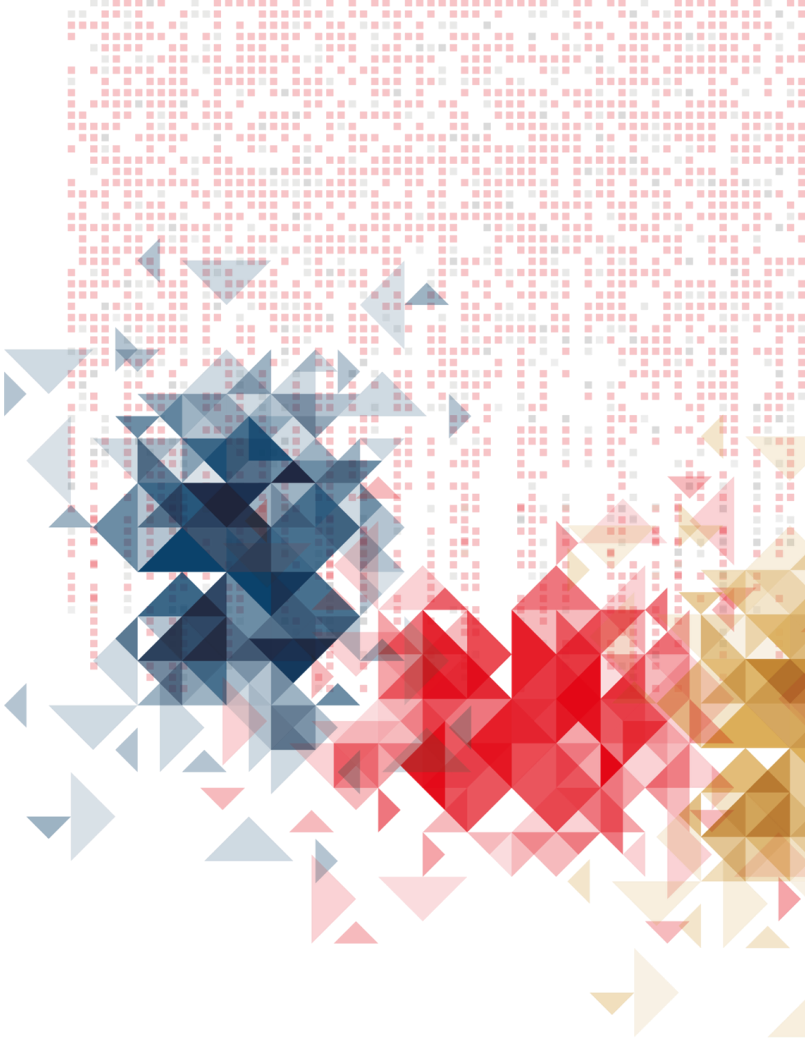
2021 ESMO congress

Are circulating and tissue markers going to help in the future?

Dr Naureen Starling
Consultant Medical Oncologist in Gastrointestinal Cancer
Royal Marsden Hospital, London, UK
September 2021

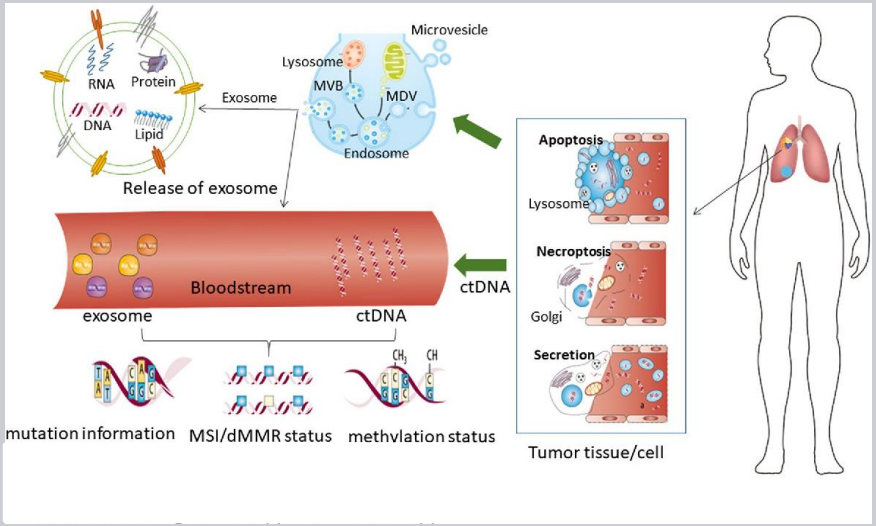


DECLARATION OF INTERESTS

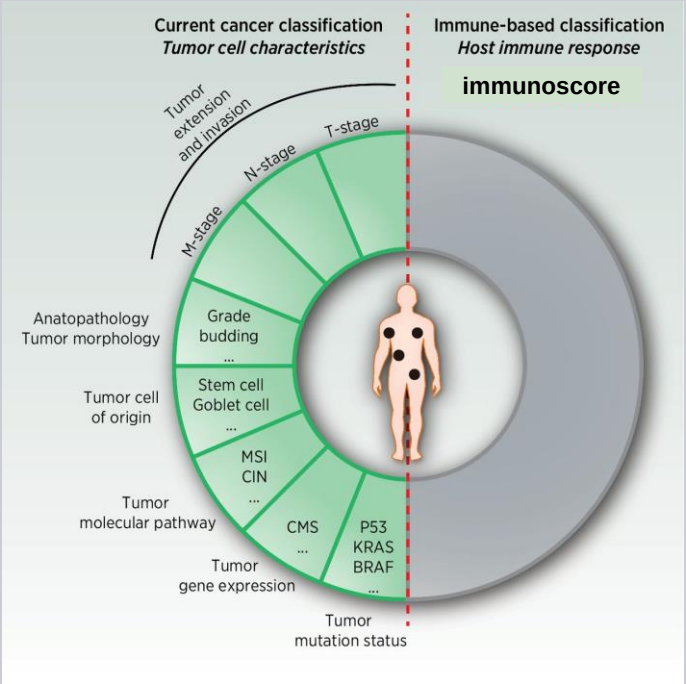
- Research funding: BMS, Astra Zeneca, Pfizer, Merck Serono
- Honorarium: Eli-Lilly, Astra Zeneca, MSD, Merck Serono, Pierre Fabre
- Advisory Board: Pfizer, Astra Zeneca, Servier

