Adjuvant treatment in colon cancer: new ideas

Stefania Kokkali
Medical Oncologist
Saint-Savvas Anticancer Hospital, Athens Greece

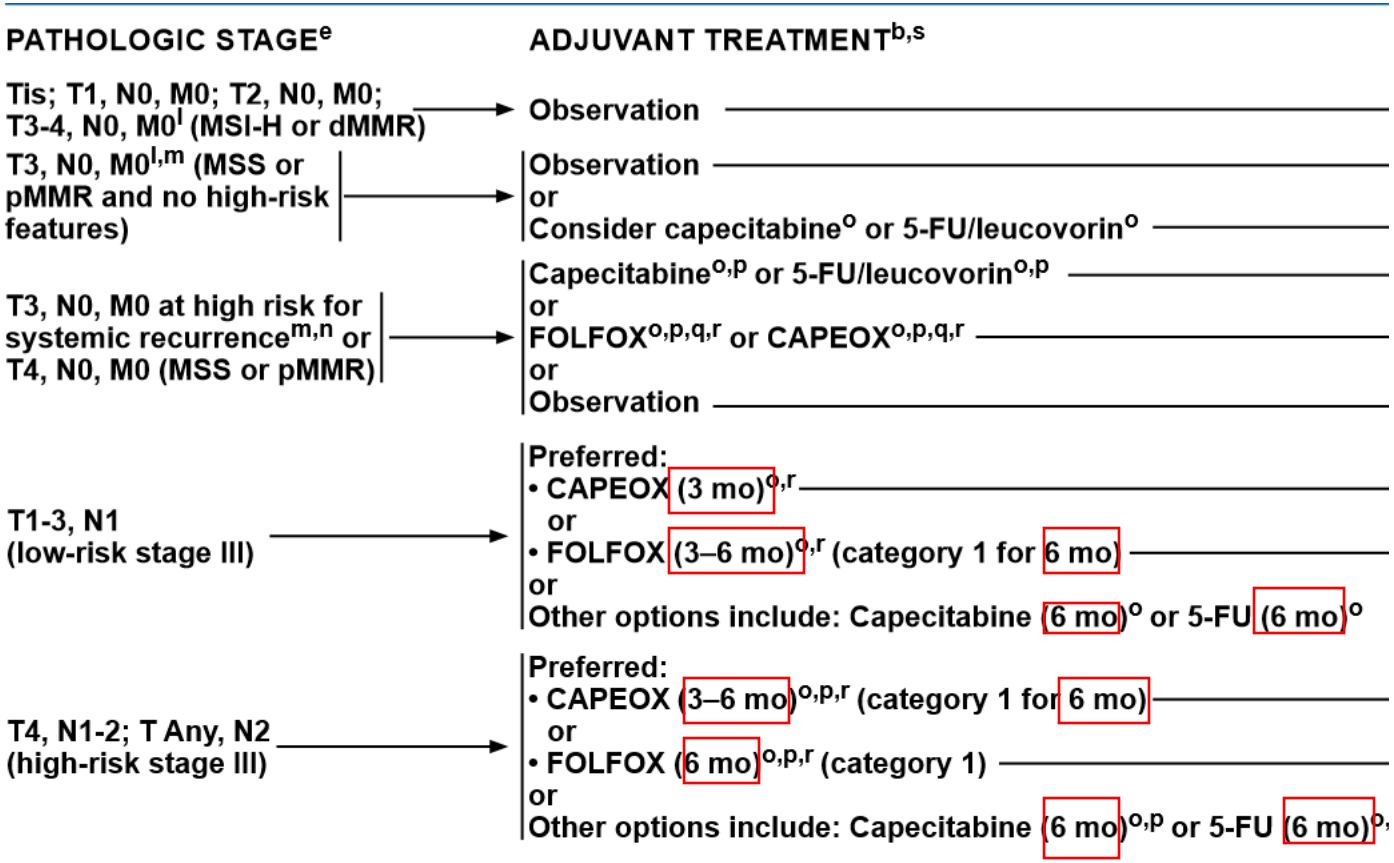
28/11/2019 Antalya

Plan

- Introduction
- Better stratification of patients: biomarkers to guide adjuvant chemotherapy decision and confer prognostic information
- Which drugs to use in the adjuvant setting
- Duration of adjuvant chemotherapy

Current treatment recommendations

- Stage I: no adjuvant treatment
- Low-risk stage II: **observation** or 5-FU/LV or capecitabine
- High-risk stage II: observation or FOLFOX or CAPEOX or 5-FU/LV or capecitabine
- Low-risk stage III: **CAPEOX or FOLFOX** (or 5-FU/LV or capecitabine)
- High-risk stage III: **CAPEOX or FOLFOX** (or 5-FU/LV or capecitabine)



Risk factors

- Extramural vascular invasion, lymphatic invasion, perineural invasion
- Grade 3
- T4 stage/perforation
- Obstructive tumors
- Mucinous tumors
- <12 lymph nodes harvested
- Tumor budding (foci of isoloated tumor cells at the invasive front): *newly implemented factor*
- (absence of MSI)

Biomarkers in early colon cancer

In which patients should I give adjuvant chemotherapy in stage II disease?

Heterogeneous prognosis in localized colon cancer

Stade UICC	Clasification TNM	Taux de survie à 5 ans (%)
Stade I	pT1N0	97,4
	pT2N0	96,8
Stade II		
IIA	pT3N0	87,5
IIB	pT4aN0	79,6
IIC	pT4bN0	58,4
Stade III		
IIIA	pT1N1a	90,6
	pT1N1b	81
	pT1N2a	68,5
	pT2N1a	90,4
	pT2N1b	83,7
IIIB	pT1N2b	68,4
	pT2N2a	81,7
	pT2N2b	60,3
	pT3N1a	74,2
	pT3N1b	65,3
	pT3N2a	53,4
	pT4aN1a	67,6
	pT4aN1b	54
IIIC	pT3N2b	37,3
	pT4aN2a	40,9
	pT4aN2b	21,8
	pT4bN1a	38,5
	pT4bN1b	31,2
	pT4bN2a	23,3
	pT4bN2b	15,7

stage III>II
(best prognosis)

AJCC 7th Edition

- Stage based
- 109 953 colon cancers
- Heterogeneity is present within the same stage

Need for other prognostic markers to better define the different patients populations and their therapeutic need

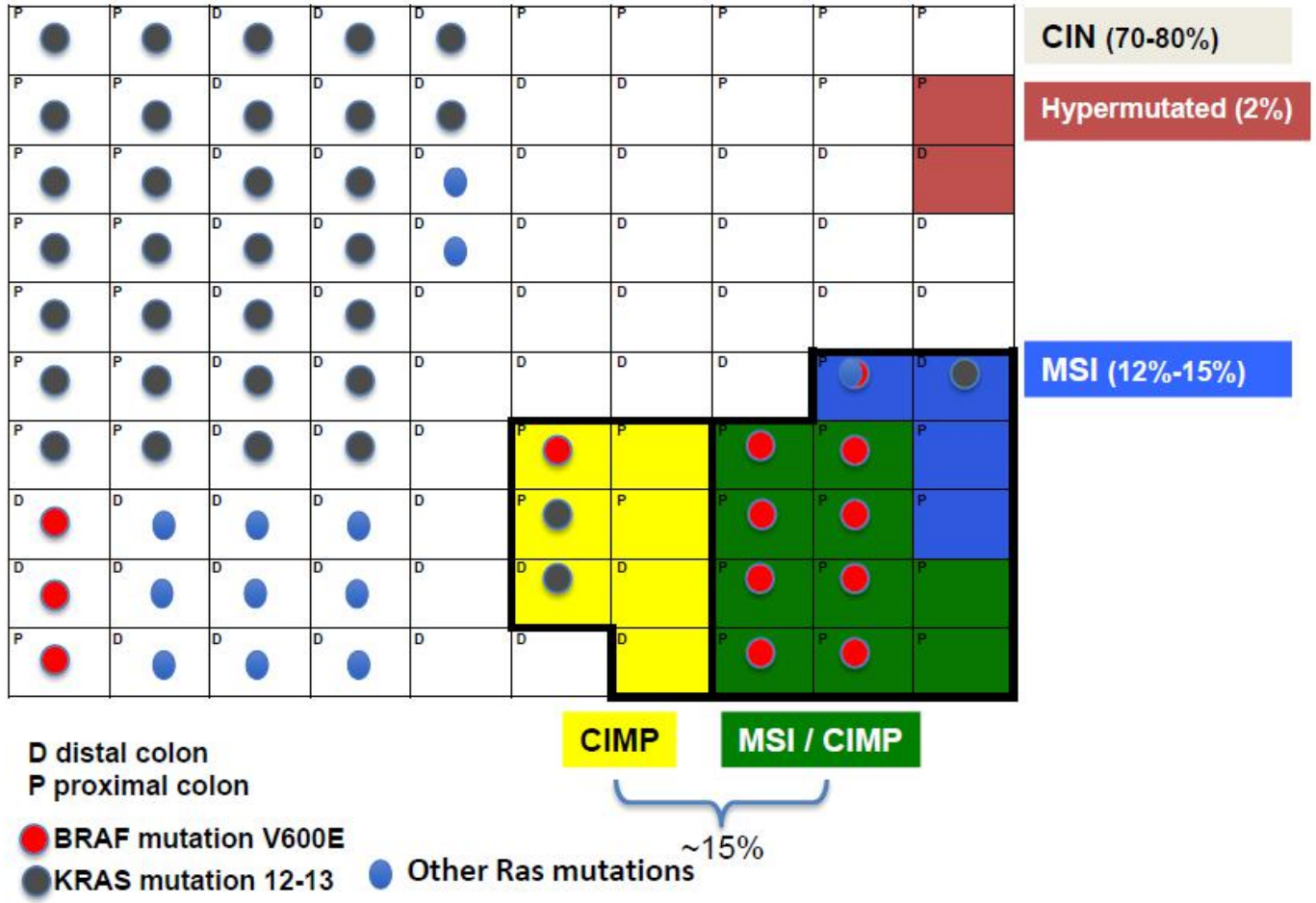
Gunderson J Clin Oncol; 2010; 28: 264-271.

Colorectal Cancer Diversity

Diversity at the **genomic level**

At least **4 distinct entities**

- Microsatellite instable (MSI)
- Chromosomal instable (CIN)
- Hypermethylated (CIMP)
- Hypermutated



Barault et al. Cancer Res 2008;68:8541-46, Barault al. Int J cancer 2008;122:2255-59; & consortium colon CIT2

Predictive value? Role in the adjuvant setting?

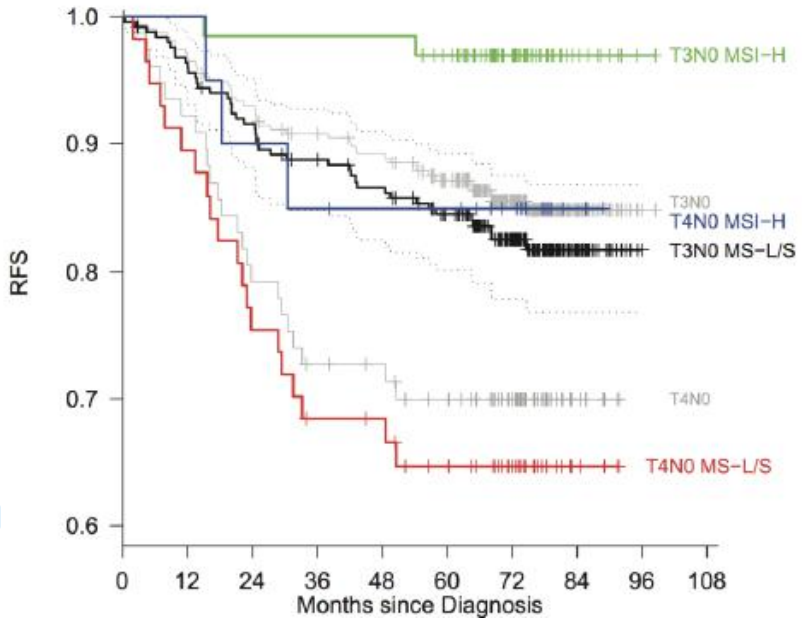
CMS1 MSI Immune	CMS2 Canonical	CMS3 Metabolic	CMS4 Mesenchymal
14%	37%	13%	23%
MSI, CIMP high, hypermutation	SCNA high	Mixed MSI status, SCNA low, CIMP low	SCNA high
BRAF mutations		KRAS mutations	
Immune infiltration and activation	WNT and MYC activation	Metabolic deregulation	Stromal infiltration, TGFβ activation, angiogenesis
Worse survival after relapse			Worse relapse-free and overall survival

Guinney, Nat Med 2015

MSI-high (MMR-deficiency)

- Avoid chemotherapy with 5-FU in stage II colon cancer (no benefit, good prognosis)
- Stage III ?, oxaliplatin-based chemotherapy ?

Stage II: **MSI patients** have low recurrence rates and good outcome without adjuvant treatment

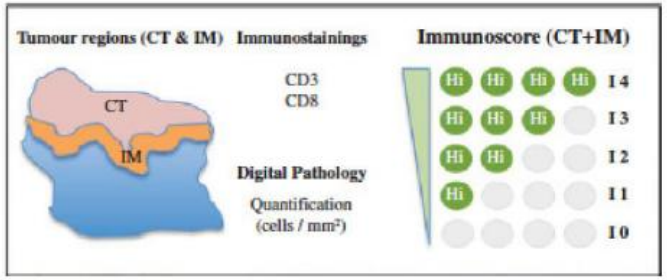


→A further step towards personalized cancer care!

