15th CONGRESS on Lung CANCER

MADRID

23&24 November 2023

#15CongressGECP

Fundación GECP lung cancer research

Liquid biopsy, ready for clinical practice?

Atocha Romero

Hospital Universitario Puerta de Hierro

BACKGROUND

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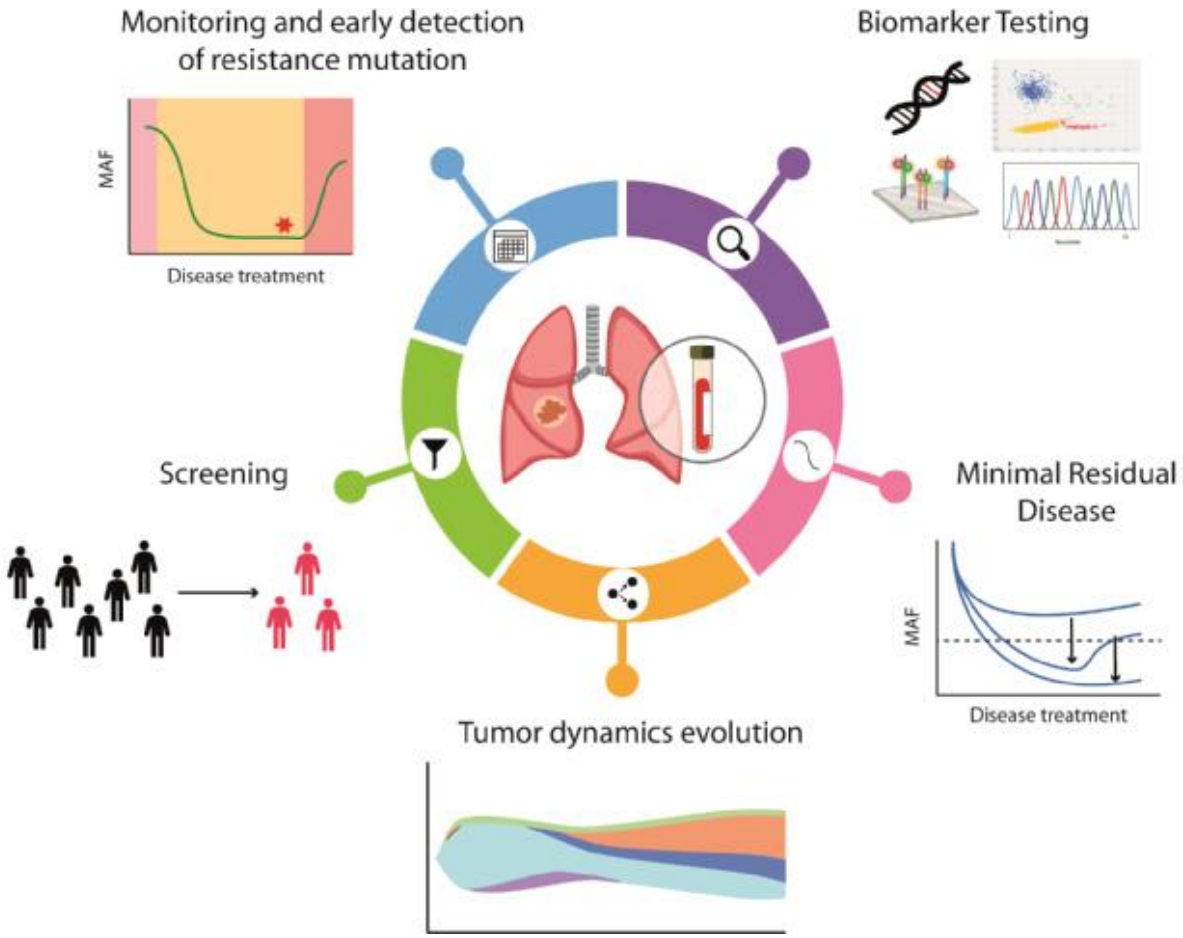

Romero, A et al. Curr Treat Options Oncol. 2021 Aug 23;22(10):86.

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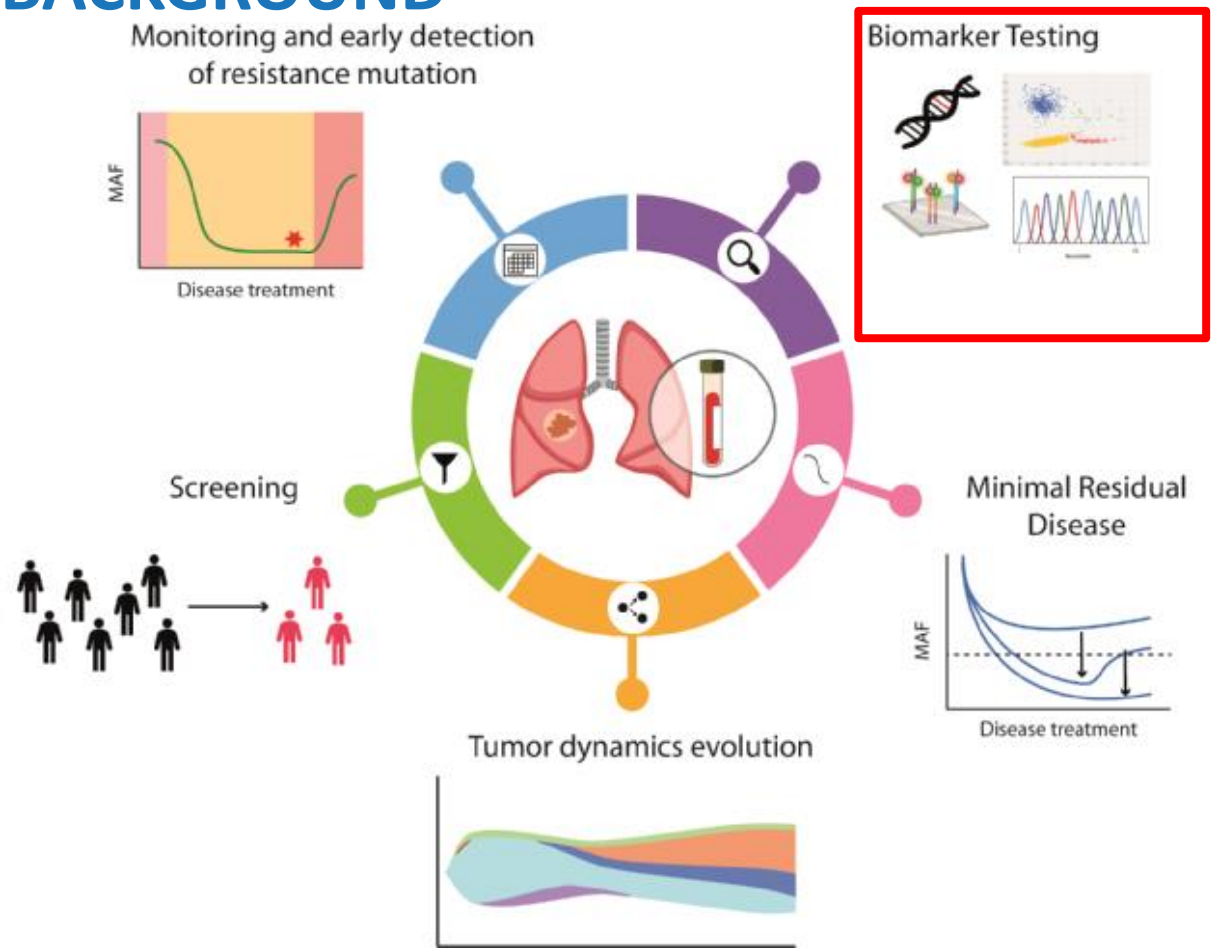

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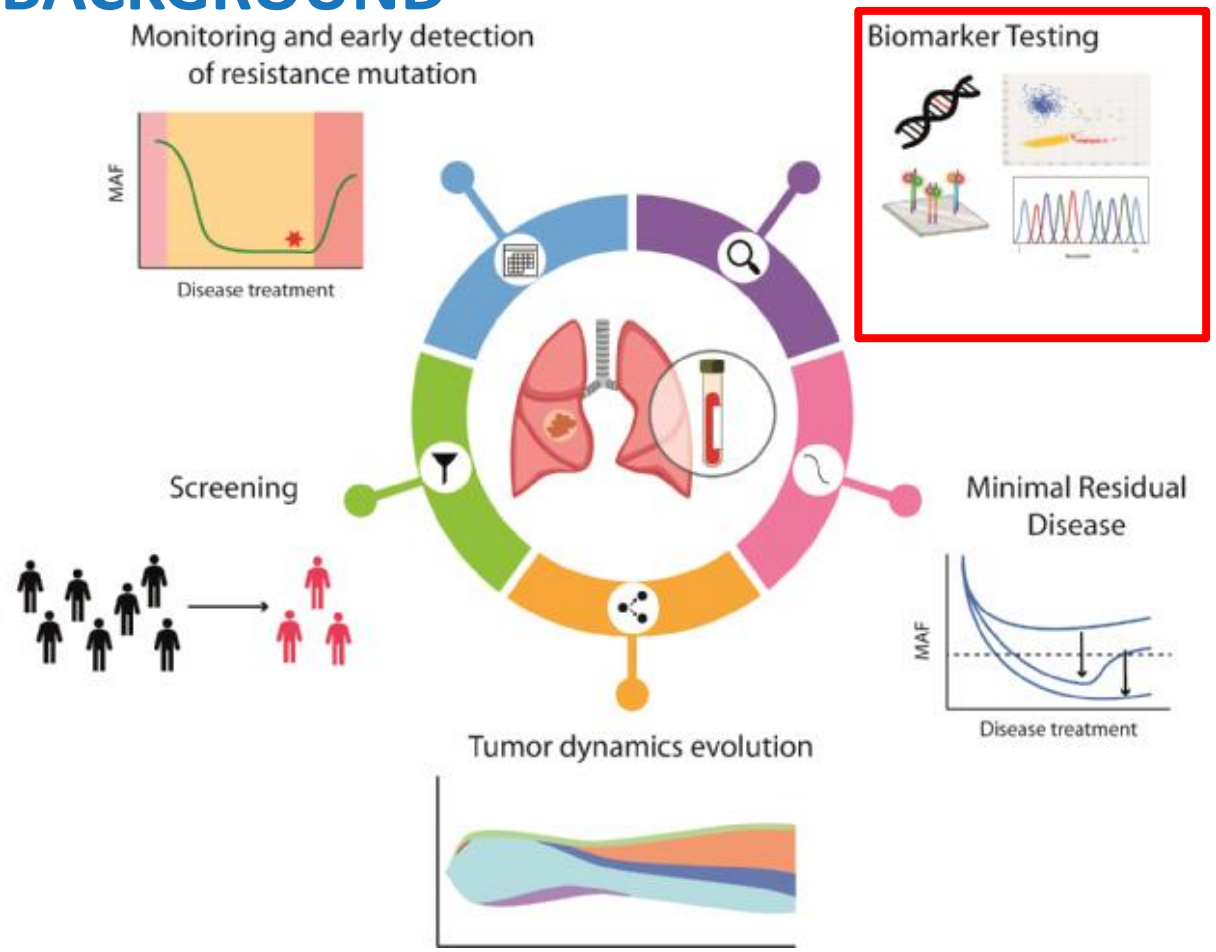

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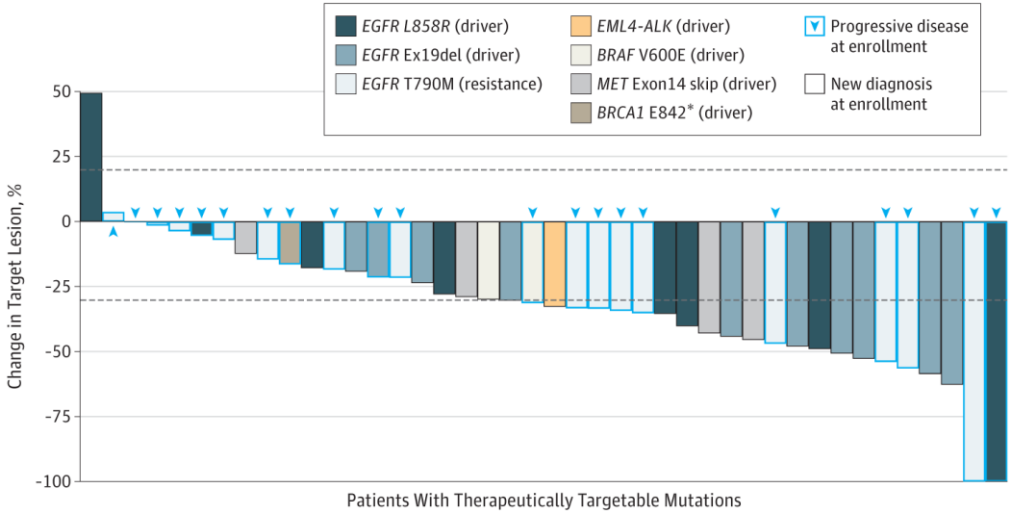

JAMA Oncol. 2019;5(2):173-180. doi:10.1001/jamaoncol.2018.4305

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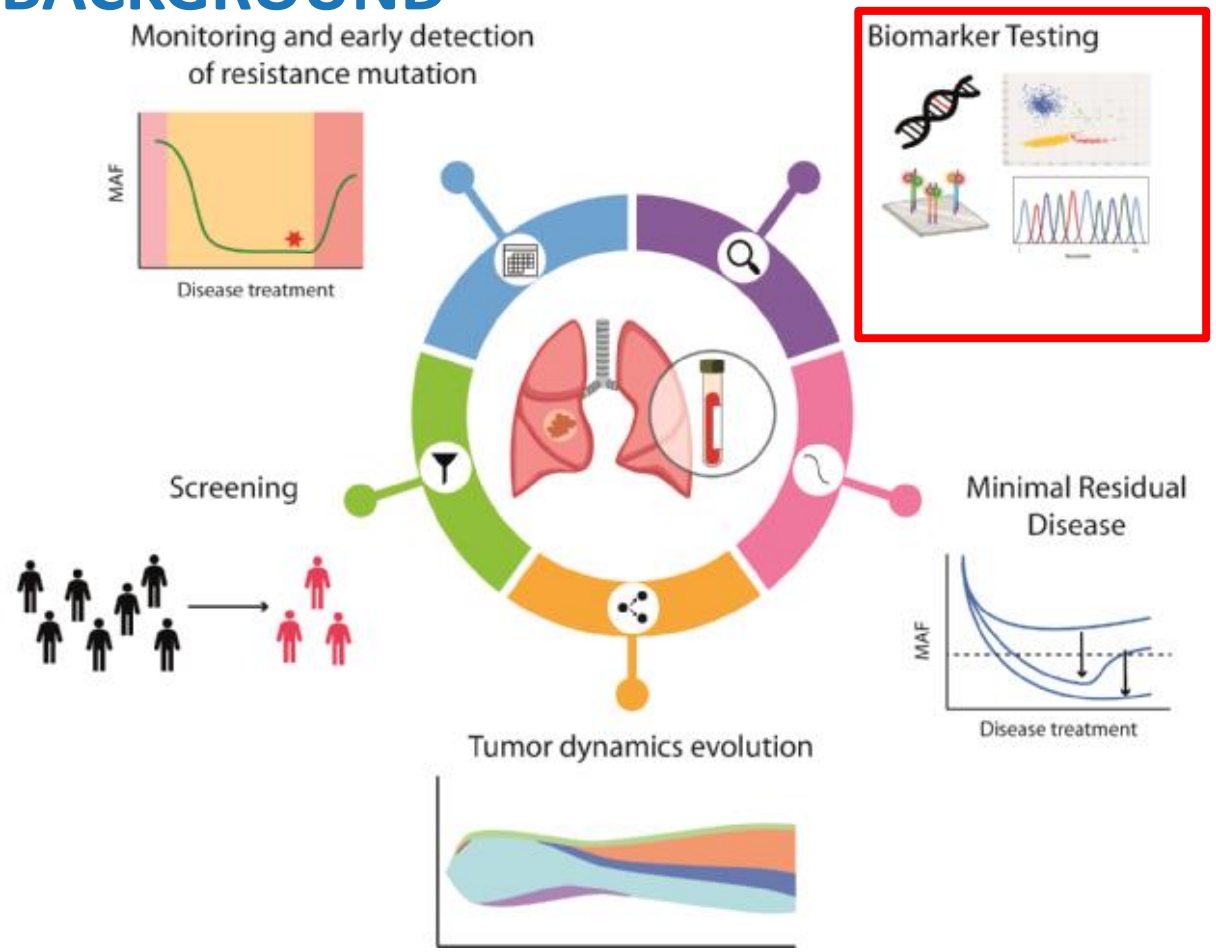

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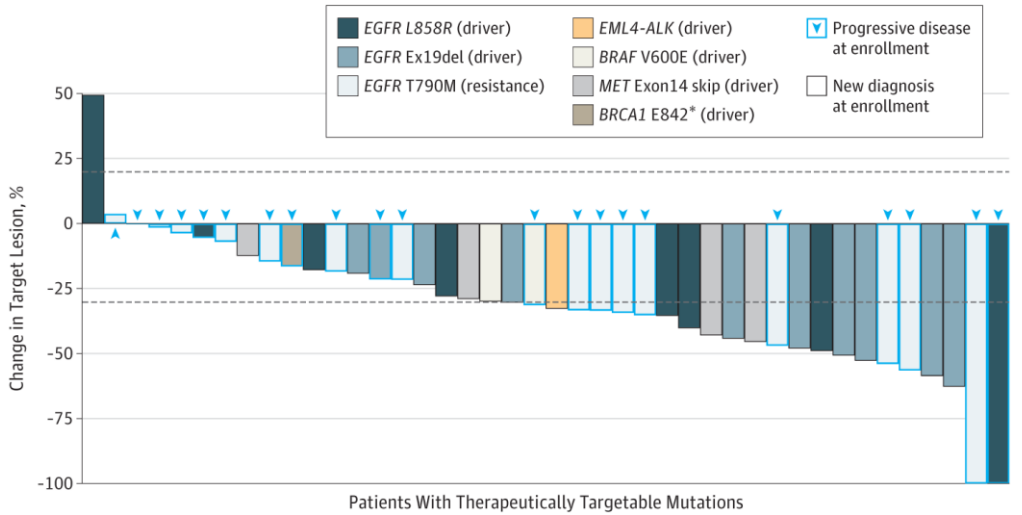

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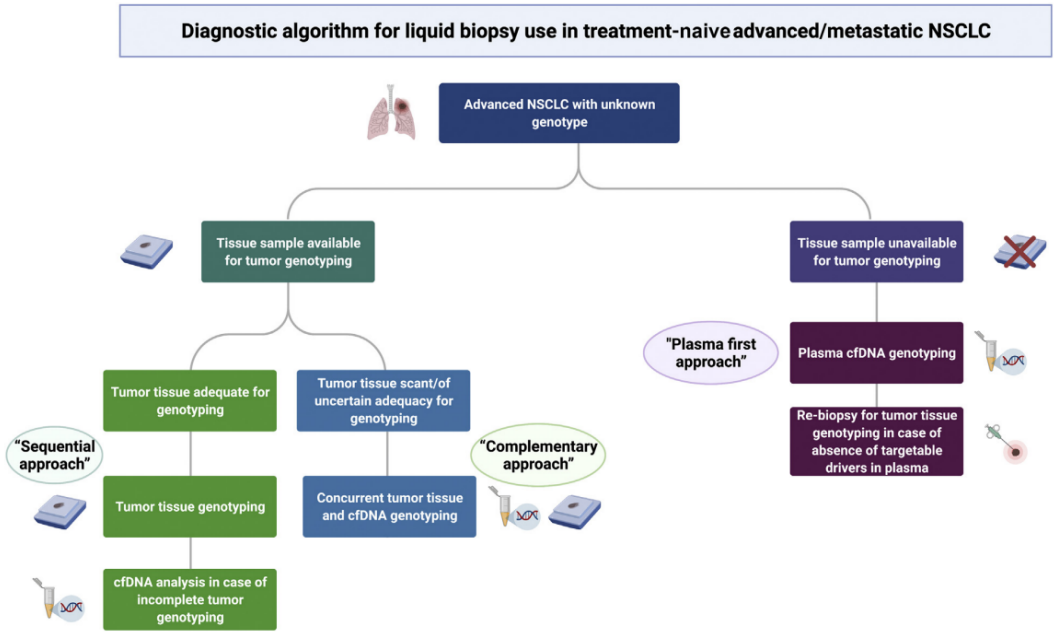
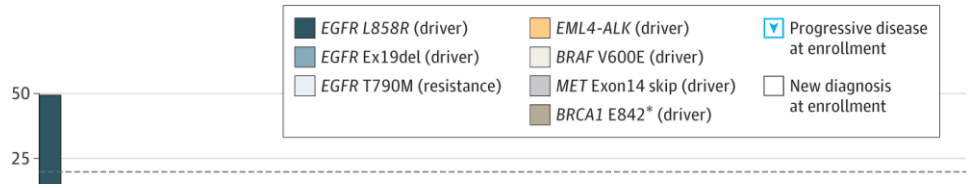


https://pubmed.ncbi.nlm.nih.gov/34246791/

BACKGROUND

Monitoring and early detection of resistance mutation

Biomarker Testing



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

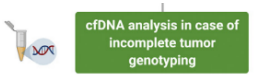
ANNALS OF ONCOLOGY

SPECIAL ARTICLE

ESMO recommendations on the use of circulating tumour DNA assays for patients with cancer: a report from the ESMO Precision Medicine Working Group

J. Pascual[1], G. Attard[2], F.-C. Bidard[3,4], G. Curigliano[5,6], L. De Mattos-Arruda[7,8], M. Diehn[9], A. Italiano[10,11,12], J. Lindberg[13], J. D. Merker[14], C. Montagut[15], N. Normanno[16], K. Pantel[17], G. Pentheroudakis[18], S. Popat[19,20], J. S. Reis-Filho[21], J. Tie[22,23], J. Seoane[24,25], N. Tarazona[26,27], T. Yoshino[28] & N. C. Turner[19,20*]

Romero, A et al. Curr Treat Options Oncol. 2021 Aug 23;22(10):86.



