Adjuvant chemotherapy for colon cancer

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Confict of interest

Honoraria :

Merck

Pfizer

Roche

BMS

Consultant for:

EMA

Aims

Adjuvante Chemotherapy is indicated in stage IIII (N+)

- **Capecitabine or (inf.) FU/LV are options for all patients**
- **FOLFOX / CapeOx are options for patients < 70y**

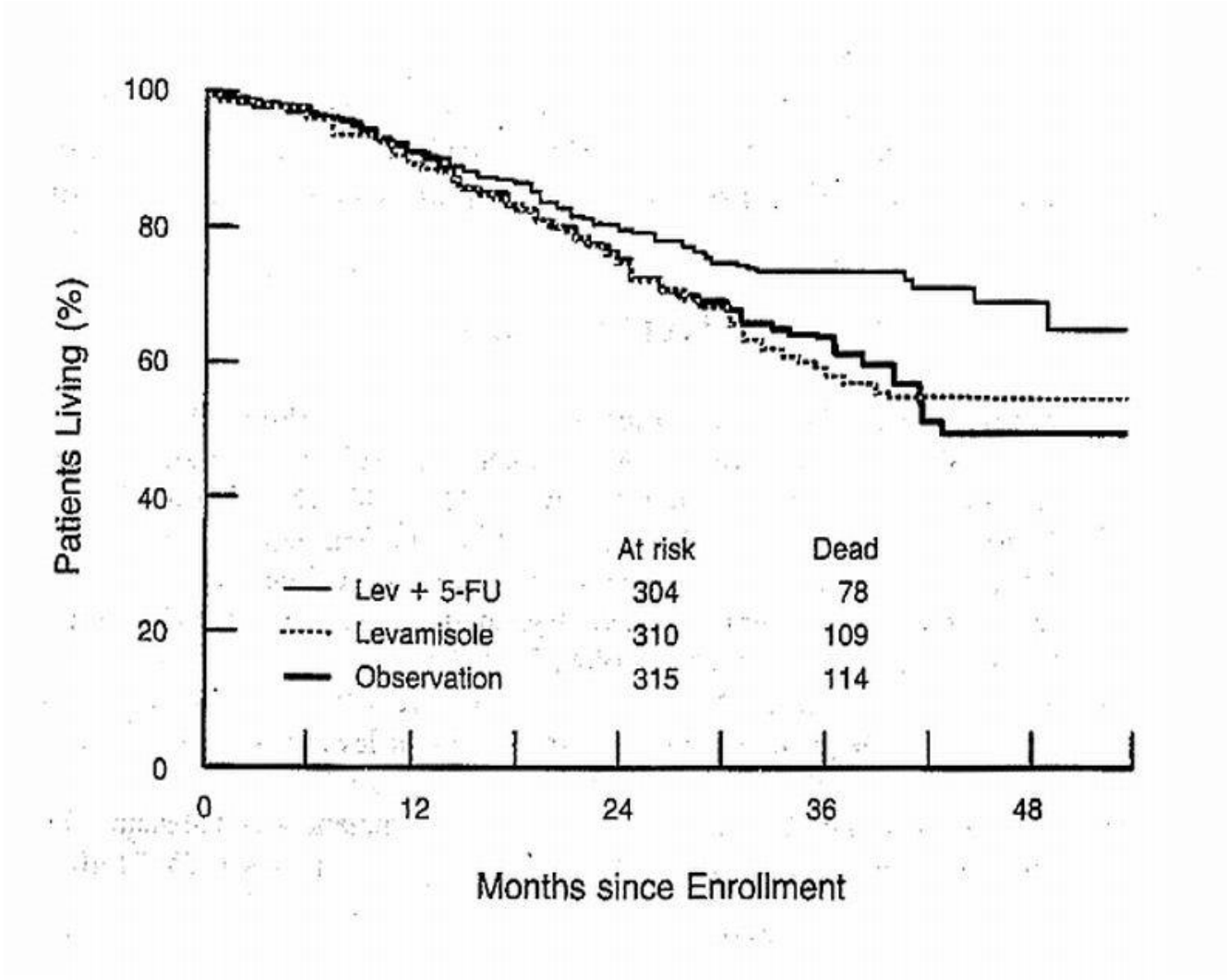
Adjuvant chemotherapy may be considered in high risk stage II patients, but most likely not with FOLFOX

Biologicals are no therapeutic option

Gen signatures are prognostic, ? but predictive ?

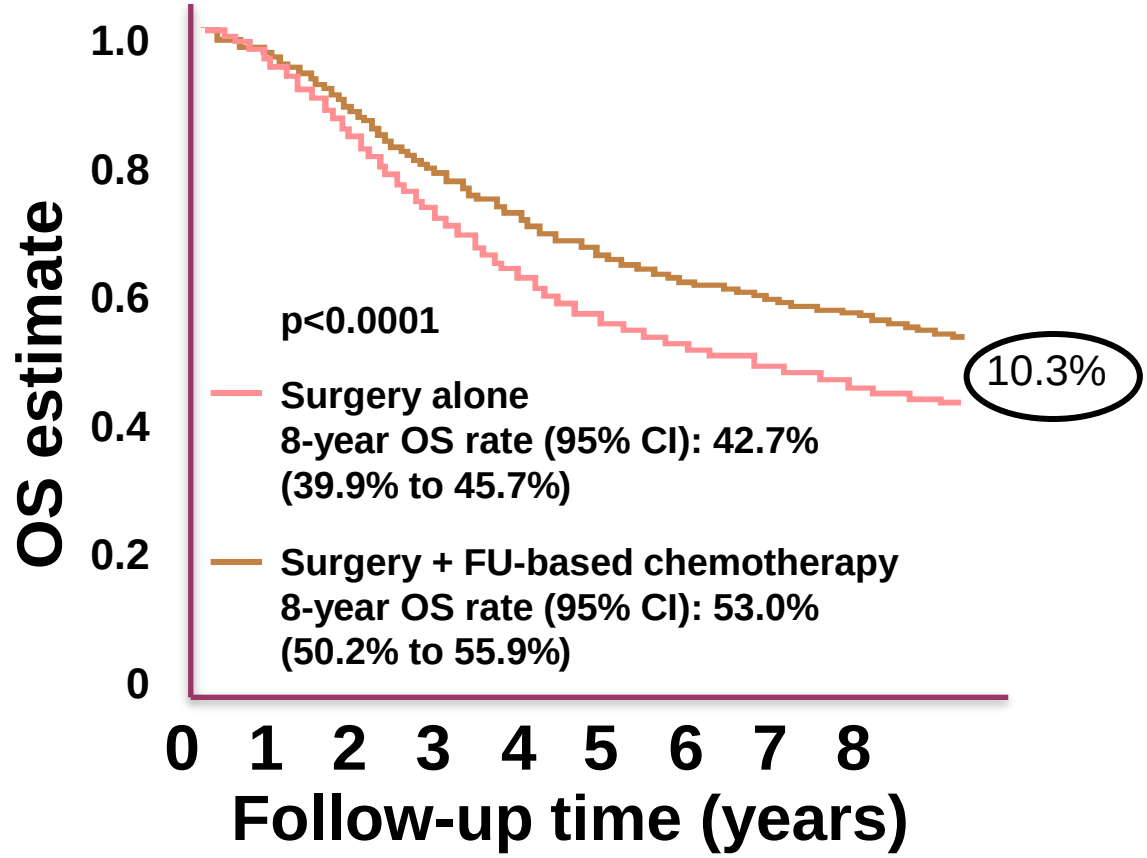
The decision for adjuvant therapy has to balances the risk of cancer and other competing risks

Benefits of adjuvant therapy in stage III colon cancer



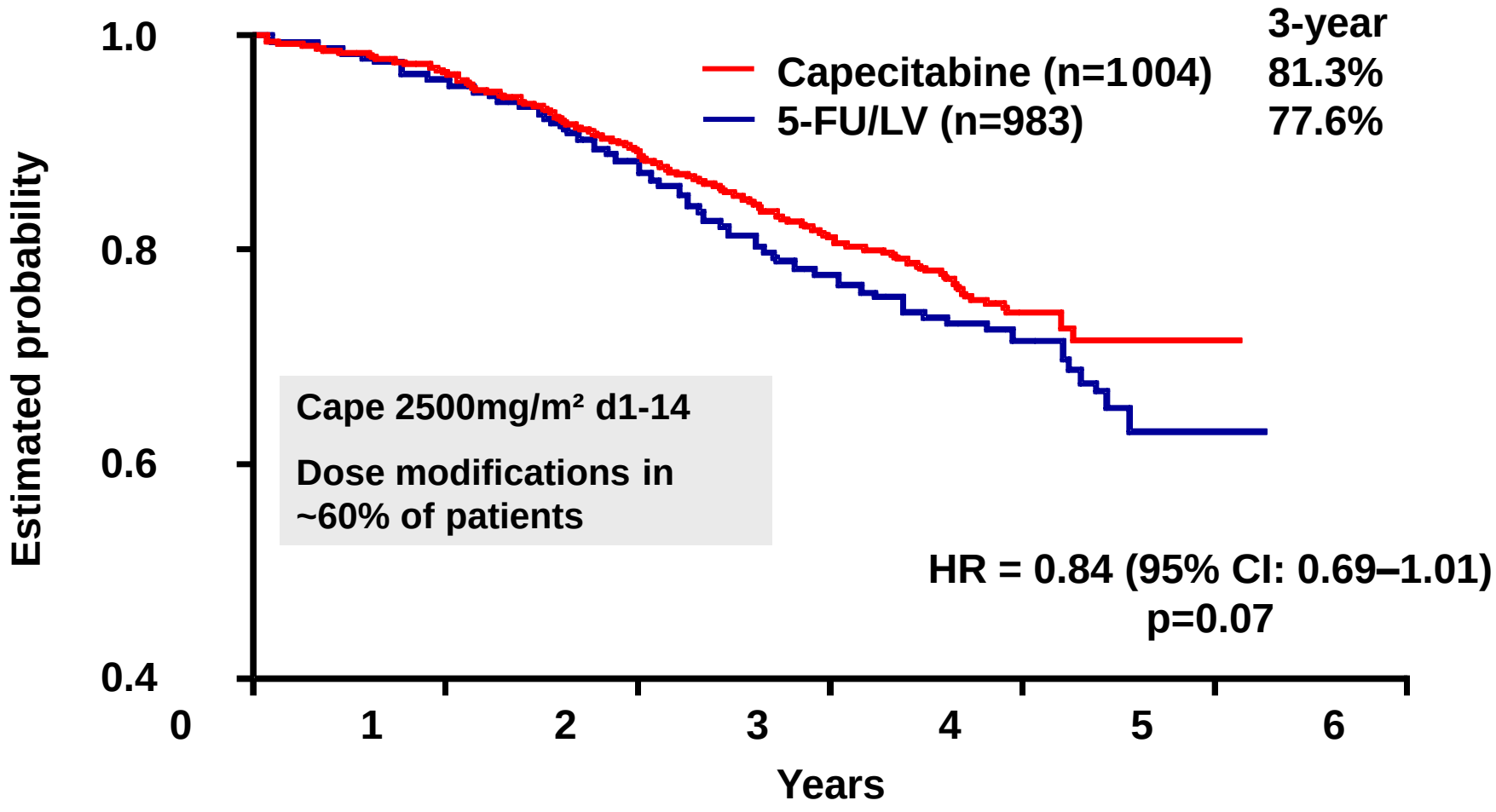
Moertel et al NEJM 1990

5FU Increases OS and Cure in Stage III colon cancer patients
Evidence in 13,793 Patients with Stage III



