INSTITUT HOSPITALIER FRANCO-BRITANNIQUE

Au-delà du soin, vous comprendre

How to improve the adjuvant treatment of colon cancer?

Aimery de Gramont
Franco-British Institute
Levallois-Perret

Disclosure

- Sanofi
- Roche

How to improve the adjuvant treatment of colon cancer?

Our achievments

What is ongoing?

Biomarkers

Improving our therapies

Imrproving our clinical research

How to improve the adjuvant treatment of colon cancer?

Our achievments

Chemotherapy agents in adjuvant colon

Chemotherapy	Results	Studies
LV5FU	Stage II MSS Stage III	Moertel - IMPACT - QUASAR - NSABP C03/C04 …
Capecitabine	Stage III	X-ACT
Oxaliplatin + FP	High-risk Stage II - Stage III	MOSAIC - NSABP C07 - XELOXA
UFT	Non-inferiority	NSABP C06
Irinotecan+FP	Failed	PETACC3 - CALGB 89803 - ACCORD 02
Raltitrexed	Failed	PETACC 1
S1	Failed	JCOG 0910
TAS 102	Not tested	

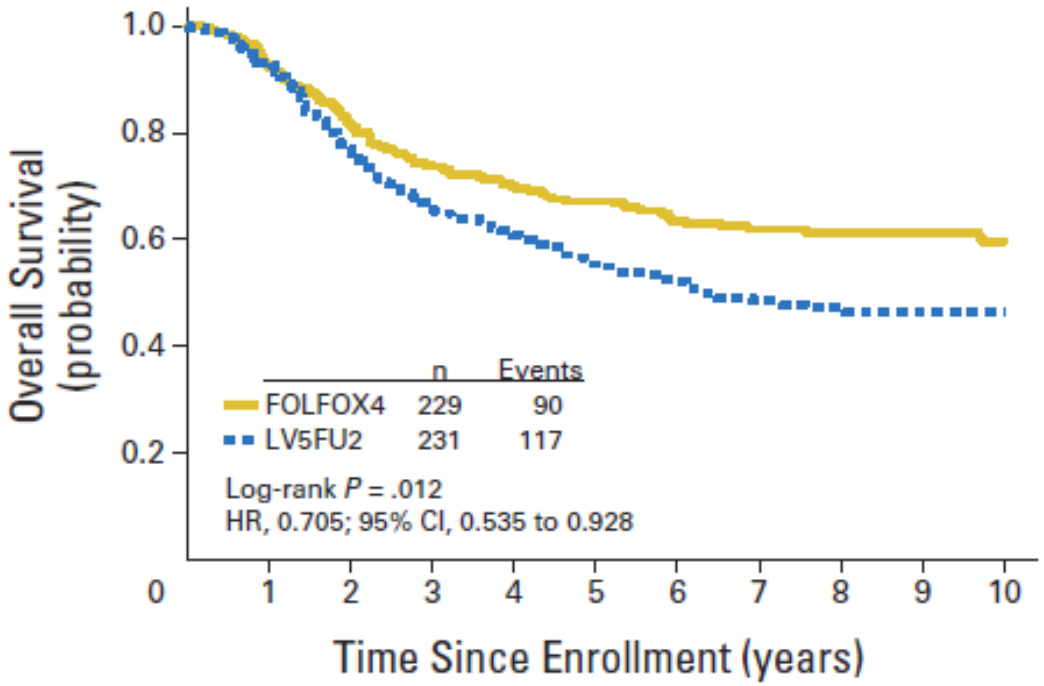
Fluoropyrimidines +/- oxaliplatin

Tageted therapies in adjuvant colon

Targeted therapy	Results	Studies
Bevacizumab	Failed	NSABP C08 - AVANT
Cetuximab	Failed	N0147 - PETACC 8
Regorafenib	On going	NSABP C13
Panitumumab	Not tested	
Ramucirumab	Not tested	

Other failures:
Interferon alpha
Edrecolomab

Oxaliplatin in stage IIIC



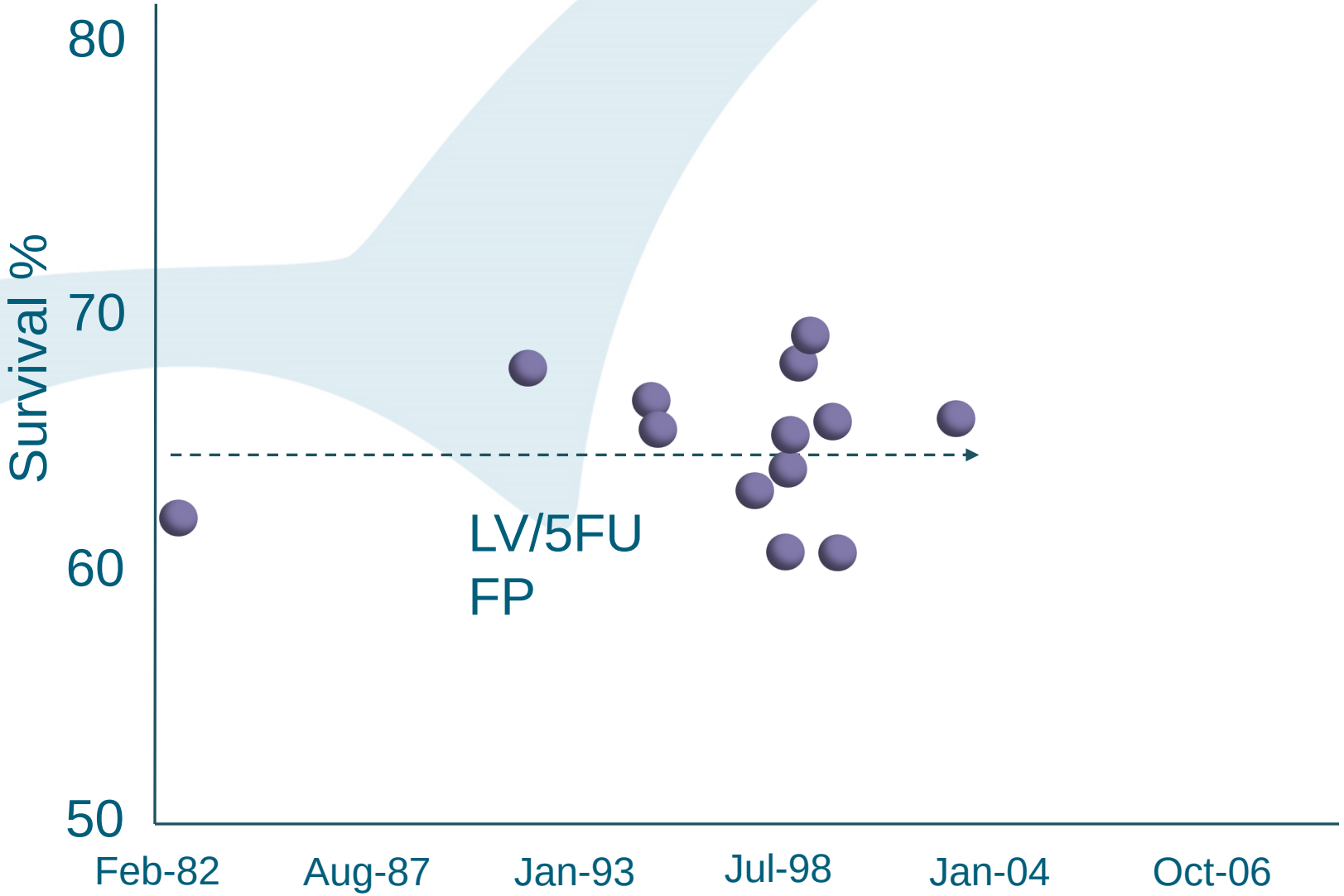
FOLFOX4											
No. at risk	229	209	180	161	153	146	136	106	81	77	63
Events	0	18	43	60	68	74	81	84	85	85	87
LV5FU2											
No. at risk	231	211	171	149	134	119	108	83	69	62	48
Events	0	17	54	76	89	100	107	114	117	117	117

Stage III N2

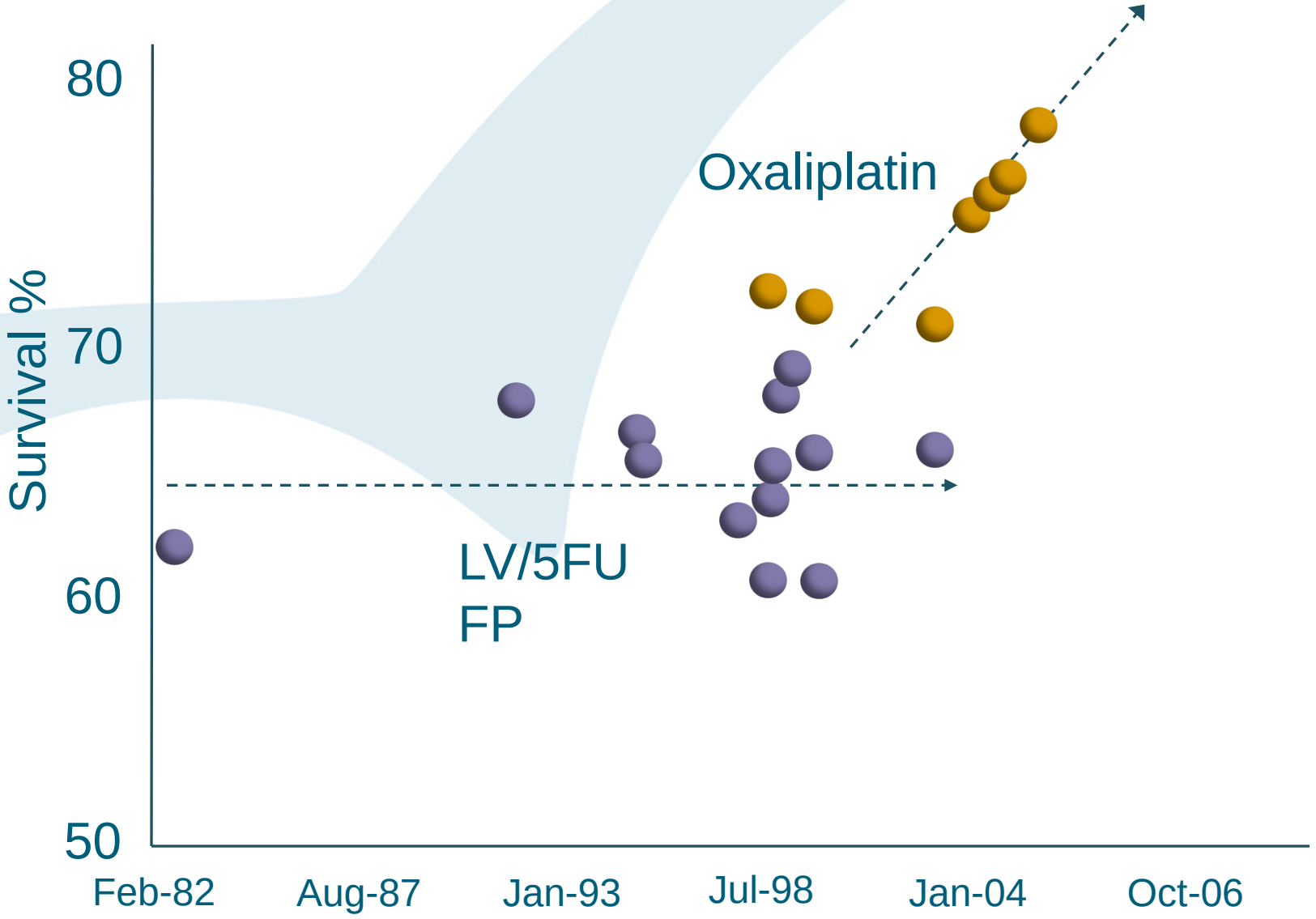
15% absolute benefit

André T et al, JCO 2015

3-Yr DFS in Stage III: Results over time



3-Yr DFS in Stage III: Results over time



Will Rogers'effect

Stage Migration

Recent trials vs. MOSAIC in Stage III

	MOSAIC 2004		XELOXA 2011	NCCTG N0147 2012	AVANT 2012
Regimen	LV5FU2	FOLFOX4	XELOX	mFOLFOX6	FOLFOX4
3yr OS	81.3%	84.3%	86.0%*	87.9%	90.0%

* from curves

FOLFOX4 MOSAIC vs. FOLFOX4 AVANT

	3-yr DFS	5-yr OS	3-yr DFS <4LN	3-yr DFS ≥4LN
MOSAIC	73%	76%	72%	56%
AVANT	77%	85%	85%	66%
	+4%	+9%	+13%	+10%

Elderly - ACCENT

ACCENT analysis	Hazard ratio (95% CIs)* DFS	OS
<70 years, n=3877	0.77 (0.68,0.86)	0.81 (0.71,0.93)
≥70 years, n=703	1.04 (0.80,1.35)	1.19 (0.90,1.57)

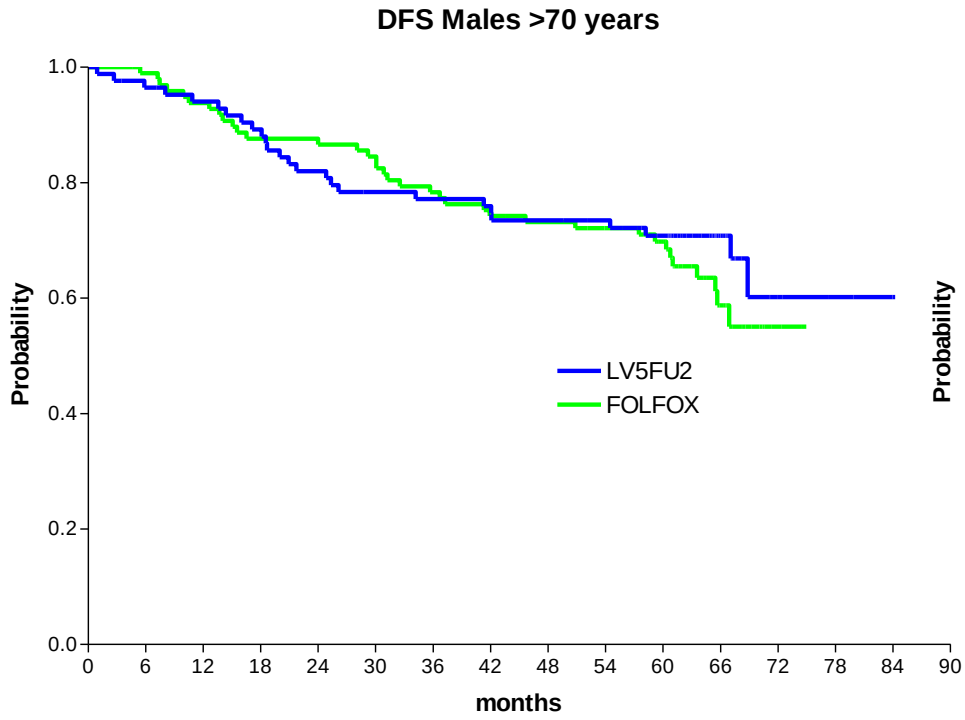
*Values <1 favor oxaliplatin-based therapy vs. 5-FU/LV.
†Data for oxaliplatin-based regimens.