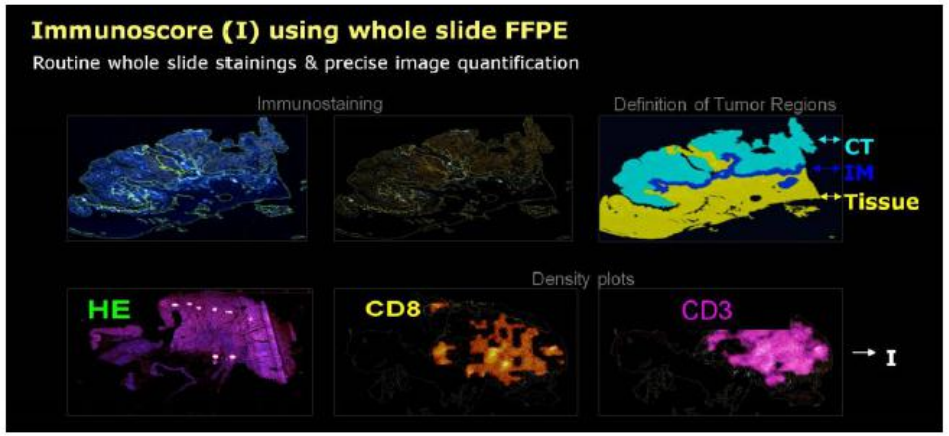
Hutchins, JCO 2012 (QUASAR); Gavin, CCR 2012 (NSABP C07 and C08); Roth, JNCI 2012 (PETACC3); Sargent, ASCO 2014 (ACCENT); Sinicrope JNCI 2011

Immunoscore

Prognostic Lymphocite inflitrate score
Immunoscore



CT: Tumor Center
IM: Invasive Margin



Immunoscore is standardized, objective, quantitative

Article

Immunity

Integrative Analyses of Colorectal Cancer Show Immunoscore Is a Stronger Predictor of Patient Survival Than Microsatellite Instability

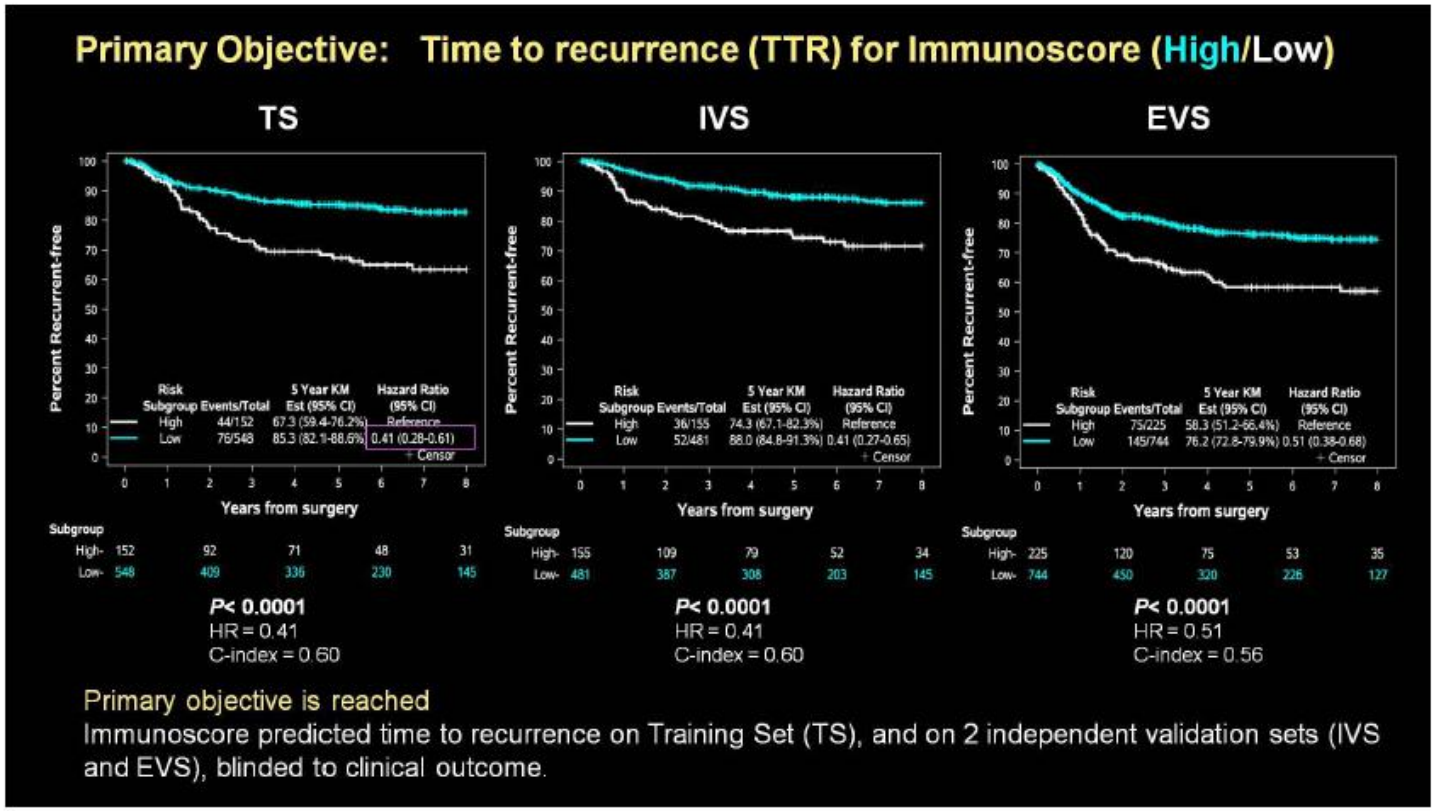
CANCER

The tumor microenvironment and Immunoscore are critical determinants of dissemination to distant metastasis

Bernhard Mlecnik,[1,2,3]* Gabriela Bindea,[1,2,3]* Amos Kirilovsky,[1,2,3]* Helen K. Angell,[1,2,3,4] Anna C. Obenauf,[5] Marie Tosolini,[1,2,3] Sarah E. Church,[1,2,3] Pauline Maby,[1,2,3] Angela Vasaturo,[1,2,3] Mihaela Angelova,[1,2,3] Tessa Fredriksen,[1,2,3] Stéphanie Mauger,[1,2,3] Maximilian Waldner,[6] Anne Berger,[7] Michael R. Speicher,[5] Franck Pagès,[1,2,3,8] Viia Valge-Archer,[9] Jérôme Galon[1,2,3]†

Galon et al., ASCO 2016

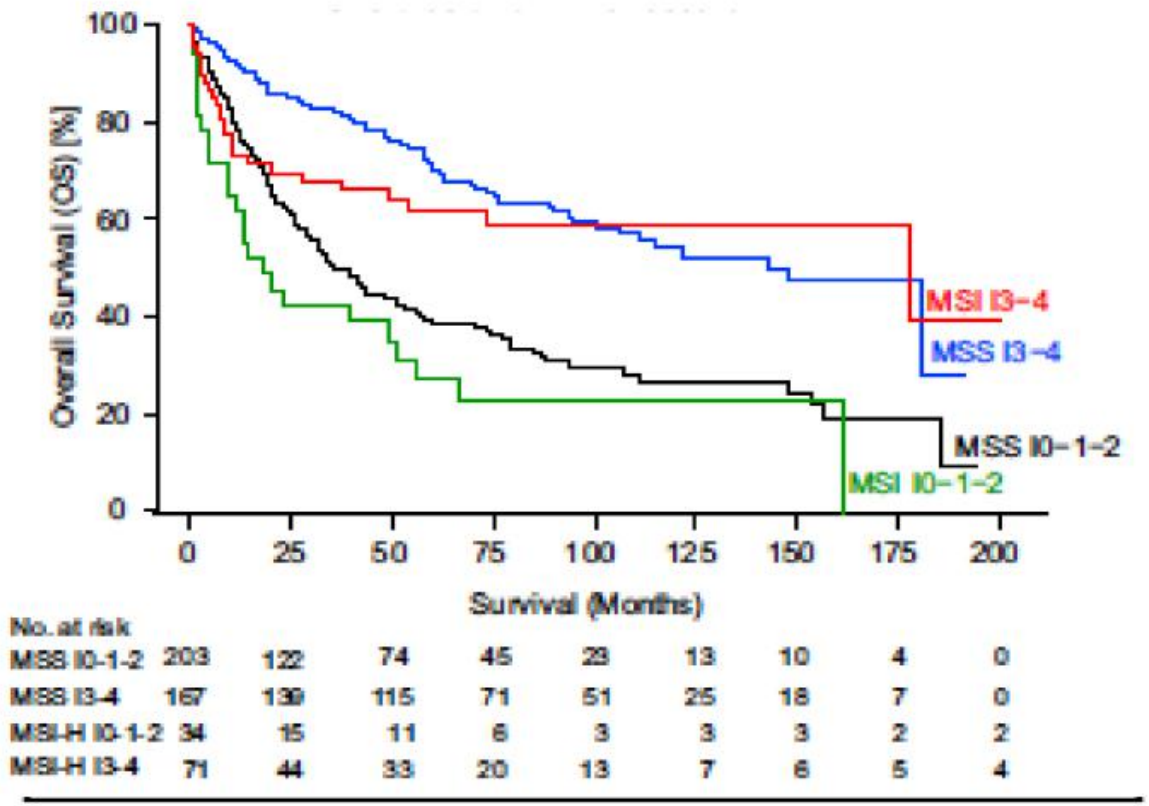
Immunoscore as a prognostic marker in stage II/III CC



Galon, ASCO 2016

MSI vs immunoscore status

- Subset of MSS tumors have high immunoscore and good prognosis
- Immunoscore is superior to MSI in predicting DFS



Mlecnik et al. Immunity 2016

Genomic profiling

- Oncotype Dx
- Coloprint
- ColDX
- Colo Guide EX
- Onco Defender-CRC

Not available in the clinical practice, need validation..

Other biomarkers in the tumor

- BRAF V600E: independent prognostic factor in early stage colon cancer
- KRAS mutations: bad prognosis in stage III colon cancer (II ?)
- PI3K mutation: predictive of benefit from aspirin

Liao, NEJM 2012; Domingo, JCO 2013

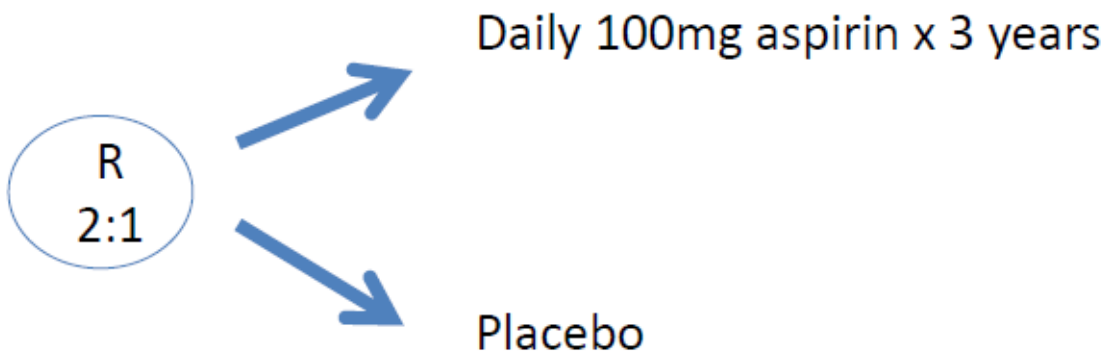
Popovici, BMC 2013; Gavin CCR 2012; Lochhead, JNCI 2013

Imamura, CCR 2012; Yoon, CCR 2014; Blons, Ann Oncol 2014; Hutchins, Jco 2011

Adjuvant aspirin treatment in PIK3CA mutated colon cancer patients
Randomized double-blinded placebo-controlled phase III trial

(EORTC-SAKK 41/13; NCT02301286)

Stage II / III
- Ressected
- PIK3CA mut



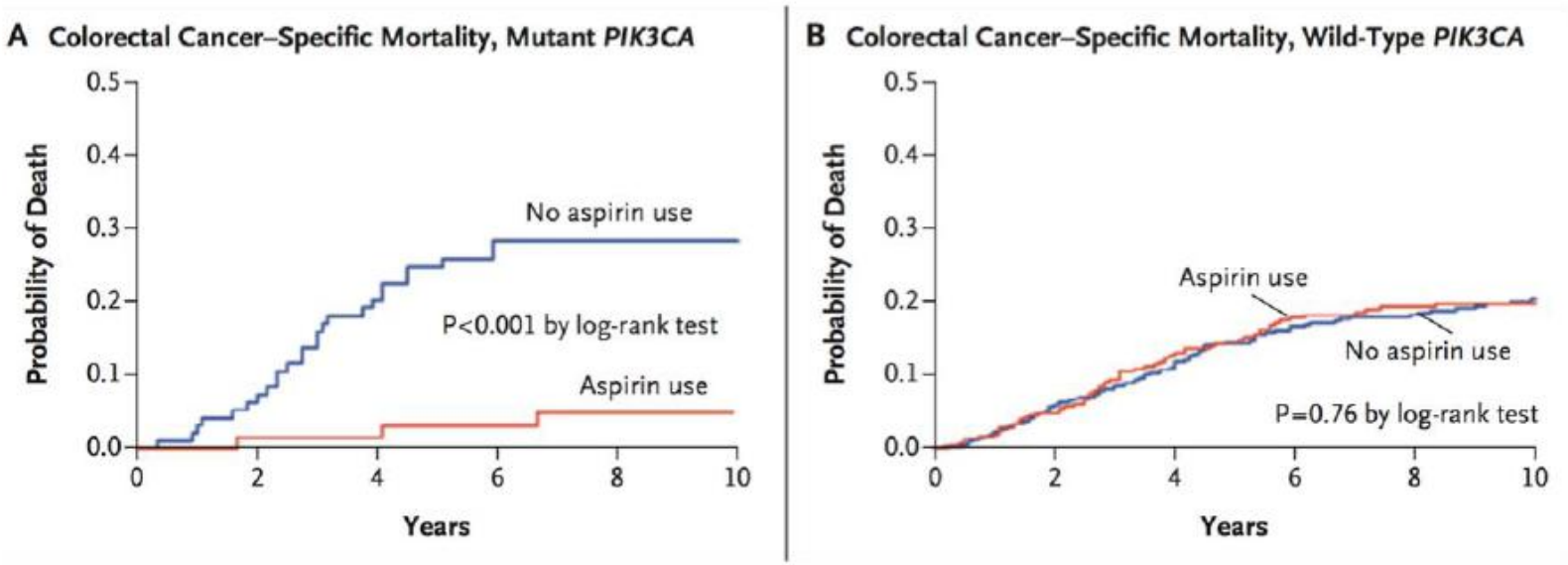
Aspirin is independent from administration of adjuvant chemotherapy

Primary Endpoint: **DFS**
Secondary Endpoints: Time-to-recurrence (TTR), OS, cancer specific survival (CSS), tolerability

Results by 2022

PIK3CA mutations

- Protective effect of regular use of aspirin in colon cancer
- Inhibition of COX2 by aspirin regulates PI3K signaling activity
- VICTOR trial (stage II-III) and prospective cohort (stage I-IV): Regular use of low-dose aspirin after diagnosis of CC decreased risk of tumor relapse in patients with PIK3CA mutated early-stage tumors, but not in PIK3CA wild-type