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FUSION TESTING IS CHALLENGING

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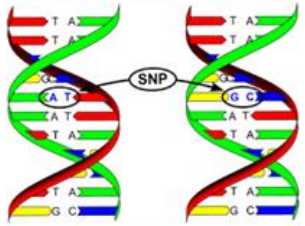


Indel examples

wild-type sequence

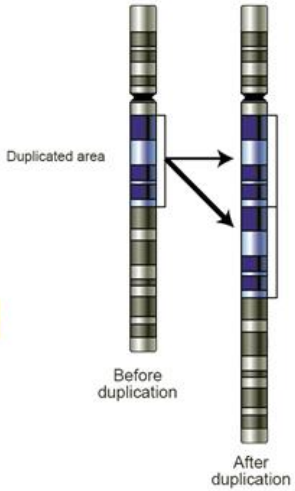
ATCTTCAGCCATAAAAGATGAAGTT

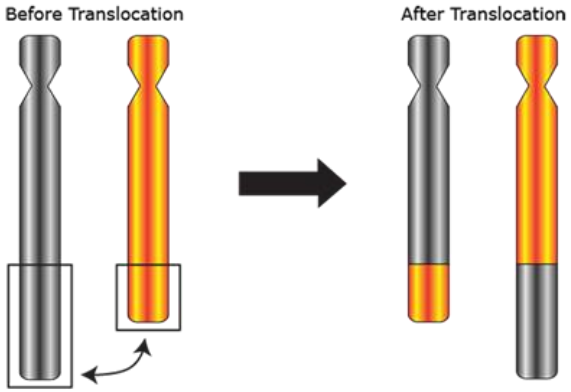
3 bp deletion

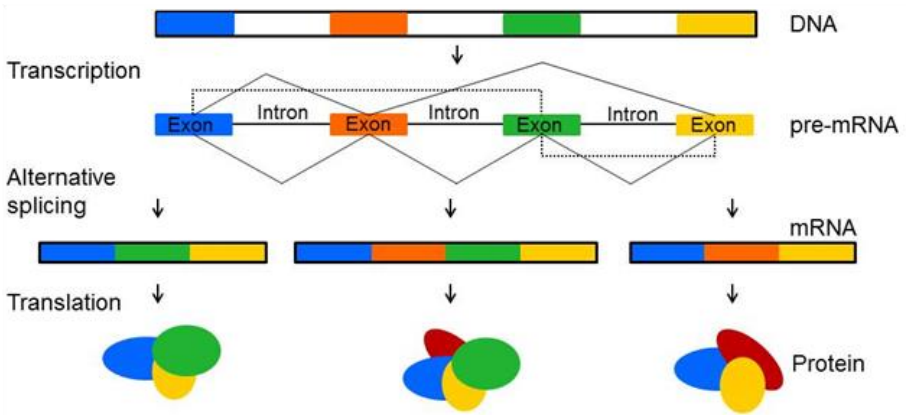
ATCTTCAGCCAAAGATGAAGTT

4 bp insertion (orange)

ATCTTCAGCCATATGTGAAAGATGAAGT





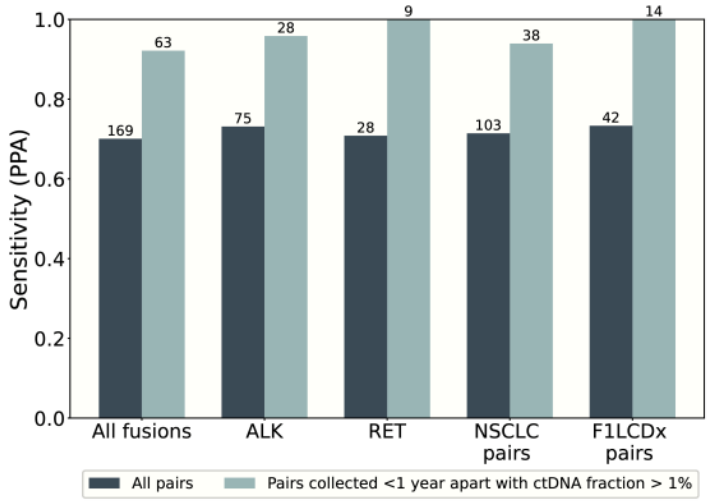


FUSION TESTING IS CHALLENGING

Molecular Methods	Variant Types: Point Mutations	Small Deletions, Insertions	Copy Number Alterations	Rearrangements	Sensitivity (%)	Turnaround Time
Sizing assays	+/–	✓				2 to 3 days
PCR and Sanger sequencing	✓	✓			20–50	3 to 4 days
PCR and pyrosequencing	✓	+/–			20–50	3 to 4 days
PCR and mass spectrometry	✓	+/–			1–10	3 to 4 days
PCR and single-base extension	✓				1–10	3 to 4 days
qPCR and digital PCR	✓	✓		✓	0.00001	2 to 3 days
Allele-specific PCR	✓					1 to 2 days
FISH			+/–	✓	<1	2 to 3 days
NGS: targeted amplicon capture	✓	✓			1–10	7–10 days
NGS: targeted hybridization capture	✓	✓	✓	+/–1	1–5	15–20 days
NGS: whole exome	✓	✓	✓	+/–1	Variable	Weeks
NGS: whole genome	✓	✓	✓	✓	Variable	Weeks

Abbreviations: PCR, polymerase chain reaction; qPCR, quantitative PCR; FISH, fluorescent in situ hybridization.

National Comprehensive Cancer Network. 2023



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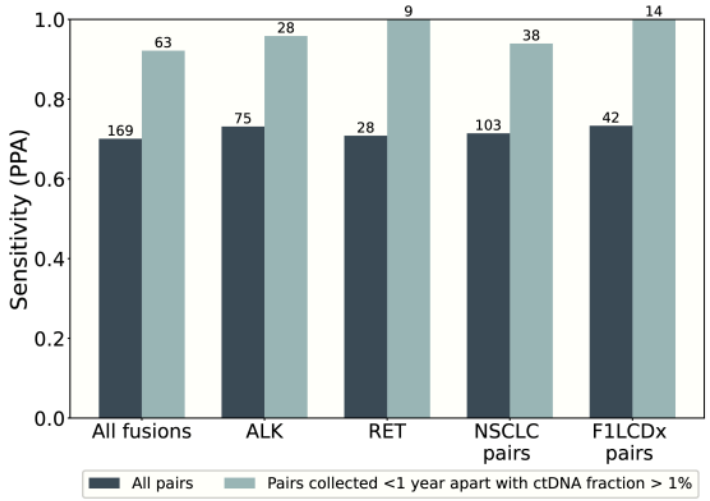

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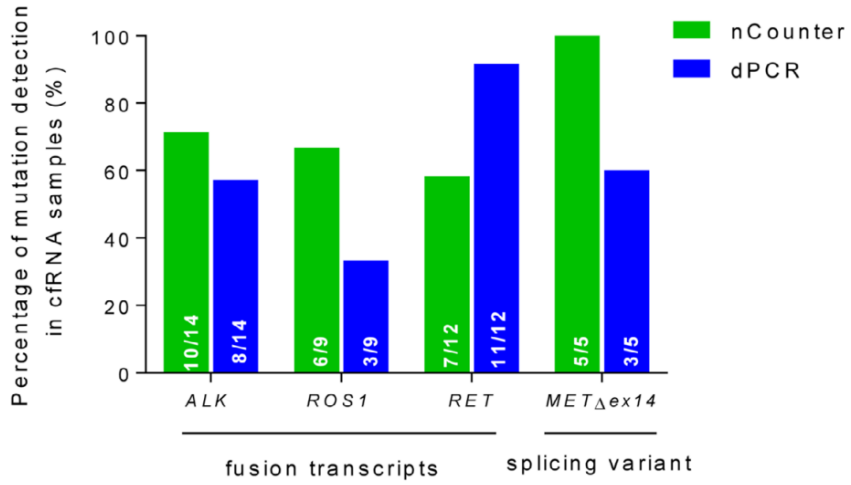

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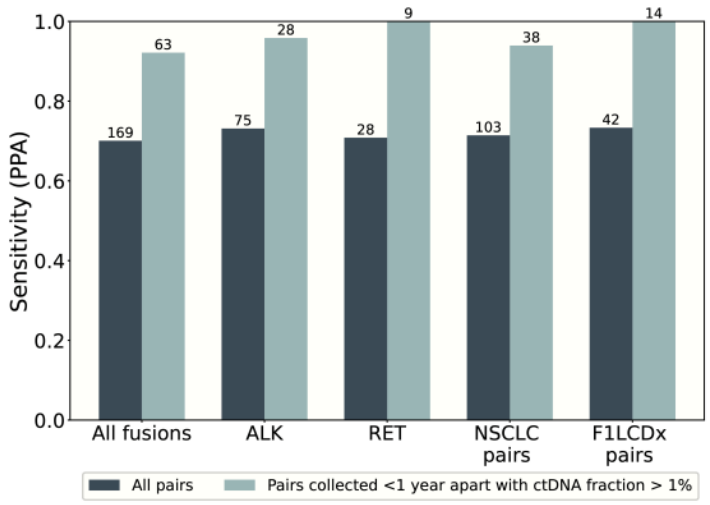

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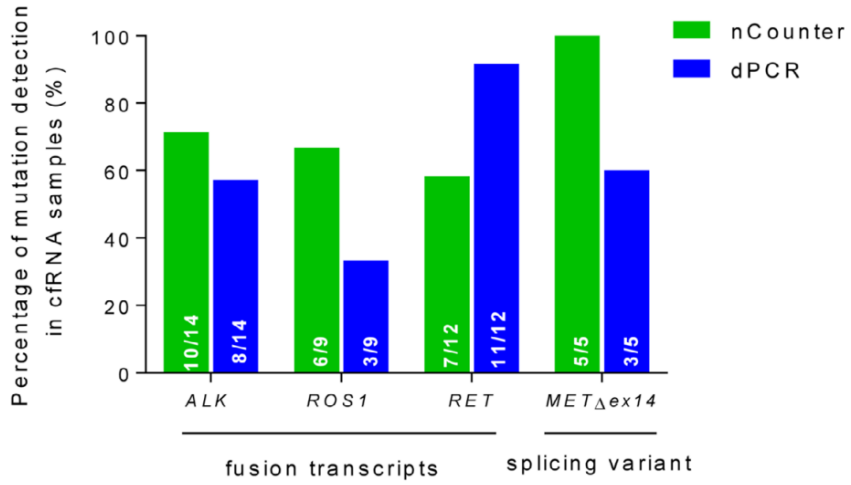

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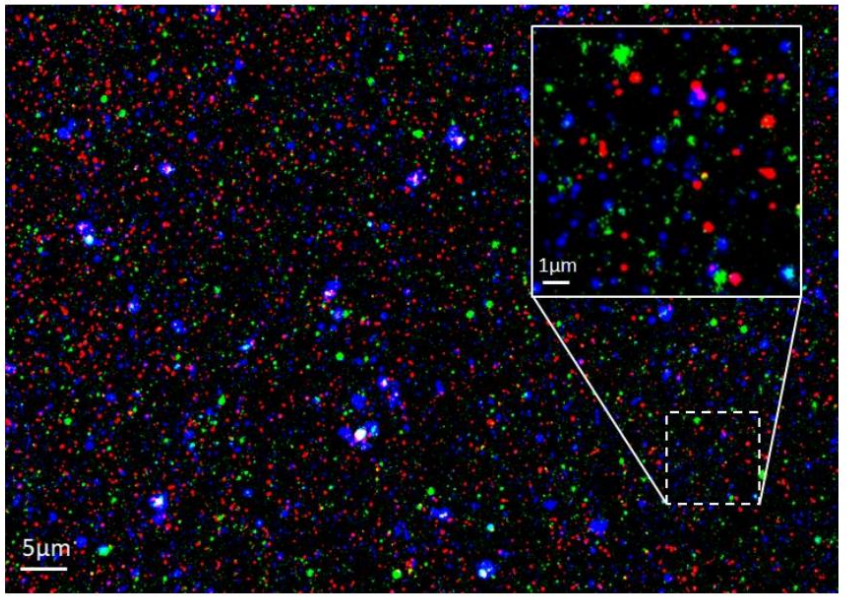
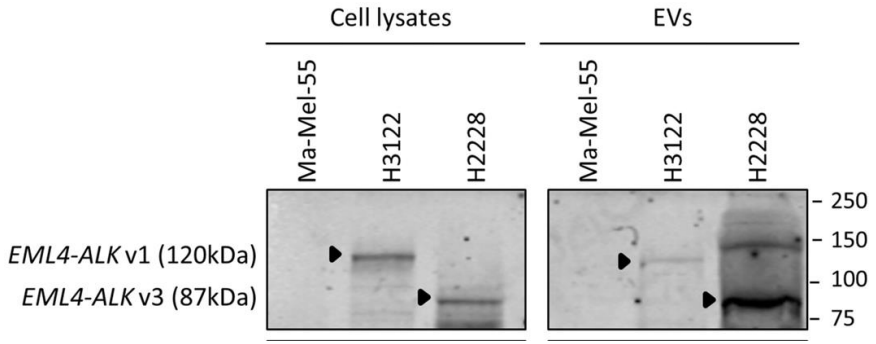


Figure S2. Characterization of EV-enriched preparations from NSCLC plasma samples by ExoView platform. CD9-captured EVs image in fluorescence mode: CD63 in red, CD9 in blue, *ALK** in green, CD63-*ALK** in yellow, CD63-CD9 in purple, *ALK**-CD9 in light blue, and CD63-CD9-*ALK** in white. *ALK**, *ALK* fusion protein.



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LIMITATIONS

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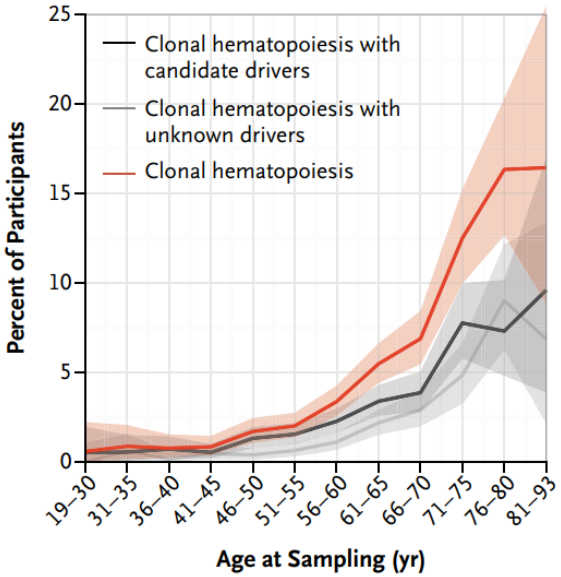
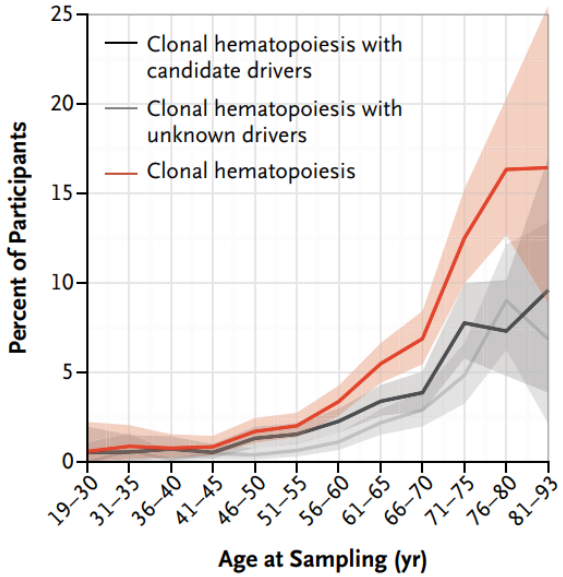


Genovese G et al. New Engj J Med 2014

LIMITATIONS



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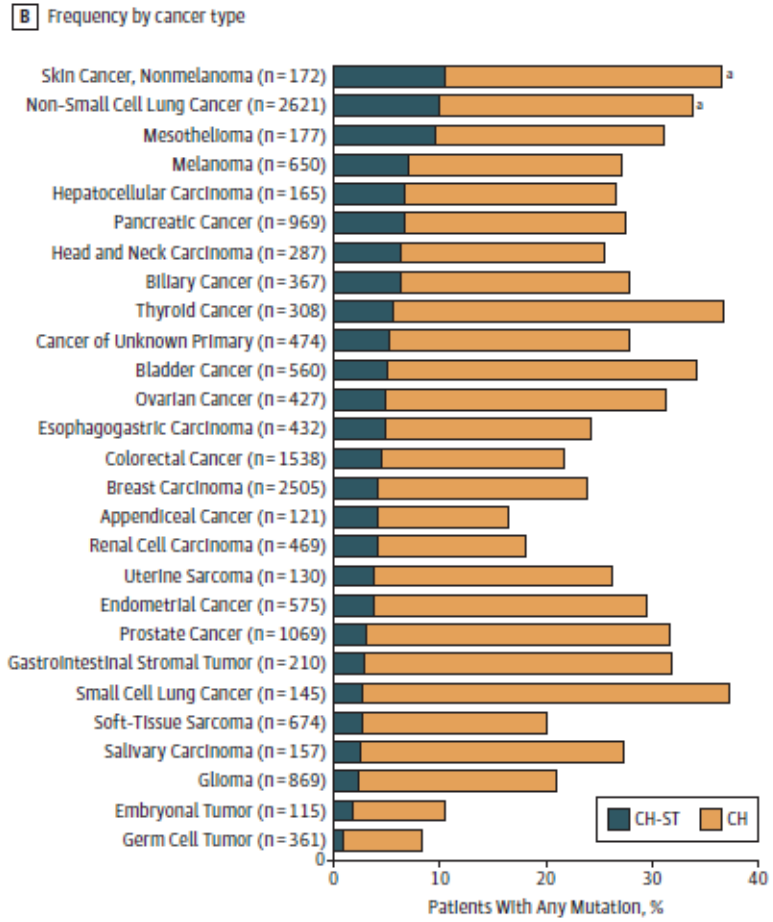

Ptashkin RN et al JAMA Oncol. 2018 Jun 5.

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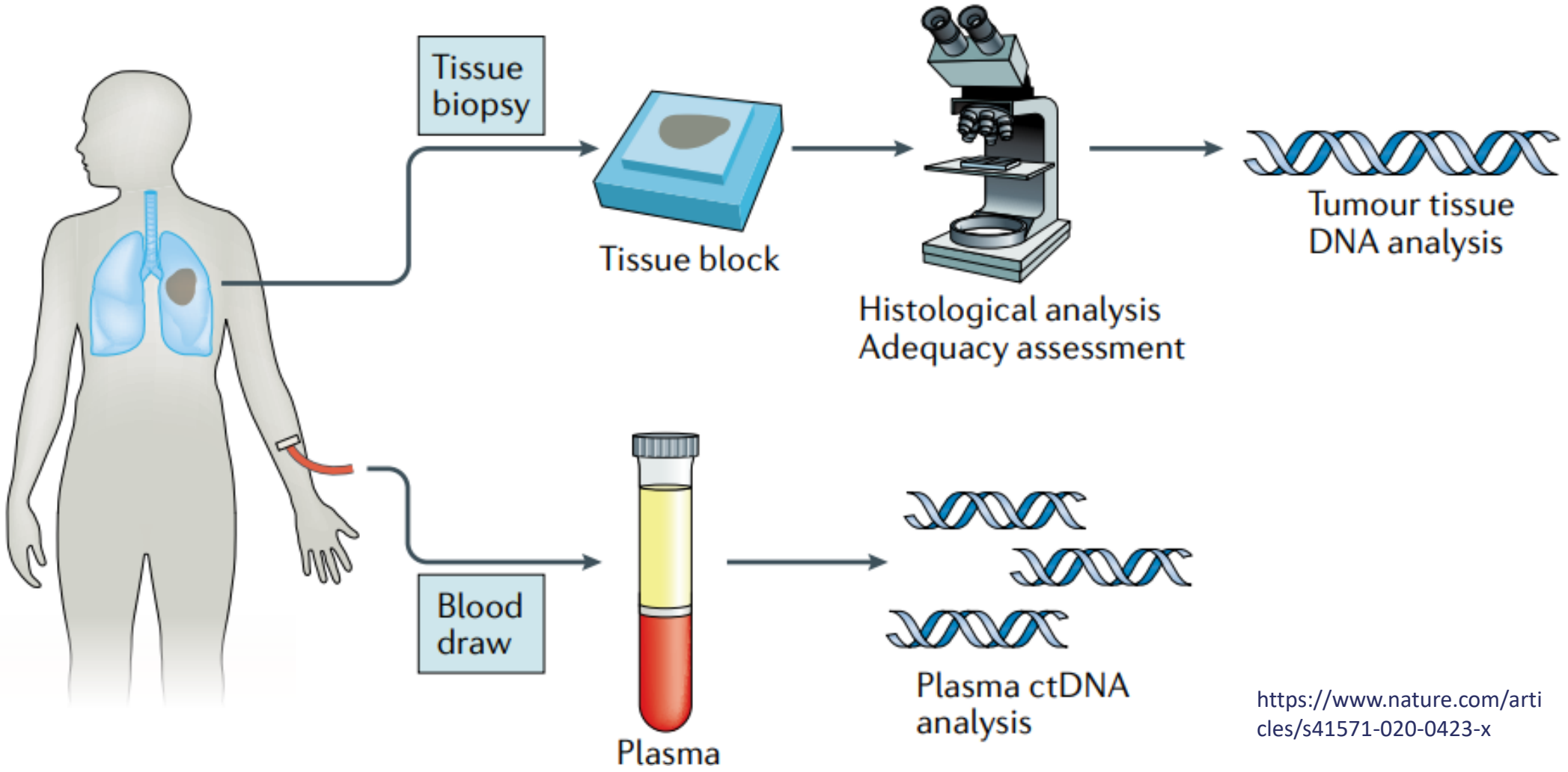
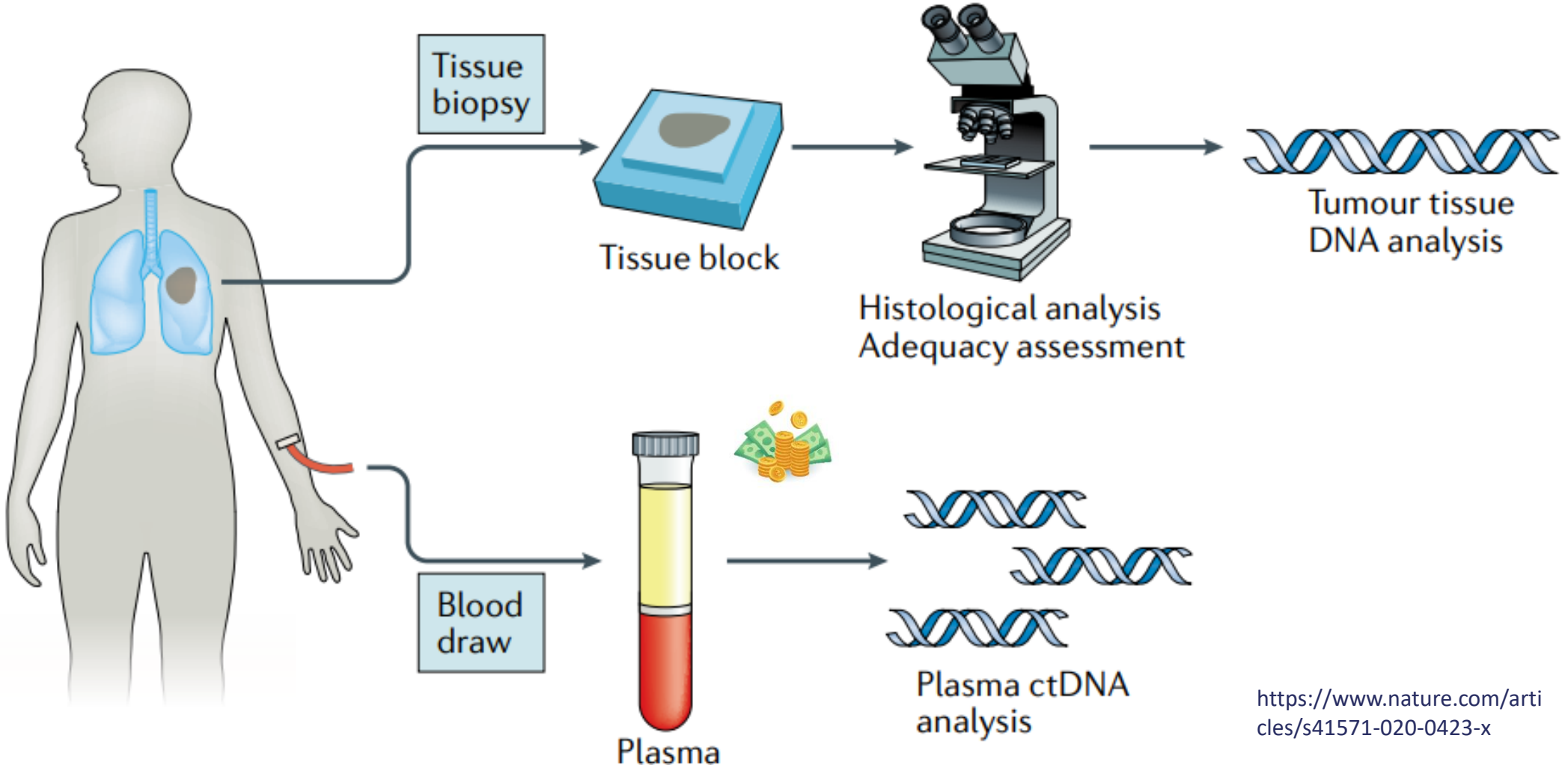