Introduction

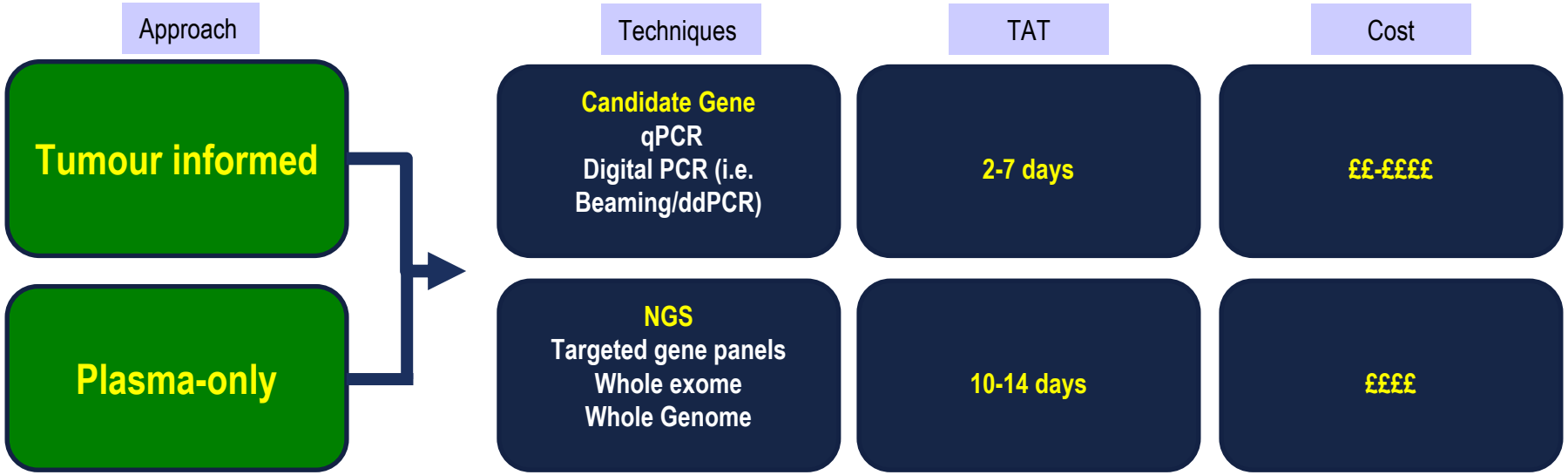
Liquid



Tissue



Liquid biopsies and ctDNA for MRD detection



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GUARDANT REVEAL

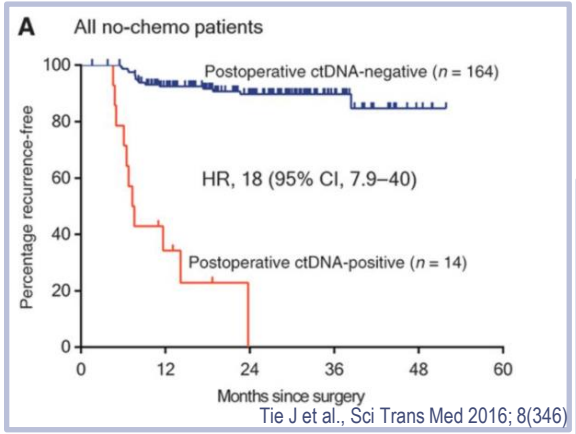
natera

Chakrabarti S et al., Cancers 2020

MRD is associated with relapse

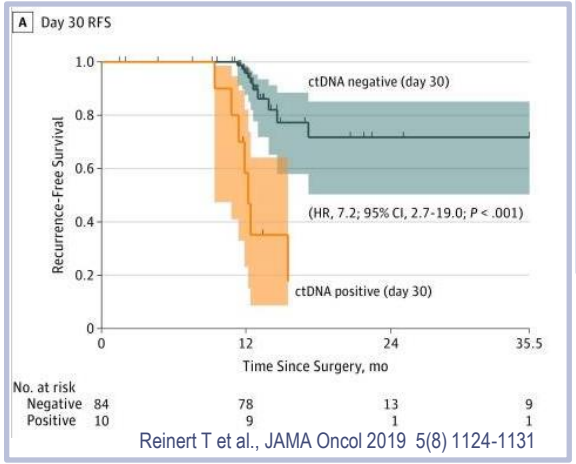
Single post-op ctDNA time point

Stage II colon cancer n=178



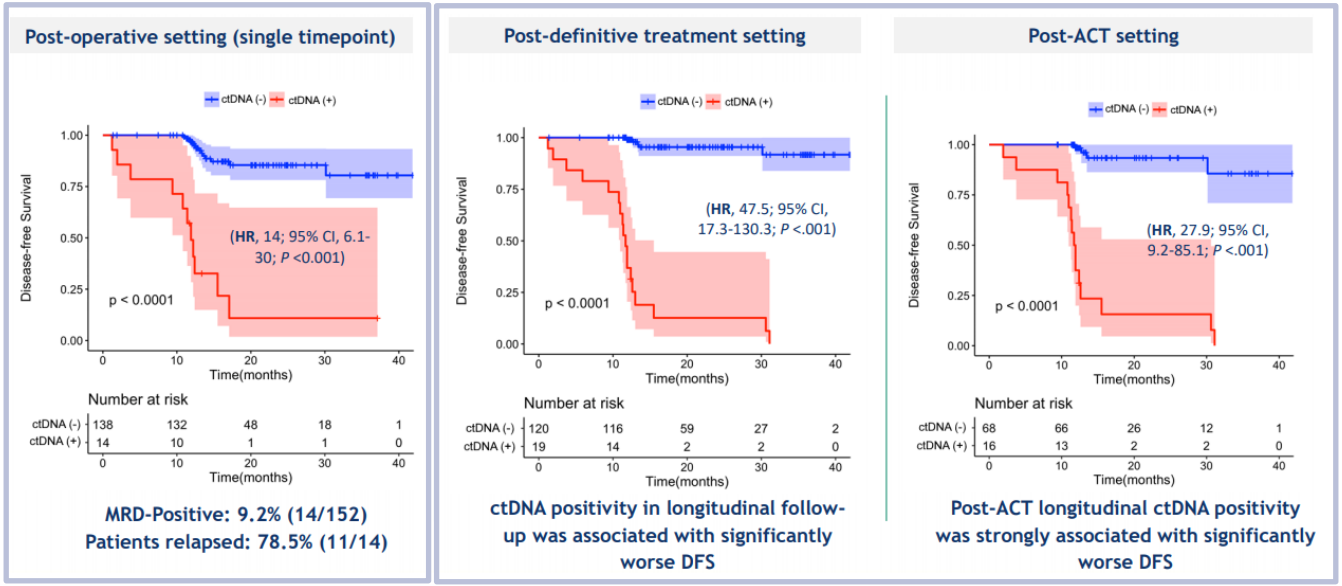
Tie J et al., Sci Trans Med 2016; 8(346)

Stage I-III colon cancer n=94



Reinert T et al., JAMA Oncol 2019 5(8) 1124-1131

Single versus longitudinal post-op ctDNA n=193

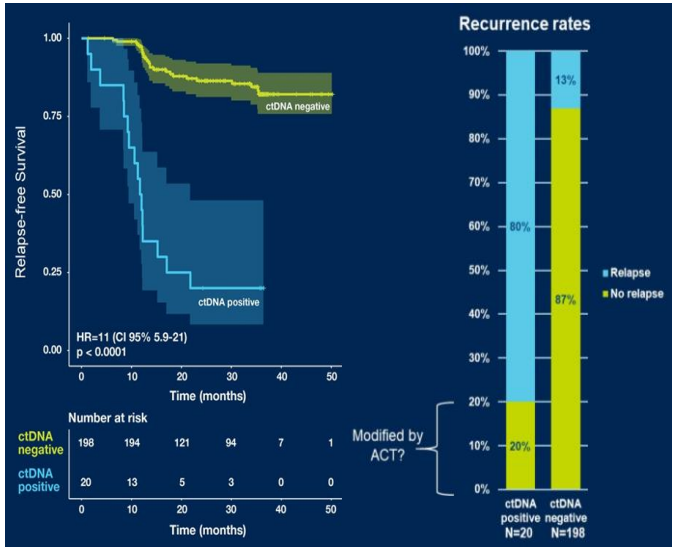


Tarazona N et al., ASCO 2020

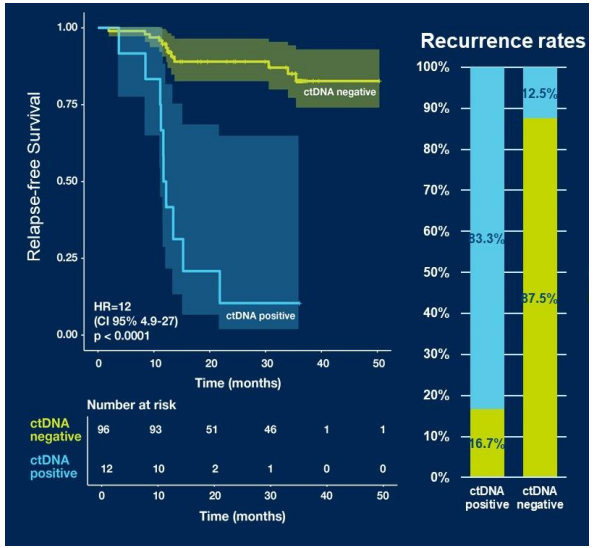
These studies utilised tumour informed analytical assays

Longitudinal ctDNA monitoring improves NPV of ctDNA in bowel cancer

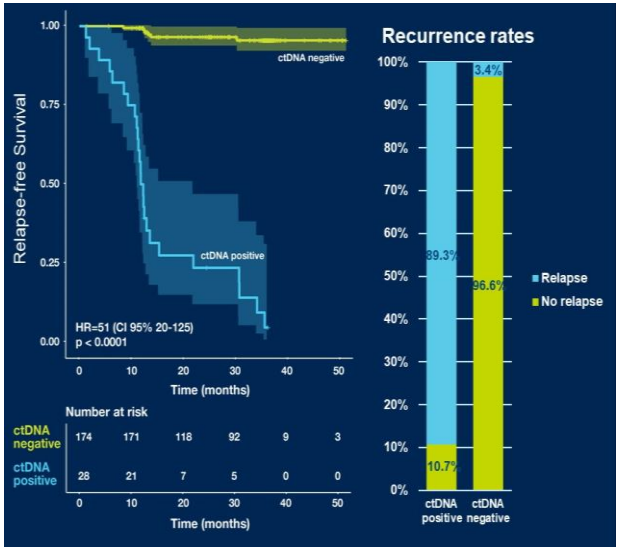
Single post-op ctDNA time point



Post ACT ctDNA



Longitudinal tracking



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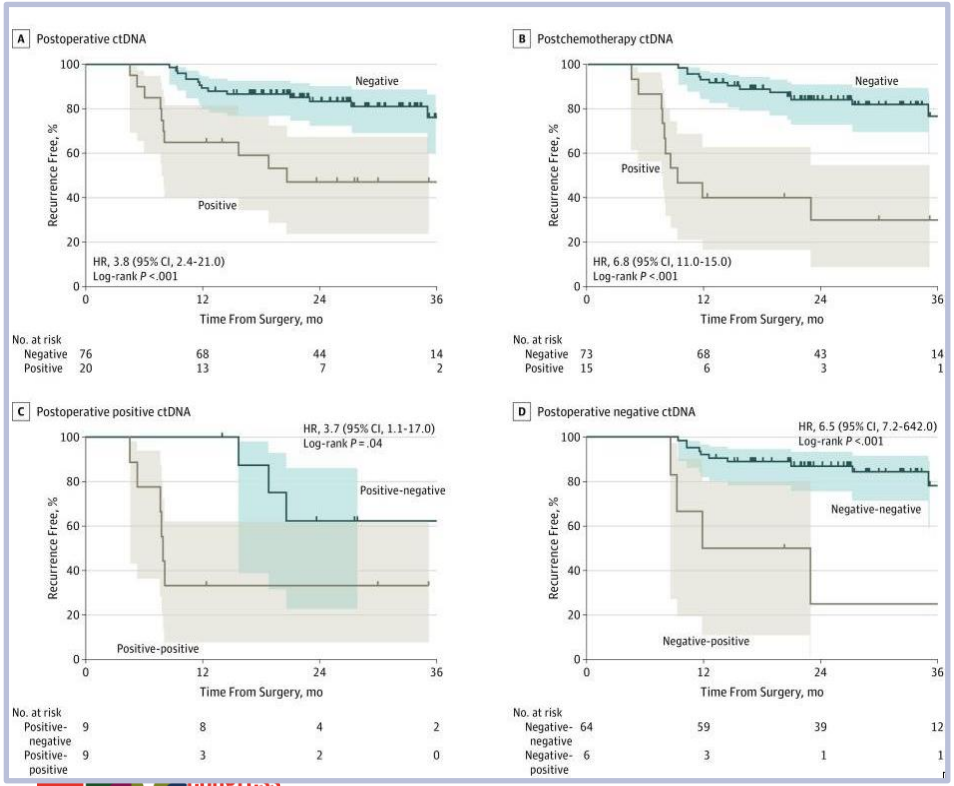
N=260: Pooled analysis Danish and Spanish cohorts, Signatera assay (tumour informed)

Vestmann et al ASCO GI 2021

Adjuvant chemotherapy can result in ctDNA clearance

ctDNA as marker of recurrence risk and benefit of ACT in stage III colon cancer N= 100



