Novel Platforms to Assess the Cancer Continuum Using Liquid Biopsy

ISLB
INTERNATIONAL SOCIETY OF LIQUID BIOPSY

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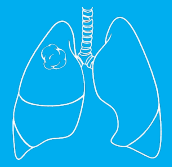

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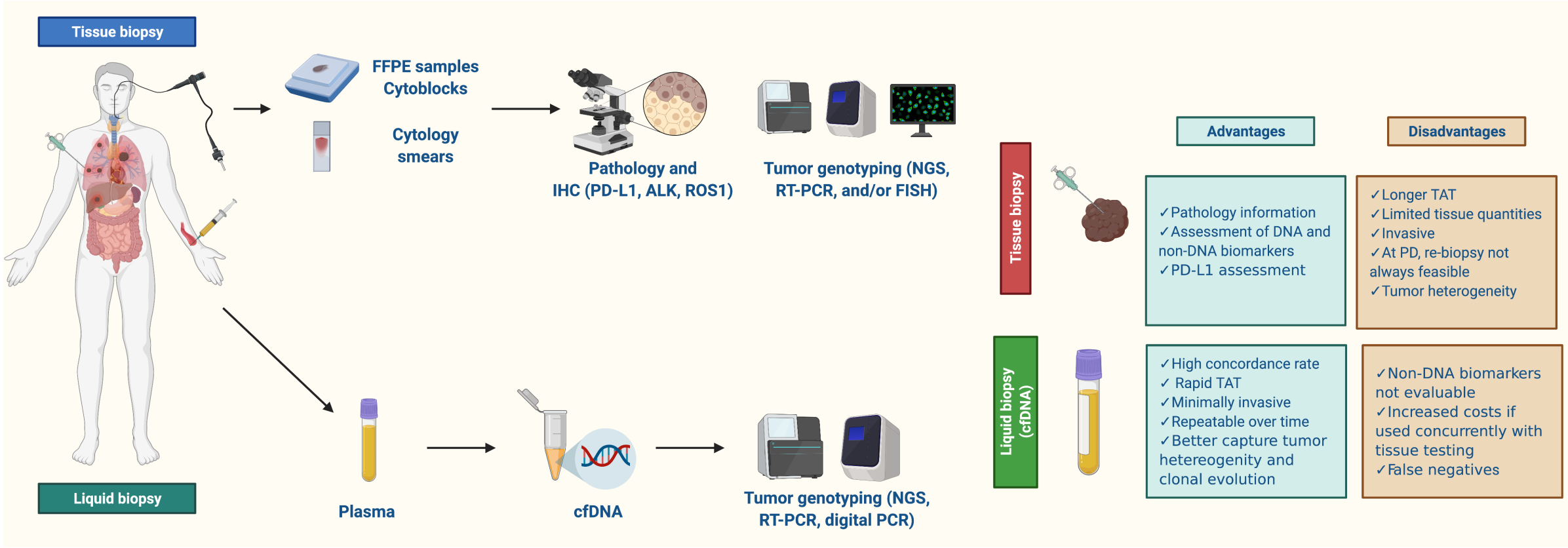
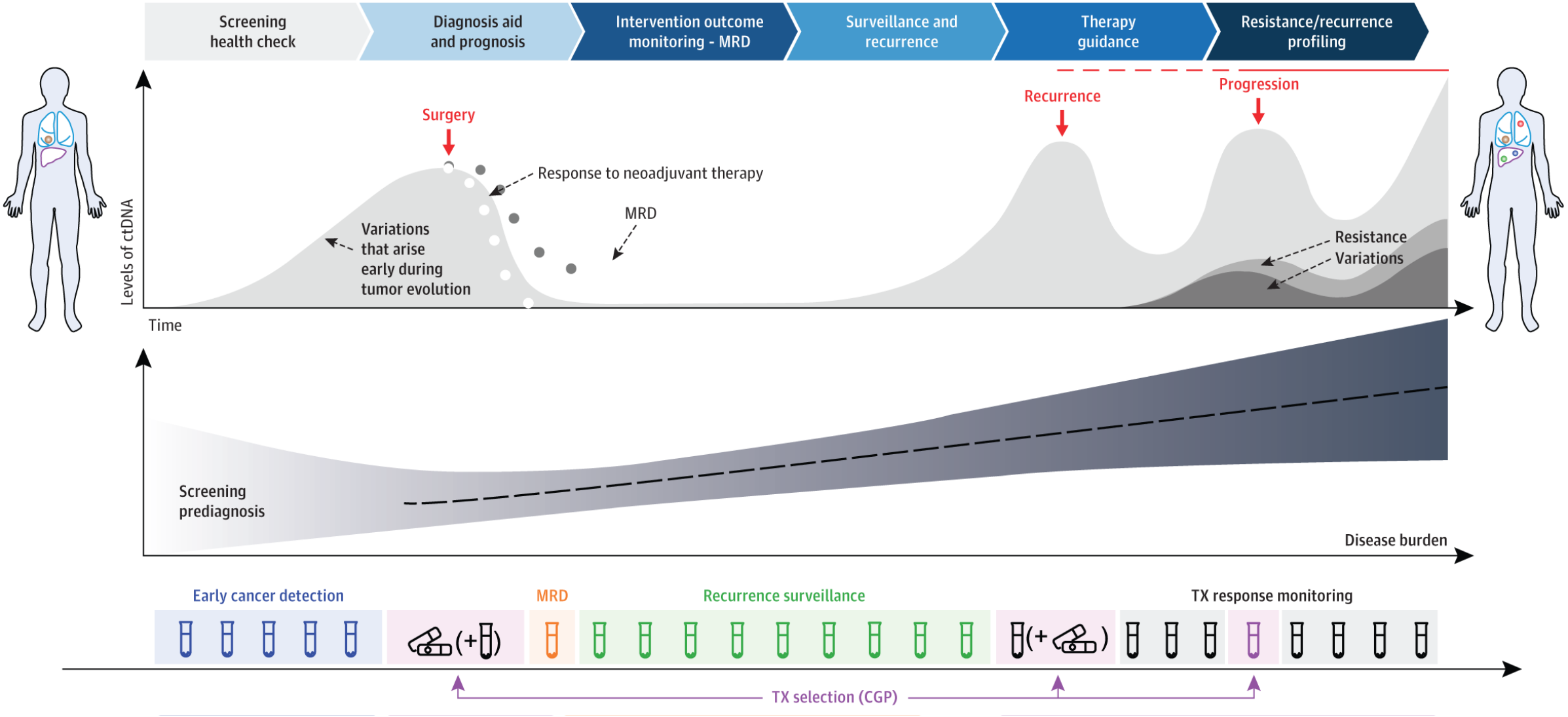
Tissue vs. Liquid biopsy



Rolfo C, et al. J Thorac Oncol 2021;16(10):1647-1662.