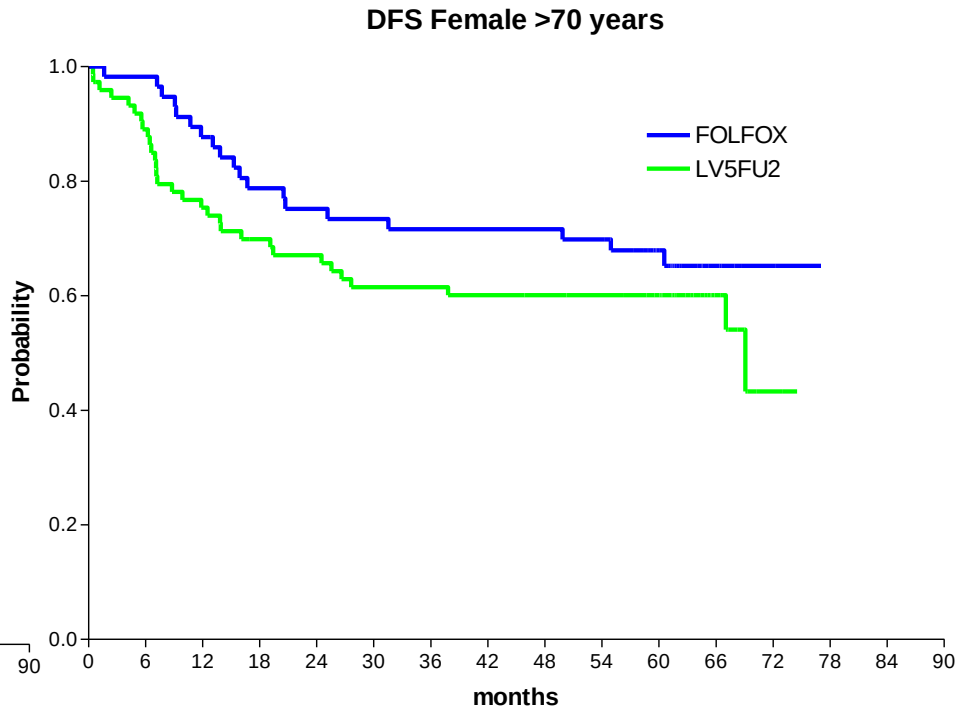
Ederly patients do not benefit of oxaliplatin

McCleary et al. ASCO 2009 (poster 4010), JCO 2014

Role of Gender in Elderly Patients

DFS (recurrence & death of other causes)





MOSAIC: elderly women did better than elderly men

80405: Sidedness is Prognostic

MCRC

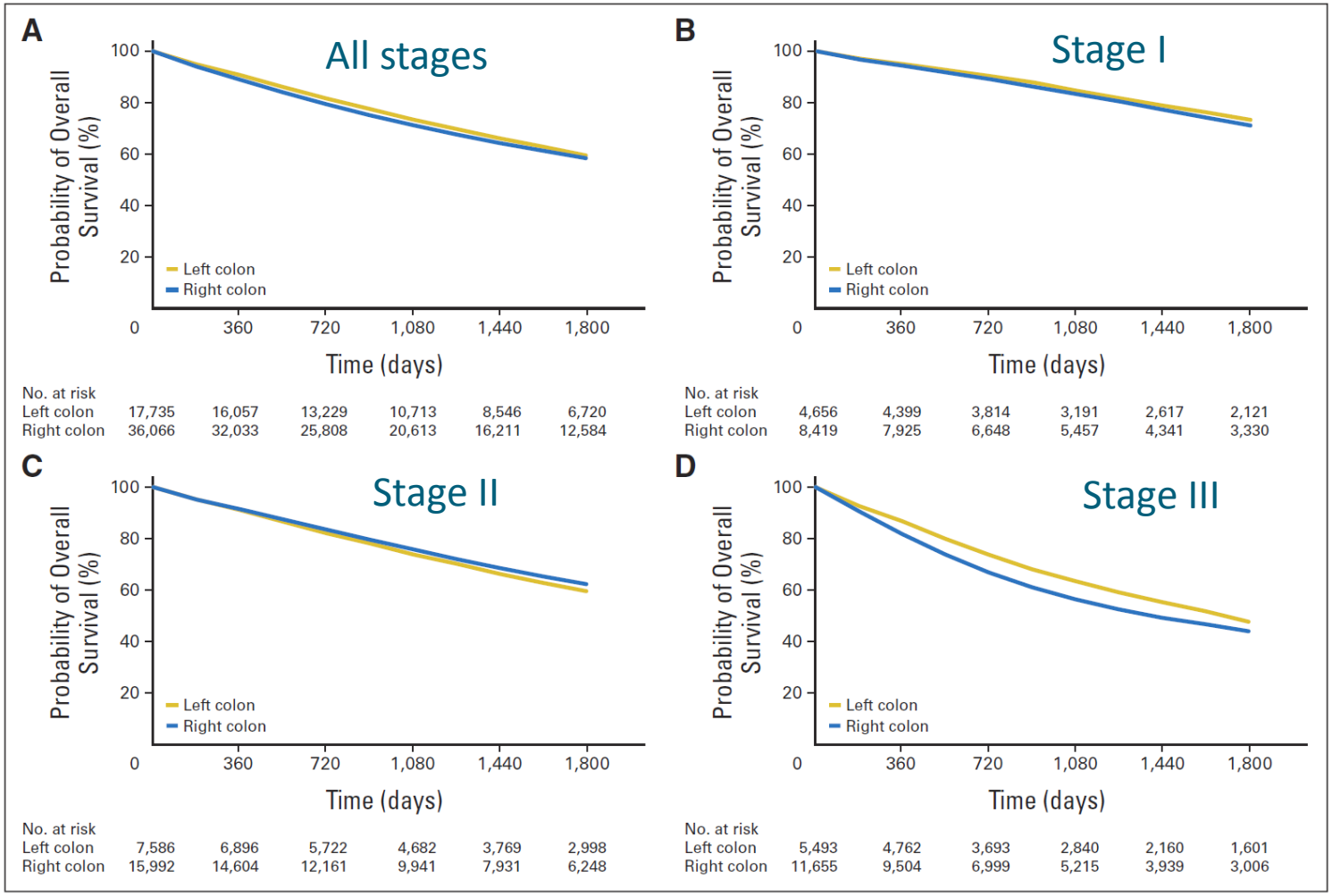
Overall Survival (OS)

KRAS wt N = 1025	Right 1° Median OS (mos)	Left 1° Median OS (mos)	Hazard Ratio 95% CI (adjusted*)	P (adjusted*)
All pts	19.4	33.3	1.55 (1.32,1.82)	P < 0.0001
Cet	**16.7**	**36.0**	1.87 (1.48, 2.32)	P < 0.0001
Bev	24.2	31.4	1.32 (1.05, 1.65)	P = 0.01