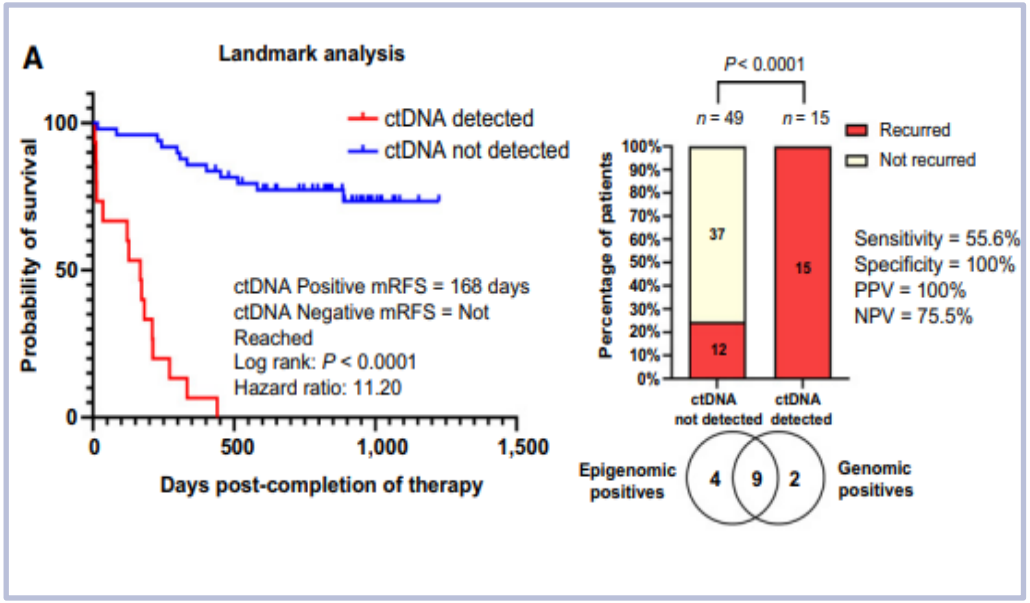
Post-surgery and post-chemotherapy ctDNA status	No. (%)
Completed at least 12 weeks of treatment (N = 78)	
Positive-Positive	7 (9)
Positive-Negative	9 (11)
Negative-Positive	6 (8)
Negative-Negative	56 (72)
Completed 24 weeks of treatment (N = 66)	
Positive-Positive	5 (7.5)
Positive-Negative	8 (12)
Negative-Positive	5 (7.5)
Negative-Negative	48 (73)

Studies suggest 20-50% ctDNA clearance. More data needed.

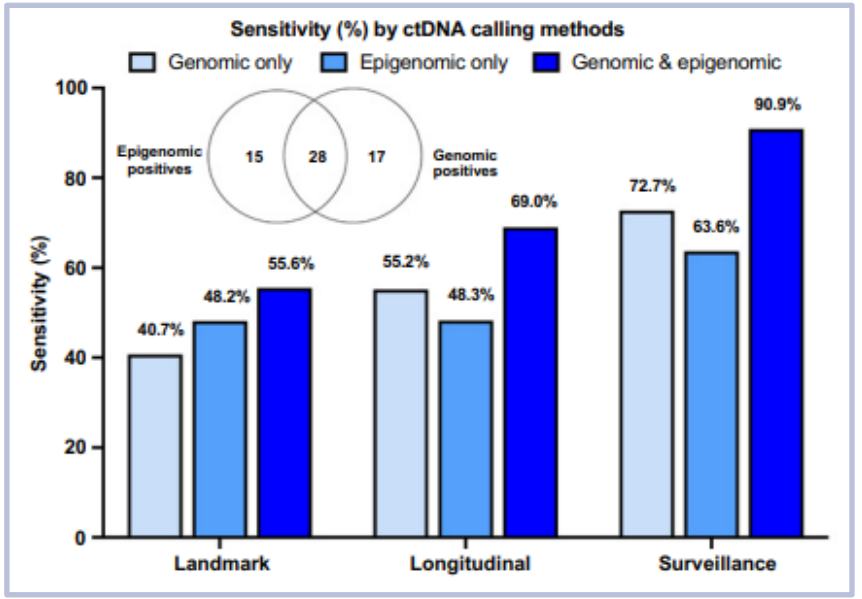
Tie et al., JAMA Oncol 2019

Plasma only MRD detection: Genomic + Methylation

RFS by 1 month post-op ctDNA n=70



Recurrence sensitivity of ctDNA detection by calling methods



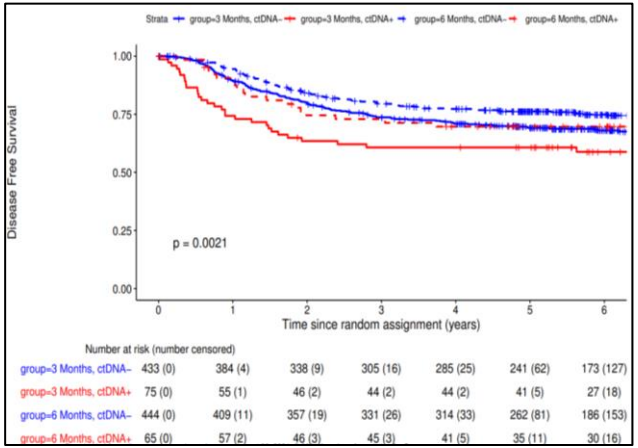
Guardant Reveal assay

Parikh A et al., Clinical Cancer Research 2021

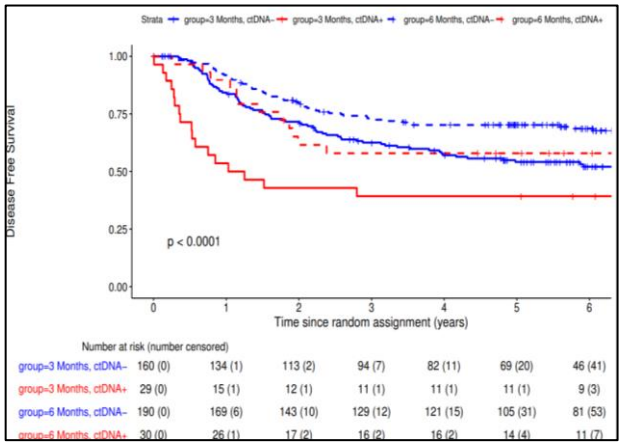
Plasma only ctDNA detection: Methylation alone – IDEA France

- Randomised N=2010 Stage III **N=1017** paired pre and post op ctDNA. Post-hoc analysis
- 90% had mFOLFOX6, 10% CAPOX
- Methylation markers WIF1 and NPY genes (ddPCR)
- Post-op ctDNA +ve 13.8%
- ctDNA independent prognostic variable in MVA (along with clinical risk stage)

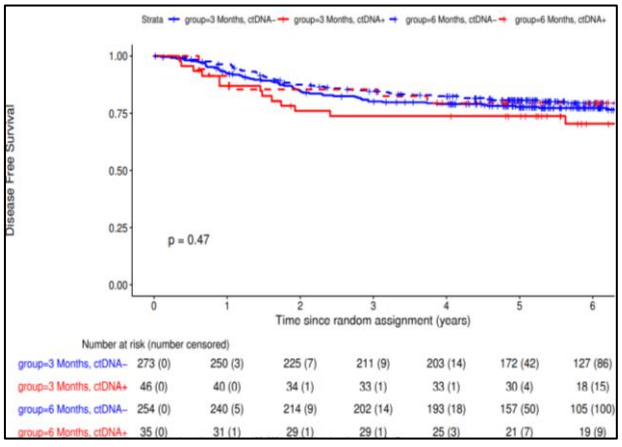
DFS by ctDNA and treatment arm



DFS by ctDNA in high risk stage III



DFS by ctDNA in low risk stage III



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Needs prospective validation. Unknown if this trend will be seen with CAPOX

Taieb J et al. CCR 2021

Selected observational studies - ctDNA in CRC MRD

Study	N	ctDNA assay	Colon or rectum	Stage	+ve ctDNA post-op	-ve ctDNA post-op	Adjuvant chemo	Lead time	Median FU
Swedish 2007-2013	58	SafeSeqS*	Both	I-III	13/58 (**22%**) 77% relapsed	45 (78%) 0% relapsed	31%	3 m	49 m
Spain 2015-2017	94	ddPCR*	Colon	I-III	14/69 (**20%**) 57% relapsed	55/69 (80%) 13% relapsed	37.2%	11.5m	24.7m
Denmark 2014-2017	130	Signatera bespoke NGS*	Both	I-III	10/94 (**11%**) 70% relapsed	84/94 (89%) 11.9% relapsed	62% +ve post chemo 4/58 (7%)	8.7m	12.5m
Australian 2011-2014	230	SafeSeqS*	Colon	II	14/178 (8%) 78.6% relapsed	164/178 (92%) 9.8% relapsed	23%	5m	27m (no chemo)
Australian 2014-2017	96	SafeSeqS*	Colon	III	20/96 (**21%**) ---	76/96 (79%) ---	100% +ve post chemo 15/88 (17%)	nr	28.9m
France IDEA	805	**metddPCR WIF1/NPY**	Colon	III	109/805 (**14%**) 64% relapsed	696/805 (86%) 17% relapsed	100%	nr	Min 24m
US 2021	103	**Guardant Reveal**	Both	I-IV	17/70 (**24%**)	49/70 (70%)	53.6%	**	Min 12m
UK (TRACC) 2016-present	122	Signatera bespoke NGS*	Both	II-III	14/107 (**13%**)	93/107 (87%)	**	**	**
US (BESPOKE) 2020-present	535	Signatera bespoke NGS*	Both	II-III	38/300 (**13%**)	262/300 (67%)	**	**	**
Japan (CIRCULATE) 2021	400	Signatera bespoke NGS*	Colon	I-IV	65/363 (**18%**)	298/363 (82%)	**	**	**

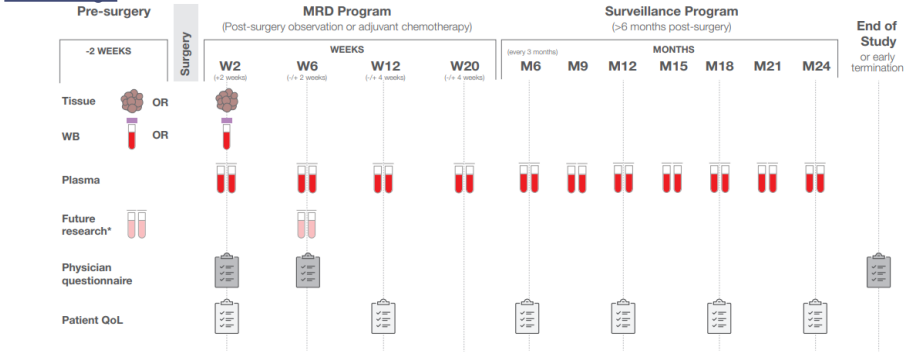
*Tumour informed assay
**Not reported

Ongoing observational studies: BESPOKE

Tumour-informed (Signatera) assessment of MRD in stage I-III CRC

NCT04264702

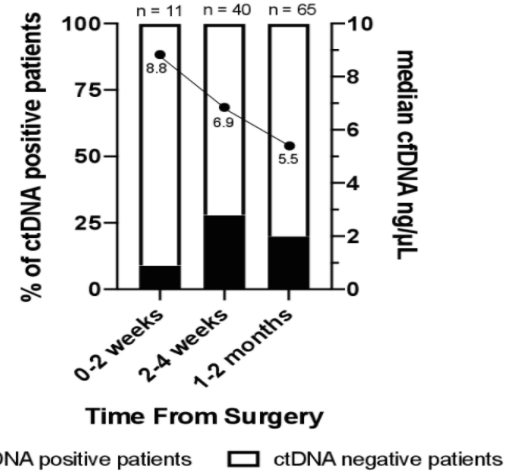
Trial design



MRD rates and ctDNA quantity in patient with locoregionally advanced (stage I-III) CRC (n=300)