Liquid biopsy in cancer patients journey



Krebs et al (Rolfo), JAMA Oncology OCT 2022

Clinical utility of liquid biopsy in oncogene-addicted NSCLC

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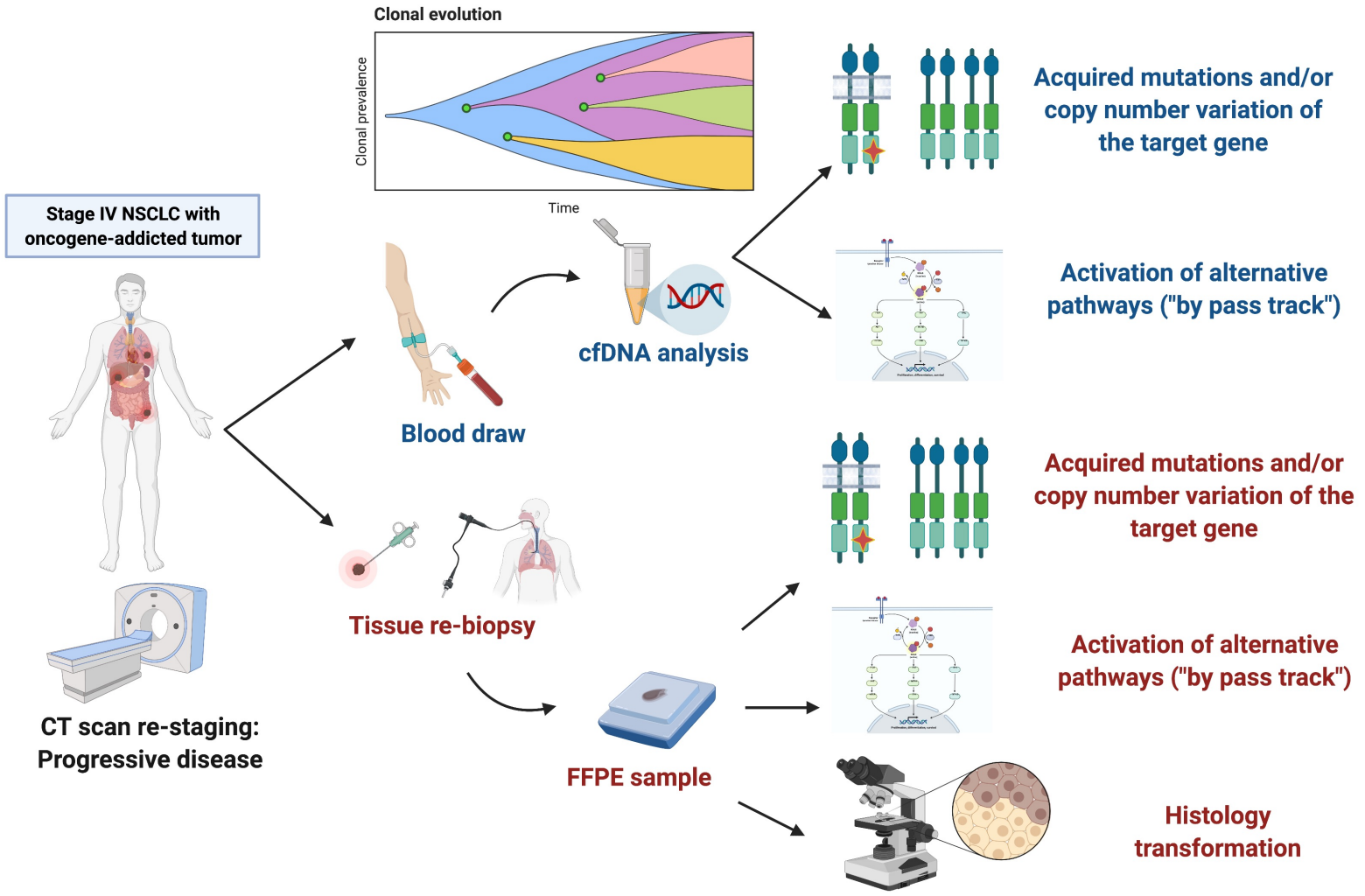
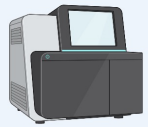
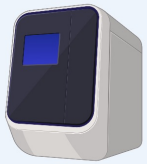


Main liquid biopsy techniques used



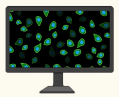
NGS-based approaches:
- ✓High sensitivity
- ✓Multiplex
- ✓Gene rearrangements
- ✓Gene amplifications



PCR-based approaches:
- ✓Variable sensitivity
- ✓Single gene testing
- ✓Only for mutations

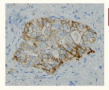
Main techniques used for tumor tissue

NGS-based approaches:
- ✓High sensitivity
- ✓Multiplex
- ✓Gene rearrangements
- ✓Gene amplifications



FISH:
- ✓Gene rearrangements & amplifications

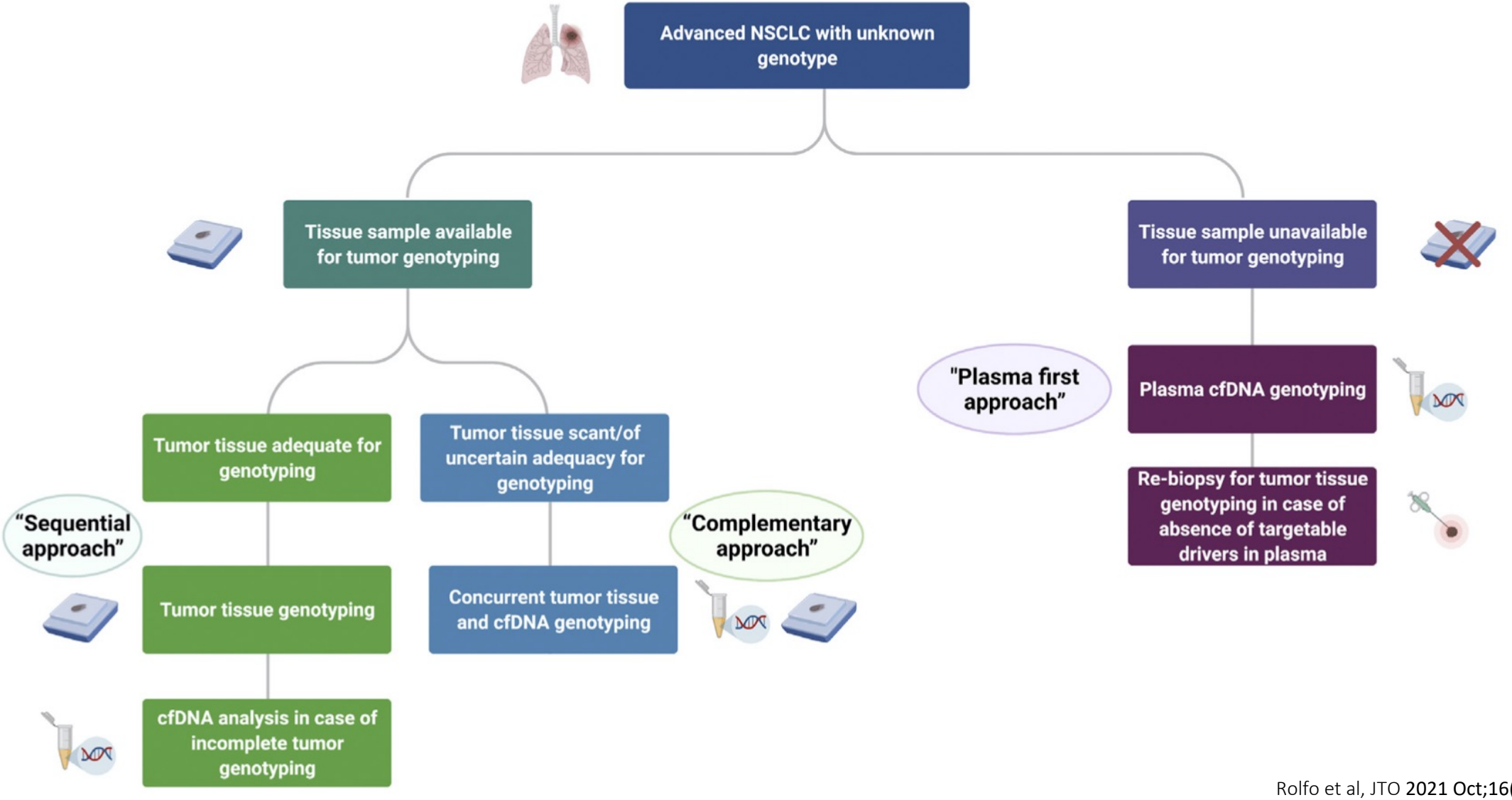
PCR-based approaches:
- ✓Variable sensitivity
- ✓Single/Multiplex gene testing
- ✓Only for mutations



IHC:
- ✓Protein expression

Rolfo C, et al. J Thorac Oncol 2021

Diagnostic algorithm for liquid biopsy use in treatment-naive advanced/metastatic NSCLC



