ctDNA in Adjuvant and Metastatic Therapy for GI Cancers: Prime Time?

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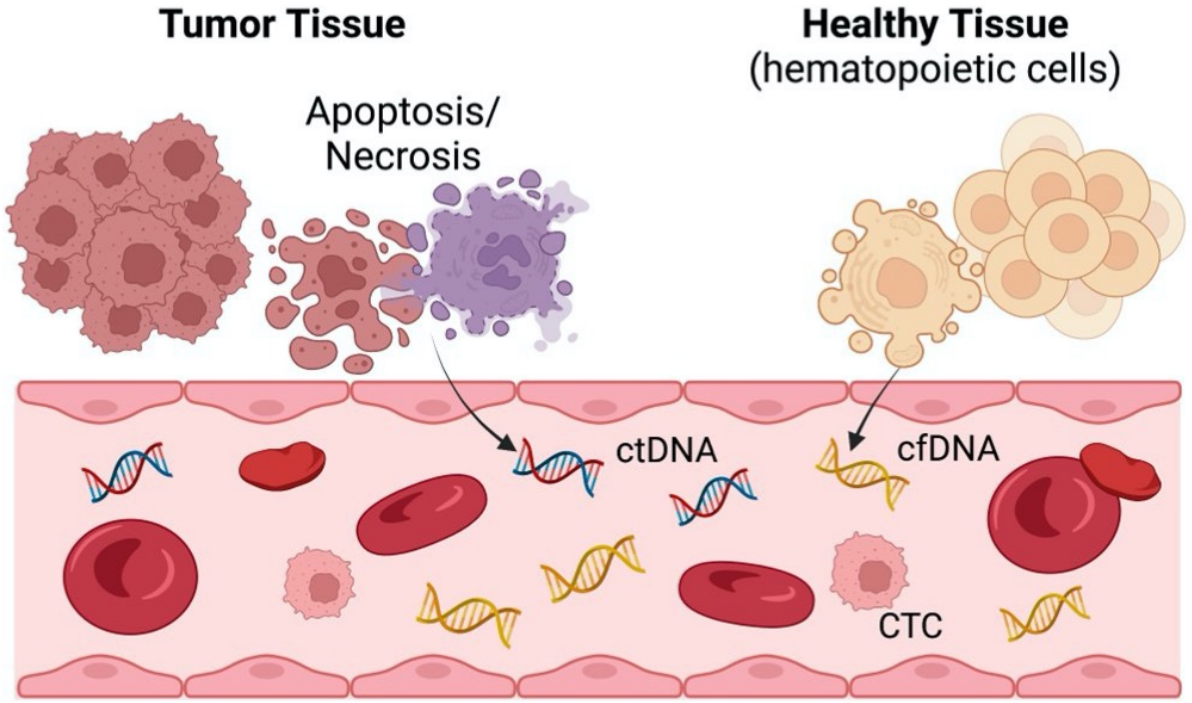
Learning Objectives:

- Brief primer on ctDNA
- Discuss the expanding role of ctDNA in the management of patients with GI malignancies
- Highlight ctDNA as an emerging biomarker in clinical trials

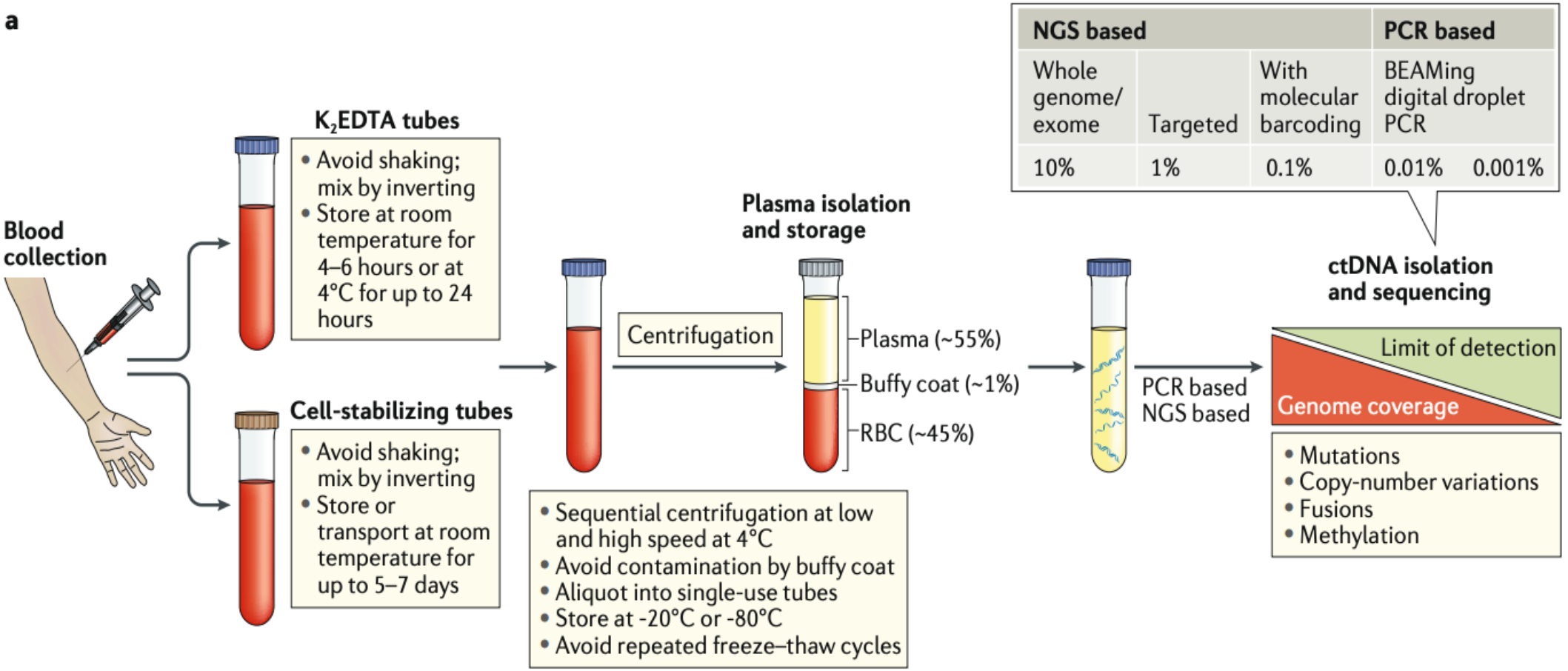
What is Circulating Tumor DNA?

- Cell-free DNA (cfDNA) = small DNA fragments (160-200 bp) in circulation
- Released into bloodstream via cell death
- Healthy adults - cfDNA mainly from hematopoietic cells
- **ctDNA** = small DNA fragments in circulation released from tumors in cancer patients
- ctDNA shorter fragment (143-145bp) vs normal cfDNA (~ 166bp)
- Short half-life ~ 2hrs → dynamic tracking of tumor burden



Courtesy – Jeanine Tie, MD

Introduction

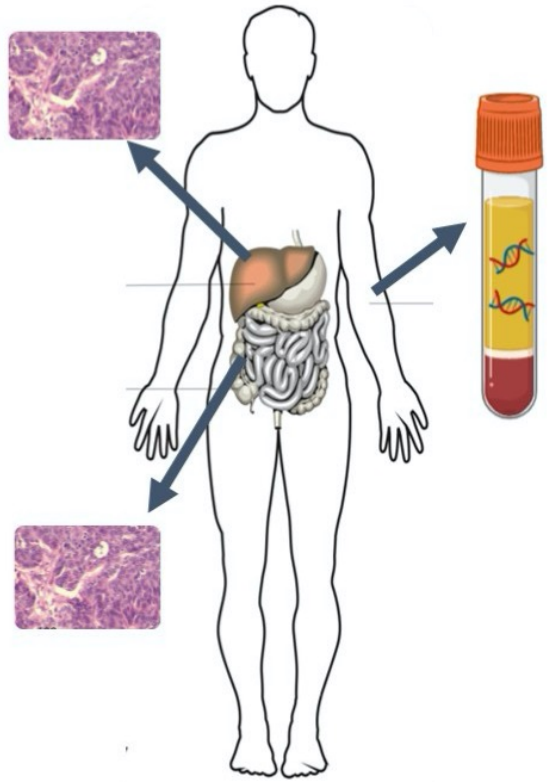


Dasari, A et al. Nat Rev Clin Oncol 17, 757–770 (2020)

ctDNA versus Tumor Tissue Testing

Tumor Tissue Assay

- Invasive, biopsy risk, serial biopsy more difficult
- Represent one small tumor region
- Uses existing tissue processing approaches
- No assessment of tumor load



ctDNA Assay

- Less invasive, easy serial testing
- More representative of whole tumor or all metastatic sites
- Requires special processing or use cell stabilizing tubes
- Quantitative analysis correlates with tumor load

Courtesy – Jeanine Tie, MD

Introduction

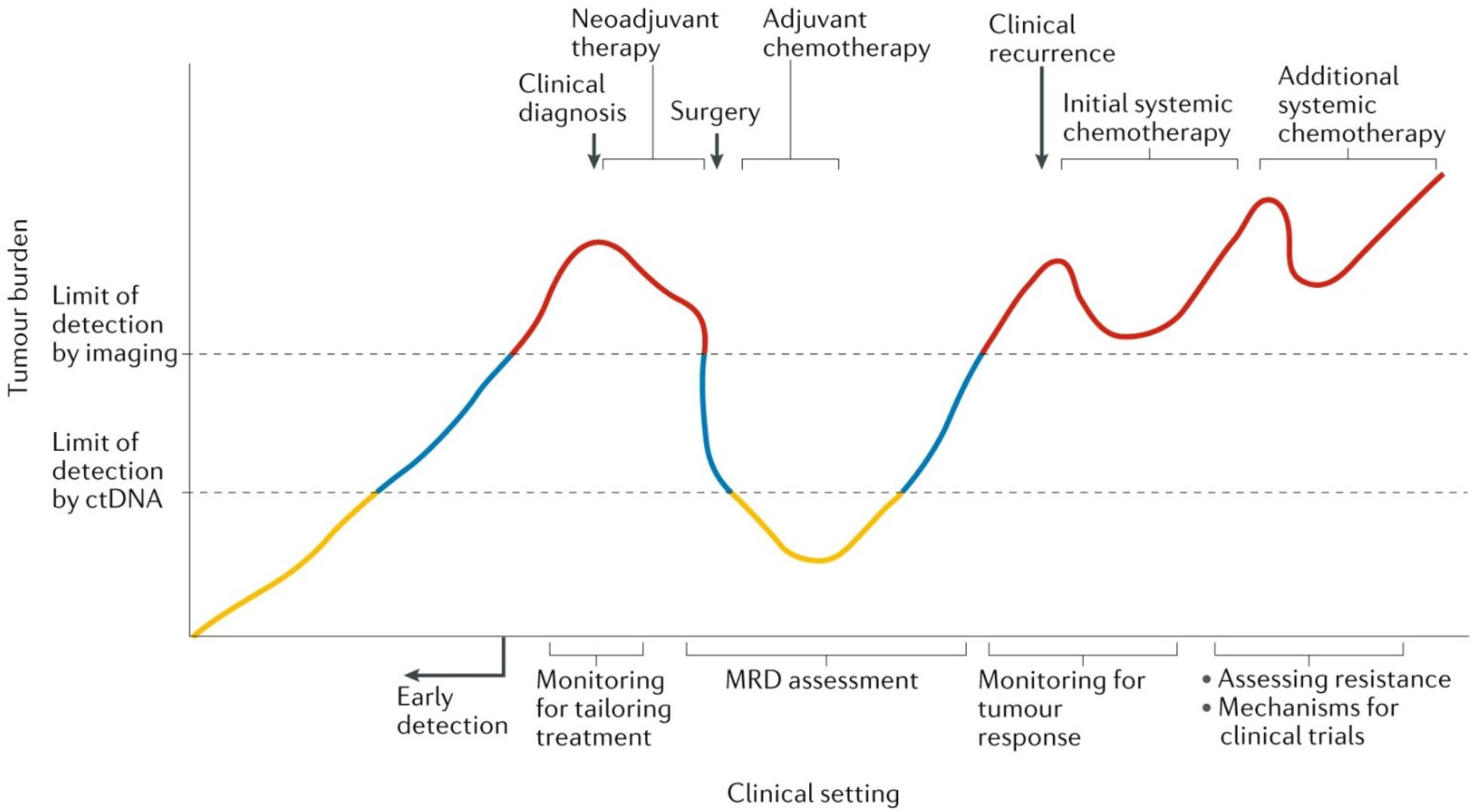
Liquid biopsy and other emerging ctDNA technologies represent a paradigm shift in cancer diagnostics because they allow for

- Detection of minimal residual disease (MRD) in patients with early-stage disease
- Improved risk stratification
- Captured tumor heterogeneity and genomic evolution
- Enhanced ctDNA-guided adjuvant and palliative cancer therapy

Alese OB, Cook N, Ortega-Franco A, Ulanja MB, Tan L, Tie J. Am Soc Clin Oncol Educ Book. 2022 Apr;42:1-20.