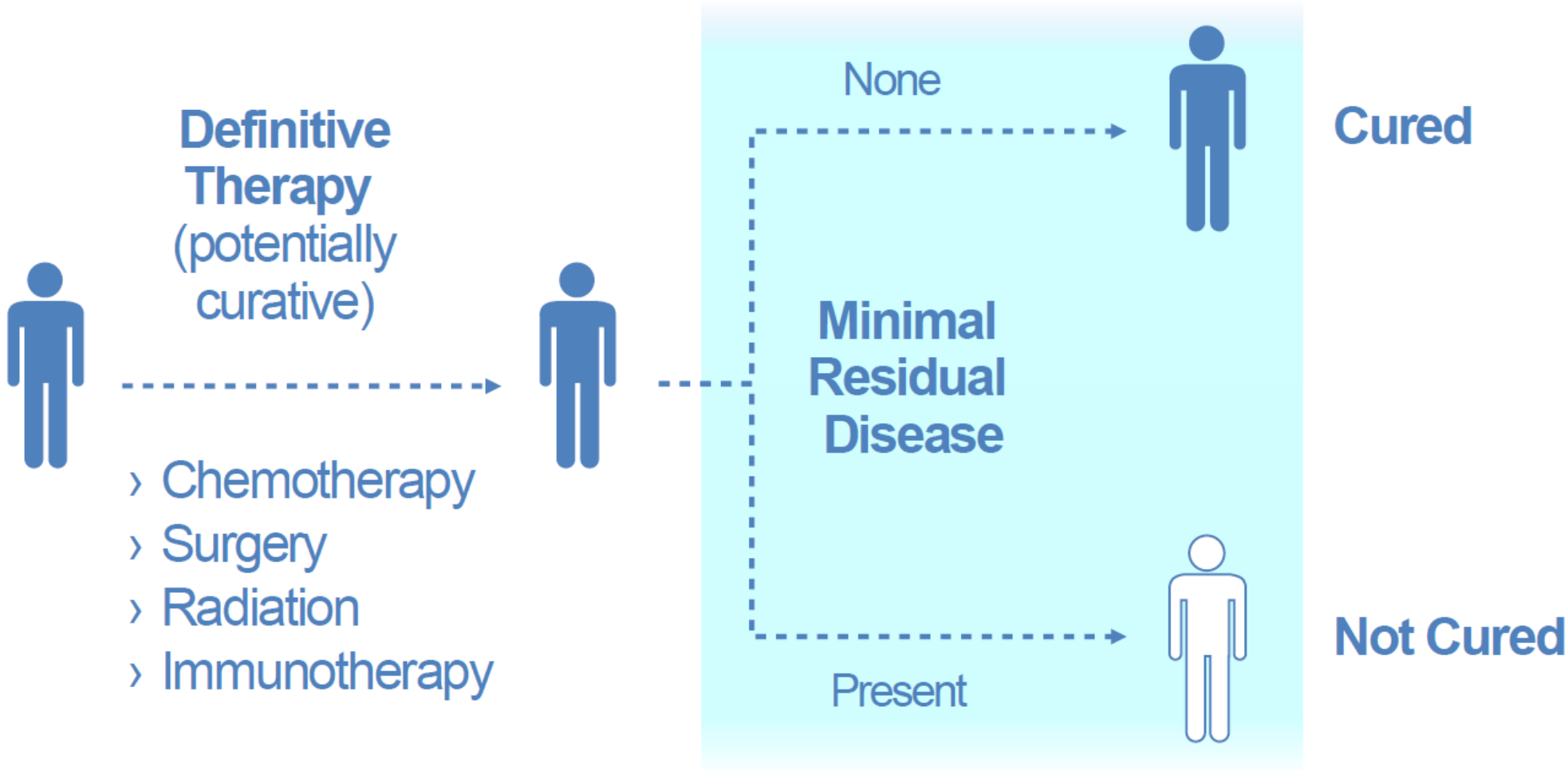
Liao, NEJM 2012; Domingo, JCO 2013

Prognostic biomarkers in the blood, not used in clinical practice

- CTCs **preoperatively** (association with OS, DFS) > postoperatively
- ct-DNA (IDEA trial): bad prognosis (mainly in the advanced setting)
- miRNAs: miR-21 associated with shorter DFS, miR-320e associated with recurrence, other .. (miR-20a-5p, miR103a-3p, miR-106a-5p..)

Boussios et al, J of Person Med 2019

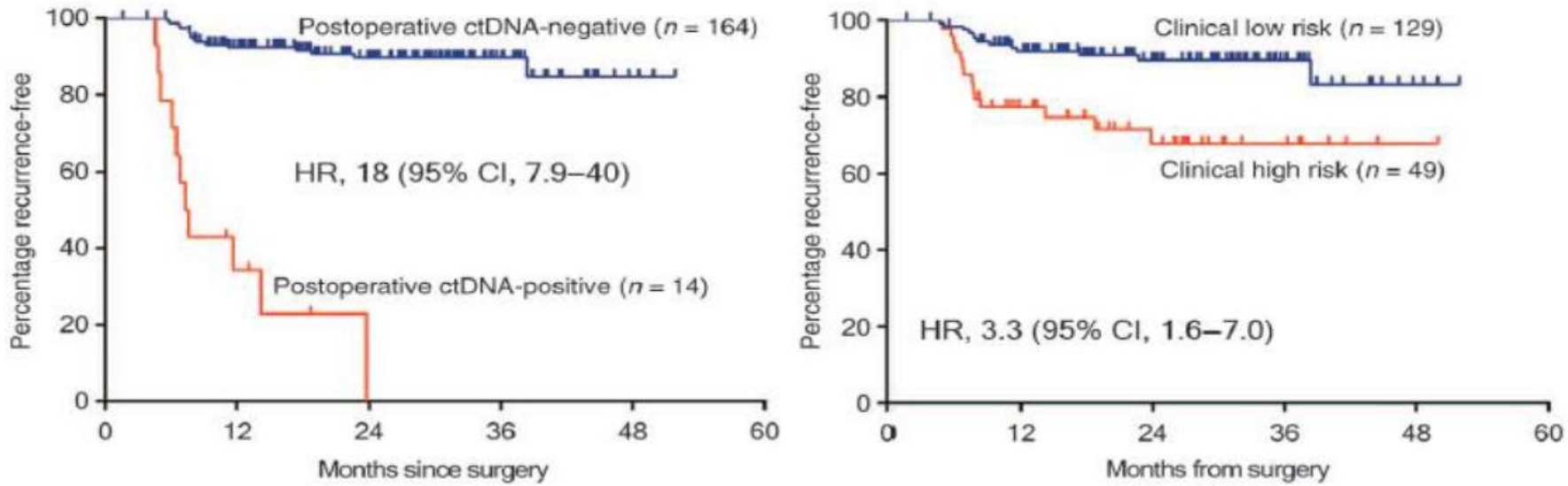
Minimal Residual Disease (MRD) Defined



ctDNA > prognostic markers > TNM?

- in patients plasma, tumor specific mutations are present as circulating tumor DNA, ctDNA
- Patients with colon cancer who are positive for ctDNA (still) after resection, have a very unfavourable prognosis
- In contrast, the prognosis of postoperatively ctDNA negative patients is very good

ctDNA and outcomes



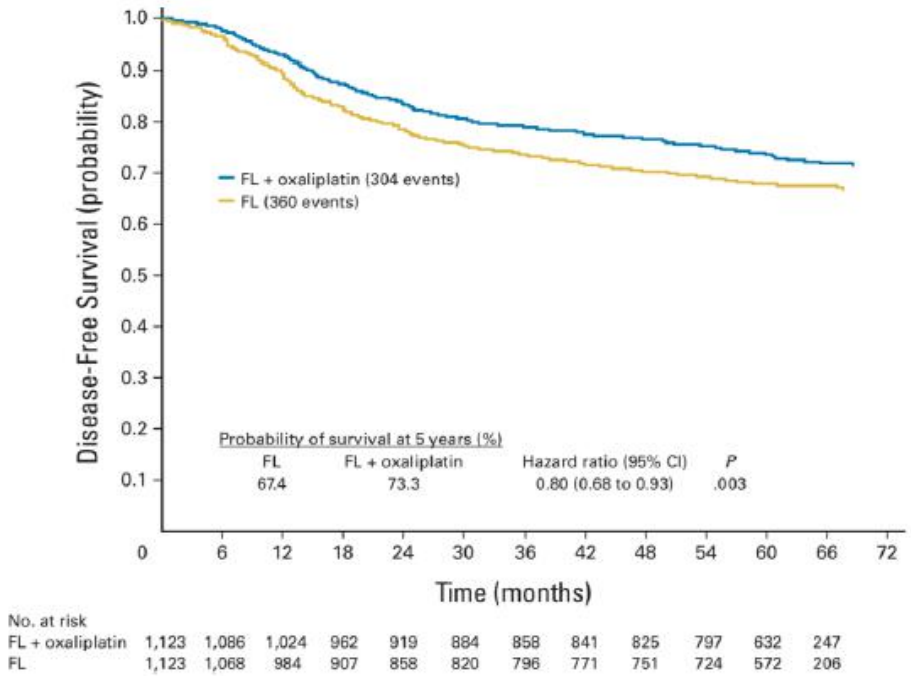
In patients with colon cancer stage II, plasma was sampled few weeks after resection and analyzed for the presence of mutations that were known from the mutational analysis of the resection specimen of the primary tumor. The Kaplan Meier curves demonstrate the survival of patients who did no receive chemotherapy.

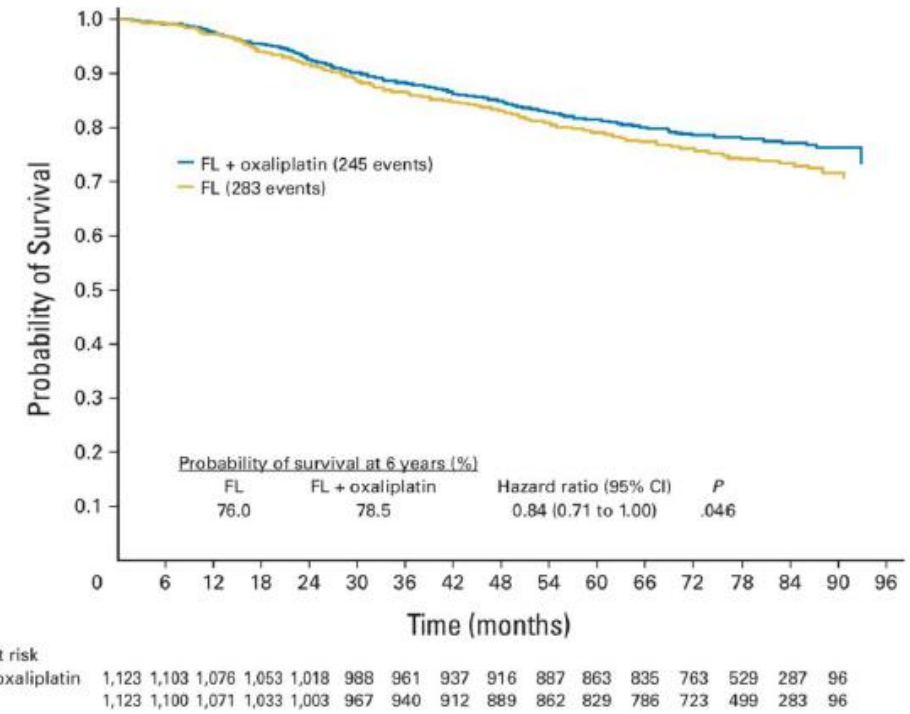
Tie, Sci Transl Med 2016

Which drugs to use in the adjuvant setting

Adjuvant chemotherapy for stage III Colon Cancer

Fluoropyrimidine and oxaliplatin combination is the standard of care





André, NEJM 2004; Yothers JCO 2011; Haller JCO 2011; André JCO 2009

Fluoropyrimidines and oxaliplatin

(X-ACT, MOSAIC, NSABP C07, XELOXA)

Benefit in **stage III** patients:

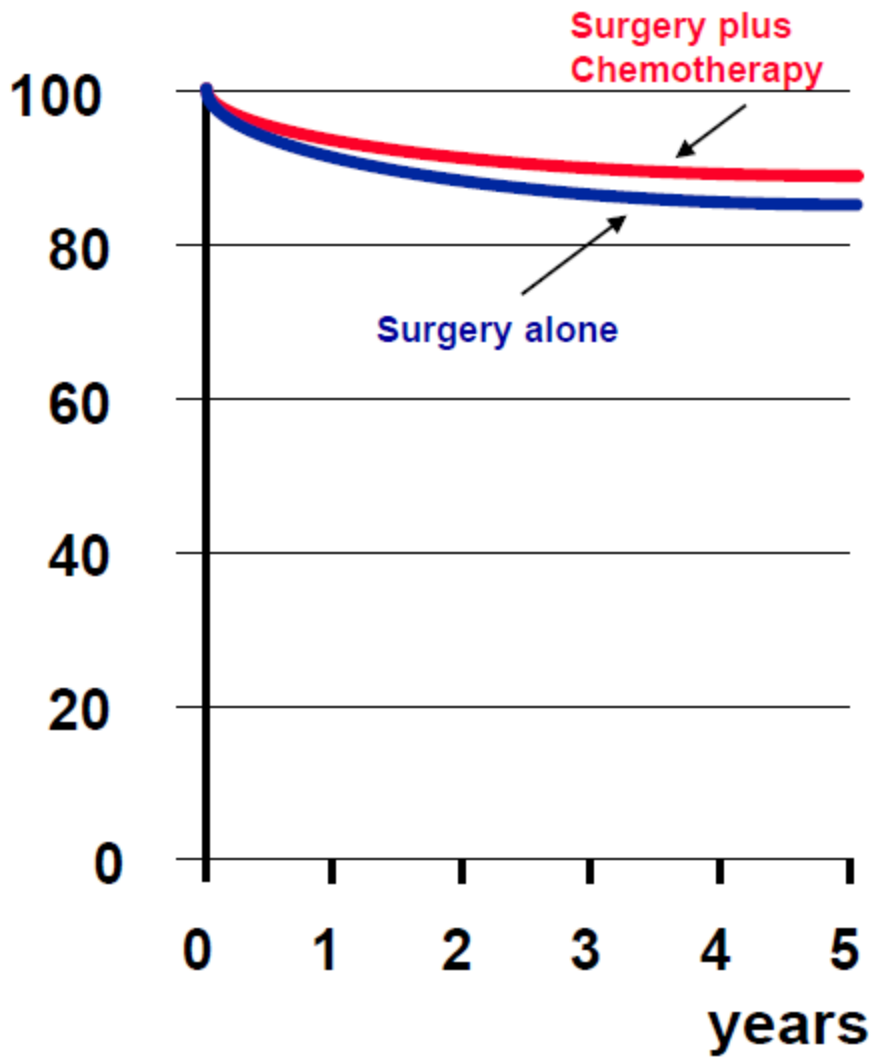
- Fluoropyrimidines risk of death reduction: 10-15%
- OXA addition to risk of death reduction: 4-6%
- Both FOLFOX and XELOX (CAPOX) acceptable
- Neurological toxicity is an issue