Rolfo et al, JTO 2021 Oct;16(10):1647-1662

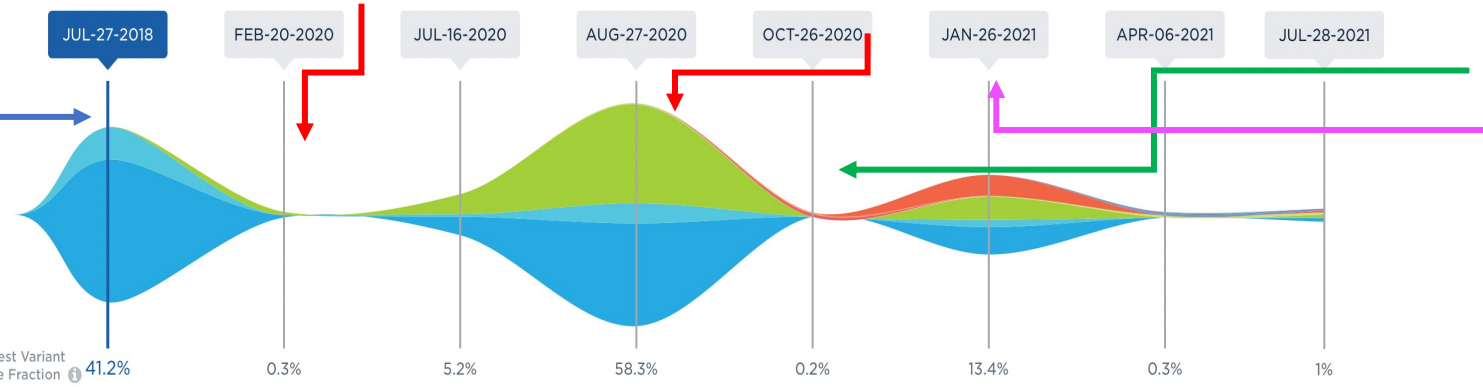
Monitoring and tailoring treatment with Liquid Biopsy

Osimertinib start with an intracranial CR and extracranial PR

After 18 mos oligo-PD (LN mets) → SBRT and continued osi

Further disease progression → osimertinib stopped; switch to erlotinib

52-year-old never smoker female; diagnosed in July 2018 with cT4 N3 M1c lung adenocarcinoma (stage IVB).



PET/CT in Nov. 2020: CR

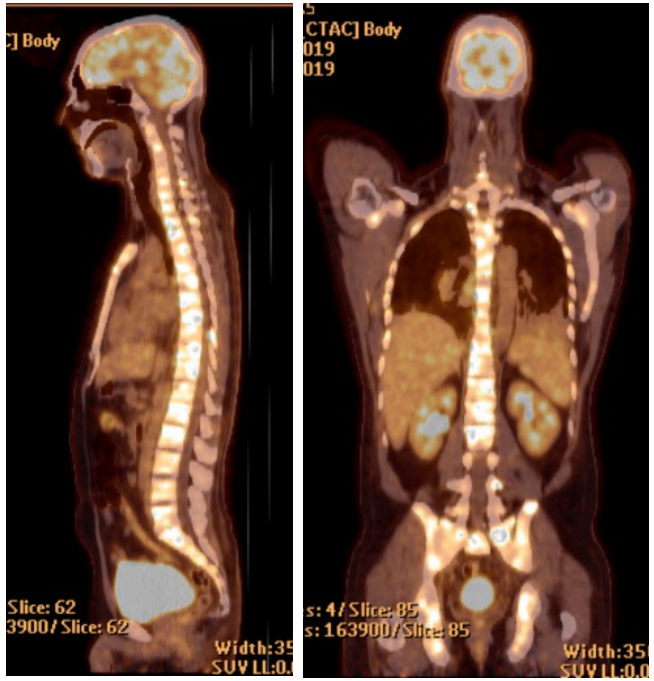
Erlotinib discontinuation → platinum-based chemo start

Genetic Alteration	% cfDNA or amplification							
EGFR E746_A750del	41.2%	0.2%	4.7%	58.3%	ND	13.4%	ND	1%
EGFR C797S	ND	0.3%	5.2%	55.6%	ND	10.7%	ND	0.7%
ARID1A Q456Q	ND	ND	ND	0.2%	ND	0.2%	0.3%	0.6%
EGFR T790M	ND	ND	ND	ND	ND	9.6%	ND	0.4%
TP53 C275Y	ND	ND	ND	ND	ND	ND	0.1%	0.2%
ARID1A F1728F	ND	ND	ND	ND	ND	ND	0.3%	0.2%
TP53 S127F	6.5%	ND	0.4%	7.6%	ND	2.6%	ND	0.2%
***BRAF* Amplification**	2.2%	ND	ND	ND	ND	ND	ND	ND
***CDK6* Amplification**	2.2%	ND	ND	ND	ND	ND	ND	ND
***EGFR* Amplification**	3.4%	ND	ND	4.2%	ND	ND	ND	ND
***NTRK2* L699L**	-	-	-	-	0.2%	ND	ND	-
***EGFR* N338N**	ND	ND	ND	ND	0.1%	ND	ND	ND
***FGFR1* V795I**	ND	ND	ND	ND	ND	ND	0.1%	ND

Rolfo C, et al. Unpublished data

Monitoring and tailoring treatment with Liquid Biopsy

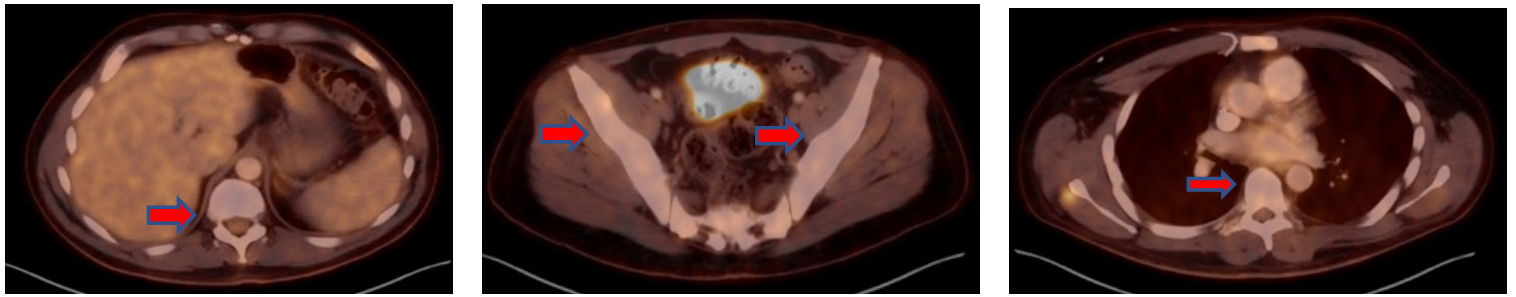
38 y.o. male never smoker
RET - KIF5B fusion



RET - KIF5B fusion and TP53 mutation; PDL-L1 high (TPS 70%);
10/2020 Started **Selpercatinib** by FDA emergency authorization **ECOG 2-3**
Hb 8.2, PLT 36.000, LDH 1496. Reduced dose to 80 mg BID due to general condition