19.3 MONTHS IS A BIG DIFFERENCE !!

Venook ASCO 2016

Left and Right Colon

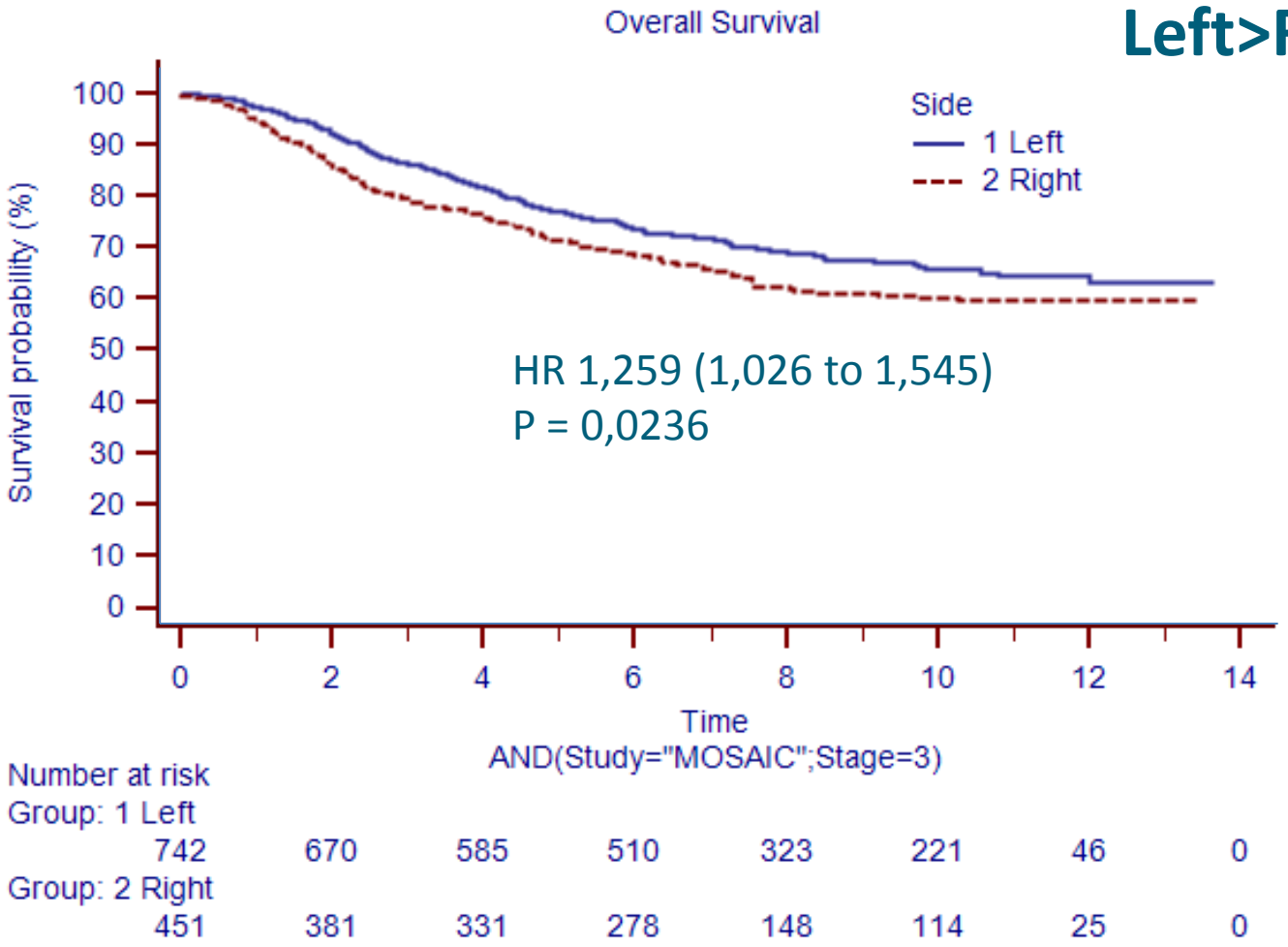


SEER database

Weiss JM et al. JCO 2011

Left and Right Colon

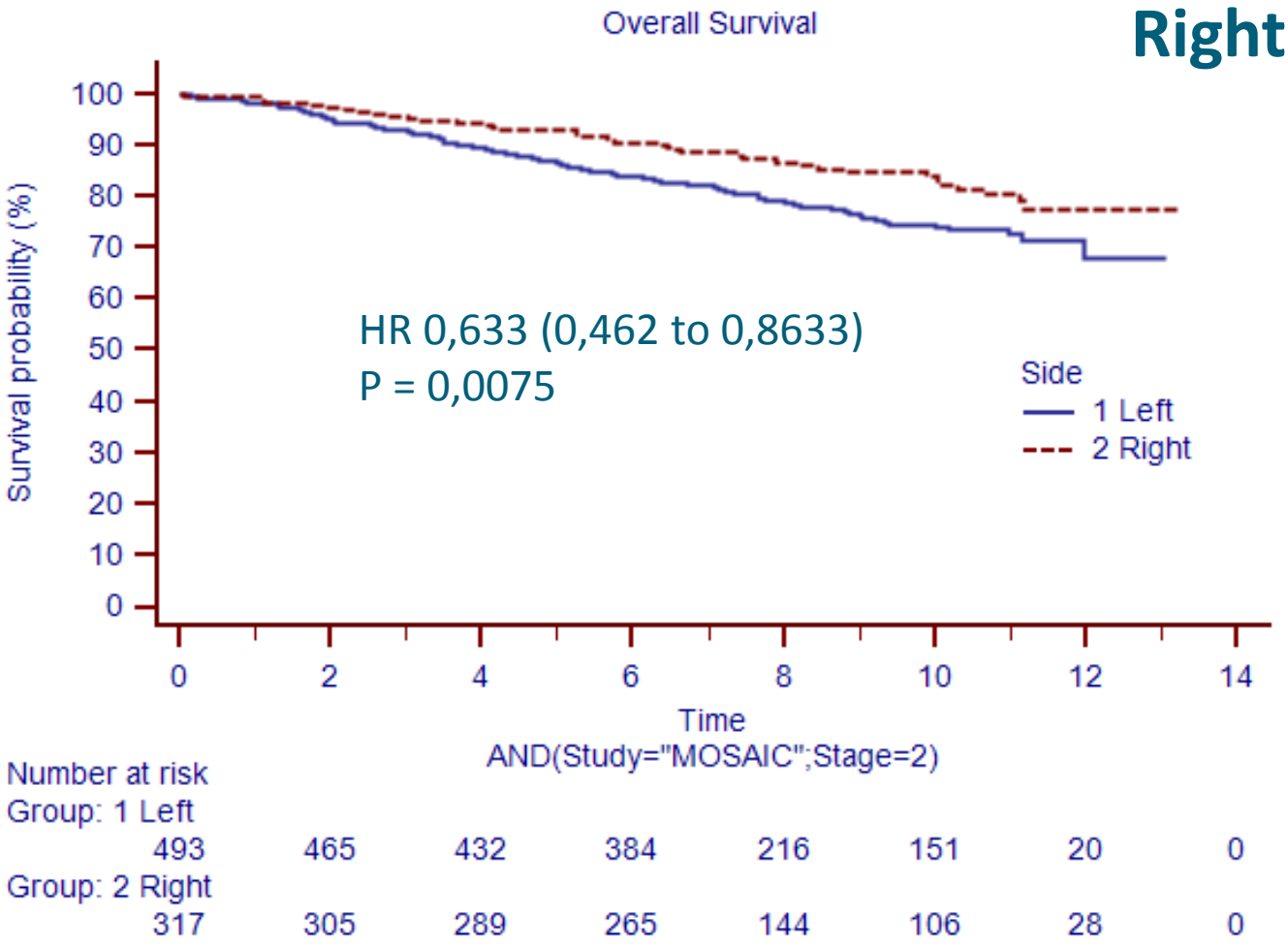
Stage III
Left>Right



MOSAIC

Left and Right Colon

Stage II
Right>Left

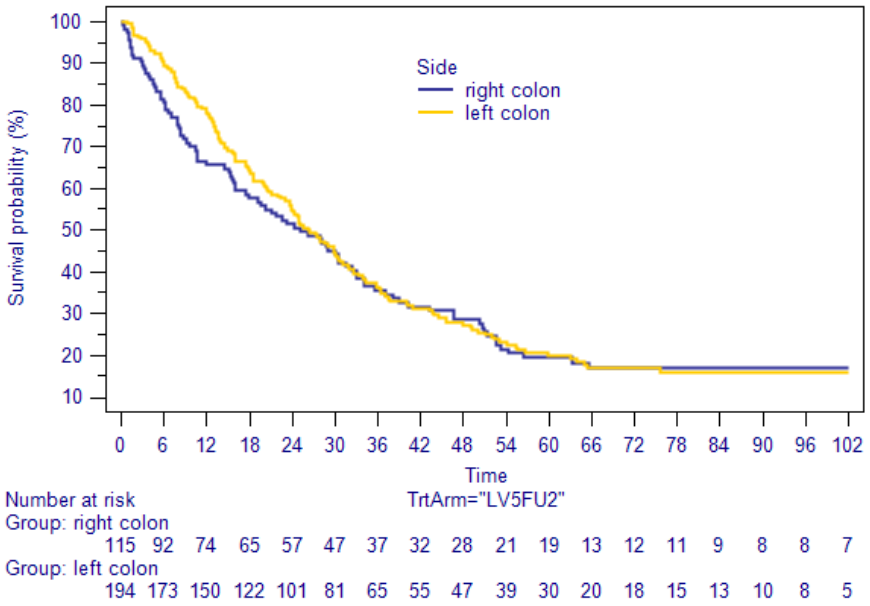


MOSAIC

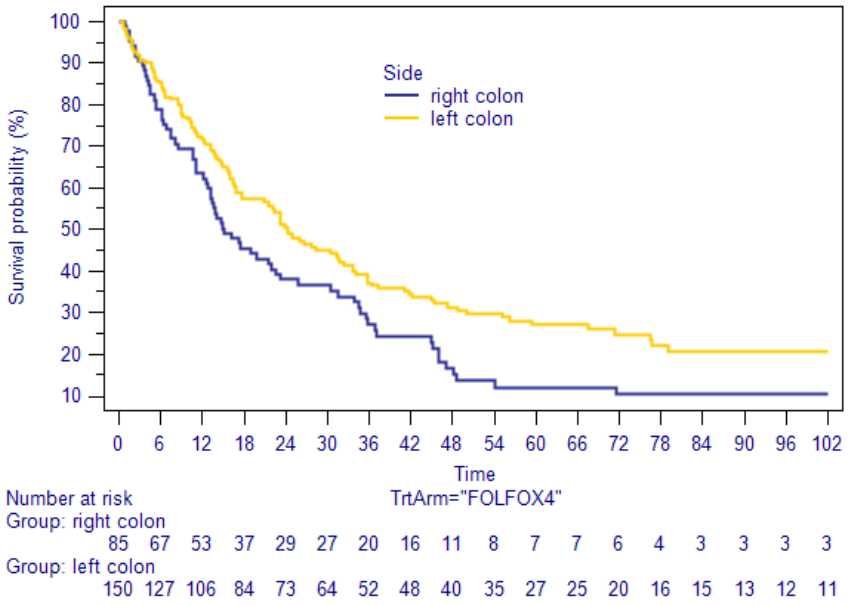
Left and Right Colon

Survival after relapse

LV5FU2



FOLFOX4



MOSAIC

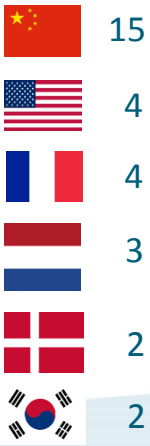
André A et al. JCO 2015

How to improve the adjuvant treatment of colon cancer?

What is ongoing?

What is ongoing?

Clinical trials June 2016



« adjuvant colon cancer »
N=250

Ongoing studies
N=99

Adjuvant colon, unpublished
Updated or ongoing
N=43

Therapy
N=17

IDEA/IDEA like n=3
Aspirin n=5
Regorafenib n=2
Liver/peritoneal n=3
Maintenance n=1
FOLFIRI vs FOLFOX n=1
Elderly N=1
Traditional medicine n=1

Strategy
N=7

Neoadjuvant n=6
pN0micro+ n=1

Immunology
N=5

CIKC n=3
GM-CSF n=1
Vaccine n=1

Support
N=3

Neurotoxicity n=2
Behavorial n=1

Pathology
N=1

LN detection n=1

Biomarkers
N=6

microRNA n=3
Immunoscore n=1
Coloprint n=1
Free DNA/CTC n=1

Physical activity
N=3

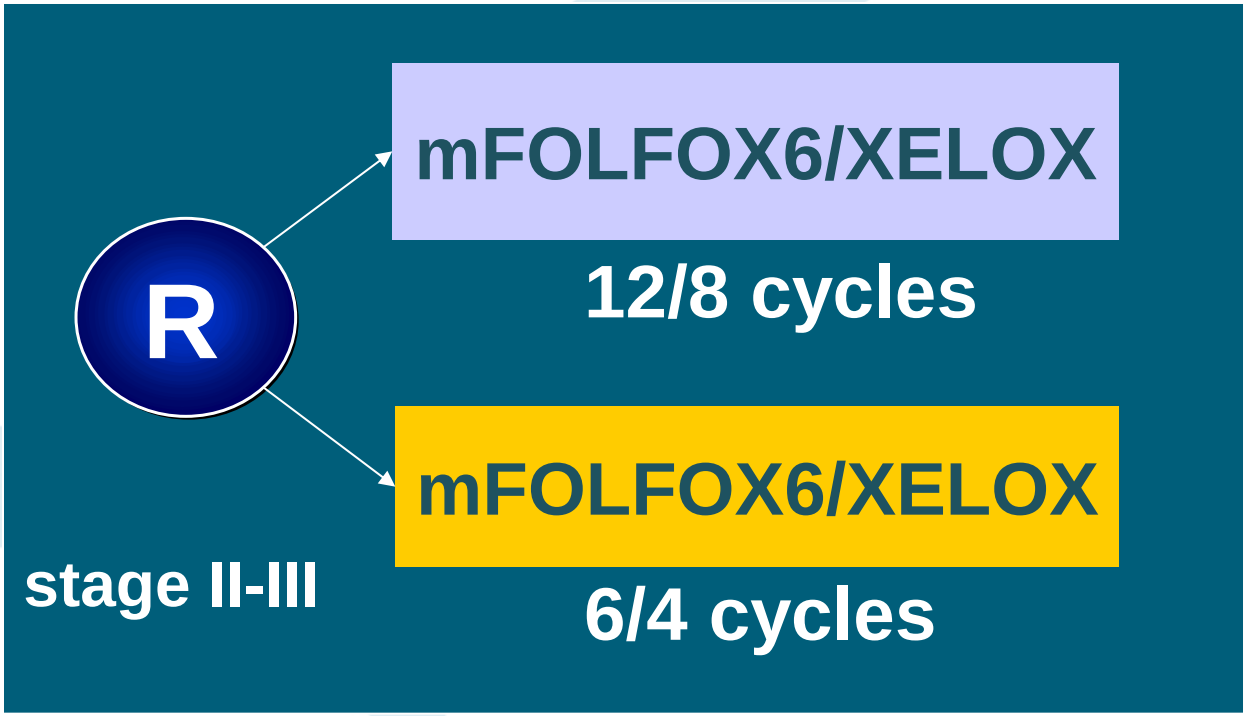
IDEA – Meta-Analysis

N= 4081

GERCOR

IDEA

N= 2020



TOSCA

N= 2436

Non inferiority trial (HR<1.12)

N= 10500 N= 12626

CALGB/SWOG 80702

N= 1364

HORG

N= 656

ACHIEVE

N=1313

What's Involved?

If you decide to participate in this study you will be in one of two treatment groups.

Group 1:

Physical Activity Program and General Health Education Materials

You will take part in a three-year individualized physical activity program to increase the amount of physical activity you do in your free time. The program will include a combination of counseling and education sessions about your physical activities and supervised physical activity sessions at a fitness centre. Both types of sessions will be led by a qualified exercise specialist that is linked with the cancer centre that you attend. You will also be provided with handouts about diet and physical activity.

Group 2:

General Health Education Materials

You will be provided with handouts containing recommendations for diet and physical activity.

All participants will undergo fitness testing at different time points.

Sponsored by:

NCIC Clinical Trials Group
NCIC Groupe des essais cliniques

Cancer Clinical Trials Division
Cancer Research Institute
Queen's University
10 Stuart Street
Kingston ON Canada K7L 3N6

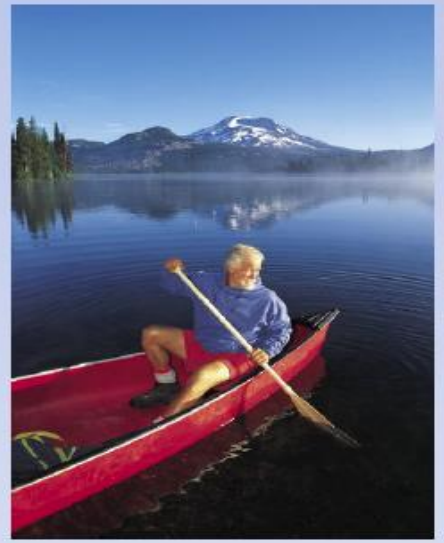
Talk to your doctor if you are interested in participating in the CHALLENGE study.

The NCIC Clinical Trials Group (NCIC CTG) is a cancer clinical trials cooperative group that conducts phase I-III trials testing anti-cancer and supportive therapies across Canada and internationally. It is one of the national programmes and networks of the Canadian Cancer Society Research Institute, and is supported by the Canadian Cancer Society. The NCIC CTG's Central Office is located at Queen's University in Kingston, Ontario, Canada.

Initiated 2008
Feasibility reported at ASCO 2016
Inclusions > 400
Target 962 (HR 0,75)

CHALLENGE TRIAL

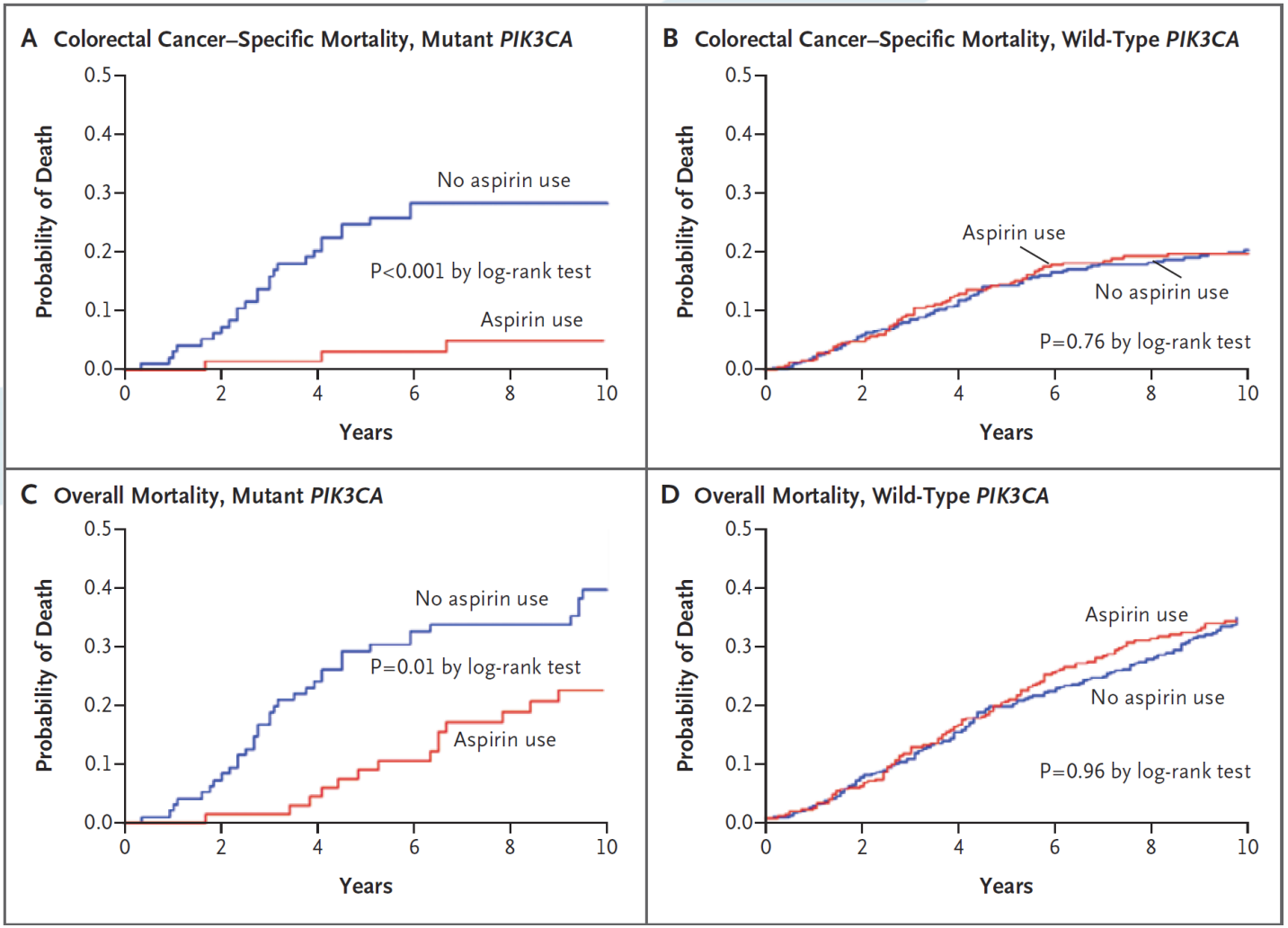
This phase III clinical trial is currently recruiting participants, both adult men and women.