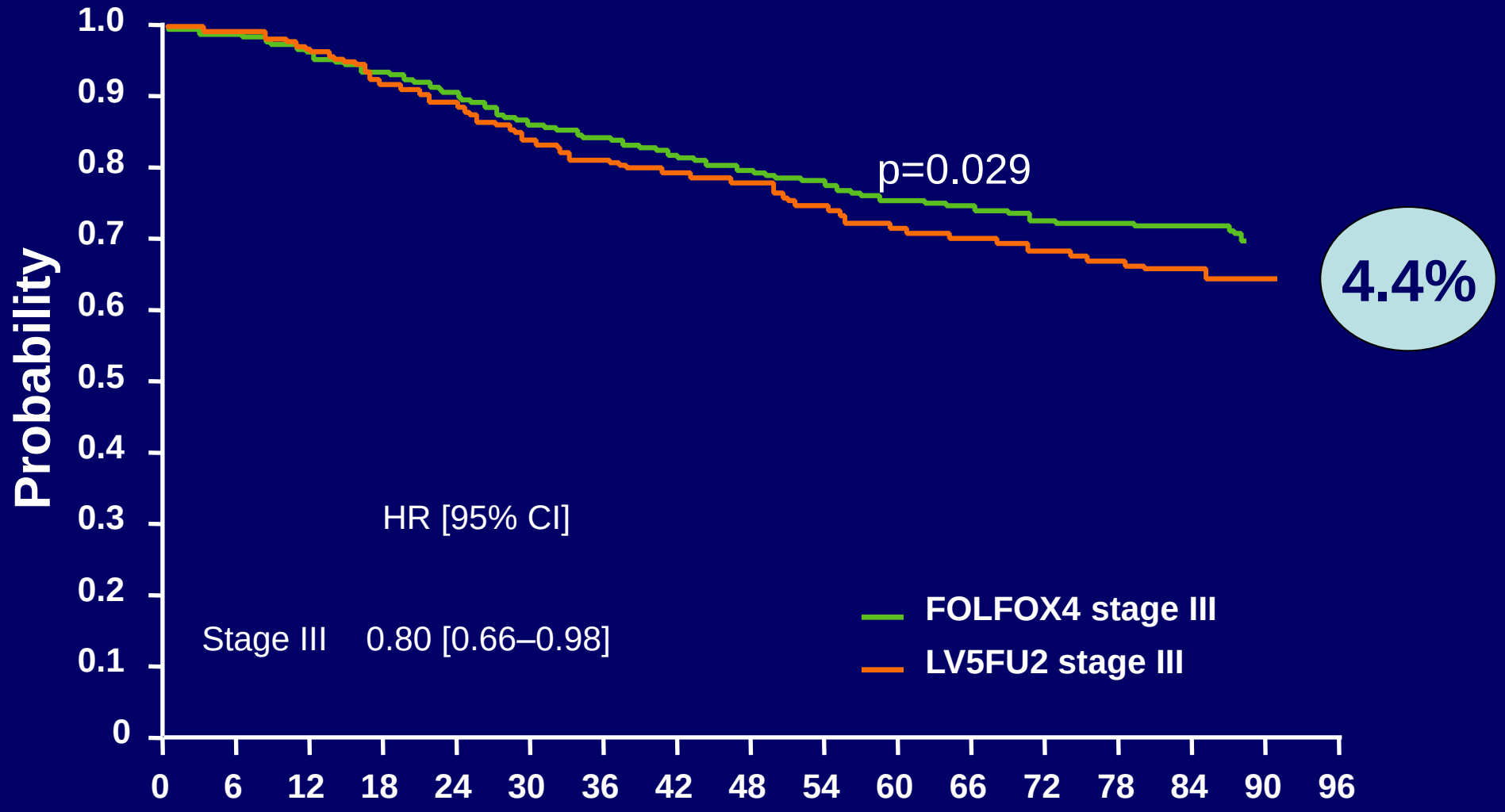
Sargent D, J Clin Oncol 2009

Stage III X-ACT: Overall Survival



Twelves et al. NEJM 2005

MOSAIK Study
Survival: Stage III



Data cut-off: January 2007

De Gramont et al. ASCO 2007

Fluoropyrimidines ± Oxaliplatin Stage III

	HR for DFS	P value	DFS Δ (%)	HR for OS	P value	OS Δ (%)
MOSAIC (1)	0.78 CI, 0.65-0.93 @ 5 year	0.005	Δ 7.5% 58.9% vs 66.4% @ 5 year	0.80 CI, 0.65-0.97 @ 6 year	0.023	Δ 4.2% 68.7% vs 72.9% @ 6 year
NSABP C-07 (2)	0.78 CI, 0.68-0.90 @ 5 year	0.0007	Δ 6.6 % 57.8% vs 64.4% @ 5 year	0.85 CI, 0.72-1.00 @ 5 year	0.052	Δ 2.7% 73.8% vs 76.5% @ 5 year
XELOXA (3)	0.80 CI, 0.69-0.93 @ 3 year	0.0045	Δ 4.4% 66.5% vs 70.9% @ 3 year	0.87 CI, 0.72-1.05 @ 5 year	0.1486	Δ 3.4% ND (57 months FU)

1 André T, J Clin Oncol. 2009
2 Yothers G, J Clin Oncol 2011
3 Haller D, J Clin Oncol 2011

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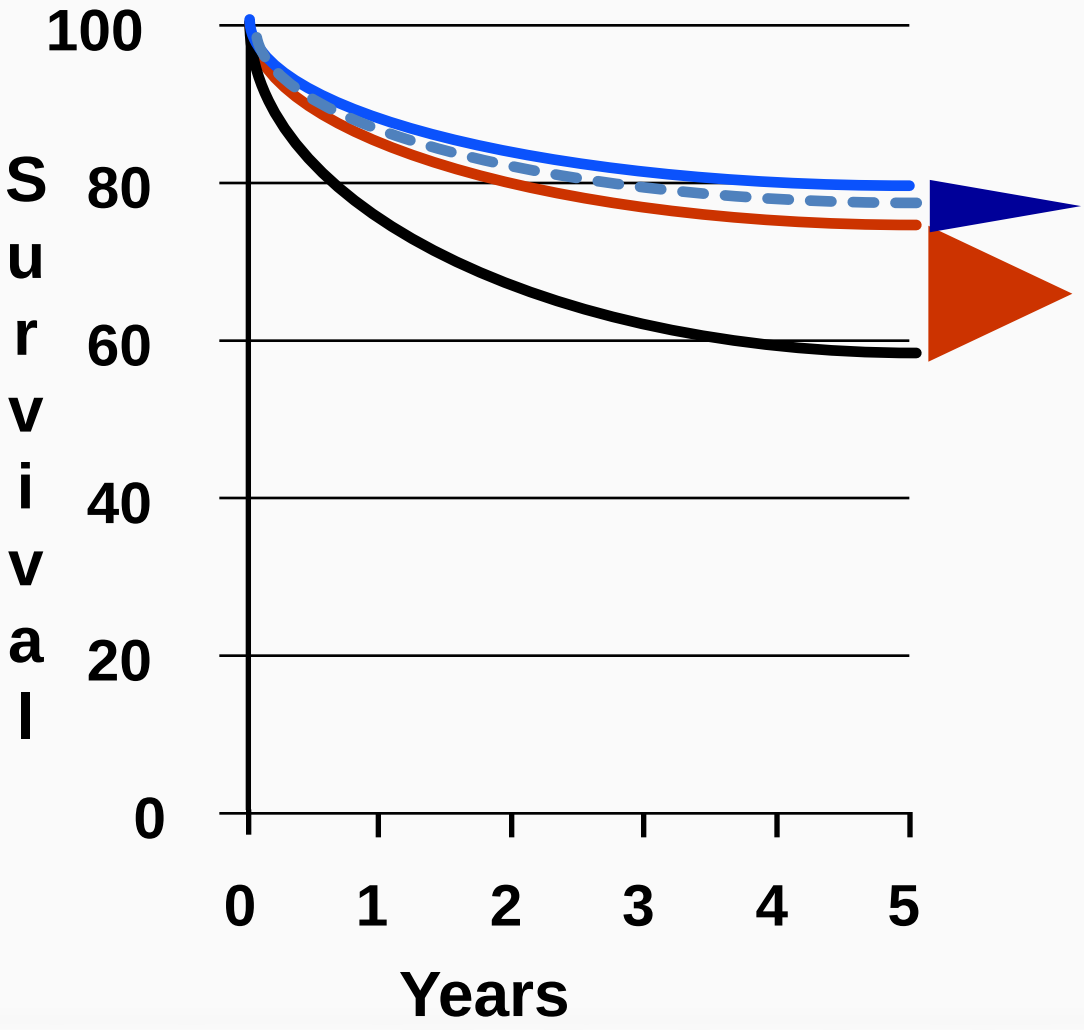
X-ACT FU/FA bolus vs. Capecitabine	**0.87** CI, 0.75-1.00 @ 3y	0.0528	**Δ 3.6%** 60.6% vs. 64.2% @ 3y	**0.84** **CI: 0.69–1.01** **@3y**	**p=0.07**	**Δ 3.7%** **77.6% vs. 81.3%** **@3y**

1 André T, J Clin Oncol. 2009
2 Yothers G, J Clin Oncol 2011
3 Haller D, J Clin Oncol 2011

The achievements:
Adjuvant chemotherapy for stage III colon cancer



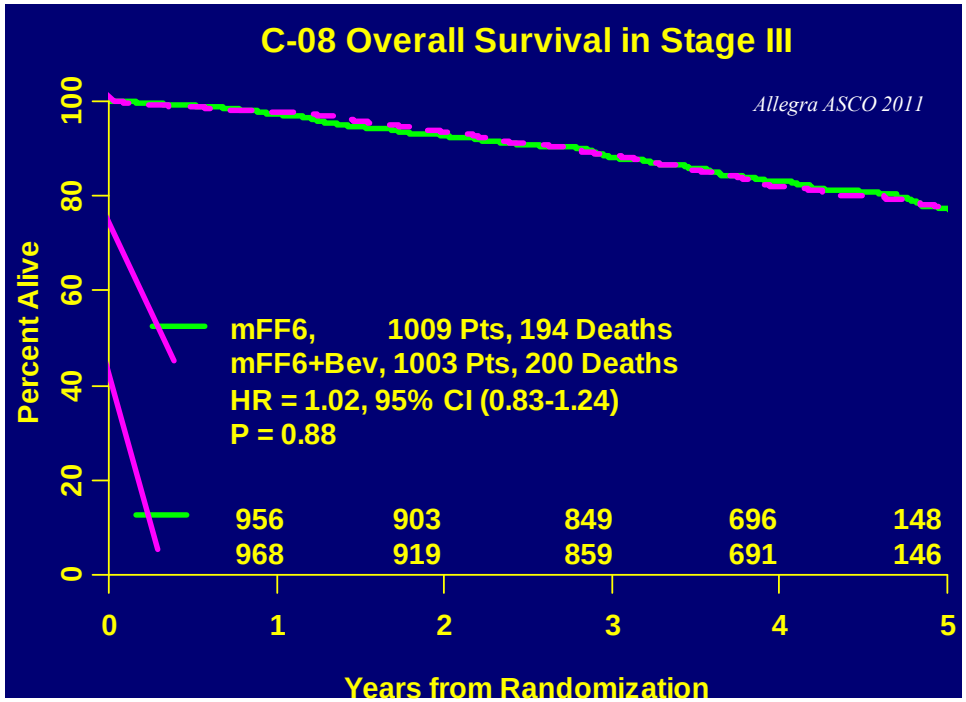
FOLFOX + 4%

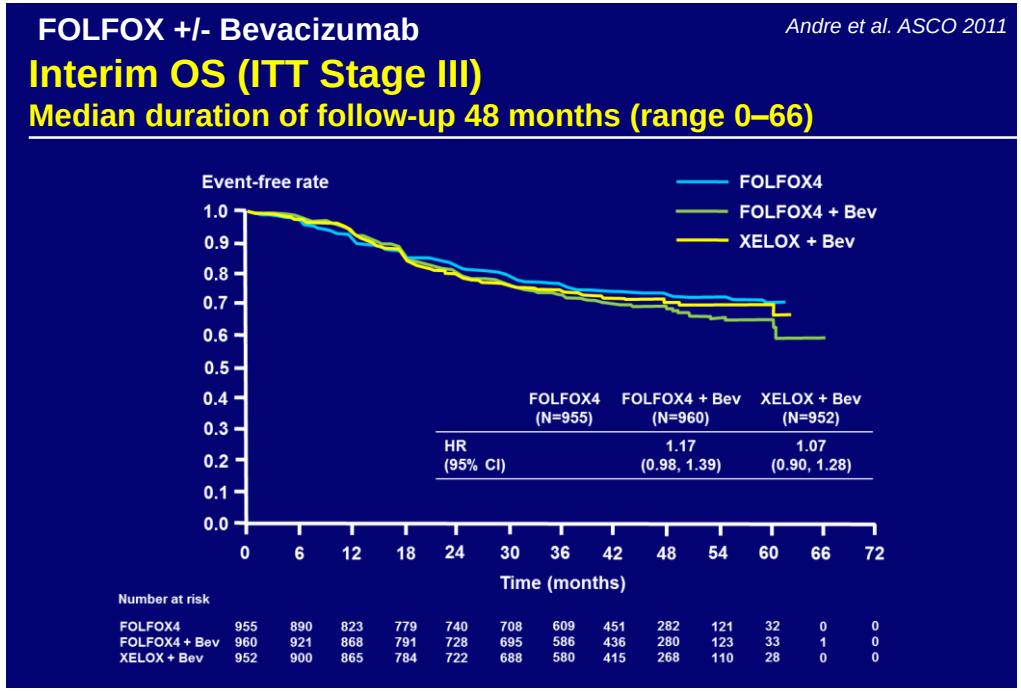
(Cape ? + 3%)

