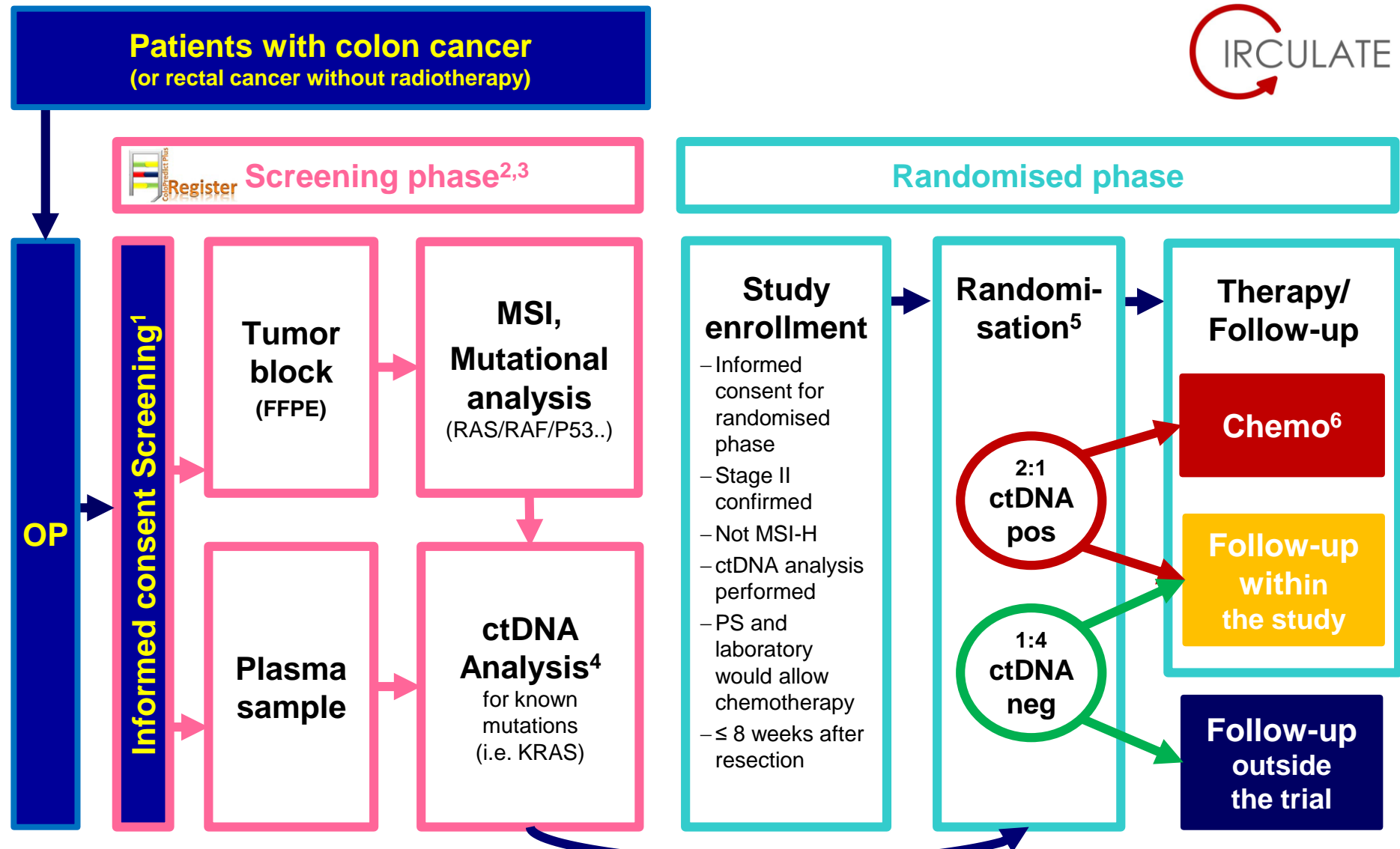
Clinical High-Risk

(pMMR + at least one poor prognostic features)



