



**GASTRO**  
JournalClub

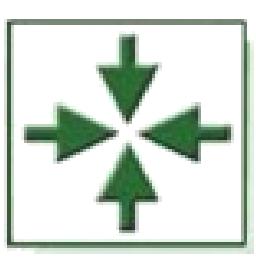
L'importanza della ricerca in Oncologia

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**10-11 OTTOBRE 2019 - ROMA**

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VOI Donna Camilla Savelli Hotel - Via Garibaldi, 27



# TERAPIA ADIUVANTE: COSA ABBIAMO IMPARATO

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*Dipartimento di Oncologia Medica*

*Fondazione IRCCS Istituto Nazionale dei Tumori*

*Milano*

Trattamento locoregionale: *chirurgia e linfadenectomia standard vs radioterapia*

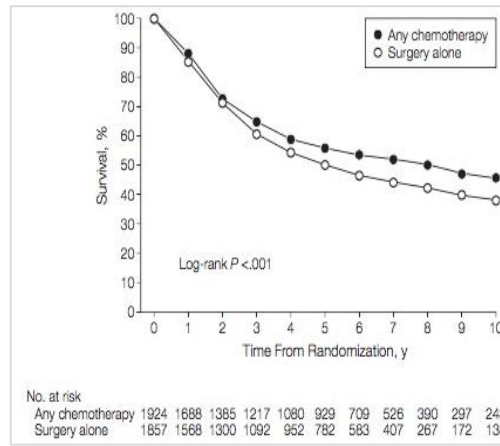
Chemioterapia: *quale schema e quanti farmaci*

Caratterizzazione biologica del tumore: *marcatori molecolari*

Selezione dei pazienti: *minimal residual disease*

## 2006 MAGIC

ECF x 3 – Surgery – ECF x 3  
vs Surgery

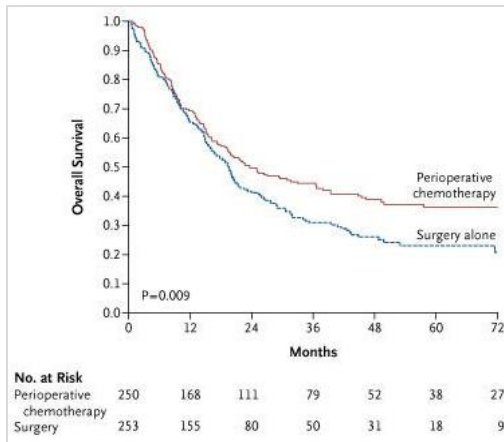


**Δ: 5.7%**

5-YR OS  
SURG: 49.6%  
ADJUV: 55.3%

## 2019 FLOT4/AIO

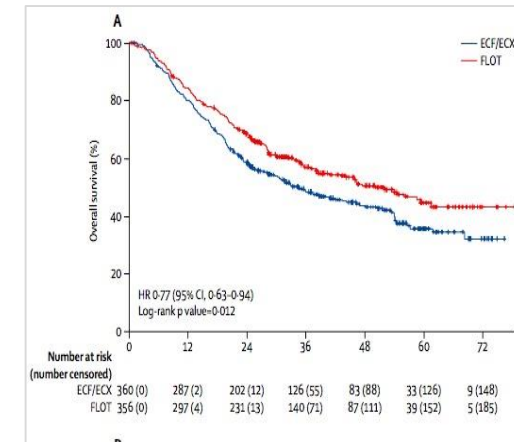
FLOT x 4 – Surgery – FLOT x 4  
Vs ECX x 3 – Surgery – ECX x 3



**Δ: 13%**

5-YR OS  
SURG: 23%  
PERIOP: 36%

## 2010 GASTRIC Group Meta-analysis



**Δ: 9%**

Estimate 5-YR OS  
ECF: 36%  
FLOT: 45%

**THERAPY EVOLUTION IN OPERABLE GC**

OPERABLE  
GASTRIC  
CANCER

PERIOPERATIVE TREATMENT

$\Delta$  +22% in 5-yrOS

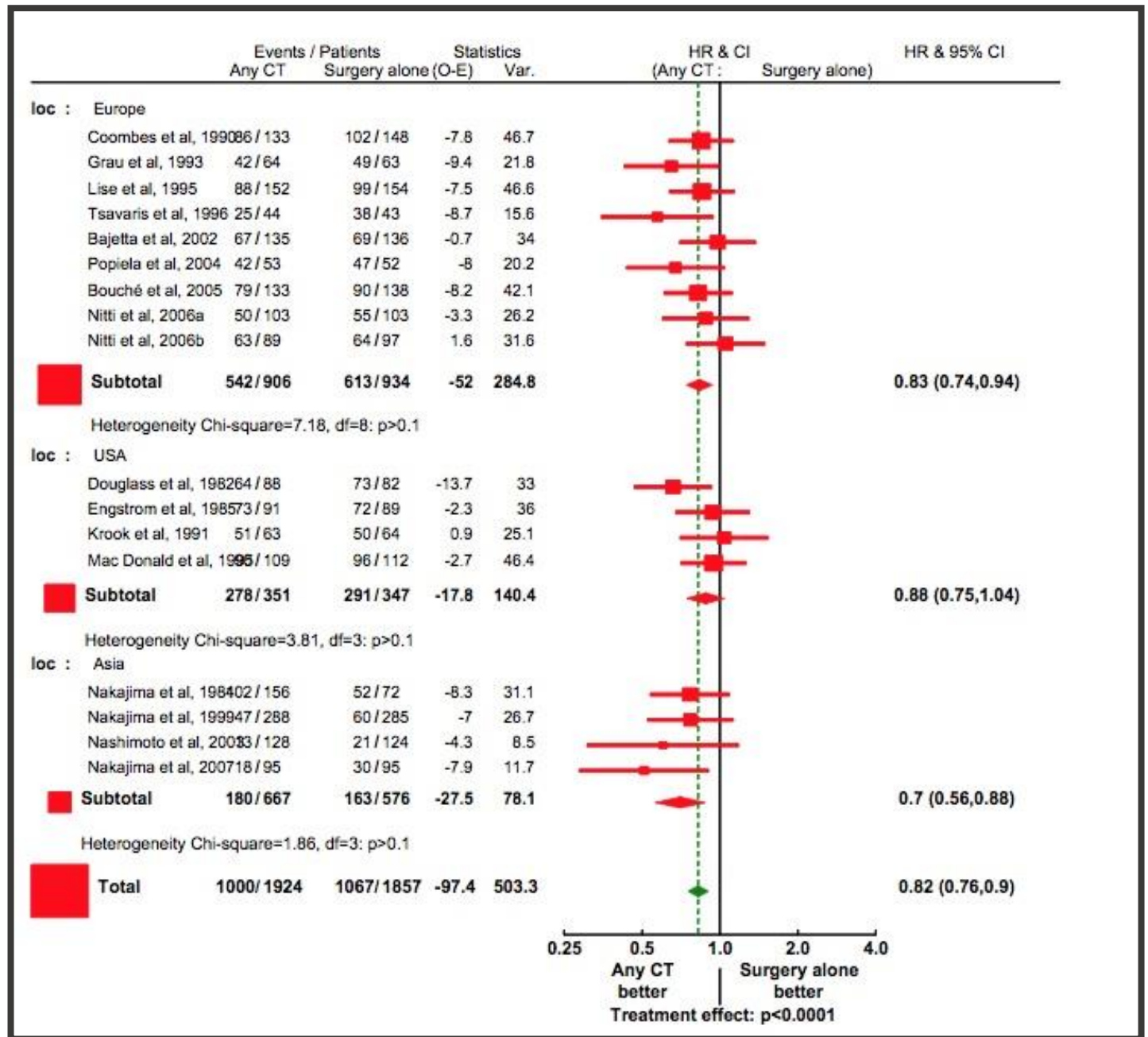
ADJUVANT TREATMENT

$\Delta$  +5.7<sup>1</sup>%- 11%<sup>2</sup>-9%<sup>3</sup> in 5-yrOS

1. Pignon et al, JAMA, 2010
2. Sakuramoto et al, NEJM, 2007
3. Bang et al, Lancet, 2012



COMINCIO'  
COSI'.....

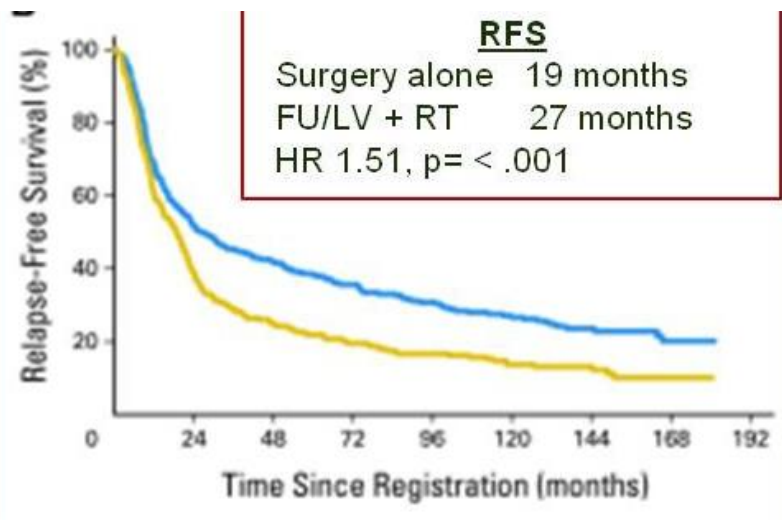
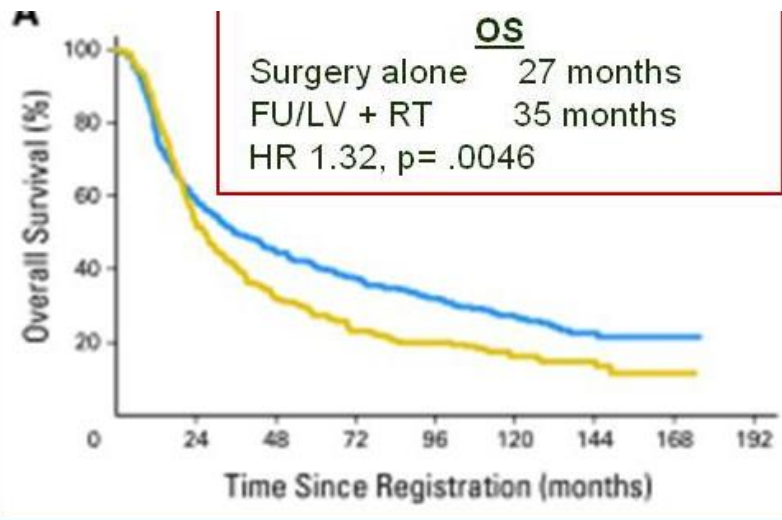


(The Gastric Collaboration, JAMA, 2010)

IL  
CONTRIBUTO  
ITALIANO

Autore	Bajetta, 2002	Cascinu, 2007	Di Costanzo, 2008	De Vita, 2007
Stadio	T3-4/N+	T3-4/N+	T3-4/N+	I-IIIB
N. Pz	137/137	196/201	128/130	112/113
Tratt sperimentale	EAP→FU/LV	PELFWk	PELF	ELFE
controllo	Follow-up	FU/LV	Follow-up	Follow-up
Local: III sup/medio,inf	18%/72%	30%/70%	8%/82%	13%/87%
HR	0.93	0.95	0.90	0.91
5-y OS controllo	49%	50%	48.7%	43.5%