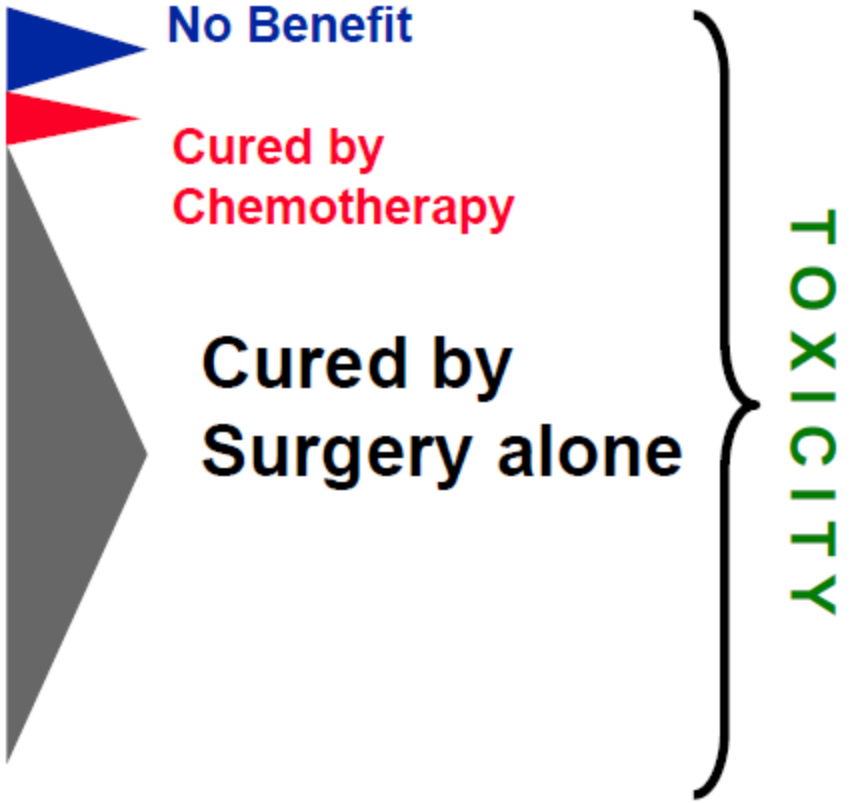
Twelves c, NEJM 2005 Andrè T et al, JCO 2011 Yothers g et al, JCO 2011 Schmoll H-J, JCO 2015

Findings in stage II

- Benefit of monotherapy
  - 3-4% in 5 yr DFS and 5% in 8 yr OS
  - Clinically meaningful?
- Additional benefit of Oxaliplatin
  - No benefit in overall survival
  - ~8% DFS in high risk stage II
- Need to improve tools (molecular biology, immuno profile) to inform decision
- Every decision must be discussed and shared with the patient

Stage II colon cancer

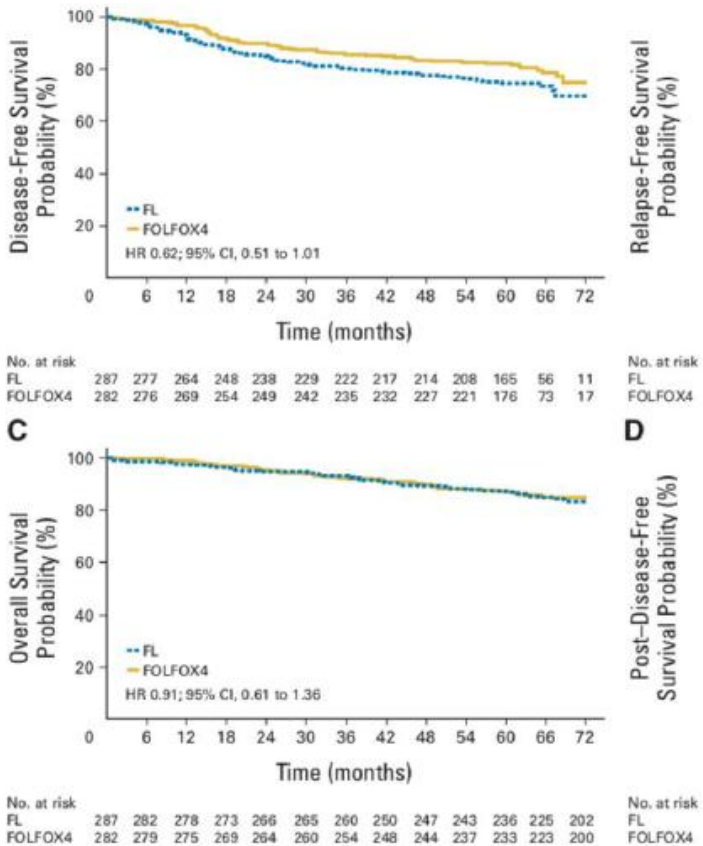


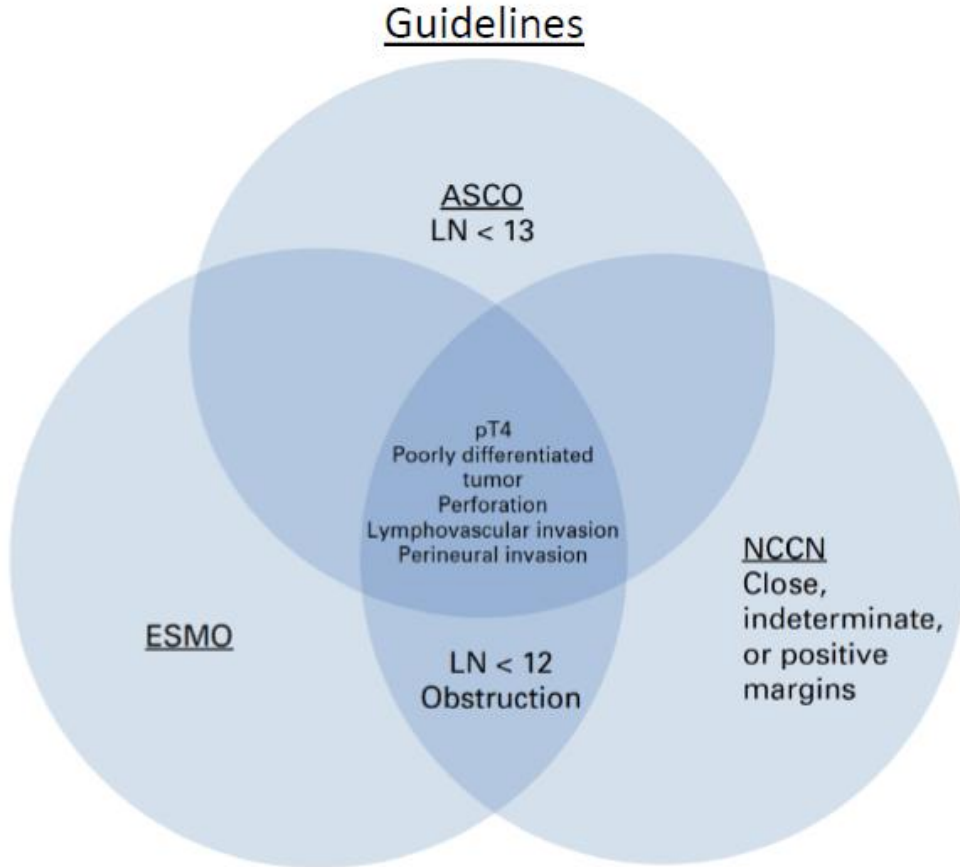


Adjuvant chemotherapy for stage II Colon Cancer

Benefit remains uncertain

Recommendation: Stage II with consensus definition for clinico-pathological high-risk features / discuss with patient / 5FU alone

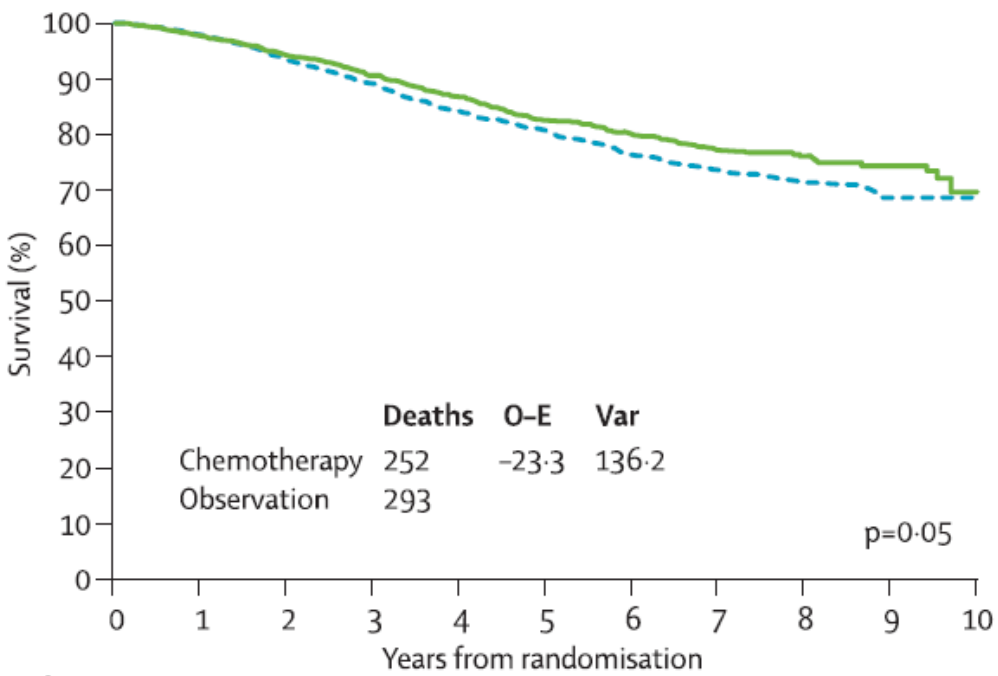




Gray, Lancet 2007 (QUASAR); Kannarkatt, J Oncol Pract 2017; O'Connor, JCO 2011; Tournigand, JCO 2012 (MOSAIC)

Adjuvant Therapy in Stage II (FU/FA)

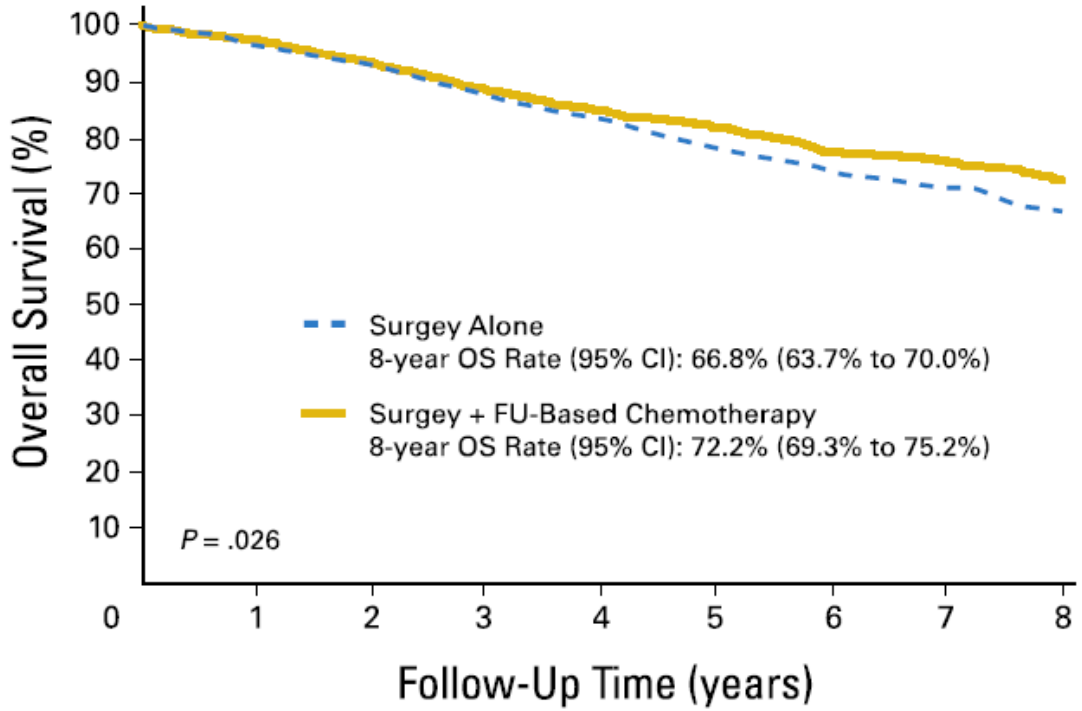
QUASAR
randomised trial N=2963
FU+/-FA d1-5qd28 or regimen +Lev



Estimated absolute gain
@ 5 years ~3%

Group. Lancet 2007; 370:2020.

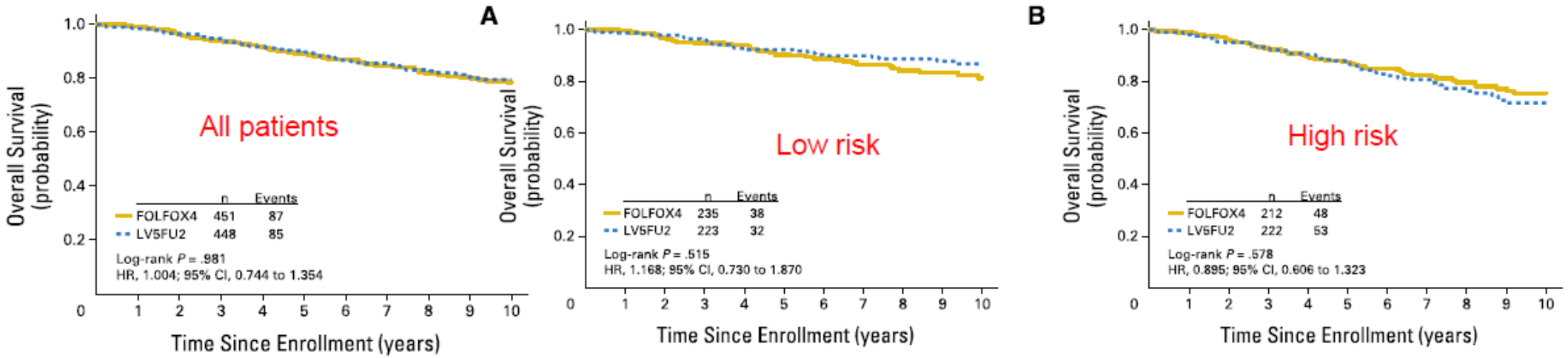
ACCENT Study
Data of ~6900 Stage II
from 18 randomised trials
Different regimens



Estimated absolute gain
@ 8 years ~5%

Sargent D, Sobrero A, Grothey A et al.et al. J Clin Oncol 2009; 29:872-877

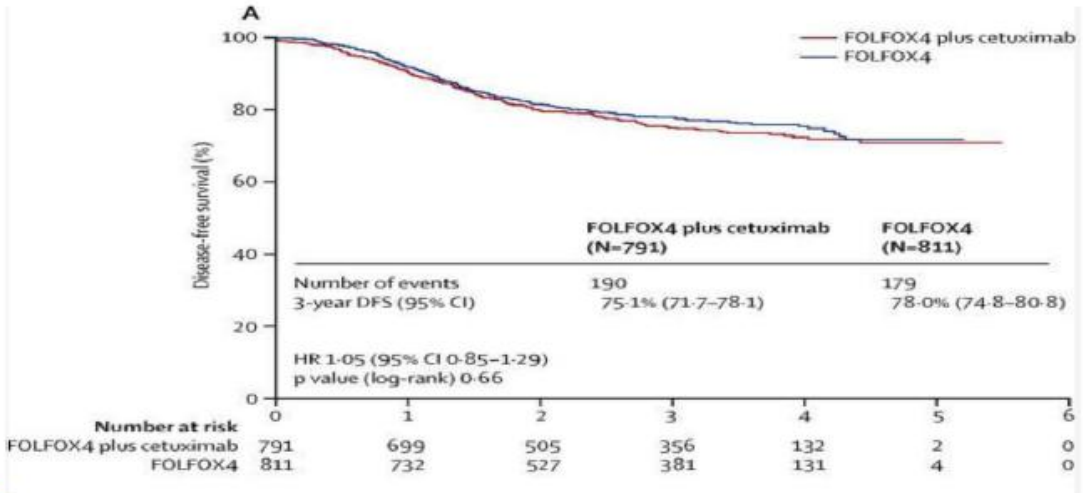
Updated MOSAIK Data Low Risk & High Risk Stage II FOLFOX vs. FU/LV