Introduction

From: ctDNA applications and integration in colorectal cancer: an NCI Colon and Rectal–Anal Task Forces whitepaper



Dasari, A et al. Nat Rev Clin Oncol 17, 757–770 (2020)

Colorectal Cancer - Adjuvant

- *Relatively low survival benefit and the risk of substantial adverse effects with adjuvant chemotherapy*
- *Imperative to identify which individuals require adjuvant chemotherapy versus close monitoring alone*

Study	Patient population	Blood Sample Collection Time Points	Key findings
Tie et al 2016 [1]	Resected stage II CC, n=230	4 - 10 weeks postop, then every 3 months for 2 years	--ACT associated with poor RFS if ctDNA+; median interval between ctDNA detection and radiologic recurrence - 5.5 months
Tie et al 2019[2]	Stage III CC, n=96	4 - 10 weeks postop (pre-ACT) and within 6 weeks of the final cycle of chemotherapy.	--Post chemotherapy ctDNA+ with 3-year RFI of 30%; 77% with undetectable ctDNA. -Postsurgical ctDNA status independently associated with RFI
Reinert et al 2019[3]	Stages I to III CRC, n=96	Pre-op, 30 days post-op, and every 3rd month for 3 years	--30-day postop ctDNA+ was 7x more likely to relapse --Immediate post ACT ctDNA+ was 17X more likely to relapse --All 7 patients ctDNA+ after ACT relapsed --Surveillance ctDNA+ > 40 x likely to relapse
Tarazona et al 2019[4]	Localized CC, n=150	At baseline, 6-8 weeks after surgery, and every 4 months for up to 5 years	--Postop and follow up ctDNA+ associated with worse DFS --ctDNA + post-ACT associated with early relapse, --ctDNA+ preceded radiological recurrence with median lead time of 11.5 months
Taieb et al 2019[5]	Stage III CC, n=805	N/A	--ACT for 6 months was superior to 3 months for both ctDNA– and ctDNA+ patients --ctDNA+ ACT x 6 months similar prognosis with ctDNA- ACT x 3 months

Alese OB, Cook N, Ortega-Franco A, Ulanja MB, Tan L, Tie J. Am Soc Clin Oncol Educ Book. 2022 Apr;42:1-20.

Colorectal Cancer - Adjuvant

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JUNE 16, 2022 VOL. 386 NO. 24

Circulating Tumor DNA Analysis Guiding Adjuvant Therapy in Stage II Colon Cancer

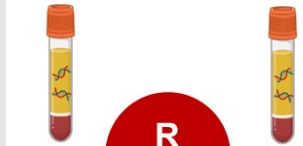
DYNAMIC Study Design

ACTRN12615000381583

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

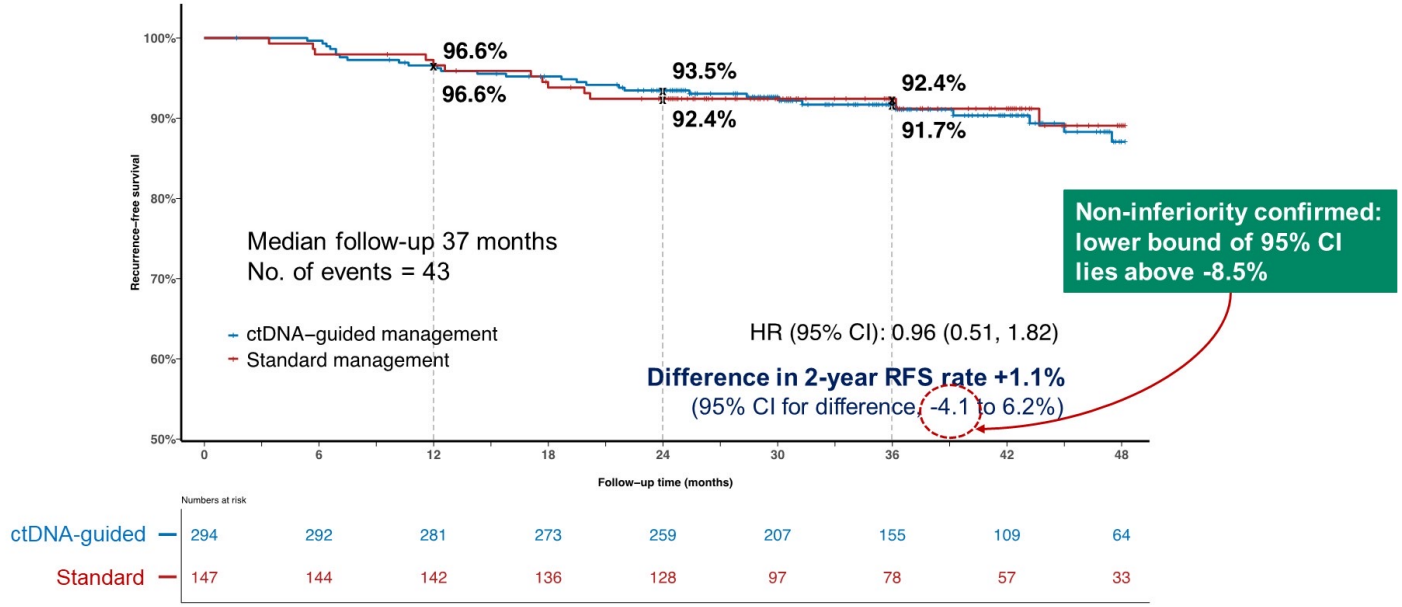
Secondary
- RFS by ctDNA status for ctDNA-guided arm
- TTR
- OS

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

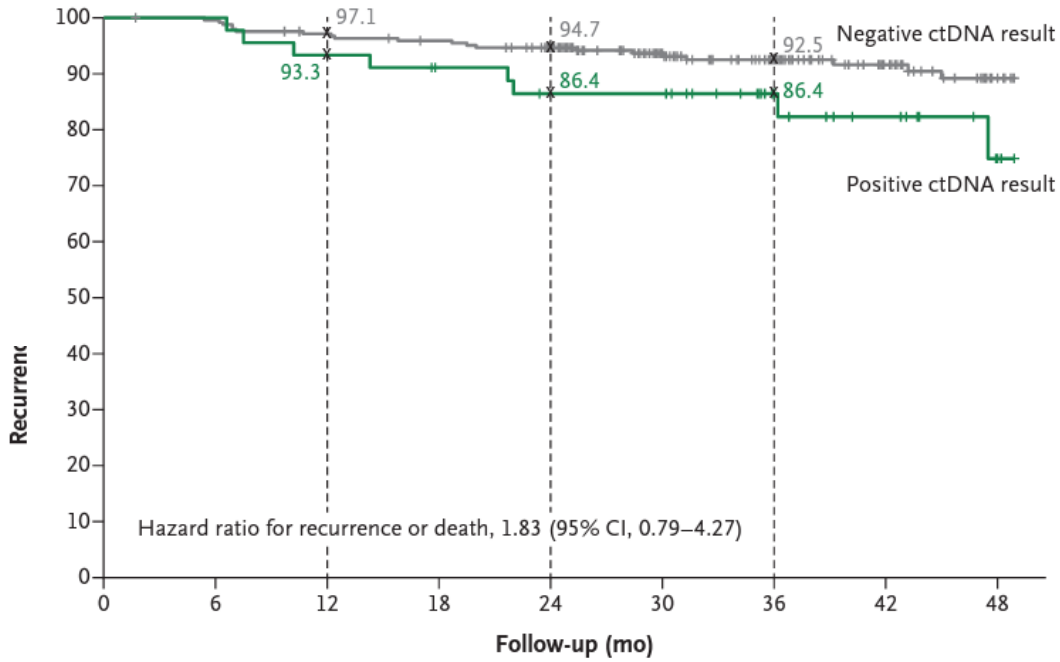
Surveillance:
- CEA → 3-monthly for 24M, then 6-monthly for 36M
- CT C/A/P → 6-monthly for 24M, then at 36M

Tie J et al. *N Engl J Med*. 2022;386(24):2261-2272.

Recurrence-Free Survival



Outcomes with ctDNA-Guided c.f Standard Management in the ITT pop.



Recurrence-free Survival in the ctDNA-Guided Group per ctDNA Status

Tie J et al. *N Engl J Med*. 2022;386(24):2261-2272.

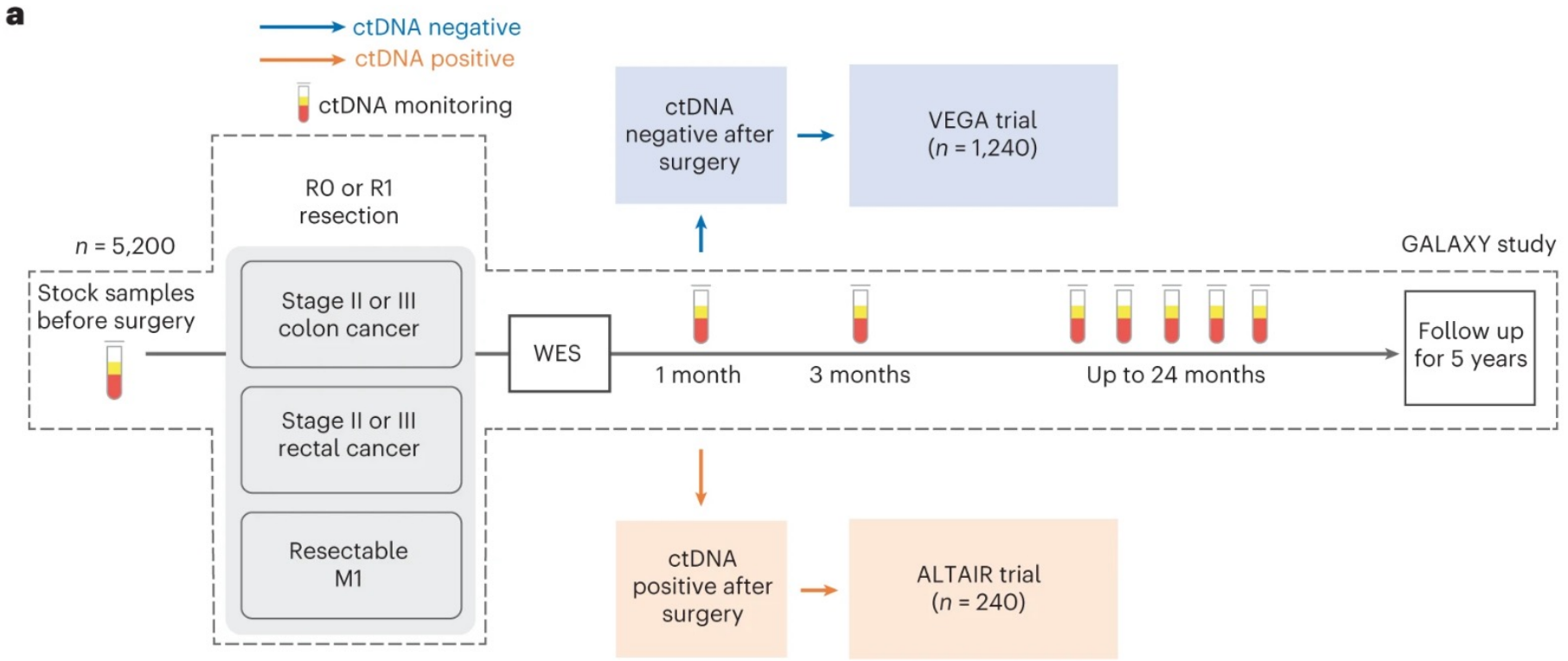
GALAXY Study (CIRCULATE-Japan)

nature medicine

Article

https://doi.org/10.1038/s41591-022-02115-4

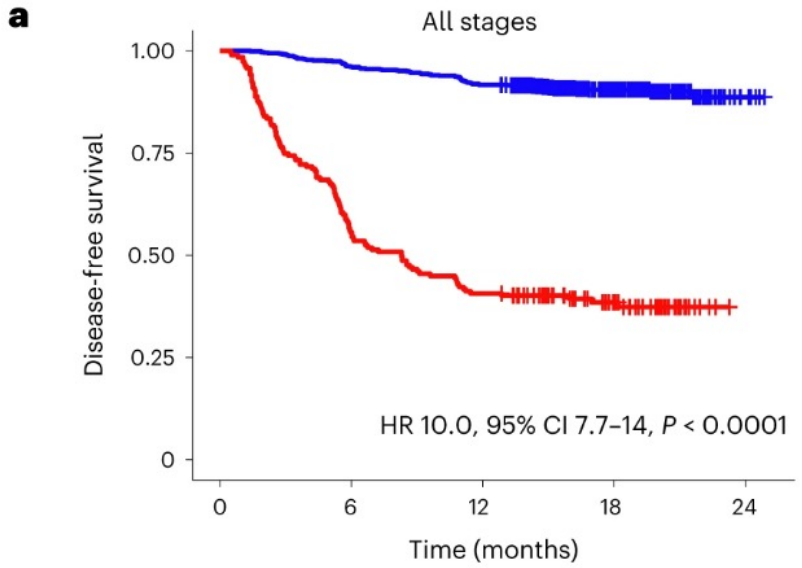
Molecular residual disease and efficacy of adjuvant chemotherapy in patients with colorectal cancer



Kotani D et al. Nat Med 29, 127–134 (2023)