# ADJUVANT CHEMORADIATION ..... REDUCES LOCAL FAILURE

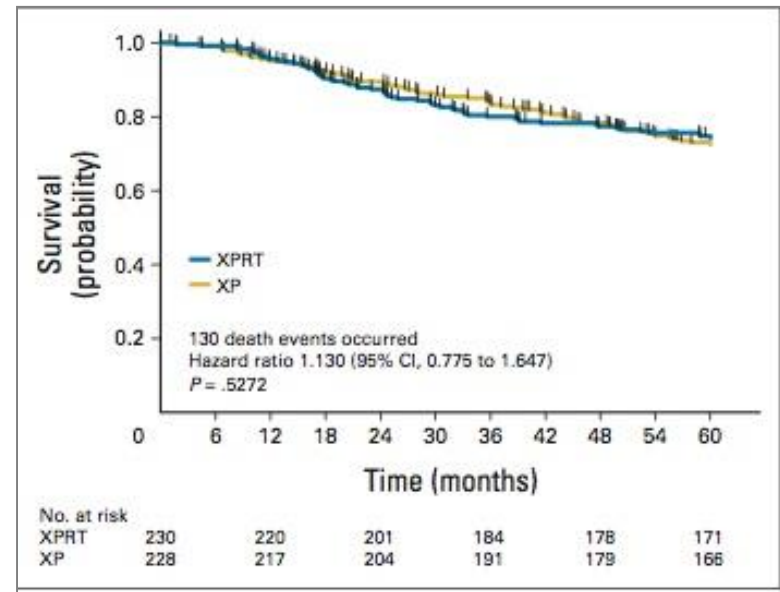
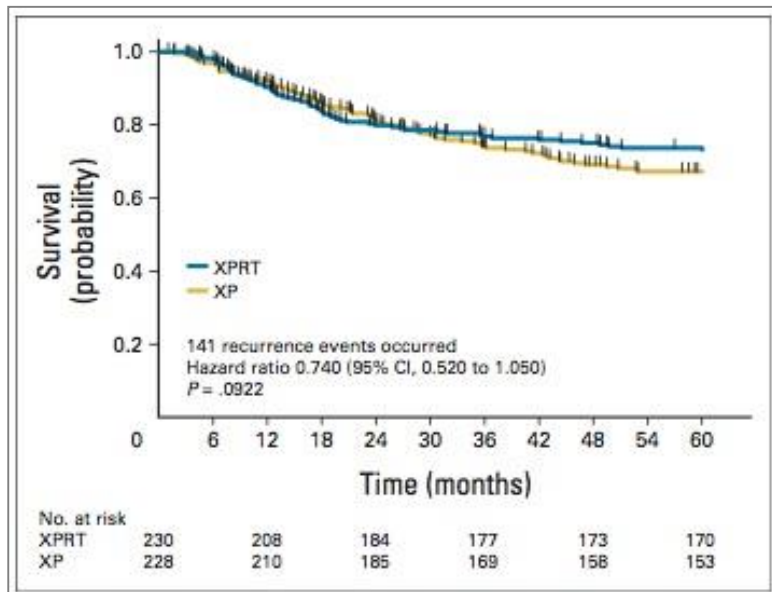


Following D0/1 dissection



Macdonald, NEJM 2010

Following D2 dissection



(Lee J, JCO 2012)



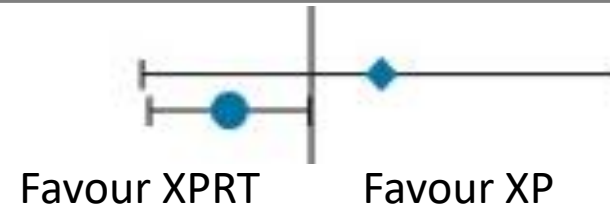


# Refining the Role for Adjuvant Radiotherapy in Gastric Cancer: Risk Stratification Is Key

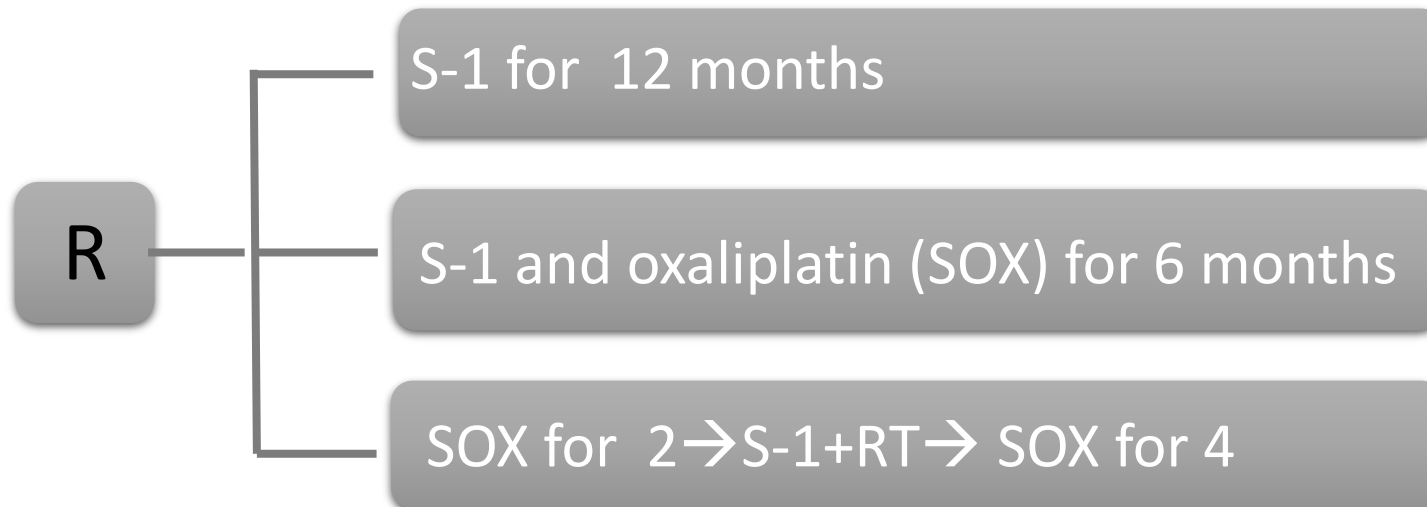
Karyn A. Goodman, Memorial Sloan Kettering Cancer Center, New York, NY

(*J Clin Oncol* 2015)

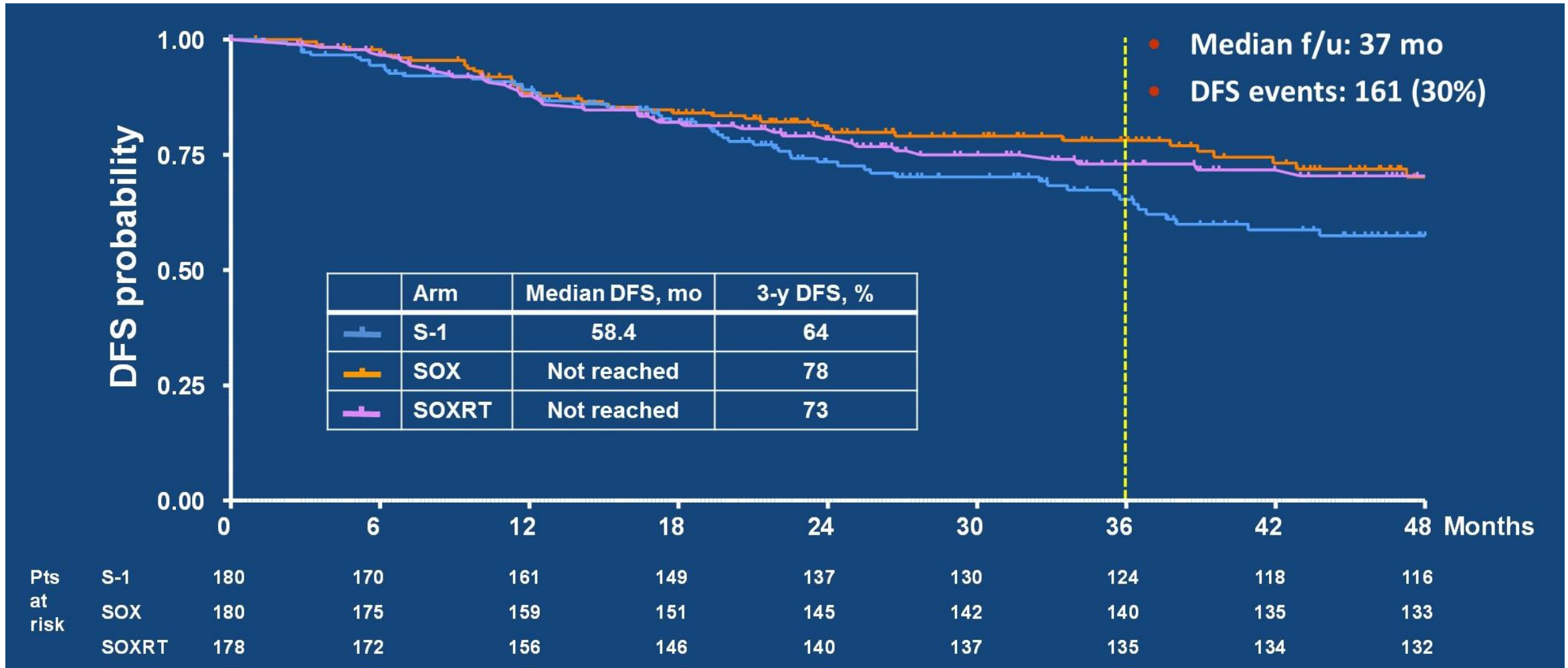
LN		
Negative	1.359	0.477 to 3.876
Positive	0.700	0.493 to 0.994