OCT 2019

FEB 2020



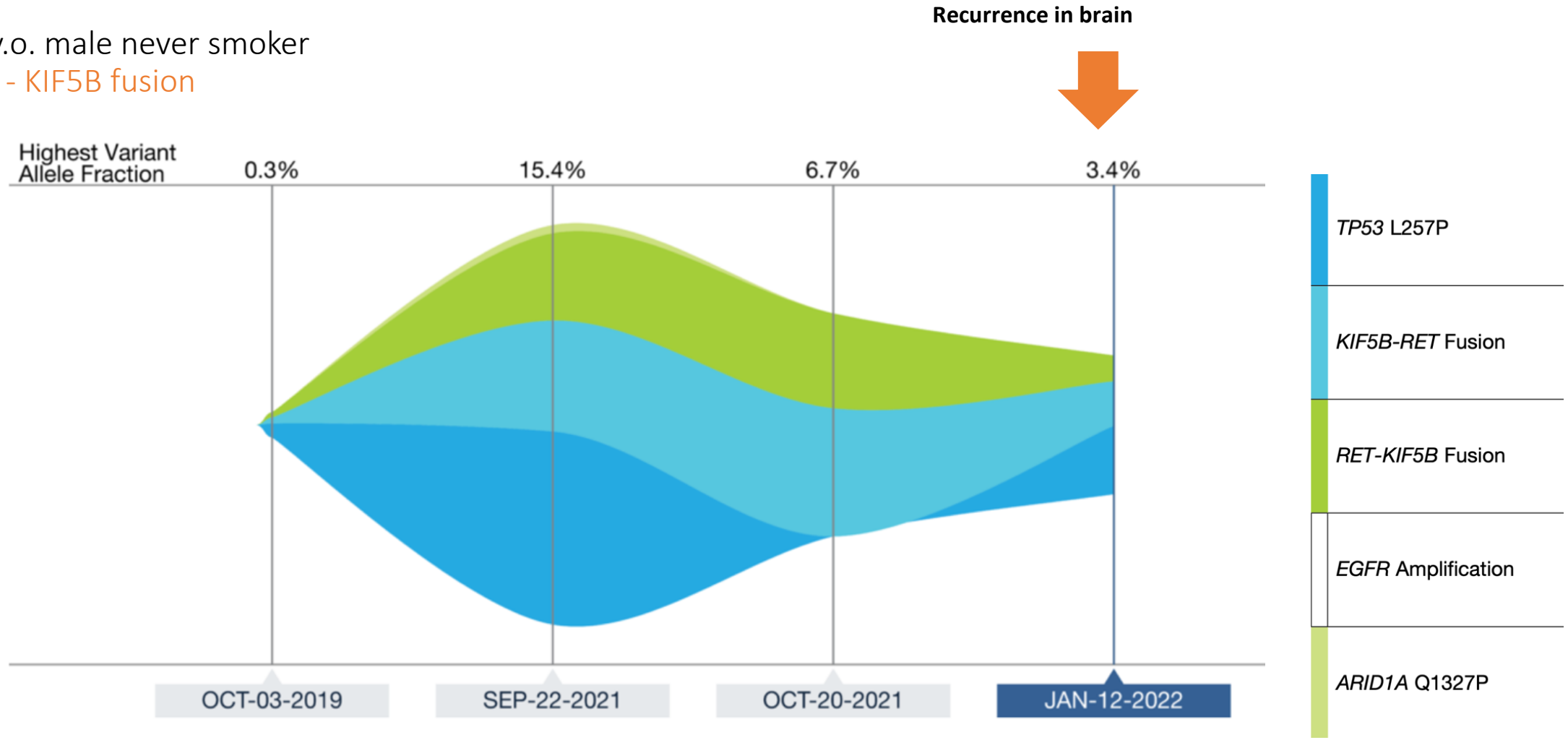
Complete resolution of bone marrow invasion, **ECOG 0**, continue in response,
04/2020 : **Hb 14.9, PLT 240.000, LDH 91** current dose 160 mg BID since 12/2020

Courtesy of Christian Rolfo

Monitoring and tailoring treatment with Liquid Biopsy

38 y.o. male never smoker

RET - KIF5B fusion



Courtesy of Christian Rolfo

Liquid biopsy – a not plasma only approach!
CSF NGS analysis at recurrence

38 y.o. male never smoker
RET - KIF5B fusion

IMPAKT NGS CSF by MSKCCC

Somatic alterations detected in this sample:

Gene	Type	Alteration	Location	Additional Information
Mutations				
TP53	Missense Mutation	L257P *(c.770T>C)*	exon 7	MAF: 45.7%
Copy Number Alterations				
PHF6	Whole gene	Amplification	Xq26.2	FC: 3.2
CCNQ	Whole gene	Amplification	Xq28	FC: 3.2
Structural Variants				
KIF5B-RET	Fusion	c.1725+1180:KIF5B_c.2136+909:RE Tinv	KIF5B exon 15 to RET exon 12	1 a

Courtesy of Christian Rolfo

Minimal Residual Disease assessment by Liquid Biopsy

Retrospective Data From ~900 NSCLC Patients demonstrate that pre- and post-treatment MRD is a strongly prognostic biomarker

Study	N	Stage	Treatment(s)	ctDNA assay
Chaudhuri *Cancer Discov* 2017	37	IB-IIIB	RT and/or surgery +/- chemo	CAPP-Seq
Abbosh *Nature* 2017	24	IA-IIIB	Surgery +/- chemo	Natera
Chen *CCR* 2019	25	I-III	Surgery +/- chemo	cSMART
Moding *Cancer Discov* 2020	48	IIB-IIIB	chemoRT +/- IO	CAPP-Seq
Abbosh *AACR* 2020	88	I-III	Surgery +/- chemo	ArcherDx
Zviran *Nat Med* 2020	22	I-III	Surgery +/- chemo	MRDetect
Waldeck *Mol Oncol* 2021	16	IA-IIIB	Surgery +/- chemo, RT	Custom NGS
Xia *CCR* 2021	329	I-III	Surgery +/- chemo	Custom NGS
Gale *Ann Oncol* 2022	59	I-III	RT and/or surgery +/- chemo	Inivata
Zhang *Cancer Discov* 2022	245	I-III	Surgery +/- chemo, IO, TKI	Custom NGS

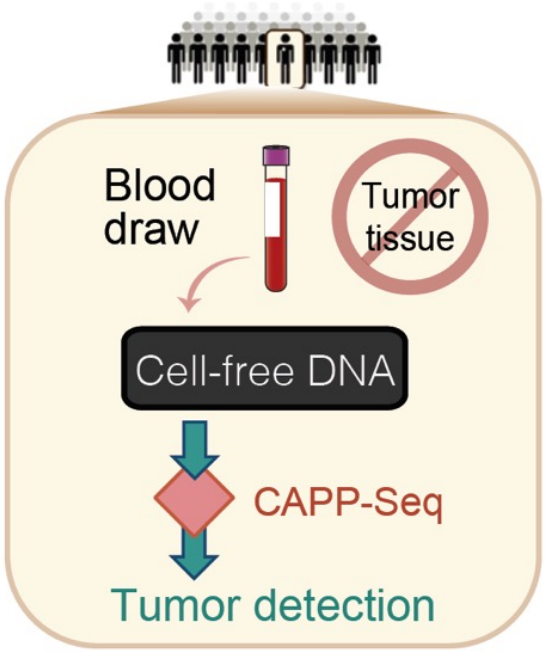
***Several studies including different population, treatment and assays

Courtesy Dr. Max Diehn & Dr. Natasha Leigh

Different types of ctDNA MRD Assays

Tumor-naïve:

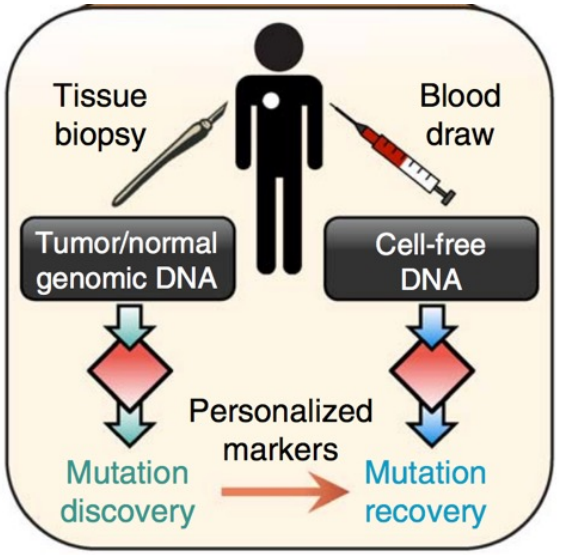
only liquid biopsy



- Genotyping with no knowledge of tumor mutations (“off the shelf”)
- Faster, less expensive
- Limit of detection ~0.1%

Tumor-informed:

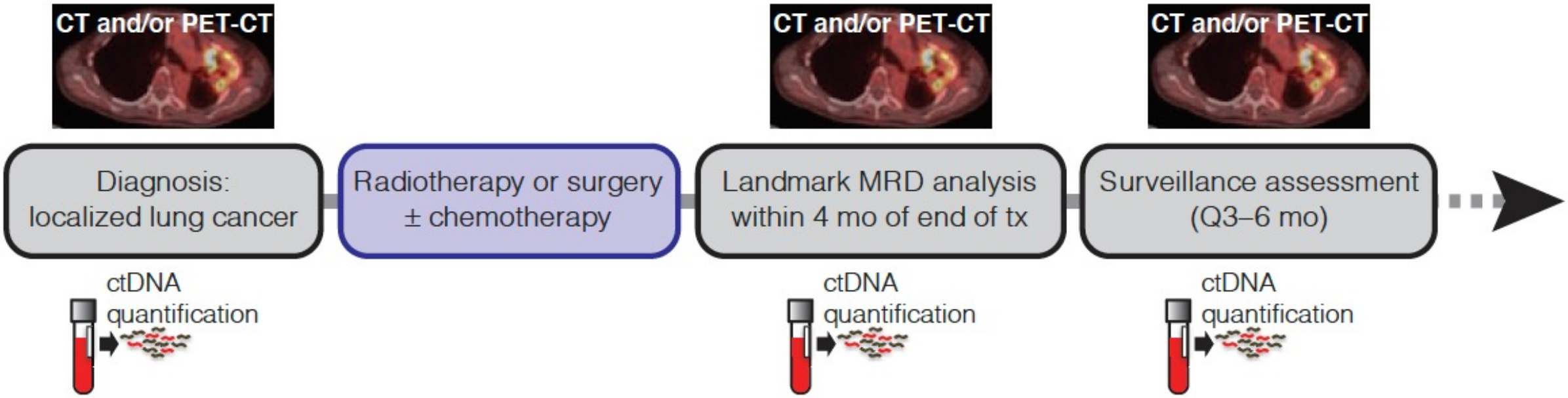
Departing from tissue biopsy and following with liquid biopsy



- Tracking multiple known mutations (bespoke or personalized)
- Requires tumor tissue, time, $$
- Limit of detection ~0.01%

Courtesy Dr. Natasha Leighl

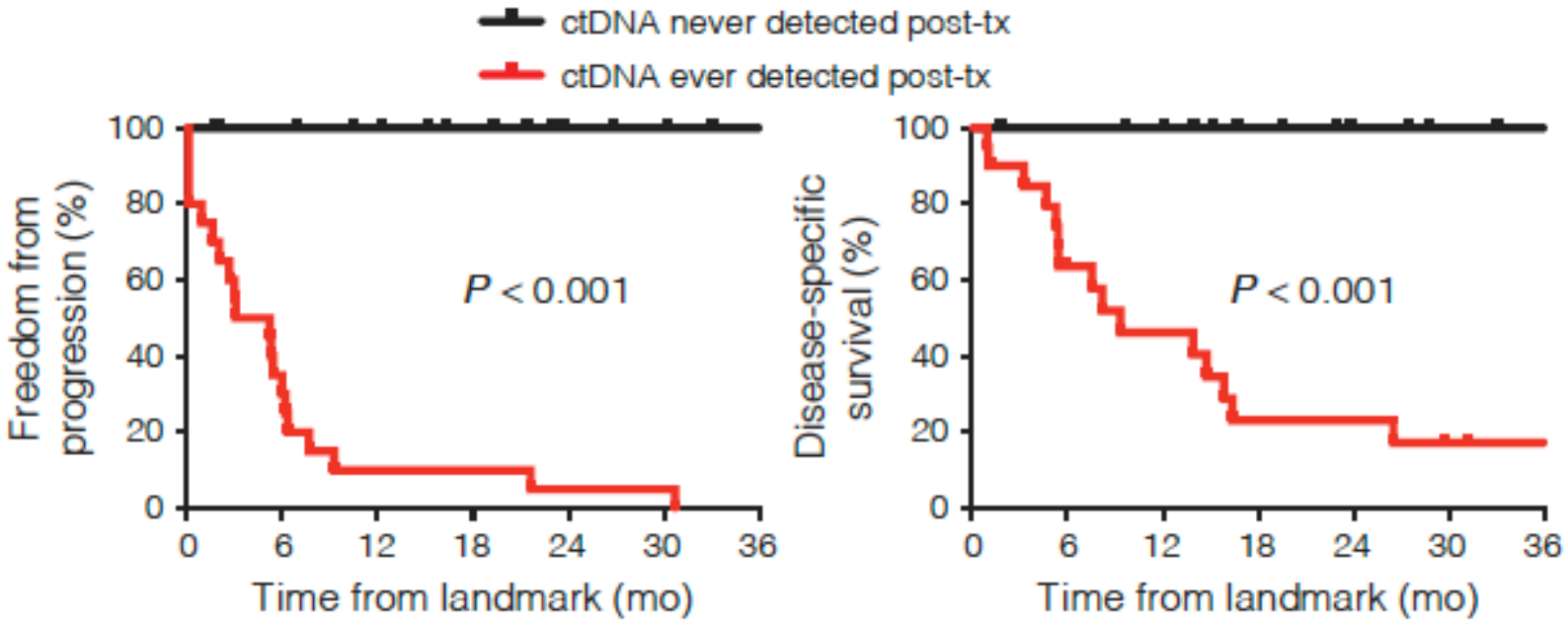
Early Detection of MRD in Localised Lung Cancer by CAPP-Seq



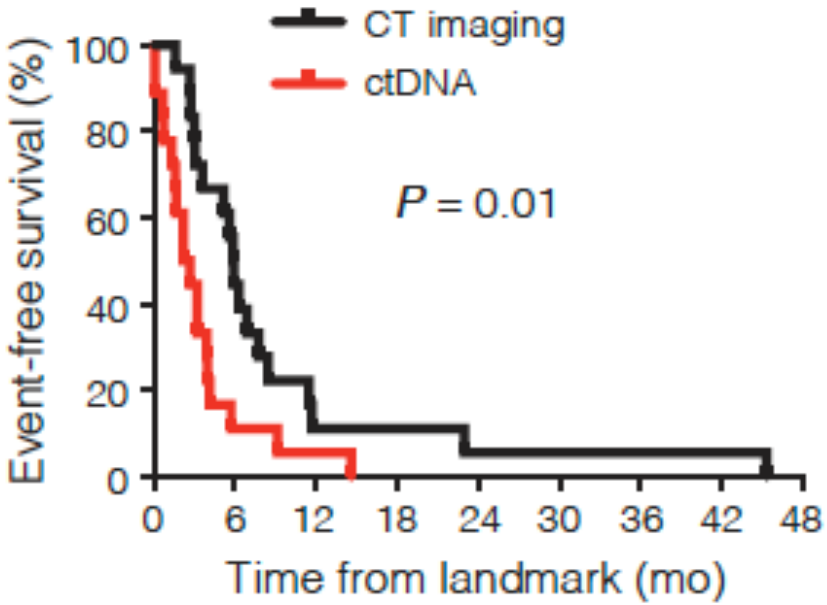
ctDNA analysis can robustly identify posttreatment MRD in patients with localized lung cancer, identifying residual/recurrent disease earlier than standard-of-care radiologic imaging, and thus could facilitate personalized adjuvant treatment

Chaudhuri AA, *et al. Cancer Discov* 2017;7(12):1394-1403.