Setting	MRD Rates	Quantity of ctDNA (MTM/mL)		
		Mean	Median	Range
Neoadjuvant setting	4/5 (80%)	21.04	11.69	0.24-60.55
Post-surgery MRD (Stage I)	2/15 (13%)	2.65	2.65	0.13-5.18
Post-surgery MRD (Stage II)	7/68 (10%)	78.5	1.33	0.31-543.77
Post-surgery MRD (Stage II, T3N0)	**3/53 (5.6%)**	1.63	1.74	1.33-1.84
Post-surgery MRD (Stage II, T4N0)	**4/14 (28.6%)**	136.24	0.44	0.31-543.77
Post-surgery MRD (Stage III)	19/71 (26.7%)	48.81	1.23	0.13-872.2
Post-surgery MRD (Stage III, low-risk: T1-3N1)	**3/32 (9.3%)**	2.43	0.40	0.23-6.67
Post-surgery MRD (Stage III, high-risk: T4, N1-2, T Any, N2)	**15/38 (39.4%)**	61.17	1.23	0.13-872.2
During Adjuvant Therapy	2/38 (5.2%)	1.37	1.37	0.27-2.47
Surveillance	4/103 (3.8%)	36.65	4.76	2.29-134.8

% of ctDNA positive vs. timing from surgery & cfDNA Stage I-III CRC patients



Also ctDNA informed study n=1000: Stage II & III colon & rectal

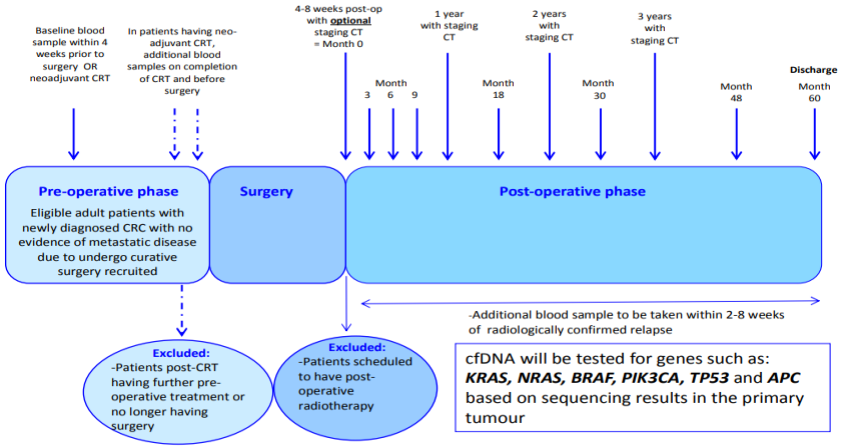
Iº end point = rate of recurrence, impact of ctDNA on ACT treatment detection

Kasi PM et al ASCO 2020

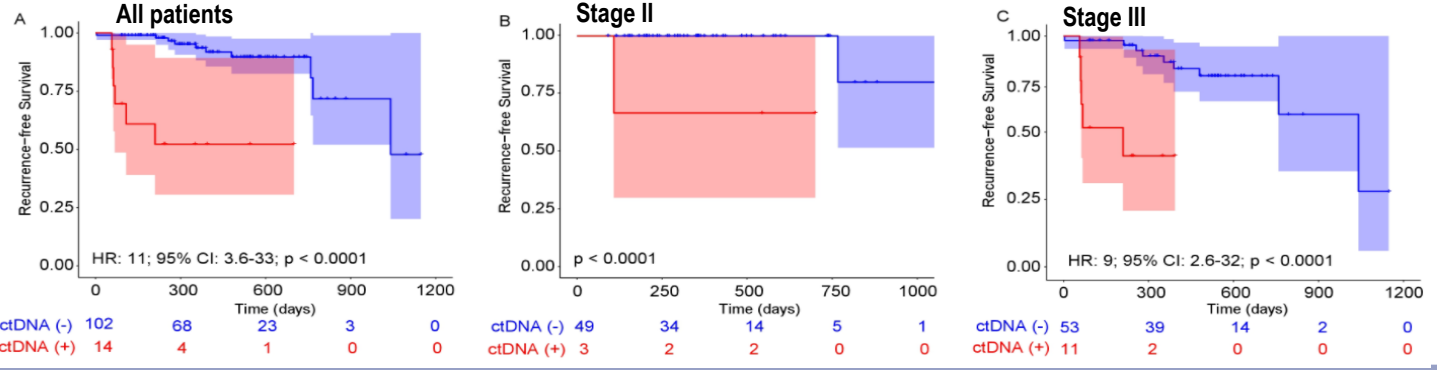
Ongoing observational studies: TRACC

Tumour-informed (Signatera) assessment of MRD in stage I-III CRC

NCT04050345



Setting	N=122	MRD detection rates at the first post-op time point	Recurrence rates	
			MRDpos	MRDneg
Stage II (Low risk)		1/31 (3.2%)	0/1 (0%)	0/30 (0%)
Stage II (High risk)		2/15 (13.3%)	1/2(50%)	0/13 (0%)
Stage III (Low risk)		3/20 (15%)	0/3 (0%)	2/17 (11.7%)
Stage III (High risk)		7/19 (36.8%)	4/7 (57.1%)	3/12 (25%)
TMT group		1/22 (4.5%)	1/1 (100%)	3/21 (14.2%)



