XXXIII SIMPOSIO INTERNACIONAL
INTERNATIONAL SYMPOSIUM
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OVIEDO

Selección de pacientes para tratamiento adyuvante en cáncer de colon: ¿es posible ir más allá de las variables clínicas?

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Agenda

Agenda

1

Signatures
KRAS/BRAF
Immunoscore

Agenda

1

Signatures
KRAS/BRAF
Immunoscore

2

Microsatellite instability (MSI)

Agenda

1

Signatures KRAS/BRAF Immunoscore

2

Microsatellite instability (MSI)

3

Circulating tumour DNA (ctDNA)

Agenda

1

Signatures KRAS/BRAF Immunoscore

2

Microsatellite instability (MSI)

3

Circulating tumour DNA (ctDNA)

4

PIK3CA

1. Gene expresión signatures, KRAS/BRAF, immunoscore

SEOM:

(Pericay 2024)

Not recommended for routine practice

ESMO:

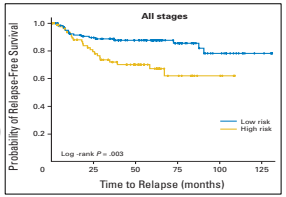
(Argiles 2020)

Not recommended for routine practice

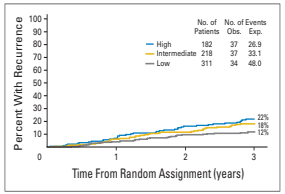
Could be considered

Signatures

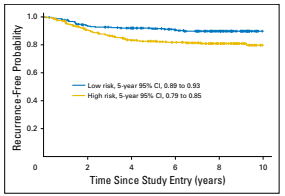
Coloprint
(Salazar, JCO 2011)



Oncotype DX
(Gray, JCO 2011)



GeneFx Colon
(Niedzwiecki, JCO 2016)

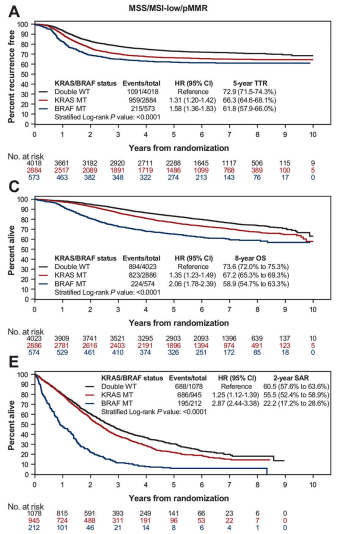


KRAS and BRAF

TTR

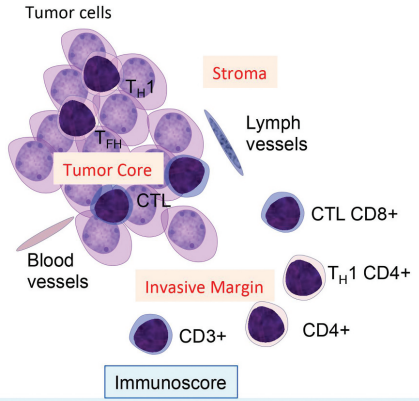
OS

SAR



Taieb, Ann Oncol 2023

Immunoscore



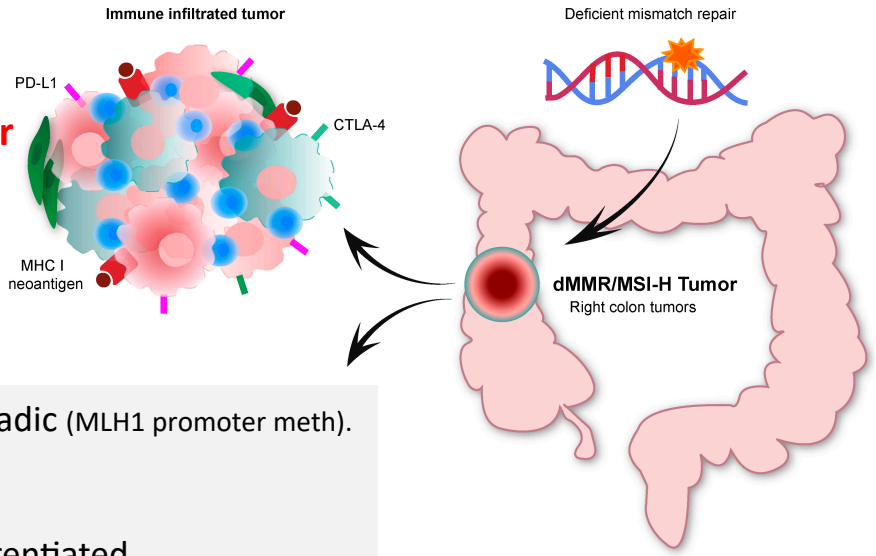
CD3+, CD8+ cells in the tumor and at the invasive margin
Full slide quantification with the Immunoscore software

Lanzi, Oncoimmunology 2020
Mlecnik, J Clin Oncol 2020
Pagés, Ann Oncol 2020

2. Microsatellite instability (MSI)

dMMR/MSI-H: hypermutated tumors

Immunogenic tumor microenvironment



- Mostly sporadic (MLH1 promoter meth).
- Right-sided.
- Mucinous.
- Poorly differentiated.
- BRAF mutations (1/3).

TMB
Frameshift mutations
BRAF V600E mutation
CMS1 subtype

Hypermutated: 10-100x somatic mutations

↓

Large amounts of neoantigens 10-50x

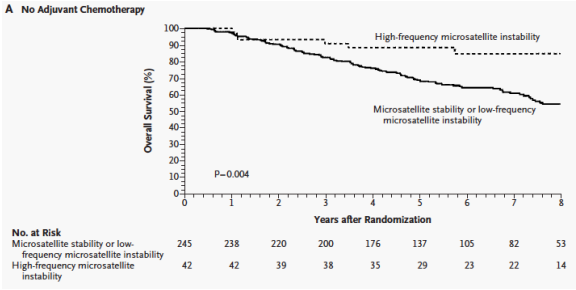
↓

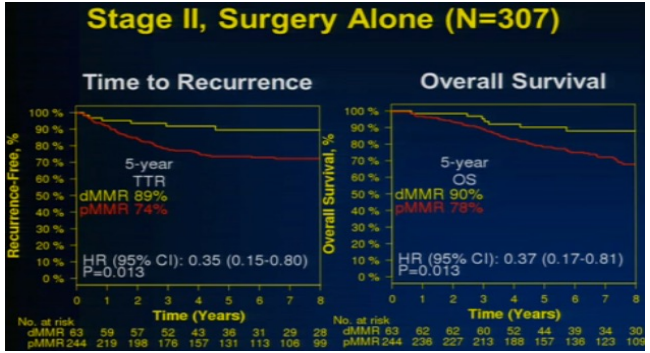
Stage II: 20%
Stage III: 12%
Stage IV: 4%

Mulet et al, Cancers 2023

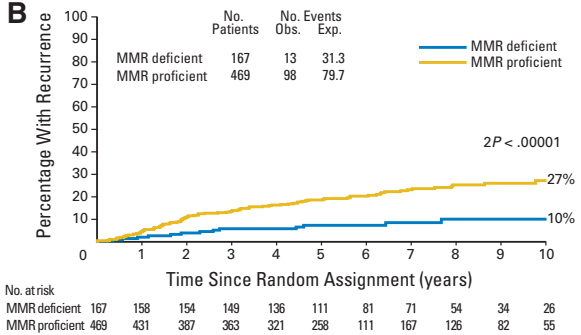
Untreated MSI patients have a better prognosis than MSS, with a trend toward stronger effect in stage II

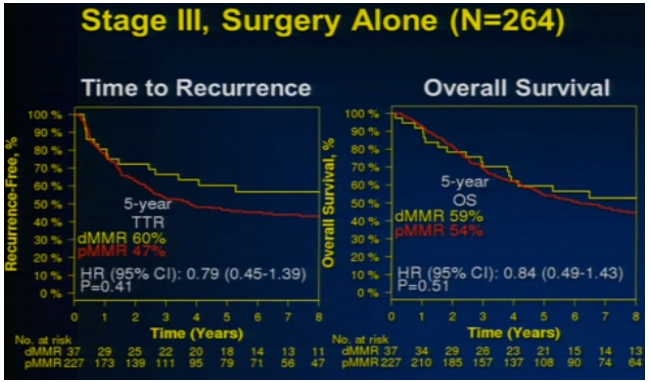
Stages II and III (5 trials)