## ARTIST 2: GC N+, D2 dissection

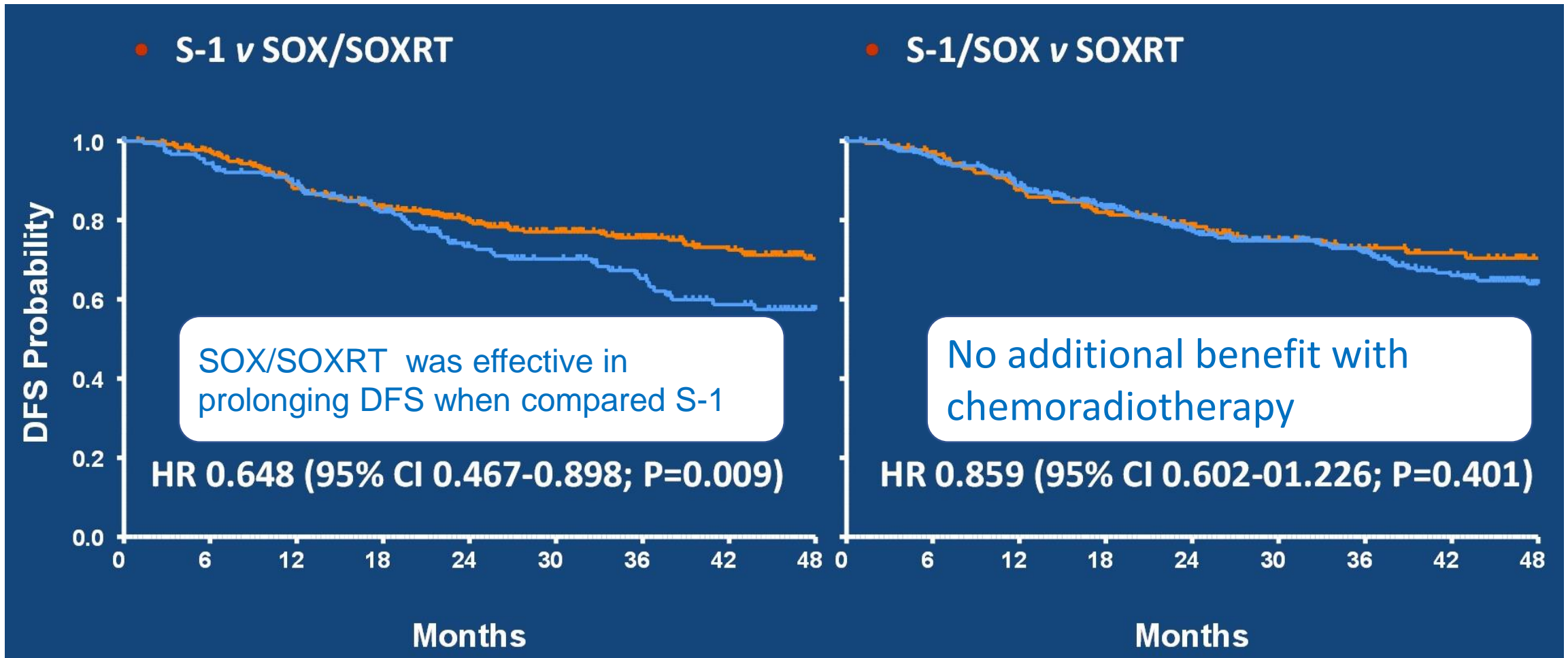


# ARTIST 2: Primary Endpoint



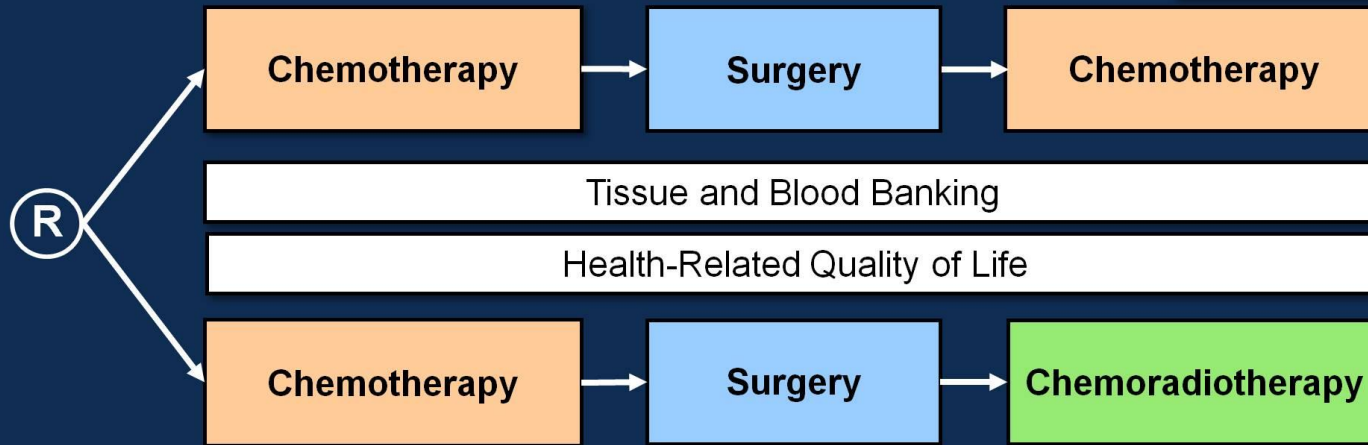


# ARTIST 2: Subgroup Analysis of DFS

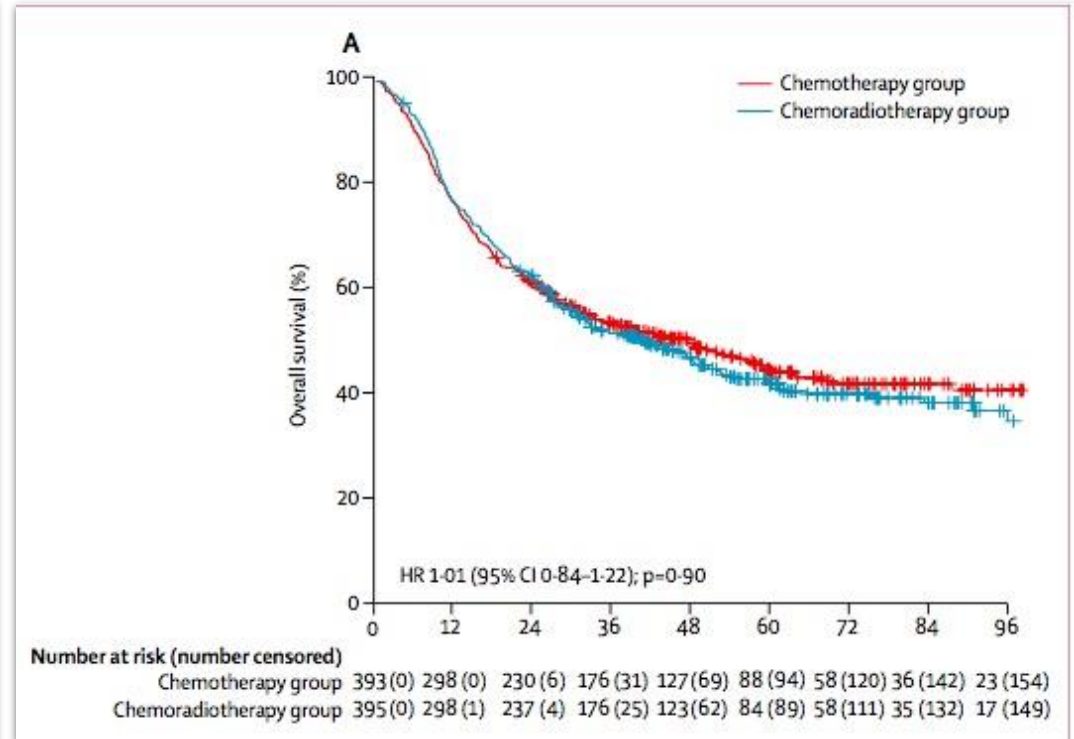


# CRITICS: NO DIFFERENCE IN OS HAS BEEN OBSERVED

## Trial design



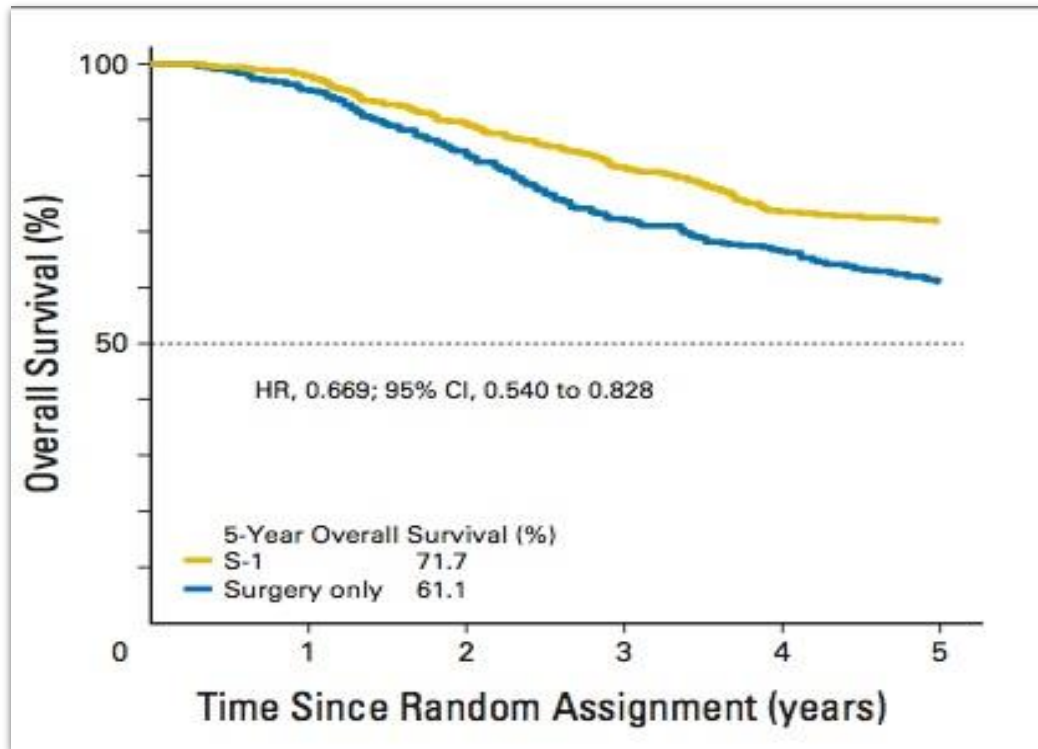
Stratified for: Center, Histological type, Tumor localization