FU/FA +15%

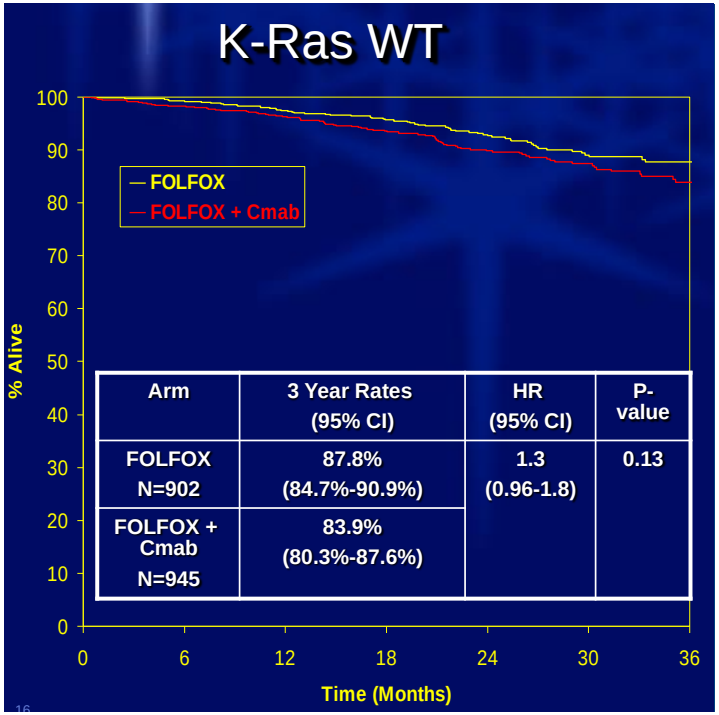
Total ~ 20%

Bevacizumab for adjuvant therapy in Colon Cancer
- negative data -

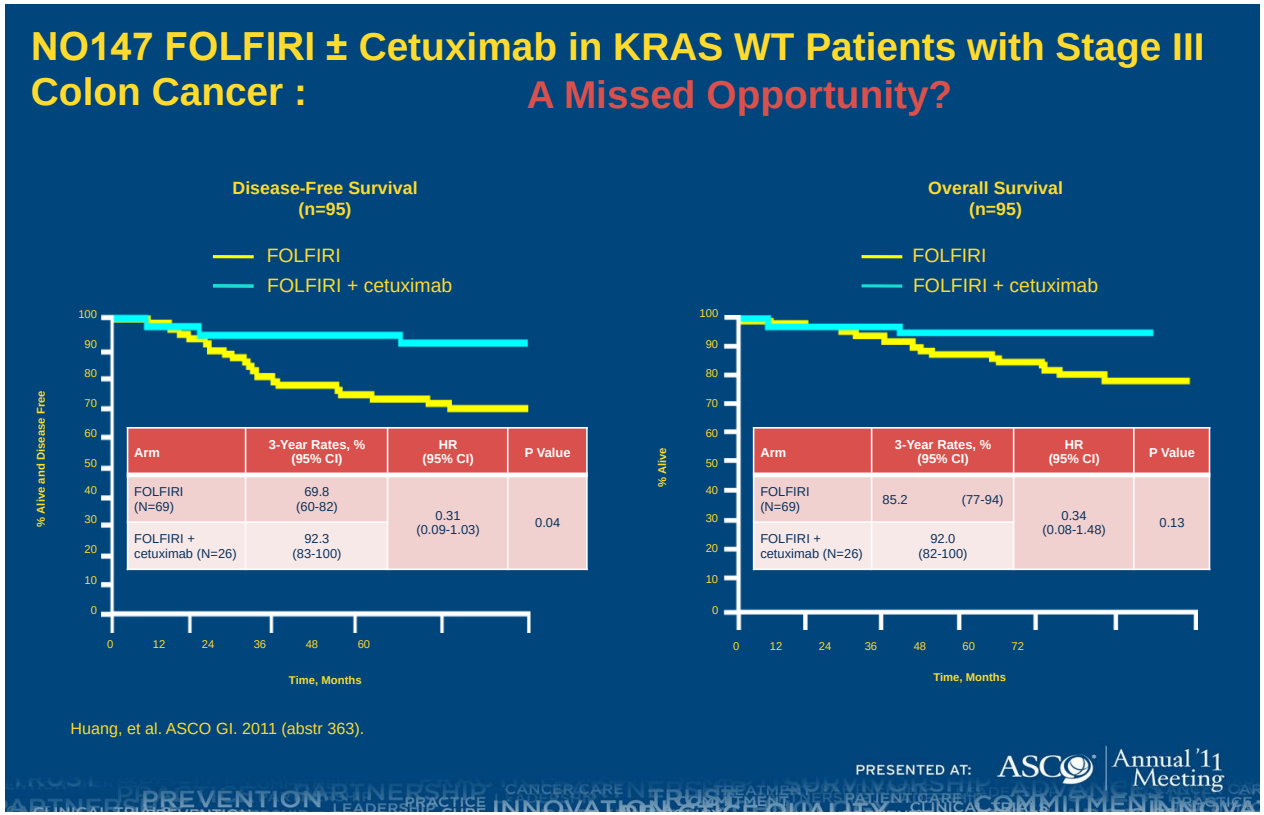




Cetuximab for adjuvant therapy in Colon Cancer
- negative data for FOLFOX –
- FOLFIRI a missed opprotunity ? -

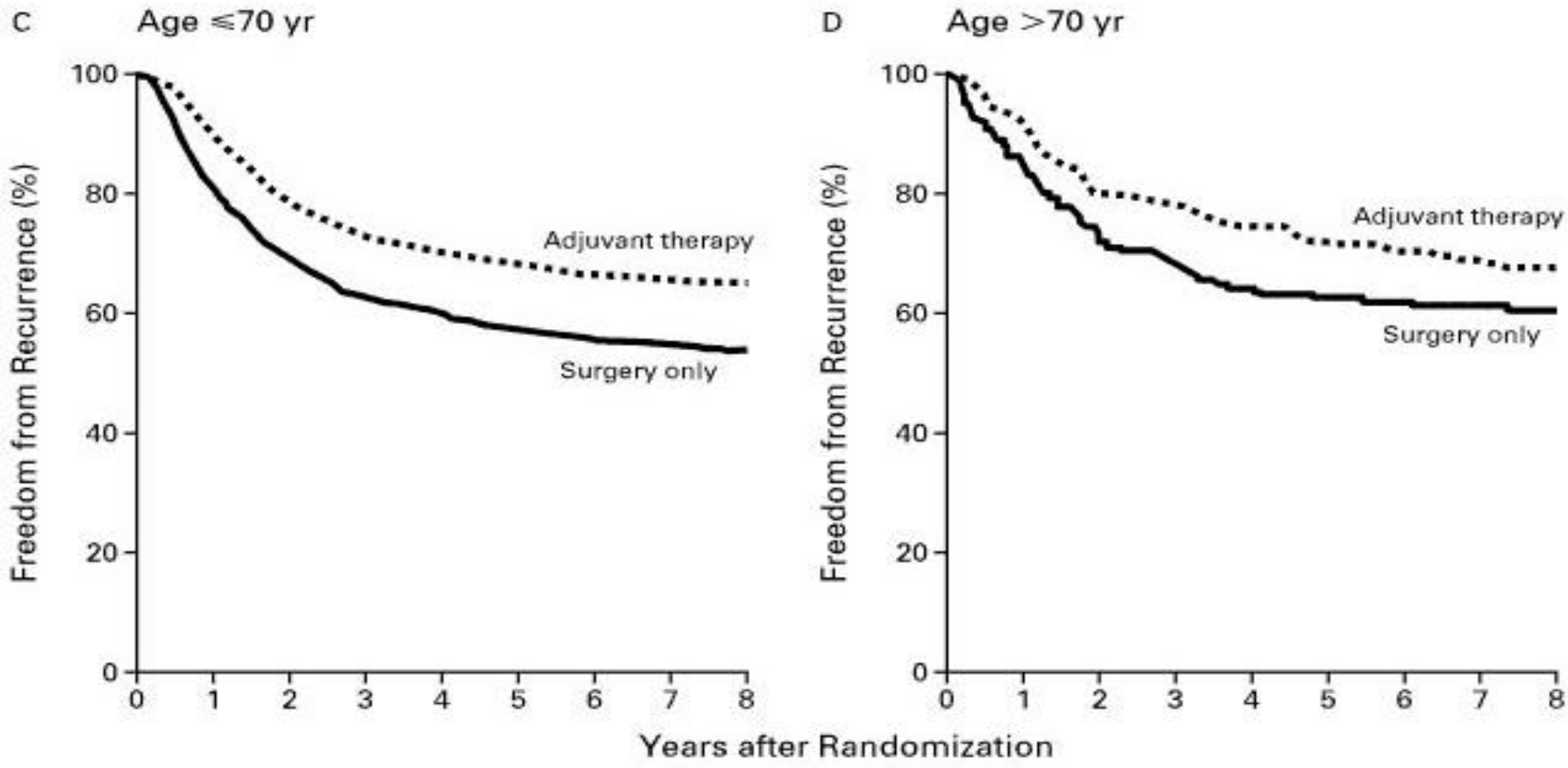


Goldberg et al. ASCO 2010



Huang et al. ASCO 2011

Elderly patients
Treatment with FU plus LV or levamisol
n= 3351 (15% > 70y) 7 trials



Sargent et al. NEJM 2001

Elderly patients and Oxaliplatin
ACCENT analysis and NO16968 data

	Hazard ratio (95% CIs)*	
	DFS	OS
ACCENT analysis[4†]		
<70 years (n=3877)	0.77 (0.68–0.86)	0.81 (0.71–0.93)
≥70 years (n=703) 18%	1.04 (0.80–1.35)	1.18 (0.90–1.57)
Interaction of age by treatment	p=0.016	p=0.037
NO16968 (XELOXA) n= 1886		
<70 years (n=1477)	0.79 (0.66–0.94)	0.86 (0.69–1.08)
≥70 years (n=409) 28%	0.87 (0.63–1.18)	0.94 (0.66–1.34)
Interaction of age by treatment	p=0.6222	p=0.7065

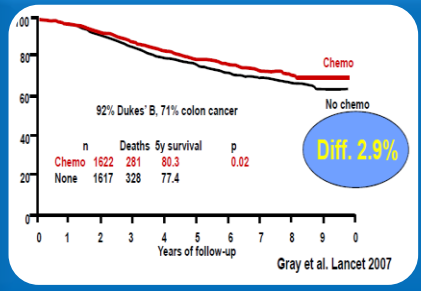
†CO7 + MOASAIK

Elderly and adjuvant FOLFOX vs. FU/LV
Updated MOSAIK data srage II and stage III

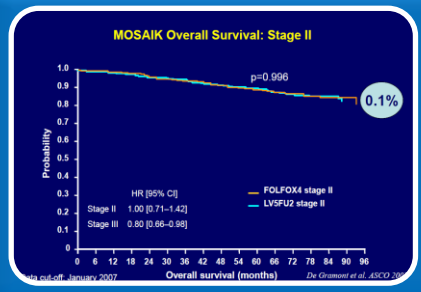
		5 y DFS		6y OS	
Age	**NPat**	**HR**	**P-value**	**HR**	**P-value**
< 70y	**1931**	**0.78** .66-.92	**.003**	**.80** .66-.97	**.020**
> 70y	**315 (16%)**	**.93** .64-1.35	**.710**	**1.10** **.73-1.65**	**.661**

Tournigant et al. JCO 2012

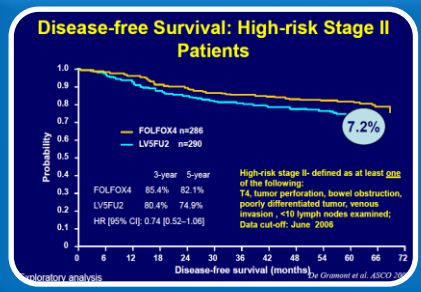
Stage II



Small survival benefit (3%) with 5-FU



No further improvement with FOLFOX



?? Does a Clinically defined high risk group benefit from FOLFOX (PFS) ??

Stage II Colon Cancer a heterogenous disease

Stage I	T	N	5y OS
II A	T3	N0	88 %
II B	T4a	N0	80%
II C	T4b	N0	58%

T4a: tumor penetrate the surface of the visceral peritoneum
T4b: tumor directly invades or is histologically adherent to other organs/structure

Controversy of Adjuvant Treatment of Stage II Disease due to

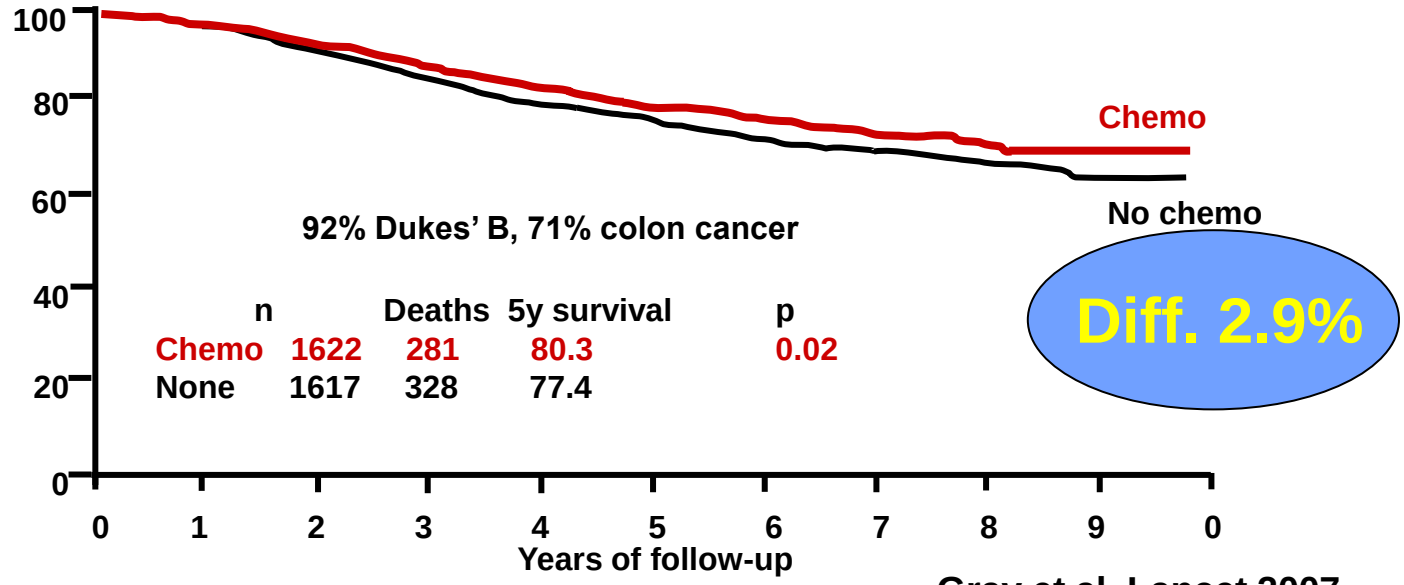
- **Lack of purely stage II randomized trials in CRC**
- **Small survival benefit (2-3%)**

Clinical Data in Stage II Colon Cancer

- Randomized trials: Stage II subsets

Study	N	Arms	5y OS
Intergroup 0035	935	5FU/LV vs. Obs.	72% vs. 72%
QUASAR	3238	FU vs. Obs.	80% vs. 77%
IMPACT B2	1016	5FU vs. Obs.	82% vs. 80%