Stage II (QUASAR)





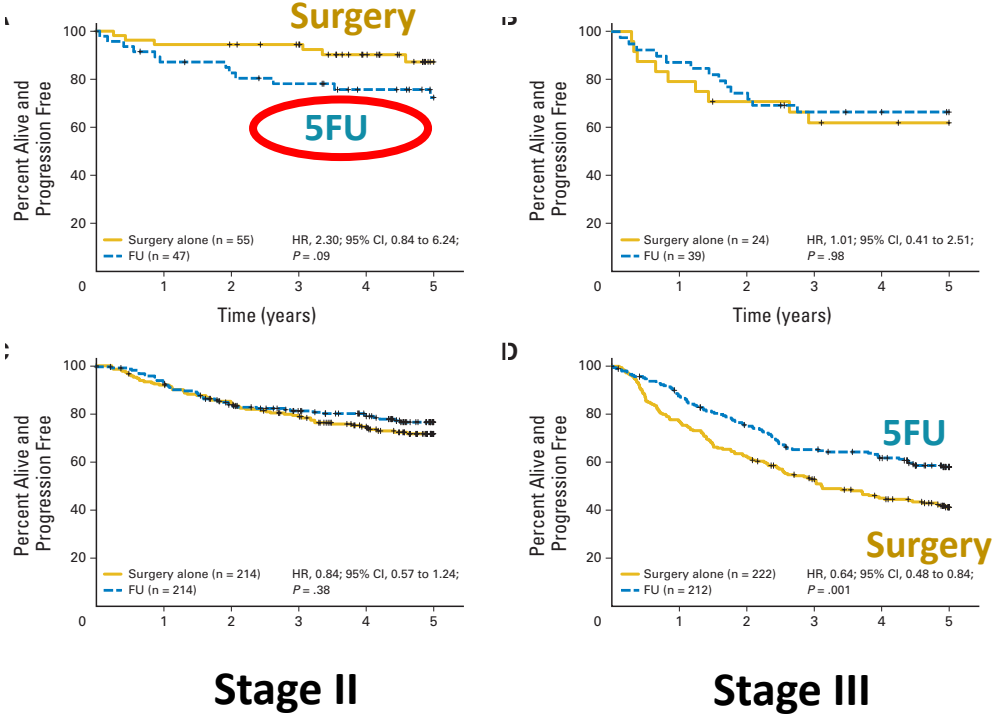
Ribic et al, N Engl J Med 2003
Hutchins et al, J Clin Oncol 2011

Sargent et al, ASCO 2014

MSI do not seem to benefit from adjuvant FP, even a suggestion of harm in OS (5 trials of adj FU vs observation)

dMMR

pMMR



Stage II **Stage III**

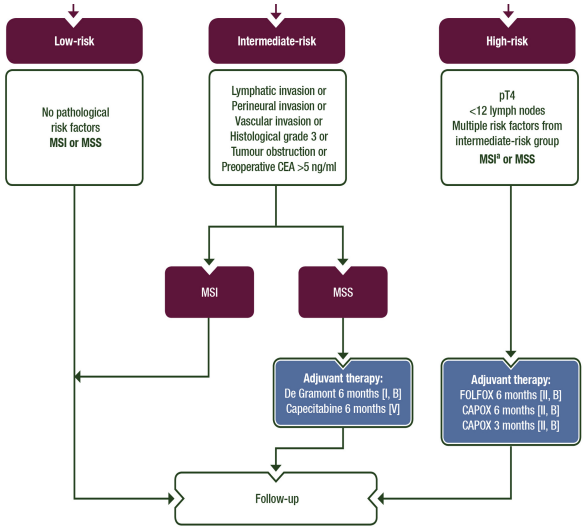
Sargent et al, J Clin Oncol 2010

Stage II

IMS

ESMO

Argilés et al, Ann Oncol 2020



ASCO

Baxter et al, J Clin Oncol 2022

MSS: Adj CT should be offered to IIB and IIC (T4).

May be offered to IIA with high-risk factors: <12 ln, PNI, LVI, G3-4, obstruction, perforation, BD3 tumor budding (≥ 10 buds)

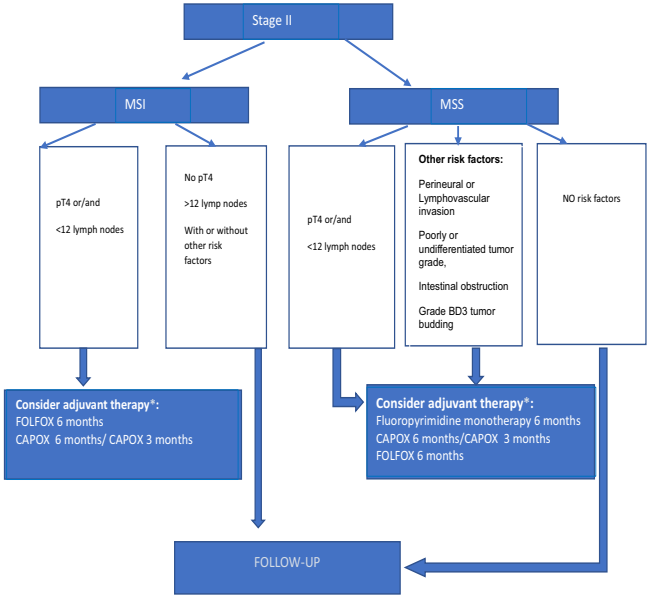
Nº of risk factors should be considered.

Insufficient evidence to routinely recommend oxali to high-risk MSS.

MSI and T4/other high-risk features (exception: G3): Oxaliplatin.

SEOM

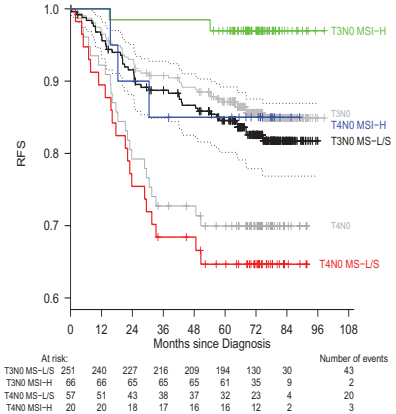
Pericay et al, Clin Transl Oncol 2024



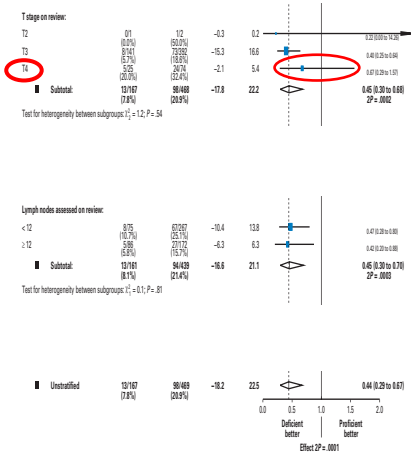
*Individualize according to age and comorbilities