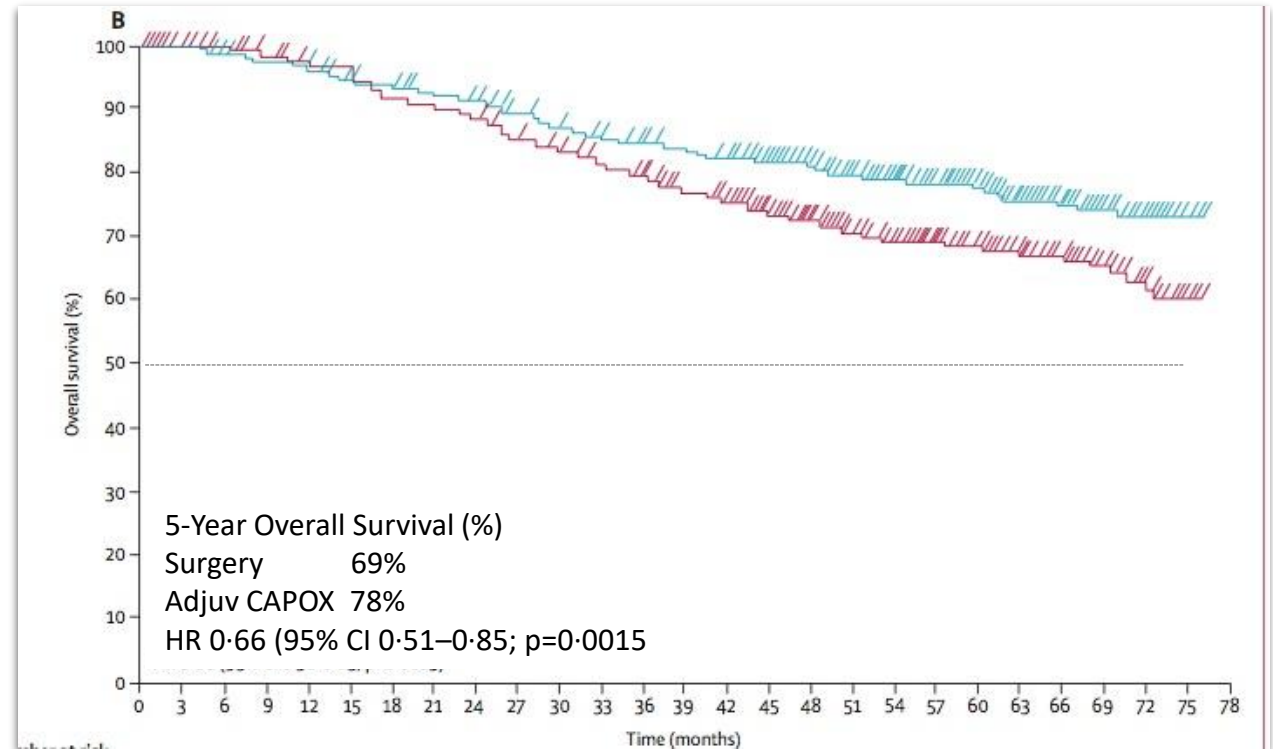
# ADJUVANT CHEMOTHERAPY IN ASIA .....STANDARD CARE



## ACTS-GC<sup>1</sup>



## CLASSIC<sup>2</sup>



# ADJUVANT .....NEGATIVE PHASE III TRIALS



SAMIT: Sequential adjuvant chemotherapy did not improve DFS

## T4a/b GC D2 dissection

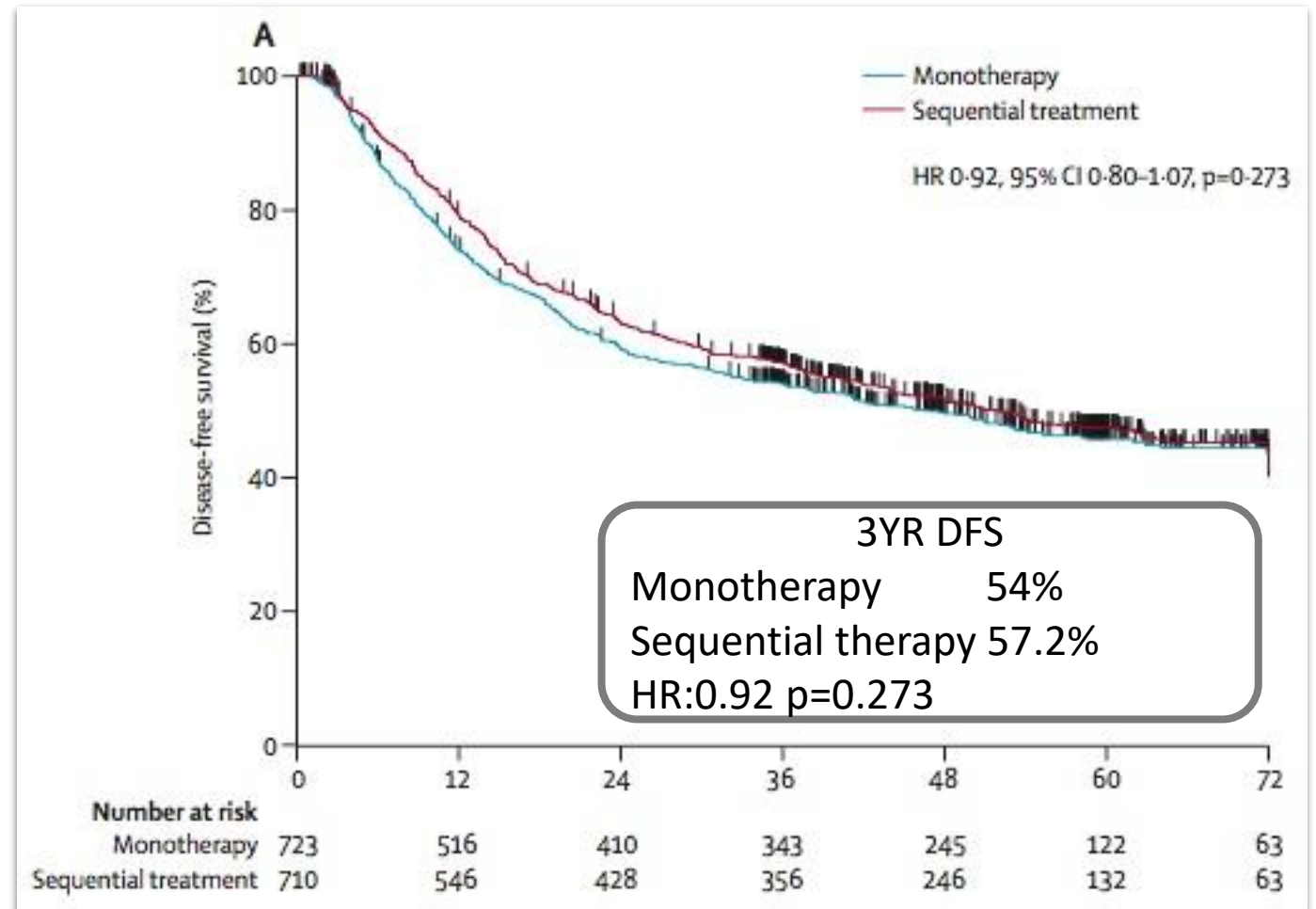
UFT alone  
n.374

S1 alone  
n.374

Paclitaxel then UFT  
n.374

Paclitaxel then S1  
n.373

R





# ADJUVANT .....NEGATIVE PHASE III TRIALS



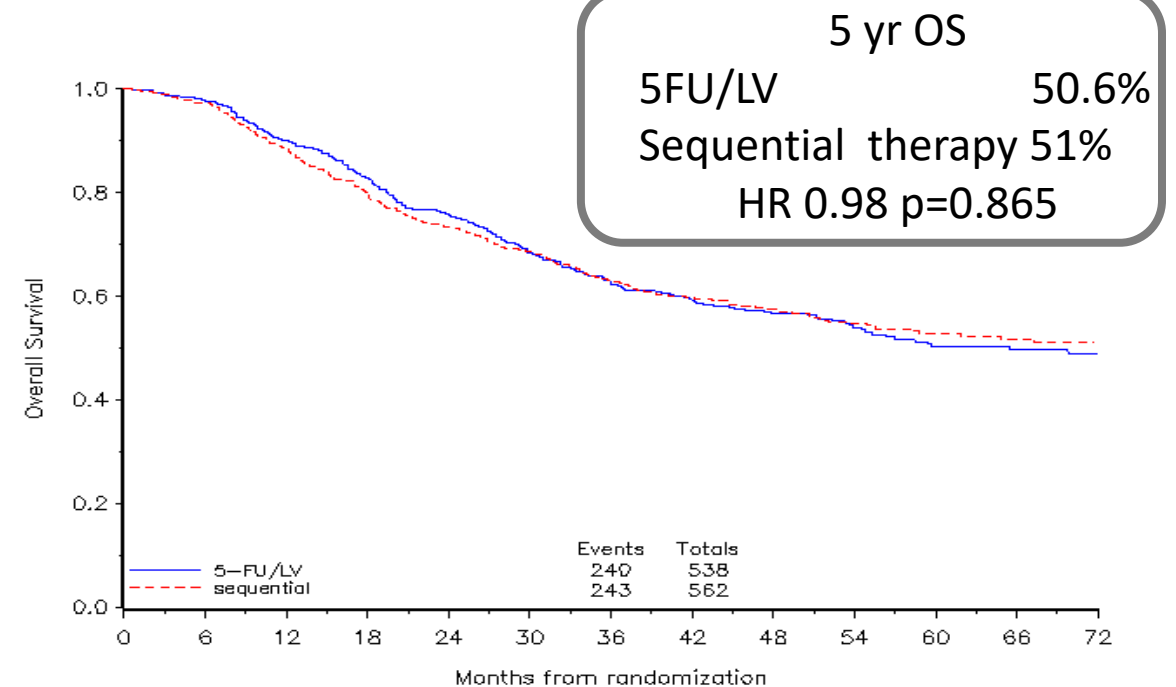
ITACA-S: Intensification of chemotherapy did not improve DFS or OS

**T3-4/N+ GC  $\geq$  D1 dissection**

R

de Gramont x 9  
n.538

FOLFIRI x4->CDDP/DXTx 3  
n.562



Patients at Risk	Months from randomization												
	0	6	12	18	24	30	36	42	48	54	60	66	72
5-FU/LV	538	514	468	429	383	341	294	248	198	160	115	77	53
sequential	562	538	482	428	385	352	315	267	216	168	114	84	55

# PRODIGY STUDY : TOMORROW NEW STANDARD CARE IN ASIA?

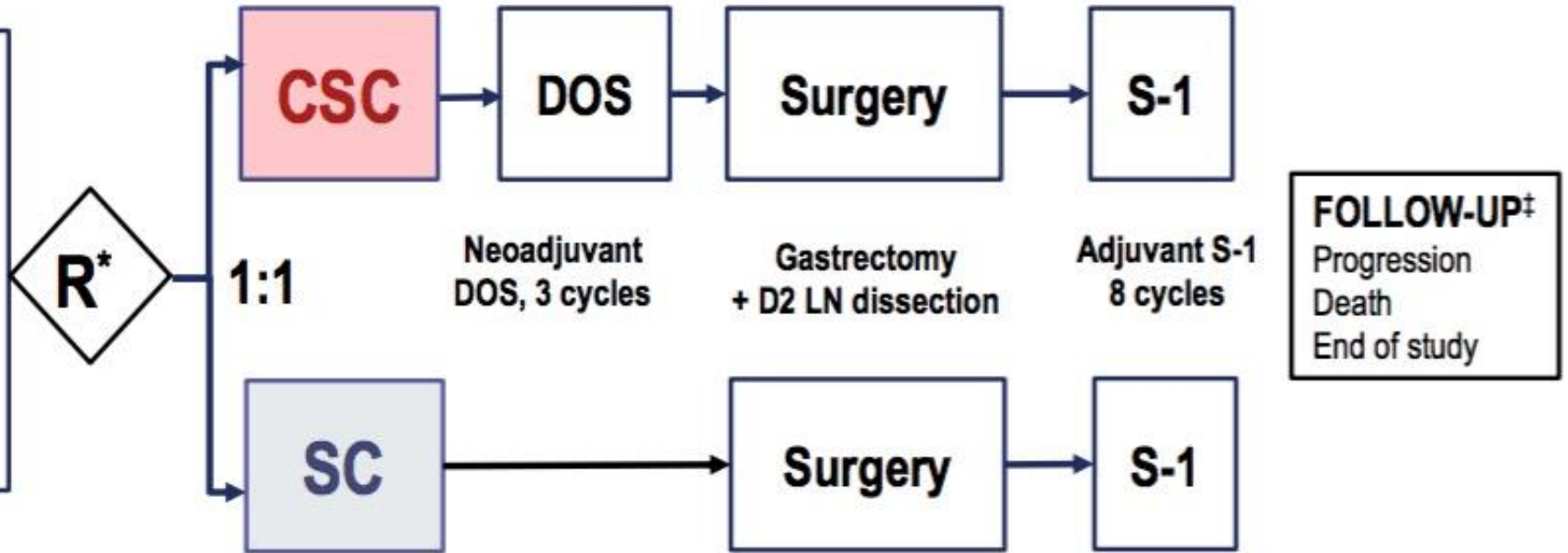


## STUDY DESIGN

**CSC arm:** Neoadjuvant Chemotherapy + Surgery + Adjuvant Chemotherapy  
**SC arm:** Surgery + Adjuvant Chemotherapy

**Key Eligibility Criteria**

- Newly diagnosed locally advanced gastric or GEJ adenocarcinoma
- cTNM stage: cT2,3/N[+]M0 or cT4/N[any]M0 (AJCC 7<sup>th</sup> edition)
- ECOG PS 0 or 1
- Adequate organ function

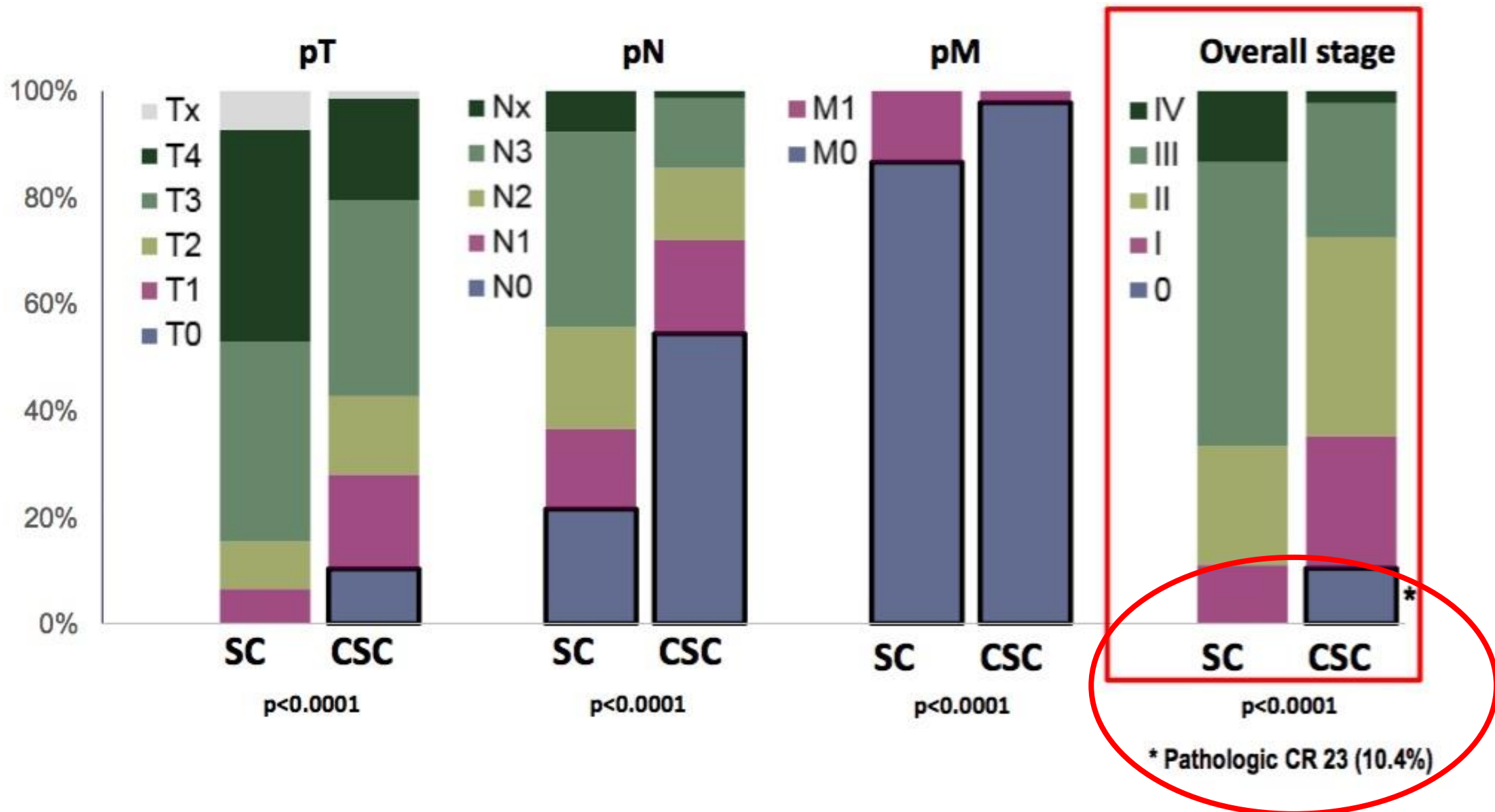


**\* Stratification factors**

- 1) Study site
- 2) cTNM stage (cT2/N+, cT3-4/N+, cT4/N-)

Primary endpoint	Secondary endpoints
<ul style="list-style-type: none"> <li>• 3-year PFS in FAS</li> </ul>	<ul style="list-style-type: none"> <li>• R0 resection rate</li> <li>• Post-operative pathological stage</li> <li>• OS</li> <li>• Safety</li> </ul>

# PRODIGY STUDY: POST-OPERATIVE PATHOLOGY

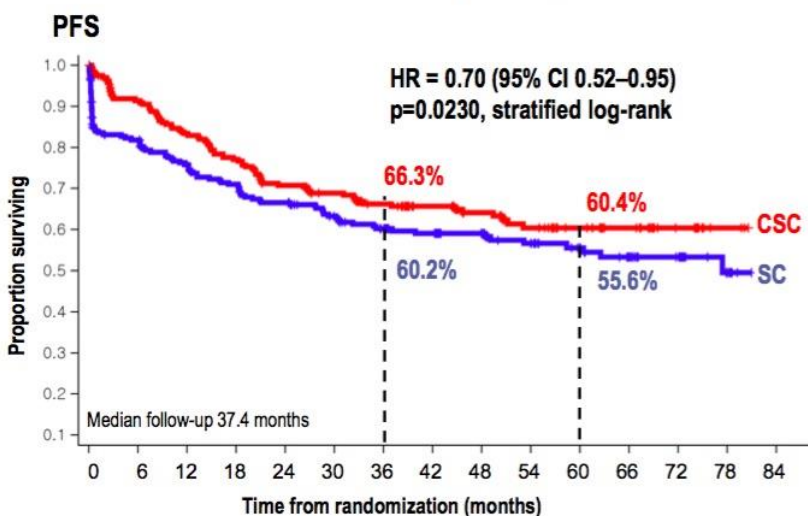


(Kang from ESMO2019)