https://www.nature.com/articles/s41571-020-0423-x

LIMITATIONS



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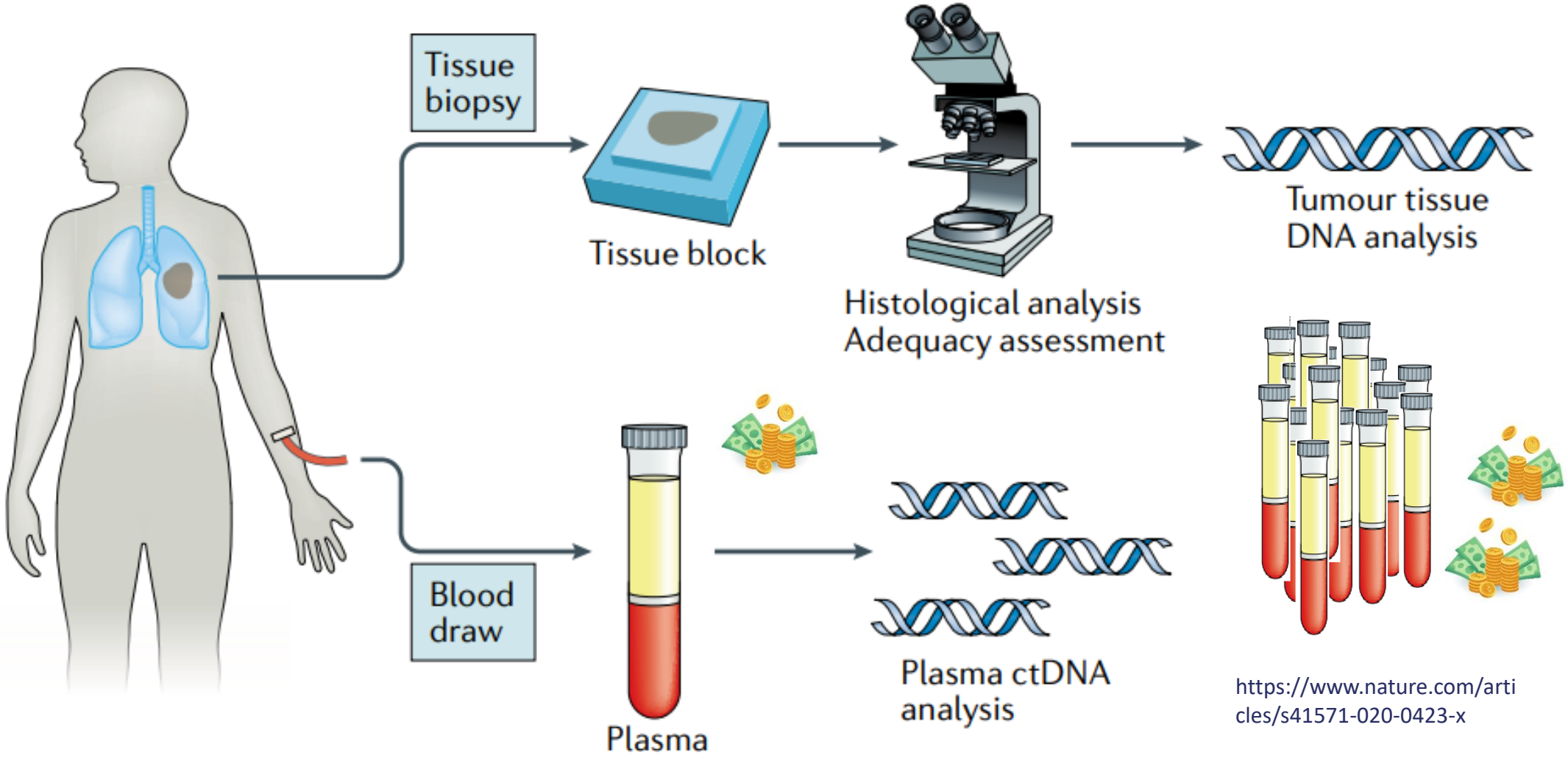

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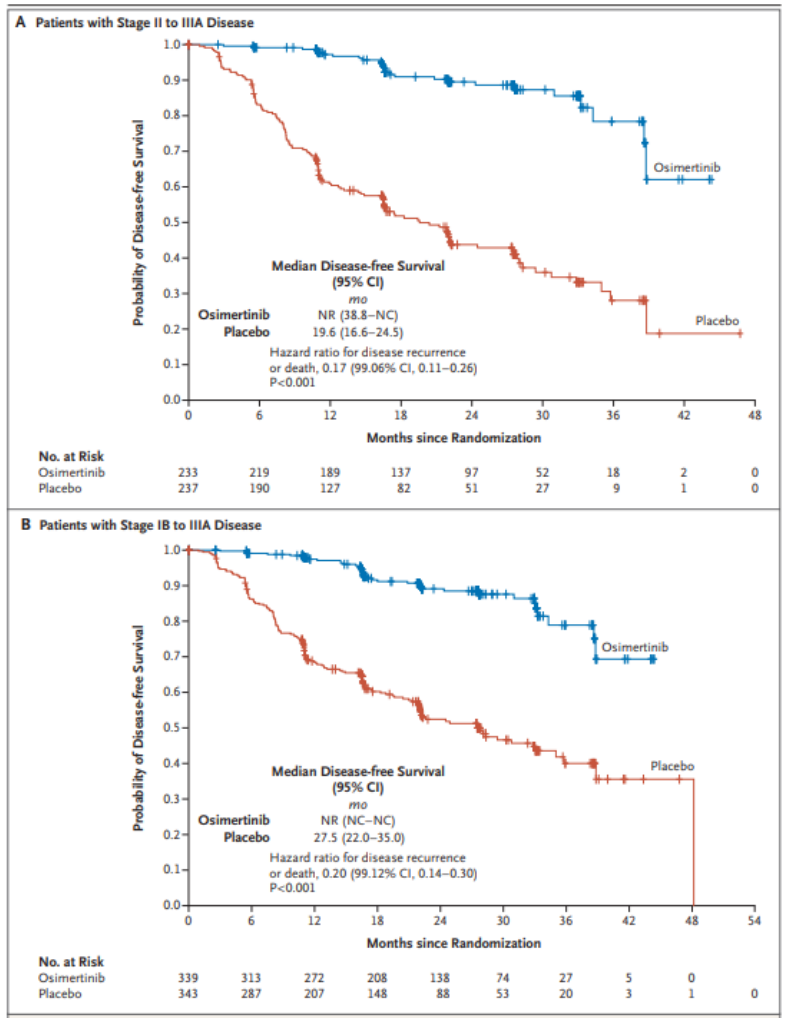
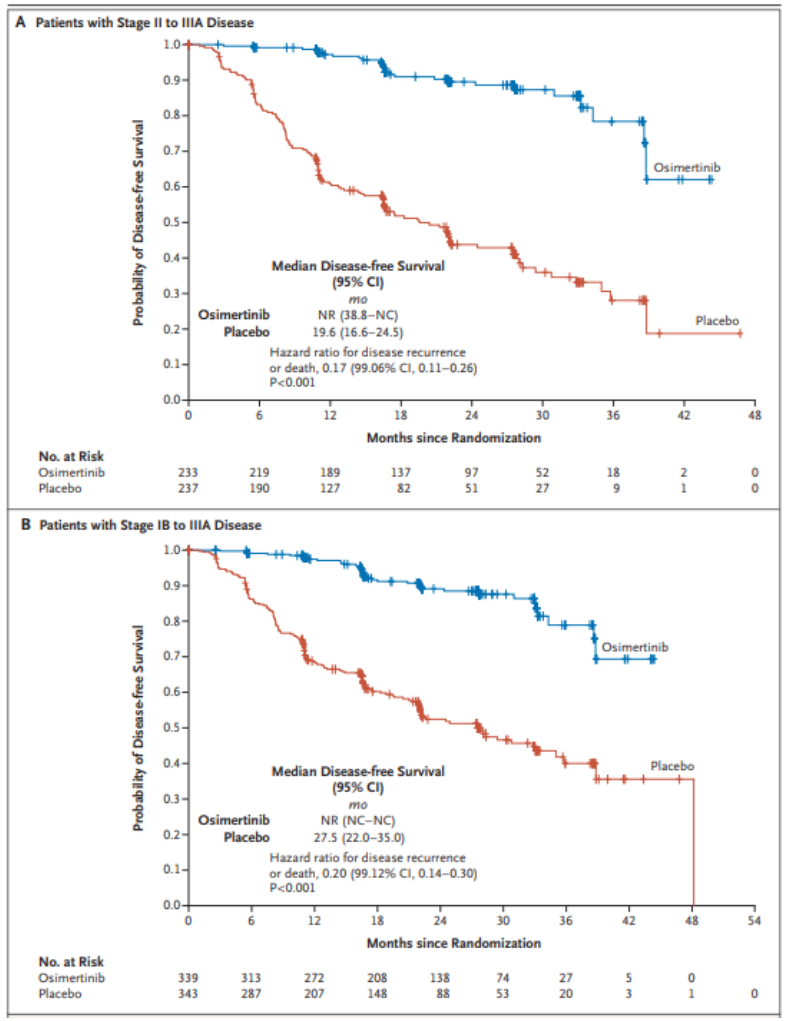
Challenges

Challenges



Wu et al. NEJM 2020

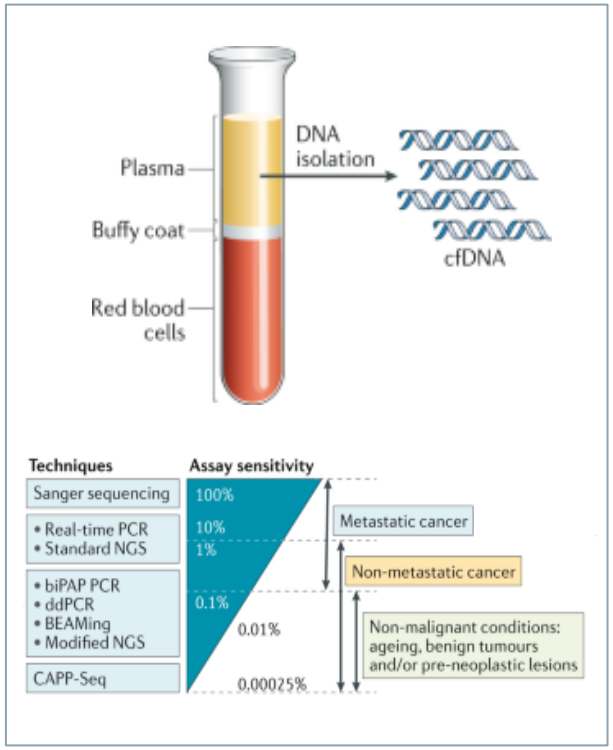
Challenges

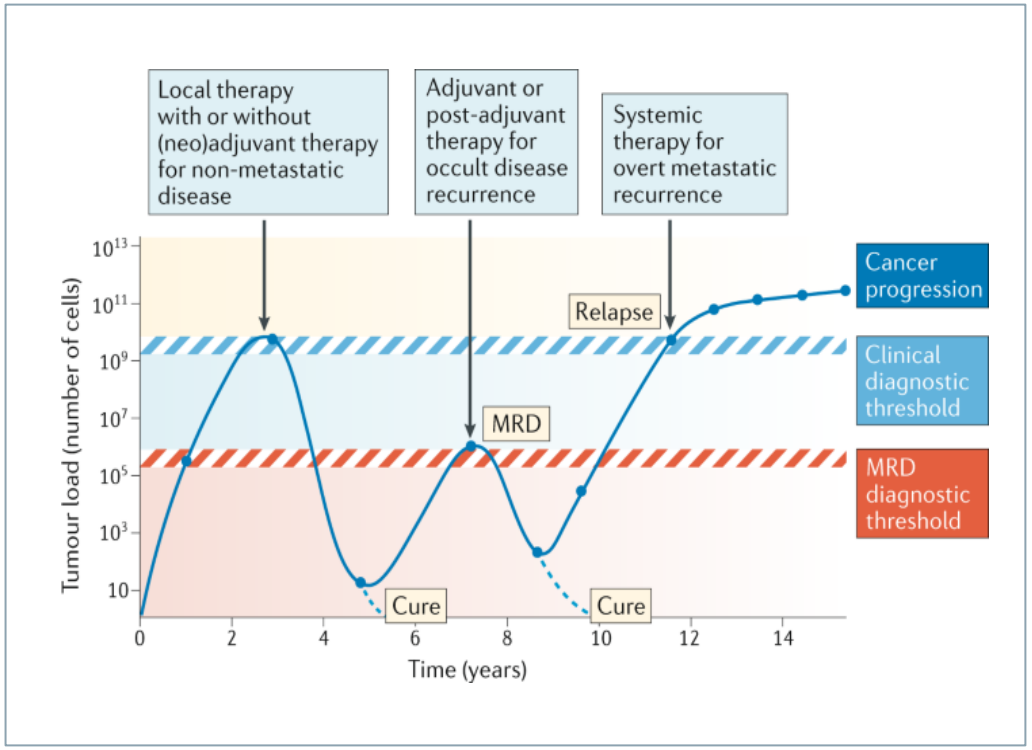


Wu et al. NEJM 2020

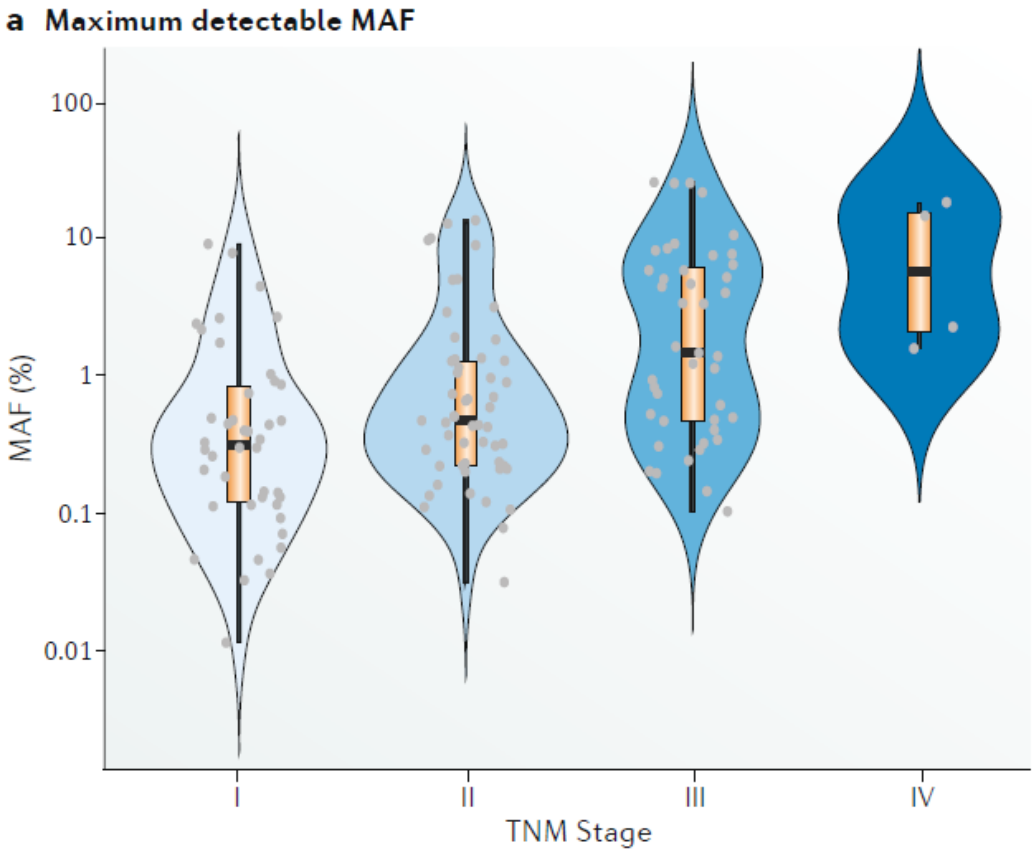
Clinical Trial	Phase	N° pts [a]	Years	Stage	Treatment Arms	DFS	OS
BR19 [10] (NCT00049543)	III	503 (EGFRm-unselected)	2002–2005	IB-IIIA	Gefitinib × 2 y vs. placebo (after adj CT) (1:1)	No difference (HR 1.22, 95% CI 0.93–1.61, p = 0.15)	No difference (HR 1.24, 95% CI 0.94–1.64, p = 0.14)
ADJUVANT-CTONG1104 [11] (NCT01405079)	III	222	2011–2014	II-IIIA	Gefitinib × 2 y vs. adj CT (1:1)	30.8 vs. 19.8 m (HR 0.56, 95% CI 0.40–0.79, p = 0.001)	75.5 vs. 62.8 m (HR 0.92, 95% CI 0.62–1.36, p = 0.674)
IMPACT [12] (UMIN000006252)	III	234	2011–2015	II-III	Gefitinib × 2 y vs. adj CT (1:1)	35.9 vs. 25.1 m (HR 0.92, 95% CI 0.67–1.28, p = 0.63)	No difference (HR 1.03, 95% CI 0.65–1.65, p = 0.89)
RADIANT [13] (NCT00373425)	III	973 ('EGFR-positive')	2007–2010	IB-IIIA	Erlotinib × 2 y vs. placebo (after adj CT) (2:1)	50.5 vs. 48.2 m (HR 0.90, 95% CI 0.74–1.10, p = 0.324)	Not reached (HR 1.13, 95% CI 0.88–1.45, p = 0.335)
SELECT [14] (NCT00567359)	II	100	2008–2012	IA-IIIA	Erlotinib × 2 y (after adj CT)	Not reached (5-year DFS rate 56%)	Not reached (5-year OS rate 86%)
EVAN [15,16] (NCT01683175)	II	102	2012–2015	IIIA	Erlotinib × 2 y vs. adj CT (1:1)	42.4 vs. 21.0 m (HR 0.27, 95% CI 0.14–0.53, p < 0.0001)	84.2 vs. 61.1 m (HR 0.32, 95% CI 0.15–0.67)
EVIDENCE [17] (NCT02448797)	III	322	2015–2019	II-IIIA	Icotinib × 2 y vs. adj CT (1:1)	47.0 vs. 22.1 m (HR 0.36, 95% CI 0.24–0.55, p < 0.0001)	Not reached (HR 0.91, 95% CI 0.42–1.94)
ADAURA [18,19] (NCT02511106)	III	682	2015–2019	IB-IIIA	Osimertinib × 3 y vs. placebo (after adj CT or not) (1:1)	Not reached vs. 27.5 m (HR 0.20, 99% CI 0.14–0.30, p < 0.001) [b]	Not reached (2-year OS rate 98% vs. 85%) [b]