Which is the strongest factor in stage II? MSI vs T4

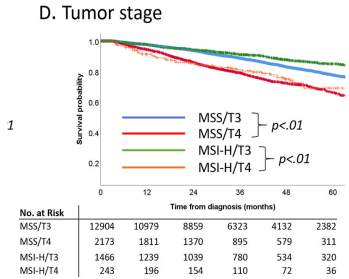
PETACC3
Roth, J Natl Cancer Inst 2012

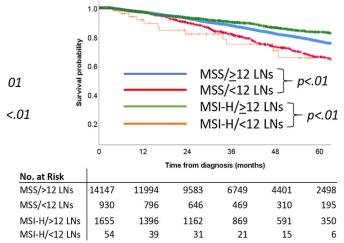


QUASAR
Hutchins, J Clin Oncol 2011



NCDB
Cavallaro, Dis Colon Rectum2021





FOXTROT
Platt, ESMO 2024

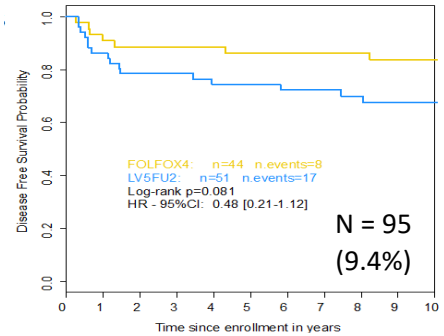
Table 5. Univariable Analysis for Time to Recurrence According to MMR Status

		pMMR		dMMR	
Radiological Feature		**Hazard ratio (95% CI) [c]**	**P value [c]**	**Hazard ratio (95% CI) [c]**	**P value [c]**
Tumour side [a]	Right	1.0		1.0	
	Left	0.76 (0.56-1.05)	0.10	1.33 (0.55-3.19)	0.53
T stage [b]	T3	1.0		1.0	
	T4	1.35 (0.95-1.92)	0.10	2.11 (1.10 – 4.06)	0.03
Depth of tumour extension	Continuous	1.03 (1.01-1.05)	0.0005	1.02 (0.98-1.05)	0.39
	≤7	1.0		1.0	
	>7	1.74 (1.26-2.38)	0.001	1.18 (0.61-2.26)	0.62
Maximum tumour thickness	Continuous	1.14 (1.00-1.29)	0.05	1.19 (1.00-1.40)	0.045
	≤25	1.0		1.0	
	>25	1.51 (1.08-2.12	0.02	2.26 (1.18-4.34)	0.01
N stage [b]	N0	1.0		1.0	
	N1	1.03 (0.69-1.54)	0.88	1.83 (0.61-5.49)	0.28
	N2	1.19 (0.77-1.84)	0.42	3.09 (1.04-9.20)	0.04
Node ≥10mm	No	1.0		1.0	
	Yes	1.35 (0.98-1.87)	0.07	1.72 (0.90-3.32)	0.10
EMVI	Absent	1.0		1.0	
	Present	1.32 (0.95-1.83)	0.10	1.82 (0.86-3.85)	0.12

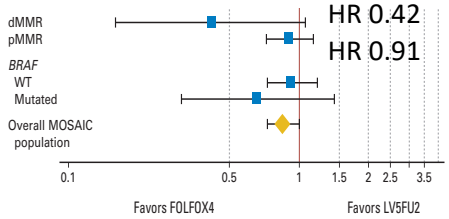
Oxaliplatin provides benefit in dMMR tumors

MOSAIC

André, J Clin Oncol 2015



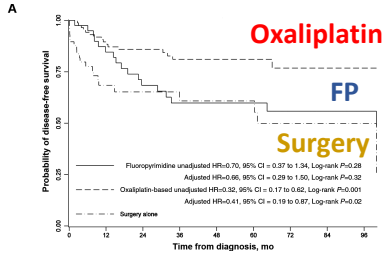
10-y DFS (stages II and III)



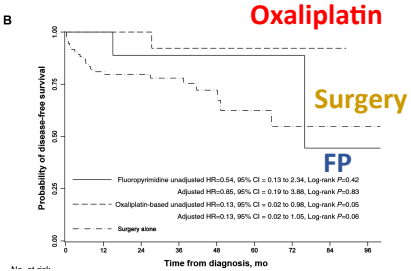
Forest plot OS

AGEO

Tougeron, J Natl Cancer Inst 2016



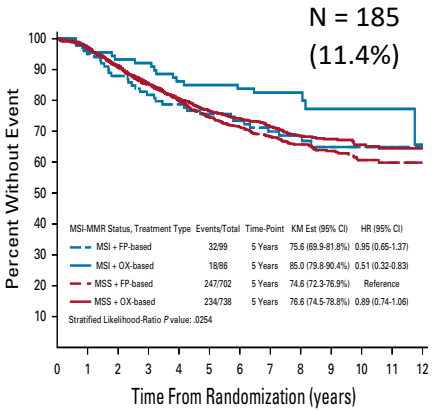
Stage III (N=187)



High Risk Stage II (N=246)

ACCENT (MOSAIC, C-07)

Cohen, J Clin Oncol 2021

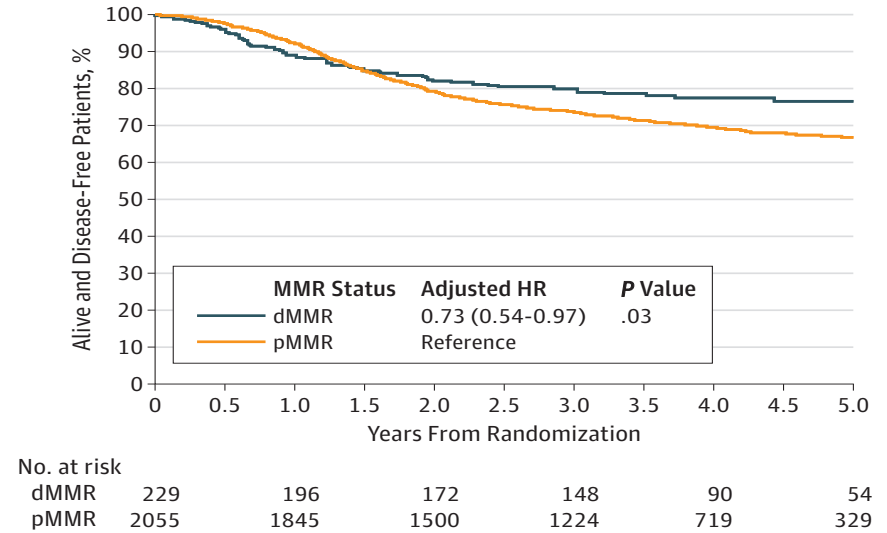


OS (stage III)

Significant benefit from oxaliplatin, aHR for OS:
MSI: 0.52 (95% CI, 0.28-0.93)
MSS: 0.89 (95% CI, 0.74-1.06)

dMMR/MSI remains a favorable prognostic factor in stage III receiving adjuvant FOLFOX (N0147 and PETACC8)

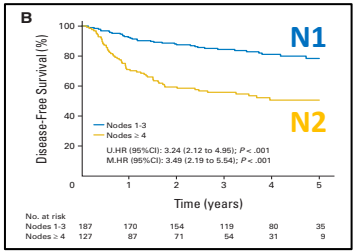
Figure 2. Disease-Free Survival



Zaanan et al, JAMA Oncol 2018

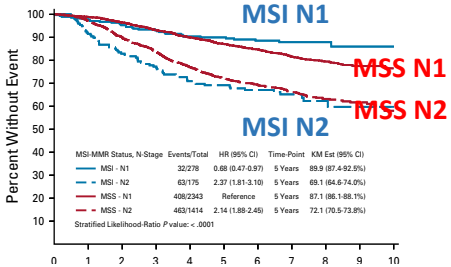
Among dMMR/MSI: distal, N2 and ctDNA+ have poor outcome

N2



N0147

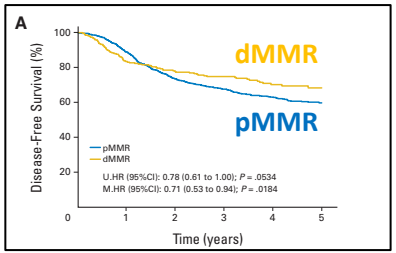
(Sinicrope, J Clin Oncol 2013)



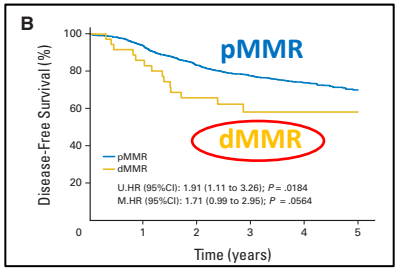
ACCENT

(Cohen, J Clin Oncol 2021)

Distal



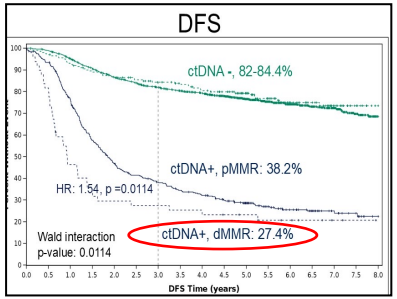
Proximal

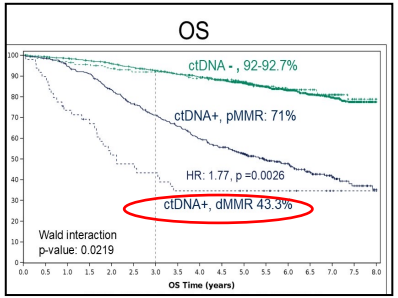


Distal

(Sinicrope, J Clin Oncol 2013)