# PRODIGY STUDY: results and subgroup analysis

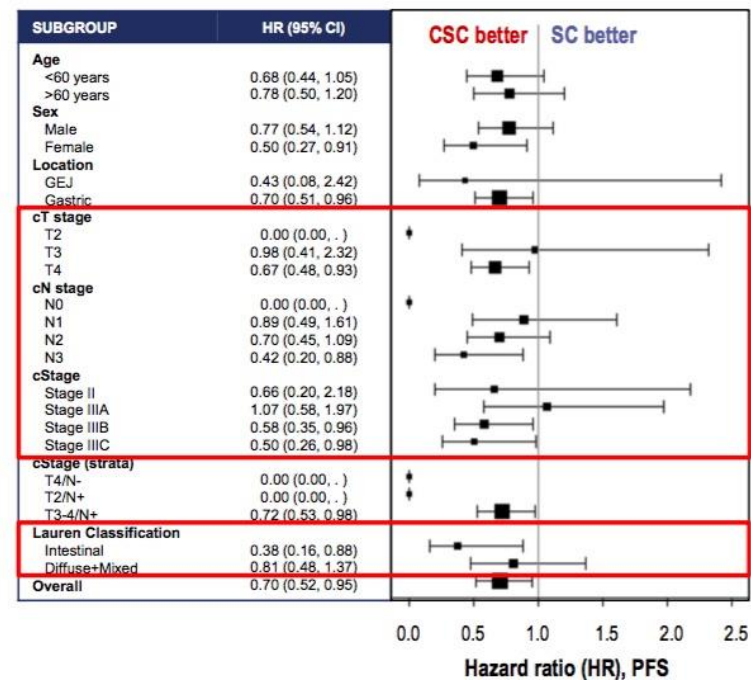
Δ +6% in 3-yrPFS

## PROGRESSION-FREE SURVIVAL (FAS)



	CSC	238	206	186	172	155	138	110	95	78	62	51	37	17	3	0
SC	246	193	174	161	150	132	113	96	81	67	52	42	31	11	0	

## PFS: SUBGROUPS

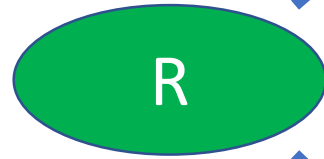


FAS: Full analysis set

(Kang from ESMO2019)

# RESOLVE STUDY: STUDY DESIGN

Histologically cT4aN1  
or cT4bN<sub>any</sub> gastric or  
GEJ adenocarcinoma



340 pz

Arm A: D2 surgery-->CAPOX x 8 cycles

340 pz

Arm B: D2 surgery-->SOX x 8 cycles

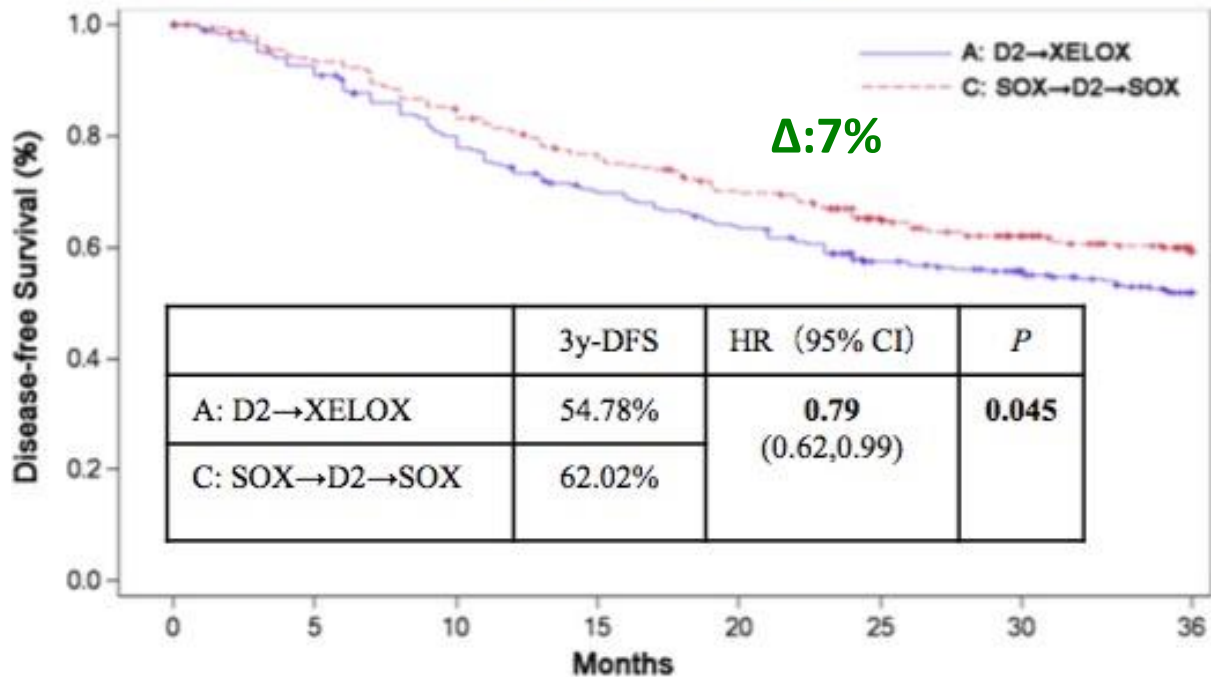
337 pz

Arm C: SOXx3→D2 surgery-->SOX x 5—S1 x3

Primary endpoint: 3-yr DFS  
Arms C vs A superiority  
Arm A vs B non-inferiority