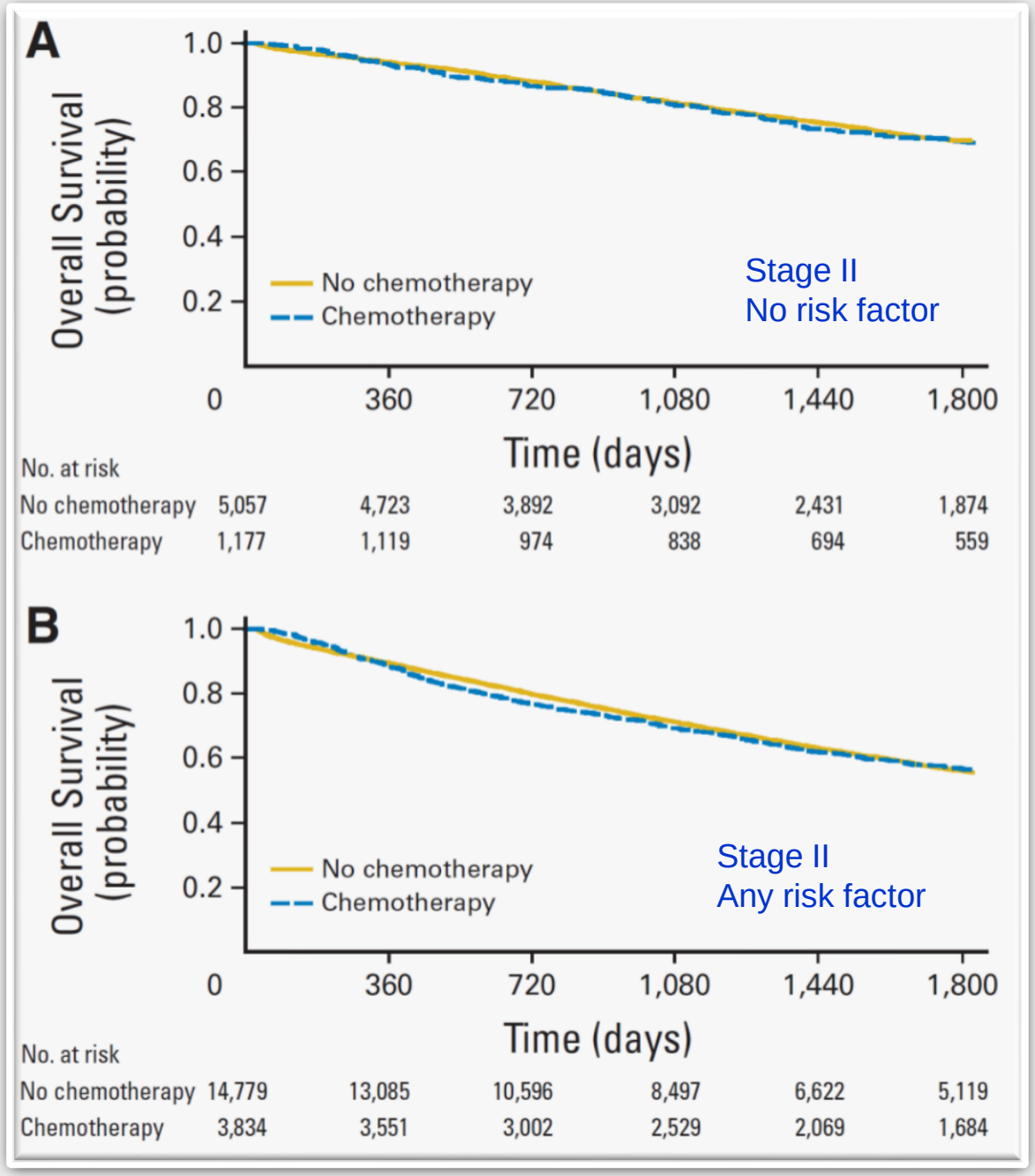
- **QUASAR-1:superior OS with adjuvant therapy for stage II disease**

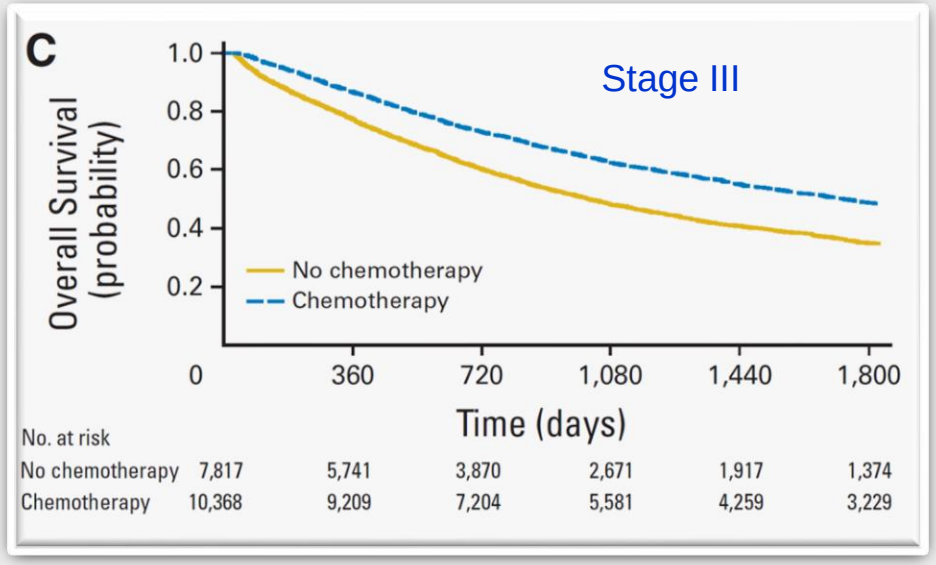


Gray et al. Lancet 2007

SEER (Medicare) Database
Patients > 65y
Stage II and III

n=43032 1992-2005

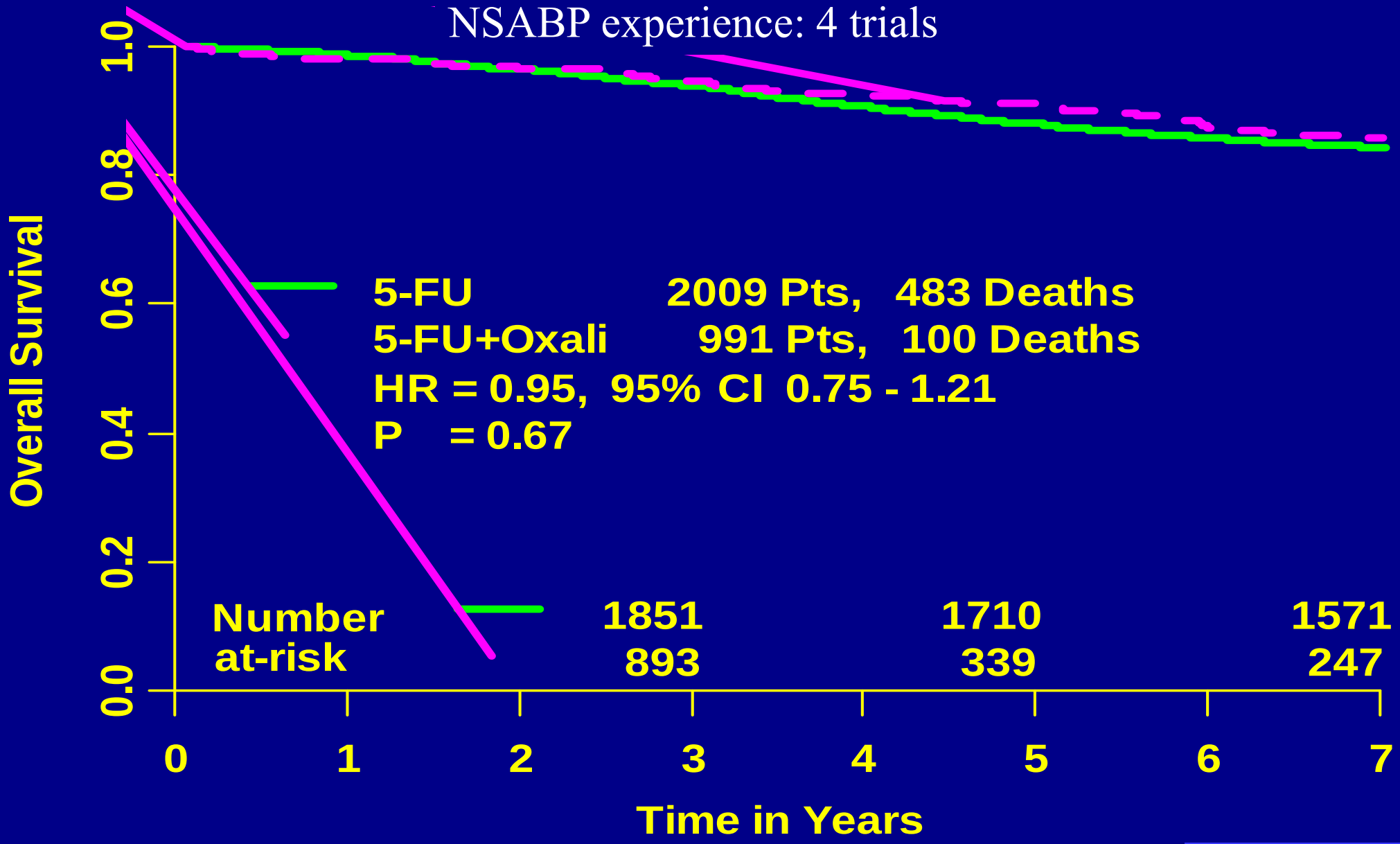




O'Connor et al. JCO 2011

Adjusted* Kaplan Meier Estimate of OS in Stage II

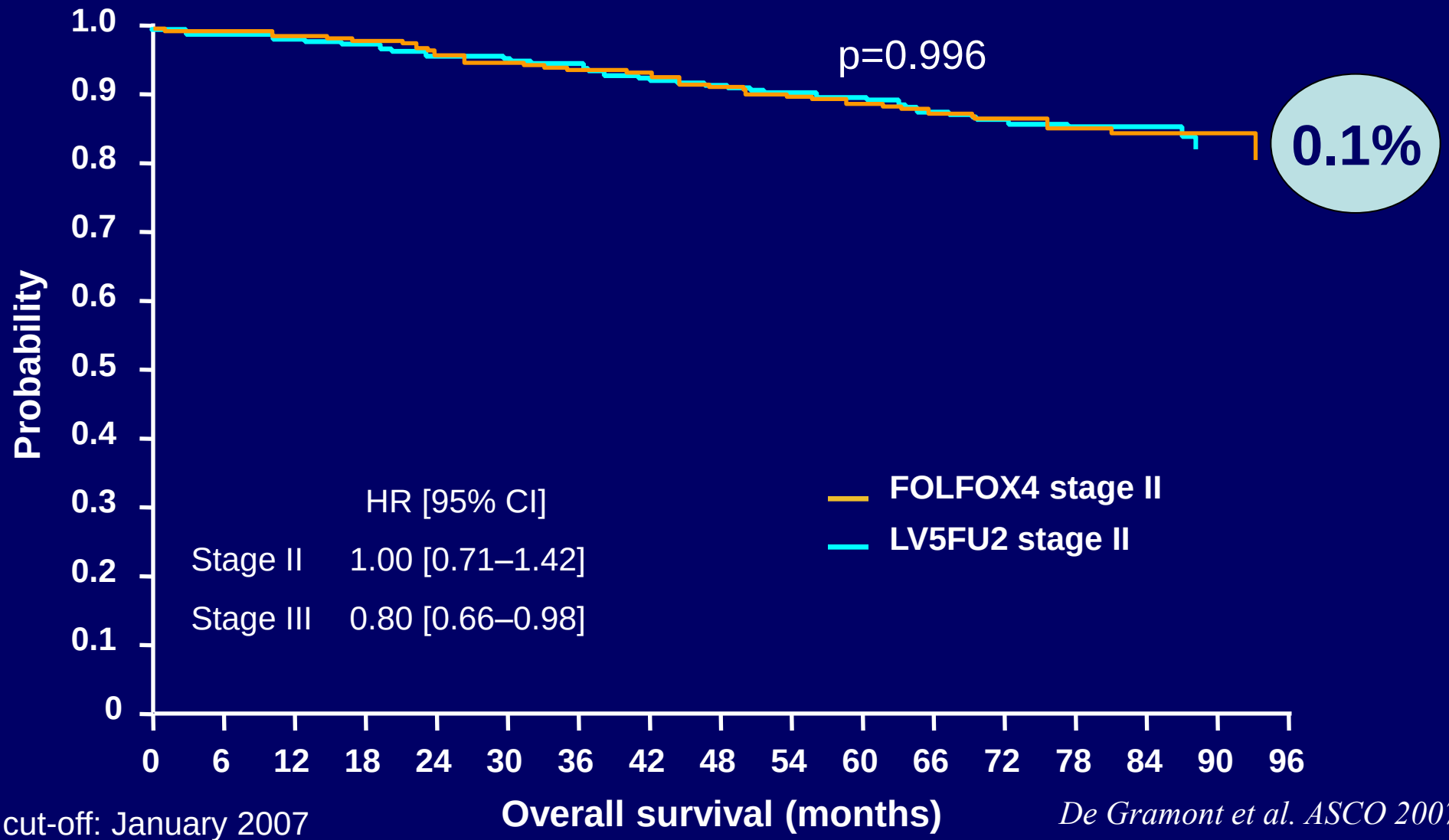
NSABP experience: 4 trials



*Adjusted for age, gender, race, nodes examined, and T-stage

Yothers ASCO 2011

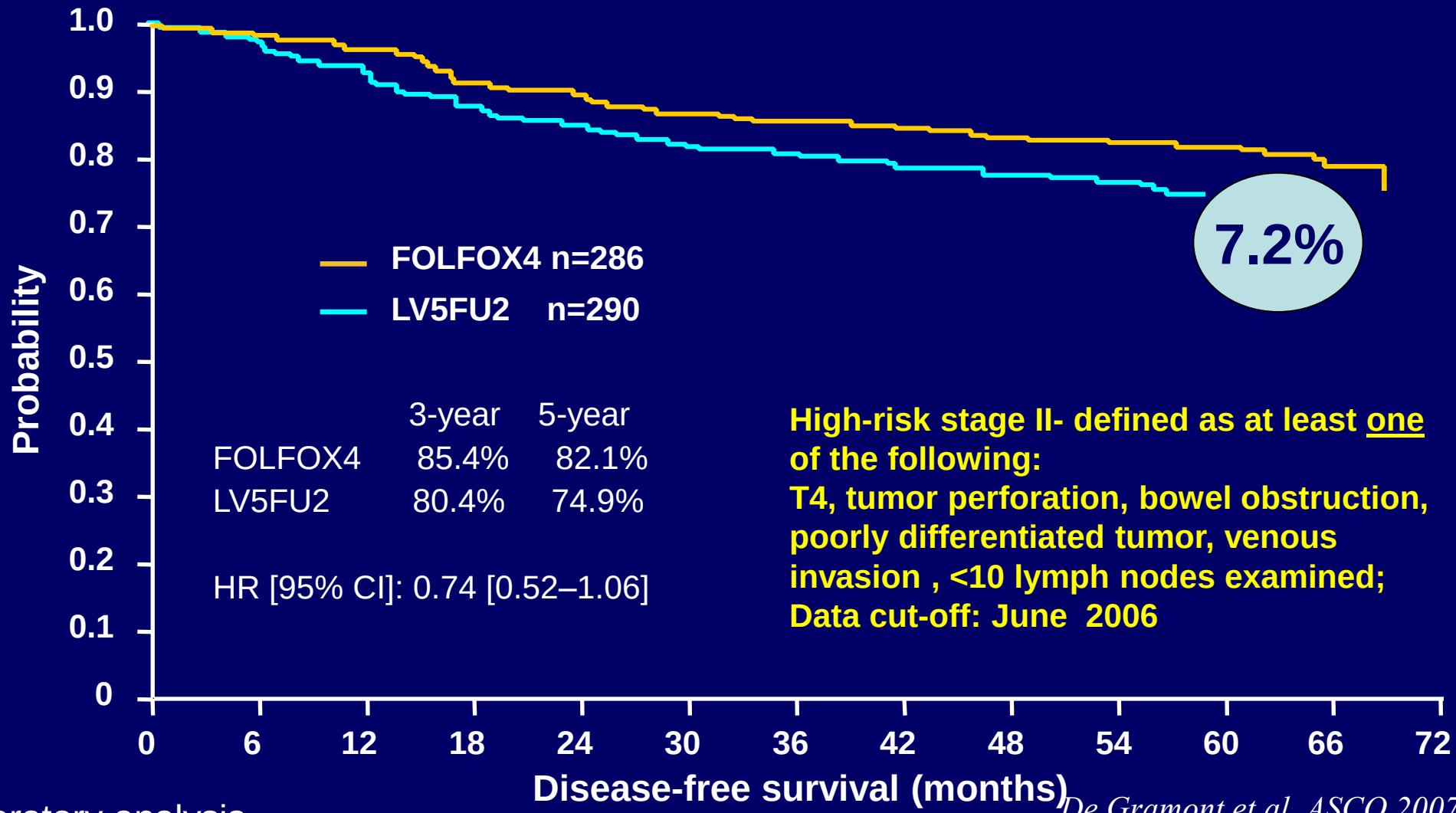
MOSAIK FOLFOX vs. FU/LV
Overall survival all stage II patients