Application of ctDNA analysis for post-treatment surveillance in patients with localised lung cancer



KM curves stratified by ctDNA detection status during posttreatment surveillance

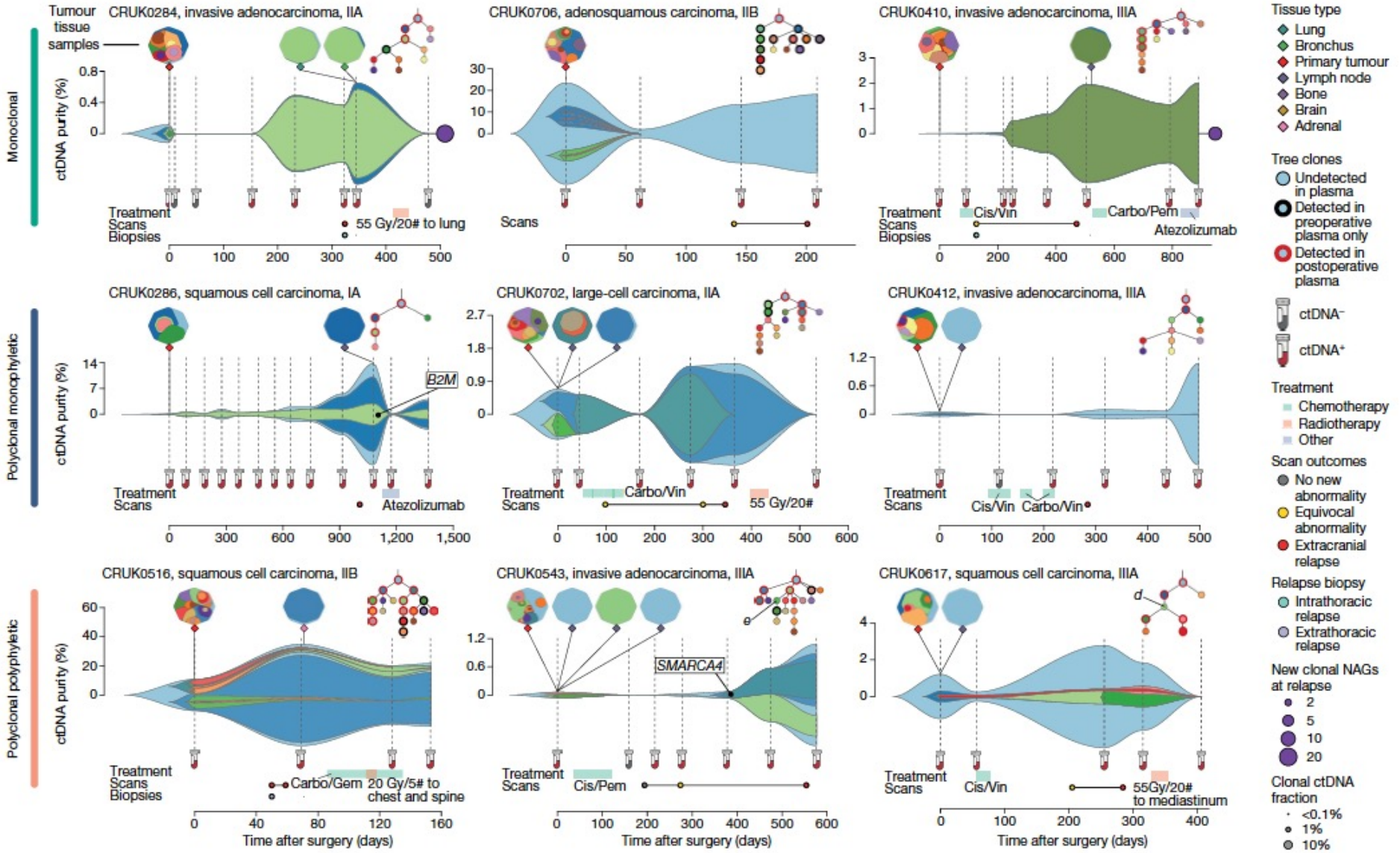


ctDNA detection and time to imaging progression

Chaudhuri AA, *et al. Cancer Discov* 2017;7(12):1394-1403.

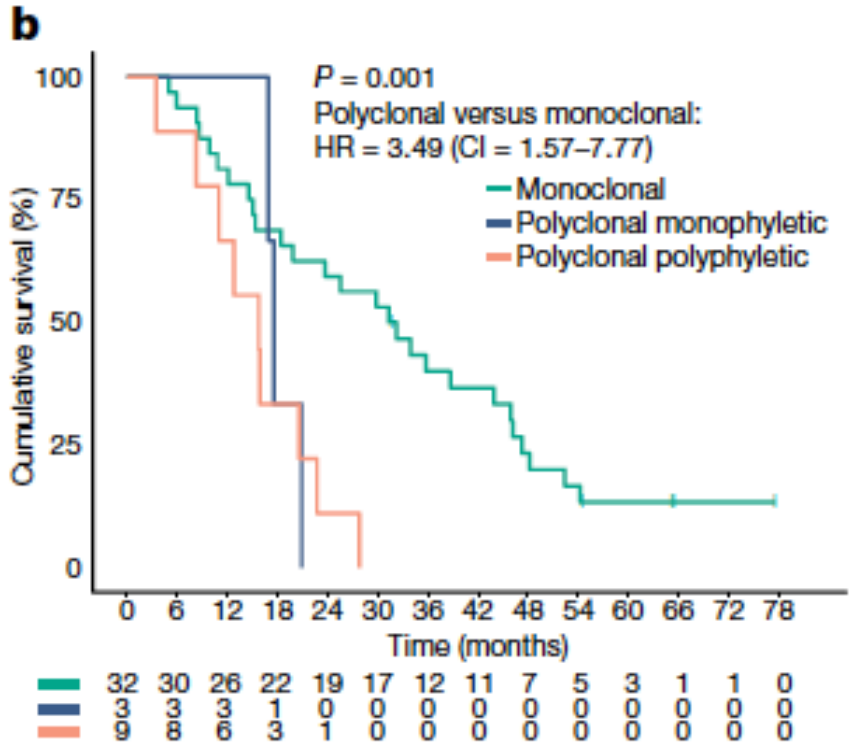
Longitudinal measurements of clonal evolution in the plasma from surgery to therapy and recurrence

Depictions of longitudinal tumour evolution for examples of monoclonal, polyclonal monophyletic and polyclonal polyphyletic metastatic dissemination patterns.

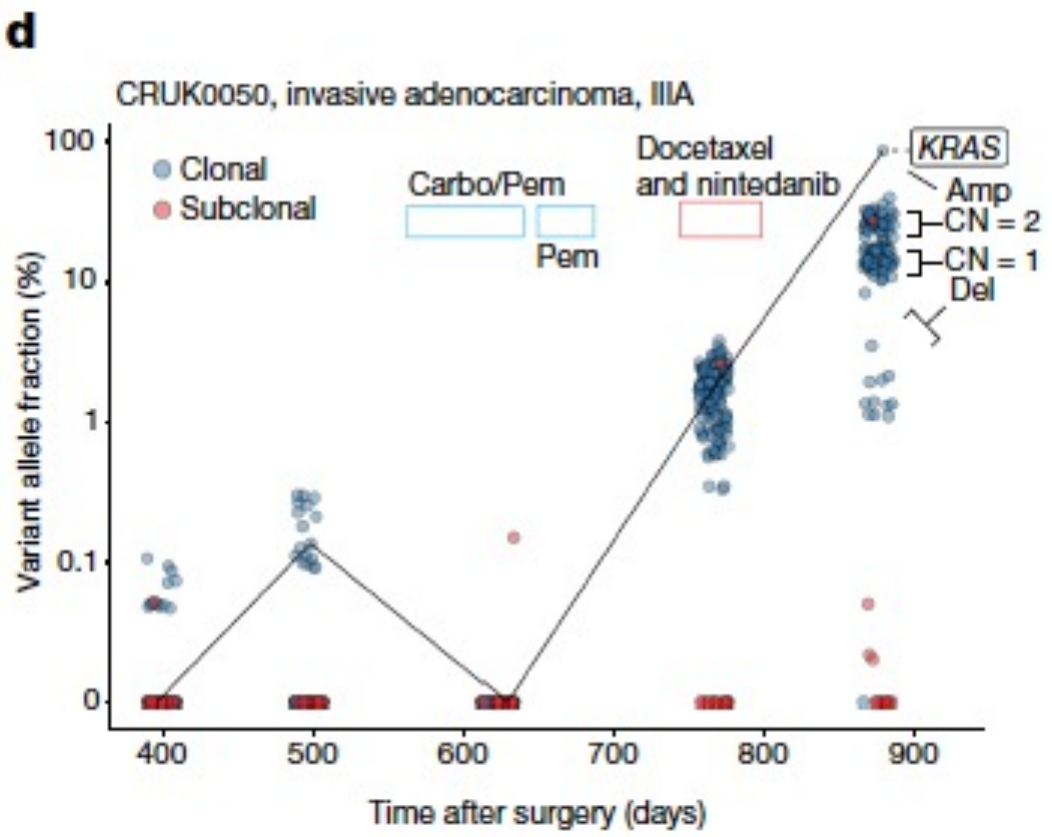


Abbosh C, et al. Nature. 2023 Apr;616(7957):553-562

Longitudinal measurements of clonal evolution in the plasma from surgery to therapy and recurrence