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

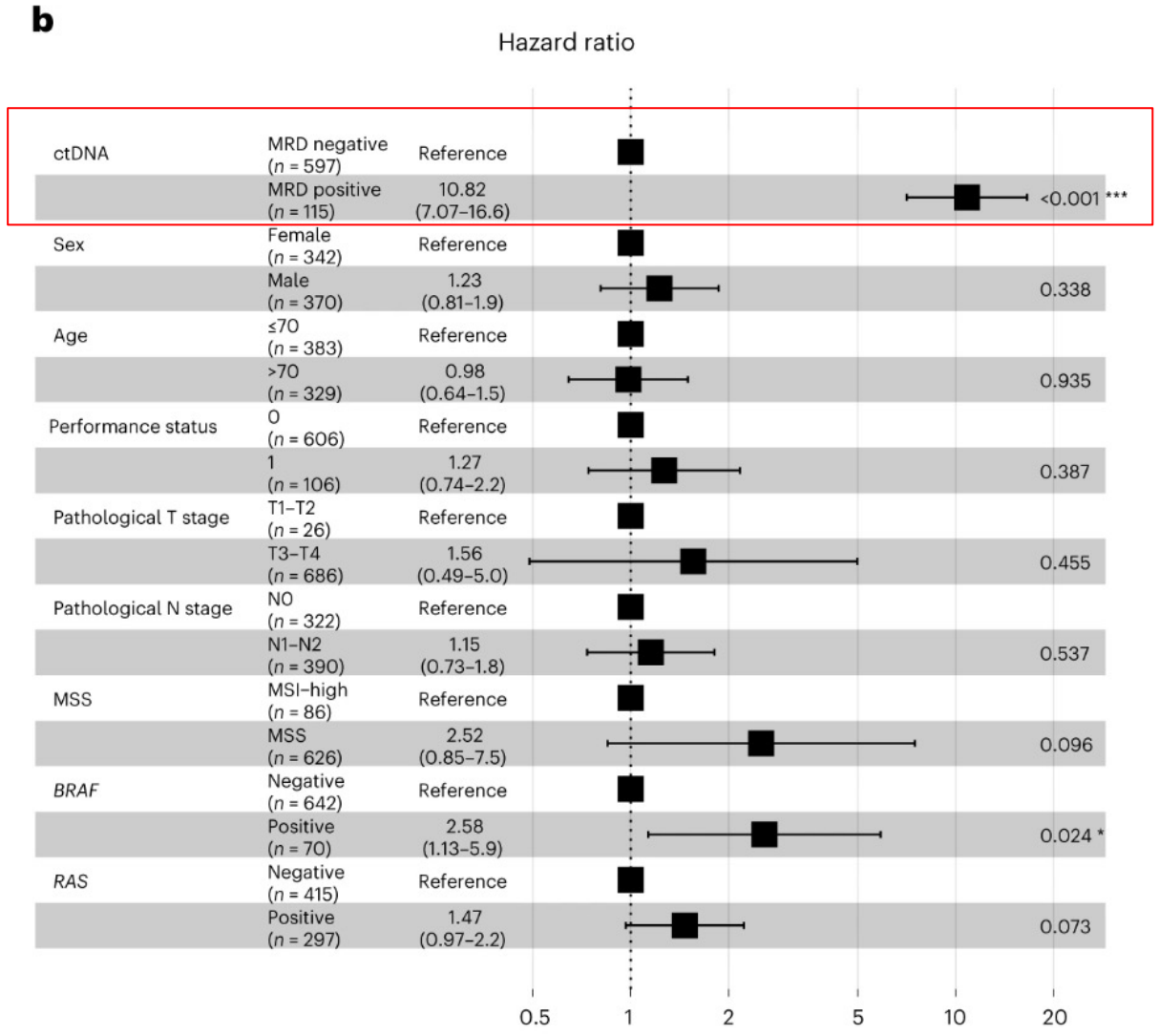
GALAXY Study (CIRCULATE-Japan)



Number at risk

ctDNA negative	852	819	781	347	5
ctDNA positive	187	104	76	37	0

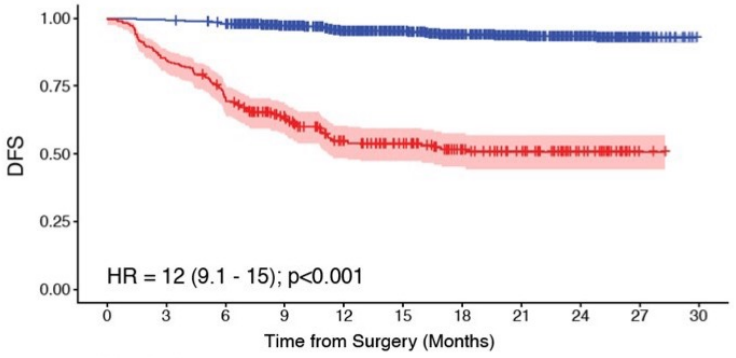
ctDNA	Number of events	6M-DFS (95% CI)	12M-DFS (95% CI)	18M-DFS (95% CI)
ctDNA negative	81 out of 852	96.1% (94.6–97.2)	91.7% (89.6–93.3)	90.5% (88.3–92.3)
ctDNA positive	115 out of 187	55.6% (48.2–62.64)	40.6% (33.6–47.6)	38.4% (31.4–45.5)



Kotani D et al. Nat Med 29, 127–134 (2023)

ctDNA dynamics between weeks 4 and 12 post surgery is prognostic of DFS

ctDNA status at 4-weeks MRD time point

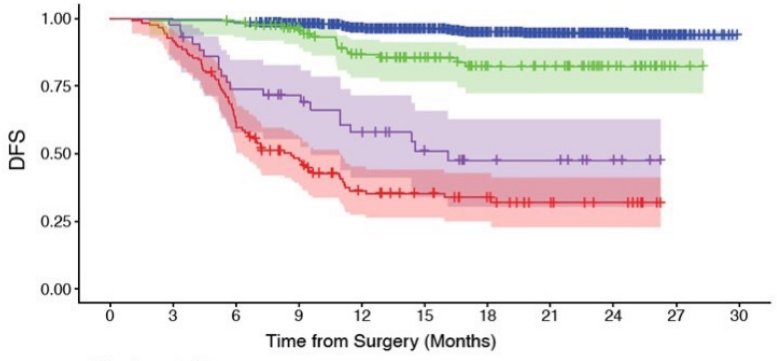


Number at risk

ctDNA (-)	1797	1786	1756	1568	1323	1054	731	502	231	37	0
ctDNA (+)	286	242	200	158	113	93	62	49	27	2	0

Dynamics	ctDNA Negative	ctDNA Positive
Events (n)	96/1797 (5.3%)	130/286 (45.5%)
18M - DFS	93.9 (92.5 - 95)	51.6 (45.2 - 57.6)
HR	Reference	12
95% CI	Not applicable	9.1 - 15
P	Not applicable	<0.001

ctDNA Dynamics from 4 weeks to 12 weeks



Number at risk

Persistently Negative	1529	1524	1508	1391	1176	938	648	439	204	35	0
Converted Negative	112	111	109	95	74	60	42	36	19	2	0
Converted Positive	43	42	31	27	21	14	9	8	4	0	0
Persistently Positive	124	114	76	52	33	27	18	11	7	0	0

Dynamics	Persistently Negative	Converted Negative	Converted Positive	Persistently Positive
Events (n)	69/1529 (4.5%)	16/112 (14.3%)	20/43 (46.5%)	78/124 (62.9%)
18M - DFS	94.9 (93.5 - 96)	82.2 (72.3 - 88.9)	47.4 (30.4 - 62.7)	33.8 (25 - 42.8)
HR	Reference	3.5	14.5	25.4
95% CI	Not applicable	1.9 - 5.8	8.8 - 23.8	18.3 - 35.3
P	Not applicable	<0.001	<0.001	<0.001

Eiji Oki et al. Journal of Clinical Oncology 2023 41:16_suppl, 3521-3521

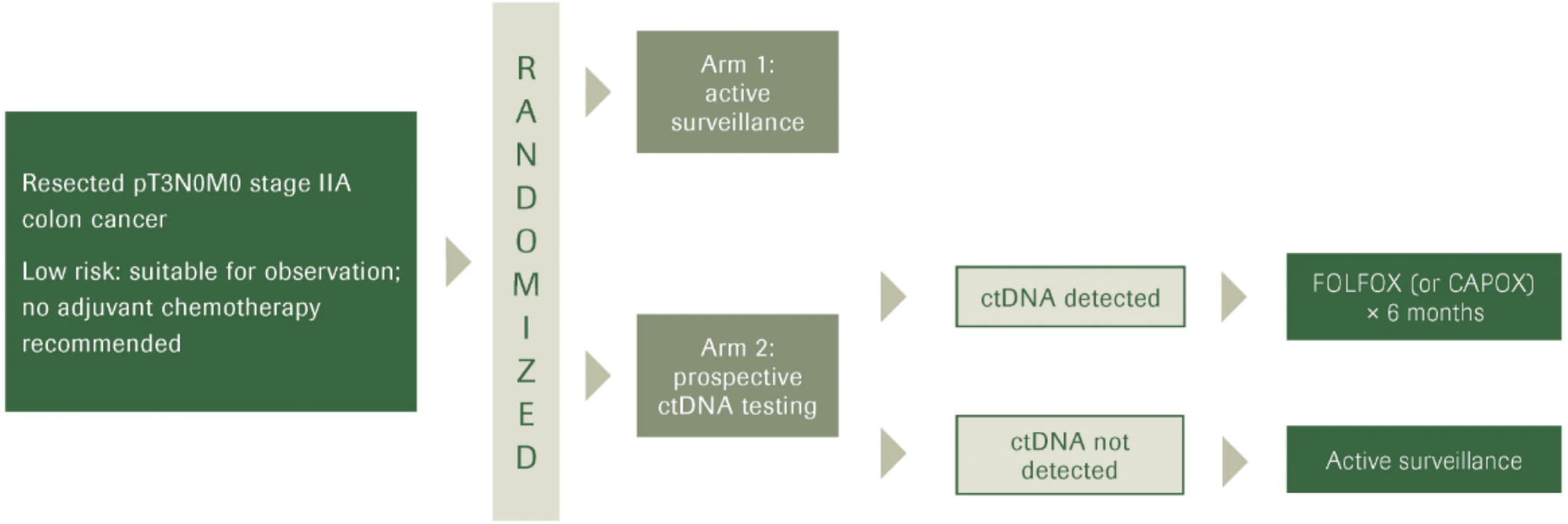
Colorectal Cancer - Adjuvant

Study Identifier	*Study Design*	*Study population*	*Sample size*	*Timepoint of ctDNA analysis*	*Primary Endpoint*	*Secondary/exploratory endpoints*
NCT04120701 (PRODIGE 70 – CIRCULATE)	Phase III	Resected Stage II CRC	1980	≥2 weeks post-op and up to <8 weeks	3-year DFS in ctDNA +patients	2-yr DFS, overall survival, and toxicity, time to recurrence (TTR)
COBRA study (NCT0406810, NRG-GI005)	Phase II/III	Stage IIA CRC after surgery	1408	Post op	-Clearance of ctDNA +/- ACT up to 6 months from baseline (phase II) -RFS in ctDNA + patients +/- ACT (phase III)	-OS, Time to recurrence, Compliance with ACT and/or active surveillance - Incidence of ctDNA + post resection - Cost effectiveness of ctDNA vs. SOC -Rates of compliance with assigned intervention (all up to 3 years)
TRACC (NCT04050345)	Phase II/III	High risk stage II, stage III CRC And subset of rectal cancer patients	1621	Pre-op, first post-op visit, 3mos after being on ACT, and 3 mos after de-escalation to single agent ACT based on ctDNA results at 3mos	3-year DFS	-Relationship between ctDNA detection before, during and after treatment -OS, neurotoxicity, quality of life and health economics
MEDOCC-CrEATE (NL6281 / NTR6455)	Phase III	Stage II CRC	1320	Immediately after surgery in interventional arm, end of trial in control arm	Proportion of patients receiving ACT when ctDNA is detectable after resection	-2-year recurrence rate -OS -DFS -cost-effectiveness
CIRCULATE AIO-KRK-0217 (NCT04089631)	Phase II	Stage II CRC	4812	Post op; within 5 weeks after resection	DFS in ctDNA-positive patients treated or not treated with adjuvant chemotherapy	
VEGA (UMIN000039205)	Phase III	ctDNA negative high risk stage II, low risk stage III colon cancer	1240	Postop week 4, end of ACT (3mos)	RFS in ctDNA-negative patients treated or not treated with adjuvant chemotherapy	-ctDNA clearance -OS

Alese OB, Cook N, Ortega-Franco A, Ulanja MB, Tan L, Tie J. Am Soc Clin Oncol Educ Book. 2022 Apr;42:1-20.

Colorectal Cancer - Adjuvant

NRG-GI005 (COBRA): Phase II/III study of circulating tumor DNA as a predictive biomarker in adjuvant chemotherapy in patients with stage II colon cancer

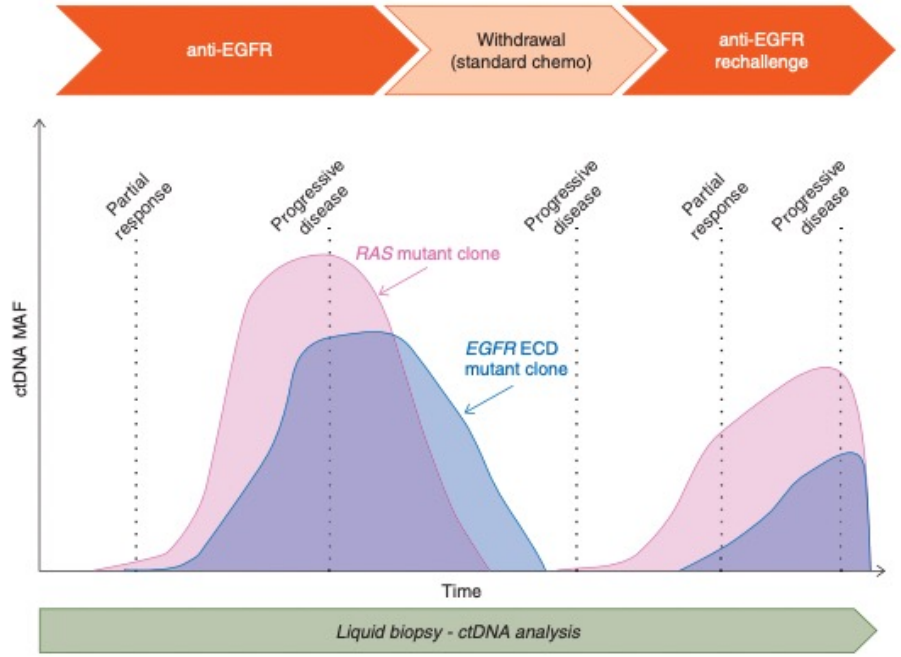


NCT04068103

Principal Investigator: Van K Morris

Colorectal Cancer - Metastatic

RAS and *EGFR* relative mutant allele frequency decays exponentially with a cumulative half-life of 4.4 months.