Data cut-off: January 2007

De Gramont et al. ASCO 2007

MOSAIK: disease free survival
High-risk Stage II Patients



	3-year	5-year
FOLFOX4	85.4%	82.1%
LV5FU2	80.4%	74.9%

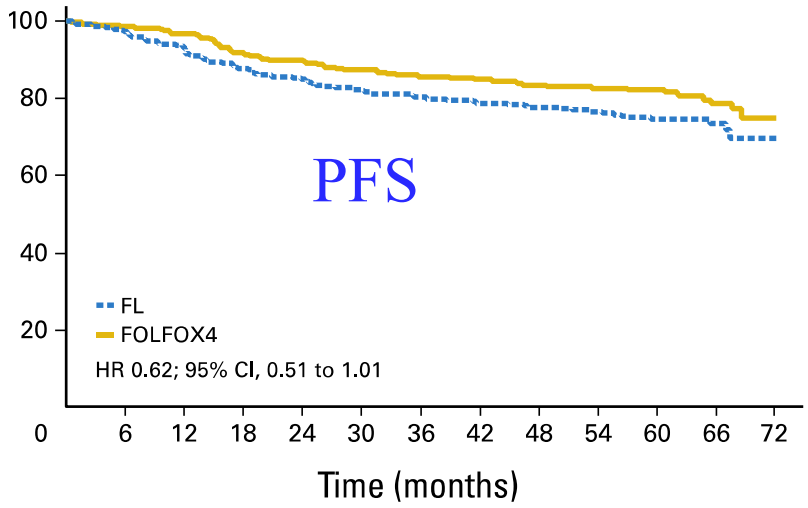
HR [95% CI]: 0.74 [0.52–1.06]

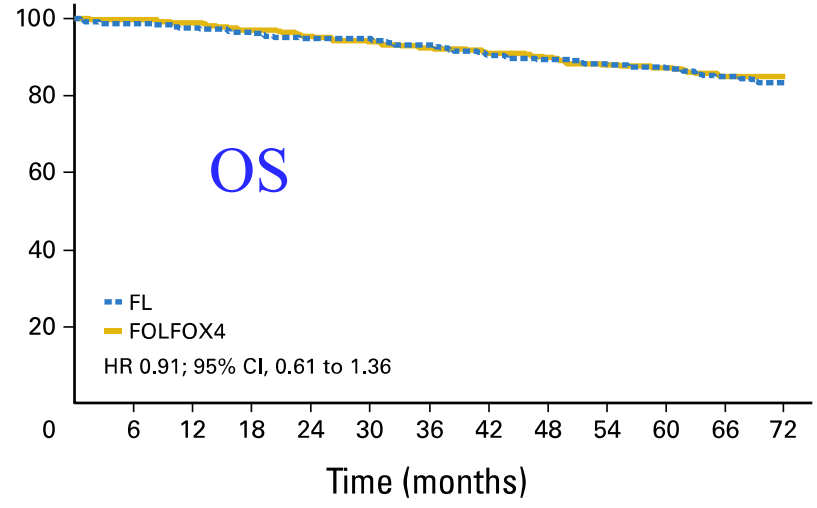
High-risk stage II- defined as at least one of the following:
T4, tumor perforation, bowel obstruction, poorly differentiated tumor, venous invasion , <10 lymph nodes examined;
Data cut-off: June 2006

Exploratory analysis

De Gramont et al. ASCO 2007

Updated MOSAIK data High Risk Stage II FOLFOX vs. FU/LV

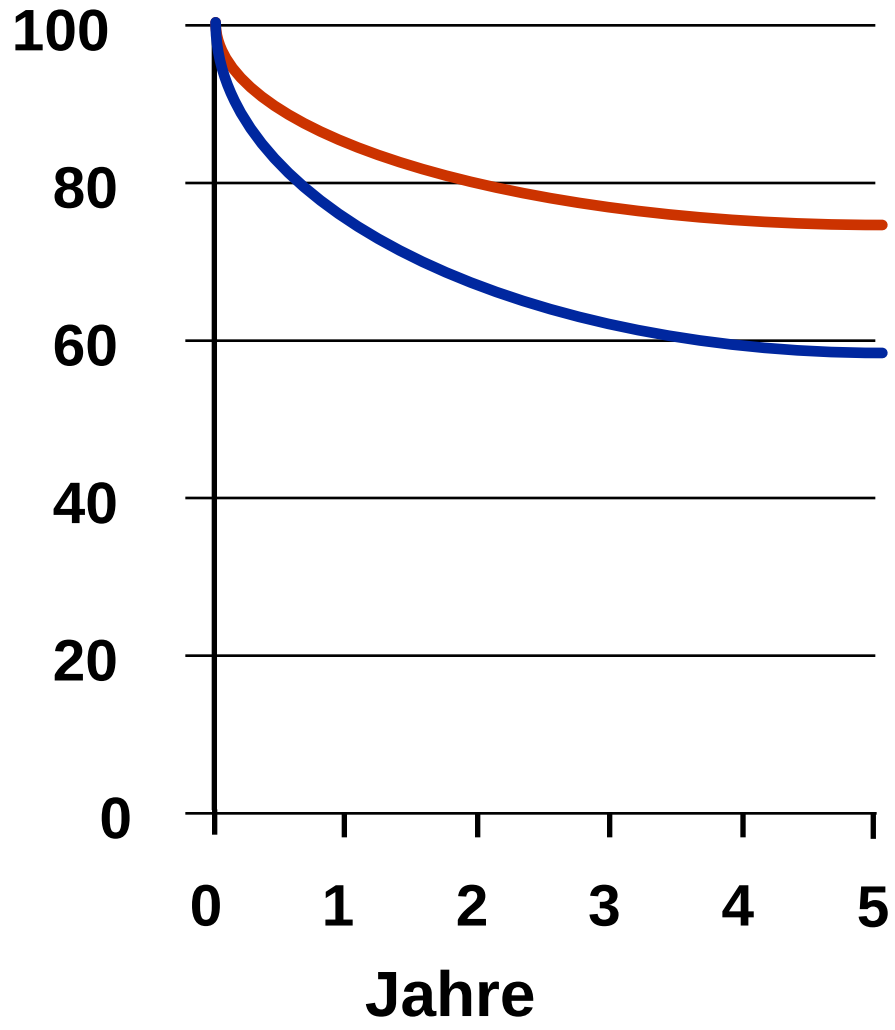




		5 y DFS		6y OS	
Age	**N Pat**	**HR**	**P-value**	**HR**	**P-value**
high risk	**569**	**0.72** **0.51-1.01**	**.062**	**0.91** **0.66-.97**	**.648**
low risk	**330**	**1.36** **0.76-2.45**	**1.01**	**1.36** **0.67-2.5**	**.399**

Tournigant et al. JCO 2012

Patient groups in adjuvant Therapy



No benefit

cured

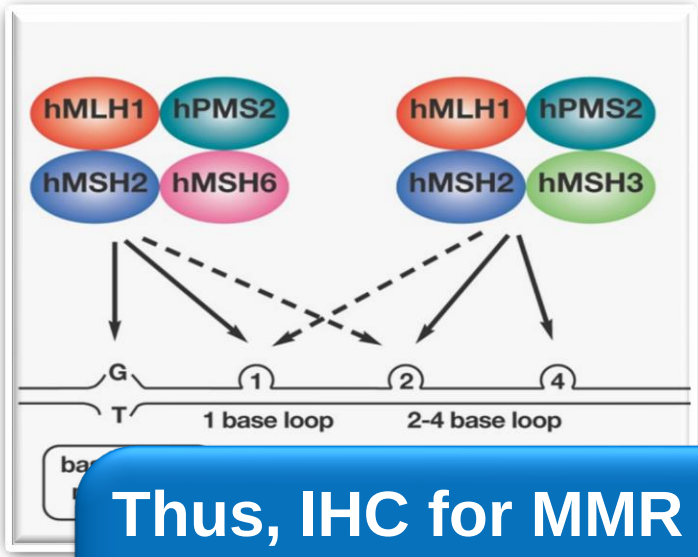
Cured by surgery already

TOXICITY

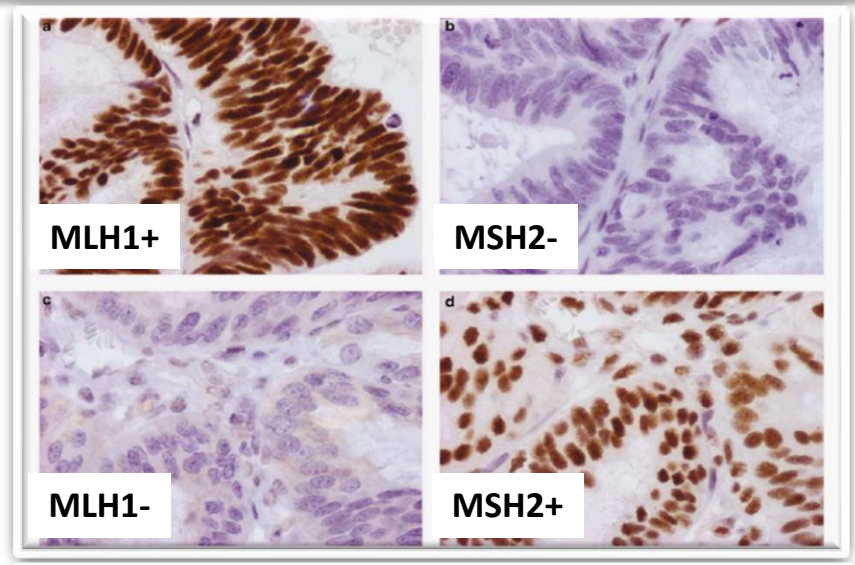
Stage II Colon Cancer

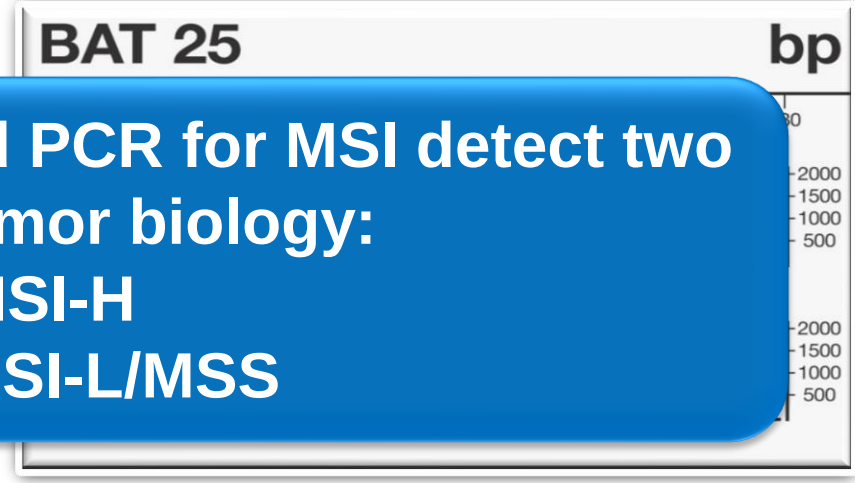
Are there subgroups that might benefit from adjuvant chemotherapy ?

Mismatch Repair Deficiency (MMR-D): Unique Biological Subgroup of Colon Cancer



IHC for MMR protein status





Thus, IHC for MMR proteins and PCR for MSI detect two manifestations of the same tumor biology:

- **MMR-D is synonymous with MSI-H**
- **MMR-P is synonymous with MSI-L/MSS**

Imai K, et al. *Carcinogenesis*. 2008;29:673-680.
Umetani N, et al. *Ann Surg Oncol*. 2000;7:276-280.
Rosen DG, et al. *Mod Pathol*. 2006;19:1414-1420.