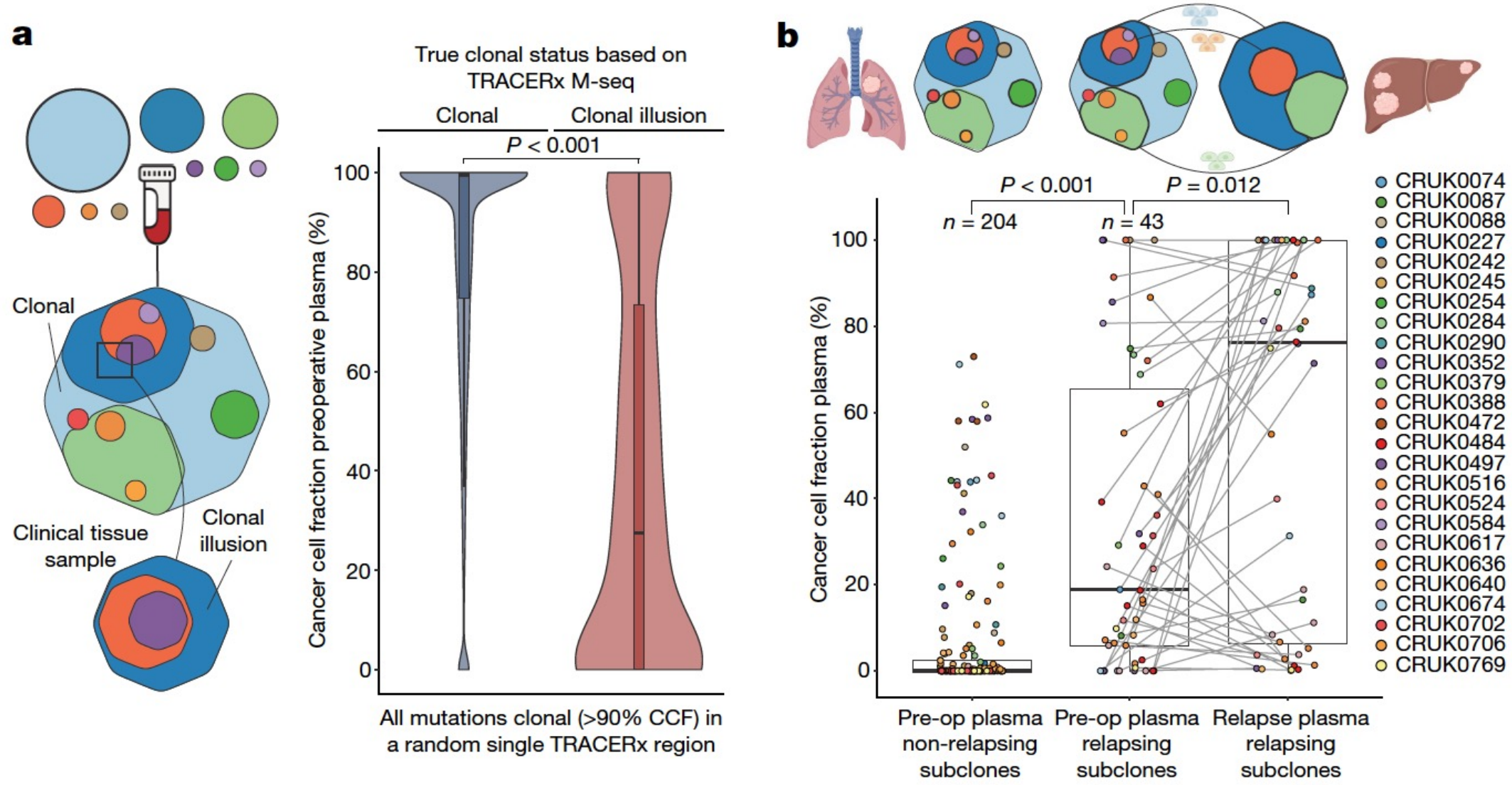
Kaplan–Meier plot depicting differences in the overall survival between metastatic dissemination classes



Variant allele fractions for mutations tracked in patient CRUK0050 at recurrence.

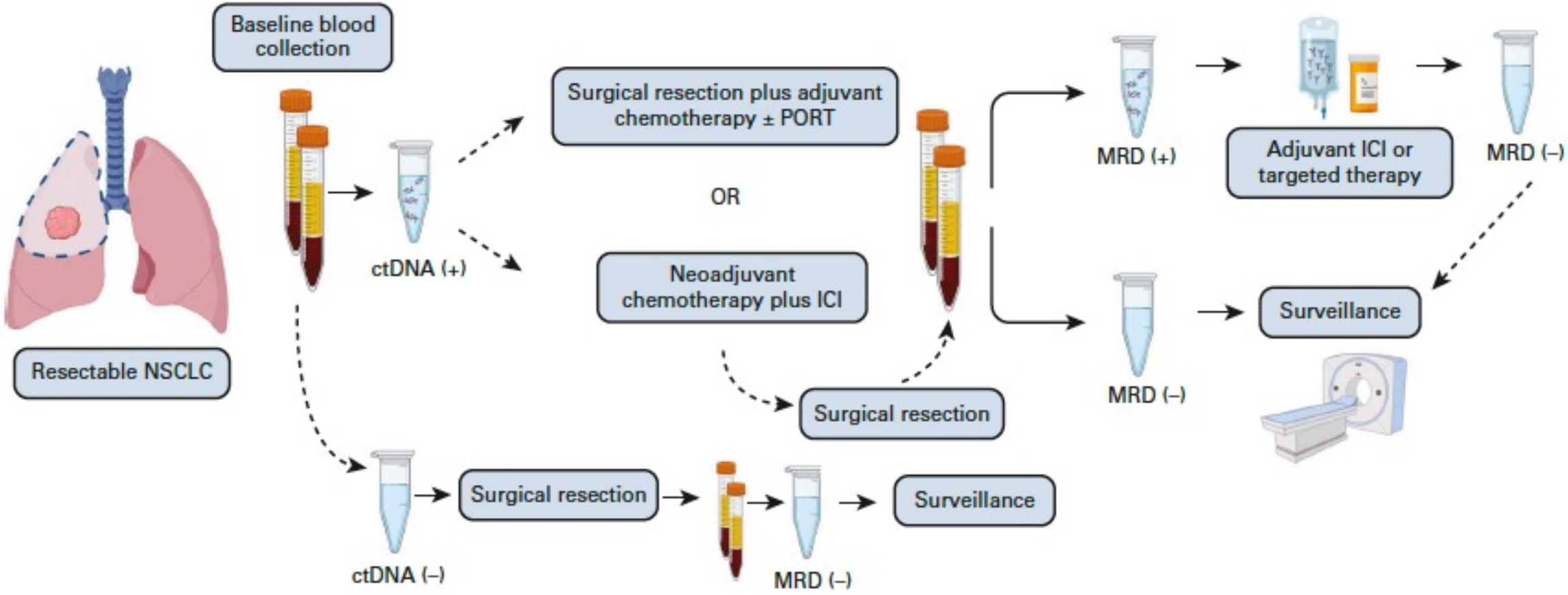
Abbosh C, et al. Nature. 2023 Apr;616(7957):553-562

Clonality measurements in preoperative plasma overcome sampling bias from a single tissue sample and predict metastatic seeding