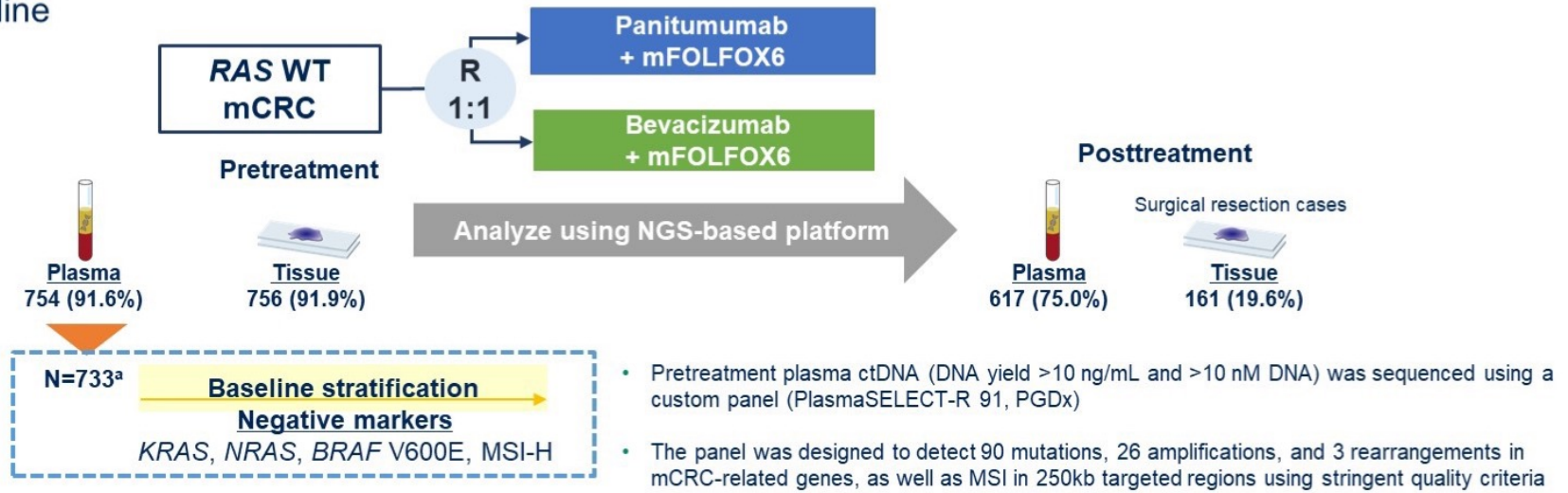


PANIRINOX (NCT02980510)[g]	II, randomized	209	Stage IV first-line therapy	*RAS* and *BRAF* wild type	mFOLFOX6 plus panitumumab *v* FOLFIRINOX plus panitumumab	CR rate in FOLFIRINOX plus panitumumab arm	France
CHRONOS (NCT03227926)[h]	II	129	Stage IV third-line therapy[i]	*RAS*-extended mutational load between basal and rechallenge mutation load checkpoints	Rechallenge with panitumumab	ORR	Italy
NCT03087071[j]	II, randomized	84	Stage IV cetuximab-refractory disease	Treatment allocation according to *RAS*, *BRAF*, and *EGFR* mutational status	Panitumumab *v* panitumumab and trametinib	ORR	USA
TRIUMPH (UMIN000027887)[k]	II	36	Stage IV refractory disease	*ERBB2* amplification	Trastuzumab plus pertuzumab	ORR	Japan

Parseghian CM et al. *Ann Oncol*. 2019;30(2):243-249; Siravegna G and Bardelli A. *Ann Oncol*. 2019;30(10):1671; Antoniotti C et al. *JCO Precis Oncol*. 2019;3:1-14.

PARADIGM biomarker study

- The PARADIGM biomarker study (NCT02394834) was designed to investigate molecular biomarkers of primary and secondary resistance to each therapy based on testing of tumor tissue and ctDNA
- Based on current guideline recommendations regarding clinically relevant biomarkers for first-line mCRC,[1,2] we report clinical outcomes for patients with MSS or MSI-L and *RAS* (*KRAS*/*NRAS*)/*BRAF* V600E WT in ctDNA at baseline

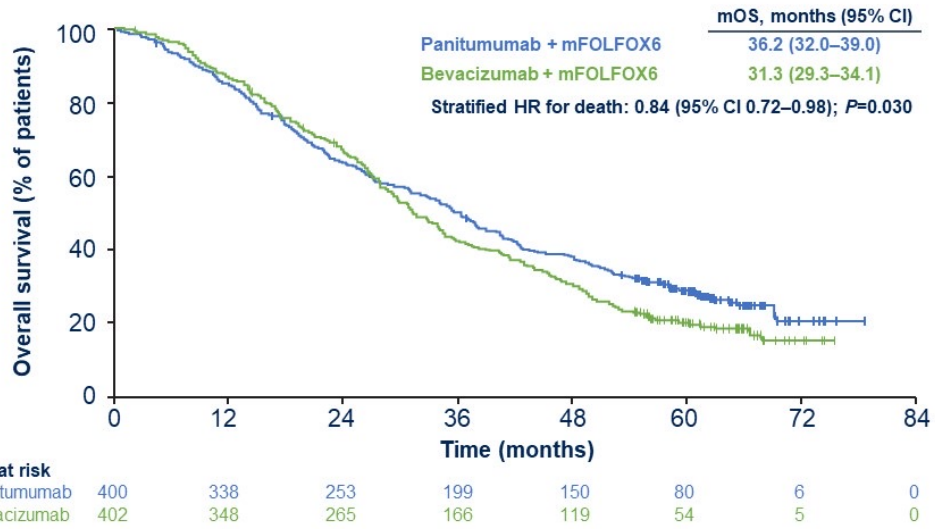


- Pretreatment plasma ctDNA (DNA yield >10 ng/mL and >10 nM DNA) was sequenced using a custom panel (PlasmaSELECT-R 91, PGDx)
- The panel was designed to detect 90 mutations, 26 amplifications, and 3 rearrangements in mCRC-related genes, as well as MSI in 250kb targeted regions using stringent quality criteria
- Efficacy (OS, PFS, RR, R0 rate, and depth of response) by treatment group was evaluated according to *RAS (KRAS/NRAS)*, *BRAF* V600E, and MSI status and primary tumor location

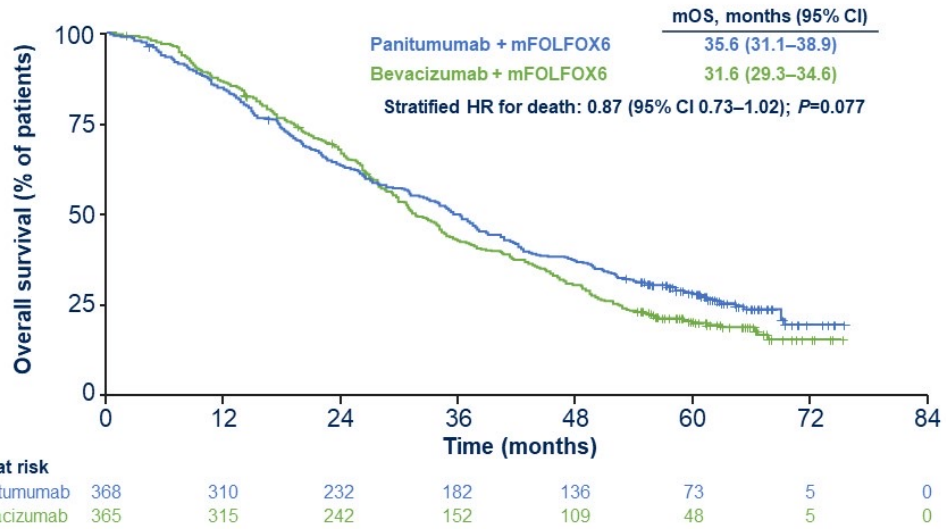
ctDNA, circulating tumor DNA; MSI, microsatellite instability; MSI-H, microsattelite instability-high; MSI-L, microsatellite instability-low; MSS, microsatellite stable; NGS, next-generation sequencing.
[a]Patients with available ctDNA among those included in efficacy analysis set in the PARADIGM study
1. Morris VK, et al. J Clin Oncol. 2023;41:678–700; 2. Cervantes A, et al. Ann Oncol. 2022;34:10–32.

Overall survival in overall population

Main study (NCT02394795; N=802)[1]



Biomarker study (NCT02394834; n=733)[a]

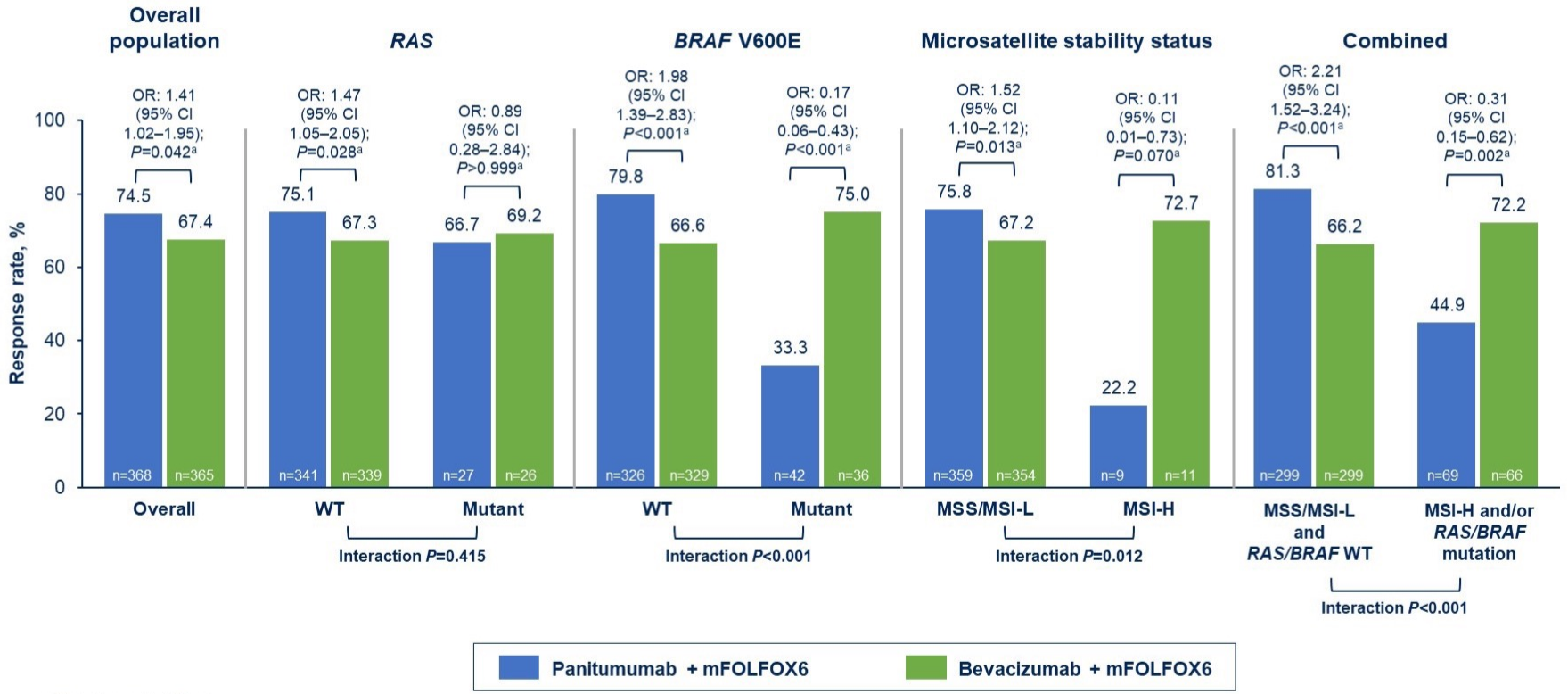


	mOS, months (95% CI)				Stratified[b] Log-rank *P*-value	Stratified HR (95% CI)
	Panitumumab + mFOLFOX6		Bevacizumab + mFOLFOX6			
Main study	**n=400**	**36.2 (32.0–39.0)**	**n=402**	**31.3 (29.3 – 34.1)**	**0.030**	**0.84 (0.21–0.98)**
Biomarker study	**n=368**	**35.6 (31.1–38.9)**	**n=365**	**31.6 (29.3–34.6)**	**0.077**	**0.86 (0.73–1.02)**