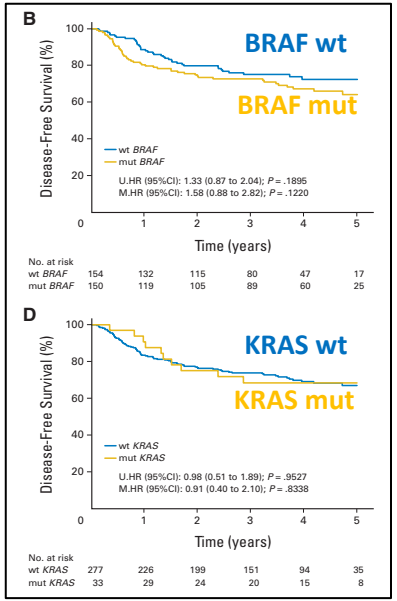
ctDNA+





(Sinicrope, ASCO 2025)

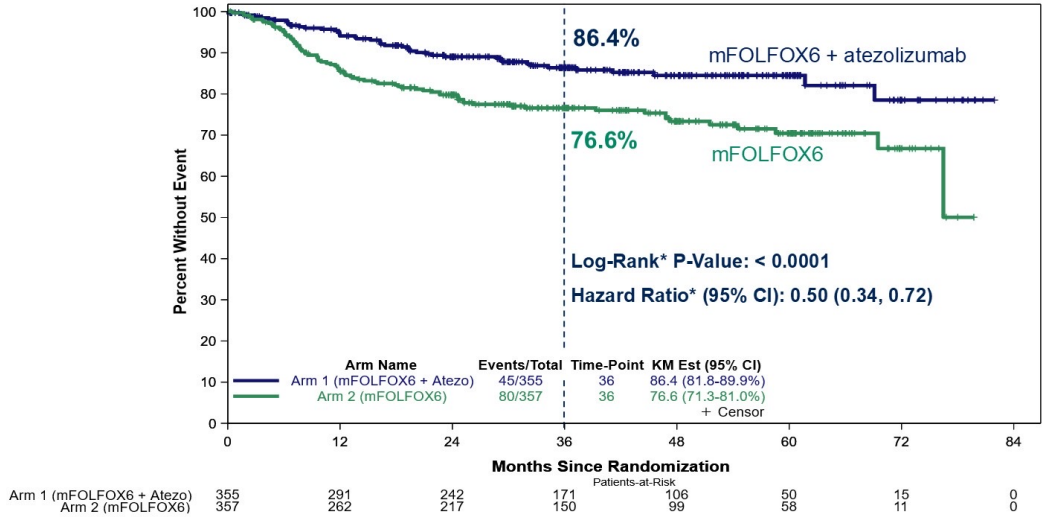
KRAS and BRAF



(Sinicrope, J Clin Oncol 2013)

ATOMIC trial (Phase III): Adding atezolizumab to mFOLFOX6 significantly improves DFS for dMMR stage III

Primary Endpoint: DFS



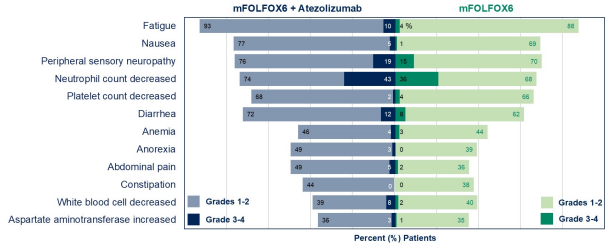
Confirmed dMMR by central reference laboratory: Log-Rank P-Value: 0.0007, Hazard Ratio (95% CI): 0.53 (0.36, 0.79)

*Stratified by randomization factors

Median follow-up = 37.2 mos

Safety Summary

Characteristics	mFOLFOX6 + Atezo (N=346)*	mFOLFOX6 (N=334)*
Any Grade AE, % (n) Treatment-related	100% (346) 99.7% (345)	95.1% (329) 94.2% (326)
Grade 3-4 AE, % (n) Treatment-related	83.8% (290) 72.3% (250)	69.1% (239) 59.2% (205)
Grade 5 AE, % (n) Treatment-related	1.7% (6) 0.6% (2)*	0.6% (2) 0.0% (0)

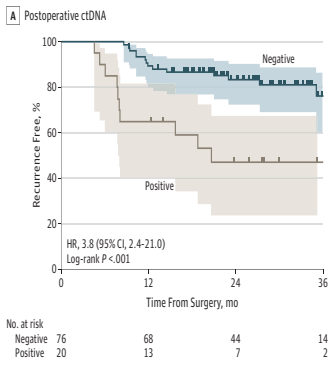


Sinicrope et al, ASCO 2025

3. Circulating tumour DNA (ctDNA)

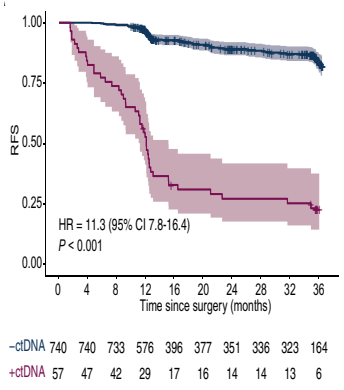
Positive ctDNA status is a strong prognostic factor for recurrence

Australian cohort
Tie, JAMA Oncol 2019



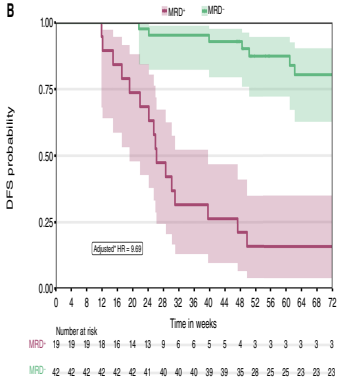
N = 100
Stage III
SafeSeq
ctDNA+ post-Sx **21%**
HR **3.8**

Danish cohort
Henriksen, Ann Oncol 2024



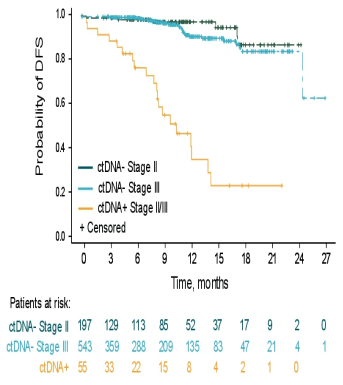
N = 851
Stage II/III
dPCR
ctDNA+ post-Sx **7%**
HR **11.3**

GALAXY
Nakamura, Clin Cancer Res 2025



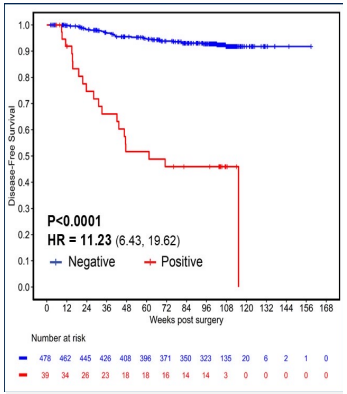
N = 80
Stage II/III
xM
ctDNA+ post-Sx **31%**
HR **9.69**