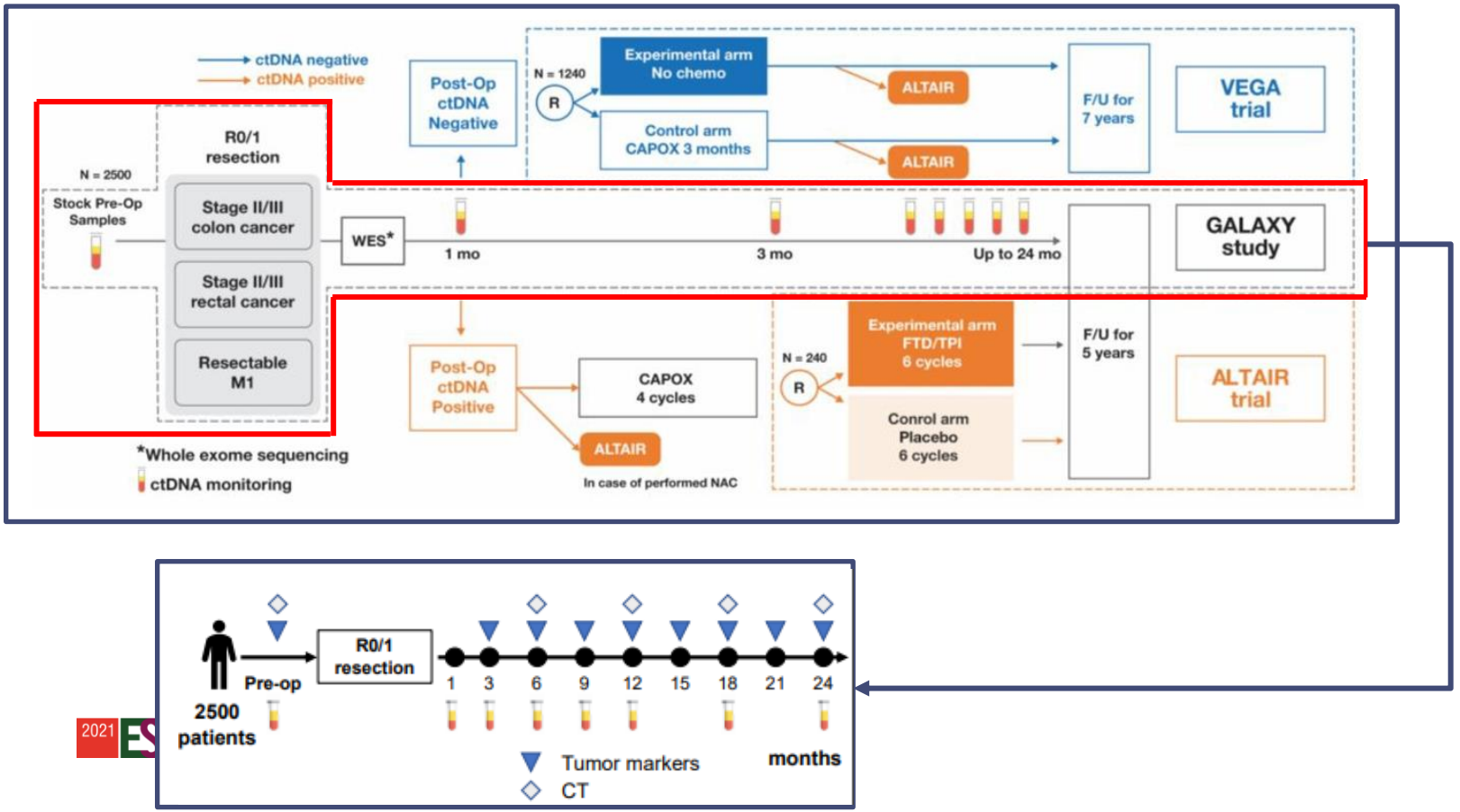
Aug 2021: 938/1000 patients recruited

Anandappa et al ASCO GI 2021

Ongoing observational studies: GALAXY

Part of CIRCULATE JAPAN: Stage II and III CRC and stage IV resectable

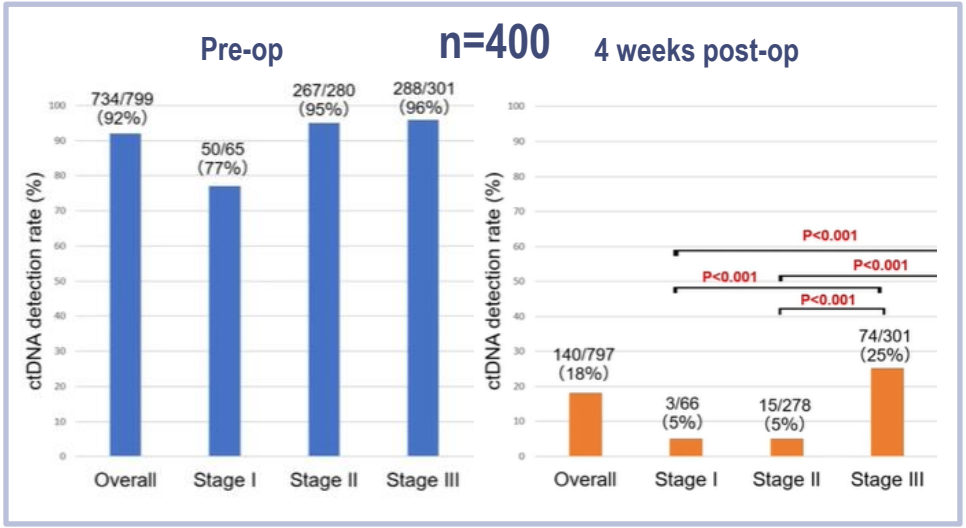
UMIN000039205

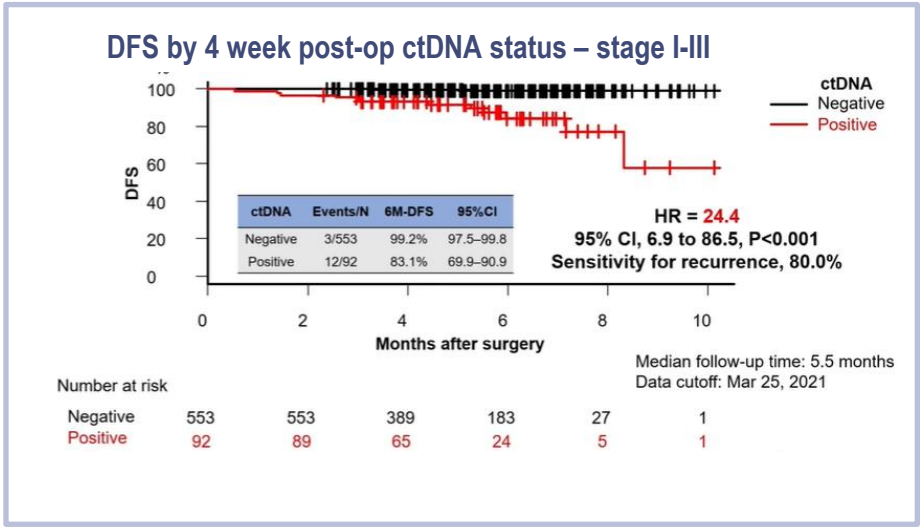


Yukami et al ASCO 2021

GALAXY – preliminary results

Tumour-informed (Signatera) assessment of MRD in stage I-III CRC





Multi-variate analysis for recurrence – stage I-III (n=107)

Covariates	HR	95% CI	P
Post-op-4w ctDNA positive vs. negative	**17.1**	**4.6–63.1**	**<0.001**
N1-2 vs. N0	7.1	0.9–57.7	0.06
RAS mt vs. wt	1.1	0.3–3.3	0.91
BRAF mt vs. wt	3.5	0.7–17.6	0.13
Gender Female vs. Male	1.5	0.5–4.2	0.46
PS 1 vs 0	1.4	0.3–6.5	0.65

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Yukami et al ASCO 2021

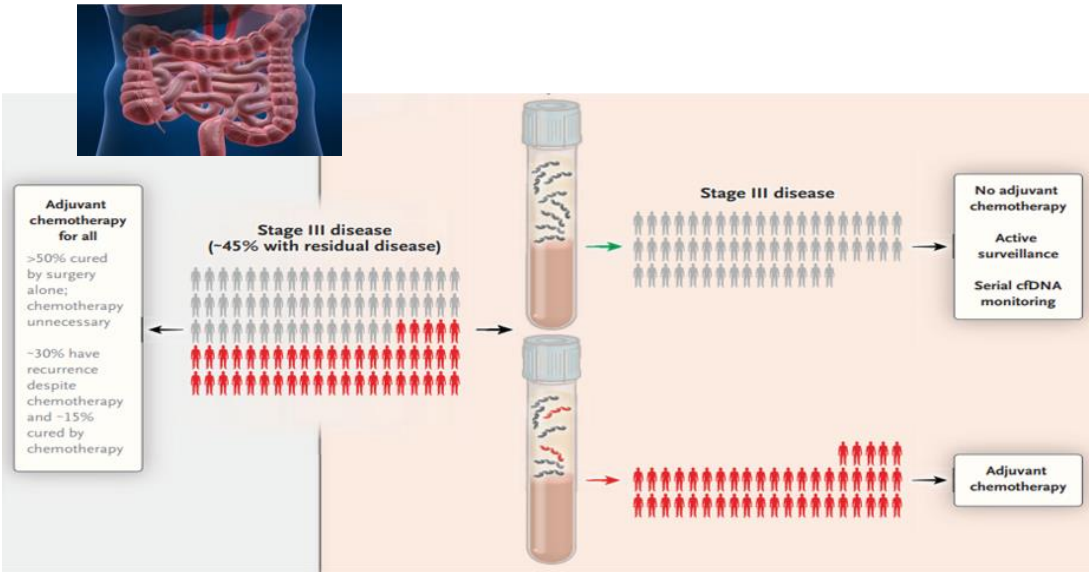
Can ctDNA inform adjuvant chemotherapy decisions?

Who can avoid it/ who should have it?

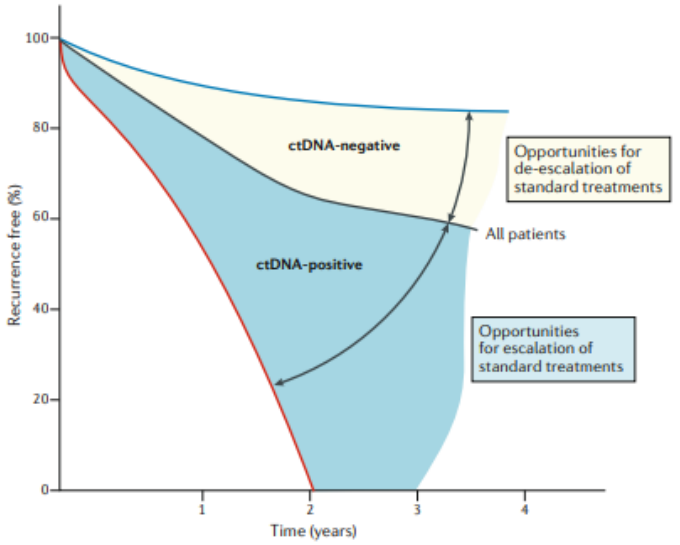
When should they start it?

What should they have?

How long should they have it for?



Corcoran, R., et al NEJM 2018



Dasari, A., et al. Nat Rev Clin Oncol. 2020

Colon cancer: selected randomised studies of ctDNA guided adjuvant therapy

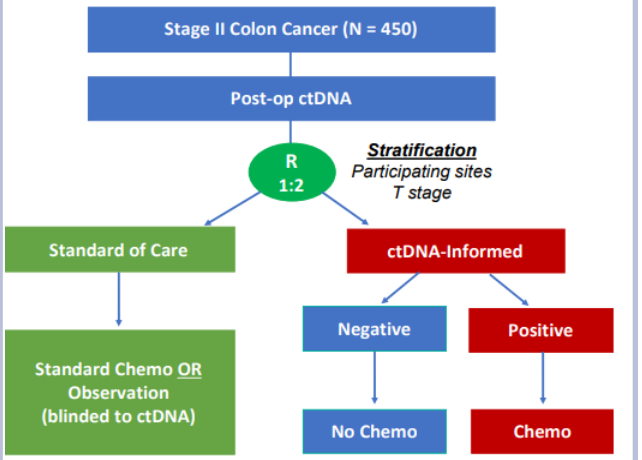
Study	Stage	N	Phase	Assay	Study Arms	1^0 endpoint
STAGE II						
IMPROVE-IT (Denmark)	I/II	64	2	T-NGS/ddPCR	Obs vs ACT	DFS
COBRA (US/Canada)	IIA	1408	2/3	REVEAL	SoC vs ctDNA guided ACT escalation if +ve	ctDNA clearance & RFS
DYNAMIC II (Australia)	II	450	2/3	Safe-Seq	SoC vs ctDNA guided ACT escalation if +ve	RFS
CIRCULATE (Germany)	II	4812	3	Tum-informed	SoC vs ctDNA guided ACT escalation if +ve	3 yr DFS
CIRCULATE (France)	II	1980	3	Methylated markers	Obs vs ctDNA guided ACT escalation if +ve	DFS/RFS
MEDOC-cREATE (Netherlands)	II	1320	3	PDGx elio™	Obs vs ctDNA guided ACT escalation if +ve	DFS/RFS
STAGE II/III						
CIRCULATE (Spain)	II/III	1000	2/3	T-NGS/ddPCR	Escalate to FOLFOXIRI if ctDNA +ve	DFS
PEGASUS (Italy/Spain)	II/III	140	2/3	REVEAL	ctDNA guided ACT (de/escalation)	No. of post-surgery and post-adjuvant false -ve cases after a double ctDNA -ve detection
VEGA (Japan)	II/III	1240	2/3	Signatera	SoC vs ctDNA guided ACT de-escalation	DFS/RFS
TRACC (UK)	II/III	1621	3	T-NGS/ddPCR	SoC vs ctDNA guided ACT de-escalation	DFS
ALTAIR (Japan)	II-IV	240	3	Signatera	Escalation if ctDNA +ve	DFS/RFS
DYNAMIC III (Australia)	III	1000	2/3	Safe-Seq		DFS
CIRCULATE (US) NRG GI008	III	1500	2/3	Signatera	SoC vs obs (if ctDNA-ve). Escalate if ctDNA +ve during surveillance	DFS/ctDNA status