Proposed prognostic and predictive marker in Stage II Colon Cancer

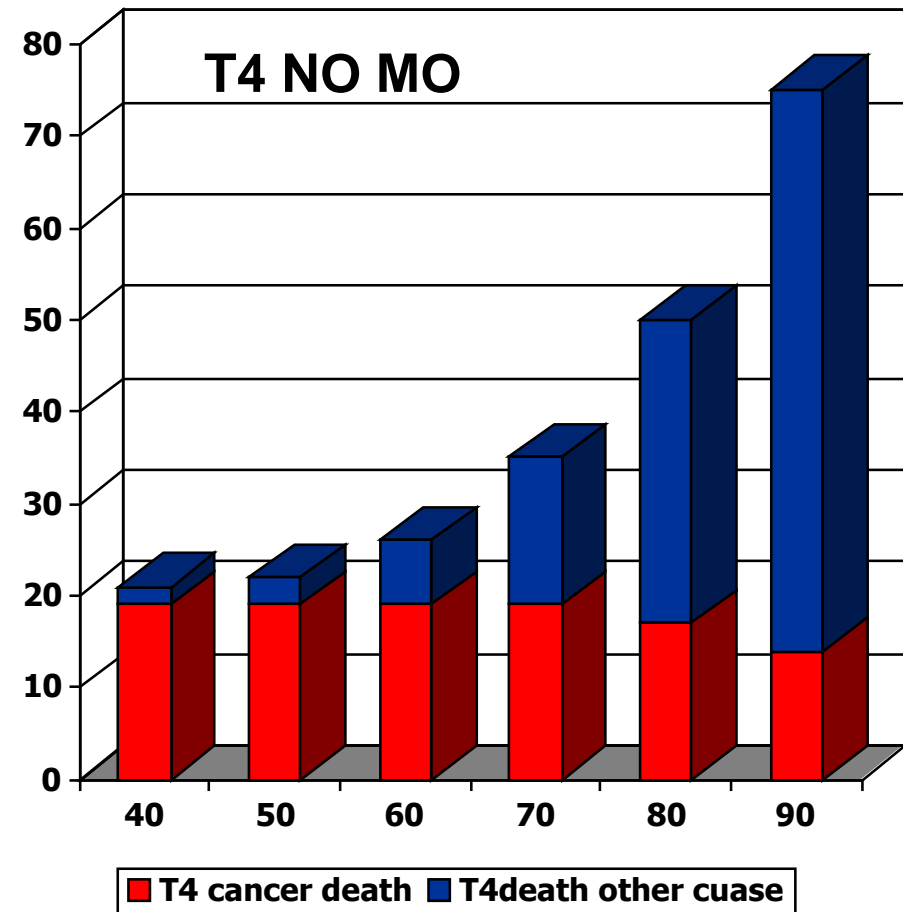
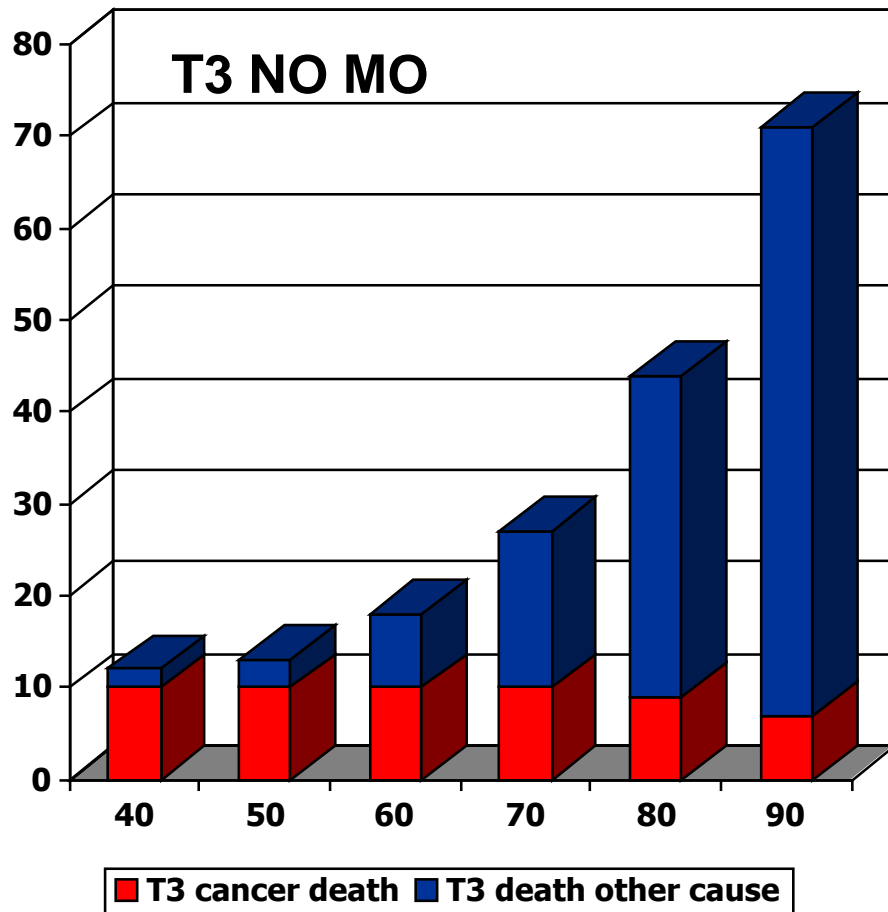
Parameter	Prognostic	Predictive for adjuvant Tx ?
Clinical (T4, N<12 etc)	yes	Not shown
Gen expression	weak	Low / intermediate risk
miRNA	yes, independent to clinical parameters	High risk group
CDX2	yes	CDX2 neg group
MSI	yes	Negative impact on MSI-H, dMMR
Immunoscore	yes, overrides MSI?	Not shown
cfDNA	Yes, very strong!	Not shown



- 1) Patients, in whom the stage is not yet known can be enrolled in screening
- 2) Preferably before discharge from surgery.
- 3) Screening may be performed in screening platforms (Germany: Colopredict).
- 4) ctDNA results will not be communicated.
- 5) Stratification: T3 vs T4, emergency resection, planned oxaliplatin.
- 6) Capecitabine based. 6 months. Oxaliplatin as investigators choice (CapOx 3 or 6 months)