BNT 000-001
Reinacher-Schick, ASCO 2024



N = 852
Stage II/III
AVENIO
ctDNA+ post-Sx **13%**
HR **13.06**

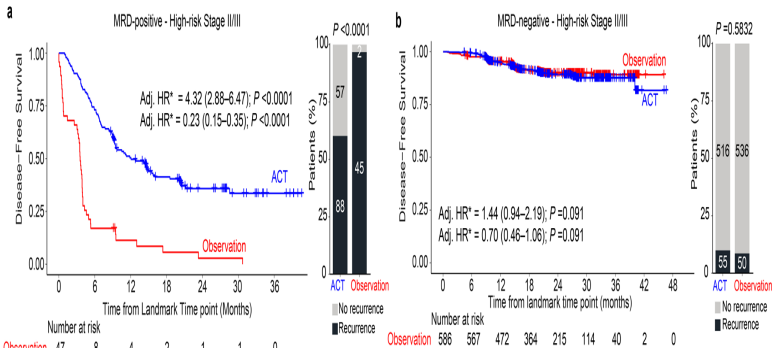
BESPOKE CRC
Shah, ASCO GI 2025



N = 1166
Stage II/III
Signatera
ctDNA+ post-Sx **8/28%**
HR **11.2/8.3**

ctDNA is also able to predict benefit from adjuvant CT

GALAXY
Nakamura et al, Nat Med 2024



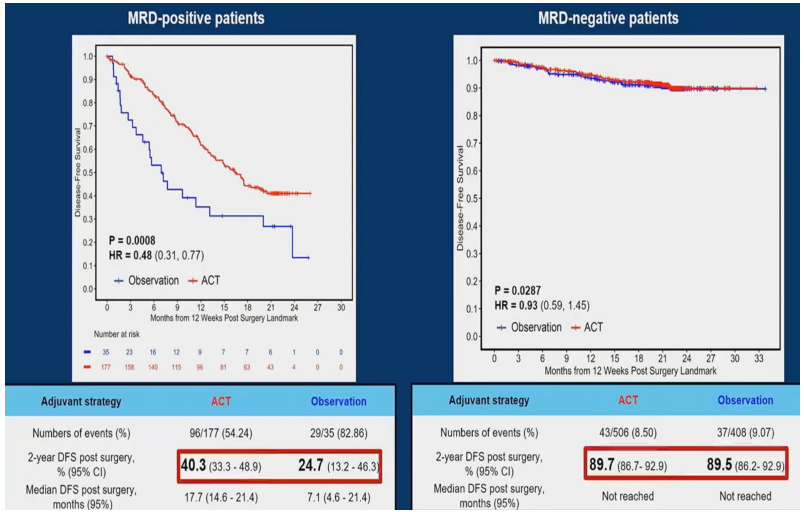
Treatment	ACT	Observation
Events %	60.68 (88/145)	95.74 (45/47)
24M-DFS % (95% CI)	35.83 (27.41–44.32)	2.84 (0.23–12.35)
mDFS (mo)	12.06 (9.30–18.57)	3.55 (3.16–3.95)

Treatment	ACT	Observation
Events %	9.63 (55/571)	8.53 (50/586)
24M-DFS % (95% CI)	89.11 (85.81–91.68)	89.9 (86.80–92.30)
mDFS (mo)	NR	NR

MRD+

MRD-

BESPOKE
Shah et al, ASCO GI 2025



Adjuvant strategy	ACT	Observation
Numbers of events (%)	96/177 (54.24)	29/35 (82.86)
2-year DFS post surgery, % (95% CI)	**40.3** (33.3 - 48.9)	**24.7** (13.2 - 46.3)
Median DFS post surgery, months (95%)	17.7 (14.6 - 21.4)	7.1 (4.6 - 21.4)

Adjuvant strategy	ACT	Observation
Numbers of events (%)	43/506 (8.50)	37/408 (9.07)
2-year DFS post surgery, % (95% CI)	**89.7** (86.7- 92.9)	**89.5** (86.2- 92.9)
Median DFS post surgery, months (95%)	Not reached	Not reached

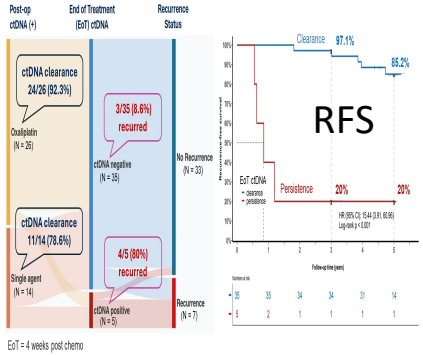
MRD+

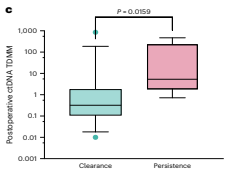
MRD-

Clearance of ctDNA as survival predictor

DYNAMIC (Stage II)

Tie, NEJM 2022; Nat Med 2025

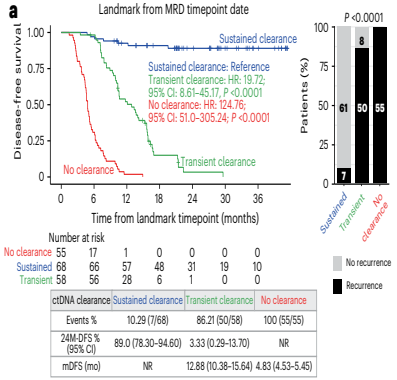




Clearance
(4w post adj CT): 87%

GALAXY (Stage I – IV)

Nakamura, Nat Med 2024

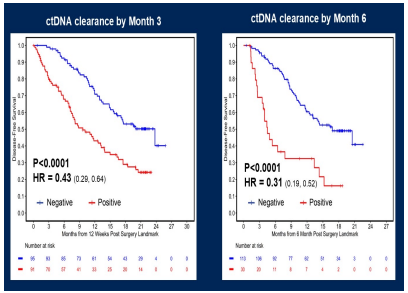


ctDNA clearance	Sustained clearance	Transient clearance	No clearance
Events %	10.29 (7/68)	86.21 (50/58)	100 (55/55)
24M-DFS % (95% CI)	89.0 (78.30–94.60)	3.33 (0.29–13.70)	NR
mDFS (mo)	NR	12.88 (10.38–15.64)	4.83 (4.53–5.45)

Clearance after adj CT: 68%
Sustained clearance: **37%**

BESPOKE (Stage II-III)

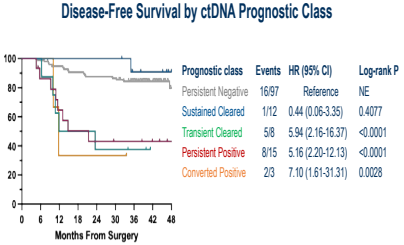
Shah, ASCO GI 2025



Clearance:
12w 49%
20w 67%
6m 73%
Overall 75%

PEGASUS (Stage II-III)

Marsoni, ESMO 2025



Prognostic class	Events	HR (95% CI)	Log-rank P
Persistent Negative	16/97	Reference	NE
Sustained Cleared	1/12	0.44 (0.06-3.35)	0.4077
Transient Cleared	5/8	5.94 (2.16-16.37)	<0.0001
Persistent Positive	8/15	5.16 (2.20-12.13)	<0.0001
Converted Positive	2/3	7.10 (1.61-31.31)	0.0026

Persistent negative: 72%
Sustained cleared: **9%**
Transient cleared: 6%
No clearance: 11%
Converted positive: 2%

DYNAMIC-II: first randomized phase II trial (stage II)

Tumor-informed: SaferSeqS

DYNAMIC

Tie et al, NEJM 2022; ASCO 2024; Nat Med 2025

Stage II Colon Cancer

- R0 resection
- ECOG 0 – 2
- Staging CT within 8 weeks
- Provision of adequate tumor tissue within 4 weeks post-op
- No synchronous colorectal cancer

Plasma Collections
Week 4 + 7 post-op

R 2:1

ctDNA-Guided Management

- ctDNA-Positive → Adjuvant Chemo (oxaliplatin-based or single agent FP)
- ctDNA-Negative → Observation

ctDNA-Positive = Positive result at week 4 and/or 7

Standard Management

Adjuvant treatment decisions based on conventional clinico-pathologic criteria

Endpoints

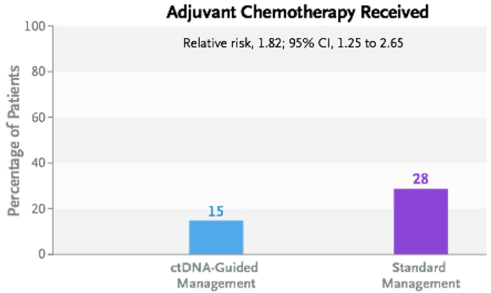
Primary
- RFS rate at 2 years

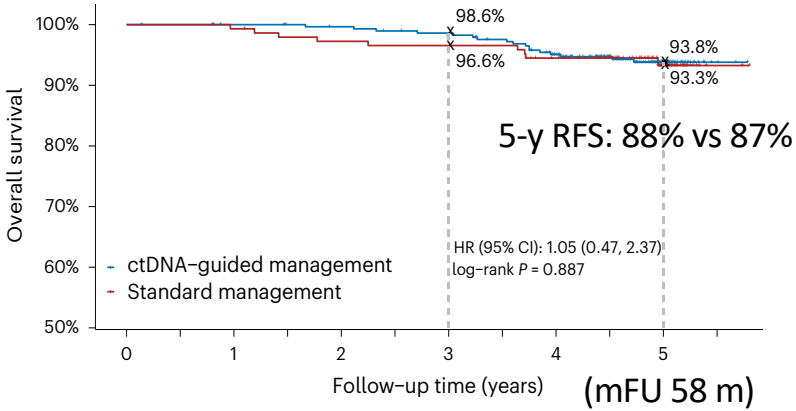
Key Secondary
- Proportion receiving adjuvant chemo