Stage II Colon Cancer: Ongoing ctDNA guided adjuvant studies

DYNAMIC II N=450

Stage II colon

Iº end point = no. of pts given ACT and RFS



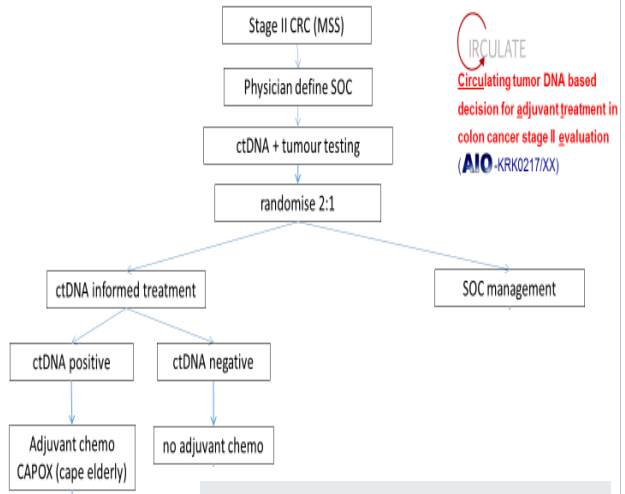
ACTRN12615000381583

Tumour informed: Safe-Seq

CIRCULATE (Germany)

Stage II colon N=4812

Iº end point = 3y DFS



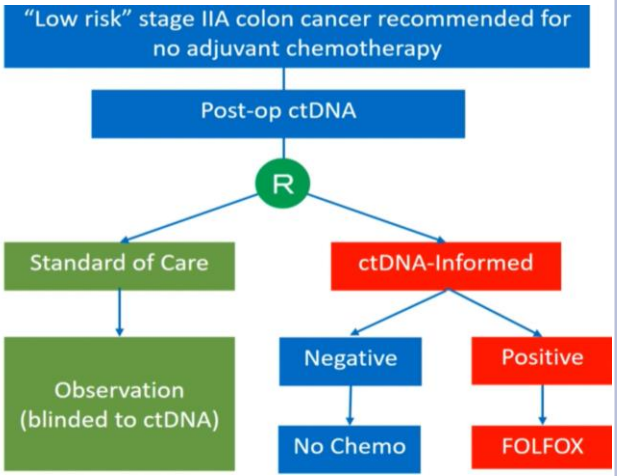
NCT04089631

Tumour informed: T-NGS/ddPCR

COBRA N=1408

Stage II colon

Iº end point = ctDNA clearance and RFS



NCT04068103

Plasma-only: REVEAL

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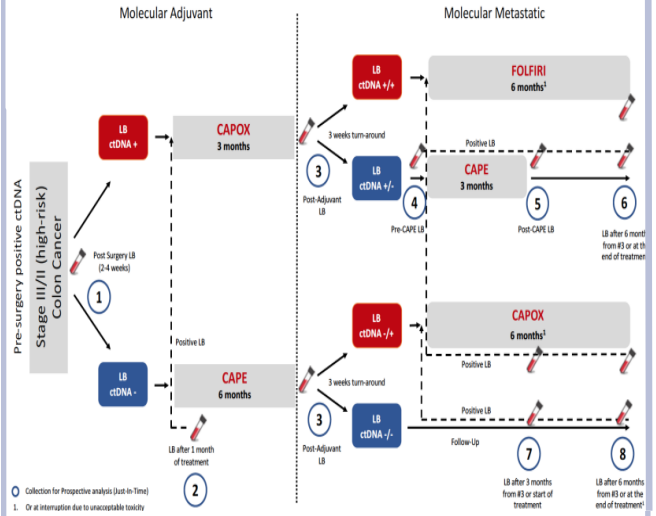
Stage III/high risk stage II CRC: ongoing ctDNA informed studies

PEGASUS N=140

High risk stage II & III colon

I° end point = No. of post-surgery and post-adjuvant false -ve cases after a double ctDNA -ve detection