CHALLENGE

NCIC CTG Trial: CO.21

Aspirin in mutant PIK3CA

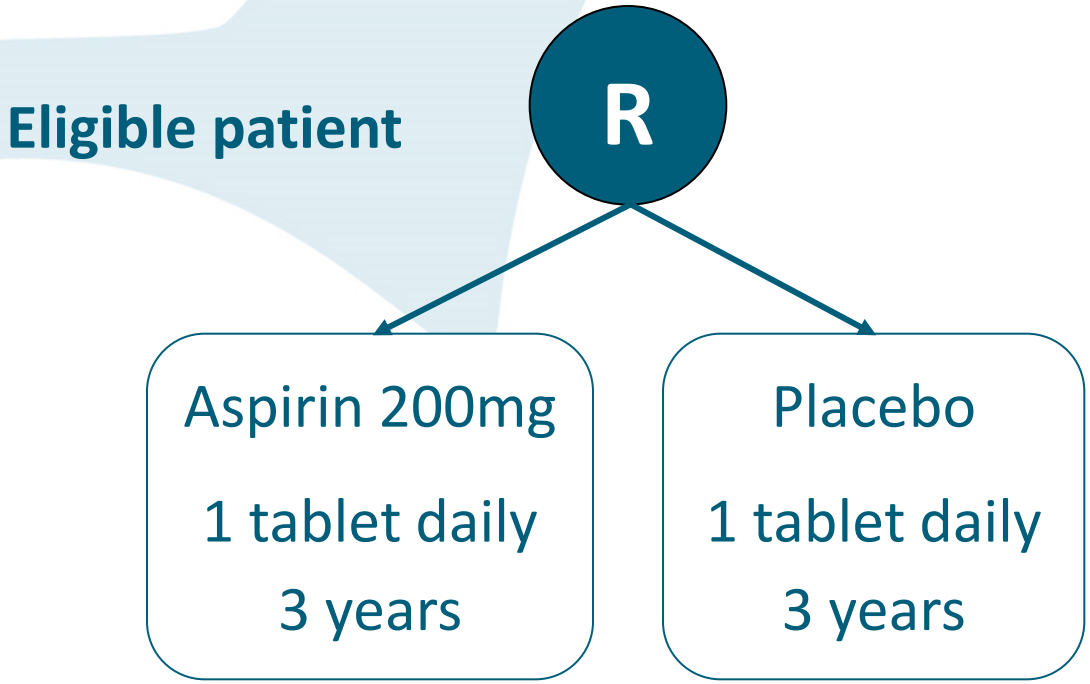


Liao X. NEJM 2012

ASPIK

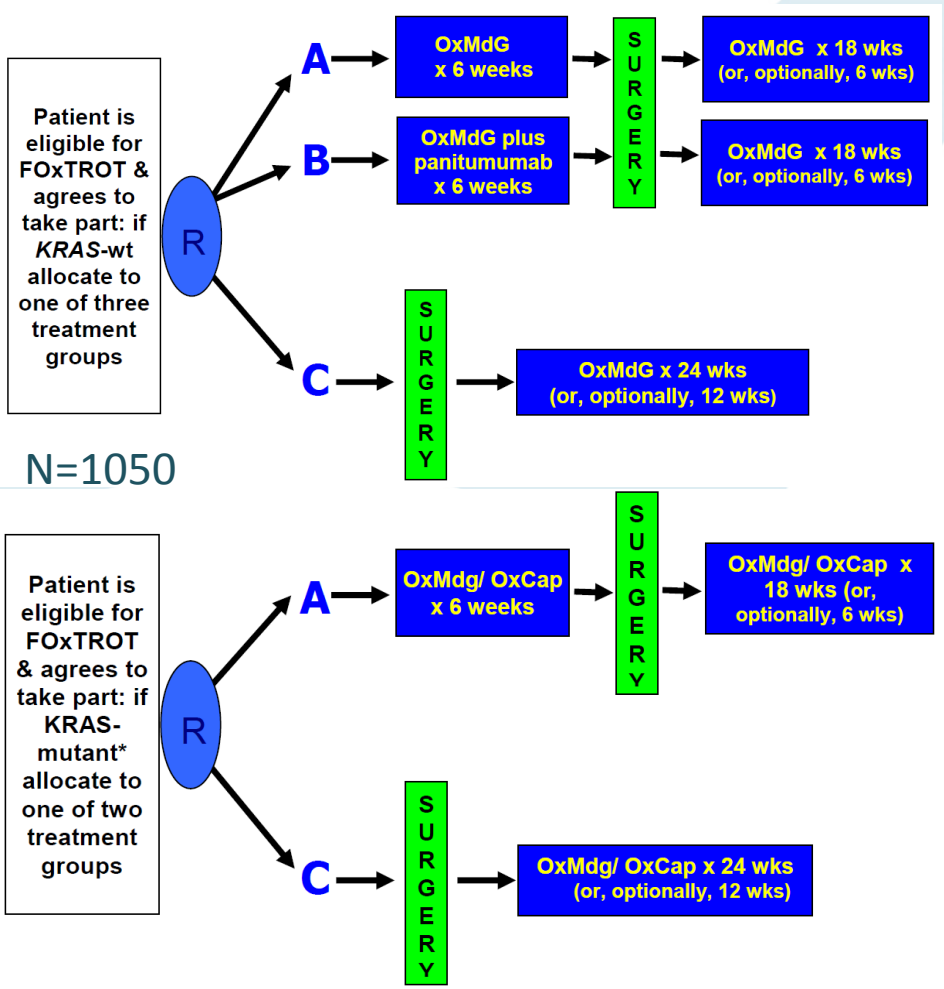
Aspirin in **PIK**3CA-mutation Selected

Patients after Resection of Colorectal Cancer



D Kerr

Neoadjuvant chemotherapy



Arm D (6w Pmab post surgery) deleted

Inadequate Rx staging

(post surgery CT group):
50% of Rx T4 were pT3
44% of Rx N+ were pN0

Time from rando to chemotherapy
13 days neoadjuvant group
61 days adjuvant group

Lancet Oncol 2012

http://www.birmingham.ac.uk/Documents/college-mds/trials/bctu/foxtrot/FOxTROTProtocolv60090712.pdf

Neoadjuvant chemotherapy PePiTA2

PET response

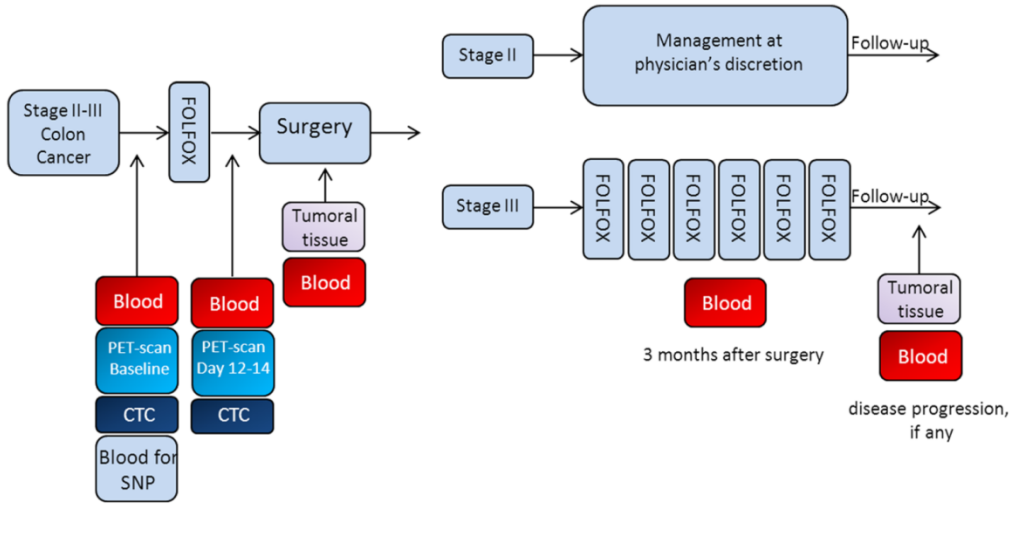


Figure 1 Study design.

H0
50% PET responders after C1
60% stage III
3-yr DFS 55% non responders vs 83% responders

N=225
BDGO

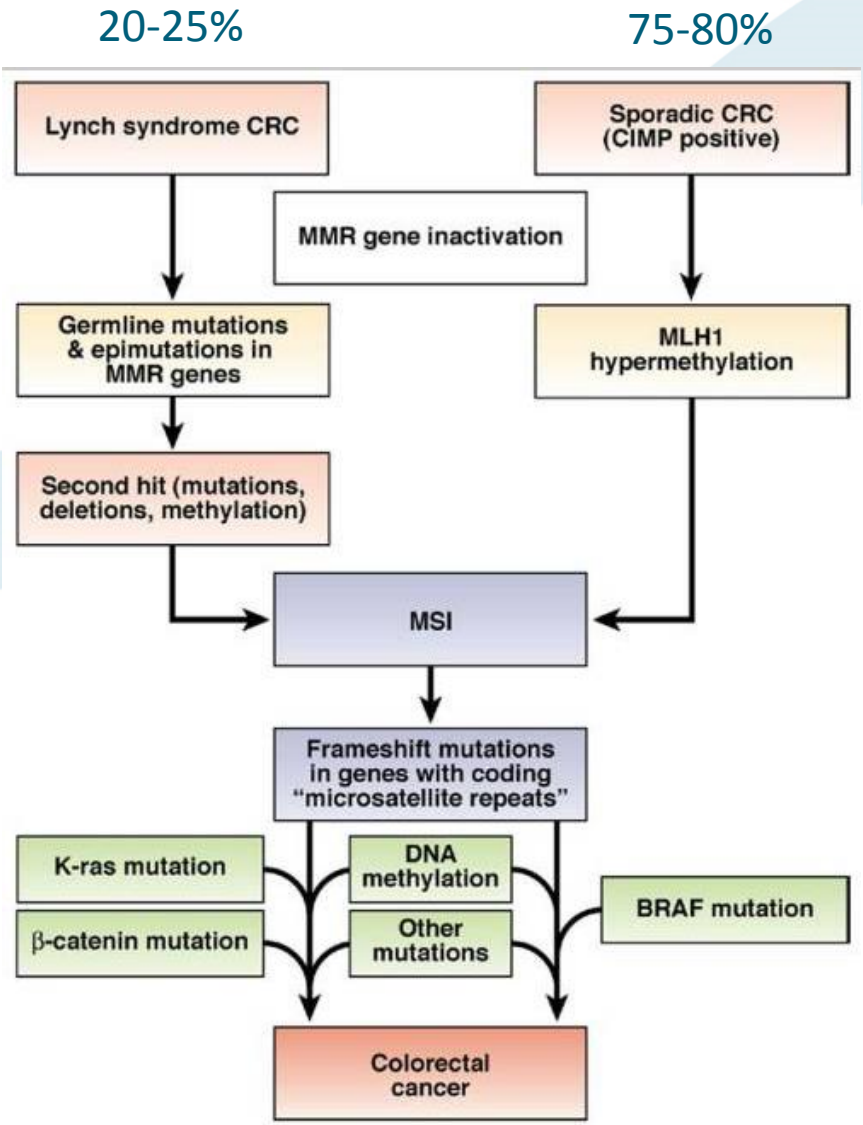
A Hendliz et al, BMC cancer 2013

How to improve the adjuvant treatment of colon cancer?