MMR-Deficiency is a Favorable Prognostic Marker

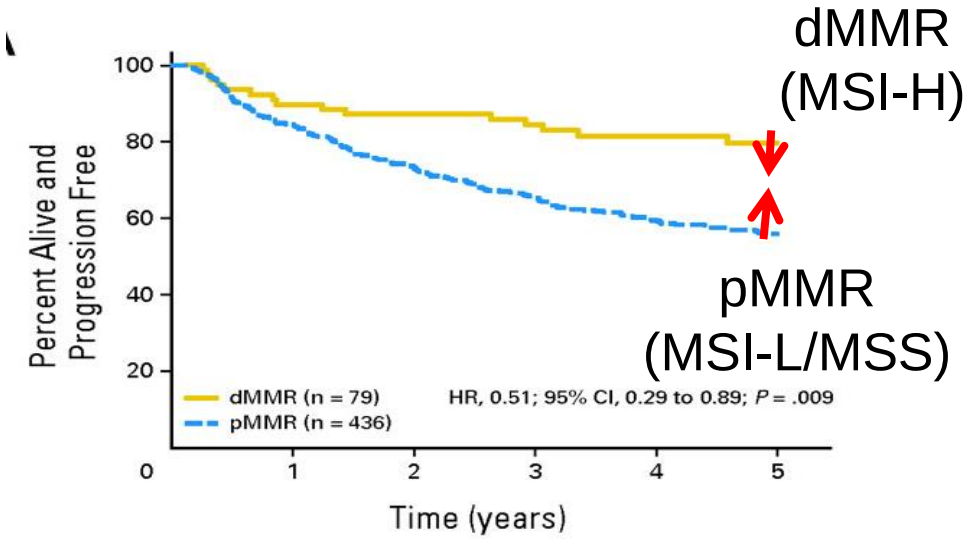
The ~15% of stage II colon cancer patients with MMR-deficient tumors have been found consistently to have a lower risk of recurrence and/or death

Source	Stage / Treatment	Endpoint	MMR-D vs MMR-P HR (95% CI); p-value
Ribic et al[1]	II/III Surgery alone	Overall survival	0.31 (0.14-0.72) p=0.004
Sargent et al[2]	II/III Surgery alone	Disease-free survival Overall survival	0.46 (0.22-0.95); p=0.03 0.51 (0.24-1.10); p=0.06
Gray et al[3] (QUASAR)	II Surgery alone	Recurrence-free interval	0.31 (0.15-0.63) p<0.001
Roth et al[4] (PETACC-3)	II 5FU ± irinotecan	Relapse-free survival	0.30 p=0.004

Ribic et al. *NEJM*2003 Sargent et al. *JCO*. 2010; Gray R, et al. *JCO* 2011 Roth AD, et al. *JCO* 2010

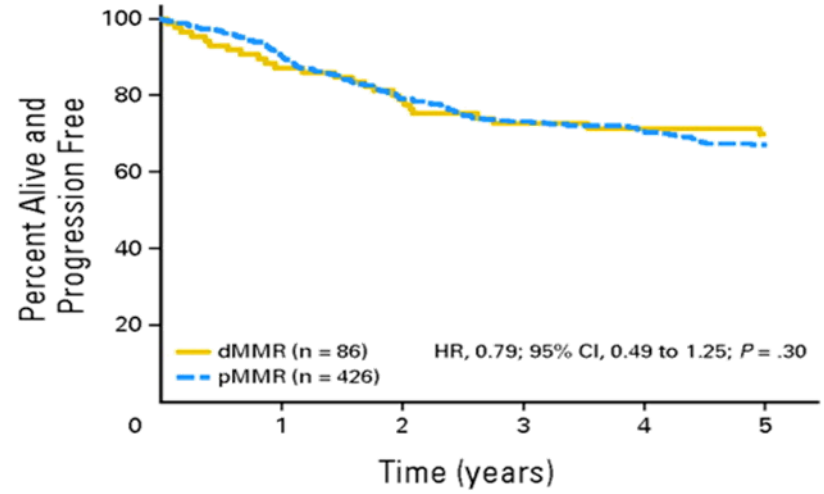
Stage II and III
MSI is prognostic and predictive

DFS by MMR status



Untreated

5Y DFS; p=.009
dMMR 80%
pMMR 56%



Treated

5Y DFS; p=.30
dMMR 70%
pMMR 67%

dMMR: deficient MMR
pMMR: proficient MMR

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

dMMR

pMMR

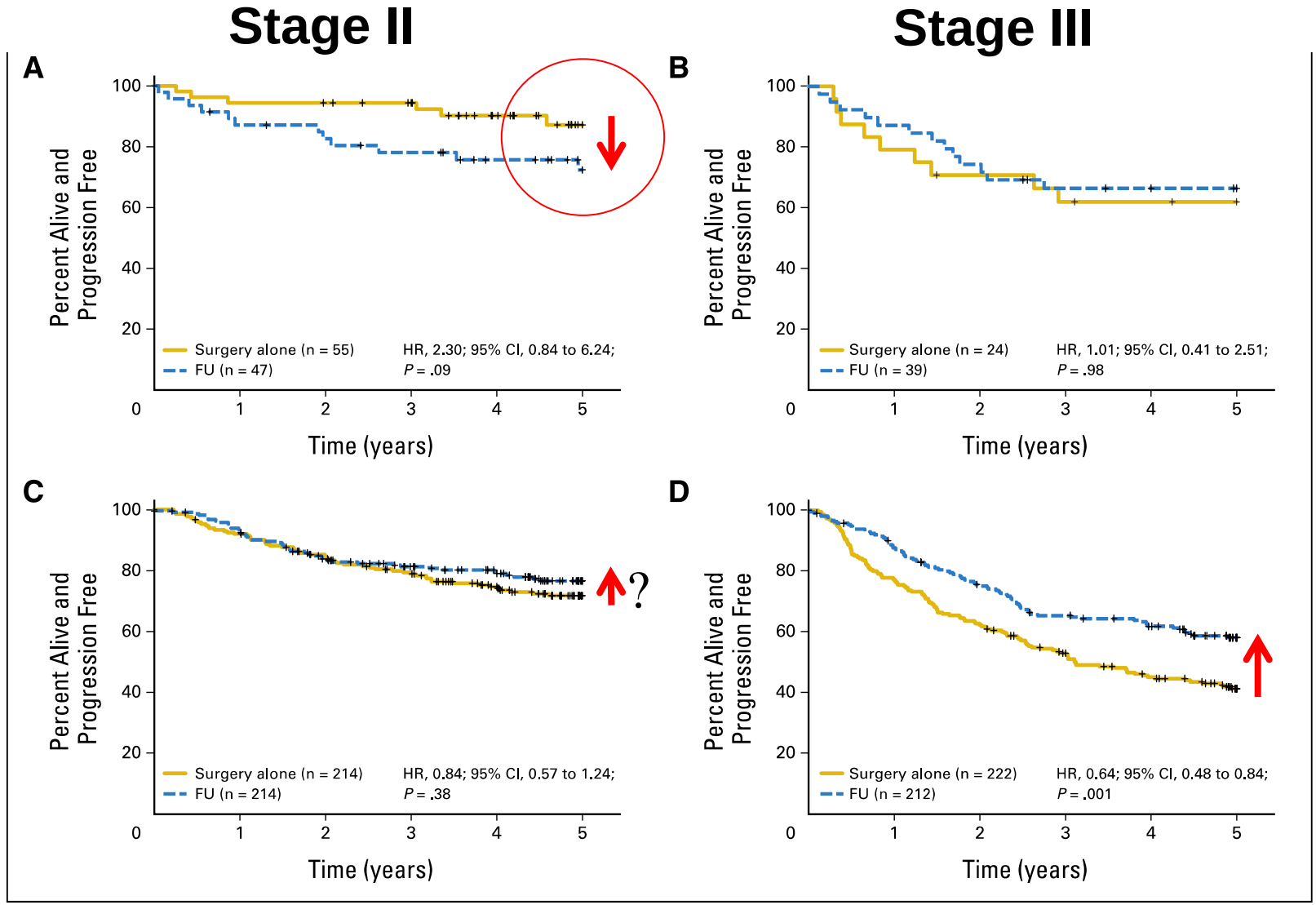


Fig 2. (A) Disease-free survival (DFS) in patients with stage II disease and defective DNA mismatch repair (dMMR) by treatment status. (B) DFS in patients with stage III disease and dMMR by treatment status. (C) DFS in patients with stage II disease and proficient MMR (pMMR) by treatment status. (D) DFS in patients with stage III disease and pMMR by treatment status. HR, hazard ratio; FU, fluorouracil.

Are stage II and Stage III different diseases?
Prognostic Value (RFS)
Multivariate Analysis in whole population

Markers	Stage II		Stage III	
	HR§	p value*	HR§	p value*
T Stage (T4 vs T3)	2.8	0.0001	1.6	0.0006
N Stage (N2 vs N1)	N/A	N/A	2.2	<0.0001
Histologic Grade (3-4 vs 1-2)	0.6	0.55	1.4	0.07
Age (>60 vs ≤60)	1.8	0.026	1.1	0.3
MSI (High vs Stable)	0.3	0.027	0.7	0.12
p53 (High)	0.7	0.27	1.3	0.015
SMAD4 (any loss)	1.0	0.9	1.6	0.0002

Treatment, Sex, Site, KRAS, BRAF,TS, 18qLOH (Stage II: HR 1.4, p=0.33), hTERT: not significant

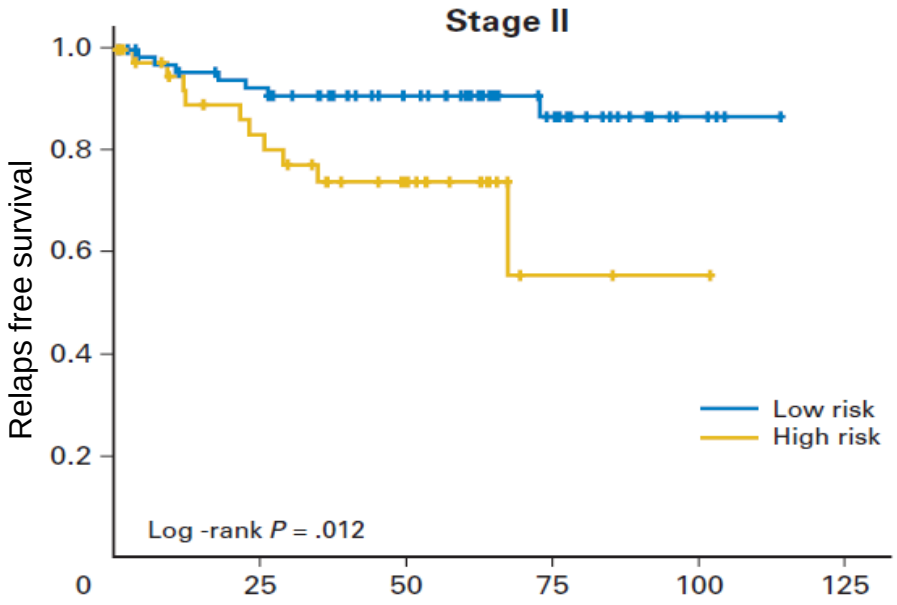
* p values from the Wald test in a multiivariate Cox regression