[a]Patients with evaluable ctDNA at baseline. [b]Stratified by age and liver metastasis

1. Watanabe J, et al. JAMA; 2023;329(15) 1271–82.

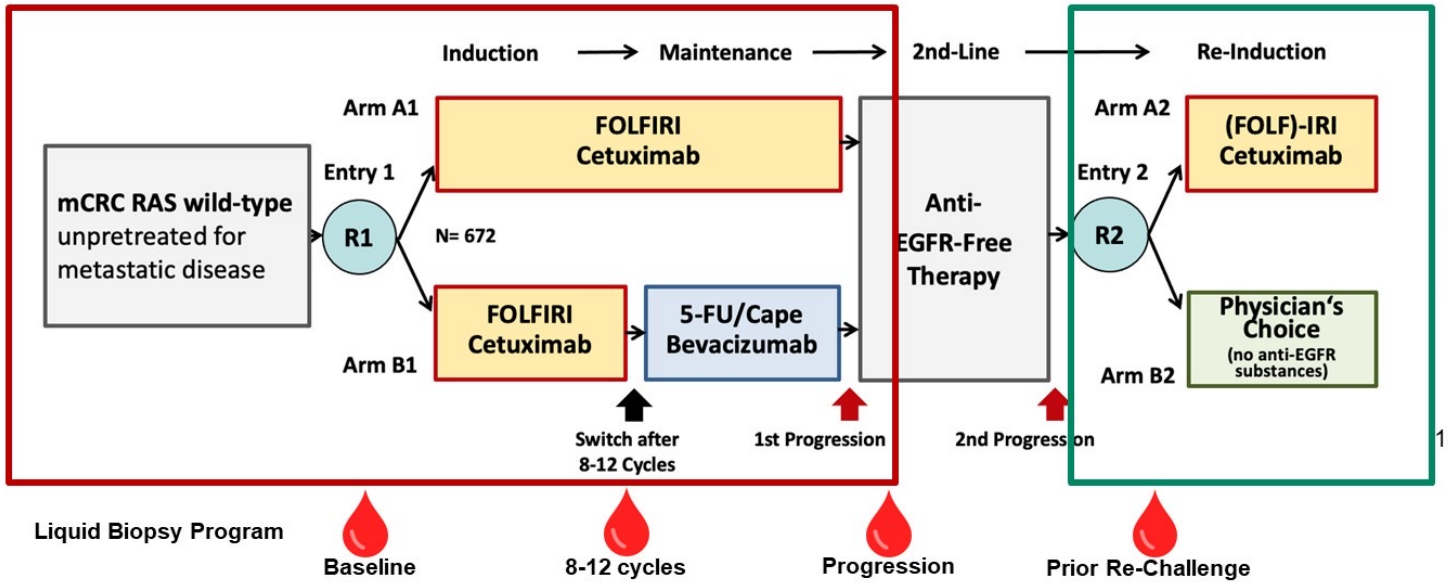
Response rate by gene alteration in the overall population



aFisher's exact test *P*-value

Takayuki Yoshino et al. Journal of Clinical Oncology 2016 34:4_suppl, TPS776-TPS776

FIRE-4: Study Design
AIO KRK-0114



130 Centres in Germany and Austria

Primary Endpoint:
Overall Survival (OS) after randomisation 2

Secondary endpoint:
Progression-free survival (PFS) in 1st-line, ORR, toxicity

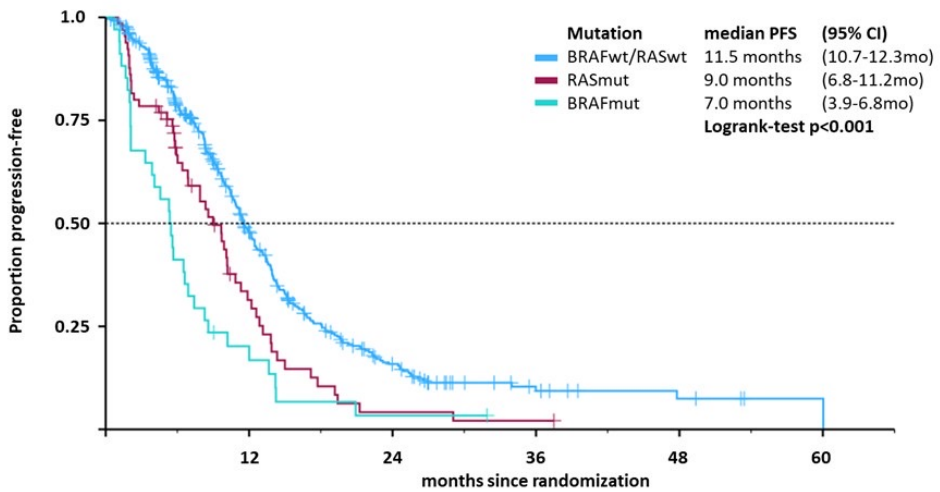
FOLFIRI: Irinotecan 180 mg/m², folinic acid 400 mg/m², 5-FU 500 mg/m² bolus, 5-FU 2,400 mg/m²
Cetuximab: Cetuximab 400mg/m² loading dose followed by 250mg/m² weekly

Stratification factors:
ECOG PS: 0 vs. 1
Leukocytes <8,000/µl vs. ≥8,000/µl
Single organ vs. muliple organ metastasis
Primary tumor sidedness: right vs. left

Sebastian Stintzing et al. Journal of Clinical Oncology 2023 41:16_suppl, 3507-3507

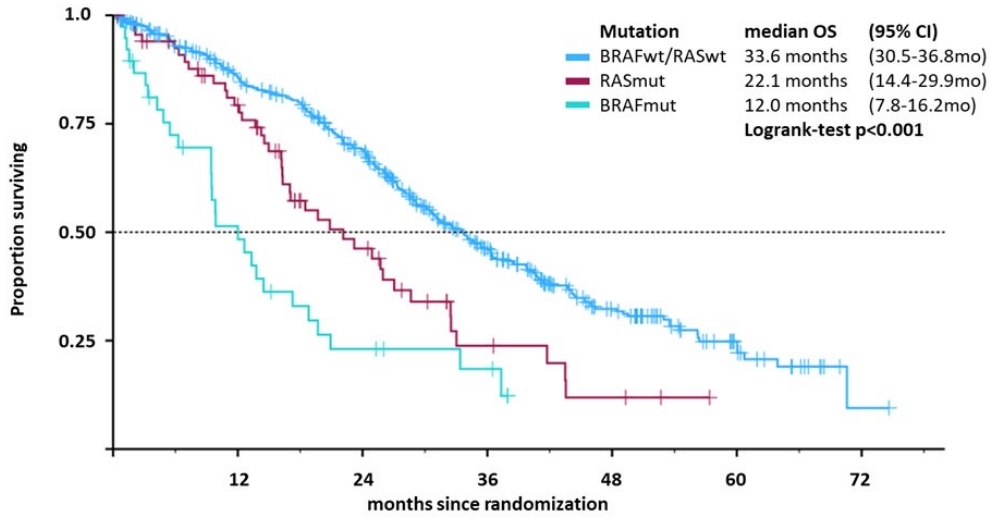
FIRE-4: Effect of baseline liquid biopsy result on survival

Progression-free survival (PFS)



Patients at risk						
BRAFwt/RASwt:	432	152	37	9	4	1
RASmut:	70	15	2	1		
BRAFmut:	38	6	1			

Overall survival (OS)



Patients at risk							
BRAFwt/RASwt:	432	333	246	131	59	19	1
RASmut:	70	47	21	7	3		
BRAFmut:	38	17	7	4			

Sebastian Stintzing et al. Journal of Clinical Oncology 2023 41:16_suppl, 3507-3507

Colorectal Cancer

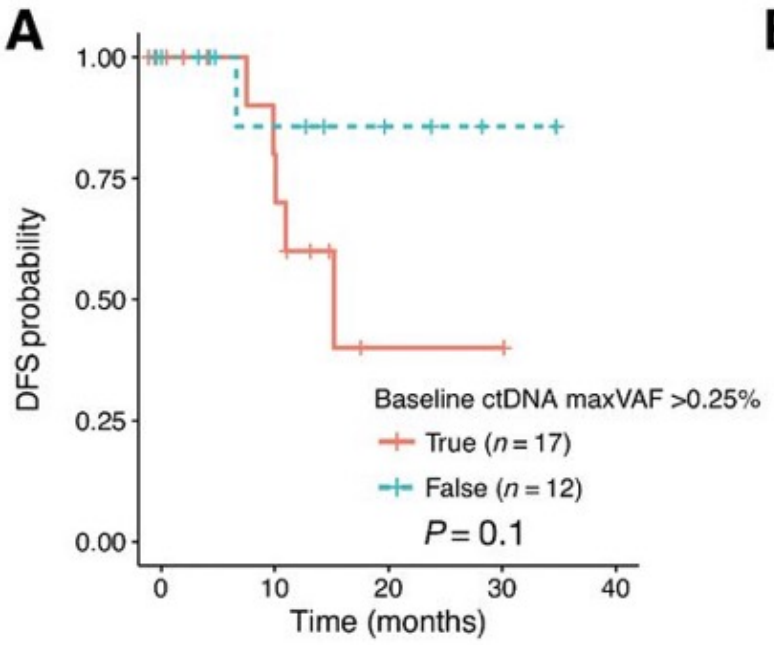
- Using clearance of ctDNA as an endpoint for escalation/de-escalation of adjuvant chemotherapy for patients considered to have high-risk disease has become an important area of research.

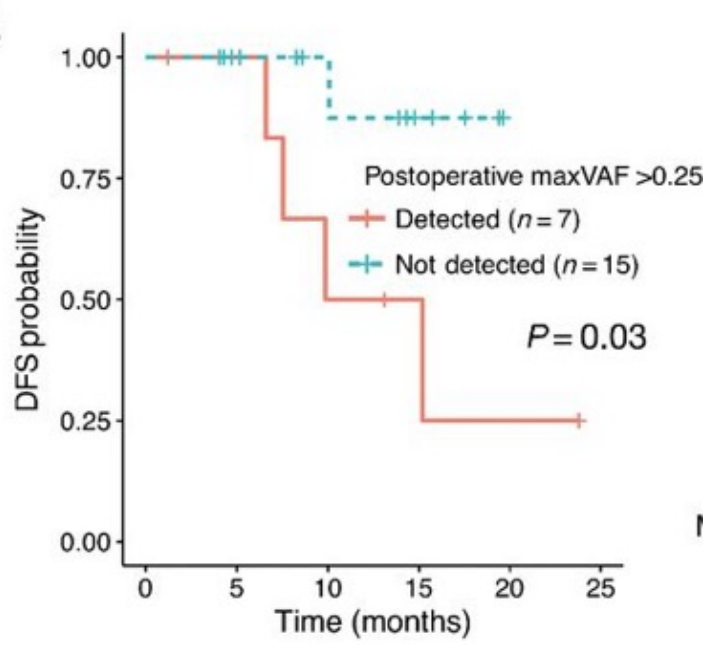
- The possibility of using ctDNA as a surrogate for treatment response (OS, PFS, DFS); arguably reduce study duration and expedite the development of new therapies.

<u>Prognostic</u>: preop detectable ctDNA = shorter DFS

(15.2 mos vs. NR; HR = 0.2; 95% CI: 0.03–2.1; p = 0.1)

- Cohort (n = 2,140 tests; 1,630 patients; 369 clinically annotated)
- Known MSI-high tumors were robustly detected with ctDNA-NGS
- Similar but not identical genomic landscape (temporospatial molecular heterogeneity)



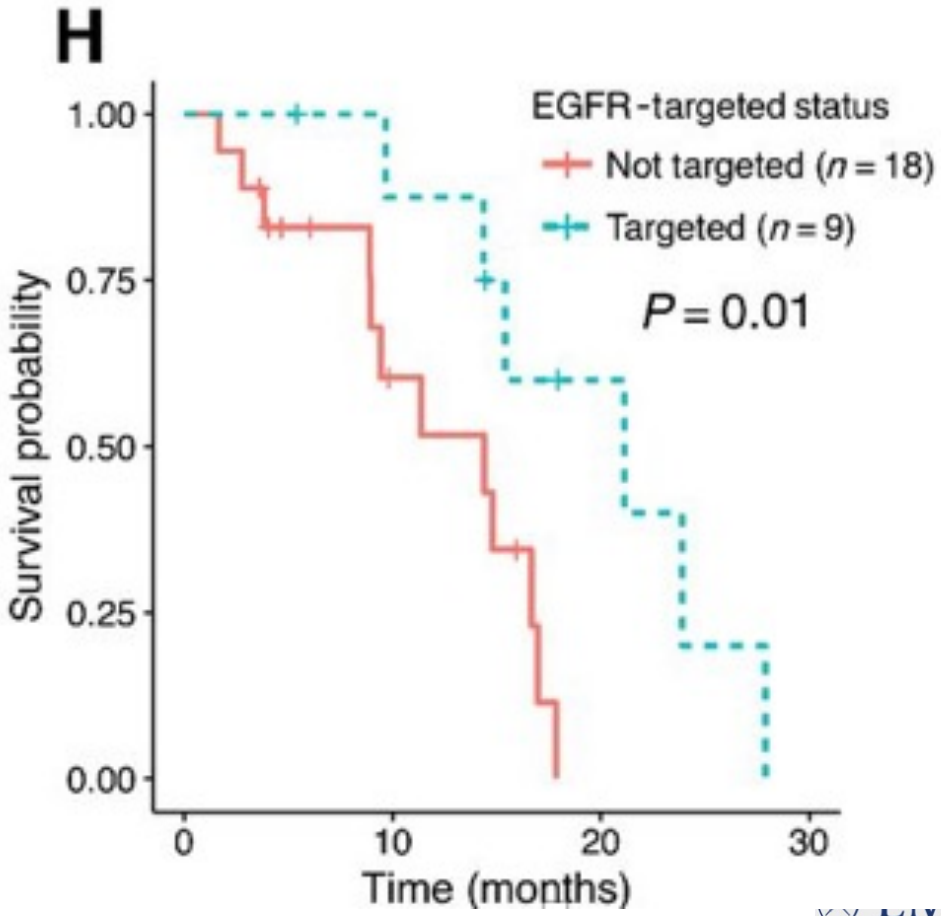


Maron SB et al. *Clin Cancer Res*. 2019;25(23):7098-7112.