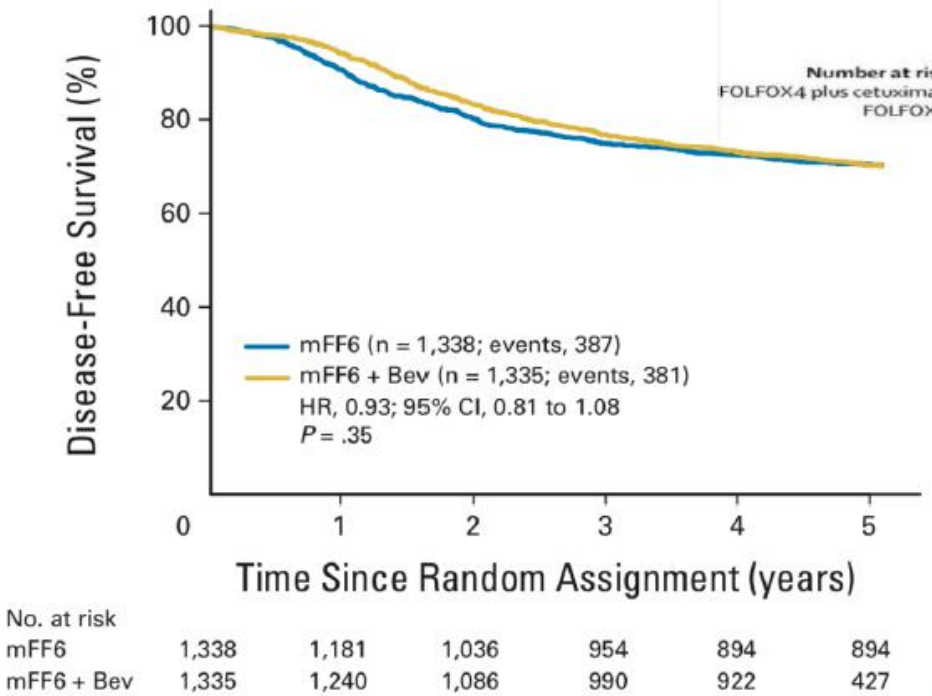


		5 y DFS		6y OS	
	N Pat	HR	P-value	HR	P-value
high risk	569	0.72 0.51-1.01	.062	0.91 0.66-.97	.648
low risk	330	1.36 0.76-2.45	1.01	1.36 0.67-2.5	.399

Tournigant et al. JCO 2015

Failure to translate benefit from cetuximab or bevacizumab from metastatic to early-stage setting





Biological differences between micro- and macro-metastatic disease

Alberts, JAMA 2012; Taieb, Lancet Oncol 2014 (PETACC-8); Allegra, JCO 2013 (NSABP-C08); DeGramont, Lancet Oncol 2012 (AVANT); Midgley, Ann Oncol 2014 (QUASAR2)

Duration of adjuvant treatment

Stage III

Evolution of duration

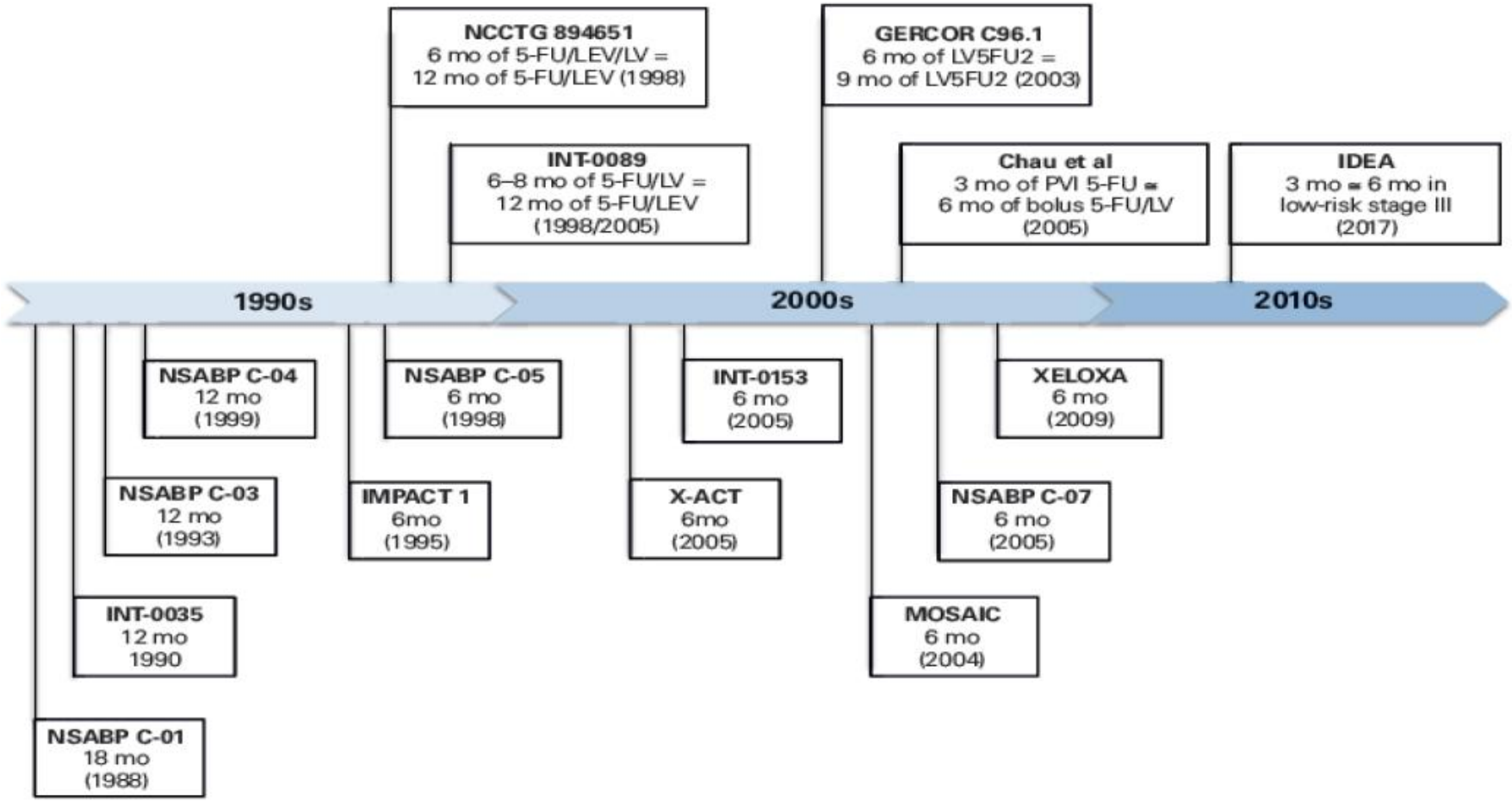
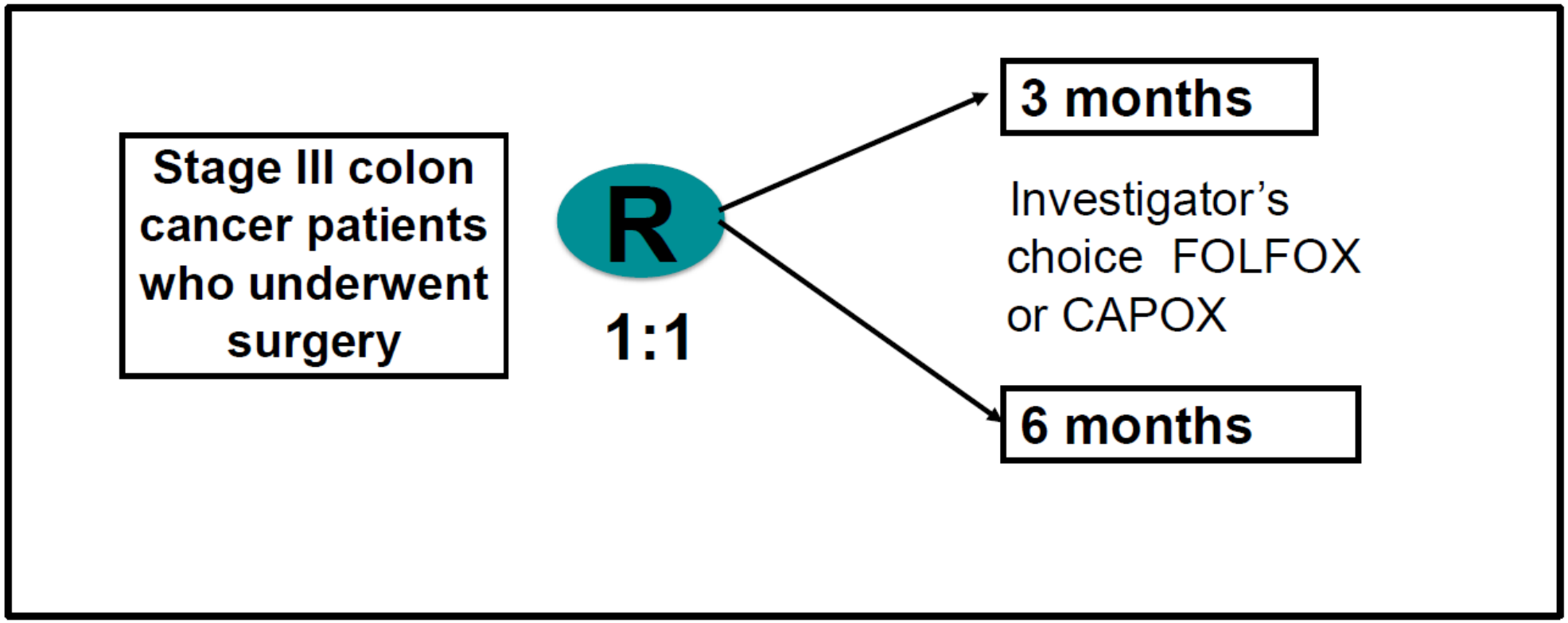


Figure. The Evolution of the Duration of Adjuvant Chemotherapy.
5-FU = fluorouracil; IDEA = International Duration Evaluation of Adjuvant; LEV = levamisole; LV = leucovorin; LV5FU2 = infusional 5-FU/LV; NCCTG = North Central Cancer Treatment Group; NSABP = National Surgical Adjuvant Breast and Bowel Project; PVI = protracted venous infusion; X-ACT = Xeloda in Adjuvant Colon Cancer Therapy.

Lee JJ, Chu E. Oncology. 2018 Sep 15; 32(9):437-42, 444. Review)

Basic Scheme for IDEA



Shi et al ASCO 2017

IDEA trial (International Duration Evaluation of Adjuvant Chemotherapy)

TABLE 1. Trials in the IDEA Collaboration

Trial	Regimen(s)	Patients With Stage II Colon Cancer	Patients With Stage III Colon Cancer	Enrolling Country
TOSCA (Three or Six Colon Adjuvant Trial)	CAPOX or FOLFOX4	1,268	2,402	Italy
SCOT (Short Course Oncology Therapy)	CAPOX or mFOLFOX6	1,078	3,983	United Kingdom, Denmark, Spain, Australia, Sweden, New Zealand
IDEA France	CAPOX or mFOLFOX6	N/A	2,010	France
CALGB/SWOG 80702	mFOLFOX6	N/A	2,440	United States, Canada
HORG (Haematology-Oncology Research Group)	CAPOX or FOLFOX4	413	708	Greece
ACHIEVE (Adjuvant Chemotherapy for Colon Cancer With High Evidence)	CAPOX or mFOLFOX6	514	1,291	Japan
Total patients		3,273	12,834	

Patient Characteristics by Study

Patient Characteristics	TOSCA (N=2402)	SCOT (N=3983)	IDEA France (N=2010)	C80702 (N=2440)	HORG (N=708)	ACHIEVE (N=1291)
Median Age, years	64	65	64	61	67	66
ECOG PS*						
0	95%	71%	74%	71%	82%	96%
1	5%	29%	25%	28%	18%	4%
T Stage						
T1-2	13%	12%	12%	18%	8%	15%
T3	75%	59%	70%	67%	78%	57%
T4	12%	29%	18%	15%	14%	28%
N Stage						
N1	73%	69%	75%	73%	67%	74%
N2	27%	31%	25%	27%	33%	26%
Median follow-up time, m	62	37	51	35	48	37

Shi et al ASCO 2017

Patient Characteristics by Duration and Regimen

Patient characteristics	FOLFOX		CAPOX	
	3m Arm (N=3870)	6m Arm (N=3893)	3m Arm (N=2554)	6m Arm (N=2517)
Median Age, years	64	64	65	65
ECOG PS*				
0	77%	77%	82%	81%
1	22%	22%	18%	19%
T Stage				
T1-2	13%	14%	13%	12%
T3	68%	67%	63%	63%
T4	19%	19%	24%	25%
N Stage				
N1	72%	73%	71%	71%
N2	28%	27%	29%	29%

*1% of PS 2 in FOLFOX treated patients

Adverse Events

Adverse Events	FOLFOX			CAPOX		
	3m Arm	6m Arm	p-value[1]	3m Arm	6m Arm	p-value[1]
Overall						
G2	32%	32%	<.0001	41%	48%	<.0001
G3-4	38%	57%		24%	37%	
Neurotoxicity						
G2	14%	32%	<.0001	12%	36%	<.0001
G3-4	3%	16%		3%	9%	
Diarrhea						
G2	11%	13%	<.0001	10%	13%	0.0117
G3-4	5%	7%		7%	9%	

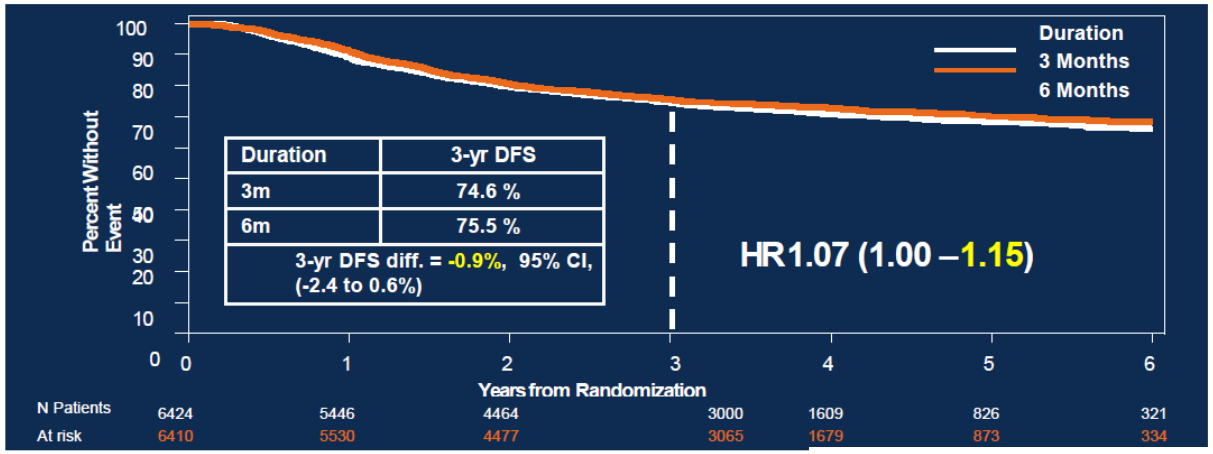
[1]Chi-squared test for trend; Total of 19 grade 5 events; Adverse events only collected on first 617 patients enrolled to SCOT trial