Biomarkers

Main goals are to define who should be treated in stage II and who should not be treated (oxaliplatin) in stage III

MSI in Colorectal Cancer



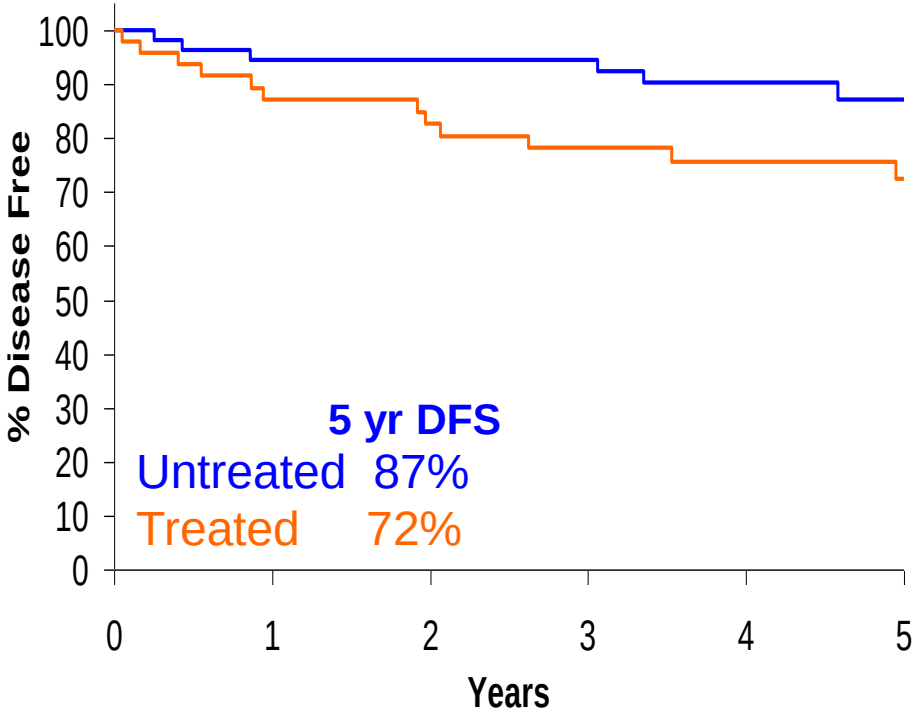
Sporadic CRC patients have a significantly worse OS compared with familial cases, while no difference was observed in DFS

Zaanan A et al, ASCO 2015

Boland CR, Goel A. Gastroenterology 2010

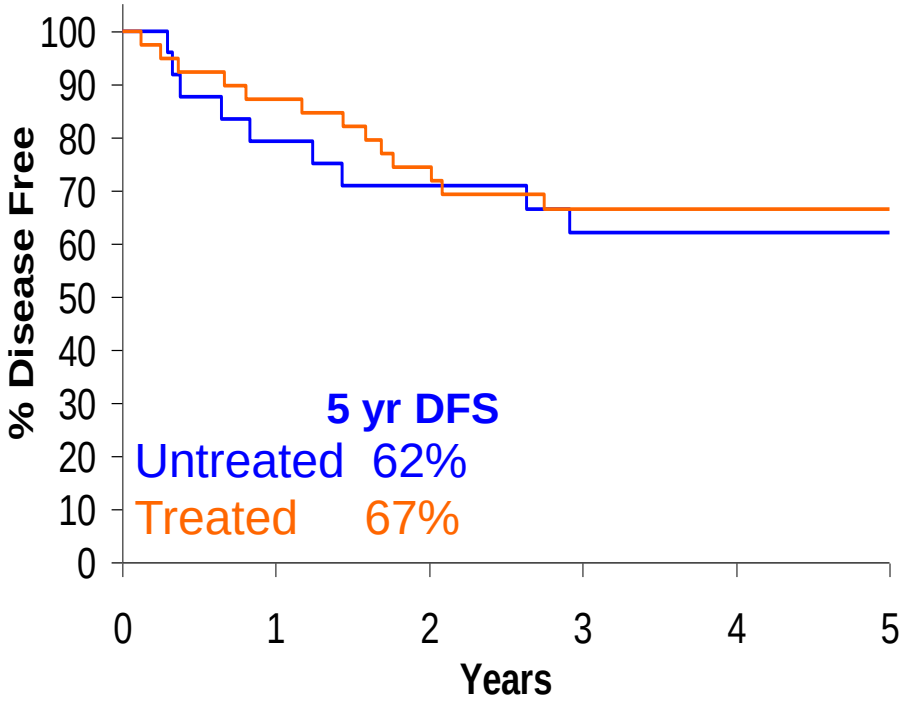
DFS in MSI patients, pooled data

Stage II (N=102)



FP alone should not be given

Stage III (N=63)

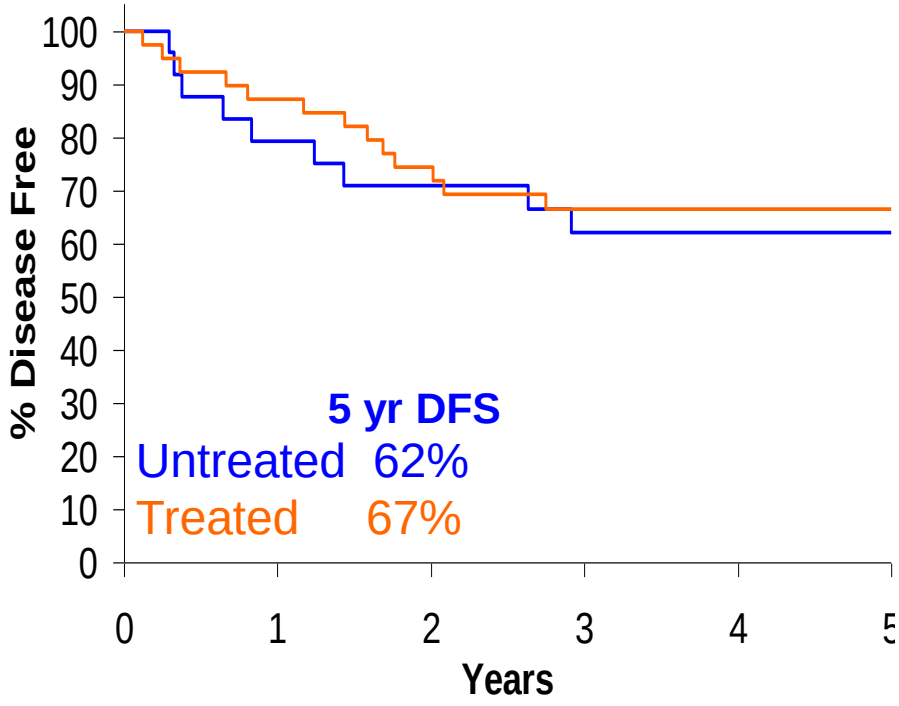


Small benefit of FP alone

Sargent, JCO 2009

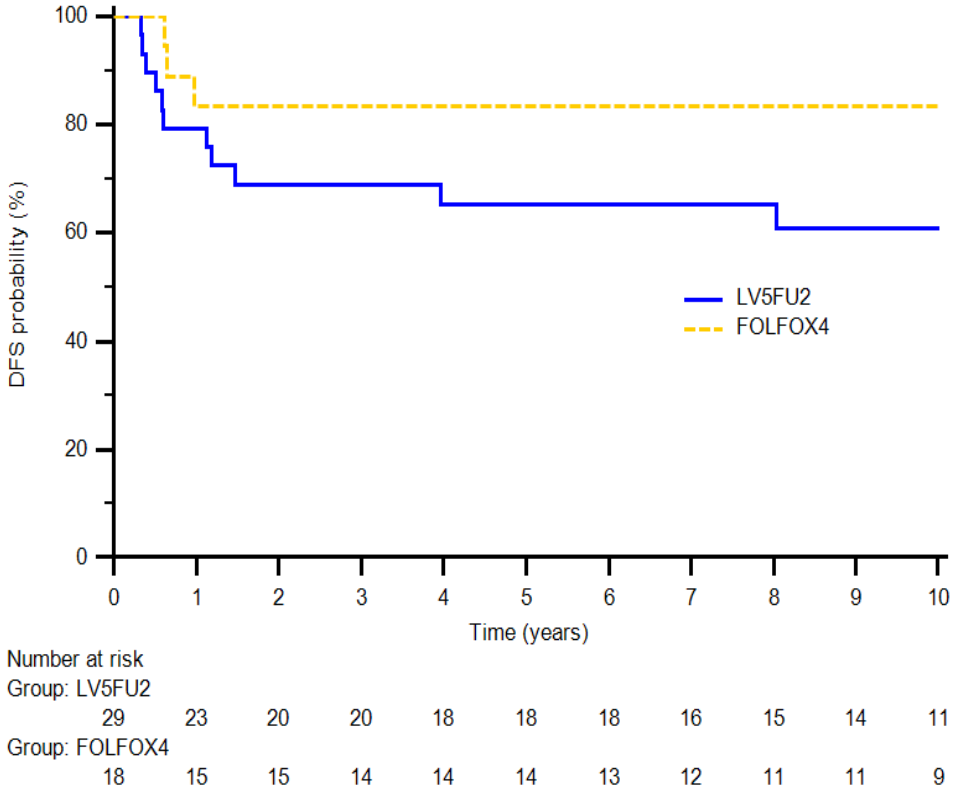
Oxaliplatin is active in Stage III MSI

Fluoropyrimidine Stage III (N=63)



Sargent, JCO 2009

FOLFOX4 Stage III (N=47)

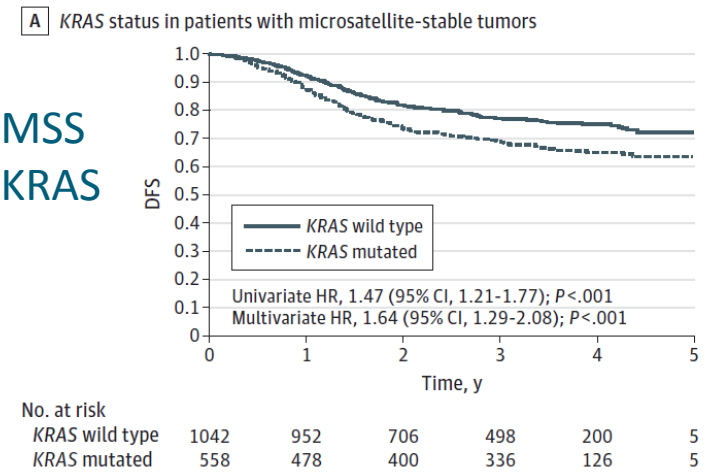


André, JCO 2015

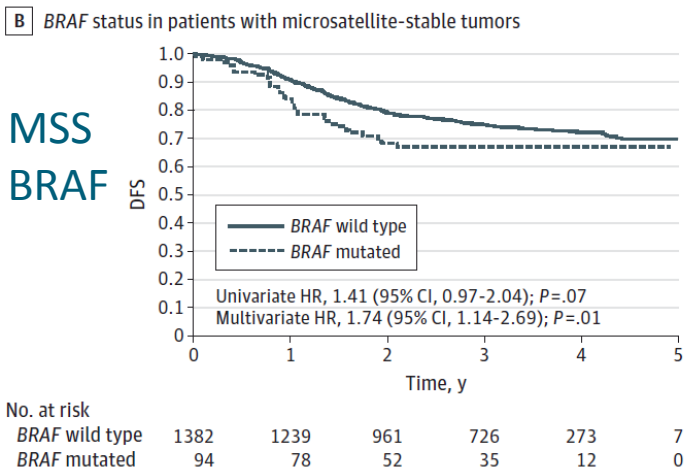
KRAS/BRAF and MS status

Figure 3. Effect of *KRAS* and *BRAF* Status on Disease-Free Survival (DFS) in Patients With Microsatellite-Stable and Microsatellite-Unstable Tumors