Scordilli et al. Int J Mol Sci. 2022;23





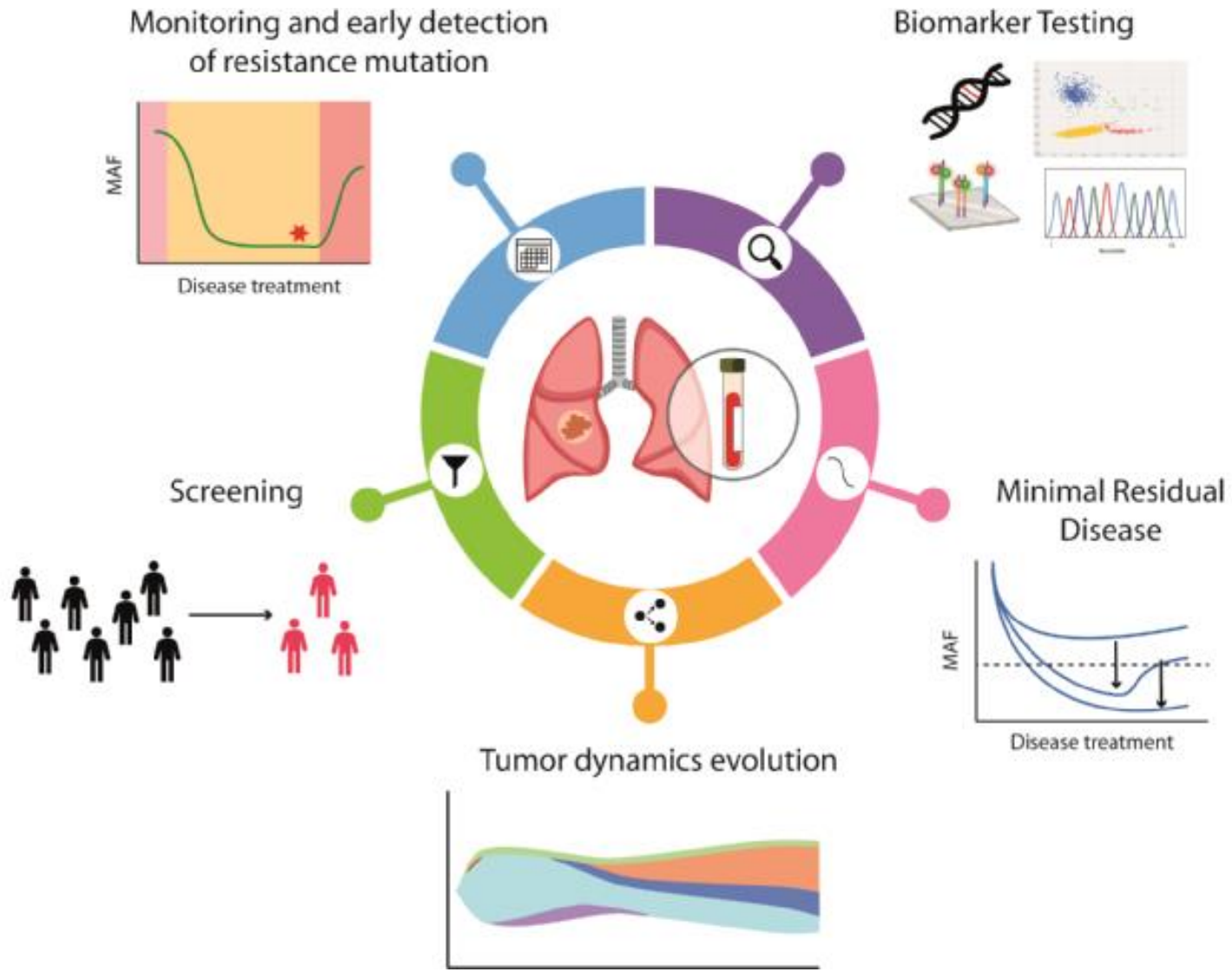
Pantel, K et al. Nat Rev Clin Oncol. 2019;16:409-424.



https://pubmed.ncbi.nlm.nih.gov/29968853/

T Tumor Size	N Lymph Node	M Metastasis	B Blood
T1 Tumor size/local invasion	**N0** Local nodes, Distant nodes No regional lymph node invasion	**M0** No distant metastasis	**B0** ctDNA No ctDNA mutations in blood
T2 Tumor size/local invasion	**N1** Local nodes, Distant nodes Tumor spead to closest or small number of regional lymph nodes	**M1** Distant metastasis	**B1** ctDNA mutations in blood (can be further defined with more detailed quantification in the future)
T3 Tumor size/local invasion	**N2** Local nodes, Distant nodes Tumor spead to an extent between N1 and N3		
T4 Tumor of any size that invades to other organs	**N3** Local nodes, Distant nodes Tumor spead to more distant or regional numerous lymph nodes		

Yang, M et al. Ann Oncol. 2018;29:311-323.



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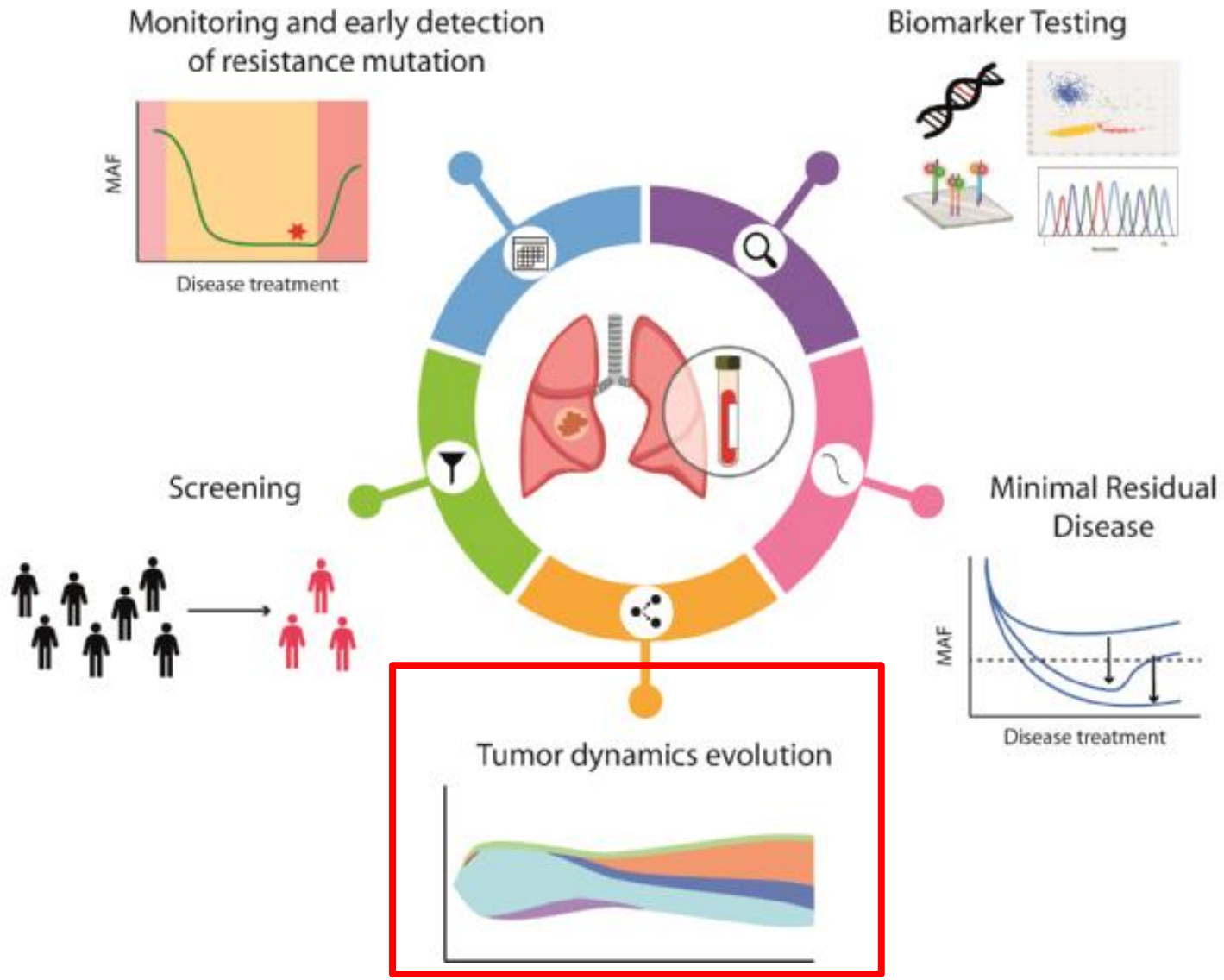
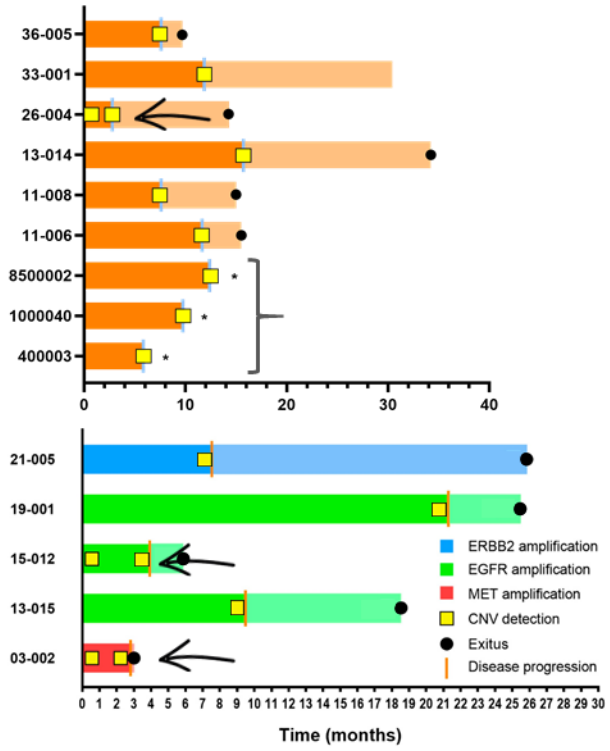


Romero, A et al. Curr Treat Options Oncol. 2021 Aug 23;22(10):86.

Resistance mechanism

Sample	Gene	Coding transcript change	Protein change	Functional classification	Location	B	3	6	P	
400003	KRAS	c.35G>T	p.G12V	missense	exonic	-	-	-	●	Unknown
1000040	KRAS	c.182A>G	p.Q61R	missense	exonic	-	-	-	●	Unknown
8500002	KRAS	c.34G>A	p.G12S	missense	exonic	-	-	-	●	Unknown
03-002	MET	CNV	CNV	CNV	-	●			●	Primary resistance
11-006	KRAS	c.34G>T	p.G12C	missense	exonic	●	●	●	●	Acquired resistance
11-008	PIK3CA	c.1633G>A	p.E545K	missense	exonic	●	●	-	●	Acquired resistance
13-014	BRAF	c.1799T>A	p.V600E	missense	exonic	●	●	●	●	Acquired resistance
13-015	EGFR	CNV	CNV	CNV	-	●			●	Acquired resistance
15-012	EGFR	CNV	CNV	CNV	-	●			●	Primary resistance
19-001	EGFR	CNV	CNV	CNV	-	●			●	Acquired resistance
21-005	ERBB2	CNV	CNV	CNV	-	●			●	Acquired resistance
26-004	KRAS	c.436G>A	p.A146T	missense	exonic	●	-	-	●	Primary resistance
33-001	KRAS	c.44G>T	p.G15V	missense	exonic	●	●	●	●	Acquired resistance
36-005	KRAS	c.183A>C	p.Q61H	missense	exonic	●	●	●	●	Acquired resistance
36-005	KRAS	c.35G>A	p.G12D	missense	exonic	●	●	●	●	Acquired resistance

● Mutation detected by dPCR and NGS ● Mutation not detected ● Not tested

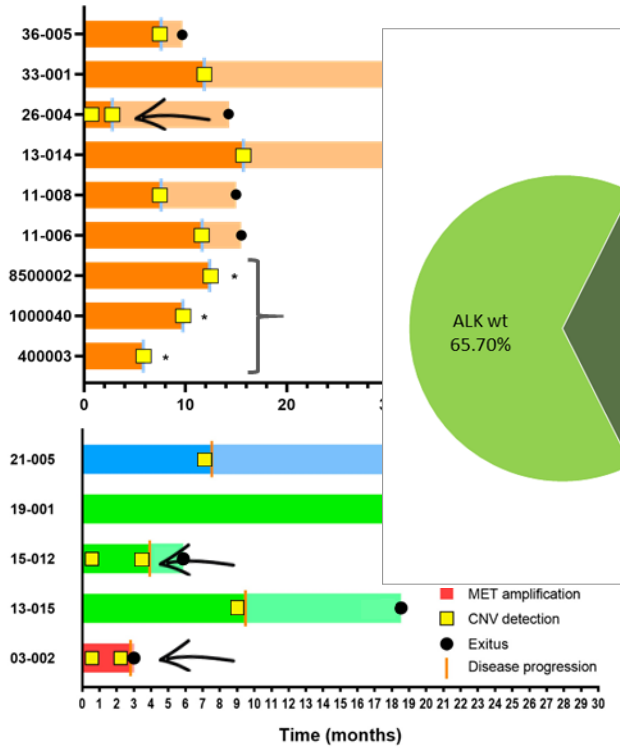


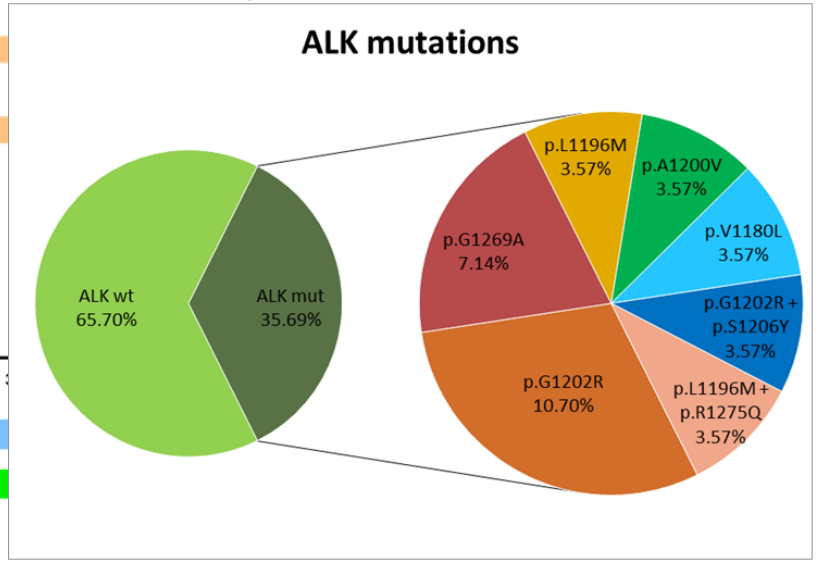
Modified from Serna-Blasco R et al. Cancers 2022 Sep 13;14(18):4446.

Resistance mechanism

Sample	Gene	Coding transcript change	Protein change	Functional classification	Location	B	3	6	P	
400003	KRAS	c.35G>T	p.G12V	missense	exonic	-	-	-	●	Unknown
1000040	KRAS	c.182A>G	p.Q61R	missense	exonic	-	-	-	●	Unknown
8500002	KRAS	c.34G>A	p.G12S	missense	exonic	-	-	-	●	Unknown
03-002	MET	CNV	CNV	CNV	-	●			●	Primary resistance
11-006	KRAS	c.34G>T	p.G12C	missense	exonic	●	●	●	●	Acquired resistance
11-008	PIK3CA	c.1633G>A	p.E545K	missense	exonic	●	●	-	●	Acquired resistance
13-014	BRAF	c.1799T>A	p.V600E	missense	exonic	●	●	●	●	Acquired resistance
13-015	EGFR	CNV	CNV	CNV	-	●			●	Acquired resistance
15-012	EGFR	CNV	CNV	CNV	-	●			●	Primary resistance
19-001	EGFR	CNV	CNV	CNV	-	●			●	Acquired resistance
21-005	ERBB2	CNV	CNV	CNV	-	●			●	Acquired resistance
26-004	KRAS	c.436G>A	p.A146T	missense	exonic	●	-	-	●	Primary resistance
33-001	KRAS	c.44G>T	p.G15V	missense	exonic	●	●	●	●	Acquired resistance
36-005	KRAS	c.183A>C	p.Q61H	missense	exonic	●	●	●	●	Acquired resistance
36-005	KRAS	c.35G>A	p.G12D	missense	exonic	●	●	●	●	Acquired resistance

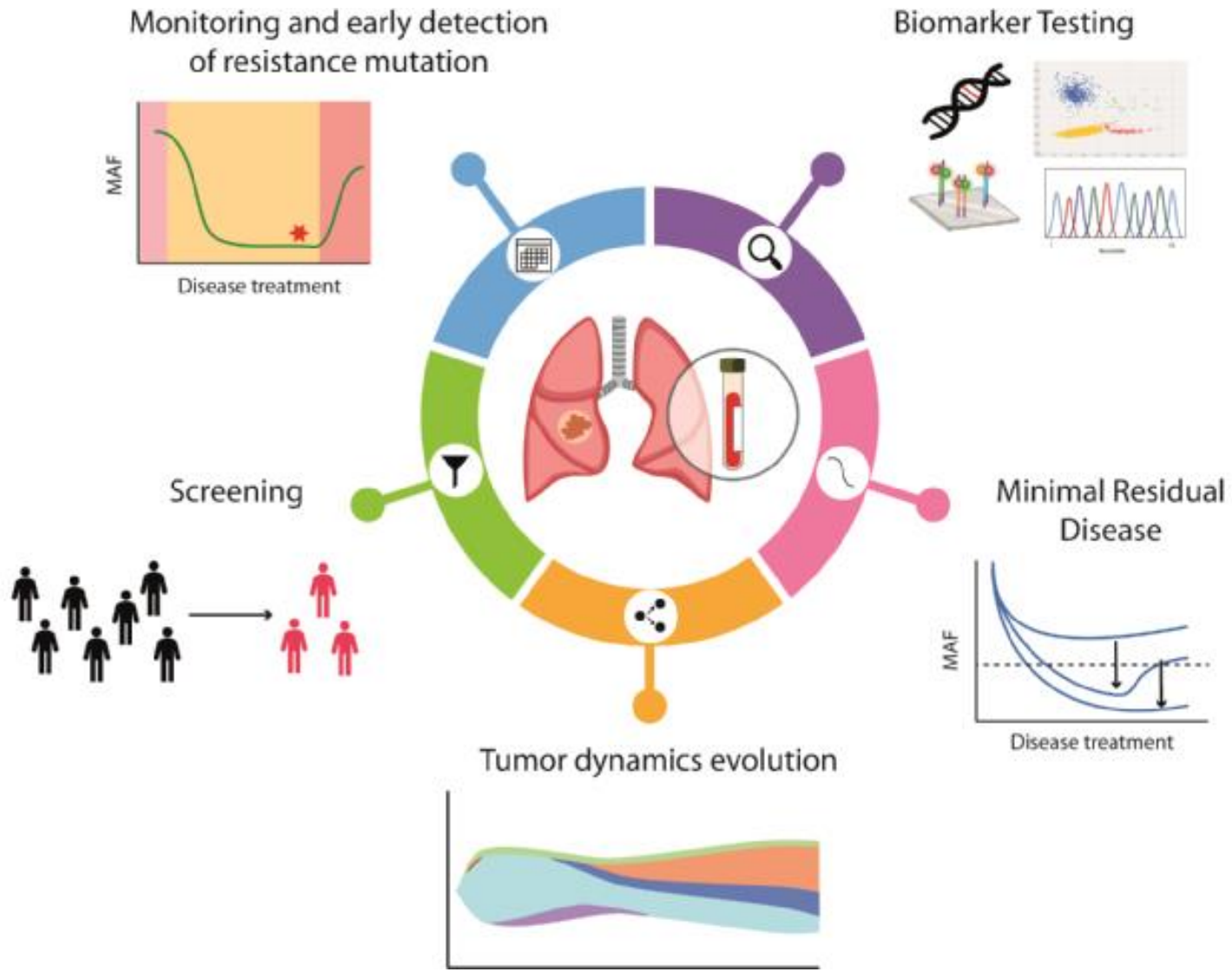
● Mutation detected by dPCR and NGS ● Mutation not detected ● Not tested