# RESOLVE STUDY: PRIMARY COMPARISON

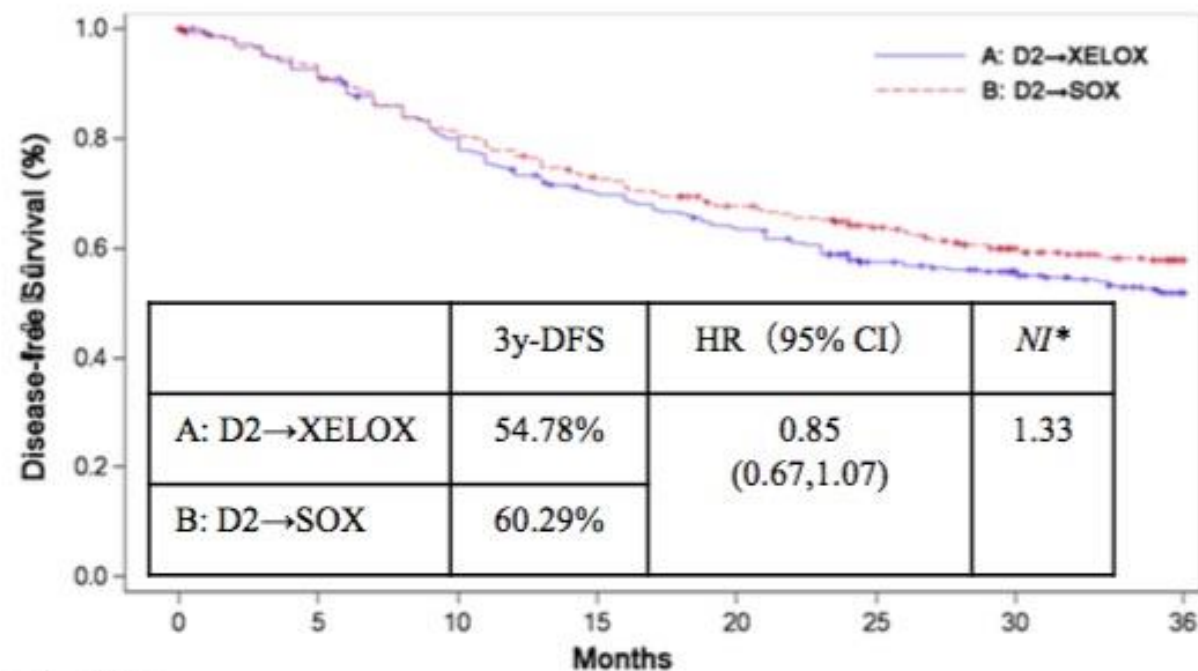
## ARMs A vs. C



No. at risk

	0	5	10	15	20	25	30	36
A	345	314	267	228	206	171	149	116
C	337	307	277	248	223	188	156	117

## ARMs A vs. B

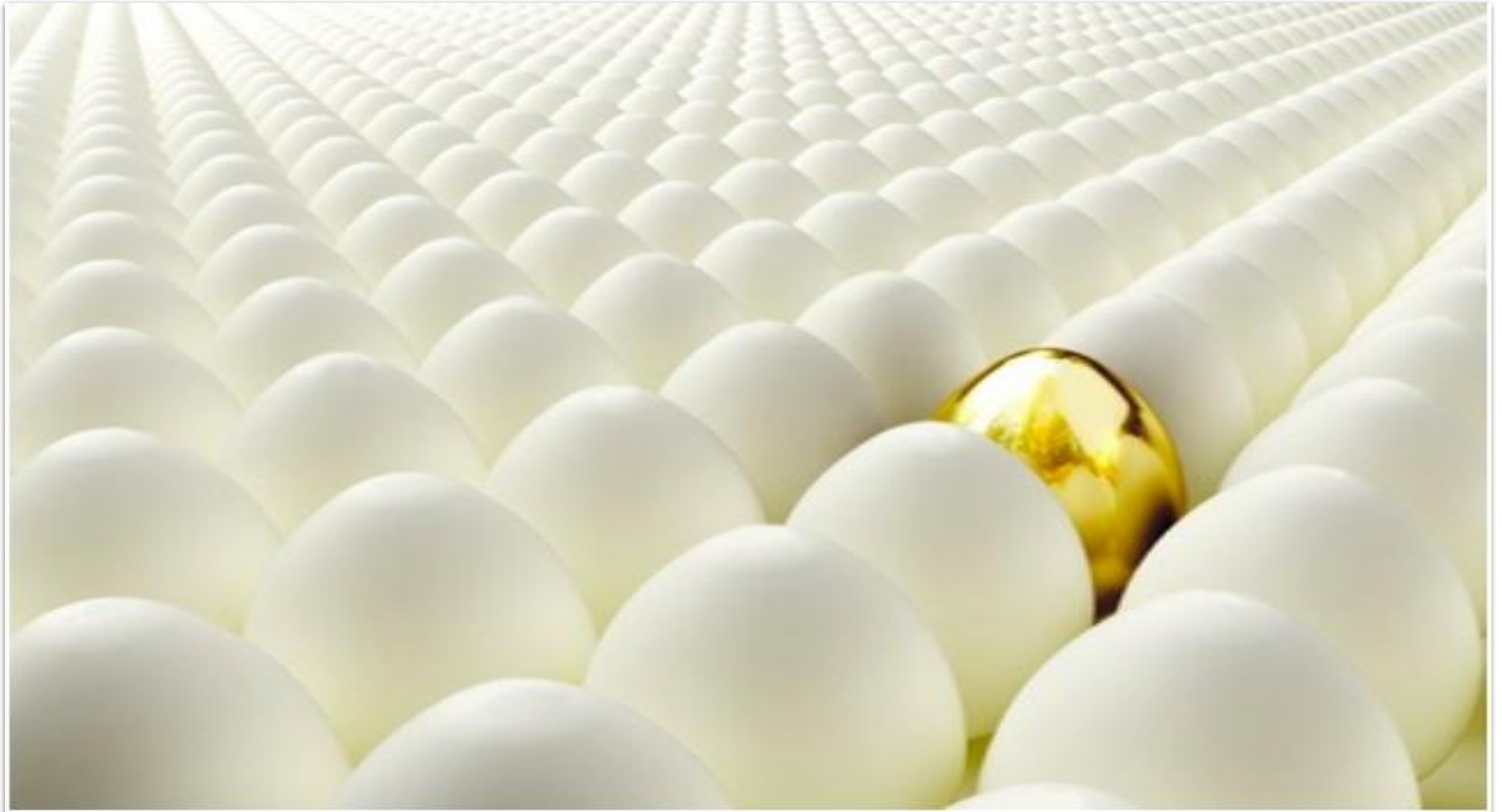


No. at risk

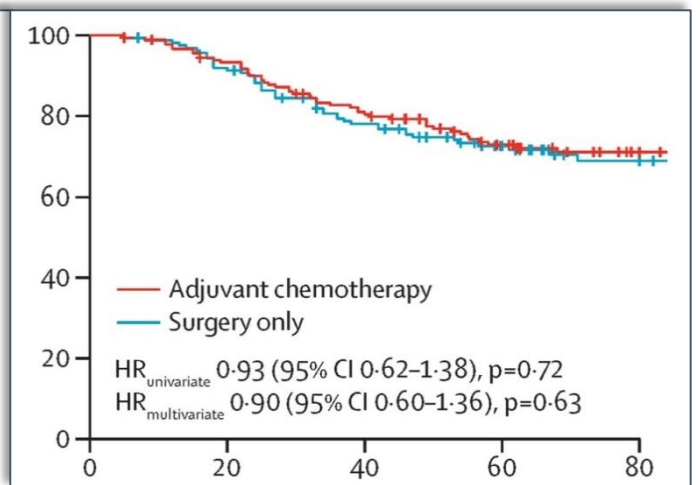
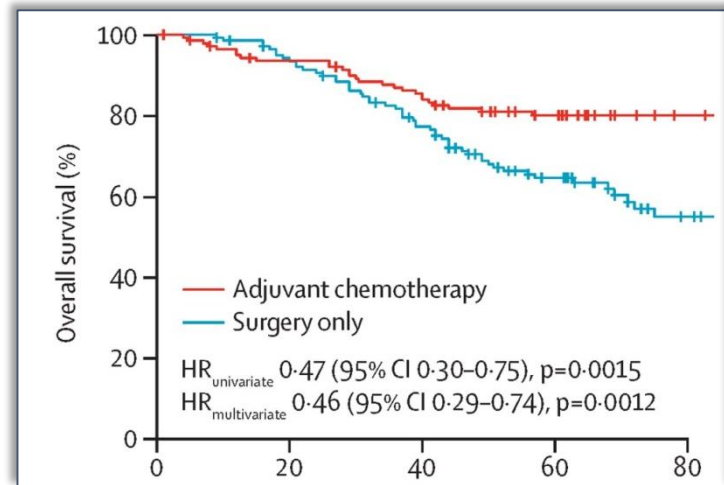
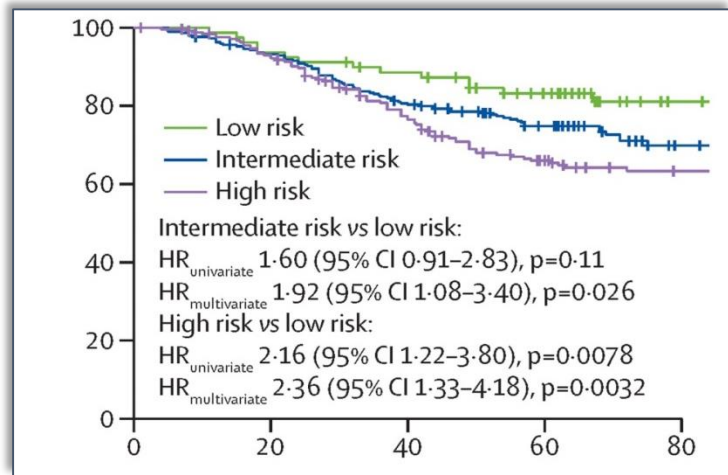
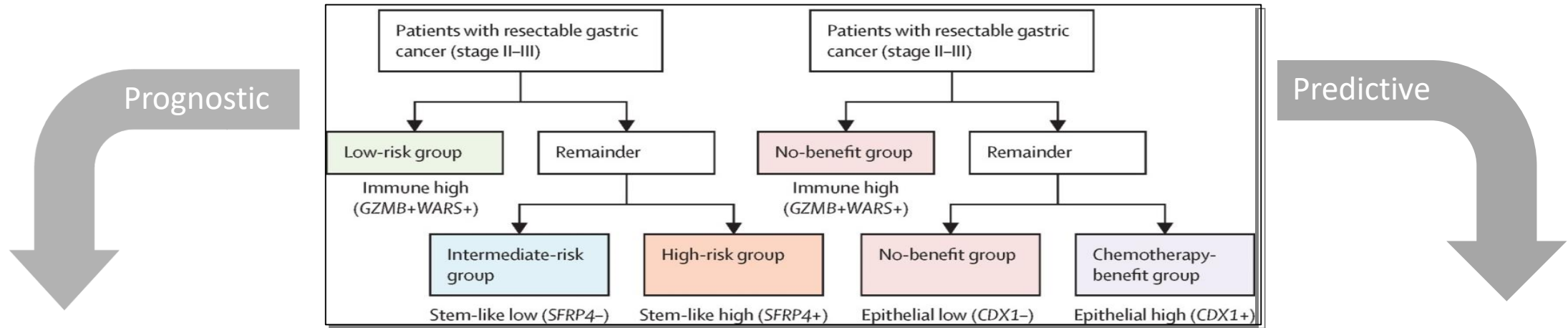
	0	5	10	15	20	25	30	36
A	345	314	267	228	206	171	149	116
B	340	309	268	237	215	188	158	123



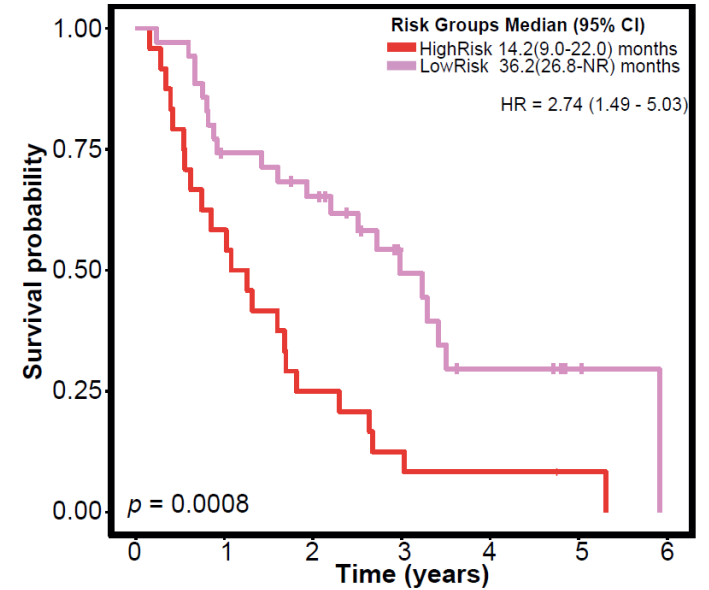
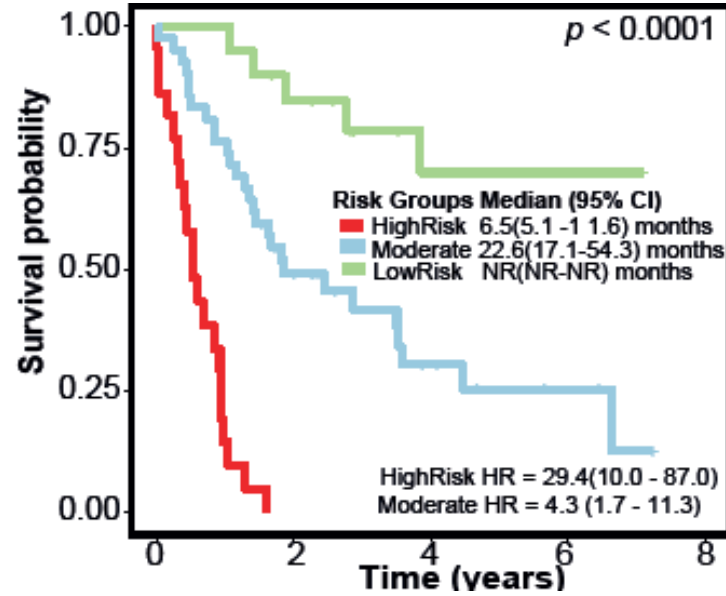
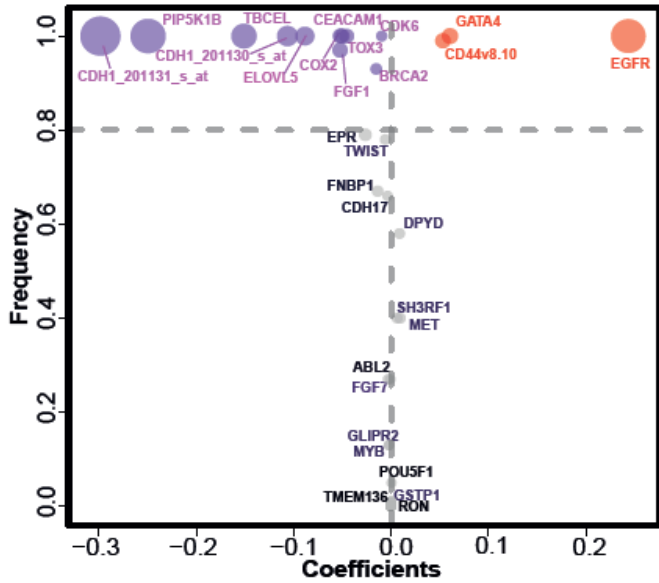
# LOOKING FOR BIOMARKERS!



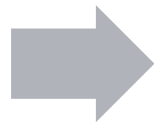
# PROGNOSTIC AND PREDICTIVE GENE SIGNATURE IN CLASSIC



# PROGNOSTIC POST-CHEMOTHERAPY 7- GENE SIGNATURE IN MAGIC



Prognostic gene selection



Risk group prognosis in MAGIC



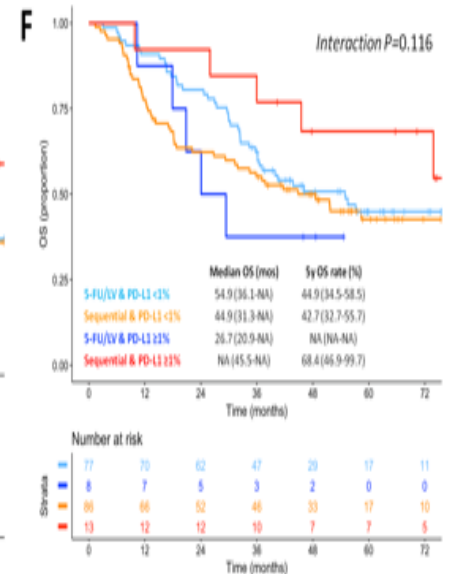
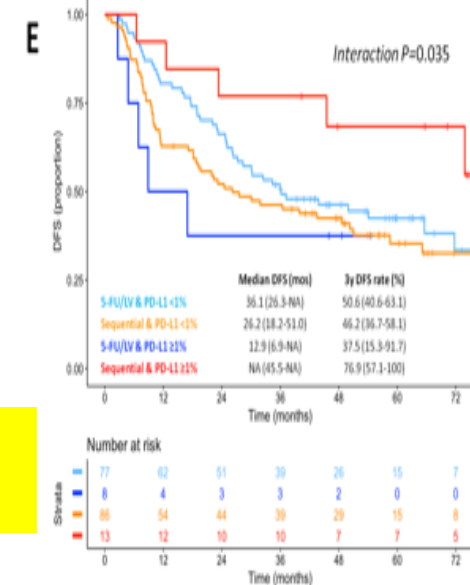
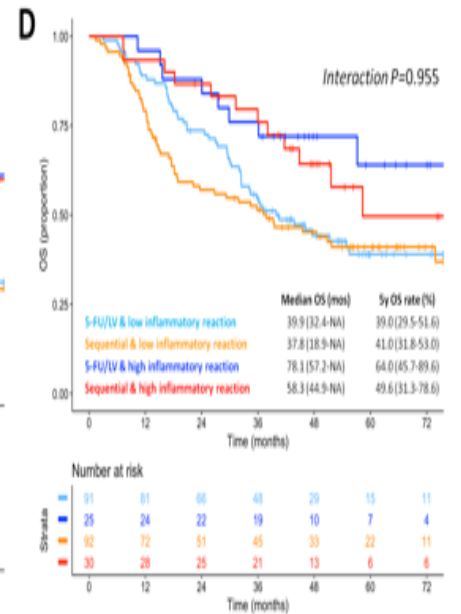
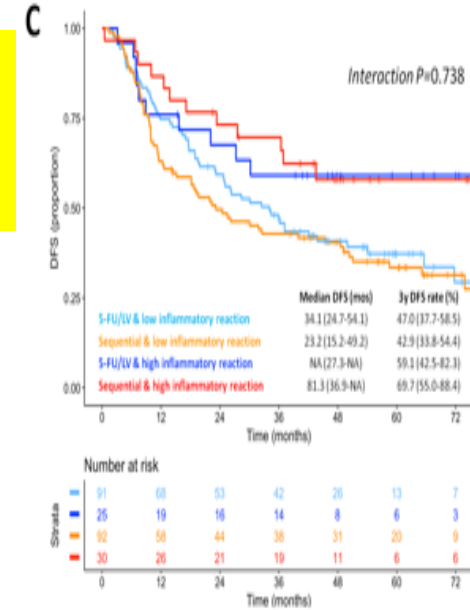
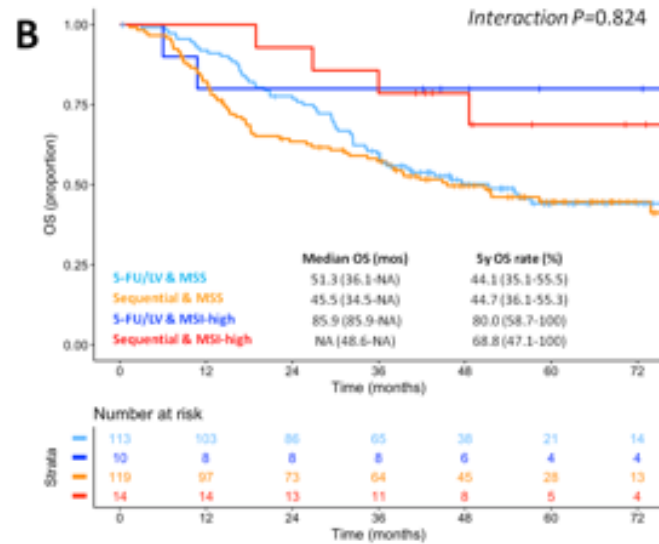
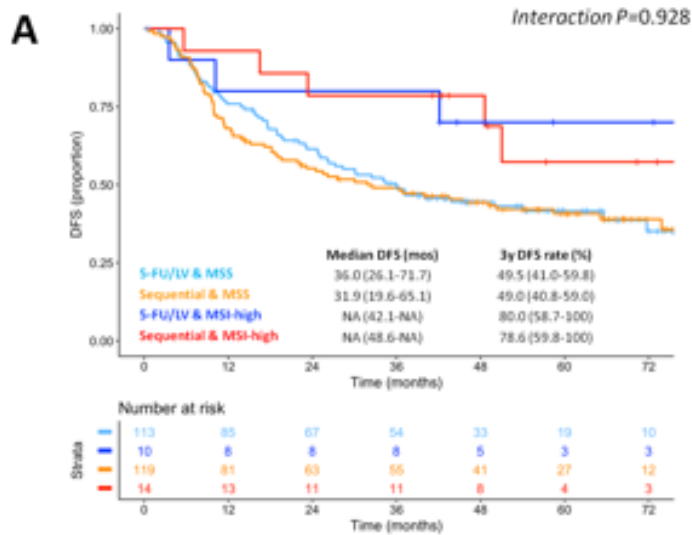
Validation using single sample predictor in independent dataset