3 y.-DFS

TABLE 2. Disease-Free Survival for Patients With Stage III Disease by Regimen and T and N Stage–Based Risk Groups

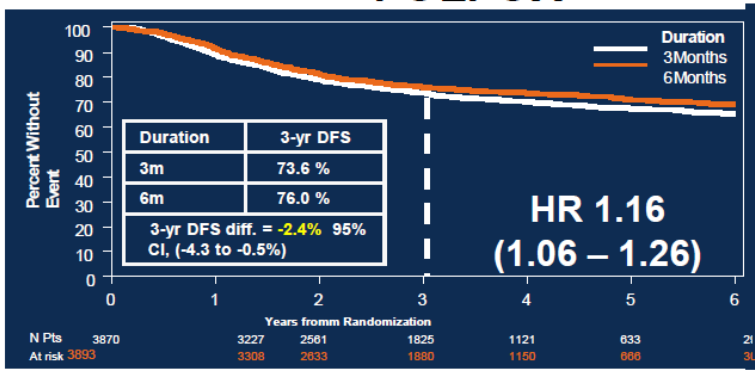
	FOLFOX/CAPOX Combined			FOLFOX Treated			CAPOX Treated		
Study Group	3 Months, %	6 Months, %	HR (95% CI)	3 Months, %	6 Months, %	HR (95% CI)	3 Months, %	6 Months, %	HR (95% CI)
Overall IDEA stage III cohort	74.6	75.5	1.07 (1.00–1.15)	73.6	76.0	1.16 (1.06–1.26)	75.9	74.8	0.95 (0.85–1.06)*
Low-risk subgroup (T1-T3, N1)	83.1	83.3	1.01 (0.90–1.12)*	81.9	83.5	1.10 (0.96–1.26)	85.0	83.1	0.85 (0.71–1.01)*
High-risk subgroup (T4, N2)	62.7	64.4	1.12 (1.03–1.23)	61.5	64.7	1.20 (1.07–1.35)	64.1	64.0	1.02 (0.89–1.17)

Primary DFS Analysis (mITT)

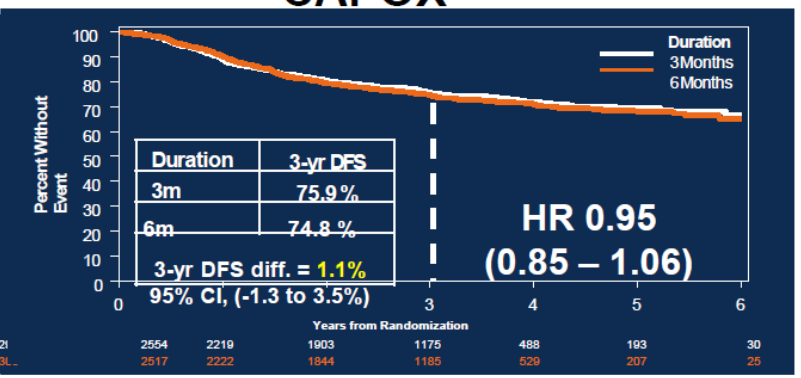


DFS Comparison by Regimen

FOLFOX

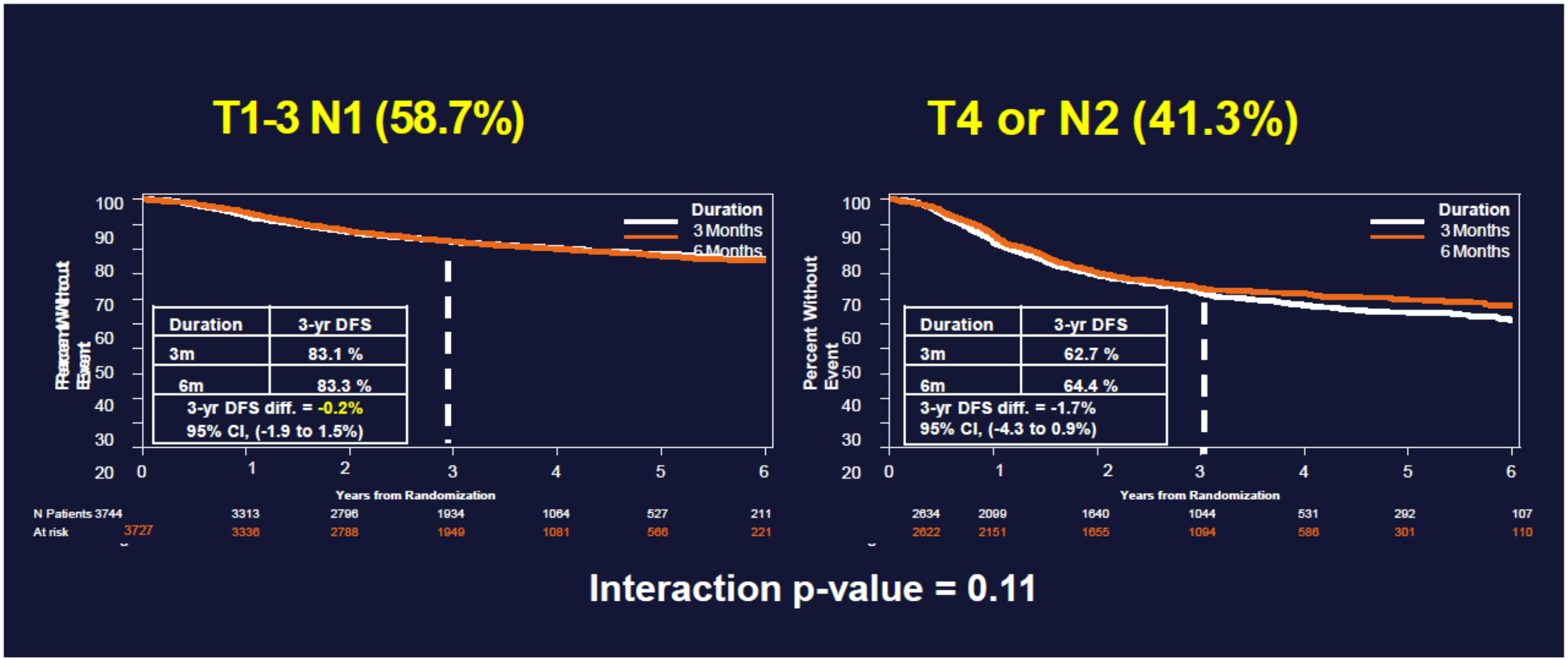


CAPOX



Interaction p-value = 0.0051

DFS Comparison by Risk Groups



Shi et al ASCO 2017

IDEA findings in one slide

3 yr DFS rate (%) and HR by risk group and regimen		Regimen								
		CAPOX			FOLFOX			CAPOX / FOLFOX Combined		
		3 yr DFS, % (95% CI)		HR (95% CI)	3 yr DFS, % (95% CI)		HR (95% CI)	3 yr DFS, % (95% CI)		HR (95% CI)
		3 m	6 m		3 m	6 m		3 m	6 m	
Risk group	Low-risk (T1-3 N1)	85.0 (83.1-86.9)	83.1 (81.1-85.2)	0.85 (0.71-1.01)	81.9 (80.2-83.6)	83.5 (81.9-85.1)	1.10 (0.96-1.26)	83.1 (81.8-84.4)	83.3 (82.1-84.6)	1.01 (0.90-1.12)
	High-risk (T4 and / or N2)	64.1 (61.3-67.1)	64.0 (61.2-67.0)	1.02 (0.89-1.17)	61.5 (58.9-64.1)	64.7 (62.2-67.3)	1.20 (1.07-1.35)	62.7 (60.8-64.4)	64.4 (62.6-66.4)	1.12 (1.03-1.23)

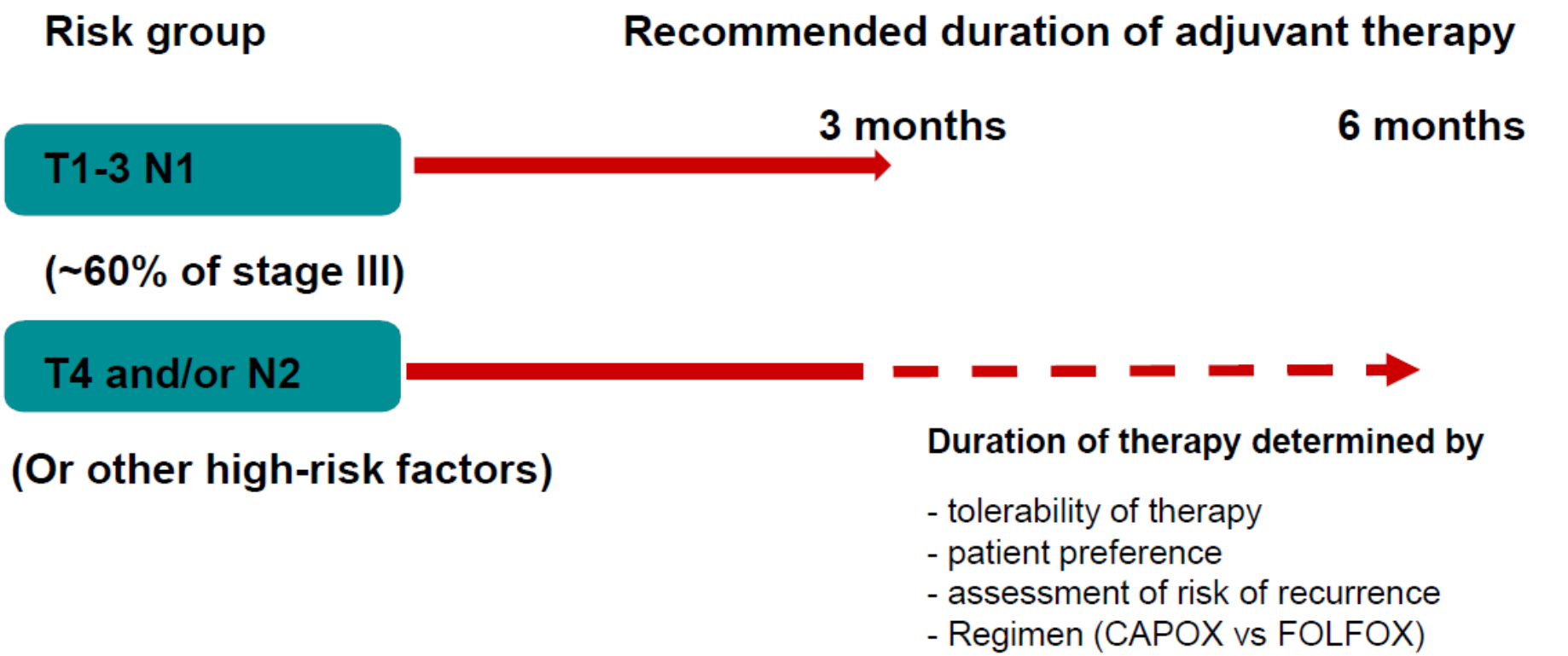
Non-inferior

Not proven

Inferior

Non-inferiority of 3 months compared with 6 months of adjuvant therapy

IDEA Clinical Consensus: Risk-based approach to adjuvant chemotherapy in stage III colon cancer



Shi et al ASCO 2017

Duration of adjuvant treatment

Stage II

IDEA in stage II colon cancer

- Prospective pooled analysis of 4 R trials investigating the duration of adjuvant treatment in patients with high-risk stage II disease
- N=3272 (1254 FOLFOX, 2019 CAPEOX)
- mF.U. 60.2 months: 5y-DFS 80.7% (3 m. treatment) v. 84% (6 m. treatment)
- Overall population HR=1.18 (3 v. 6 months)

CAPEOX HR=1.02, FOLFOX HR=1.42

- 3 months of CAPEOX are **non inferior** to 6 months, especially in the lower-risk group
- 3 months of FOLFOX are **inferior** to 6 months

Iveson, ASCO 2019

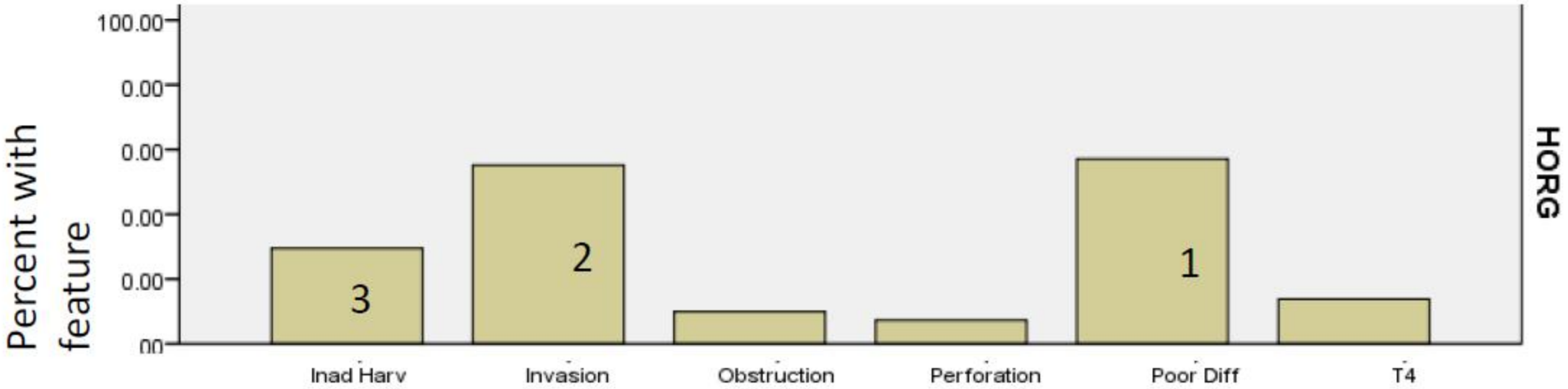
IDEA collaboration for HR stage II:

HORG TRIAL

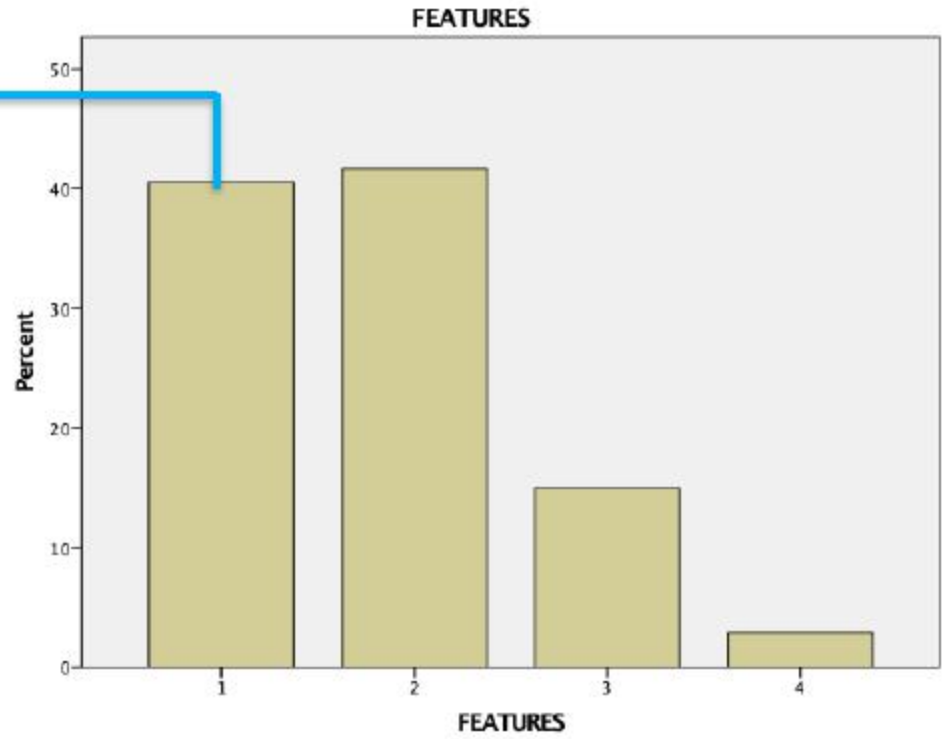
Patients' Characteristics

	FOLFOX			CAPOX		
Patient characteristics	3 Months (N=48)	6 Months (N=49)	Total (N=97)	3 Months (N=158)	6 Months (N=158)	Total (N=316)
Age, years						
Median (Range)	70.0 (40, 80)	64.0 (24, 80)	67.0 (24, 80)	66.0 (31, 81)	65.0 (36, 82)	65.0 (31, 82)
Gender, n (%)						
Male	20 (41.7%)	26 (53.1%)	46 (47.4%)	87 (55.1%)	94 (59.5%)	181 (57.3%)
Female	28 (58.3%)	23 (46.9%)	51 (52.6%)	71 (44.9%)	64 (40.5%)	135 (42.7%)
ECOG Performance Status, n (%)						
0	32 (66.7%)	46 (93.9%)	78 (80.4%)	135 (86.0%)	142 (89.9%)	277 (87.9%)
1	16 (33.3%)	3 (6.1%)	19 (19.6%)	22 (14.0%)	15 (9.5%)	37 (11.7%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)	1 (0.3%)
T Stage, n (%)						
T3	38 (79.2%)	40 (81.6%)	78 (80.4%)	139 (88.0%)	139 (88.0%)	278 (88.0%)
T4	10 (20.8%)	9 (18.4%)	19 (19.6%)	19 (12.0%)	19 (12.0%)	38 (12.0%)
Number of Lymph Nodes Examined						
Mean (SD)	18.0 (11.83)	20.9 (12.13)	19.5 (12.01)	18.6 (11.61)	19.8 (13.51)	19.2 (12.59)
Median (Range)	14.5 (3, 59)	18.0 (2, 49)	17.0 (2, 59)	16.0 (3, 79)	17.0 (2, 84)	16.0 (2, 84)

Souglakos, ESMO 2019



63% invansion

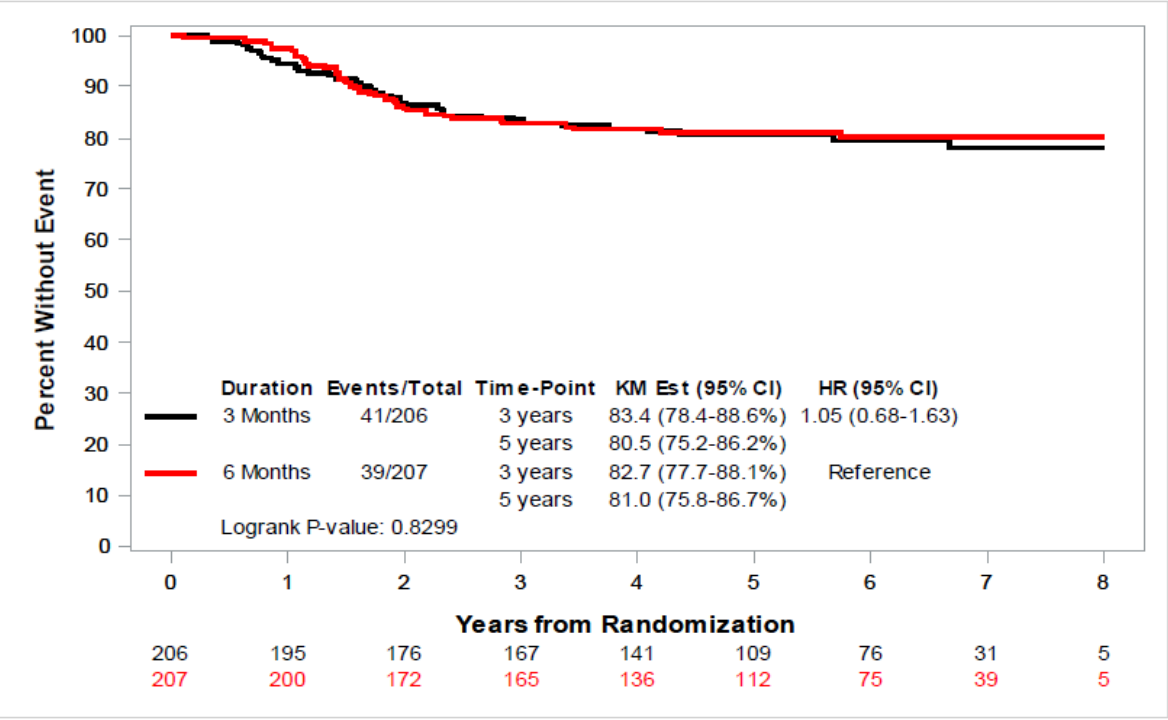


High-risk feautures

BARCELONA 2019 ESMO congress

Souglakos, ESMO 2019

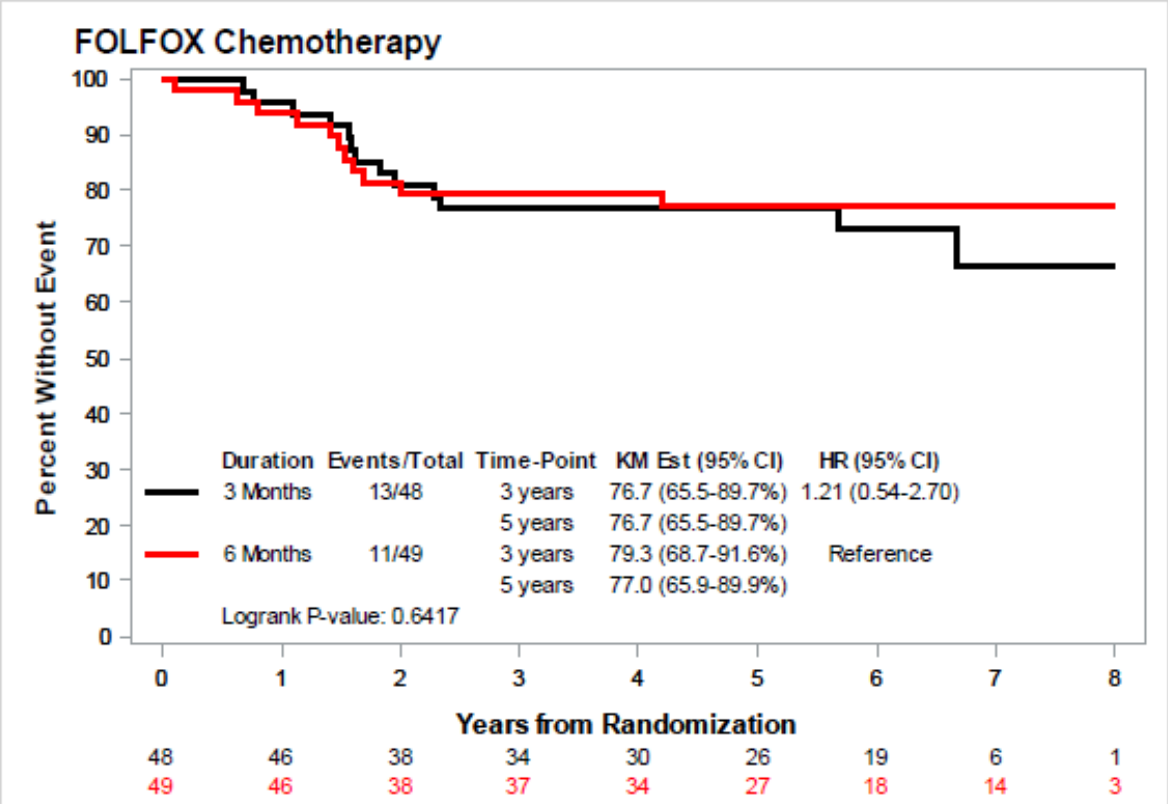
	3M (%)	6M (%)	*p*-value
Residual Neuropathy at last follow-up visit			
2	1.4	6	0.001
3	0.3	1.5	0.001

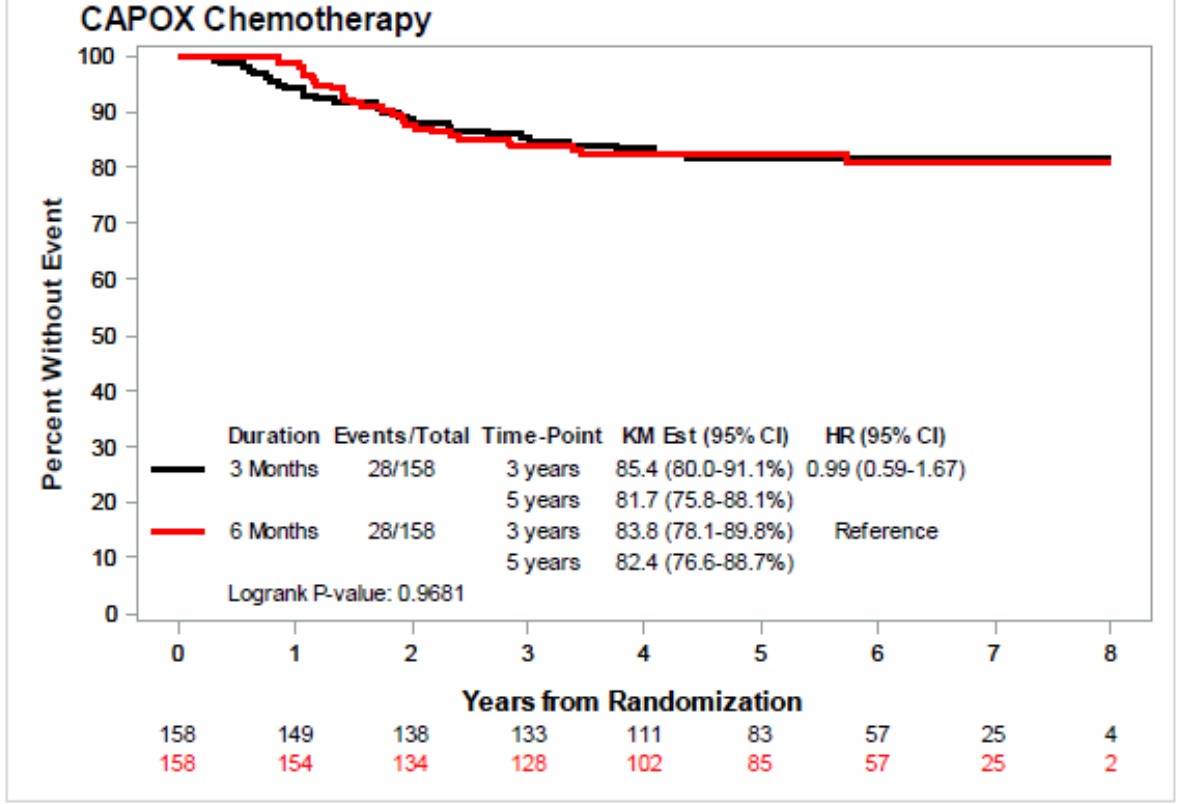


DFS at 3 and 5 years

Souglakos, ESMO 2019

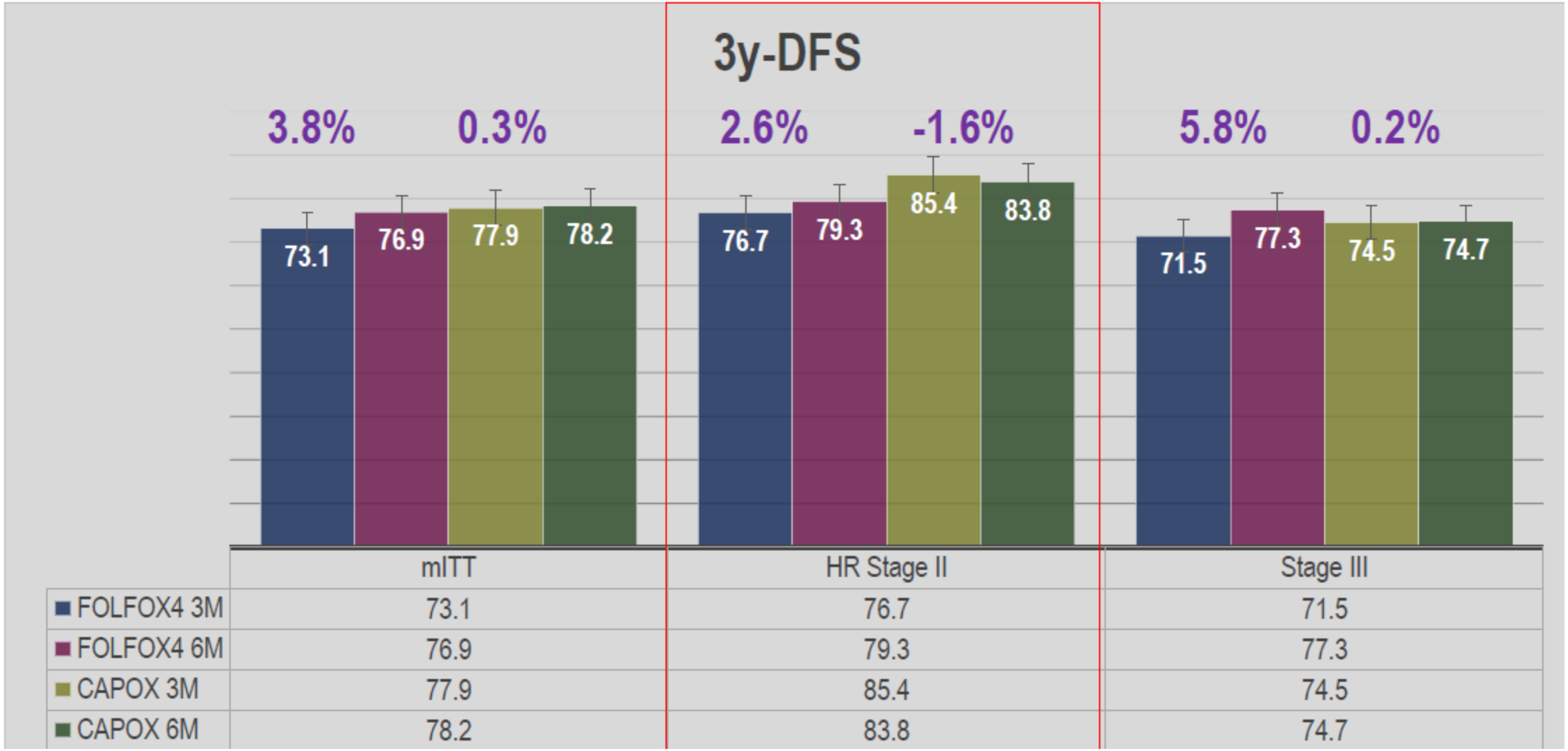
DFS according to regimen





Souglakos, ESMO 2019

Exploratory analysis of 3 y-DFS according to stage & regimen



	mITT	HR Stage II	Stage III
FOLFOX4 3M	73.1	76.7	71.5
FOLFOX4 6M	76.9	79.3	77.3
CAPOX 3M	77.9	85.4	74.5
CAPOX 6M	78.2	83.8	74.7