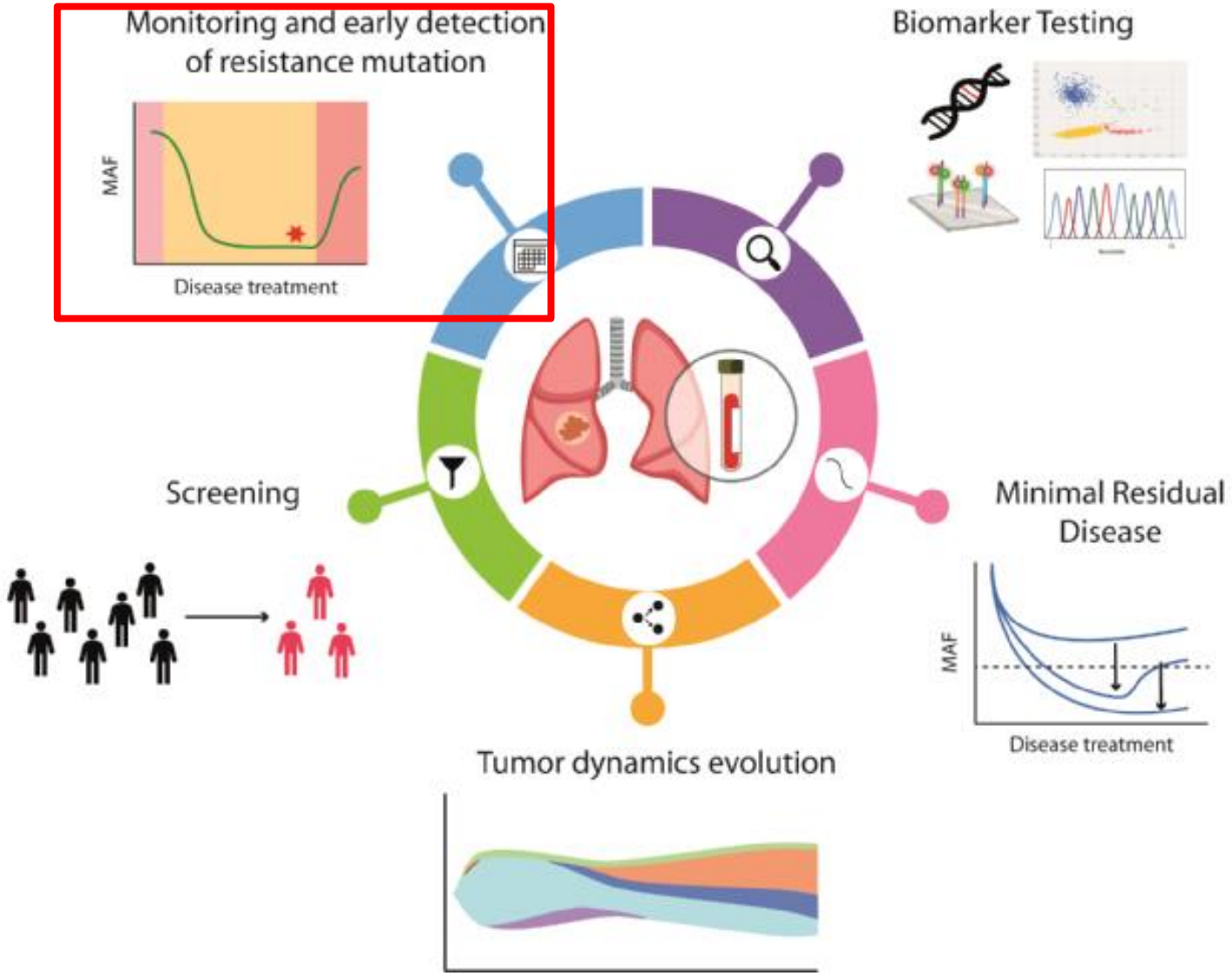


https://pubmed.ncbi.nlm.nih.gov/34058070/

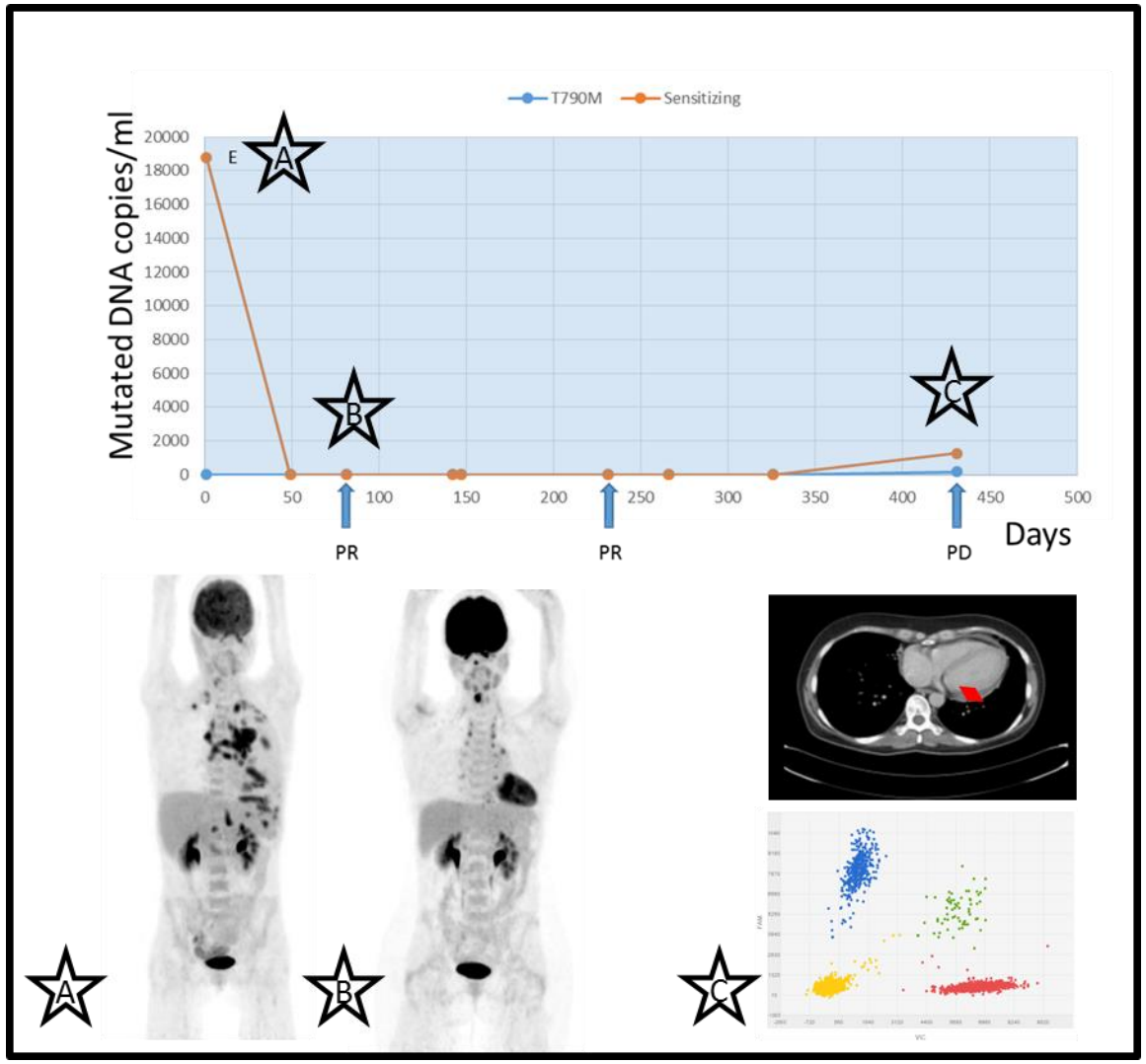
Modified from Serna-Blasco R et al. Cancers 2022 Sep 13;14(18):4446.



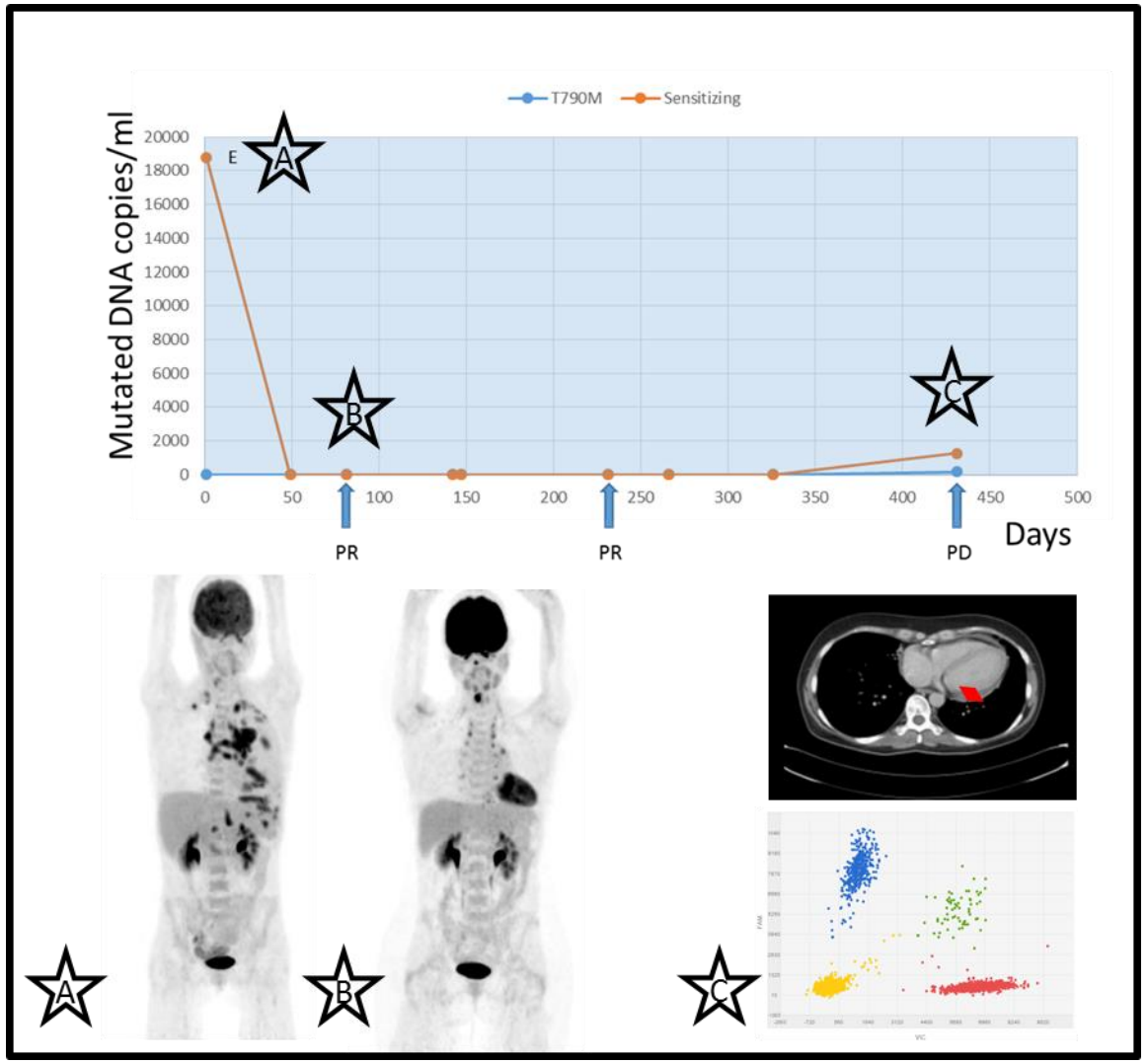
Romero, A et al. Curr Treat Options Oncol. 2021 Aug 23;22(10):86.



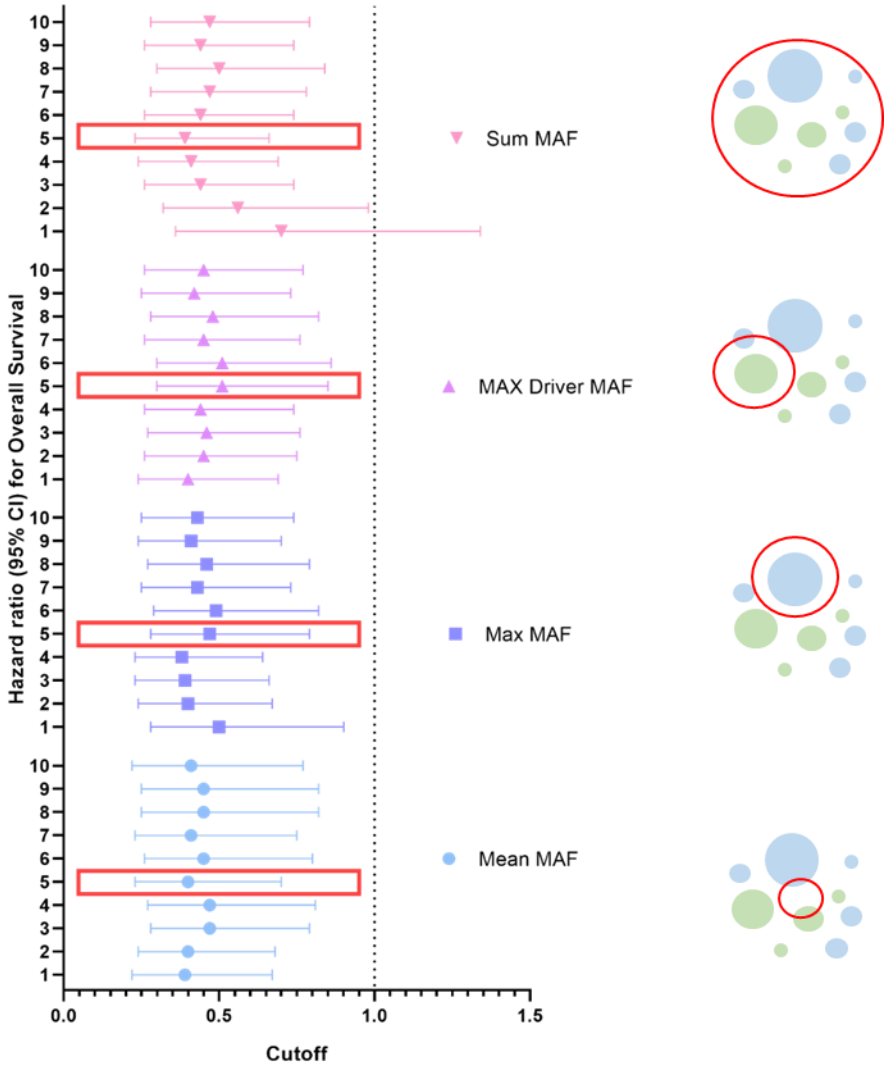
Romero, A et al. Curr Treat Options Oncol. 2021 Aug 23;22(10):86.



Provencio M , et al . Oncotarget. 2017 Aug 7;8(36):60291-60298.



Provencio M , et al . Oncotarget. 2017 Aug 7;8(36):60291-60298.



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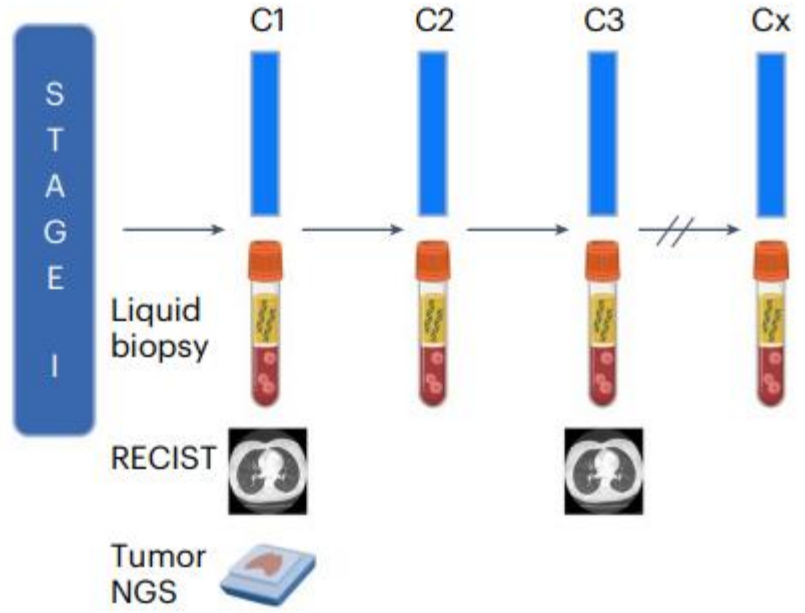
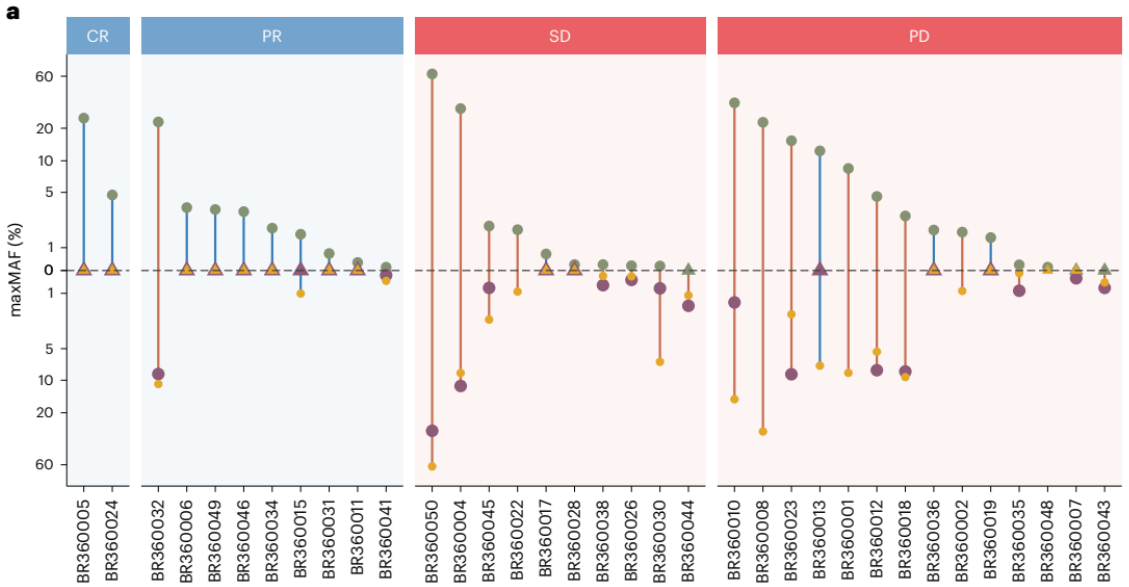


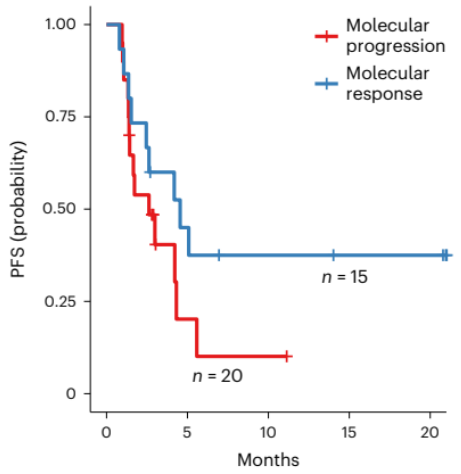
Eligibility

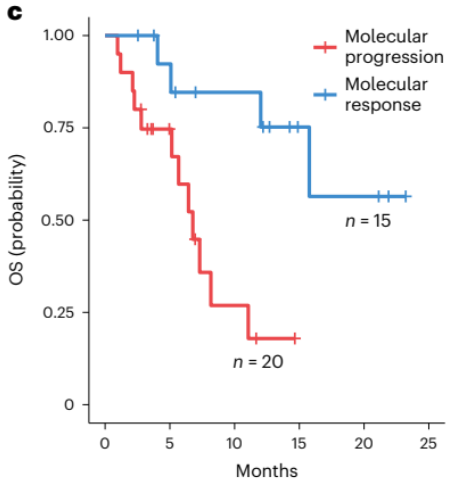
Adv/met NSCLC
ICB/chemo-naive
EGFR/ALK mut negative
PD-L1 ≥ 1%

1° endpoints

ctDNA response timing concordance btw ctDNA and RECIST response

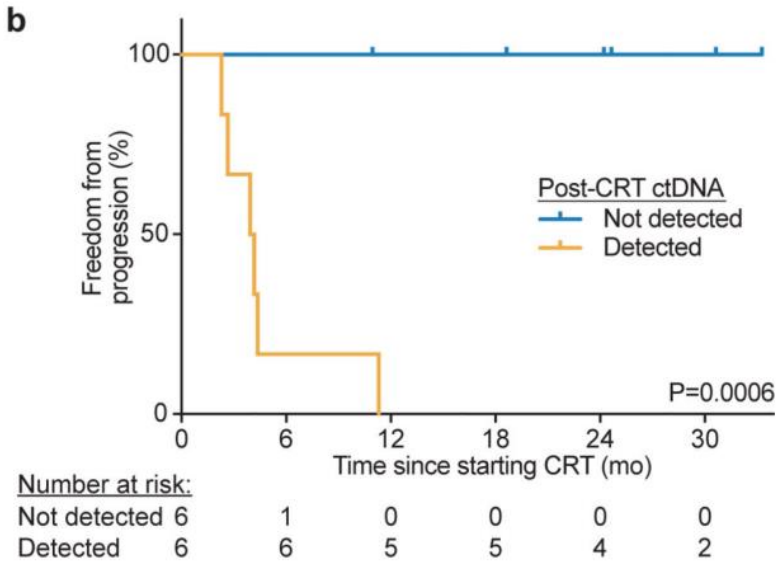


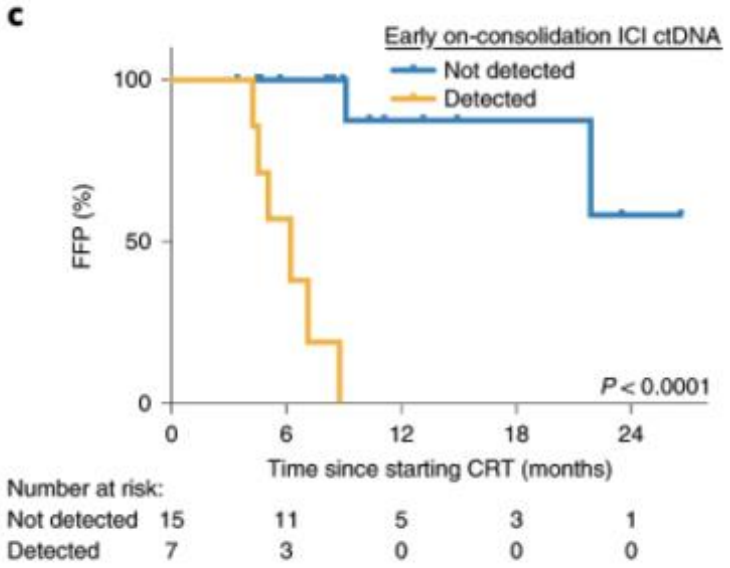


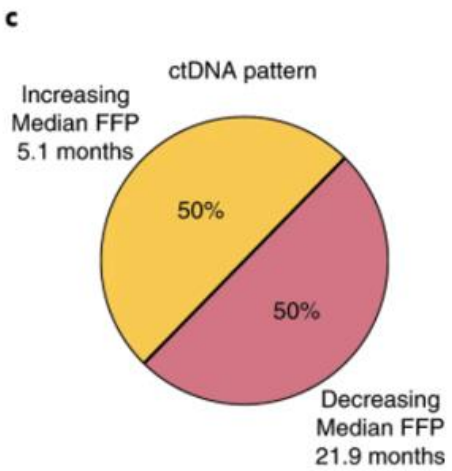


https://www.nature.com/articles/s41591-023-02598-9

ctDNA in patients treated with CRT and consolidation ICI







CAPP-Seq ctDNA analysis.
218 samples from 65 locally advanced NSCLC patients receiving chemoradiation therapy (CRT), including 28 patients receiving consolidation immune checkpoint inhibition (CICI).