MSS KRAS

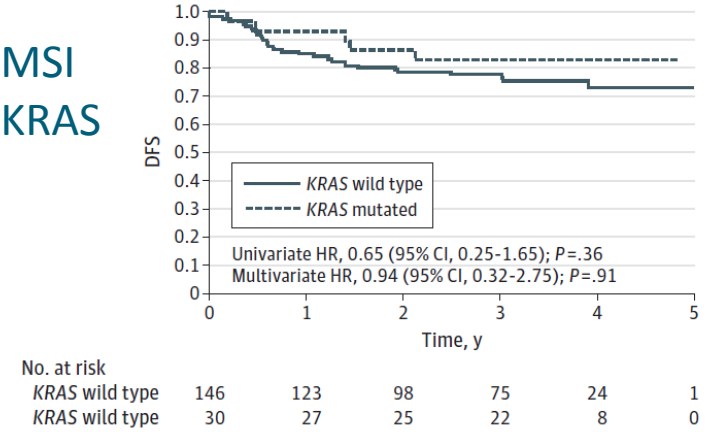


MSS BRAF

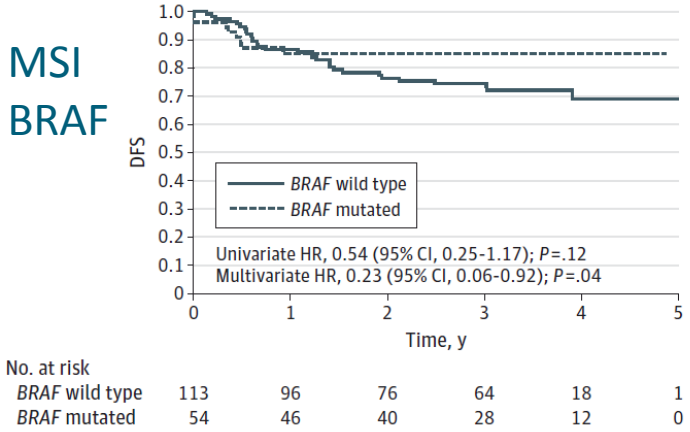


MSS poor pc of mutations

MSI KRAS



MSI BRAF

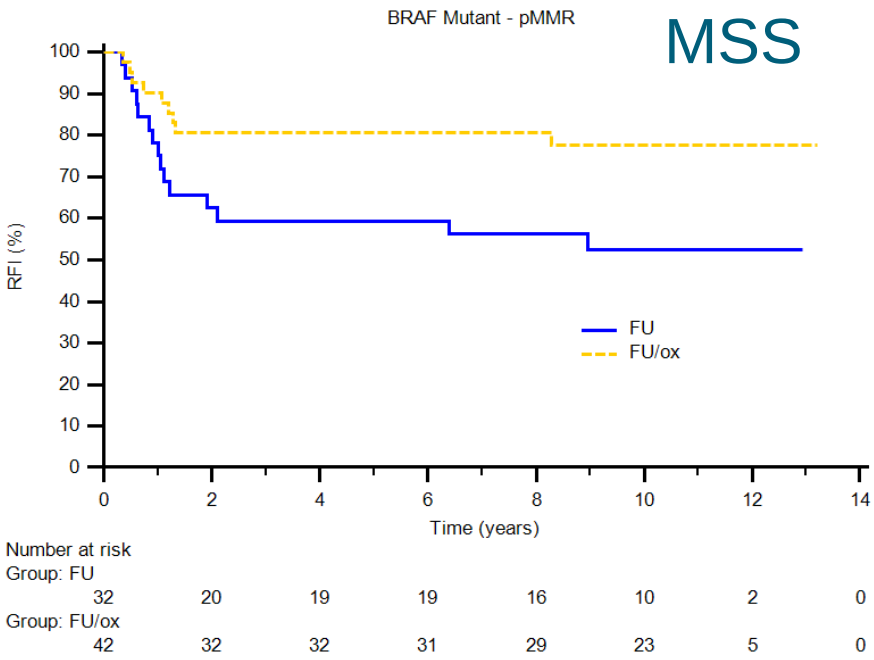


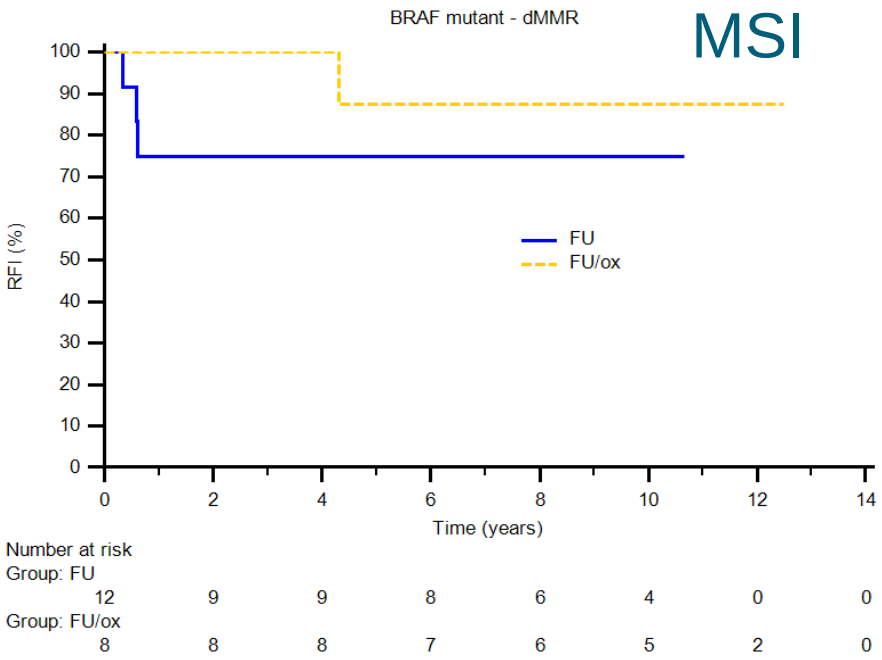
MSI good pc of mutations

Taieb J et al, JAMA Oncol 2016

Oxaliplatin is active in BRAF mut

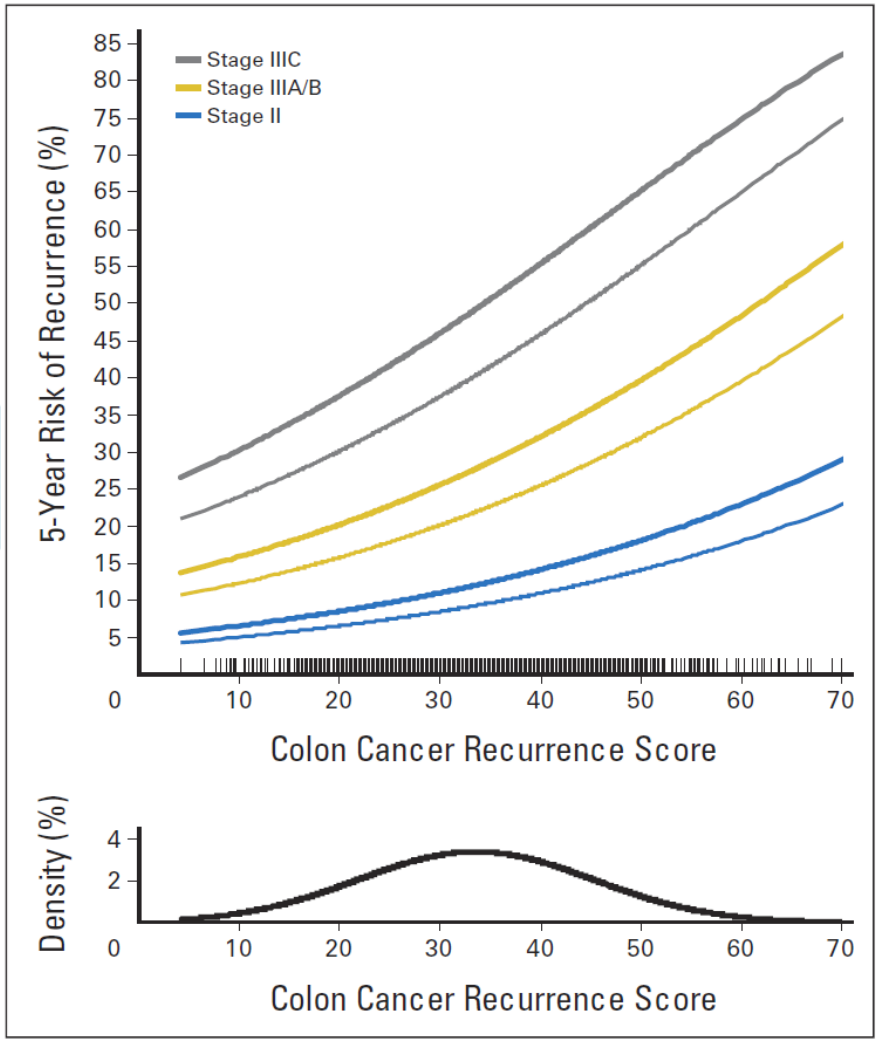
RFS Stage III





André, JCO 2015

Recurrence Score



	5 year Recurrence Risk based on Recurrence Score		
	Low	Intermediate	High
Stage IIIA/B	21%	29%	38%
Stage IIIC	40%	51%	64%

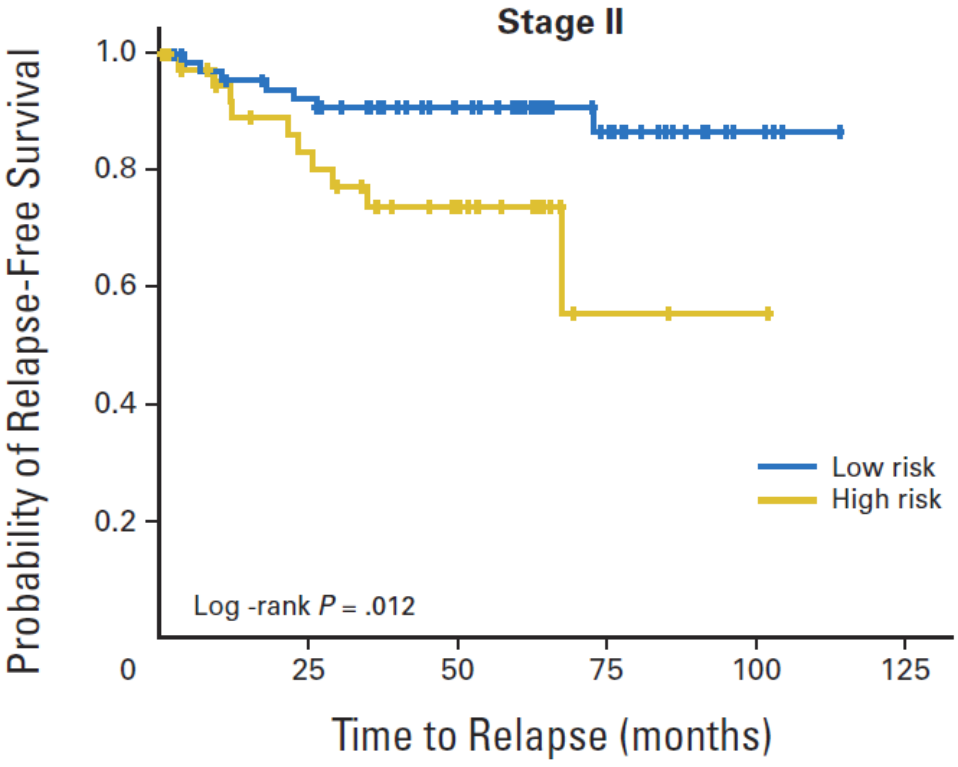
The Recurrence Score is a standardized, quantitative, reverse transcriptase polymerase chain reaction (RT-PCR) assay that measures the expression of 12 genes (seven recurrence and five reference genes) in fixed, paraffin-embedded (FPE) primary colon tumor tissue.

The recurrence genes integrate the activity of two key biologic pathways, cell cycle control and stromal response.

Gray RG et al, J Clin Oncol 2011. 29:4611-4619

Yothers G et al, J Clin Oncol 2013. 31:4512-4519.

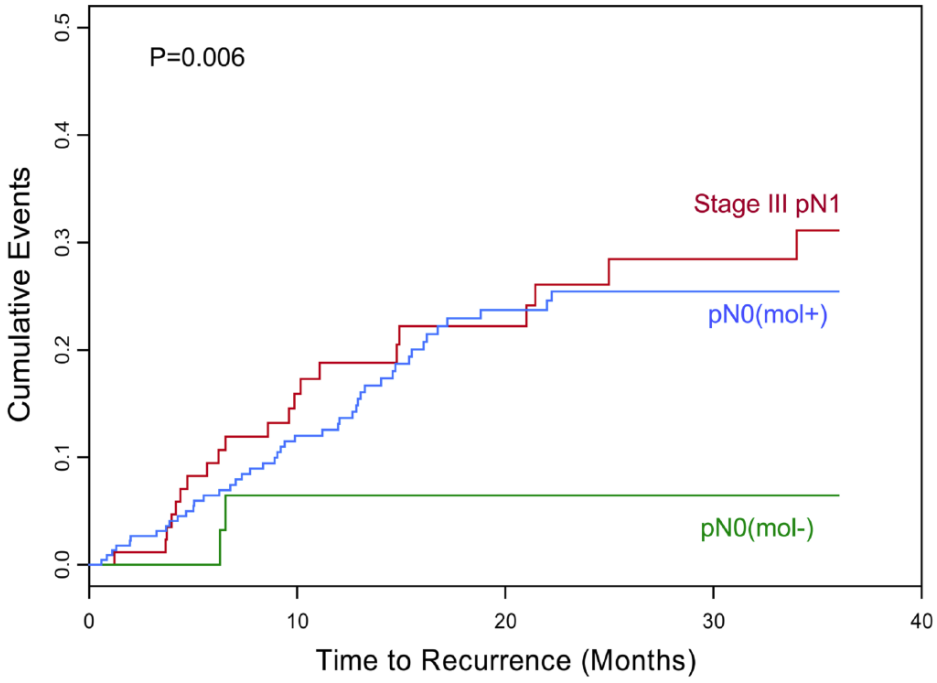
Coloprint



ColoPrint is a 18 gene expression signature identified from fresh frozen tissue to improve prognosis prediction of stage II and III colorectal cancer. 60% of patients are classified as low risk and 40% as high risk.

Salazar R et al, J Clin Oncol 2011, 29:17-24

GUCY2C Expression in Lymph Nodes



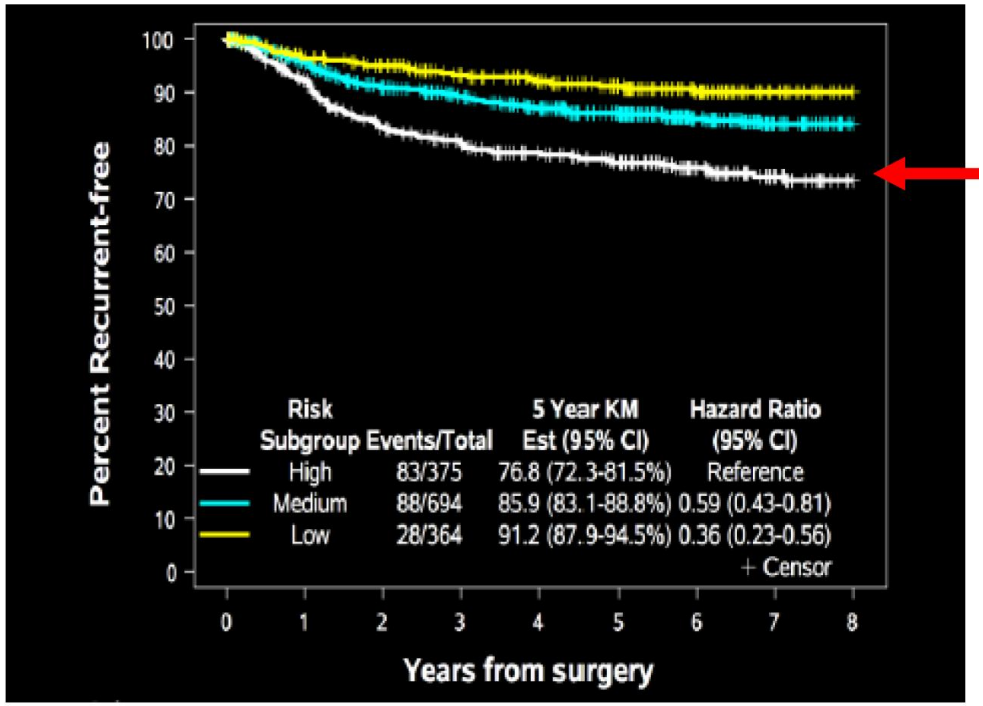
	Months	0	6	12	18	24	30	36
pN0(mol-)	Patients	32	31	28	24	21	19	13
Cumulative	Events	0	0	2	2	2	2	2
pN0(mol+)	Patients	225	195	157	102	80	57	53
Cumulative	Events	0	14	27	42	45	45	45
Stage III N1	Patients	87	75	54	44	35	26	25
Cumulative	Events	0	8	15	17	19	20	20

GUCY2C mRNA was quantified by RT-PCR, Previstage®

Waldman SA et al, JAMA 2009

Immunoscore

Presence of T cells in and around the tumor is a powerful prognosis parameter, Immunoscore combines an immuno-histochemistry (IHC) assay to quantify CD3 & CD8 positive cells in 2 zones, core tumor and invasive margin and an automated quantification using digital pathology

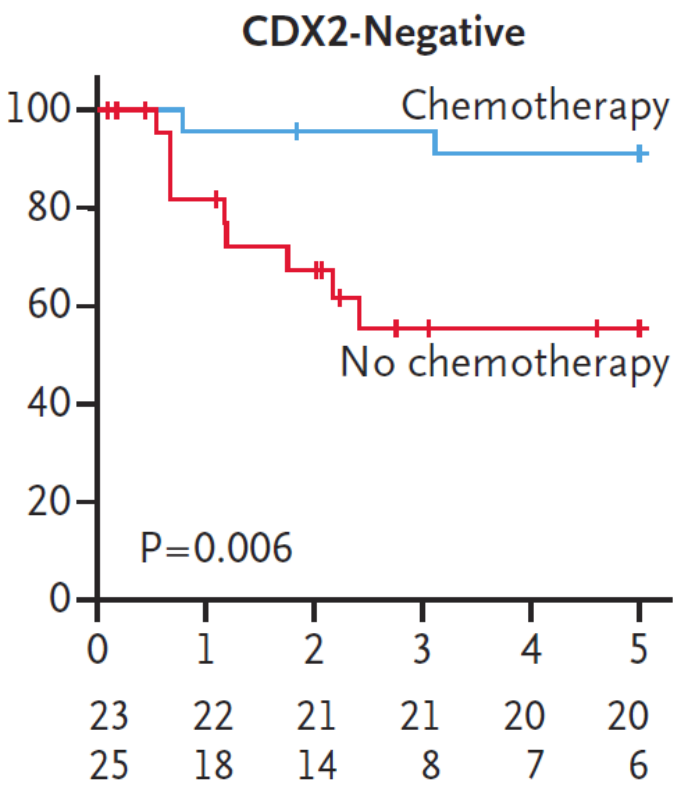


Low-IM identified a subgroup of patients with high-risk stage II CC.