Predictive

- HER2i - profound survival benefit in *HER2*-amplified patients by ctDNA-NGS ± t-NGS (mOS: 26.3 vs. 7.4 mos; HR = 0.2; 95% CI, 0.05–0.6; *p*=0.004)
- EGFRi in *EGFR*-amplified patients (mOS: 21.1 vs. 14.4 mos; *p*=0.01)

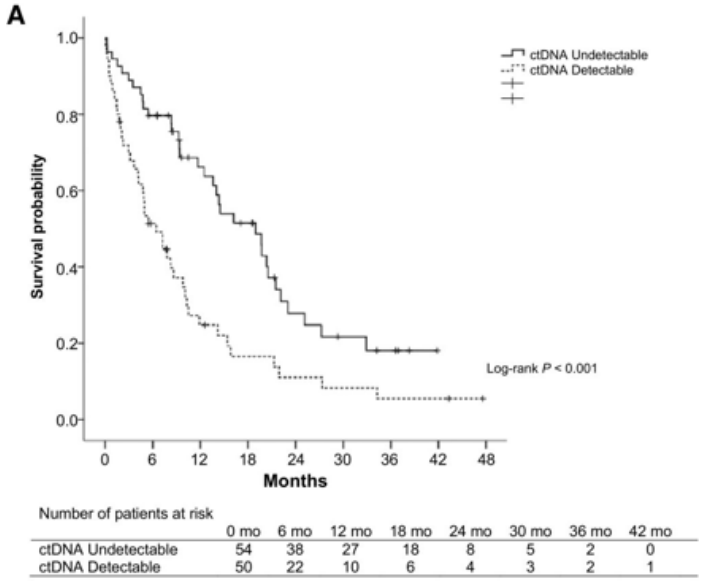
Predictive biomarker optimized by incorporating t-NGS + ctDNA-NGS in a complementary manner

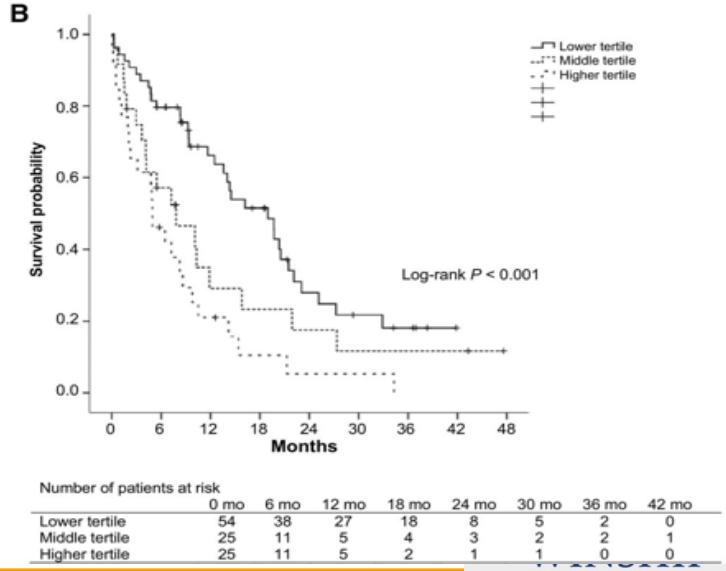


Maron SB et al. *Clin Cancer Res*. 2019;25(23):7098-7112.

Pancreatic Cancer

- *KRAS* + other mutations prevalent in pancreatic neoplasms and can be detected via ctDNA
- *Prognostic:* strongly associated with poor OS in a study of 135 patients (resectable - 23%; LAPC - 27%; mPDAC - 50%; HR, 1.96; *p*=0.007)
- *Predictive:* Day 15 assessment of 27 patients with LAPC (15%) or mPDAC (85%) – increased ctDNA levels associated with worse mPFS (2.5 vs. 7.5 mos; p=0.03) or mOS (6.5 vs. 11.5 mos; *p*=0.009).
- *? biomarker for surveillance*



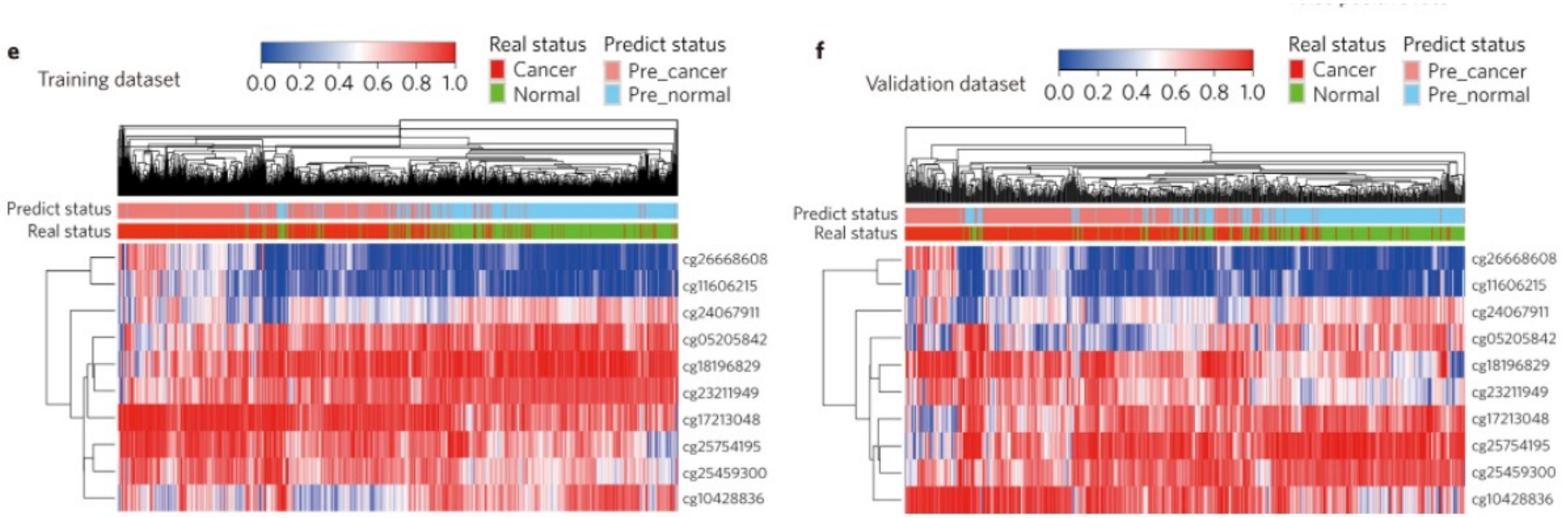


Pietrasz D et al. *Clin Cancer Res*. 2017;23(1):116-123; Del Re M et al. *Sci Rep*. 2017;7(1):7931.

Hepatocellular Carcinoma

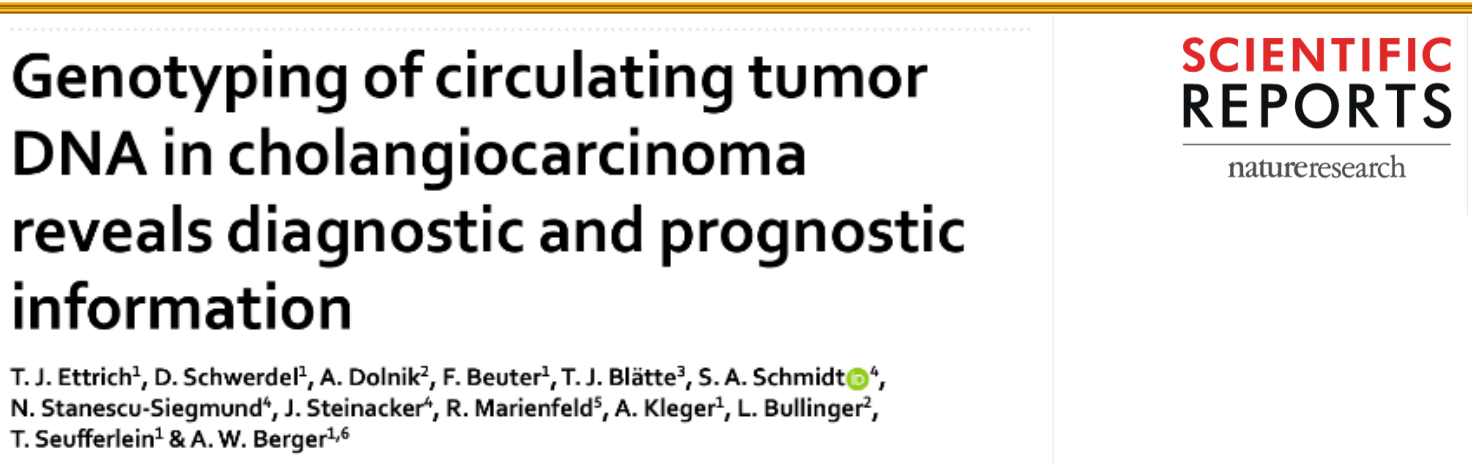
- 60% of patients experience post-resection tumor recurrence within 5 years
  - 81 patients with ctDNA (*TERT, CTNNB1* or *TP53* mutations) post curative intent hepatectomy = shorter DFS, OS; *only independent predictor of recurrence*

- *Utility of ctDNA methylation markers - levels = tumor burden and prognosis*
- *Genetic profiling when biopsy is not feasible or desirable (Rui-hua Xu et al).*



Bruix J et al. *Hepatology*. 2011;53(3):1020-1022; Xu RH et al. *Nat Mater*. 2017;16(11):1155-1161; Wang J et al. *Ann Transl Med*. 2020;8(5):237.

Biliary Tract Cancers (BTC)



Genotyping of circulating tumor DNA in cholangiocarcinoma reveals diagnostic and prognostic information

T. J. Ettrich[1], D. Schwerdel[1], A. Dolnik[2], F. Beuter[1], T. J. Blätte[3], S. A. Schmidt[4], N. Stanescu-Siegmund[4], J. Steinacker[4], R. Marienfeld[5], A. Kleger[1], L. Bullinger[2], T. Seufferlein[1] & A. W. Berger[1,6]

SCIENTIFIC REPORTS
nature research

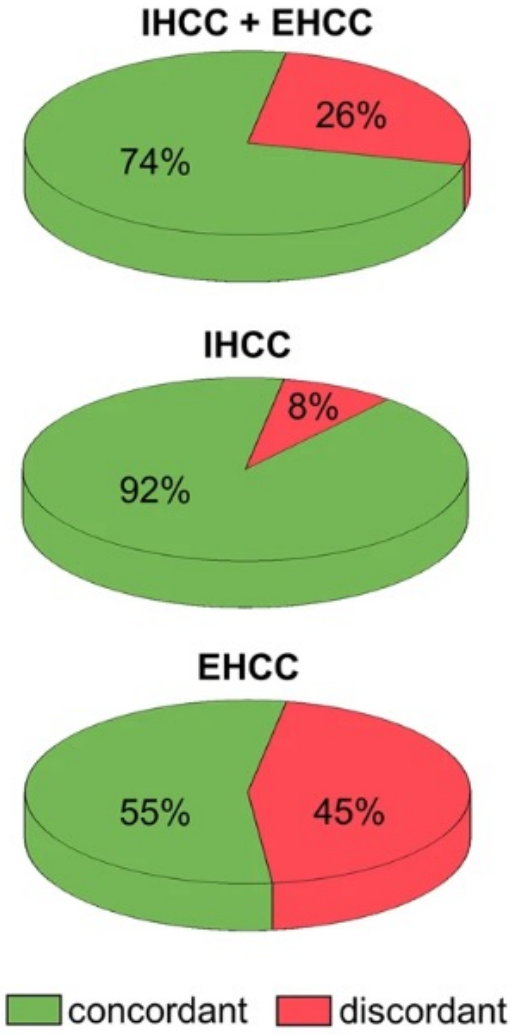
- 32 patients; ctDNA analyses at baseline, on treatment (1.7 ± 0.8 mos) and at radiologic progression
- ctDNA VAF baseline values in IHCC + EHCC correlated significantly (p=0.0433) with pretx tumor load (no correlation with number of detected mutations)
- Significant correlation between baseline ctDNA VAF and PFS in only the IHCC group (p=0.0288, r = −0.5878)

Ettrich TJ et al. *Sci Rep*. 2019;9(1):13261.