Souglakos, ESMO 2019

ACHIEVE-2 > japanese trial of stage 2, high-risk colon within IDEA

- No interaction observed between regimen and duration (but low number with FOLFOX)
- For patients with T4 tumors, 3 months → worse outcome
- For patients with T3 tumors, similar results
- Significant reduction of neuropathy with 3 months

Yoshino, ESMO 2019

JAMA Network | Open

Original Investigation | Oncology

Association Between Adjuvant Chemotherapy Duration and Survival Among Patients With Stage II and III Colon Cancer

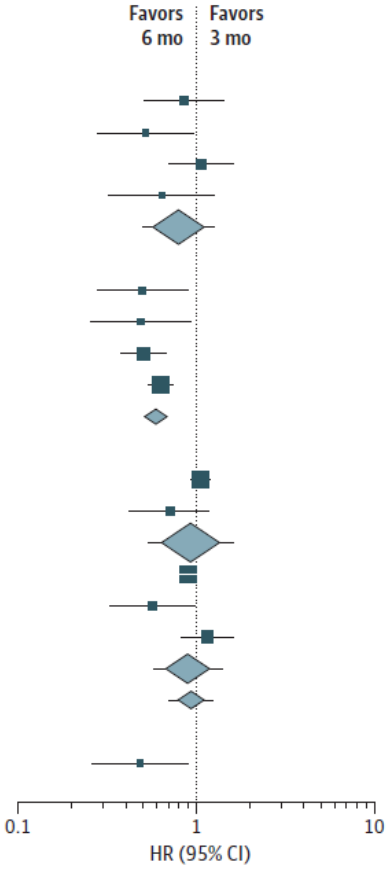
A Systematic Review and Meta-analysis

Devon J. Boyne, MSc; Colleen A. Cuthbert, PhD, RN, NP; Dylan E. O'Sullivan, MSc; Tolulope T. Sajobi, PhD; Robert J. Hilsden, MD, PhD, FRCPC; Christine M. Friedenreich, PhD; Winson Y. Cheung, MD, MPH, FRCPC; Darren R. Brenner, PhD

22 studies, N=43.671
omit stage II (factor of heterogeneity)
Monotherapy: 6 m. > 3 m.
Combination: equivalent

Figure 2. Meta-analysis of the Estimated Hazard of Death Among Patients With Stage III Colon Cancer Treated With 6 Months of Adjuvant Chemotherapy Relative to Those Who Received 3 Months of Adjuvant Chemotherapy

Source	Sample Size No.	Treatment Regimens	HR (95% CI)
Overall survival: included combination therapy			
van Erning et al,[45] 2017	161	CAPOX	0.85 (0.51-1.43)
Tsai,[44] 2016	213	FOLFOX	0.52 (0.28-0.97)
Kumar,[34] 2015	616	FOLFOX	1.07 (0.71-1.62)
Kim,[32] 2014	268	ALL	0.64 (0.32-1.27)
Random-effects model: $I^2=27.7\%$; $\tau^2=0.03$; $P=.25$			0.80 (0.58-1.09)
Overall survival: monotherapy only			
van Erning et al,[45] 2017	191	Capecitabine monotherapy	0.50 (0.28-0.90)
Chapuis,[26] 2009	104	5-Fluorouracil	0.49 (0.26-0.94)
Morris,[36] 2007	416	5-Fluorouracil	0.50 (0.38-0.68)
Neugut,[37] 2006	1579	5-Fluorouracil	0.64 (0.54-0.75)
Random-effects model: $I^2=0\%$; $\tau^2=0$; $P=.46$			0.59 (0.52-0.68)
Disease-free survival: included combination therapy			
IDEA,[1] 2018 collaboration	10 395	CAPOX	1.05 (0.93-1.19)
van Erning et al,[45] 2017	161	CAPOX	0.70 (0.42-1.18)
CAPOX only ($I^2=55.1\%$; $\tau^2=0.05$; $P=.14$)			0.93 (0.65-1.34)
IDEA,[1] 2018 collaboration	10 395	FOLFOX	0.90 (0.82-0.99)
Tsai,[44] 2016	213	FOLFOX	0.57 (0.33-0.99)
Kumar,[34] 2015	616	FOLFOX	1.16 (0.82-1.64)
FOLFOX only ($I^2=57.5\%$; $\tau^2=0.03$; $P=.10$)			0.90 (0.69-1.18)
Random-effects model: $I^2=58.2\%$; $\tau^2=0.01$; $P=.05$			0.94 (0.80-1.09)
Disease-free survival: monotherapy only			
van Erning et al,[45] 2017	191	Capecitabine monotherapy	0.48 (0.26-0.90)



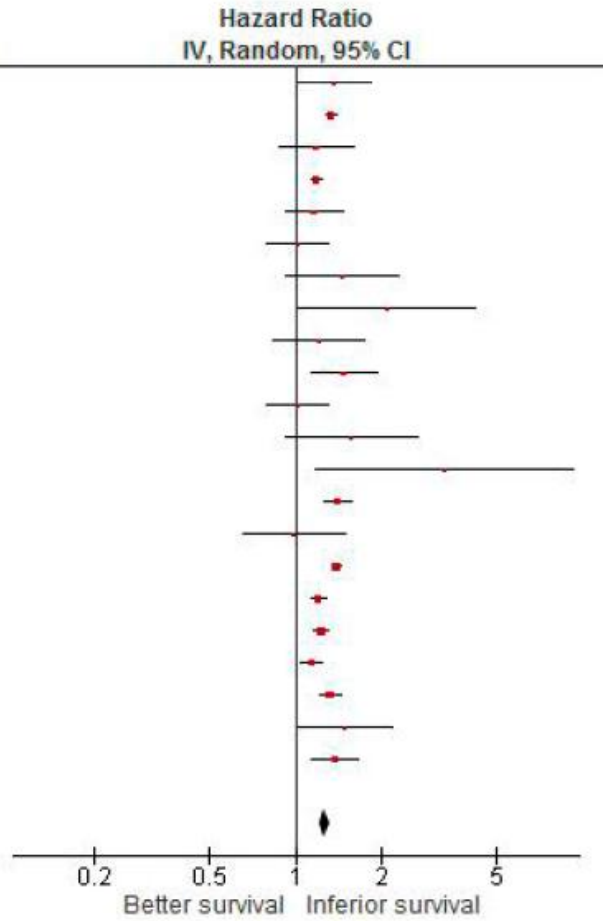
Timing of adjuvant chemotherapy

- Classically within 6-8 weeks post-surgery
- Meta-analysis to assess the effect of delay on survival (OS)

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Chau 2005	0.3148	0.1455	2.3%	1.37 [1.03, 1.82]	2005
Hershman 2006	0.2852	0.0236	10.1%	1.33 [1.27, 1.39]	2006
Berglund 2008	0.1655	0.1497	2.1%	1.18 [0.88, 1.58]	2008
Cheung 2009	0.1655	0.0221	10.2%	1.18 [1.13, 1.23]	2009
Zeig-Owens 2009	0.1484	0.1183	3.1%	1.16 [0.92, 1.46]	2009
Ahmed 2010	0.0218	0.125	2.8%	1.02 [0.80, 1.31]	2010
Lima 2011	0.3716	0.2266	1.1%	1.45 [0.93, 2.26]	2011
Bayraktar 2011	0.7275	0.3611	0.4%	2.07 [1.02, 4.20]	2011
Czaykowski 2011	0.1906	0.1862	1.5%	1.21 [0.84, 1.74]	2011
Tsai 2013	0.3853	0.1342	2.6%	1.47 [1.13, 1.91]	2013
dos Santos 2013	0.0198	0.124	2.9%	1.02 [0.80, 1.30]	2013
Kang 2013	0.4447	0.2694	0.8%	1.56 [0.92, 2.65]	2013
Day 2014	1.1878	0.5259	0.2%	3.28 [1.17, 9.19]	2014
Bos 2015	0.3365	0.0578	6.9%	1.40 [1.25, 1.57]	2015
Peixoto 2015	-0.0101	0.2069	1.2%	0.99 [0.66, 1.49]	2015
Klein 2015	0.3293	0.0187	10.5%	1.39 [1.34, 1.44]	2015
Nachiappan 2015	0.1823	0.0307	9.5%	1.20 [1.13, 1.27]	2015
Massarweh 2015	0.207	0.0299	9.6%	1.23 [1.16, 1.30]	2015
Sun 2016	0.131	0.042	8.4%	1.14 [1.05, 1.24]	2016
Becerra 2017	0.2776	0.0444	8.2%	1.32 [1.21, 1.44]	2017
Kim YW 2017	0.3988	0.1884	1.5%	1.49 [1.03, 2.16]	2017
Gao 2018	0.3148	0.0918	4.3%	1.37 [1.14, 1.64]	2018
Total (95% CI)			**100.0%**	**1.27 [1.21, 1.33]**	

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 69.82$, df = 21 ($P < 0.00001$); $I^2 = 70\%$

Test for overall effect: $Z = 9.64$ ($P < 0.00001$)

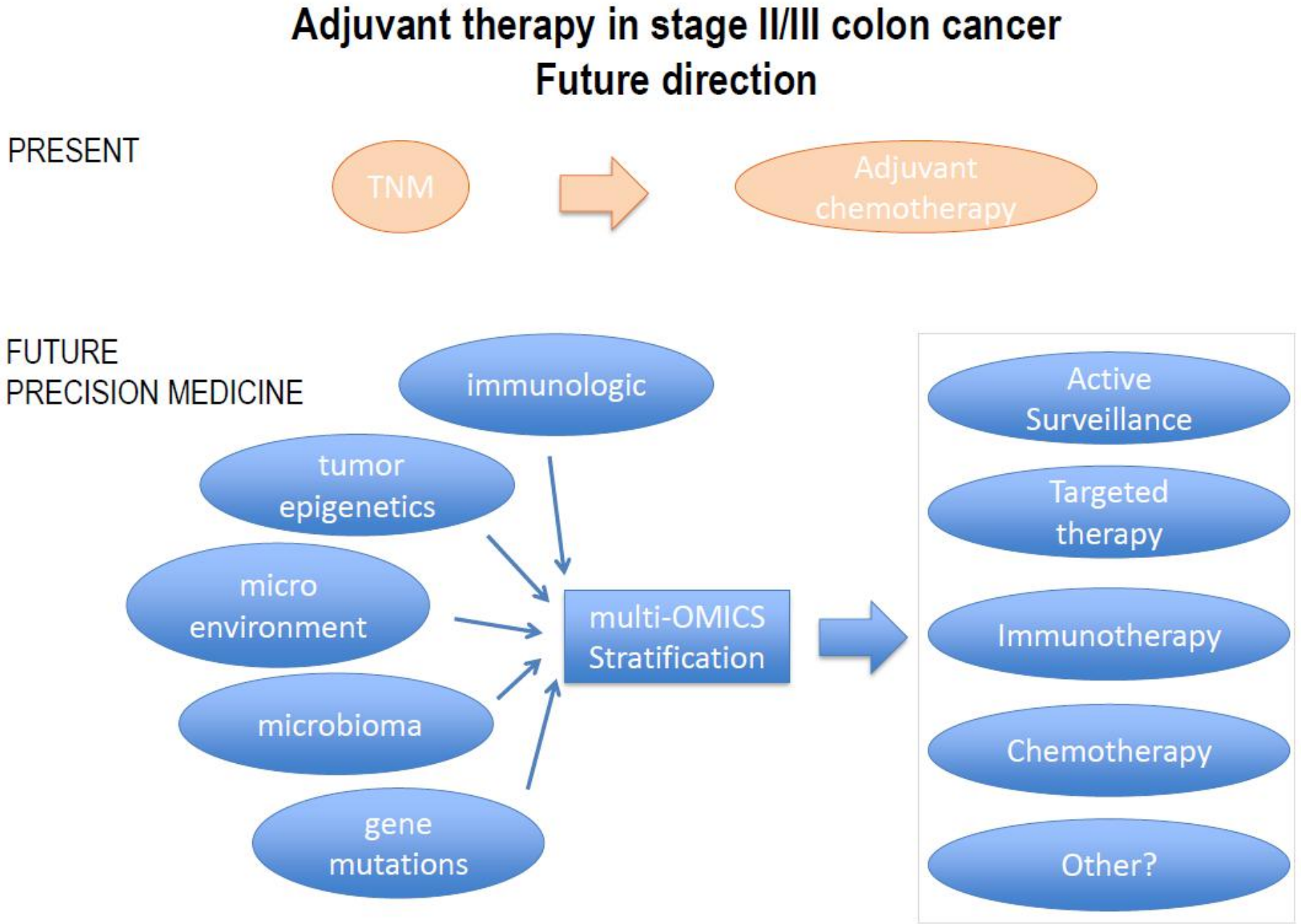


Petrelli et al., Cancers 2019

Conclusions

- In high risk stage II colon cancer there is some evidence for adjuvant chemotherapy
- Benefit from chemotherapy in stage II is limited in a small and undefined group (unknown if it is the group with poor prognostic factors) → need for **predictive** biomarkers
- Biological collections from randomized controlled trials have dramatically improved our knowledge on early colon cancer, but no valid test/biomarker in clinical practice yet
- When CAPEOX used in the adjuvant setting, it can be given for 3 months instead of 6 months (especially in low-risk stage III disease)

future


Adjuvant therapy in stage II/III colon cancer
Future direction
PRESENT
TNM
Adjuvant chemotherapy
FUTURE
PRECISION MEDICINE
immunologic
tumor epigenetics
micro environment
microbioma
gene mutations
multi-OMICS Stratification
Active Surveillance
Targeted therapy
Immunotherapy
Chemotherapy
Other?

Thank you very much for your attention.