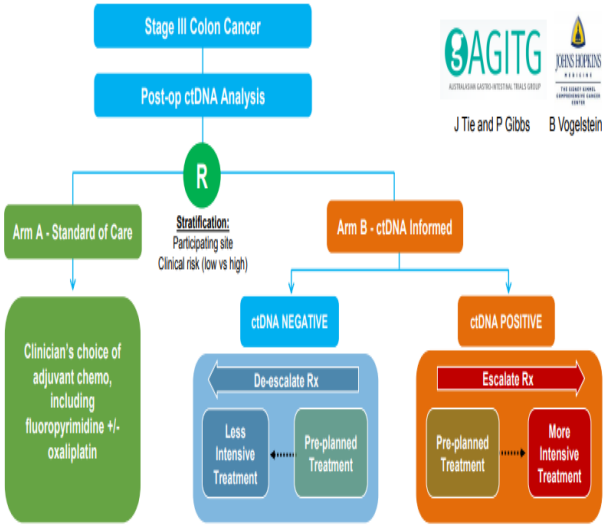
NCT04259944

Plasma-only: REVEAL

DYNAMIC III N=450

Stage III colon

I° end point = RFS, OS



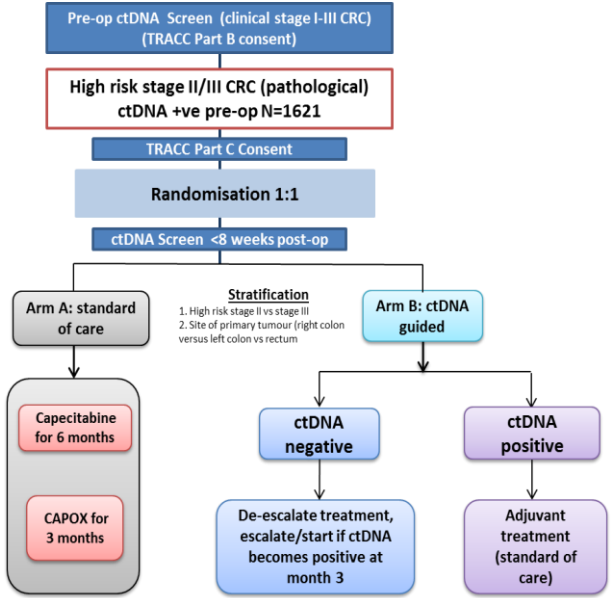
ACTRN12617001566325

Tumour informed: Safe-Seq

TRACC Interventional N=1621

High risk stage II & III colon & rectal

I° end point = 3 year DFS



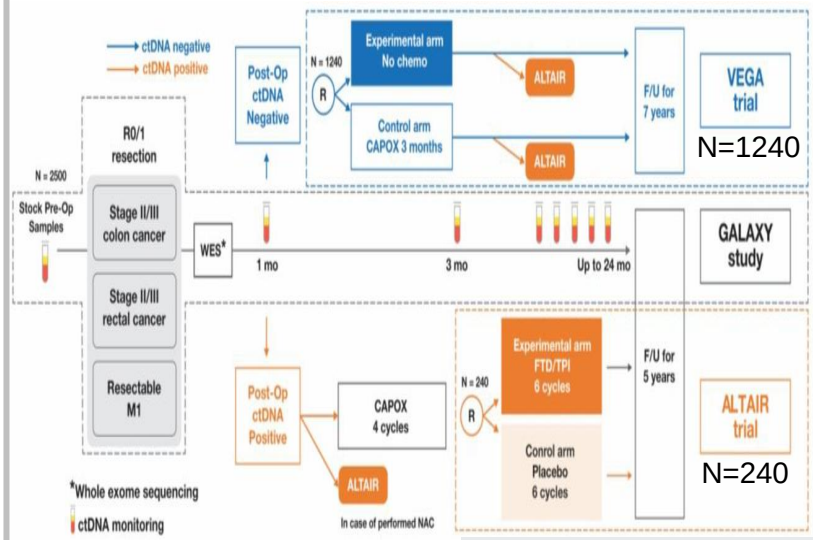
NCT04050345

Tumour informed: T-NGS/ddPCR

Stage III/high risk stage II CRC: ongoing ctDNA informed studies

CIRCULATE JAPAN: VEGA & ALTAIR

High risk stage II & III colon
Iº end point = DFS/RFS



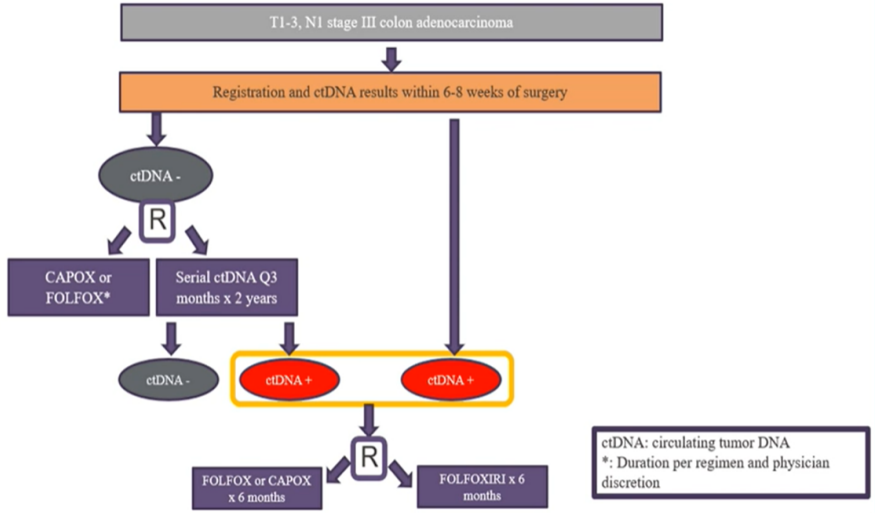
UMIN000039205

Tumour informed: Siganatera

CIRCULATE US: NRG GI008

N=1500

Low risk stage III
Iº end point = DFS/ctDNA status



Tumour informed: Siganatera

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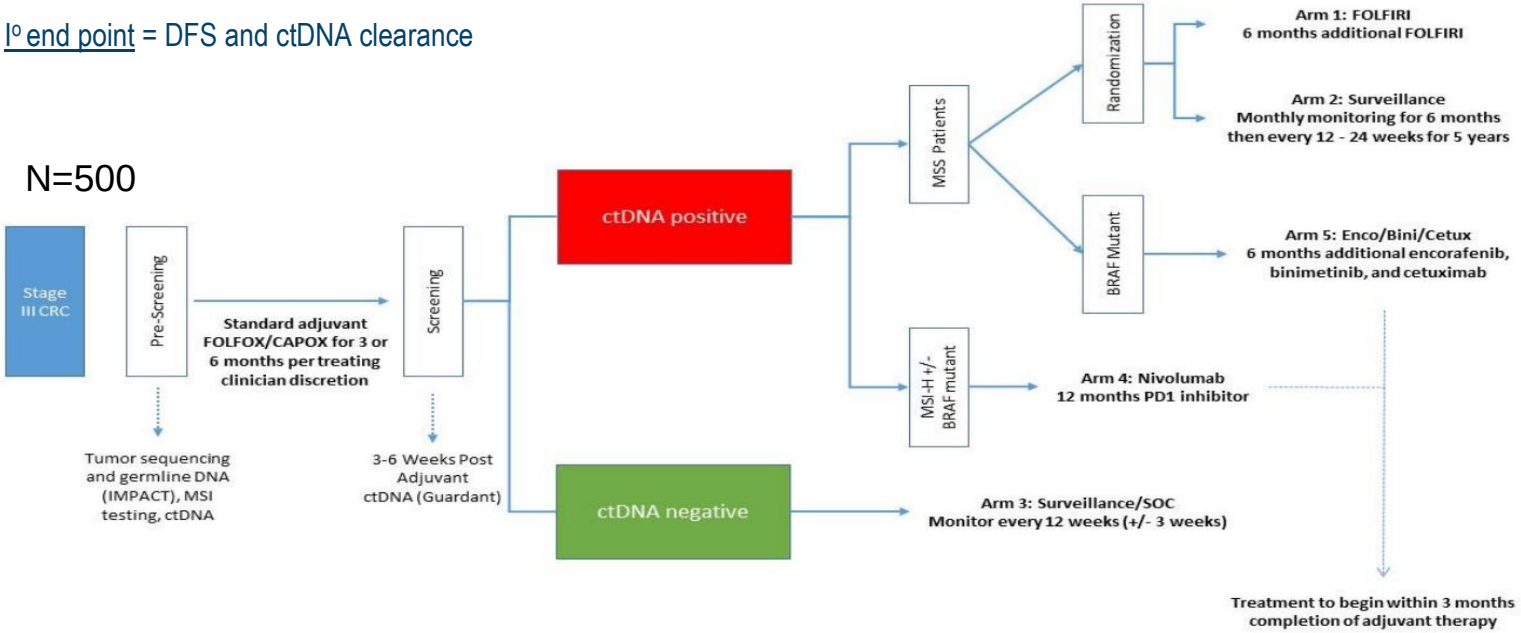
Escalation of therapy post ACT in ctDNA+ve

ACT-3 Trial

Plasma-only: REVEAL assay

Iº end point = DFS and ctDNA clearance

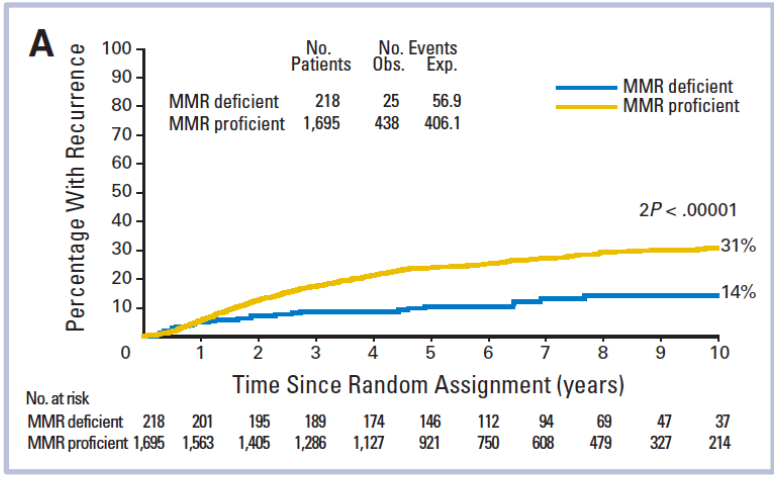
N=500



NCT03803553

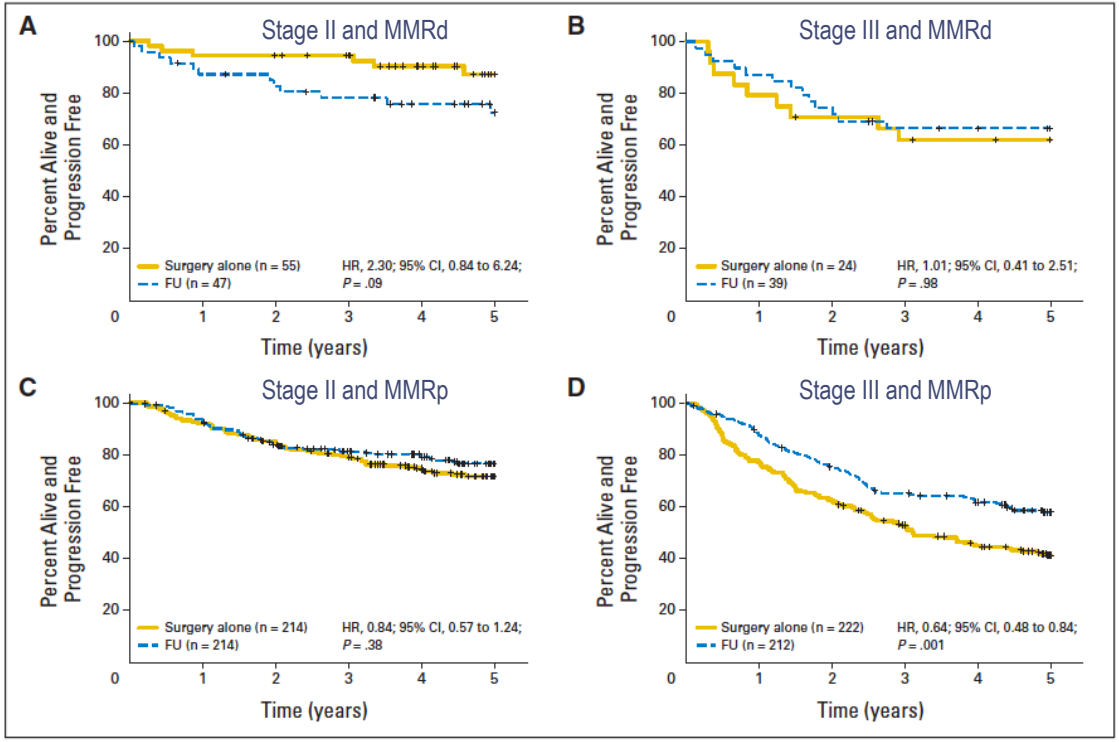
Tissue markers: MMRd and adjuvant chemotherapy