Galon, J. *et al. Science 2006,* 313, 1960–1964.
Fridman WH, et al. Nat Rev Cancer 2012,12:298-306.
Galon J et al. 2016 ASCO Annual Meeting. J Clin Oncol 34, 2016 (suppl; abstr 3500).

CDX2

Stage II



Caudaltype homeobox transcription factor 2 (CDX2) is a gene with expression in colon cancer that was negatively linked to the activated leukocyte-cell adhesion molecule (ALCAM/CD166) which is a marker of immature colon epithelial cells

7% of stage II CC are CDX2-Negative

Dalerba P et al. N Engl j Med 2016, 374:211-222,

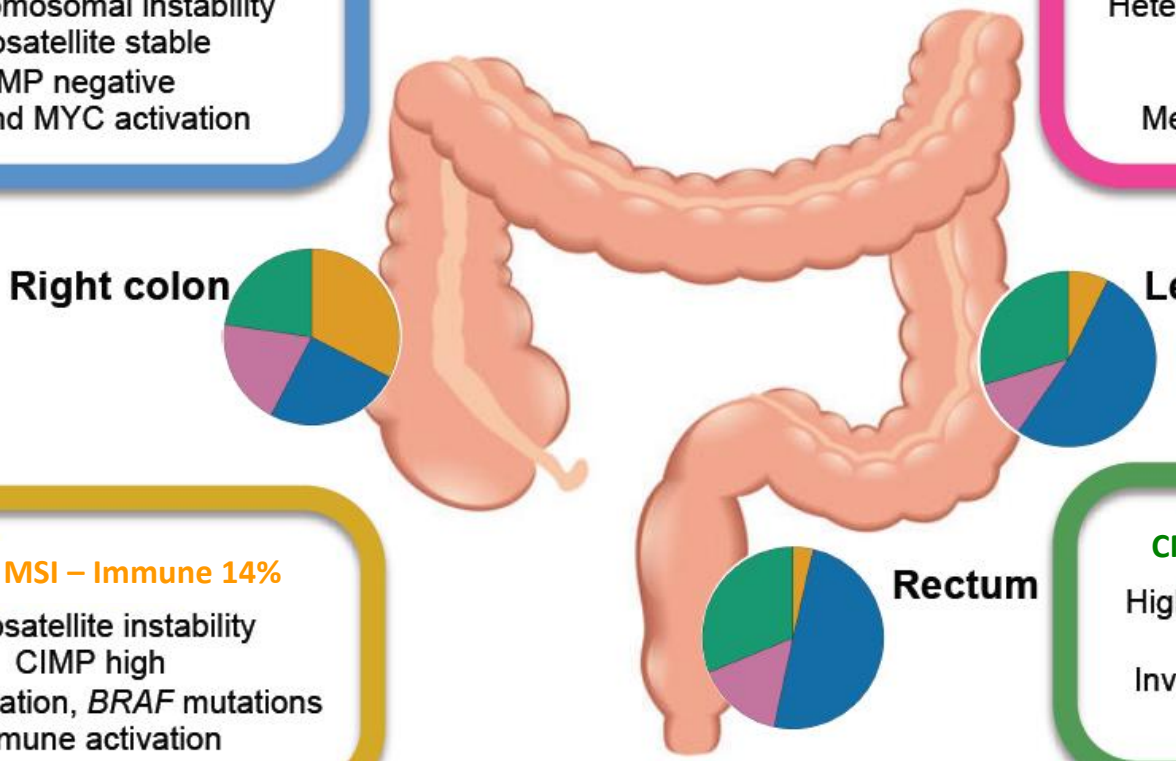
The consensus molecular subtypes of CRC

CMS2 – Canonical 37%

High chromosomal instability
Microsatellite stable
CIMP negative
WNT and MYC activation

CMS3 – Metabolic 13%

Heterogeneous chromosomal/ microsatellite status
KRAS mutations
Metabolic reprogramming



CMS1 - MSI – Immune 14%

Microsatellite instability
CIMP high
Hypermutation, *BRAF* mutations
Immune activation

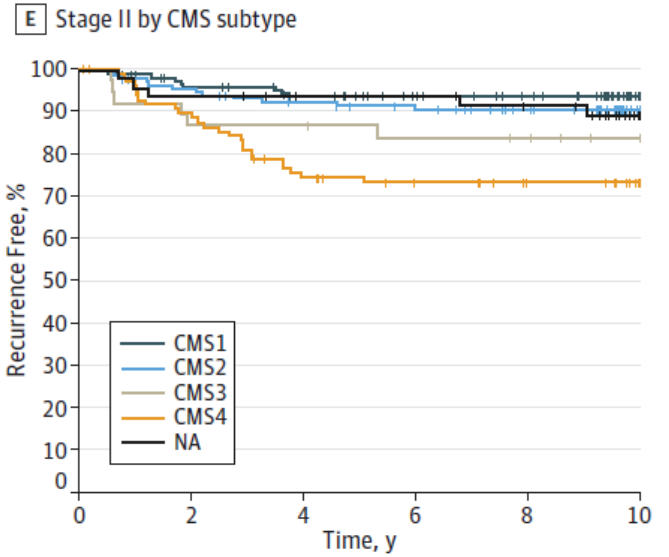
CMS4–Mesenchymal 23%

High chromosomal instability
TGFb activation
Invasion, matrix remodeling
Angiogenesis

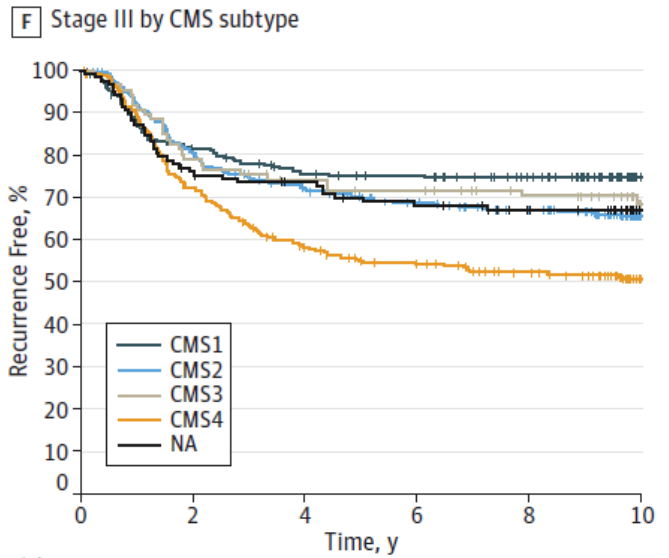
Guinney J, Dienstmann R et al. Nat Med 2015

The consensus molecular subtypes of CRC

NSABP C-07: CMS4 have the worst prognosis



No. at risk						
CMS1	141	129	120	109	103	72
CMS2	128	120	112	106	96	72
CMS3	37	32	32	30	29	26
CMS4	97	83	68	62	57	47
NA	49	46	43	43	40	28

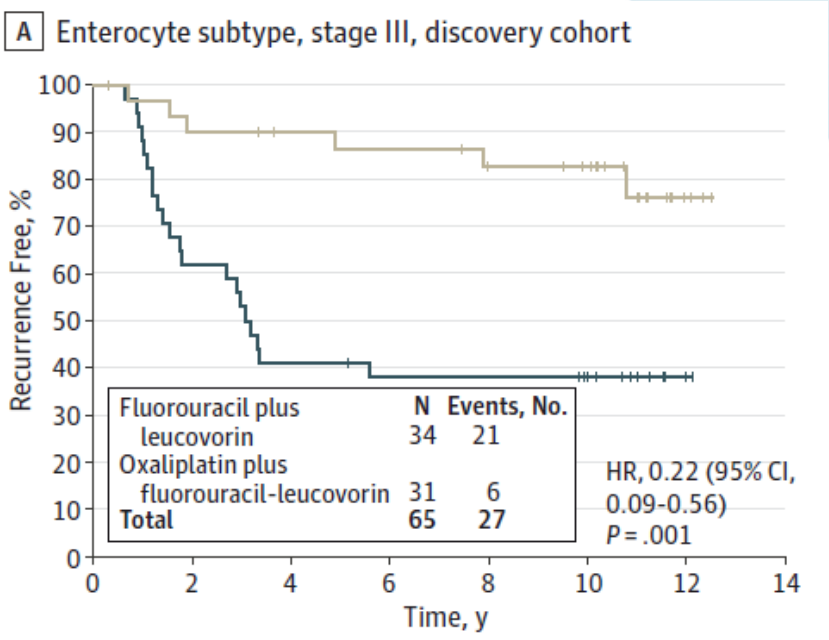


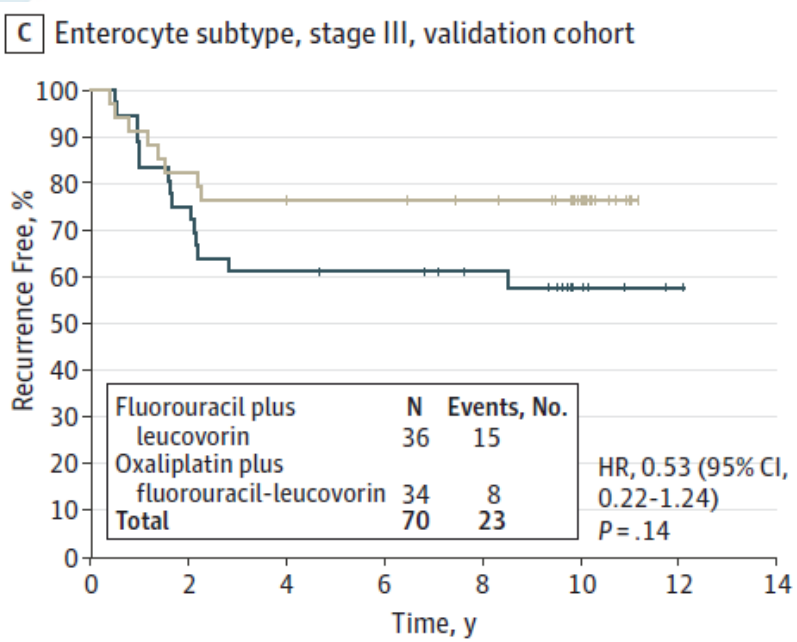
No. at risk						
CMS1	231	183	166	161	148	98
CMS2	382	301	264	241	220	153
CMS3	86	67	60	57	50	35
CMS2	334	236	185	166	147	107
NA	118	88	81	74	67	51