Secondary
- RFS by ctDNA status for ctDNA-guided arm
- TTR
- OS

Stratification Factors
- T stage (T3 vs T4)
- Type of participating center (metropolitan vs regional)

Surveillance:
- CEA → 3-monthly for 24M, then 6-monthly for 36M
- CT C/A/P → 6-monthly for 24M, then at 36M





5-y RFS: 88% vs 87%

(mFU 58 m)

DYNAMIC-III (randomised phase II/III): ctDNA-guided adjuvant CT **de-escalation** in stage III (ctDNA **negative**)

Stage III Colon Cancer

- R0 resection
- ECOG 0 – 2
- Fit for at least a fluoropyrimidine (FP)
- Staging CT within 12 weeks
- Provision of adequate tumor tissue < 6 weeks post-operation
- No synchronous colorectal cancer

Tumour-Informed ctDNA Analysis (SaferSeqS[1] targeted CRC panel)

W5-6

R 1:1

Clinicians nominate SoC Chemo

ctDNA-Informed Management

- ctDNA-Negative → De-escalate
- ctDNA-Positive → Escalate

1 cycle of pre-planned chemotherapy allowed prior to ctDNA-informed regimen

Pre-Planned SoC → De-escalation

6M FP → No chemo or 3M FP
3M Oxaliplatin + FP → 3-6M FP
6M Oxaliplatin + FP → 3M Oxaliplatin + FP or 6M FP

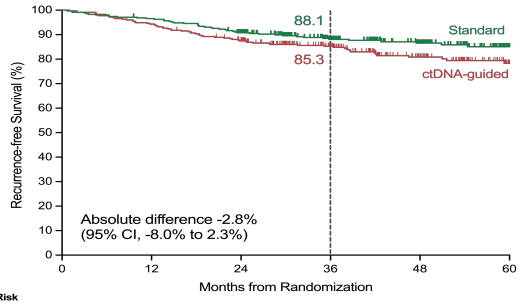
FP = fluoropyrimidine

Standard Management

Treatment per clinician's choice (blinded to ctDNA result)

Stratified by clinical risk (low vs high) and sites

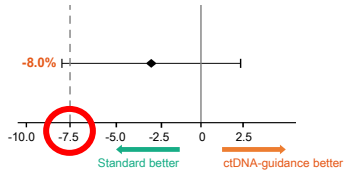
Recurrence-Free Survival



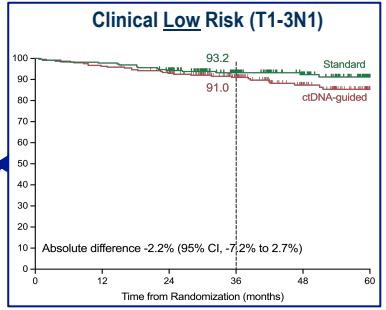
Median follow-up 47 months (0.68 - 67.0)

Arm	Total	Events	3-year RFS (95% CI)
ctDNA	353	63	85.3% (81, 89)
Standard	349	45	88.1% (84, 91)

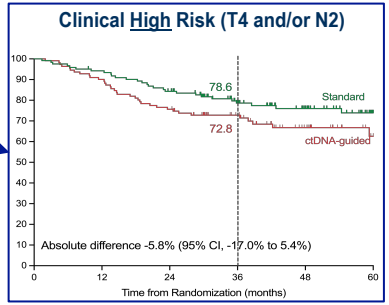
Absolute Difference in 3-year RFS (95% CI)



Clinical Low Risk (T1-3N1)



Clinical High Risk (T4 and/or N2)



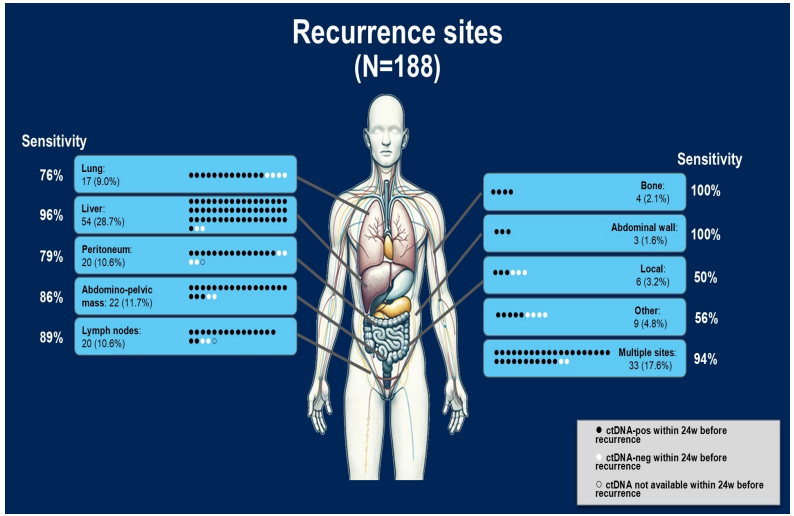
- Markedly reduced oxaliplatin exposure (88.6% → 34.8%)

Tie et al, ESMO 2025

Lung, peritoneum and local recurrences are typically not detected

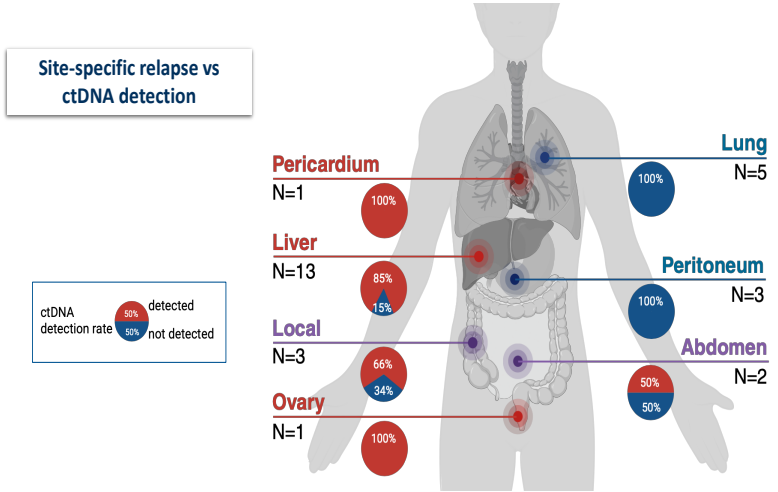
BESPOKE (Stage II-III)

Shah, ASCO GI 2025



PEGASUS (Stage II-III)

Marsoni, ESMO 2025



DYNAMIC-III (randomised phase II/III): ctDNA-guided adjuvant CT **escalation** in stage III (ctDNA **positive**)

Stage III Colon Cancer

- R0 resection
- ECOG 0 – 2
- Fit for at least a fluoropyrimidine (FP)
- Staging CT within 12 weeks
- Provision of adequate tumor tissue < 6 weeks post-operation
- No synchronous colorectal cancer

Tumor-Informed ctDNA Analysis (SaferSeqS[1] targeted CRC panel)

W5-6

R 1:1

Clinicians nominate SoC Chemo

ctDNA-Informed Management

- ctDNA-Negative → De-escalate
- ctDNA-Positive → Escalate

1 cycle of pre-planned chemotherapy allowed prior to ctDNA-informed regimen

Standard Management

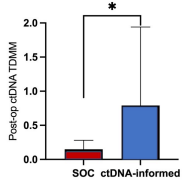
Treatment per clinician's choice (blinded to ctDNA result)