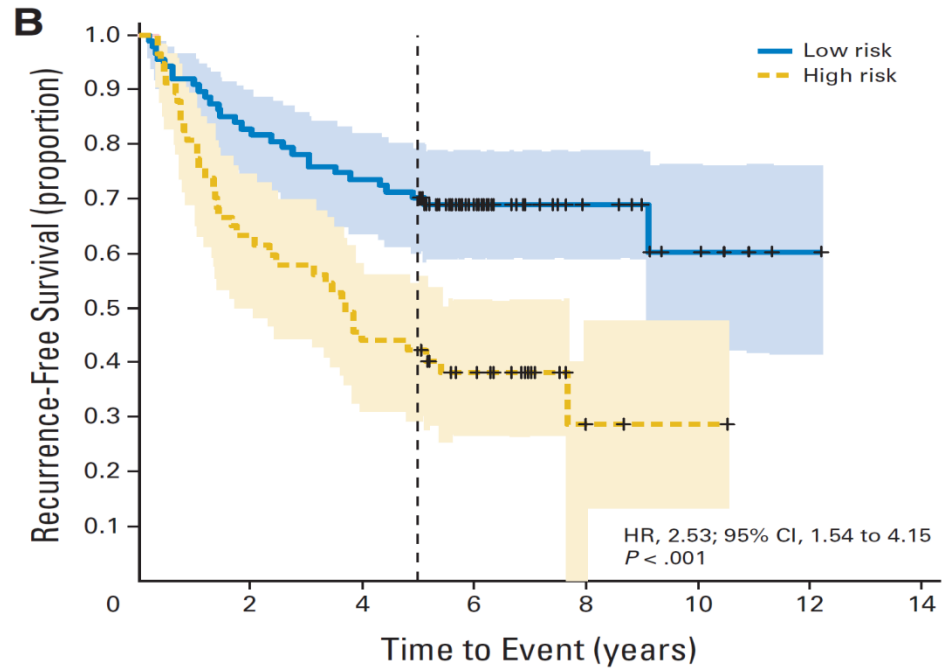
§ HR = hazard ratio

Gene expression signatures

ColoPrint / Agendia
Fresh frozen tumor tissue
N=188 stage I-IV CRC

Almac Diagnostics
Formalin-fixed paraffin-emmedded
N=144 stage II Colon Cancer

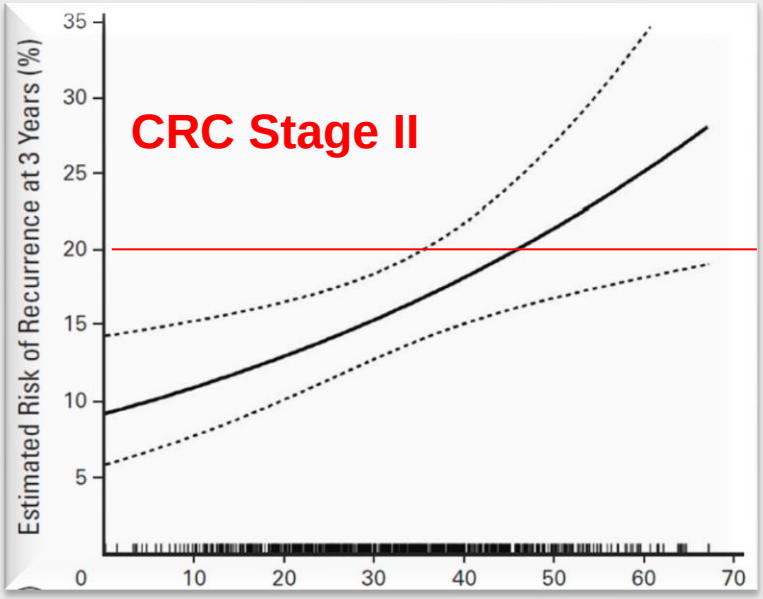


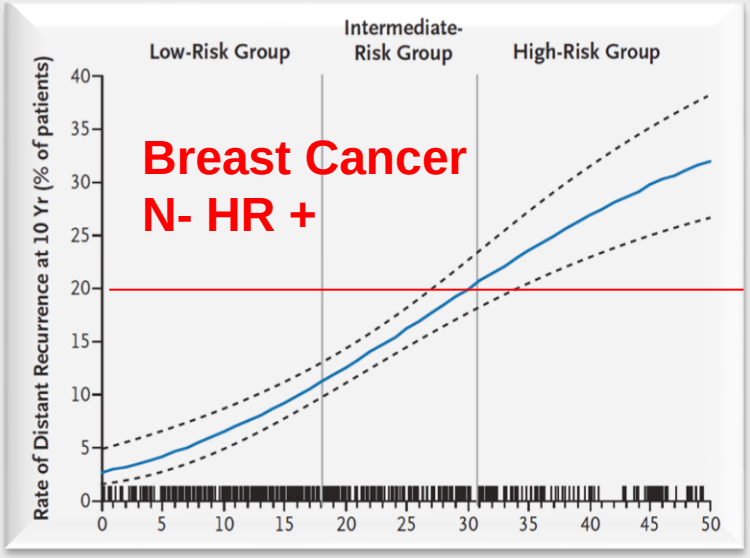


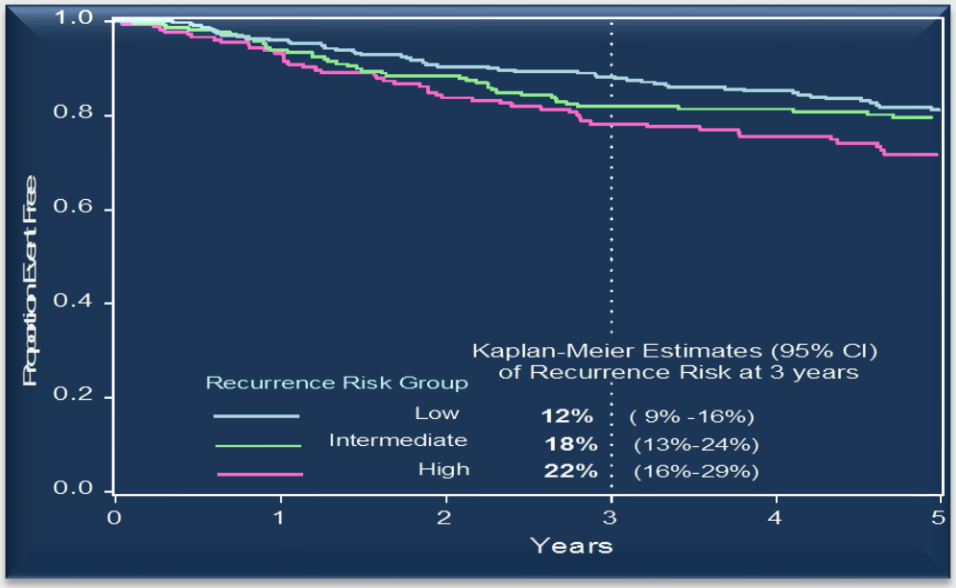
Salazar et al. JCO 2011

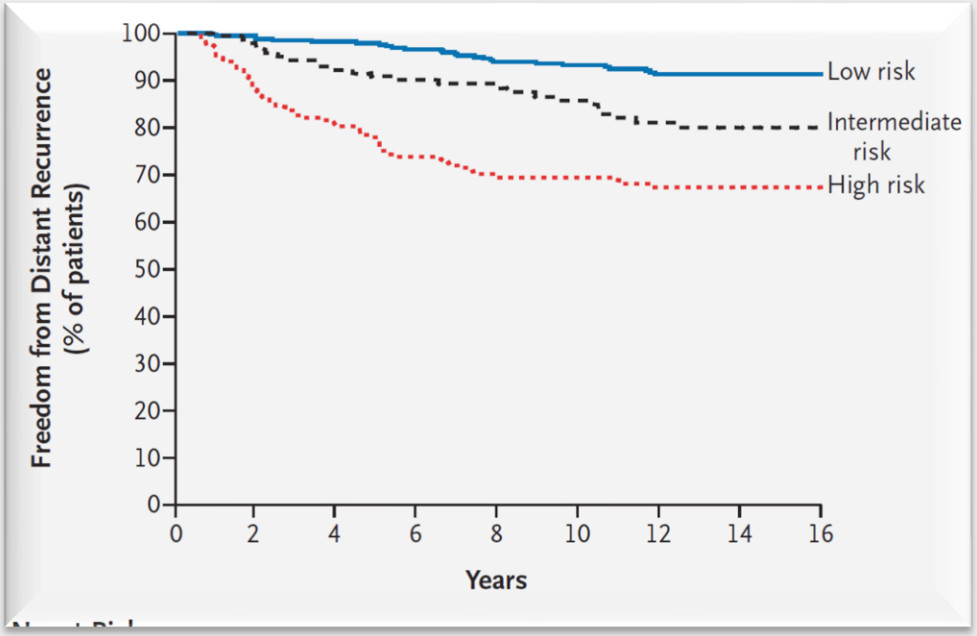
Kennedy et al. JCO 2011

Gen-Expression Assay (OncoType Dx)





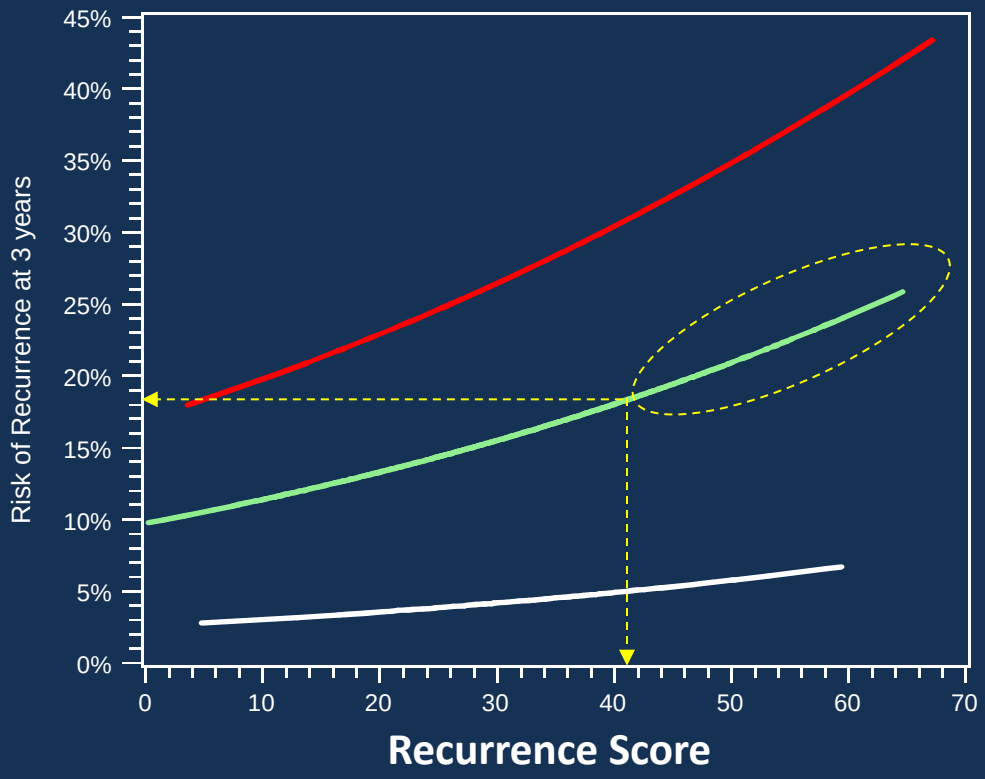




Gray et al. JCO 2011

Paik et al. NEJM 2004

Recurrence Score® Guideposts for Clinical Decisions: T3, MMR-P Patients with RS ≥ 41



T4 and MMR proficient (13%) (MSI-L/MSS)

T3 and MMR proficient (74%) (MSI-L/MSS)

T3 and MMR deficient (11%) (MSI-H)

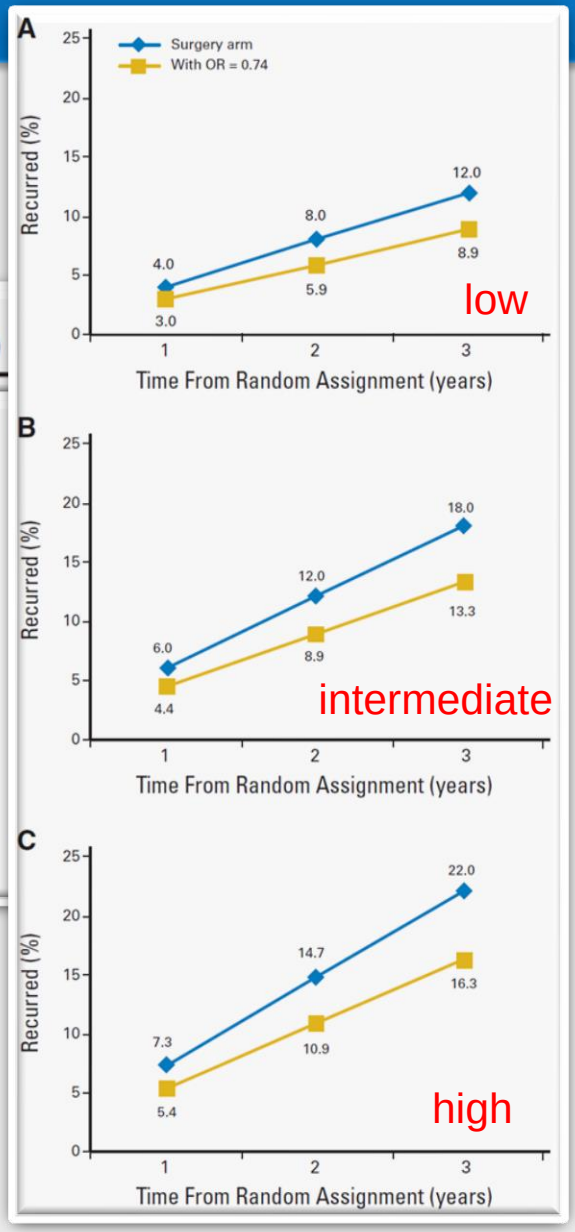
This population of patients with high Recurrence Score disease (~25% of total) has recurrence risk that overlaps with T4 patients and would be expected to have >3% benefit with adjuvant 5FU.

Gen-Expression assay not predictive for adjuvant chemotherapy

	Recurrences/Patients Chemotherapy	None	Statistics (O-E)	Var.	RR & 95% CI (chemotherapy:none)
By recurrence risk group:					
Low risk	18 of 295 (6.1%)	34 of 311 (10.9%)	-7.7	16.5	
Intermediate risk	20 of 209 (9.6%)	37 of 218 (17.0%)	-8.7	14.2	
High risk	31 of 221 (14.0%)	37 of 182 (20.3%)	-6.7	16.8	
Subtotal:	69 of 725 (9.5%)	108 of 711 (15.2%)	-23.1	47.5	