# ITACA-S: K-M CURVES ACCORDING TREATMENT ARM



HIGH vs LOW INFLAMMATORY REACTION

MSI-H vs MSS



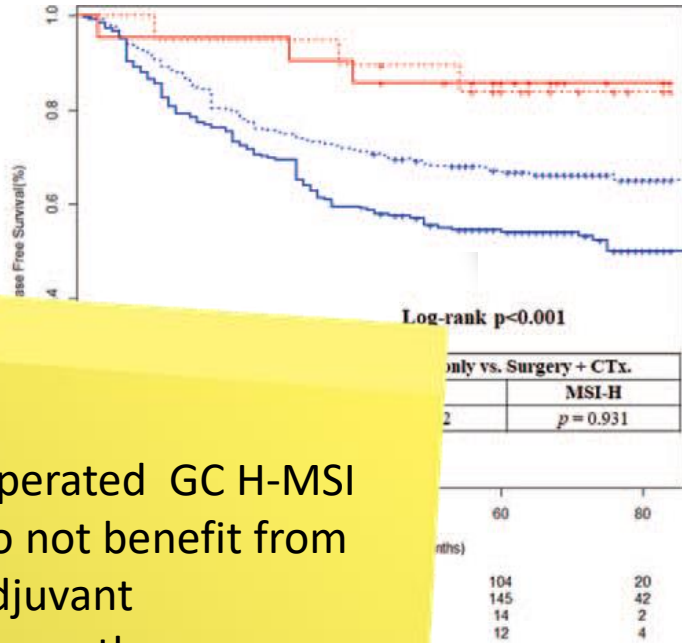
PDL-1 <1 vs PDL-1 ≥1

(Submitted for publication)

# PROGNOSTIC-PREDICTIVE ROLE OF MSI



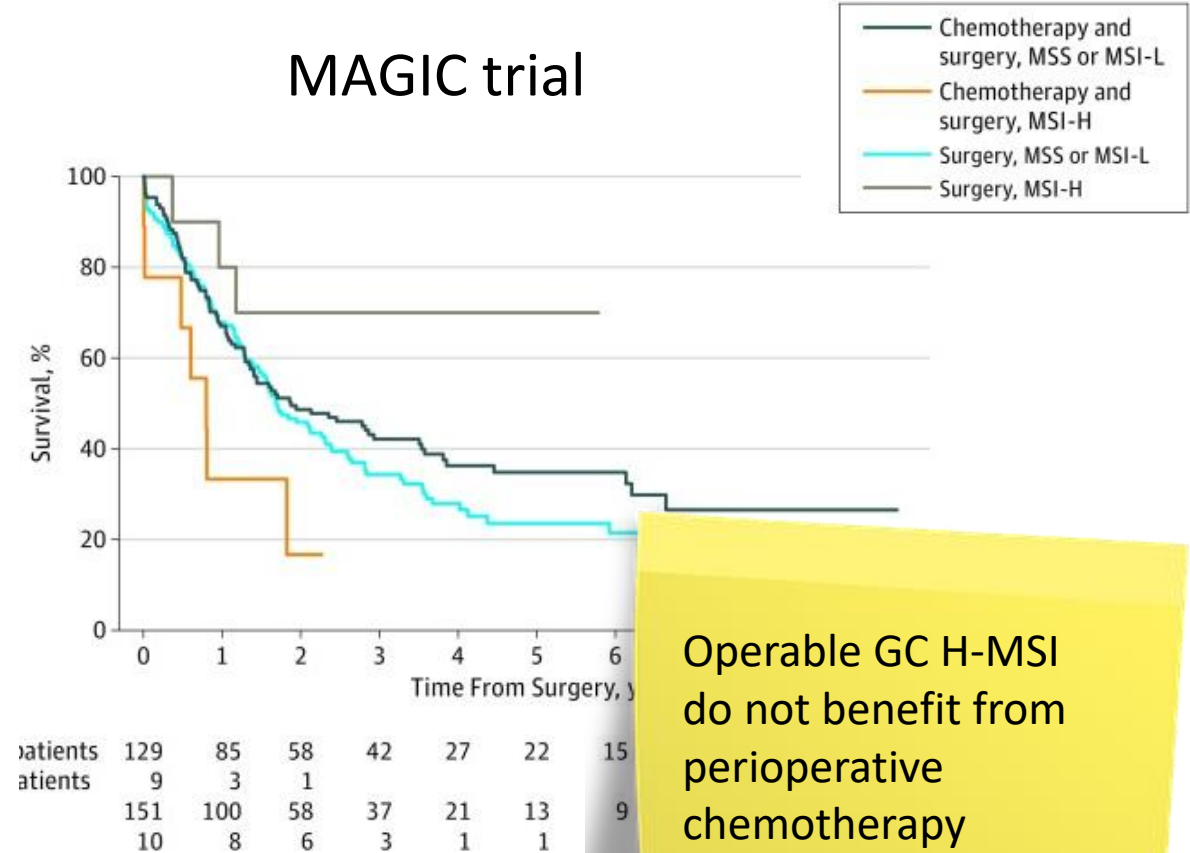
## CLASSIC trial



Operated GC H-MSI do not benefit from adjuvant chemotherapy

Surg 2018

## MAGIC trial



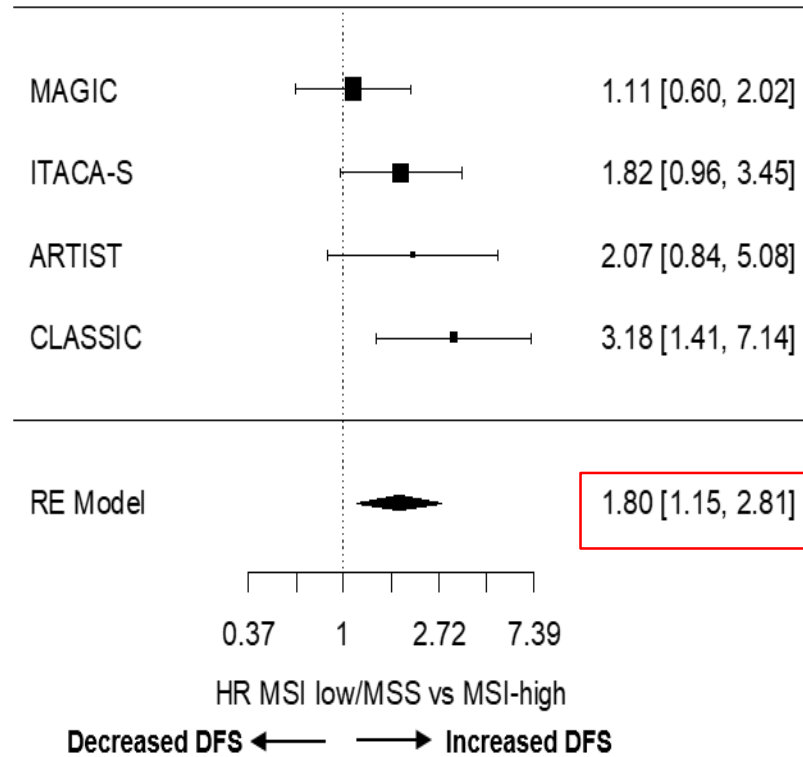
Operable GC H-MSI do not benefit from perioperative chemotherapy

Smyth et al, JAMA Oncol 2017

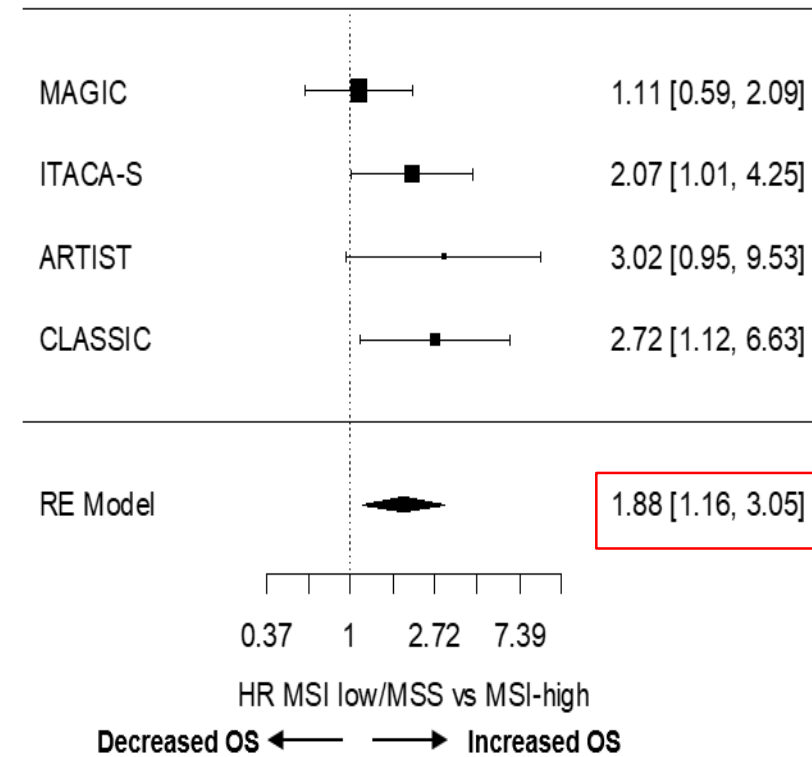
# META-ANALYSIS OF 4 RCTs: PROGNOSTIC ROLE