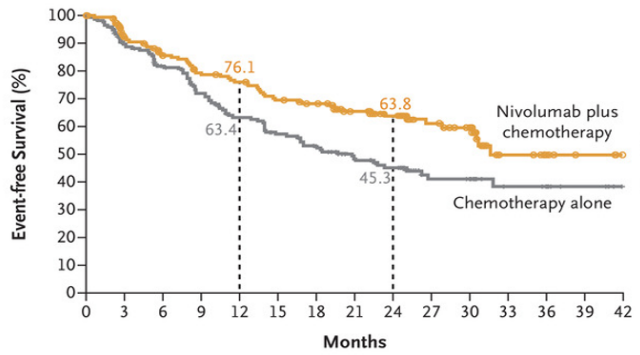
Moding E et al. Nat Cancer. 2020

Role of ctDNA in the Neoadjuvant setting

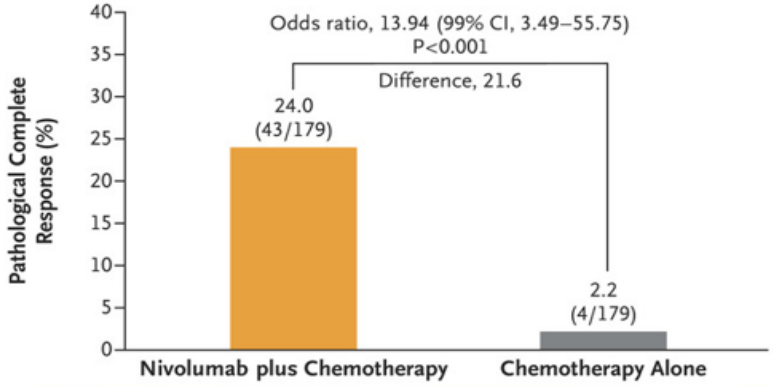
ORIGINAL ARTICLE

Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer

Patrick M. Forde, M.B., B.Ch., Jonathan Spicer, M.D., Ph.D., Shun Lu, M.D., Ph.D., Mariano Provencio, M.D., Ph.D., Tetsuya Mitsudomi, M.D., Ph.D., Mark M. Awad, M.D., Ph.D., Enriqueta Felip, M.D., Ph.D., Stephen R. Broderick, M.D., M.P.H.S., Julie R. Brahmer, M.D., Scott J. Swanson, M.D., Keith Kerr, M.B., Ch.B., Changli Wang, M.D., Ph.D., et al., for the CheckMate 816 Investigators*



No. at Risk														
Nivolumab plus chemotherapy	179	151	136	124	118	107	102	87	74	41	34	13	6	3	0
Chemotherapy alone	179	144	126	109	94	83	75	61	52	26	24	13	11	4	0

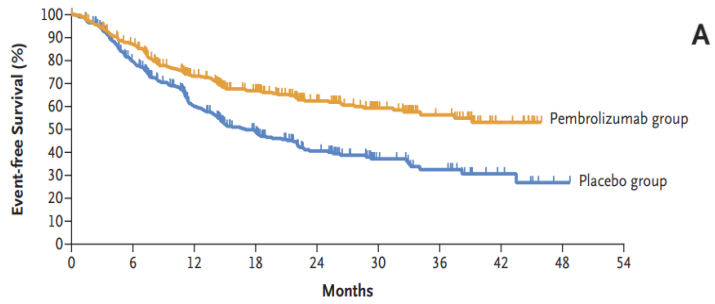


ORIGINAL ARTICLE

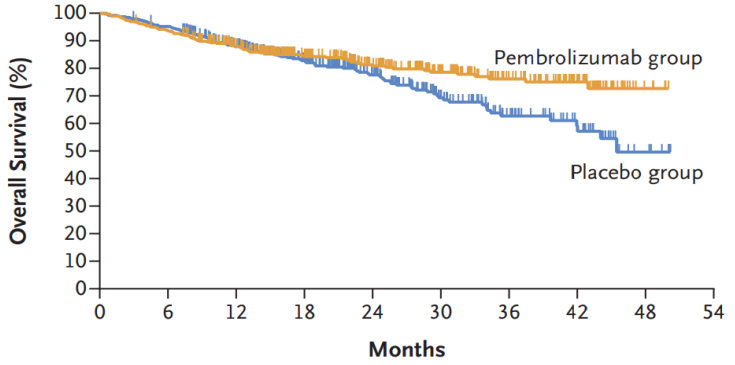
Perioperative Pembrolizumab for Early-Stage Non–Small-Cell Lung Cancer

Heather Wakelee, M.D., Moishe Liberman, M.D., Ph.D., Terufumi Kato, M.D., Masahiro Tsuboi, M.D., Ph.D., Se-Hoon Lee, M.D., Ph.D., Shugeng Gao, M.D., Ke-Neng Chen, M.D., Ph.D., Christophe Dooms, M.D., Ph.D., Margarita Majem, M.D., Ph.D., Ekkehard Eigendorff, M.D., Gastón L. Martinengo, M.D., Olivier Bylicki, M.D., Delvys Rodríguez-Abreu, M.D., Ph.D., Jamie E. Chaft, M.D., Silvia Novello, M.D., Ph.D., Jing Yang, Ph.D., Steven M. Keller, M.D., Ayman Samkari, M.D., and Jonathan D. Spicer, M.D., Ph.D. for the KEYNOTE-671 Investigators*

A Event-free Survival



No. at Risk										
Pembrolizumab group	397	330	236	172	117	72	42	11	0	0
Placebo group	400	294	183	124	74	38	24	9	1	0

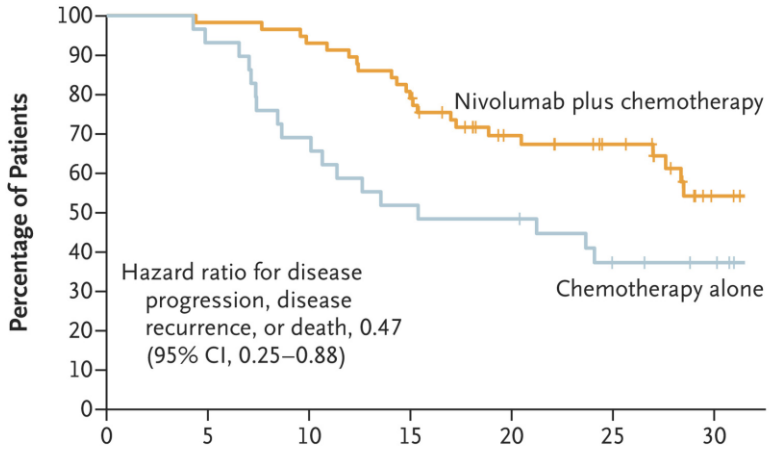


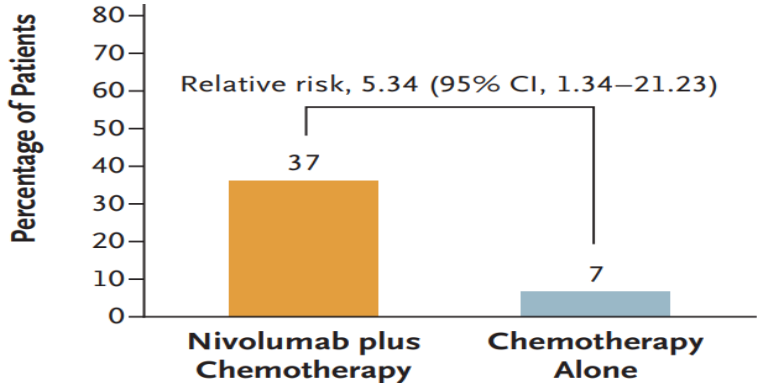
No. at Risk										
Pembrolizumab group	397	370	313	232	170	118	76	41	5	0
Placebo group	400	379	316	225	153	91	54	30	6	0

Perioperative Nivolumab and Chemotherapy in Stage III Non–Small-Cell Lung Cancer

Mariano Provencio, M.D., Ph.D., Ernest Nadal, M.D., Ph.D., José L. González-Larriba, M.D., Ph.D., Alex Martínez-Martí, M.D., Reyes Bernabé, M.D., Joaquim Bosch-Barrera, M.D., Joaquín Casal-Rubio, M.D., Virginia Calvo, M.D., Ph.D., Amelia Insa, M.D., Santiago Ponce, M.D., Ph.D., Noemí Reguart, M.D., Ph.D., Javier de Castro, M.D., Ph.D., Joaquín Mosquera, M.D., Ph.D., Manuel Cobo, M.D., Ph.D., Andrés Aguilar, M.D., Guillermo López Vivanco, M.D., Carlos Camps, M.D., Ph.D., Rafael López-Castro, M.D., Teresa Morán, M.D., Isidoro Barneto, M.D., Delvys Rodríguez-Abreu, M.D., Ph.D., Roberto Serna-Blasco, M.Sc., Raquel Benítez, Ph.D., Carlos Aguado de la Rosa, M.D., Ramón Palmero, M.D., Florentino Hernando-Trancho, M.D., Ph.D., Javier Martín-López, M.D., Alberto Cruz-Bermúdez, Ph.D., Bartomeu Massuti, M.D., and Atocha Romero, Pharm.D., Ph.D.

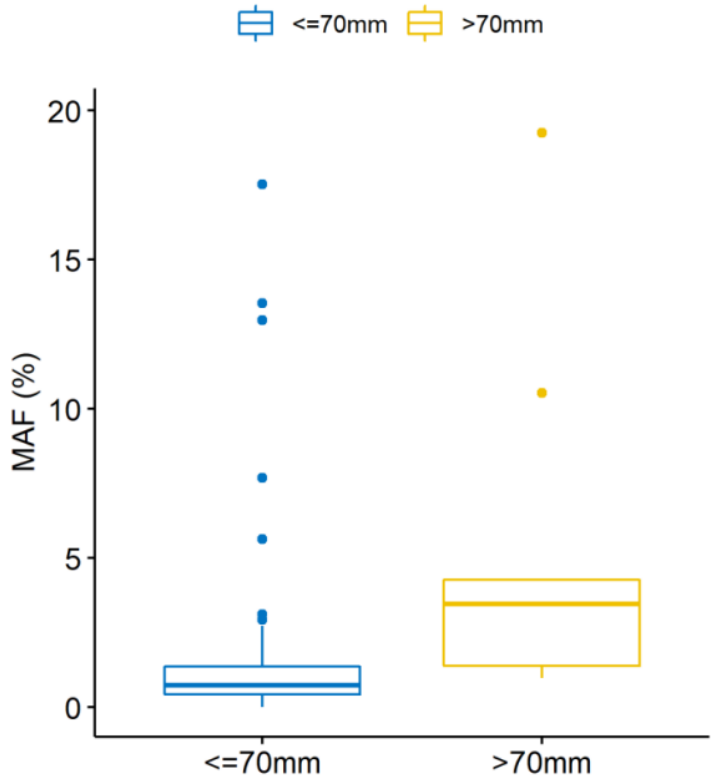
A Progression-free Survival





Baseline ctDNA is of prognostic significance

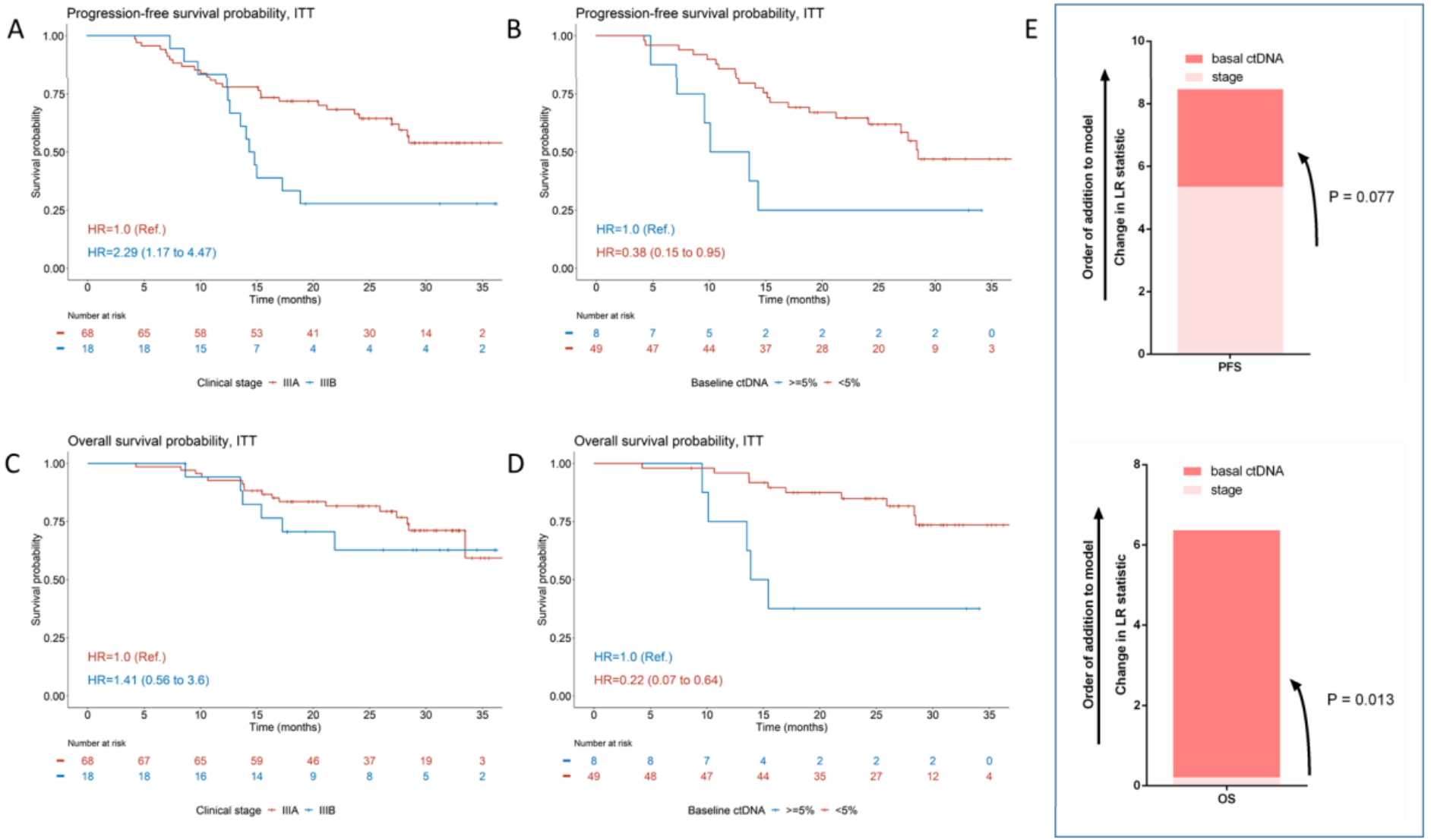
Pre-treatment ctDNA levels were significantly associated with tumor size (maximum diameter ≥ 70mm)



Pre-treatment ctDNA levels were significantly associated with progression free survival (PFS) and overall survival (OS) and regardless of the cutoff used

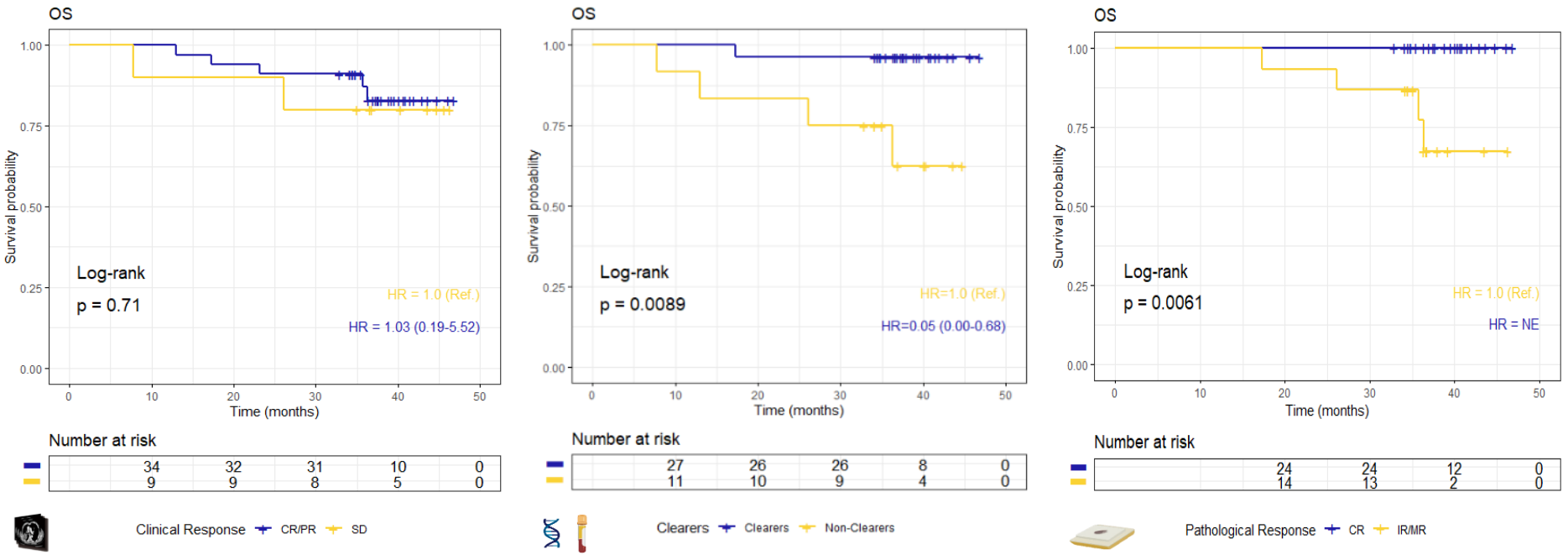
PFS		*OS*	
Cut-off	**HR (95% CI for HR)**	***Cut-off***	**HR (95% CI for HR)**
MAF 4%	0.37 (0.16-0.87)	MAF 4%	0.25 (0.085-0.75)
MAF 4.5%	0.38 (0.15-0.95)	MAF 4.5%	0.22 (0.074-0.64)
MAF 5%	0.38 (0.15-0.95)	MAF 5%	0.22 (0.074-0.64)
MAF 5.5%	0.47 (0.18-1.2)	MAF 5.5%	0.29 (0.092-0.92)
MAF 6%	0.31 (0.12-0.82)	MAF 6%	0.2 (0.064-0.65)
MAF 6.5%	0.31 (0.12-0.82)	MAF 6.5%	0.2 (0.064-0.65)
MAF 7%	0.31 (0.12-0.82)	MAF 7%	0.2 (0.064-0.65)
MAF 7.5%	0.31 (0.12-0.82)	MAF 7.5%	0.2 (0.064-0.65)
MAF 8%	0.32 (0.11-0.94)	MAF 8%	0.16 (0.05-0.51)
MAF 8.5%	0.32 (0.11-0.94)	MAF 8.5%	0.16 (0.05-0.51)
MAF 9%	0.32 (0.11-0.94)	MAF 9%	0.16 (0.05-0.51)
MAF 9.5%	0.32 (0.11-0.94)	MAF 9.5%	0.16 (0.05-0.51)
MAF 10%	0.32 (0.11-0.94)	MAF 10%	0.16 (0.05-0.51)
MAF 15%	0.12 (0.025-0.58)	MAF 15%	0.07 (0.01-0.36)