Biliary Tract Cancers (BTC)

Utility for both monitoring and prognosis

gene	Nakamura H et al. [9]	Zou S et al. [10]	Churi CR et al. [6]	Farshidfar F et al. [11]	Ross JS et al. [33]	total	current study Ettrich TJ et al.	
	tumor	tumor	tumor	tumor	tumor	tumor	tumor	ctDNA
	N=211	N=102	N=75	N=38	N=28	N=478	N=24	
TP53	24%	38%	37%	8%	32%	28%	22%	30%
ARID1A	12%	7%	16%	16%	36%	17%	9%	4%
KRAS	20%	17%	28%	5%	11%	16%	22%	9%
IDH1	4%	5%	13%	13%	32%	13%	4%	4%
BAP1	9%	1%	9%	29%	11%	12%	9%	9%
PBRM1	5%	1%	9%	21%	NA	9%	9%	4%
SMAD4	9%	4%	9%	NA	NA	7%	9%	4%
PIK3CA	7%	3%	NA	5%	4%	5%	9%	9%
FBXW7	NA	0%	8%	NA	NA	4%	4%	4%
CDKN2A	5%	0%	NA	5%	7%	4%	0%	0%
ERBB2	NA	0%	8%	5%	NA	4%	0%	0%
NRAS	4%	1%	NA	NA	7%	4%	0%	0%
IDH2	NA	0%	NA	5%	4%	3%	0%	0%
BRAF	NA	1%	NA	3%	NA	2%	0%	0%
BCL2	NA	0%	NA	NA	NA	0%	0%	0%

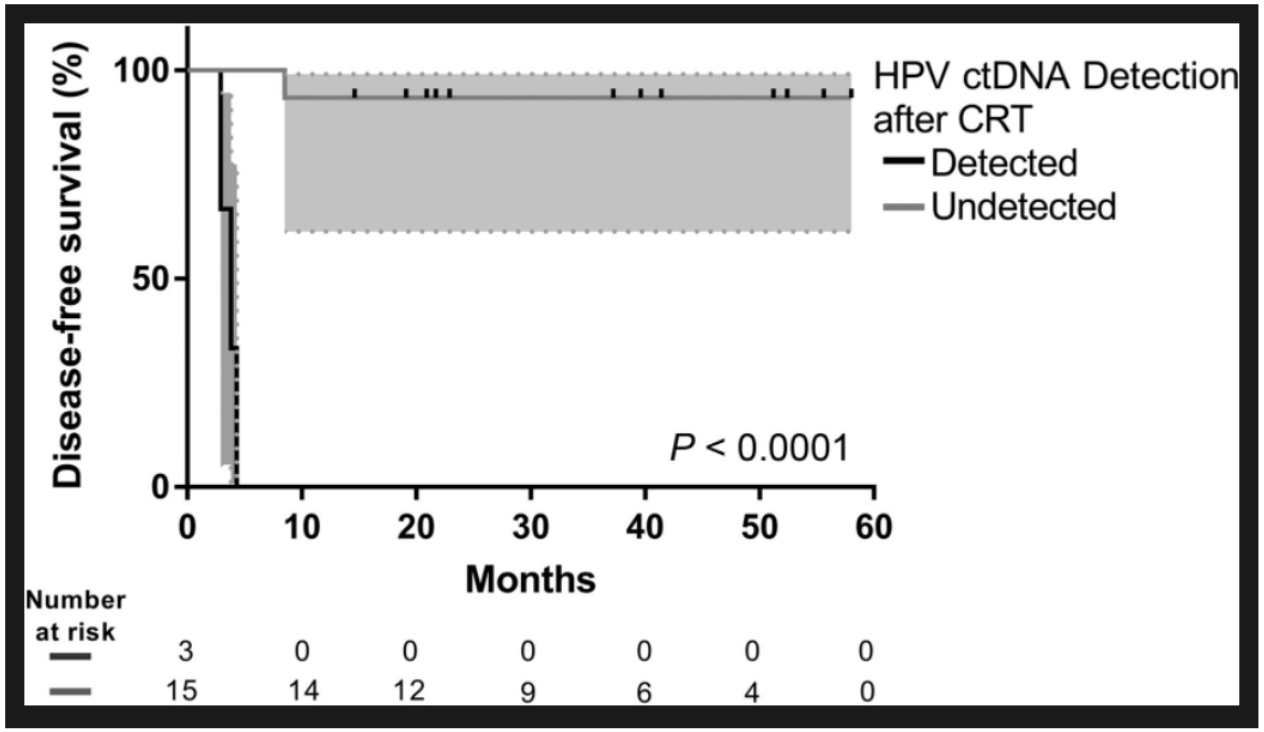


Ettrich TJ et al. *Sci Rep*. 2019;9(1):13261.

Other GI Cancers: Anal SCCa

HPV ctDNA in MRD and impact of definitive chemoradiotherapy (CRT) in anal squamous cell carcinomas (SCCa)

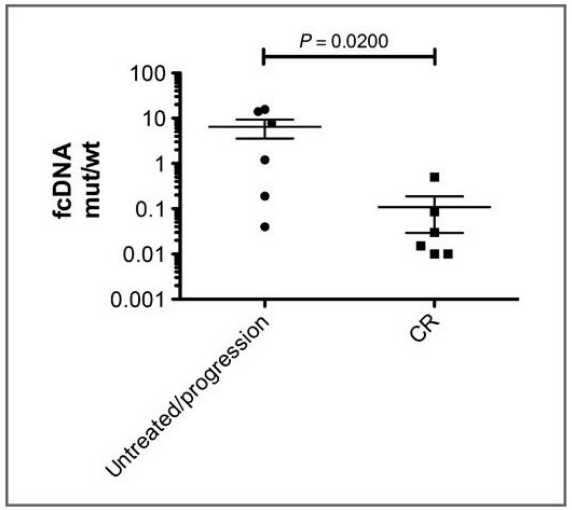
- *Positive rate = tumor stage (II: 64% and III: 100%; p=0.008) and node positive disease*
- *Positive ctDNA post-CRT = shorter DFS (p< 0.0001)*



Cabel L et al. *Clin Cancer Res*. 2018;24(22):5767-5771.

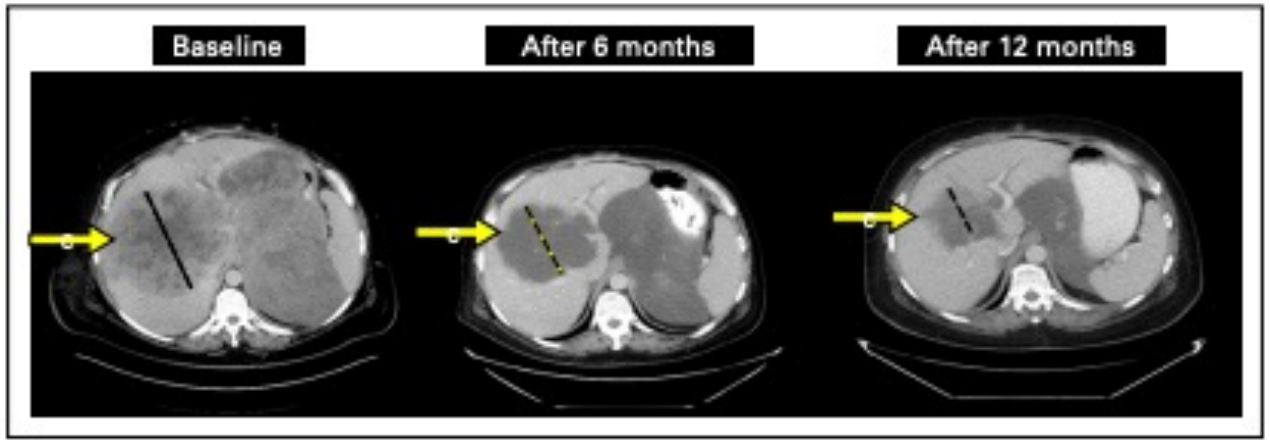
Other GI Cancers: GIST

- Active disease = higher titers of mutated ctDNA c.f. patients in complete remission (Maier J. et al)
- Detection of resistance mutations = earlier treatment changes and help avoid repeated tumor biopsies



Capture the molecular heterogeneity - whole tumor; guide treatment decisions during progression (Arshad J. et al)

55yo M; gastric GIST liver metastases; progression on imatinib, nilotinib, sunitinib, and regorafenib.
ctDNA - KIT exon 17 Y832D secondary mutation; durable response with ponatinib for nearly 2 years.



Maier J et al. *Clin Cancer Res.* 2013;19(17):4854-4867; Kang G et al. *Mol Diagn Ther.* 20(4):347-351;
Arshad J et al. *JCO Precis Oncol*. 2020;4:66-73; Namløs HM et al. *Mol Cancer Ther*. 2018;17(11):2473-2480.

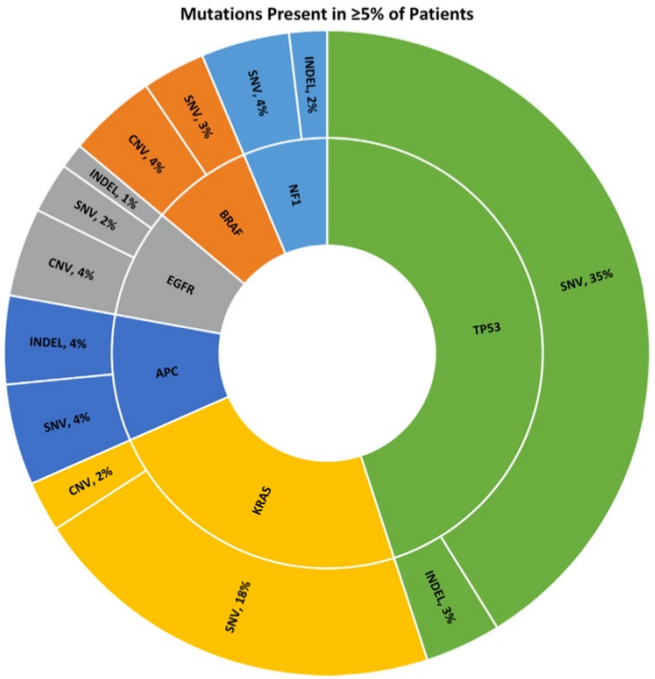
Other GI Cancers: Appendiceal Cancer

The Oncologist®

Gastrointestinal Cancer

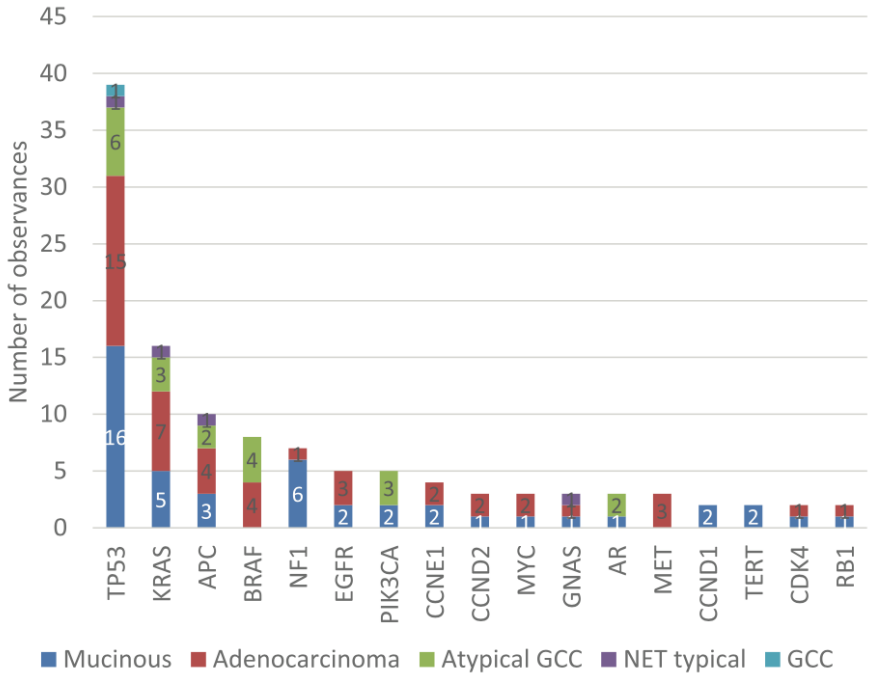
Blood-Based Next-Generation Sequencing Analysis of Appendiceal Cancers

- 303 patients; F = 56%
- Median age = 56.8yrs (25–83)
- ctDNA NGS testing was performed on 372 plasma samples
- Genomic alterations were defined in 207 (55.6%) samples



Histology	Samples, *n* (%)
Mucinous	33 (52.4)
Adenocarcinoma	14 (22.2)
Atypical GCC	14 (22.2)
GCC	1 (1.6)
NET typical	1 (1.6)

Abbreviations: GCC, goblet cell carcinoma; NET, neuroendocrine tumors.



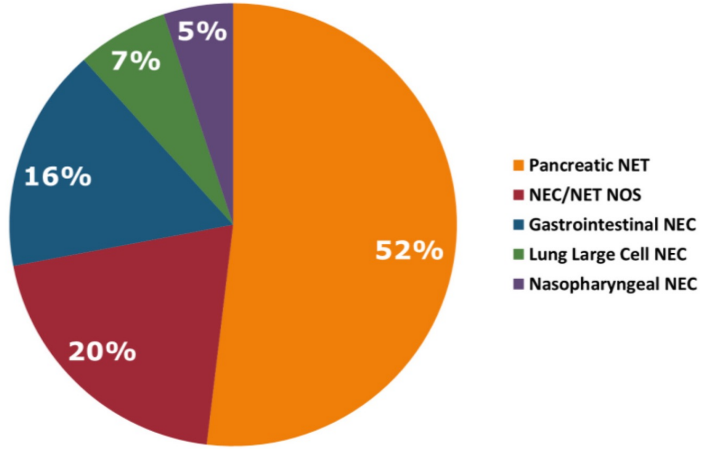
Shaib WL…Alese OB... Oncologist. 2020 May;25(5):414-421..