QUASAR – Lower risk of recurrence in MMRd patients n=1913



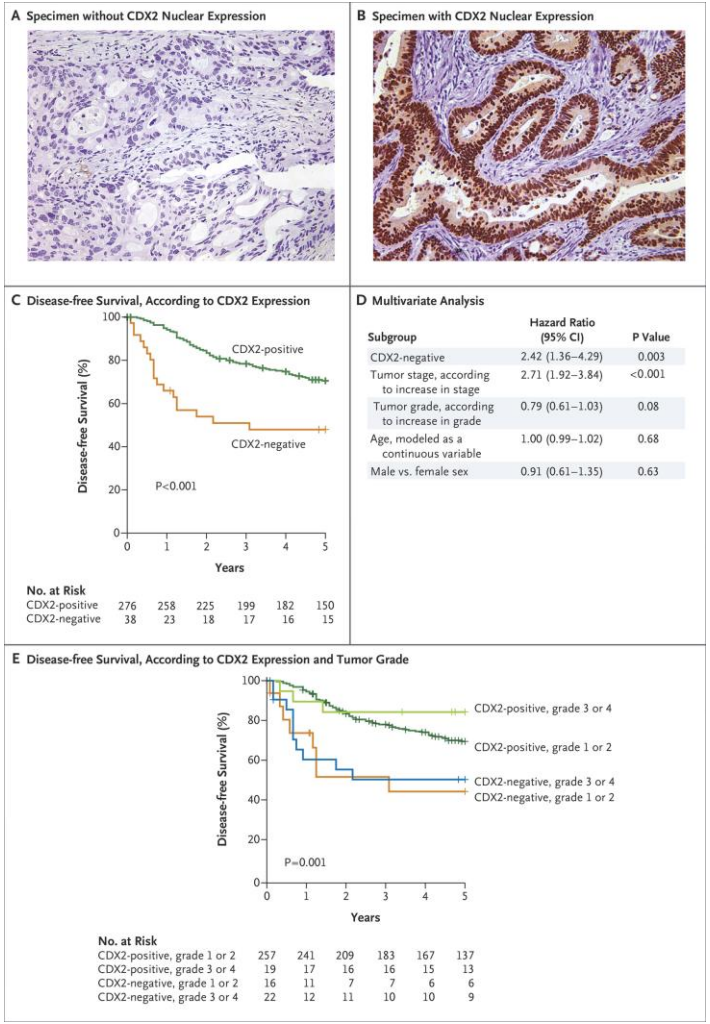
Hutchins, G., et al JCO 2011

ACT in Stage II MMRd is detrimental n=1027



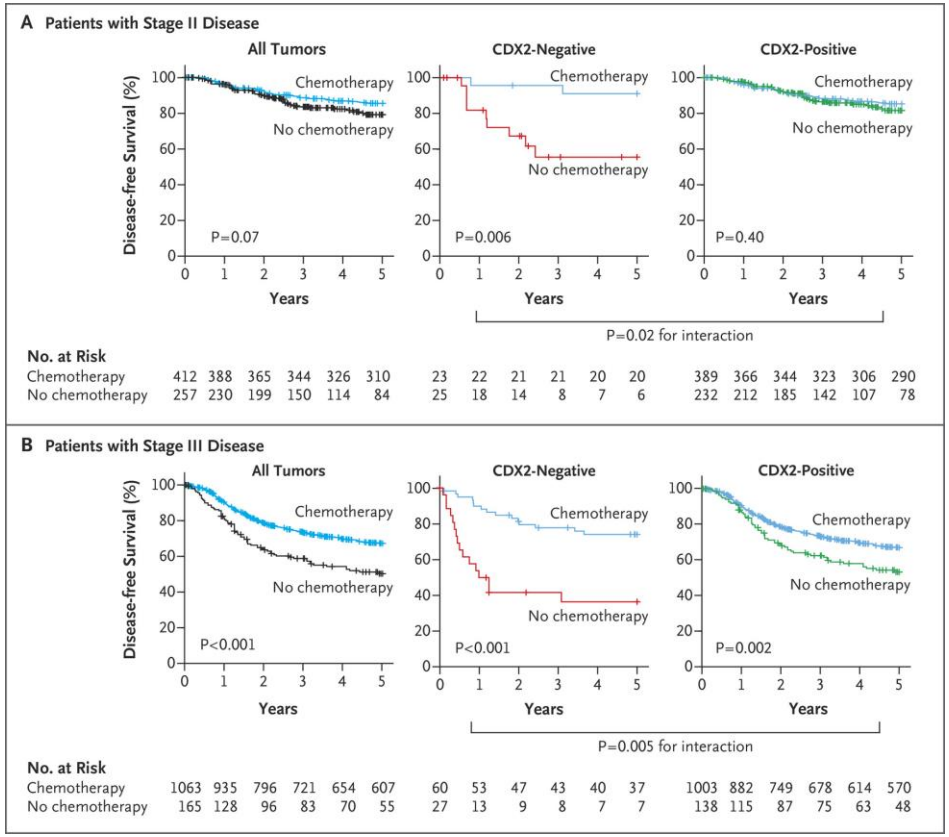
Sargent, D., et al JCO 2010

CDX2 protein expression and DFS



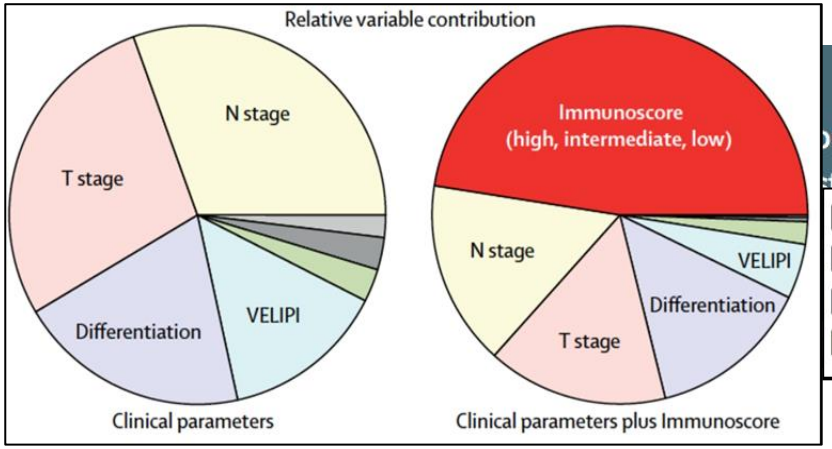
Tissue Markers: CDX2 expression

CDX2 protein expression and benefit from chemotherapy



Dalerba, P., et al. NEJM 2016

Immunoscore



Tumor histopathology

UICC-TNM Staging system

Tumor infiltrating immune cells

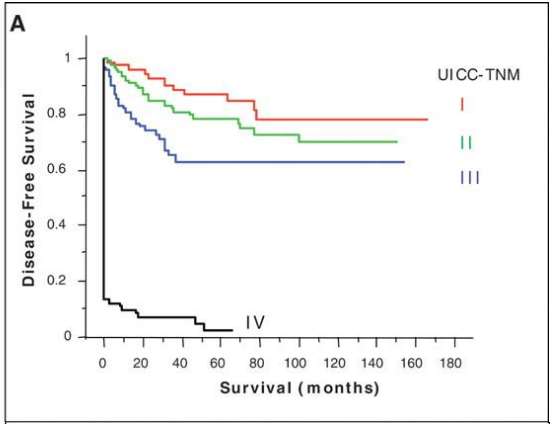
$CD3_{CT}CD3_{IM}$ evaluation

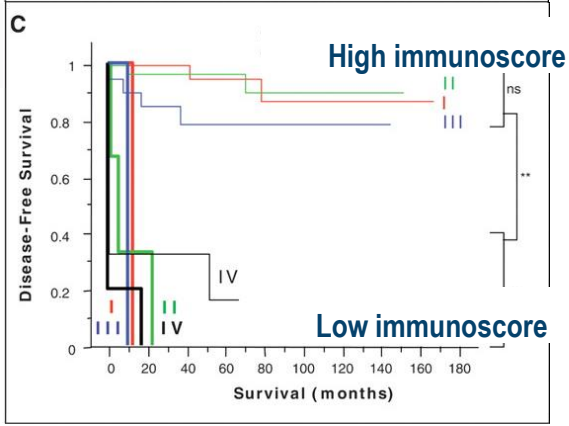
plus

$CD45RO_{CT}CD45RO_{IM}$ evaluation

- Sidedness
- Mucinous (colloid)
- MSI
- Sex

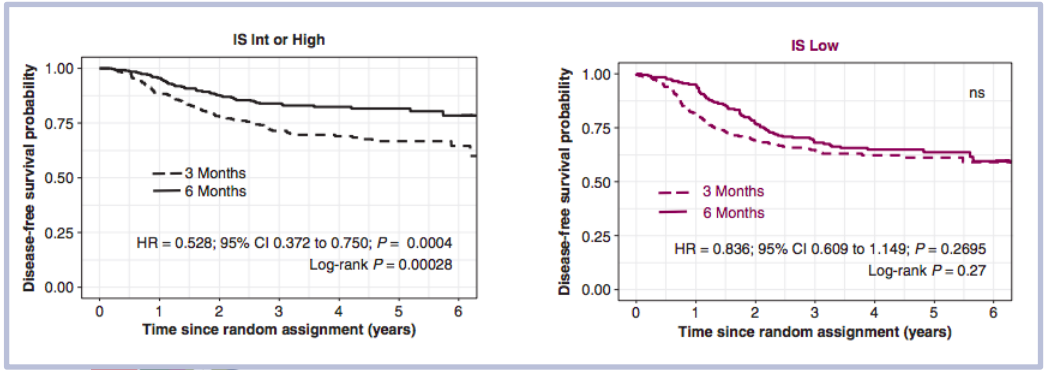
Immunoscore predicts survival regardless of TNM





Galon, J, et al., Science 2006

High Immunoscore predicts response to 6m FOLFOX in IDEA France

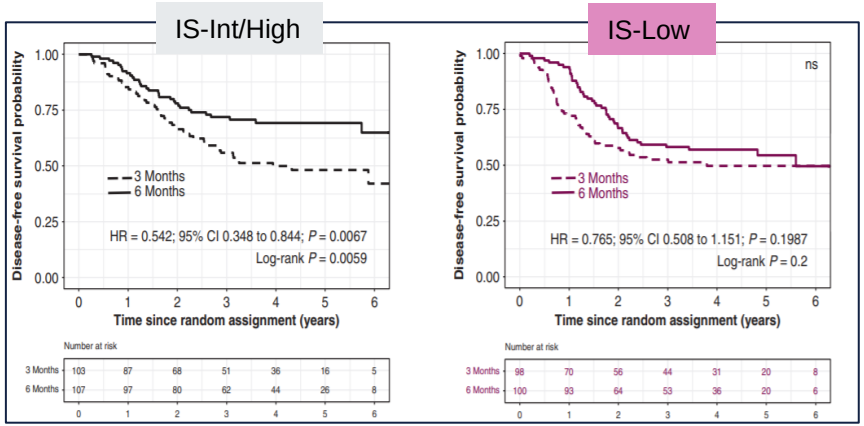


Pages, F, et al., Annals Onc 2020

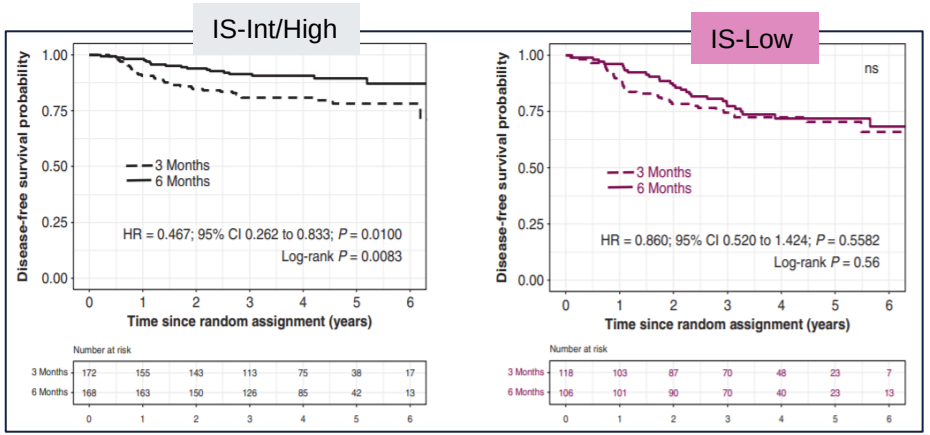
Immunoscore and 3 versus 6 m FOLFOX -IDEA France Stage III

- Randomised N=2010**, N=1322** samples available for immunoscore (IS): IS-Low versus IS intermediate/high
- 90% had mFOLFOX6, 10% CAPOX
- IS-Low 44% of study population

DFS by IS in high risk stage III (T4 and/or N2) ~40%



DFS by IS in low risk stage III (T1-3, N1) ~60%



- IS-Int/High appeared benefited from 6 m FOLFOX in High risk stage III. Unknown if this trend applies to CAPOX
- More data from other IDEA studies required re IS and duration of chemotherapy

2021 ESMO congress

Pages, F, et al., Annals Onc 2020

Conclusions

- Several prognostic tools some of which could potentially select patients for ACT: blood and the tissue
- Observational studies and translational analyses of IDEA studies will provide more insights:
  Who, how, how long, low risk vs high risk, relationship with other prognostic variables
- Integrating blood and tissue biomarkers in prospective studies
- Practice changing implications future studies – more precise selection of patients for adjuvant treatment
  - De-escalation of treatment: Save unnecessary treatment/toxicity, Save healthcare resources
  - Escalation of treatment: Improve cure rates

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