## Disease-free survival



## Overall survival





# MSI PREDICTIVE ROLE: IMPACT OF CHEMOTHERAPY IN MSI-HIGH AND MSS SUBGROUP

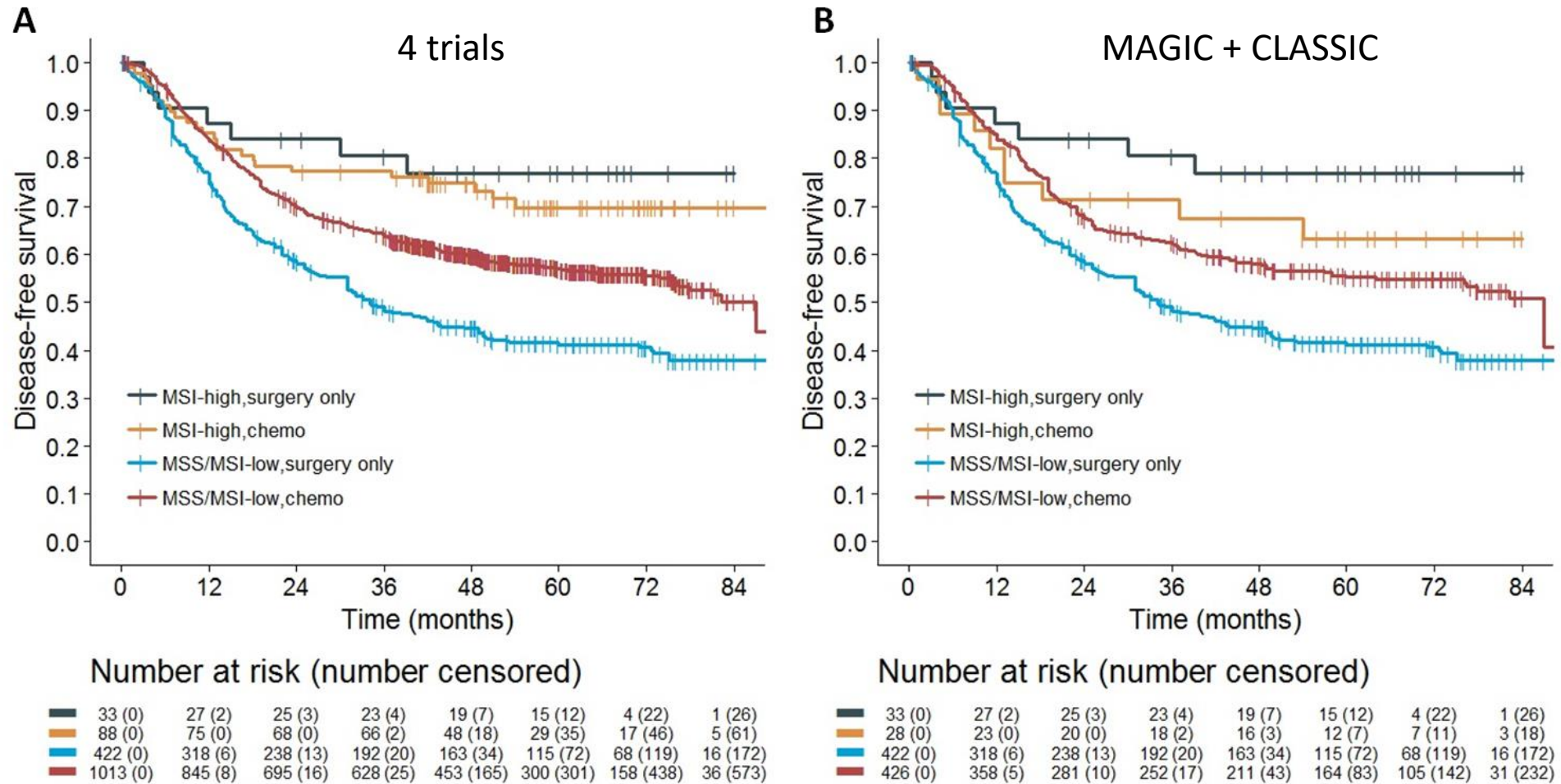


Treatment Comparison by MSI Status and Survival Type	MAGIC + CLASSIC + ITACA-S + ARTIST				MAGIC + CLASSIC			
	No. of Events	5-Year Survival, % (95% CI)	HR (95% CI)	<i>P</i> *	No. of Events	5-Year Survival, % (95% CI)	HR (95% CI)	<i>P</i> *
<b>DFS</b>								
MSS/MSI low: CT + surgery v surgery only	431 v 247	56.9 (53.8 to 60.2) v 41.2 (36.6 to 46.4)	0.65 (0.53 to 0.79)	.133	190 v 247	55.3 (50.7 to 60.4) v 41.2 (36.6 to 46.4)	0.66 (0.53 to 0.81)	.147
MSI high: CT + surgery v surgery only	25 v 7	69.8 (60.4 to 80.7) v 76.9 (63.2 to 93.6)	1.27 (0.53 to 3.04)		10 v 7	63.2 (47.4 to 84.4) v 76.9 (63.2 to 93.6)	1.45 (0.51 to 4.17)	
<b>OS</b>								
MSS/MSI low: CT + surgery v surgery only	368 v 198	62.0 (58.9 to 65.3) v 52.8 (48.0 to 58.0)	0.75 (0.60 to 0.94)	.180	156 v 198	62.4 (57.8 to 67.4) v 52.8 (48.0 to 58.0)	0.74 (0.59 to 0.93)	.070
MSI high: CT + surgery v surgery only	21 v 5	75.4 (66.4 to 85.6) v 82.8 (70.1 to 97.8)	1.50 (0.55 to 4.12)		10 v 5	63.1 (47.2 to 84.4) v 82.8 (70.1 to 97.8)	2.18 (0.69 to 6.94)	

# META-ANALYSIS: PREDICTIVE ROLE

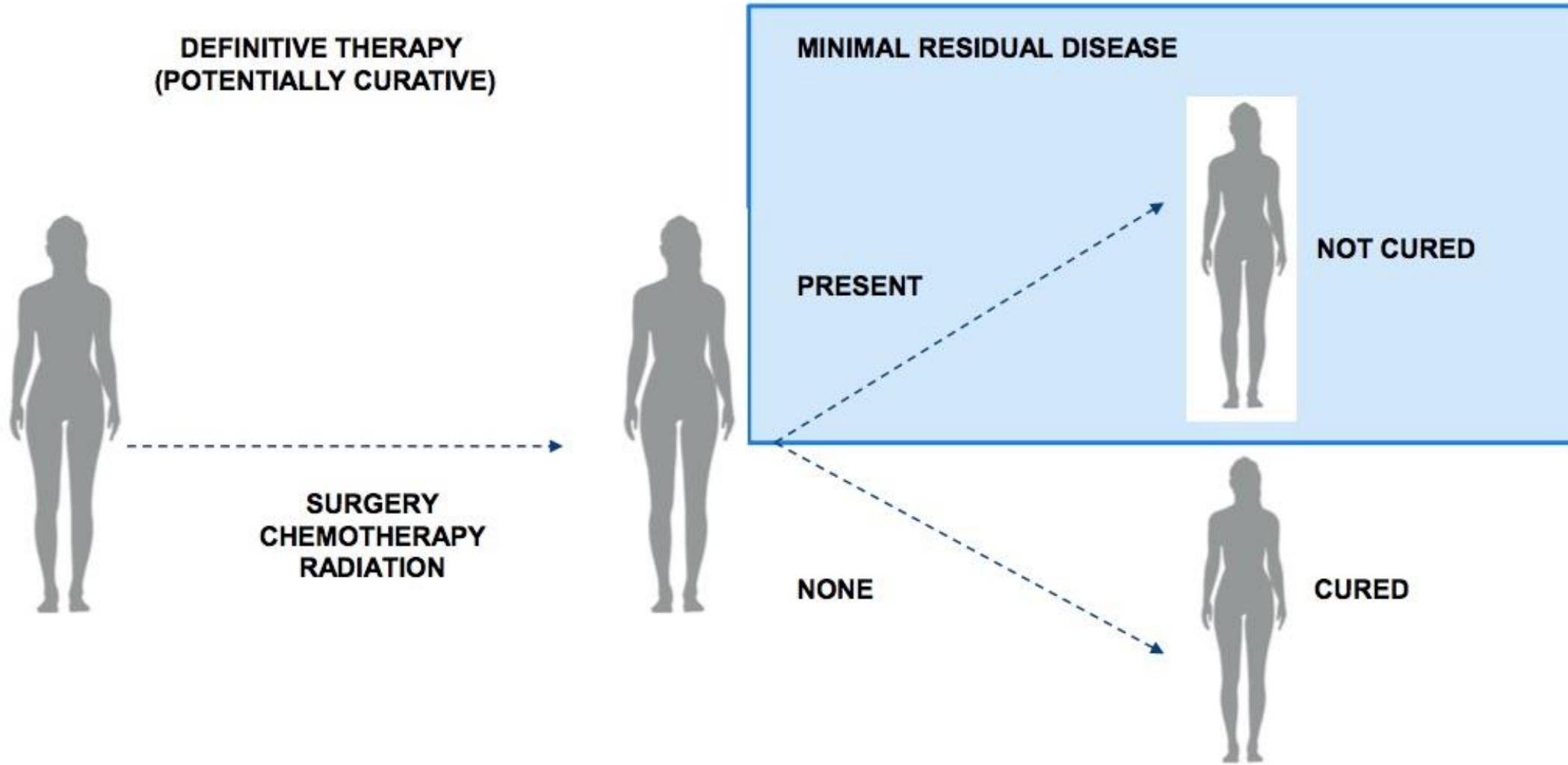


Kaplan-Meier curves of disease-free survival

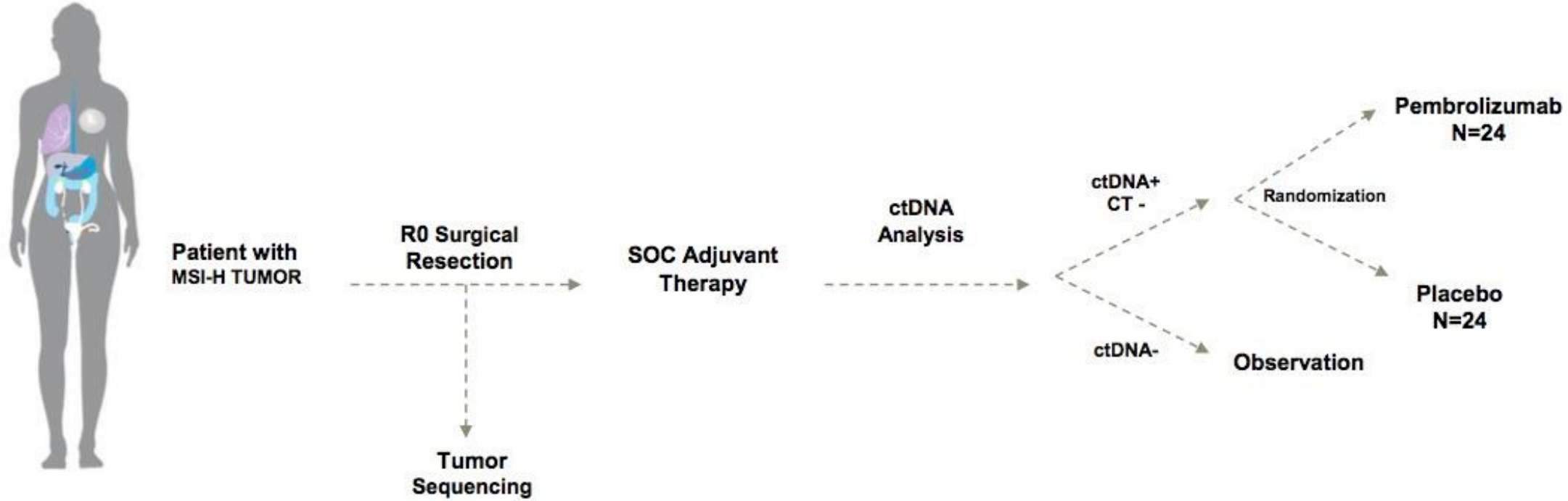


**MSI-H GC should not be treated preoperatively if resectable**

# WHAT IS MINIMAL RESIDUAL DISEASE (MRD)?



# A Randomized Double-Blind Study of Adjuvant Pembrolizumab vs. Placebo In Patients with MSI-H Tumors with Persistent ctDNA Following Surgery NCT03832569



**Year 1 Objective:** To demonstrate clearance of ctDNA at 12 months.

**Year 2, 3 and 5 Objectives:** To demonstrate improvement in DFS and OS.

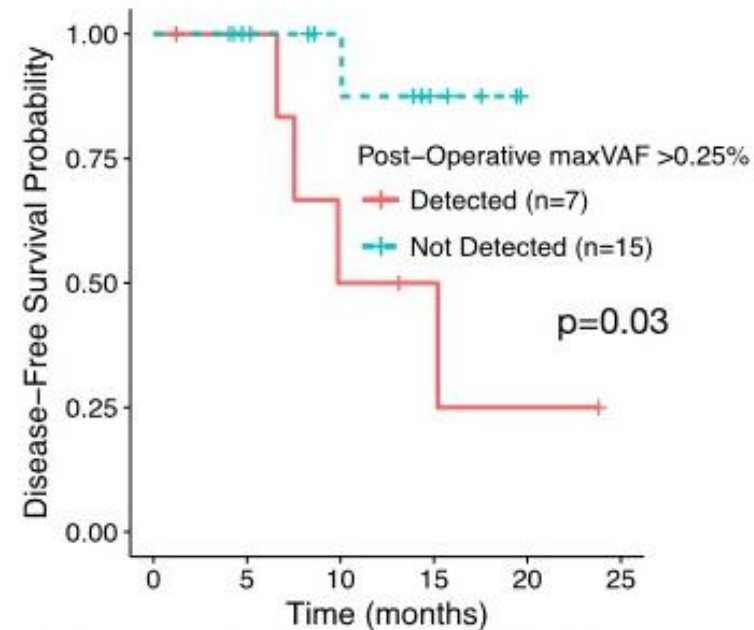


# ctDNA IN GASTRIC AND GASTROESOPHAGEAL: PROGNOSTIC, PREDICTIVE OR PRELIMINARY?



## ctDNA CAN IDENTIFY PATIENTS AT RISK FOR RECURRENCE GASTRIC CANCER

Within 6 months after surgery



Median mDFS  
12.5 vs NR month

- Detection was defined as maxVAF >0.25%

# SUMMARY



Chemoradioterapy benefits patients with limited nodal dissection.

Adjuvant chemotherapy improve survival. Doublet combination (XELOX) should be preferred.

Patients with H-MSI GC have a better prognosis and do not receive benefit from adjuvant and perioperative therapy.

Large prospective confrmatory studies are required before integrating ctDNA assessment.