Provencio M et al. N engl J Med 2023



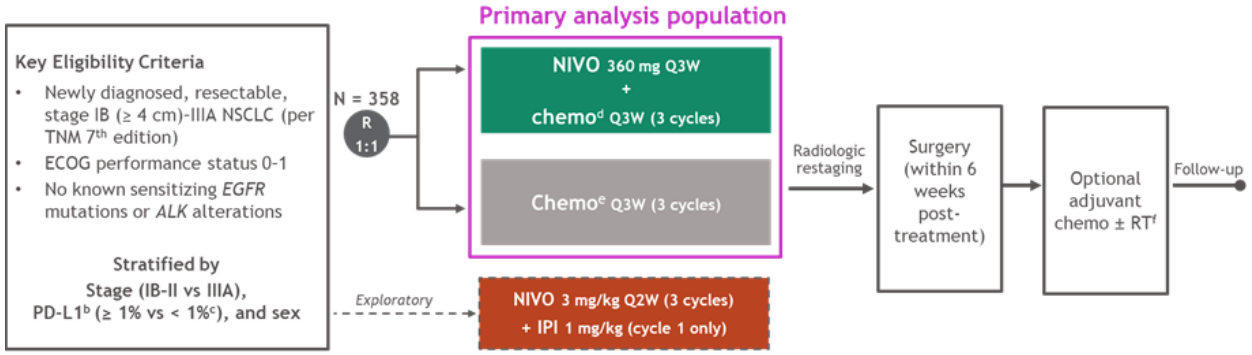
Provencio et al. N engl J Med 2023

ctDNA clearance predicts survival outcomes

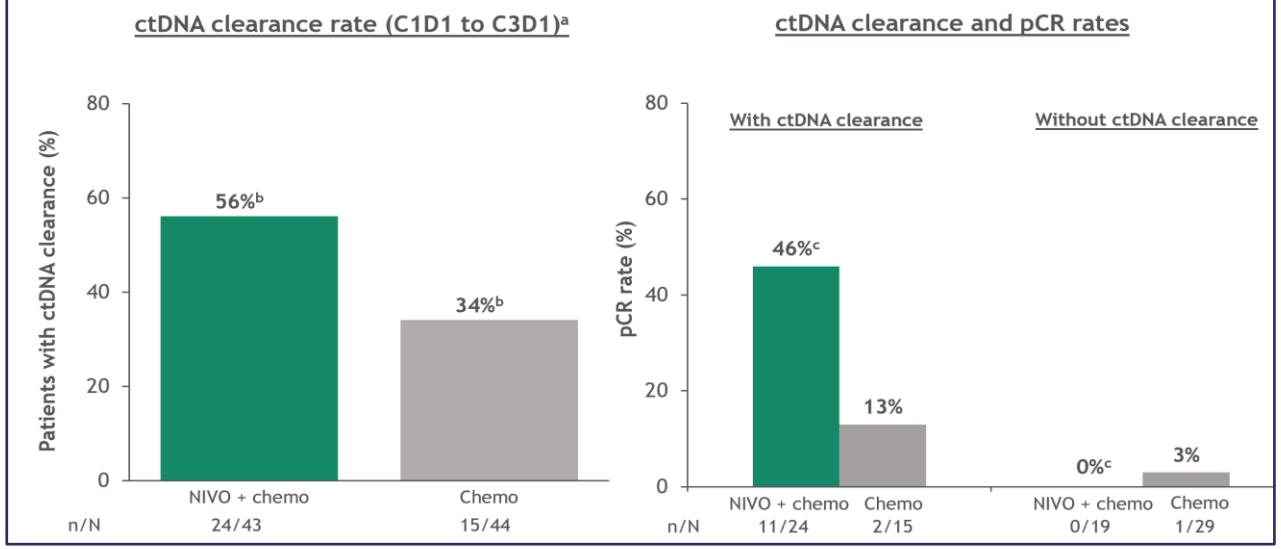


Provencio et al. J Clin Oncol 2022

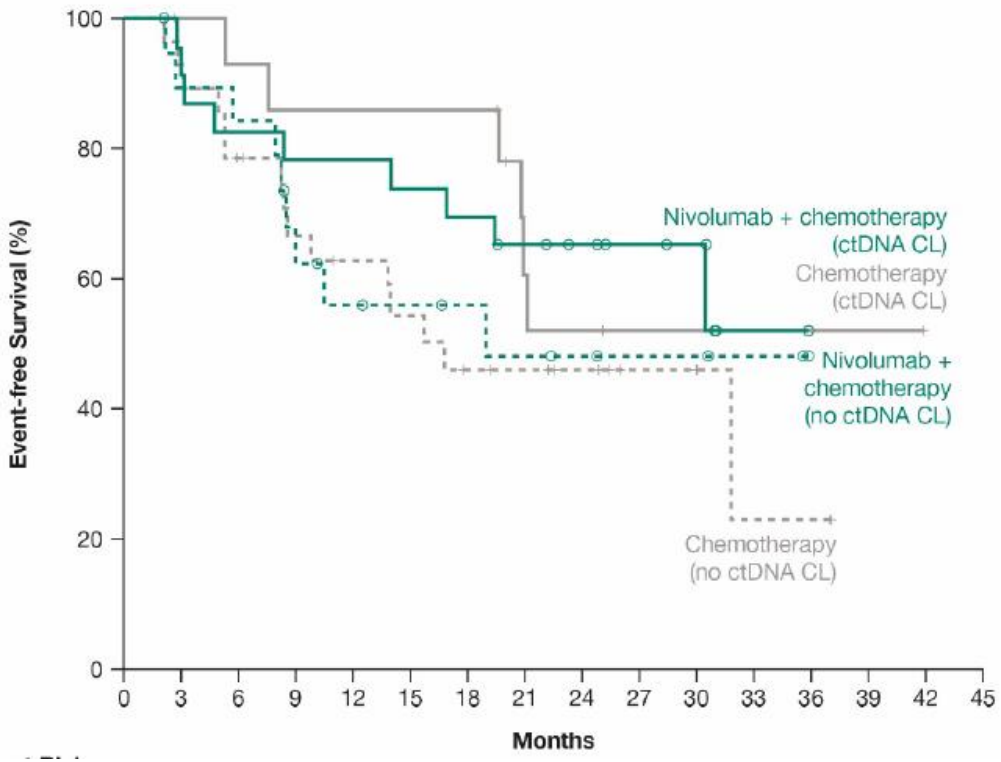
Survival surrogate	No.	HR (PFS)[a]	95% CI[a]	*P*[a]	C-index (PFS)	95% CI	HR (OS)[a]	95% CI[a]	*P*[a]	C-index (OS)	95% CI
Clinical response (CR plus PR *v* SD)	46	0.79	0.24 to 2.59	.698	0.62	0.47 to 0.77	0.87	0.20 to 3.75	.848	0.72	0.51 to 0.90
Pathologic response (pCR *v* major plus incomplete)	41	0.38	0.12 to 1.25	.111	0.63	0.47 to 0.78	0.24	0.04 to 1.33	.102	0.65	0.43 to 0.86
Undetectable ctDNA after treatment	40	0.26	0.07 to 0.93	.038	0.63	0.45 to 0.81	0.04	0.00 to 0.55	.015	0.82	0.61 to 1.00



ctDNA clearance and association with pathological response



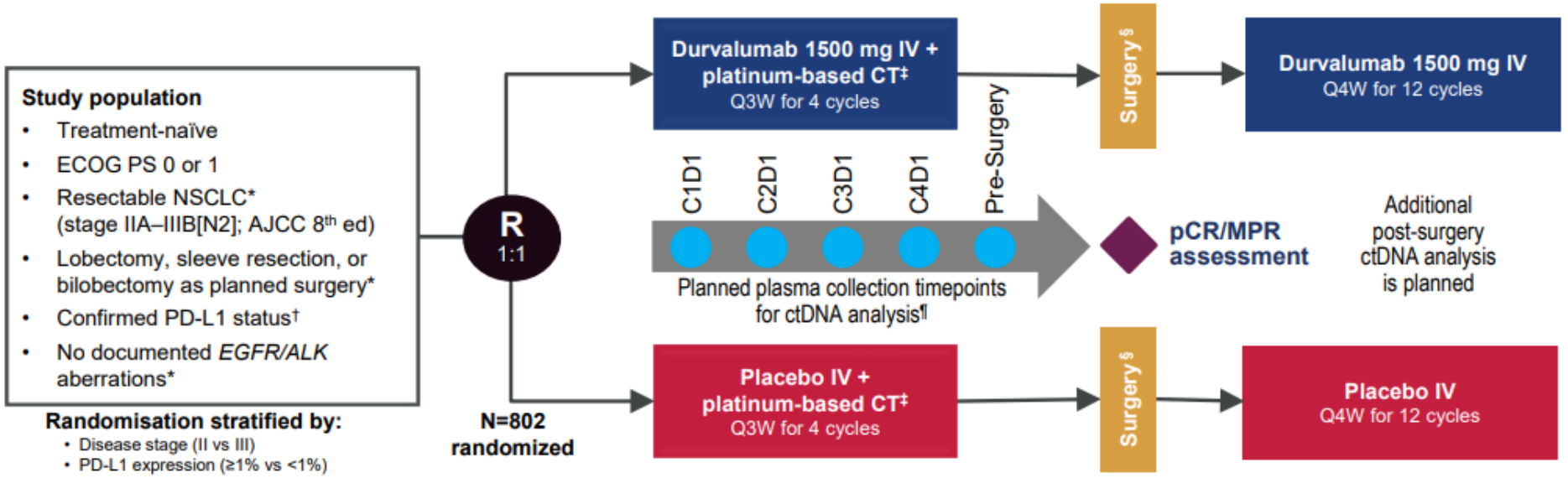
	Nivolumab + chemotherapy		Chemotherapy	
	ctDNA CL (n=24)	No ctDNA CL (n=19)	ctDNA CL (n=15)	No ctDNA CL (n=28)
Median EFS, mo (95% CI)	NR (16.8–NR)	18.9 (8.3–NR)	NR (19.6–NR)	16.8 (8.3–NR)
HR (95% CI)	0.60 (0.20–1.82)		0.63 (0.20–2.01)	



Forde P et al. NEJM 2022

Martin Reck et al.
ESMO 2023

AEGEAN Study Design



Martin Reck et al.
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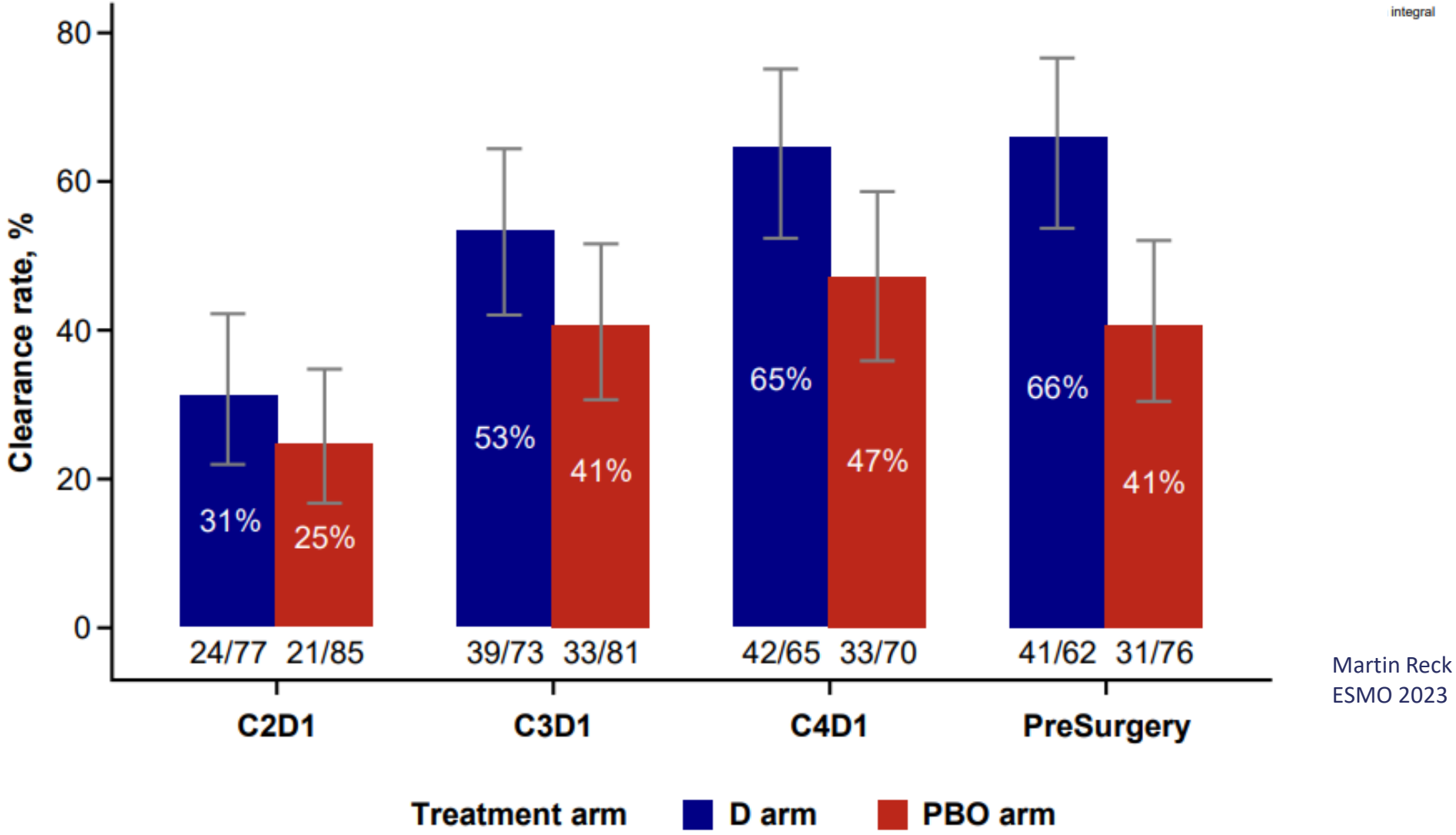
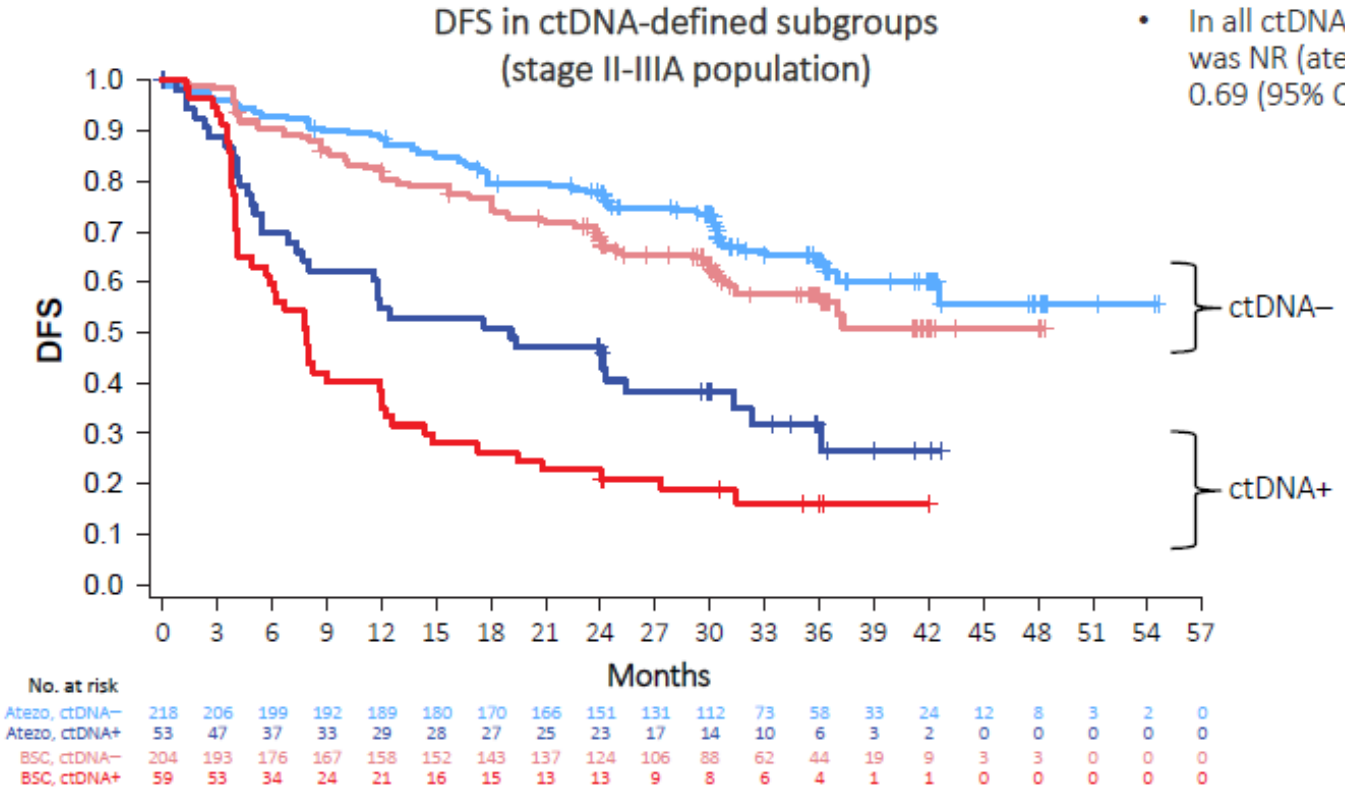
ctDNA Clearance from Baseline



Martin Reck et al.
ESMO 2023

ctDNA in the adjuvant setting

IMpower-010 Post-surgery circulating tumour ctDNA status.



- In all ctDNA-evaluable stage II-IIIA patients, mDFS was NR (atezo) vs 31.4 months (BSC), with an HR of 0.69 (95% CI: 0.53, 0.89)

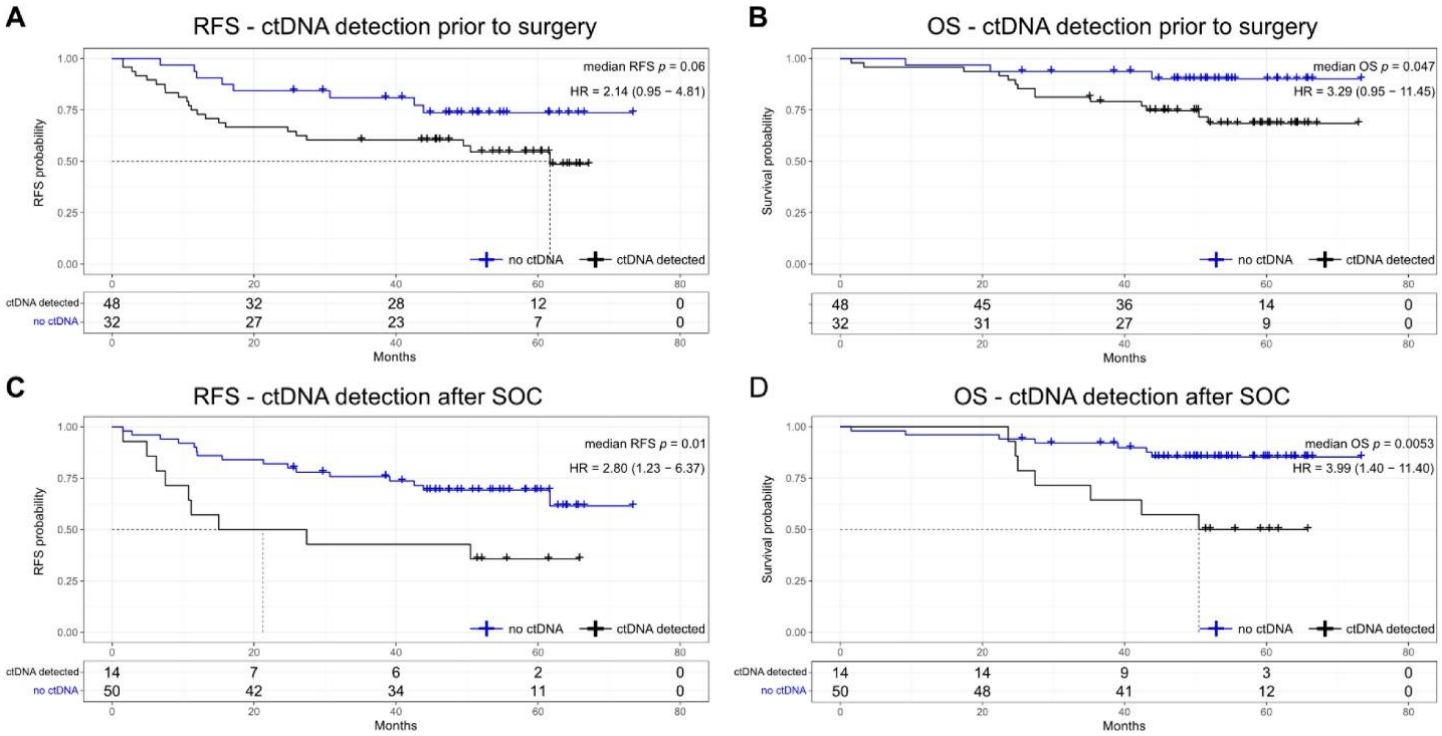
ctDNA–	Atezo (n=218)	BSC (n=204)
mDFS, mo	NR	NR
HR (95% CI)	0.72 (0.52, 1.00)	

ctDNA+	Atezo (n=53)	BSC (n=59)
mDFS, mo	19.1	7.9
HR (95% CI)	0.61 (0.39, 0.94)	

534 ctDNA-evaluable patients, ctDNA positivity increased with disease stage, being reported in 14% of patients with stage II NSCLC and 29% with stage IIIA disease.

Zhou et al. *ESMO Immuno-Oncology*. 2021

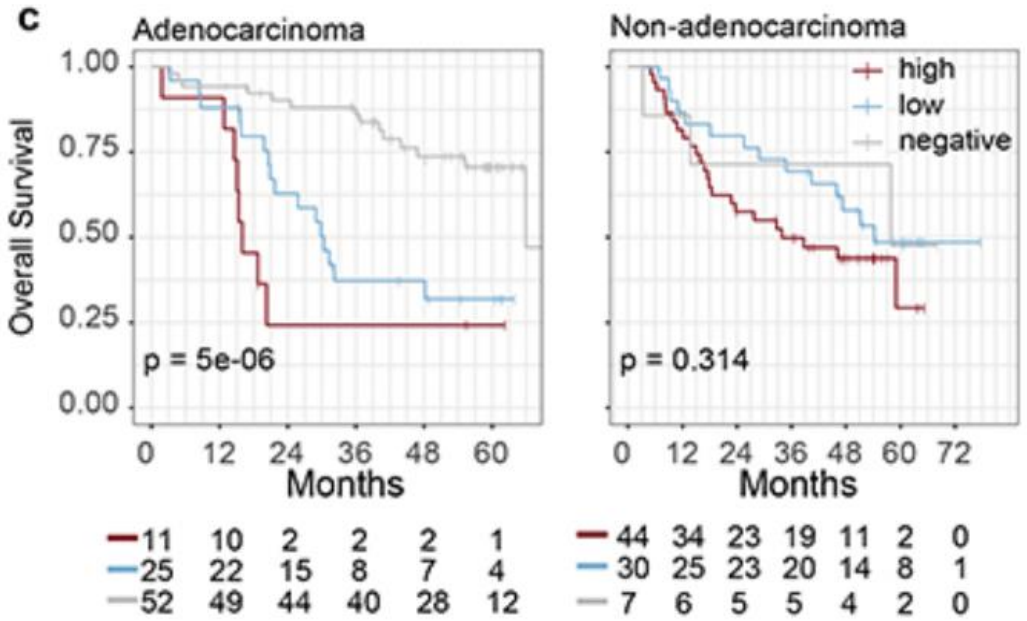
ctDNA in resected, early-stage non–small cell lung cancer



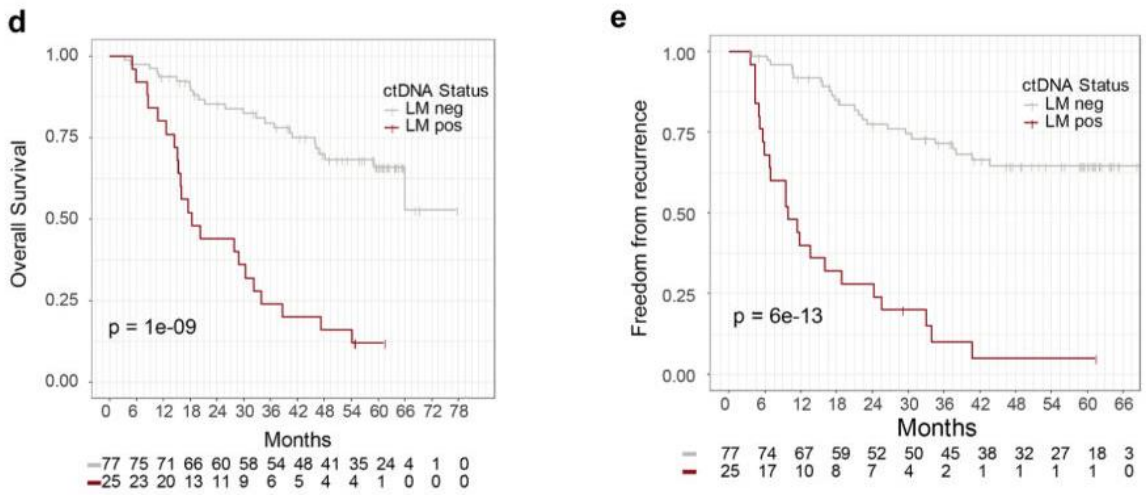
366 serial plasma samples from 85 patients who underwent surgical resections