Adjuvant! Online Prediction: Cancer and non-cancer related 5-year-Mortality

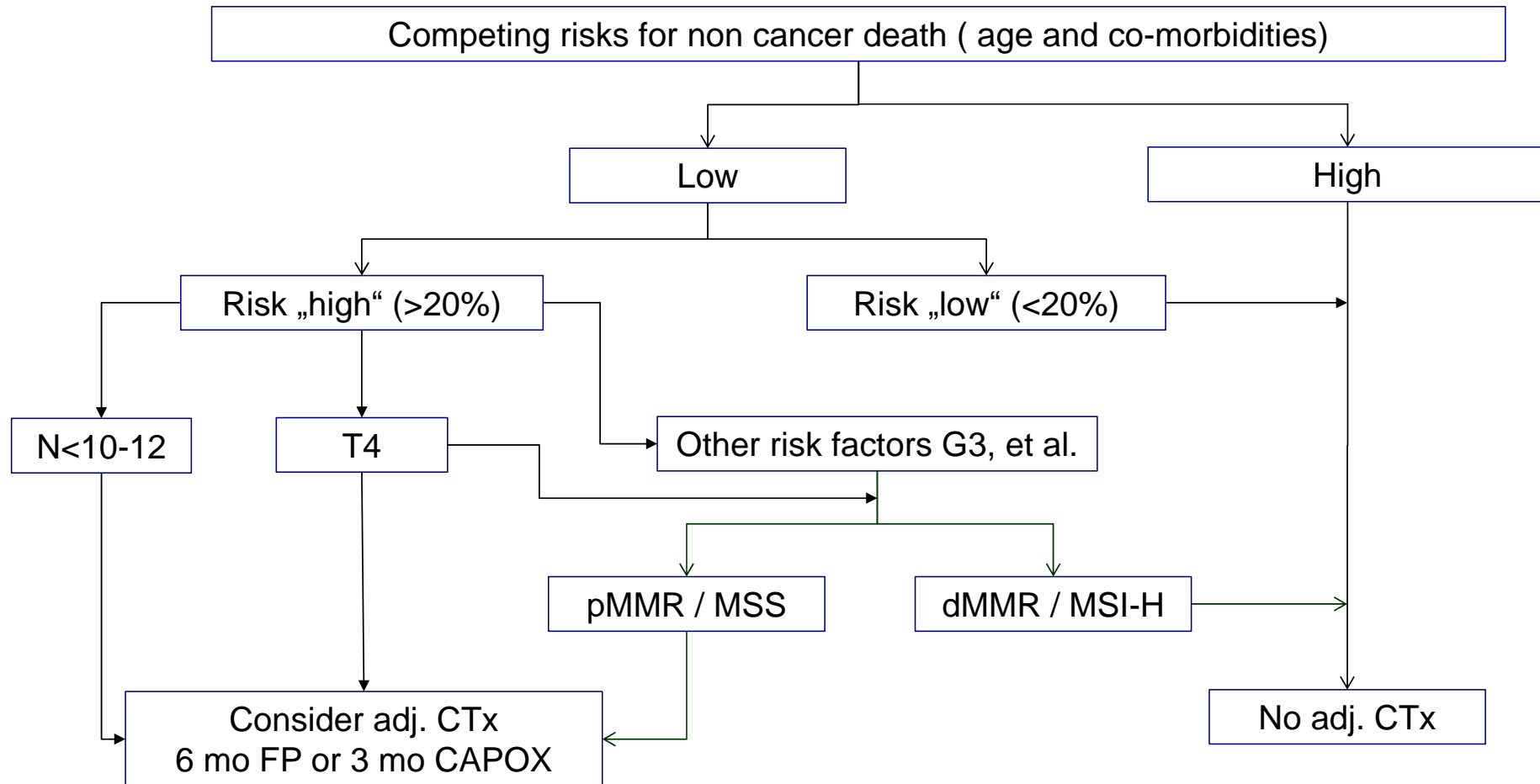
Improvement of cancer specific survival by 1.7% (FU) and 2.3% (FOLFOX)



Assumption of Gill model

- **Stadium III**
 - high risk (T4 o. N>3) 6 Monate (FOLFOX)
 - Low risk 3 Monate CAPEOX oder 6 Monate Fluoropyrimidin (FP)
- **Stadium II**
 - „High risk“ Gruppe NICHT gut definiert, z.Z. MSI-H KEINE Therapie
 - Individuelle Entscheidung zur adjuvanten CTx
 - Behandlung mit Oxaliplatin nicht gut gerechtfertigt, allenfalls 3 Monate
 - Die Entscheidung zur adjuvanten Therapie muss Co-Morbiditäten mit einbeziehen
 - Jeder Algorithmus ist als vorläufig zu betrachten
 - Aufruf zur Teilnahme an der CIRCULATE Studie der AIO (Prof. Folprecht, DD)

Algorithm for treatment decision in stage II colon cancer





Danke für die Aufmerksamkeit