Son N et al. JAMA Oncol 2016

The consensus molecular subtypes of CRC

NSABP C-07





CMS is not predictive of the benefit of oxaliplatin

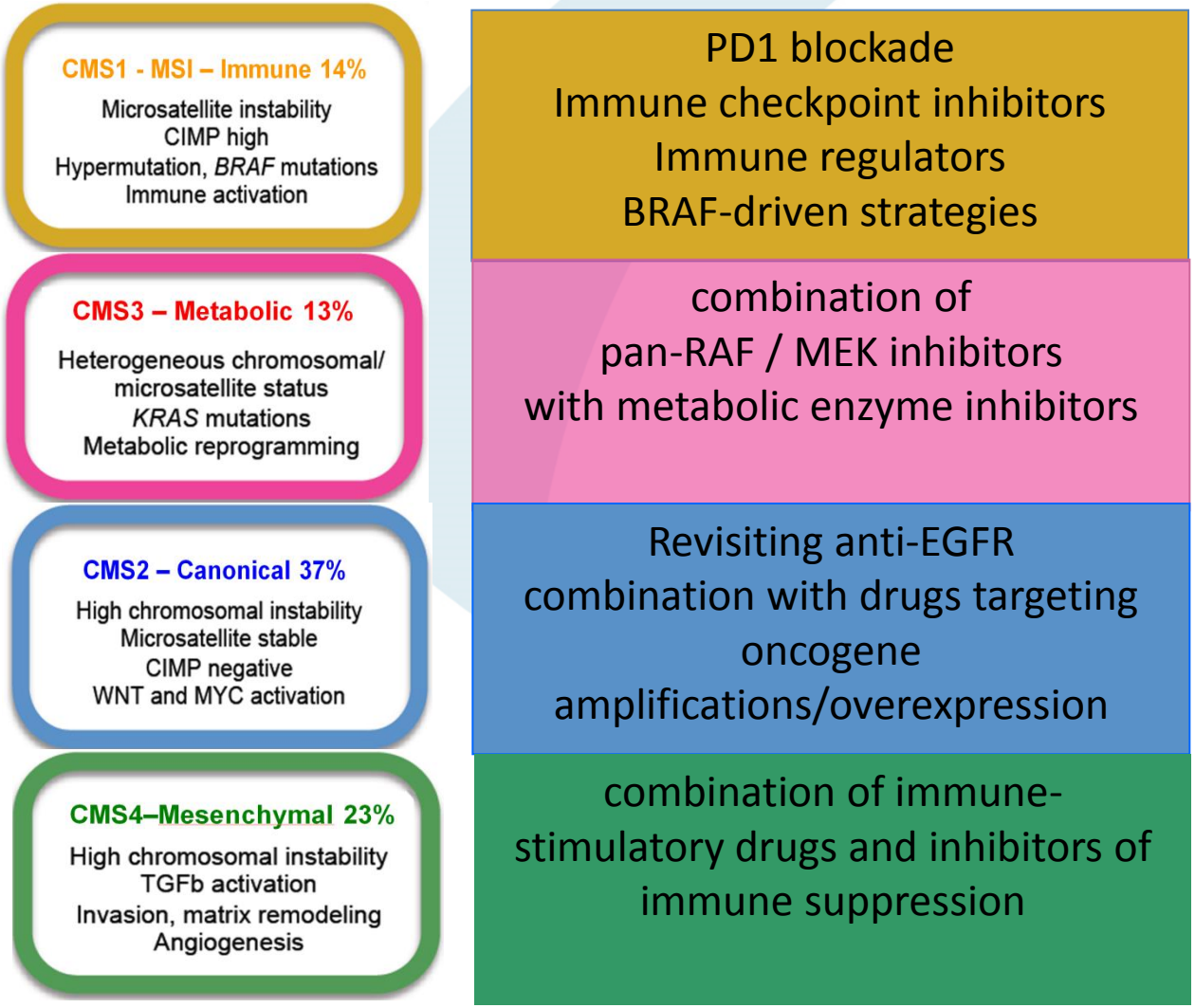
Son N et al. JAMA Oncol 2016

How to improve the adjuvant treatment of colon cancer?

Improving our therapies

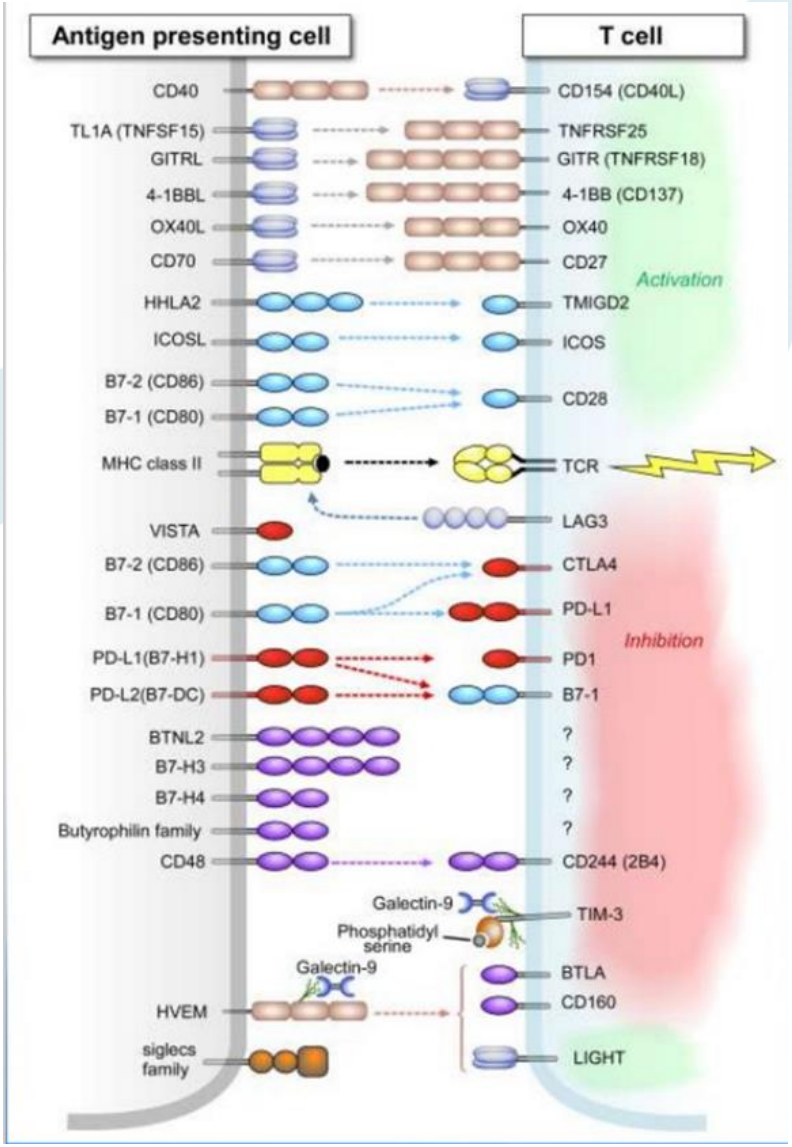
The consensus molecular subtypes of CRC

Scientific Approach

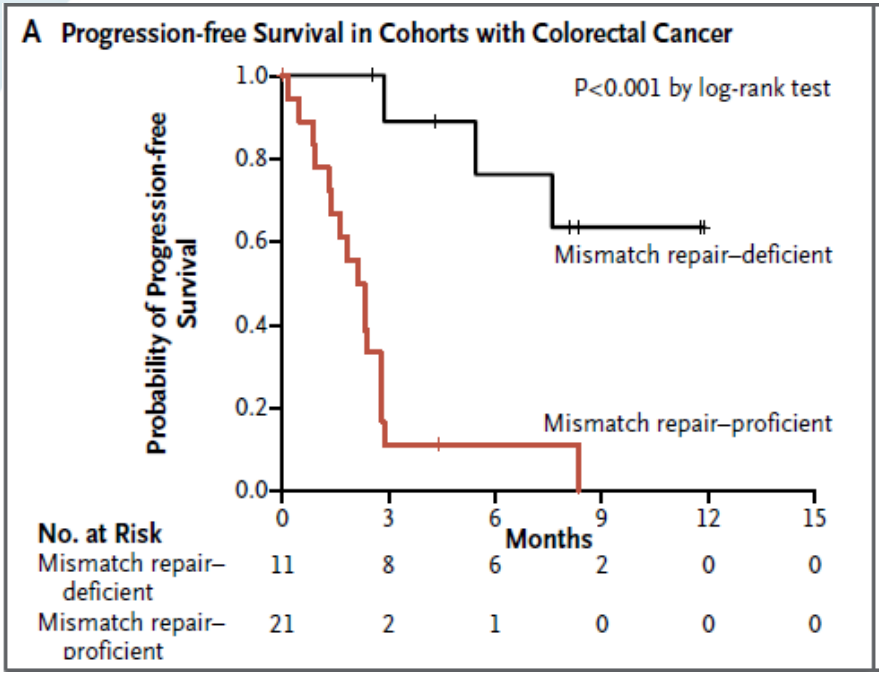


Tabernero 2016

Immunotherapy



Immune chekpoint inhibitor



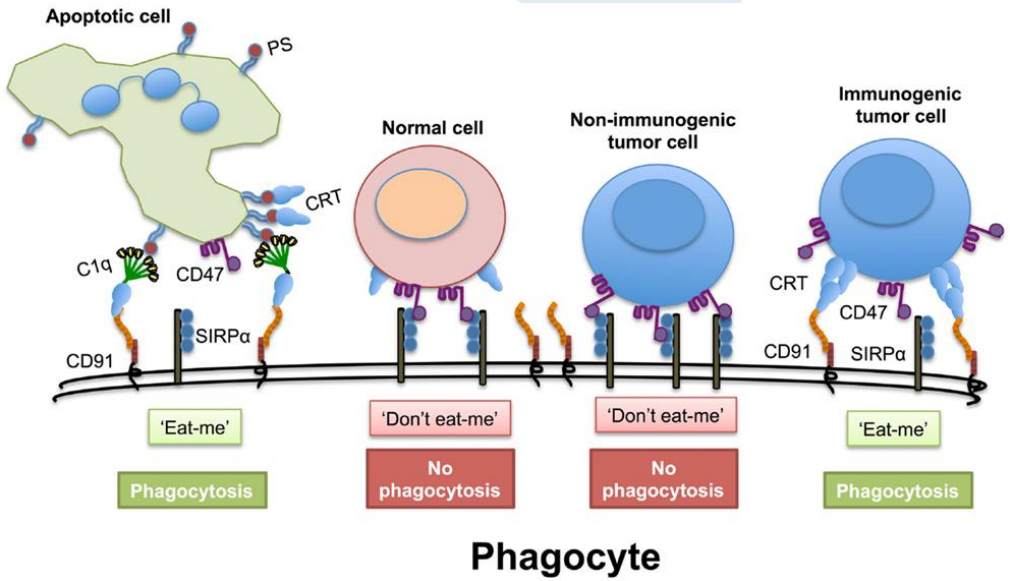
Le DT et al, NEJM 2015

http://fr.slideshare.net/PaulDRennert/the-immune-checkpoint-landscape-in-2015-combination-therapy

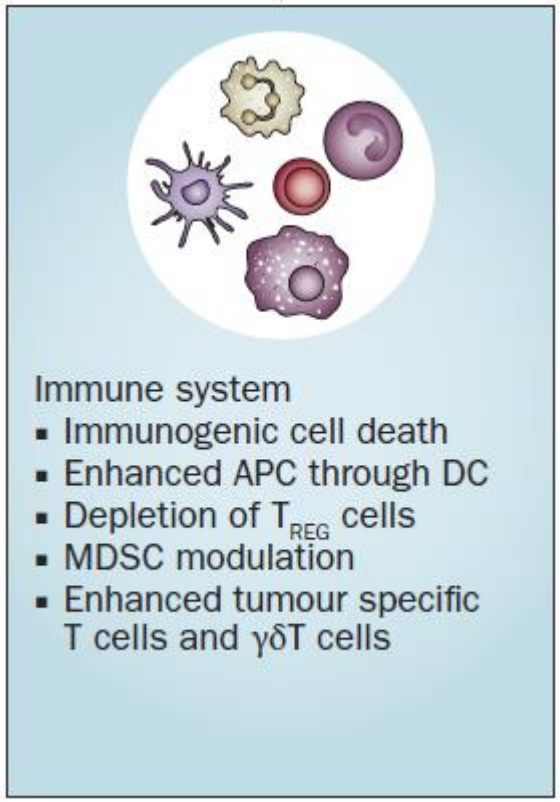
Chemoimmunotherapy

5-Fluorouracil selectively kills tumor-associated myeloid-derived suppressor cells resulting in enhanced T cell-dependent antitumor immunity.

Oxaliplatin immunogenic effects include modulation of STAT signaling; induction of an immunogenic cancer cell death through exposure of calreticulin and release of ATP and high-mobility group protein box-1 (HMGB-1); and enhancement of the effector immune response through modulation of PDL1 and mannose-6-phosphate receptor expression.



Metronomic chemotherapy



Munzone NRCO 2015

Vincent J, et al Cancer Res 2010
Yang S, Haluska FG. *J Immunol*. 2004
Hato Clin Cancer Res 2014
Wiersma Front Oncol 2015

Immunomodulation

Target	Drug	Reference
gpA33-CD3	MGD007	Moore AACR 2014
phosphatidylserine	Bavituximab	Huang ASCO 2015
CD137	Urelumab	Sanmamed Cancer Res 2015
MUC5AC/ADCC	Enzituximab	Beg ASCO 2015
β1,3β1,6 glucan	ImprimePGG	Qiu AAI 2016
Histone diacetylase	Romidepsin	Prince CCR 2012
MEKI	Cobimetinib	Bendell ASCO 2016

Target	Drug	Reference
NKG2A/HLAE	Monalizumab	Seymour Ann Oncol 2015
Autologous (patient-specific) tumor cells	Oncovax	Vermorken Lancet 1999

Adapted from Hanna, ASCO GI 2016

Other

Target	Drug	Reference
Dormancy/ Angiogenesis	Antiangiogenic agents	AVANT Lancet Oncol 2014 Naumov *Breast Cancer Res* 2003
Cancer stem cell	BBI608	Jonker ASCO 2014

How to improve the adjuvant treatment of colon cancer?

Improving our clinical research

Cost of an adjuvant trial

>100 000 000 €

Adjuvant trials

New drug

↓

Registration in advanced disease

↓

Good sales

↓

Adjuvant trial

New drug

Rationale for adjuvant

Registration in advanced disease

↓

Academic groups
Public & private fundings

↓

New Adjuvant trial

Conclusions

Stage and new prognostic biomarker	Predictive biomarkers	No predictive biomarker
Low-risk stage II & III (risk 3-10%)	MSI BRAF mut: PD1/PLD1 I PI3K mut: Aspirin	surveillance Autologous vaccin
Intermediate-risk stage II & III (risk 10-25%)	FP (II MSS) +/- oxaliplatin MSI: PD1/PLD1 I POLE: PD1/PLD1 I Her2: Trastuzumab PI3K mut: Aspirin BRAF mut: BRAFI/EGFRI/MEKI	FP +/- oxaliplatin Autologous vaccin
High-risk stage II & III (risk >25%)	FP + oxaliplatin MSI: PD1/PLD1 I CTL4 combination Immunomodulation POLE: PD1/PLD1 I CTL4 combination Immunomodulation Her2: Trastuzumab/ dual HER2 HER3 I PI3K mut: Aspirin BRAF mut: BRAFI/EGFRI/MEKI	FP + oxaliplatin Immune checkpoint inhibition + immunomodulation (CMS4) Antiangiogenics (after chemo)