Tumor-agnostic approach

https://www.annalsofoncology.org/article/S0923-7534(23)05072-X/fulltext#%20

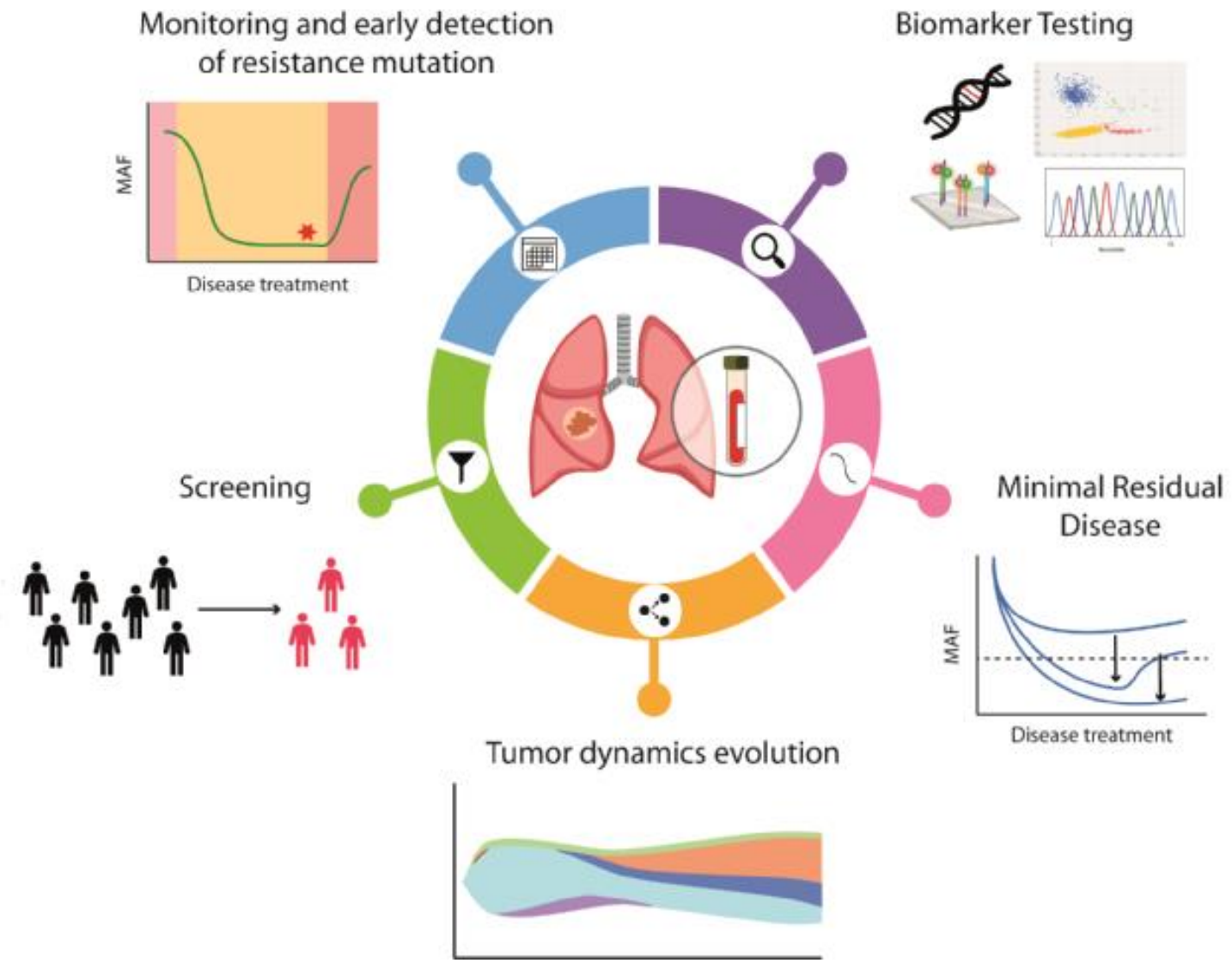


The 52 of 88 (59%) adenocarcinoma patients who were preoperative ctDNA negative had superior OS outcomes (90% 2-year OS [95% CI:82 to 99%]) compared with ctDNA low (63% 2-year OS [95% CI: 46 to 85%], n=25) or high

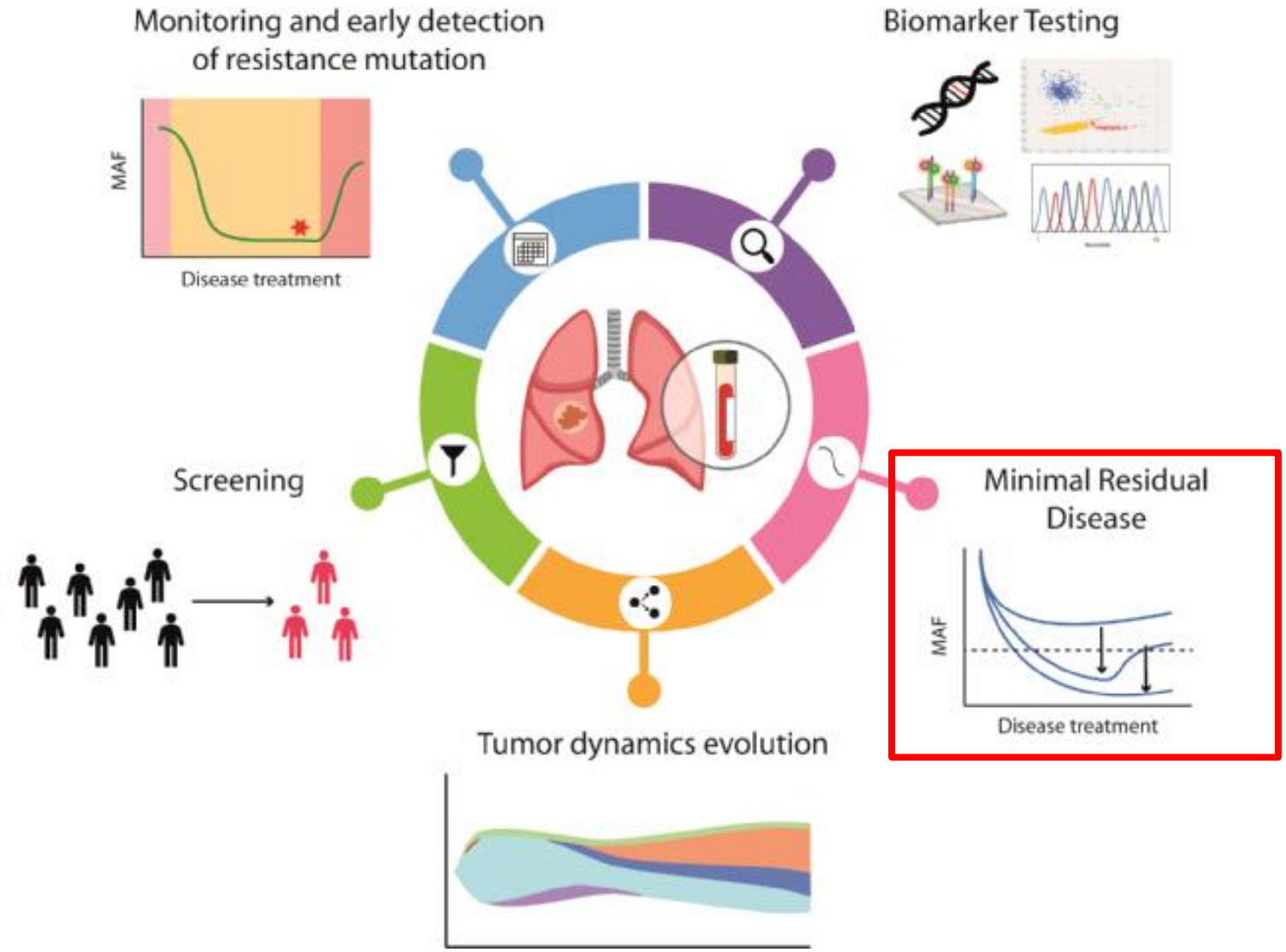


Landmark analyses of plasma samples collected within 120 days post-surgery revealed ctDNA detection in 25% of patients.

https://pubmed.ncbi.nlm.nih.gov/37055640/



Romero, A et al. Curr Treat Options Oncol. 2021 Aug 23;22(10):86.



Romero, A et al. Curr Treat Options Oncol. 2021 Aug 23;22(10):86.

Approaches for MRD assessment

Approaches for MRD assessment

Tumor-Informed	Tumor agnostic
Requires tissue biopsy	No need for biopsy
Personalized assay	Off the shelf assay
Longer turnaround time	Shorter turnaround time
Does not account for tumor heterogeneity	Can detect clonal variants that emerge during follow-up
Potential for better sensitivity and specificity	Variable sensitivity and specificity

Modified form Pellini B and Chaudhuri A. J Clin Oncol. 2022

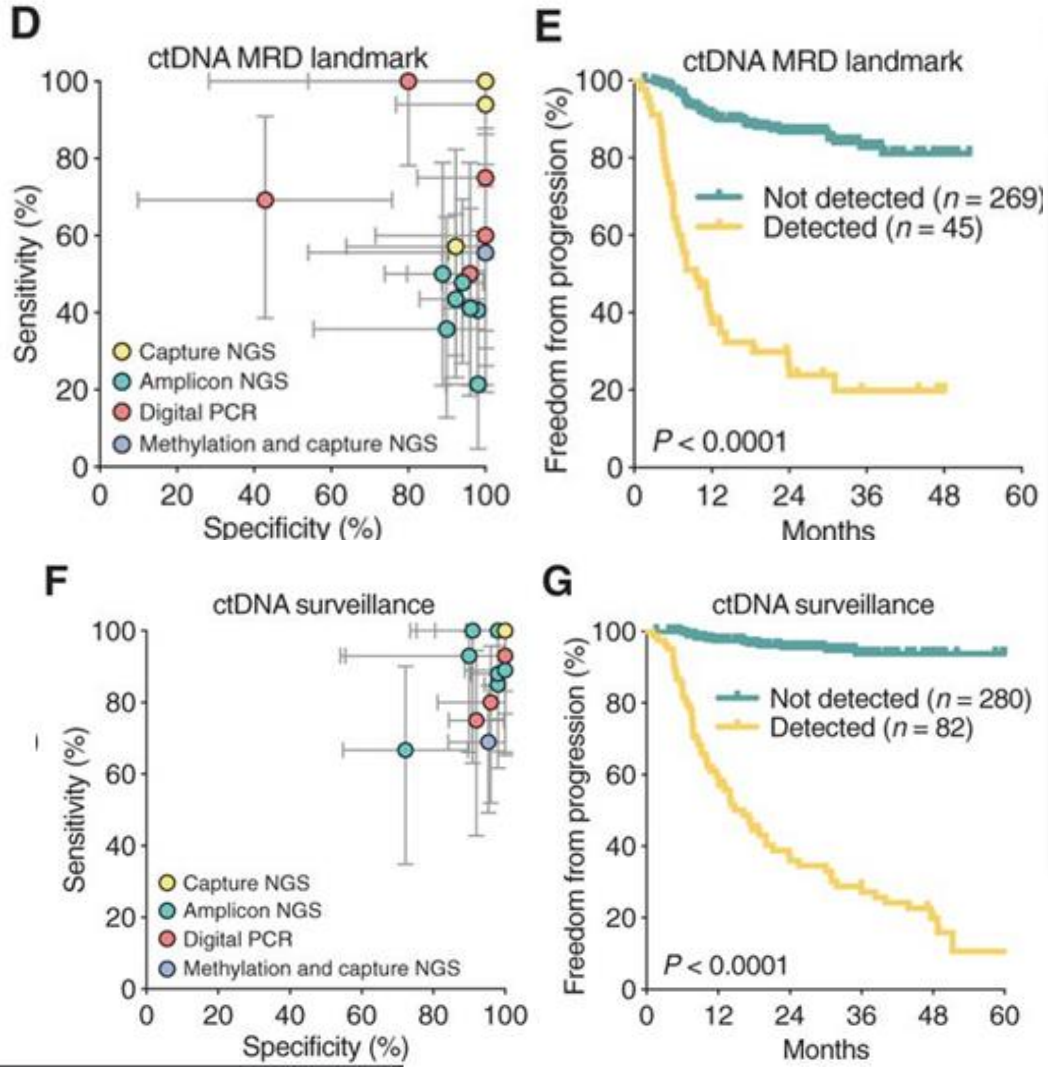


Table 1. Studies evaluating circulating tumor DNA MRD in solid cancers

Study	Tumor type	Methodology	Mutations monitored	Total patients	ctDNA MRD landmark		ctDNA surveillance	
					Sensitivity	Specificity	Sensitivity	Specificity
Peng et al. 2020 (111)	Lung	Amplicon NGS	Multiple	48	50.0%	88.9%	66.7%	72.2%
Chaudhuri et al. 2017 (62)	Lung	Capture NGS	Multiple	37	94.0%	100.0%	100.0%	100.0%
Abbosh et al. 2017 (31)	Lung	PCR NGS	Multiple	24	35.7%	90.0%	92.9%	90.0%
Moding et al. 2020 (90)	Lung	Capture NGS	Multiple	12	100.0%	100.0%	—	—
Garcia-Murillas et al. 2019 (113)	Breast	Digital PCR	Single	101	—	—	75.0%	92.1%
Coombes et al. 2019 (34)	Breast	Amplicon NGS	Multiple	49	55.6%	100.0%	88.9%	100.0%
Garcia-Murillas et al. 2015 (27)	Breast	Digital PCR	Single	43	50.0%	96.0%	80.0%	96.4%
Olsson et al. 2015 (112)	Breast	Digital PCR	Multiple	20	—	—	92.8%	100.0%
Tie et al. 2016 (91)	Colon	Amplicon NGS	Single	178	40.7%	98.0%	85.2%	98.0%
Tie et al. 2019 (92)	Colon	Amplicon NGS	Single	88	43.5%	92.3%	—	—
Wang et al. 2019 (114)	Colon	Amplicon NGS	Single	40	—	—	100.0%	90.6%
Reinert et al. 2019 (36)	Colorectal	Amplicon NGS	Multiple	94	41.2%	96.1%	87.5%	98.3%
Parikh et al. 2021 (52)	Colorectal	Methylation and Capture NGS	Multiple	72	55.6%	100.0%	69.0%	95.3%
Scholer et al. 2017 (28)	Colorectal	Digital PCR	Single	26	60.0%	100.0%	100.0%	100.0%
Diehl et al. 2008 (107)	Colorectal	Digital PCR	Single	20	100.0%	80.0%	—	—
Tie et al. 2018 (89)	Rectal	Amplicon NGS	Single	159	47.8%	94.1%	—	—
Khakoo et al. 2019 (109)	Rectal	Digital PCR	Multiple	23	75.0%	100.0%	—	—
Azad et al. 2020 (65)	Esophageal	Capture NGS	Multiple	15	55.6%	100.0%	—	—
Jiang et al. 2020 (110)	Pancreas	Capture NGS	Multiple	27	57.1%	92.3%	—	—
Sausen et al. 2015 (108)	Pancreas	Digital PCR	Single	20	69.2%	42.9%	—	—
Christensen et al. 2019 (35)	Bladder	Amplicon NGS	Multiple	66	21.4%	98.1%	100.0%	97.9%

NOTE: Clinical sensitivity (percentage of patients who relapsed in the follow-up period who were ctDNA positive) and clinical specificity (percentage of patients who did not relapse in the follow-up period who were ctDNA negative) were calculated for the first follow-up sample after completing definitive therapy (ctDNA MRD Landmark) or for repeated ctDNA analysis during follow-up (ctDNA Surveillance). Patients who received additional therapy after ctDNA analysis were excluded if noted in the study. —, not reported or unable to be calculated.

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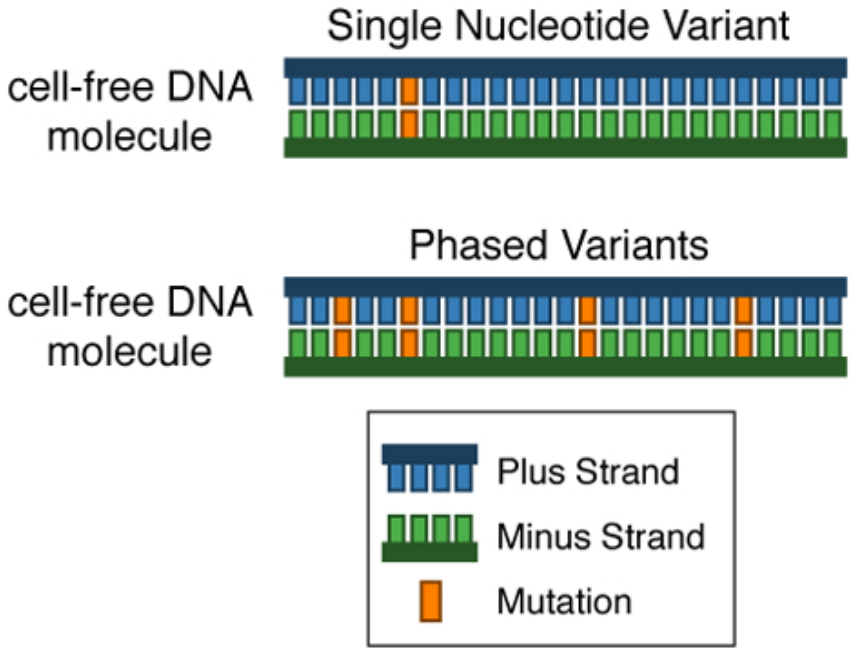
Opportunities for improvements

Opportunities for improvements

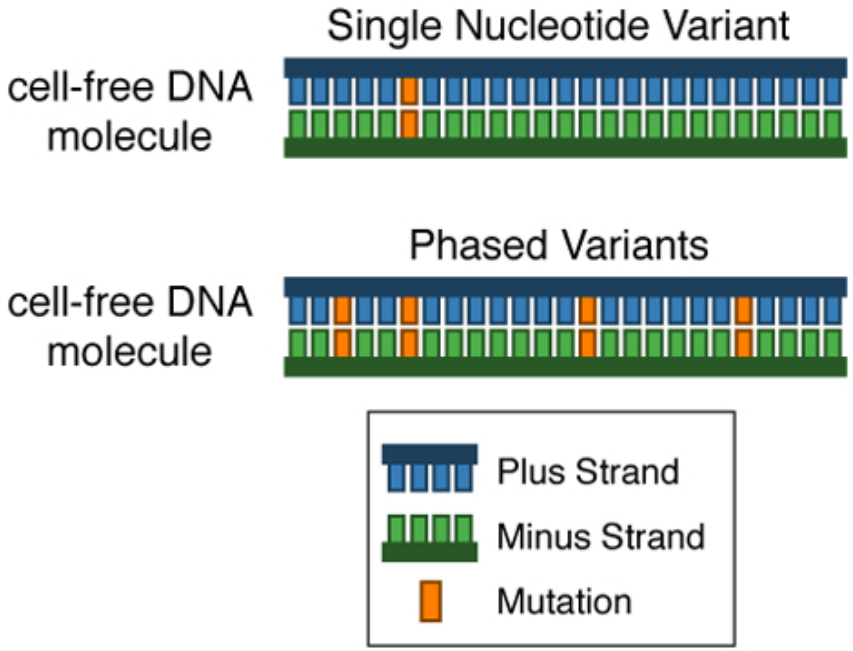
Phased variants in ctDNA



Nat Biotechnol. 2021 Dec;39(12):1537-1547

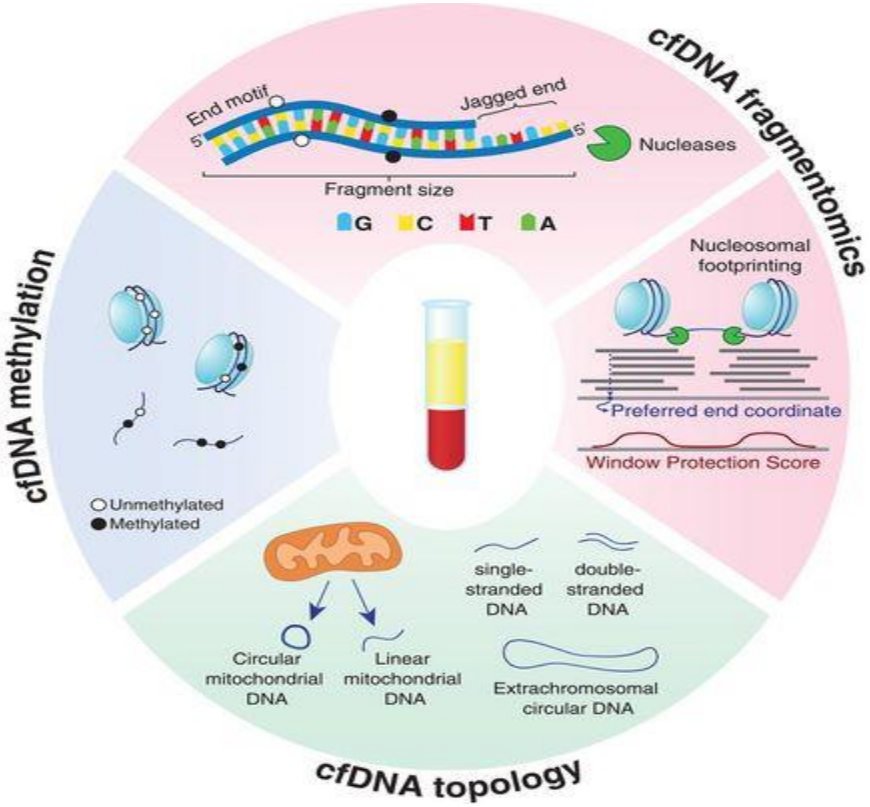
Opportunities for improvements

Phased variants in ctDNA



Nat Biotechnol. 2021 Dec;39(12):1537-1547

Non genetic cfDNA markers



Science. 2021 Apr 9;372(6538):eaaw3616

Take home message

- ctDNA profiling increases the detection of actionable mutations and can support treatment guidance in NSCLC.
- ctDNA profiling may identify oncogenic mutations underlying treatment failure.
- ctDNA levels are of prognostic significance and correlate well with survival outcomes, however ctDNA quantification is not harmonized
- ctDNA is useful to monitor disease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Muchas Gracias
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