Stratified by clinical risk (low vs high) and sites

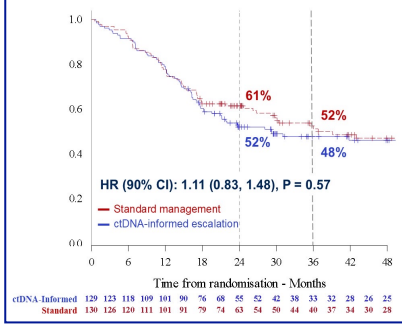
Pre-Planned SoC → Escalation
No chemotherapy → 5FU/Cape
5FU/Cape → 6M Oxaliplatin doublet
3M Oxaliplatin doublet → 6M Doublet or ≥ 3M FOLFOXIRI
6M Oxaliplatin doublet → ≥ 3M FOLFOXIRI

Imbalance in baseline ctDNA burden for T4 patients

(40% of the study population)



Recurrence-Free Survival



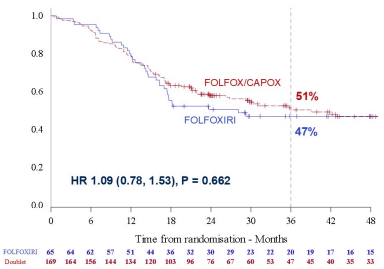
	Total	Events	Median RFS (mths)	2-year RFS (90% CI)	3-year RFS (90% CI)
ctDNA	129	66	29.24	52% (44, 59)	48% (40, 55)
SoC	130	62	36.80	61% (54, 68)	52% (44, 60)

Median follow-up 42.2 months (0.78 - 63.0)

Data cut-off: 14 Nov 2024

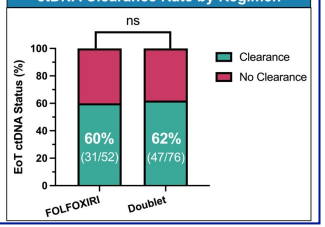
Post-Hoc Analysis: FOLFOXIRI vs FOLFOX/CAPOX

Recurrence free survival



	TDMM/mL, median (IQR)	P
FOLFOXIRI	0.28 (0.06, 1.78)	0.236
Doublet	0.15 (0.06, 0.97)	

ctDNA Clearance Rate by Regimen

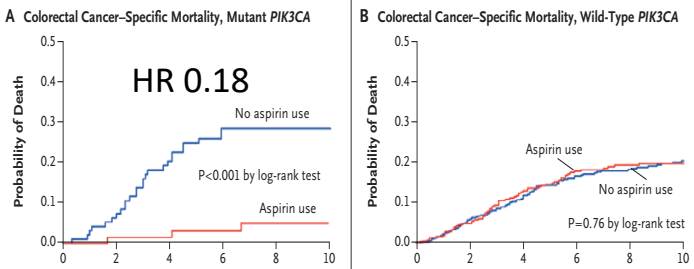


Tie et al, ASCO 2025

4. PIK3CA mutations

Aspirin and celecoxib: predictive value of PIK3CA

Liao, NEJM 2012 (Aspirin, I-IV CCR)



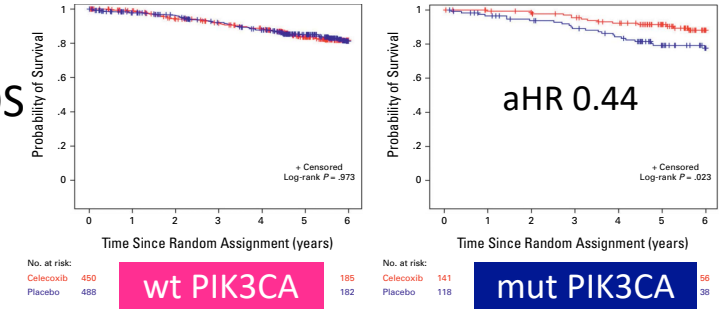
mut PIK3CA

16%

wt PIK3CA

Nowak, JCO 2024 (Celecoxib, III colon, CALGB/SWOG 80702)

OS



wt PIK3CA

Celecoxib 400 mg daily x 3y

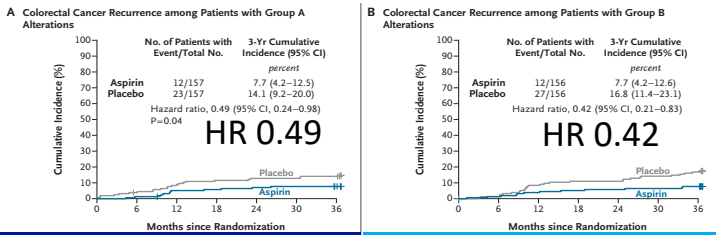
mut PIK3CA

21%

Martling, NEJM 2025 (Aspirin, I-III CCR, ALASCCA)

PIK3CA 15-30%

Aspirin 160 mg daily x 3y



PIK3CA hotspot mutations (exon 9 or 20)

Other moderate/ high-impact variants in PIK3CA, PIK3R1, PTEN

37%

Conclusions:

1) Routine use of genomic **signatures, KRAS/BRAF mutations and immunoscore** is not currently recommended to guide adjuvant treatment decisions for colon cancer in clinical practice.

2) **MSI** is the most relevant molecular factor in localised stages of colon cancer due to its prognostic and predictive value (improved survival for MSI/dMMR tumours, and lack of benefit from adjuvant fluoropyrimidines alone, particularly in stage II).

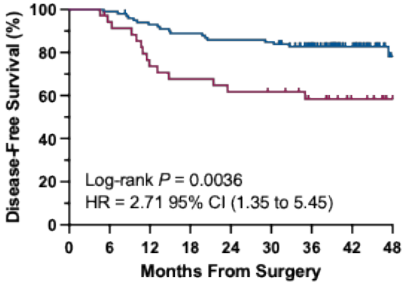
3) **ctDNA** is a powerful prognostic factor for recurrence, and it is also able to predict the benefit of adjuvant CT. Clearance of ctDNA following adjuvant CT is associated with improved survival, particularly when it is sustained over time. Ongoing clinical trials aim to enable the incorporation of liquid biopsy into routine clinical practice.

4) Activating **PIK3CA** mutations allow the selection of patients who may benefit from adjuvant aspirin, with a significantly lower incidence of colorectal cancer recurrence.

Thank you

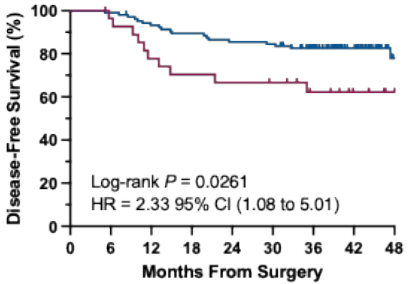
Liquid biopsy is prognostic before, during and after adjuvant treatment (PEGASUS)

POST-SURGERY
(LB1)



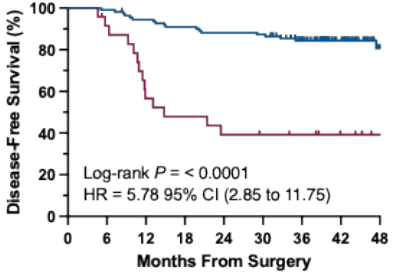
No at risk:									
ctDNA Negative	100	99	92	88	85	84	69	41	15
ctDNA Positive	35	32	25	23	21	20	16	11	6

ON –TREATMENT
(LB3)



No at risk:									
ctDNA Negative	104	103	96	92	88	87	72	43	15
ctDNA Positive	28	26	21	19	18	17	13	9	6

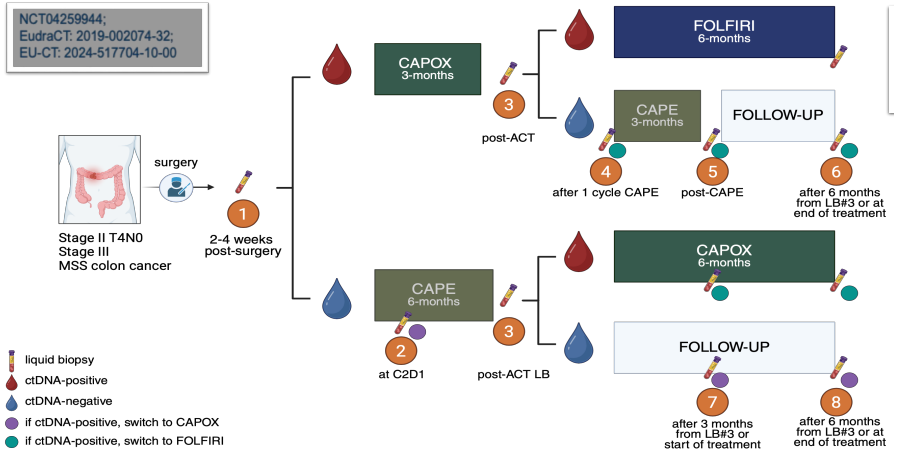
END OF TRETAMENT
(LB3, LB5, LB6, LB8)