Neuroendocrine neoplasms

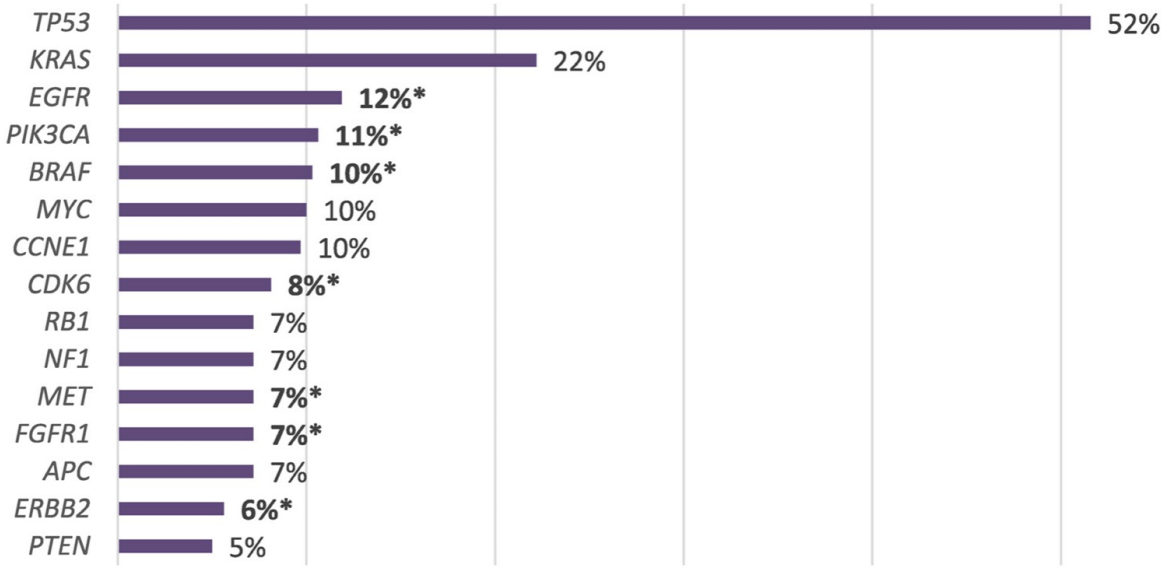
www.oncotarget.com Oncotarget, 2020, Vol. 11, (No. 19), pp: 1749-1757

Research Paper

Blood-based next-generation sequencing analysis of neuroendocrine neoplasms



- Neuroendocrine neoplasms (NENs): heterogeneous group of neoplasms – WD NET <------>NEC
- 320 NEN patients
- 338 plasma samples tested via clinical-grade ctDNA NGS
- Genomic alterations in 280 (87.5%) samples; 1,012 alterations after excluding VUS and synonymous mutations



Neuroendocrine neoplasms

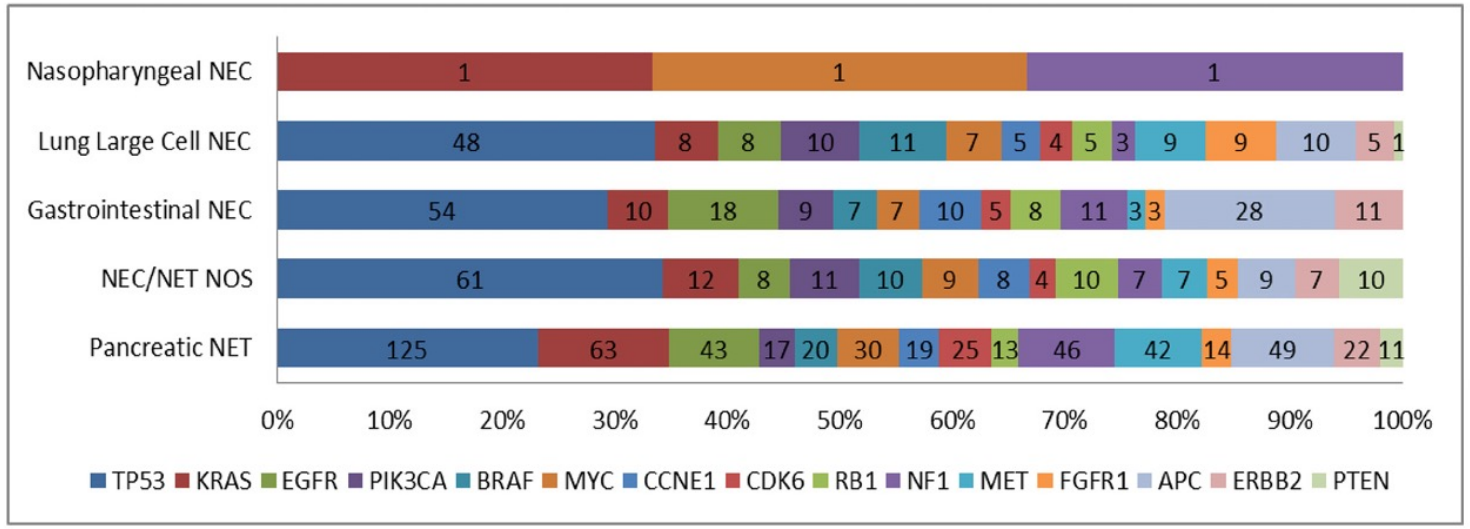


Figure 4: Genomic alterations stratified by tumor type.

Table 1: Correlation between age and gender with respect to KRAS/BRAF/ATM/BRCA/MTOR/PIK3CA

Gene	Count of Gene	Male	Female	Mean Age (Years)
KRAS	94	62/94 (66%)	32/94 (34%)	59.3
BRAF	48	29/48 (60%)	19/48 (40%)	61.5
ATM	7	4/7 (57%)	3/7 (43%)	67.1
BRCA 1	45	37/45 (82%)	8/45 (18%)	54.7
BRCA 2	48	31/48 (65%)	17/48 (35%)	58.9
MTOR	27	12/27 (44%)	15/27 (56%)	63.4
PIK3CA	47	24/47 (51%)	23/47 (49%)	58.4

Frequency of alterations with possible drug targets

- EGFR (12%, erlotinib)
- PIK3CA (11%, Alpelisib)
- BRAF (10%, Encorafenib)
- CDK6 (8%, Palbociclib)
- MET (7%, Cabozantinib)
- FGFR1 (7%, Erdafitinib)
- ERBB2 (6%, Trast/Pertuzumab)
- BRCA1/2 (15%, Olaparib)

Zakka K…Alese OB…et. al…Oncotarget, 2020, Vol. 11, (No. 19), pp: 1749-1757

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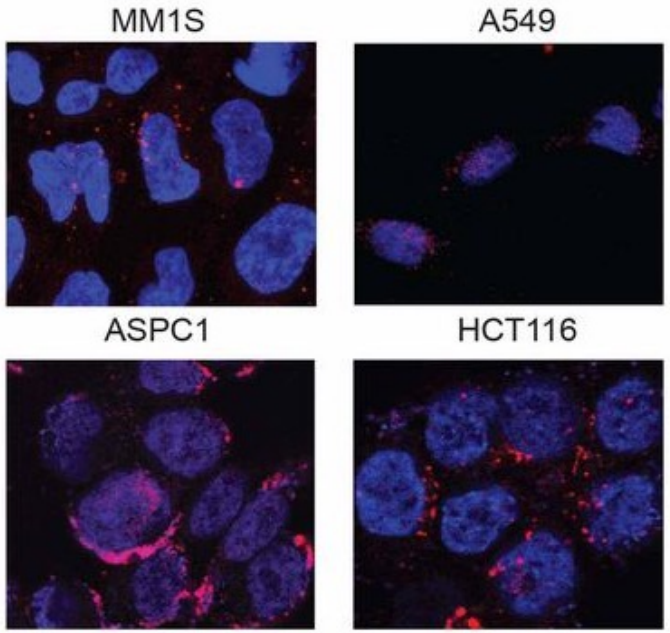
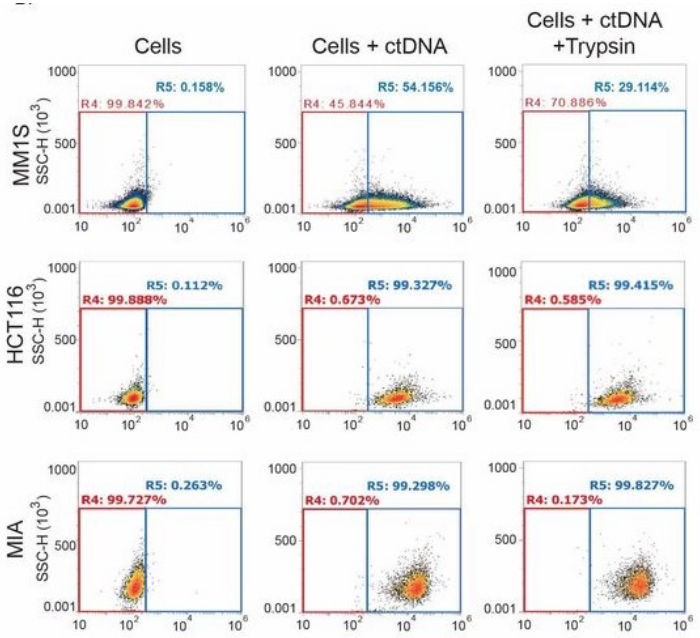
ctDNA and horizontal gene transfer

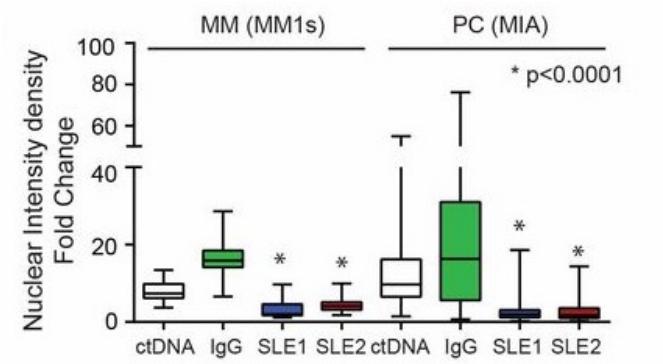
- ctDNA can promote cell-specific horizontal gene transfer (HGT) between human cancer cells
- Retrotransposons of the ERVL, SINE, and LINE families are necessary for cell targeting and the integration of ctDNA into host DNA



nuclear localization of rhodamine-labeled ctDNA (red)

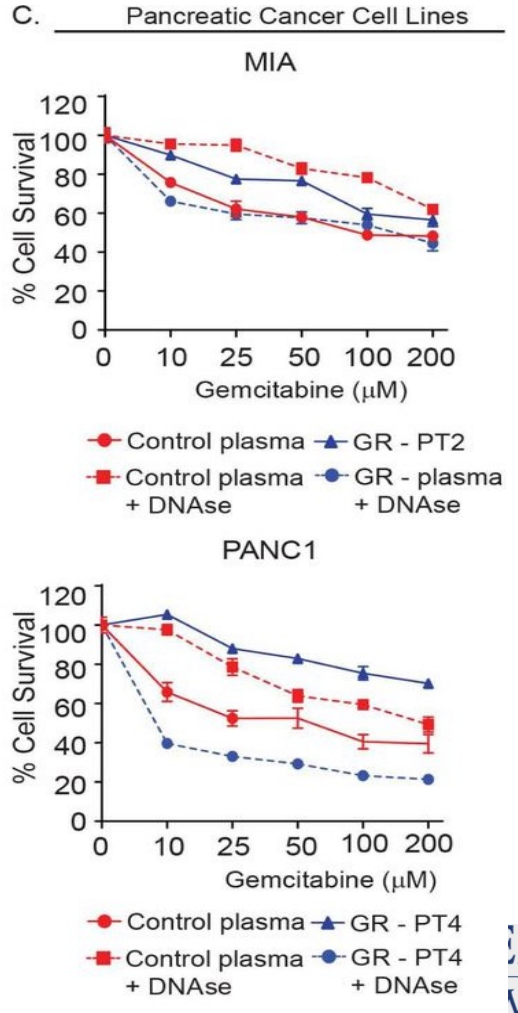


Flow cytometry assay demonstrated a high percentage of cells with ctDNA incorporation



Anti-dsDNA Ab reduce ctDNA nuclear localization

HGT likely influences treatment response in pancreatic cancer models



Cinar M…Alese OB…et. al…manuscript under review, available on bioRxiv

Conclusion

- Targeted therapies enhance personalization of GI cancer treatment, due to increasing molecular characterization
- ctDNA has a significant potential in the management of GI cancer patients
- Additional efforts regarding optimization of this tool, while exploring additional implications of ctDNA are ongoing

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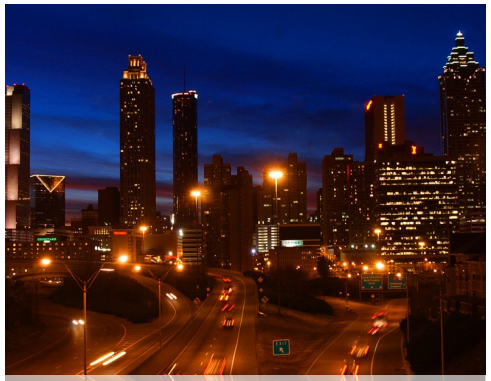

Thank you