Test for heterogeneity between subgroups: $\chi^2_2 = 0.4$; $P = .84$

Test for trend between subgroups: $\chi^2_1 = 0.0$; $P = .84$



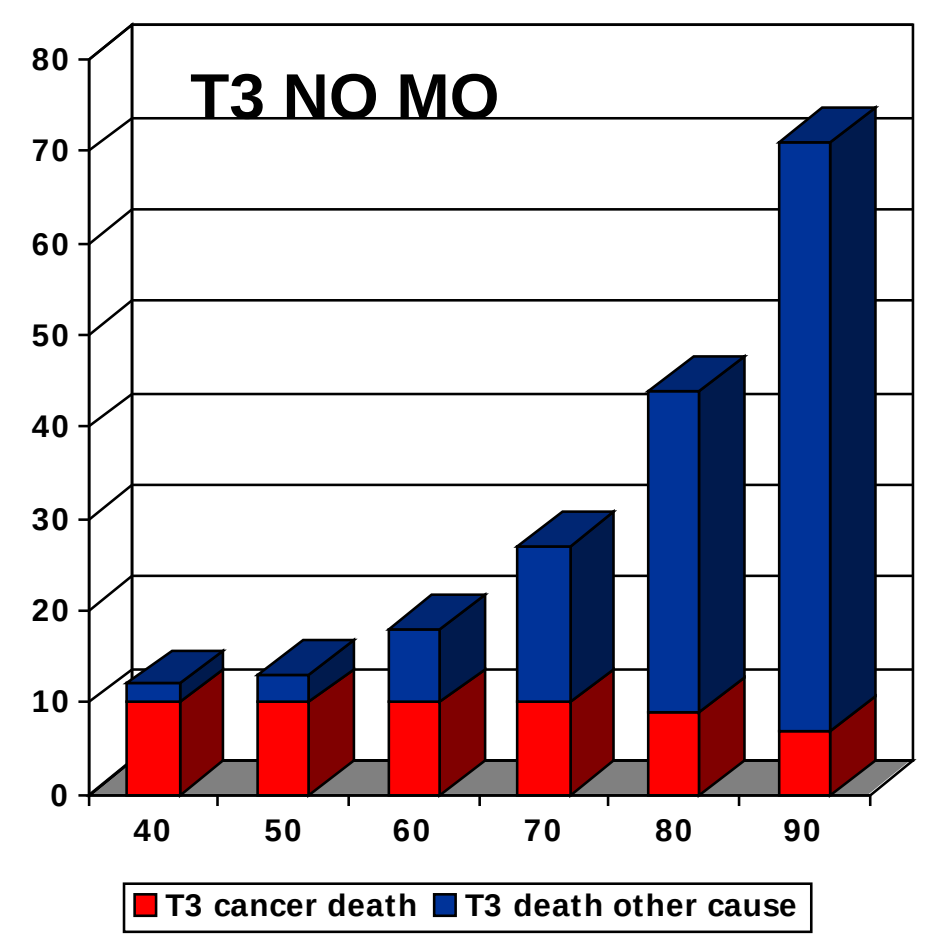
Gray et al. JCO 2011

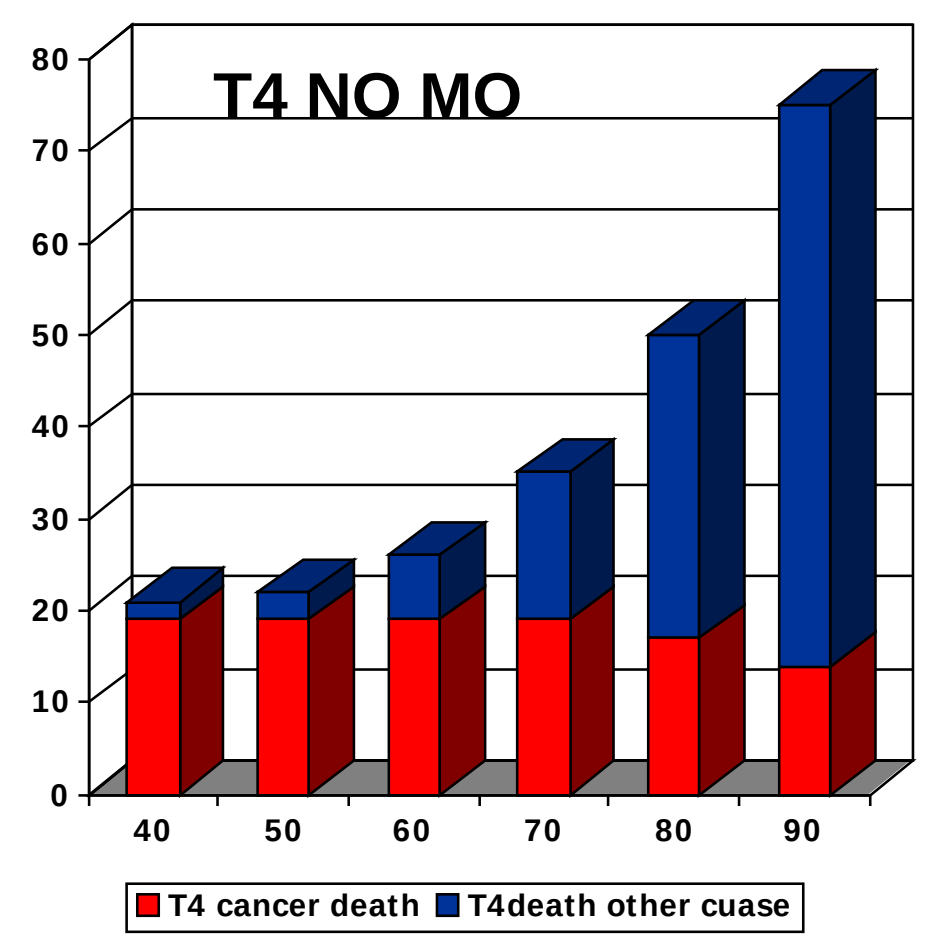
Different intentions to use Gen-Expression Assays in Breast or Colon Cancer

Tumor	Stage	Aim
Breast	N- (N1-3) HR+	Not to use chemo
Colon	N- (pMSI?)	To use chemo

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

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





Assumption of Gill model

Conclusions

Therapy

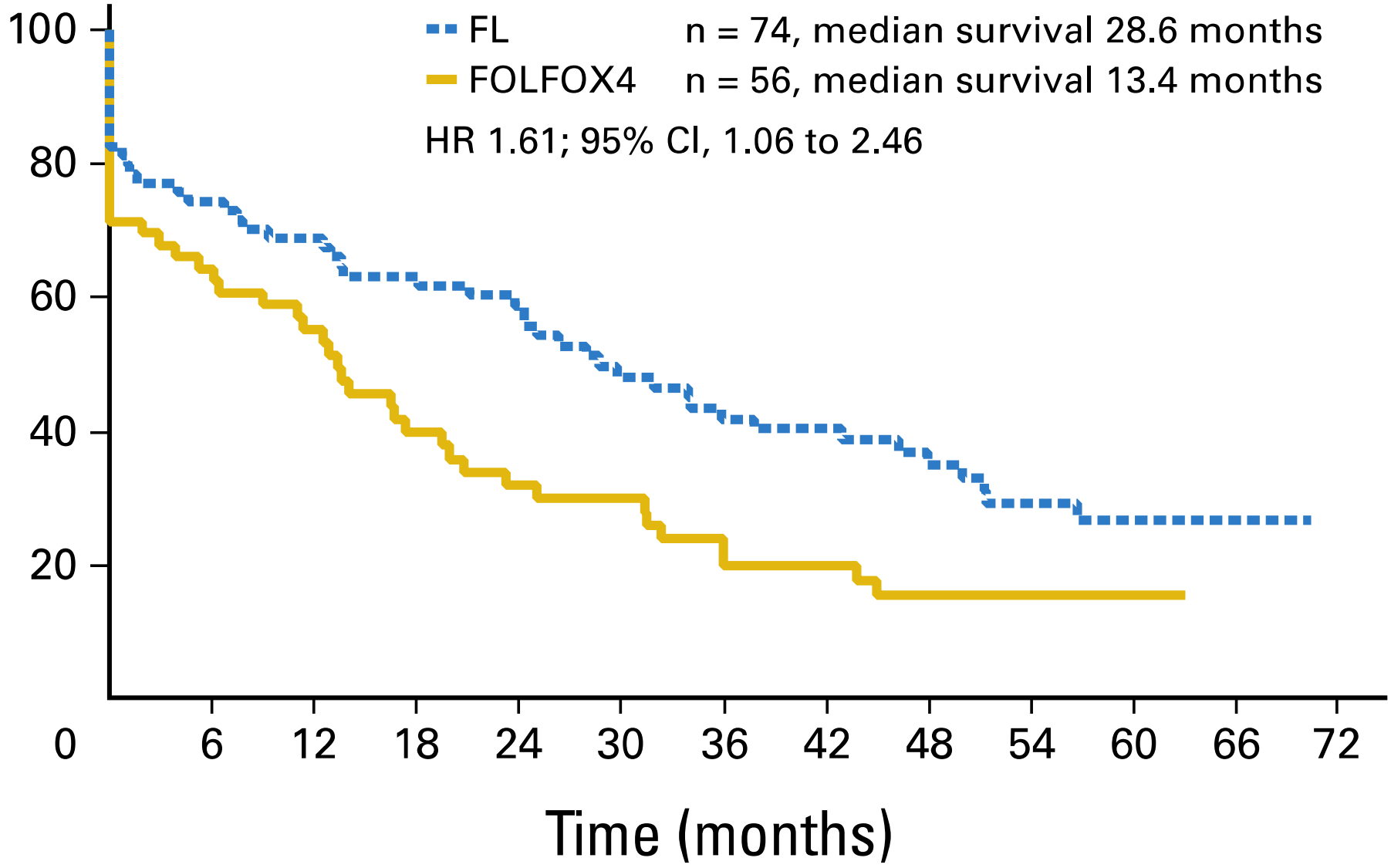
	< 70y	> 70y
Stage III	5FU/LV or Cape	
	FOLFOX	
Stage II	5FU/LV or Cape?	5-FU/LV or Cape ?
- Low risk	No adj CTx	
- High risk	5FU/LV or Cape?	

Biologicals currently no therapeutic option

Gen signatures are prognostic, but predictive?

The decision for adjuvant therapy has to balances the risk of cancer and other competing risks

MOASIK Subgroup high risk stage II analysis post relapse survival

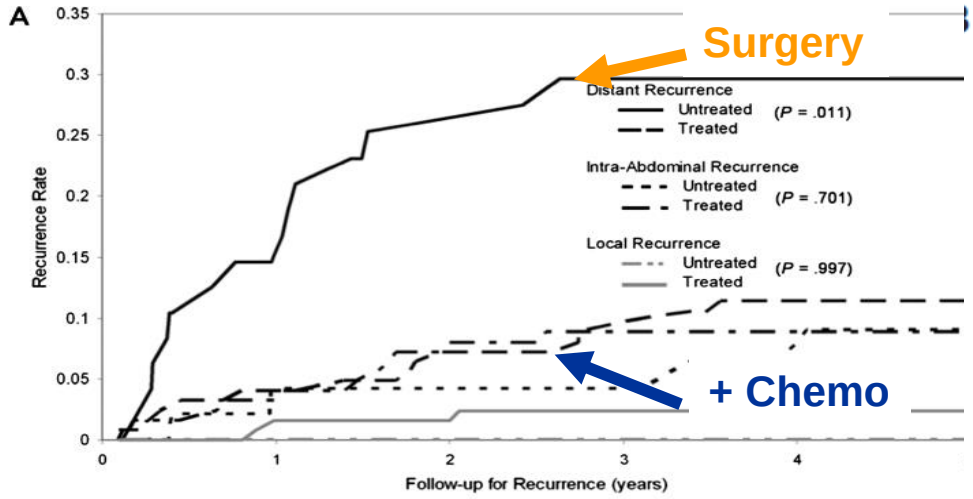


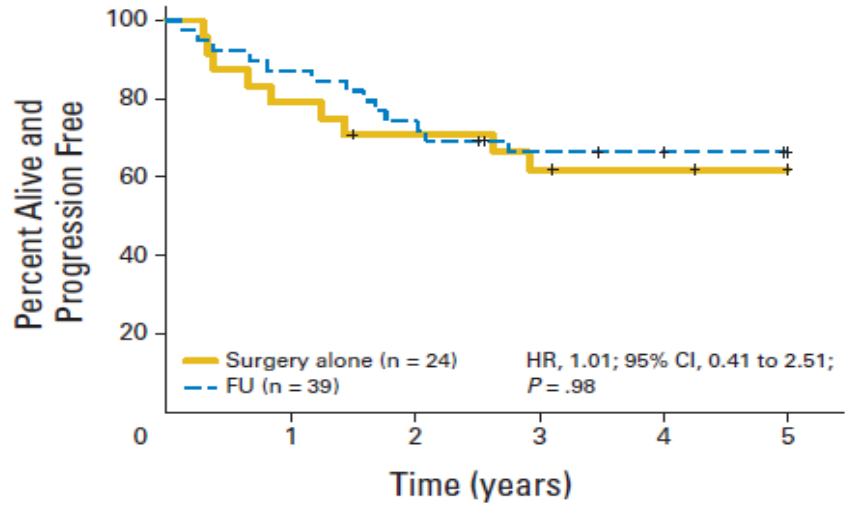
Stage III MSI is Prognostic and predictive

Relaps Stage III

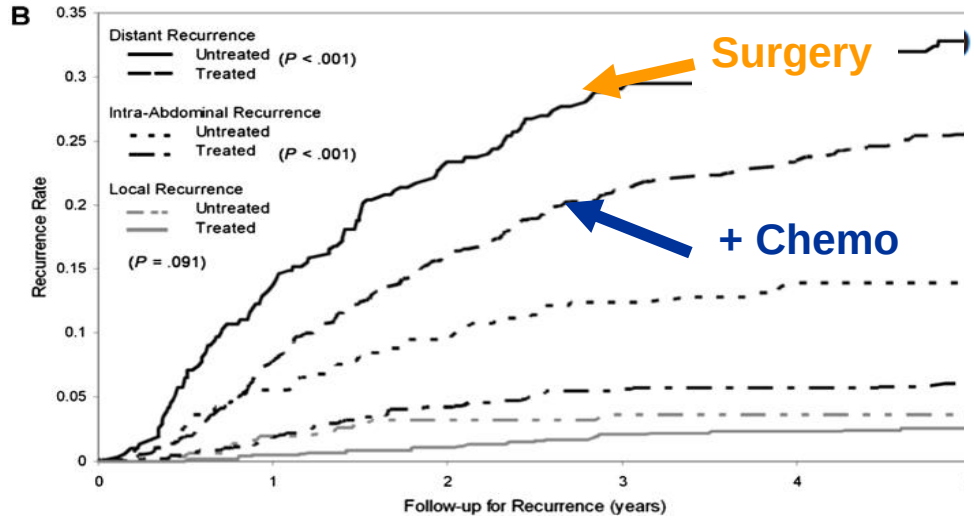
Stage III

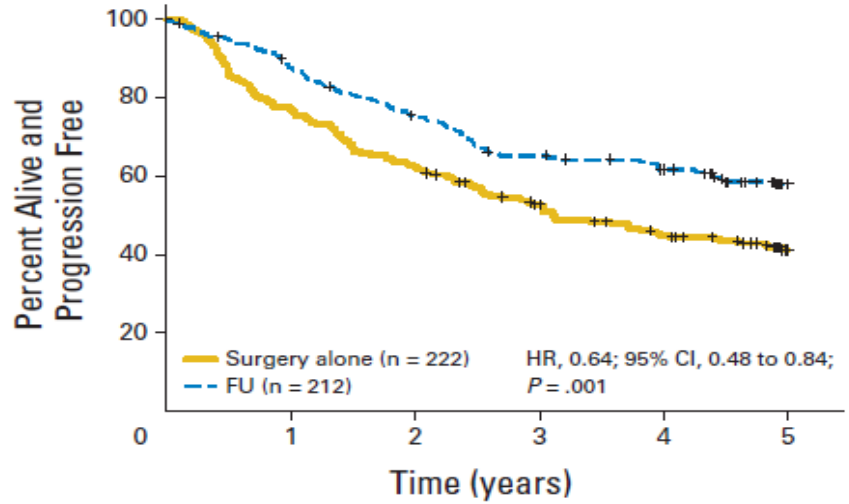
dMMR





pMMR





Sinicrope, JNCI 2011

Sargent, JCO 2010