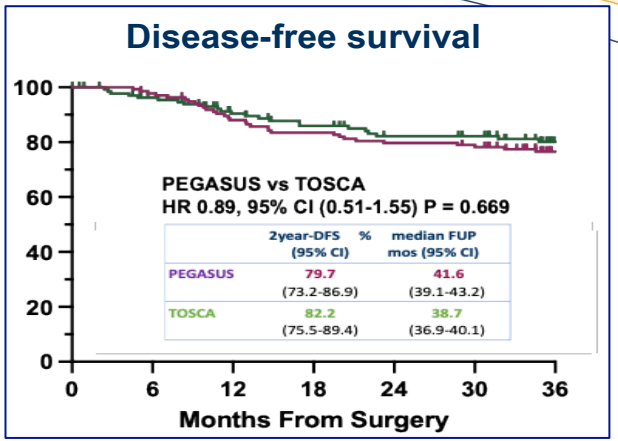


No at risk:									
ctDNA Negative	111	110	104	100	97	96	78	48	20
ctDNA Positive	24	21	13	11	9	8	7	4	1

Marsoni et al, ESMO 2025

PEGASUS: a feasibility trial (stage III and high-risk stage II)





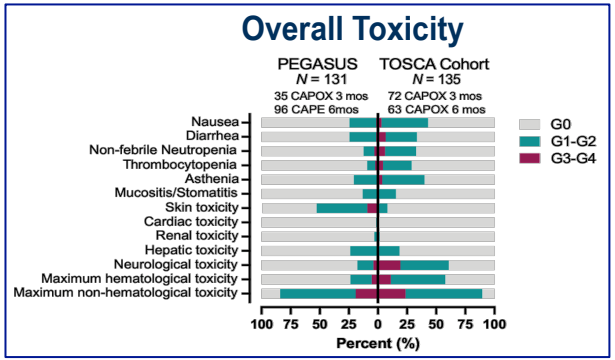
Reveal L1.2 test (Guardant Health, Inc.)

- Plasma-only assay
- Genetic | Epigenetic signal
- Early-generation version

PRIMARY ENDPOINT

Number of false negative cases within 2 years

- 100 ctDNA– patients → 12 relapses (2 local+10 distant) within 2 years
- 2-year recurrence-free rate: 88% (90% CI, 81–93)
- Primary endpoint not formally powered
- 2-year recurrence-free rate exceeded the 85% benchmarking, upper CI 93% crossed H_1 target 92% supporting clinical adequacy despite reduced power.



Marsoni et al, ESMO 2025

COBRA: Randomized phase II-III in stage IIA with <12LN

COBRA
Morris et al, ASCO GI 2024

NRG-GI005 (COBRA) Study Schema

Resected stage IIA colon cancer for which the physician decides no adjuvant chemotherapy (i.e., "suitable for active surveillance")

R 1:1

Arm 1
Standard of care (active surveillance)

Arm 2
Assay-directed therapy

All patients were followed with radiographic restaging assessments every 6 months.

ctDNA detected
Chemotherapy (mFOLFOX6 or CAPOX) x 6 months

ctDNA NOT detected
Active surveillance

NRG ONCOLOGY Abstract 433174: NRG-GI005 (COBRA)

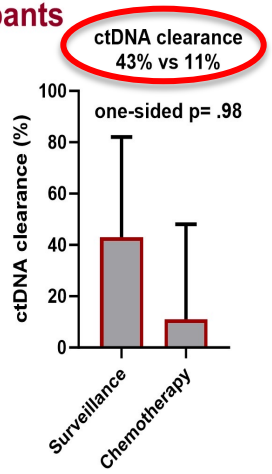
Phase II Endpoint Analysis: ctDNA(+) baseline participants

- Among 596 participants with baseline ctDNA status available, ctDNA(+) detection was observed in 33 (5.54%).

16 participants with "ctDNA detected" status at baseline
- Arm 1: Surveillance 7 participants
- Arm 2: Chemotherapy 9 participants

- Clearance of ctDNA at 6 months among ctDNA(+) participants at baseline was observed in:
  - **Arm 1 (surveillance):** 3 of 7 (43%, 95% CI 10 - 82%) participants
  - **Arm 2 (chemotherapy):** 1 of 9 patients (11%, 95% CI 0.3 - 48%) participants

- **Because the 1-sided Fisher's Exact Test yields p = 0.98 exceeded 0.35, H_0 was not rejected, and the decision rule calls for early stopping due to futility.**



NRG ONCOLOGY Abstract 433174: NRG-GI005 (COBRA)

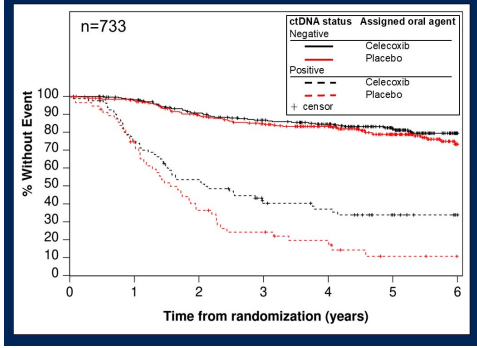
ctDNA + postCx:
5%

Guardant Lunar assay: sensitivity 56% and specificity 95% (1 month after curative therapy)

GALAXY: Spontaneous clearance rate 1.9%

Value of ctDNA in PIK3CA wt (CALGB/SWOG 80702)

Survival by ctDNA status and celecoxib use in *PIK3CA* wildtype tumors



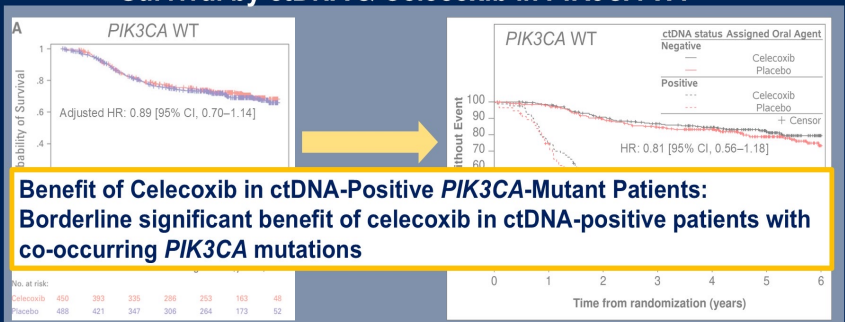
Assigned Oral Agent by ctDNA status	Events / Total	Hazard Ratio (95% CI)[1]	3 Year Survival Estimate (95% CI)[2]	P-value
Negative				0.2777[4]
Celecoxib	49/278	0.81 (0.56-1.18)	86.7 (82.7-91.0%)	
Placebo	63/318	Reference	84.8 (80.7-89.0%)	
Positive				0.0166[4]
Celecoxib	51/81	0.61 (0.41-0.92)	40.3 (30.7-52.9%)	
Placebo	45/61	Reference	24.2 (14.9-39.3%)	
Interaction P-value: 0.2217[3]				

[1] Unadjusted Cox model, [2] Kaplan-Meier method, [3] Likelihood-ratio test
[4] Log-rank test

PIK3CA status as defined in
Nowak JA, et al. J Clin Oncol. 42(24):2853-2859. 2024.

CALGB/SWOG 80702 ctDNA Analysis

Survival by ctDNA & Celecoxib in *PIK3CA* WT



Benefit of Celecoxib in ctDNA-Positive *PIK3CA*-Mutant Patients: Borderline significant benefit of celecoxib in ctDNA-positive patients with co-occurring *PIK3CA* mutations