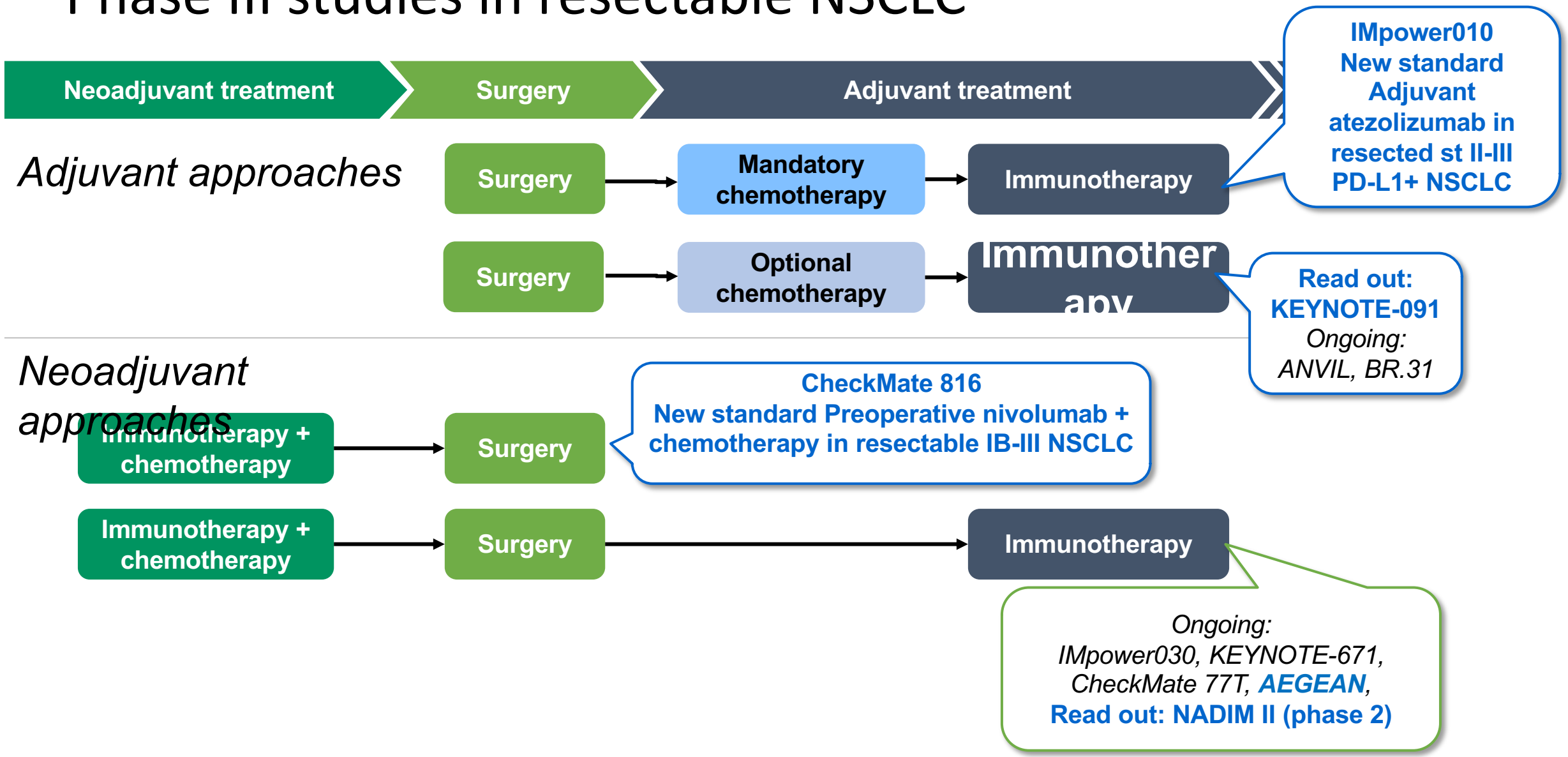
Abbosh C, et al. Nature. 2023 Apr;616(7957):553-562

Proposed clinical trial designs for early-stage NSCLC using ctDNA as a biomarker for treatment personalization



Pellini B & Chaudhuri AA. JCO 2022

Phase III studies in resectable NSCLC

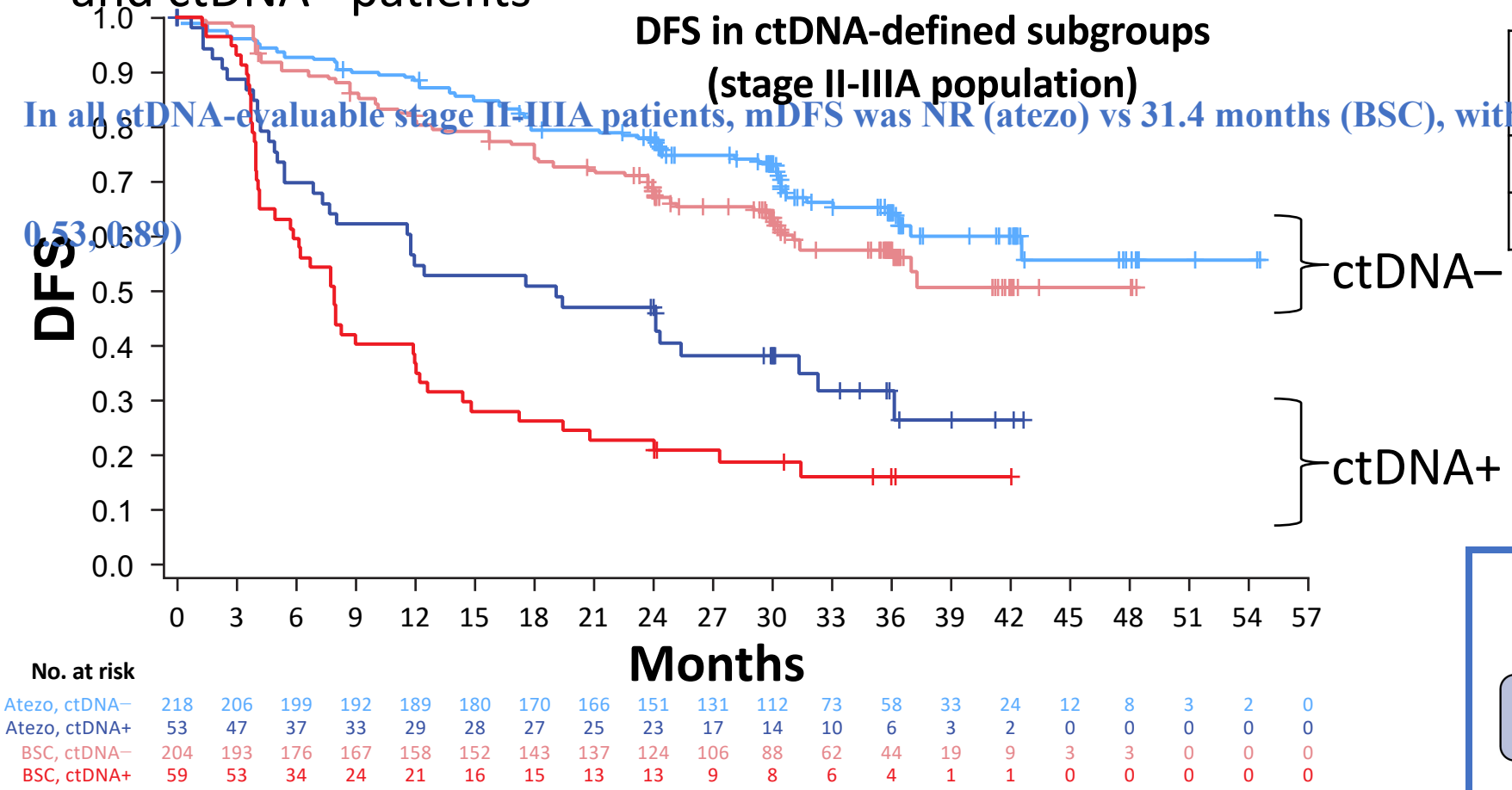


Modified from Dr. S. Peters, EPICS2022

Courtesy Dr. Natasha Leighl

ctDNA positivity was strongly prognostic, with DFS favouring atezo in both ctDNA+ and ctDNA– patients

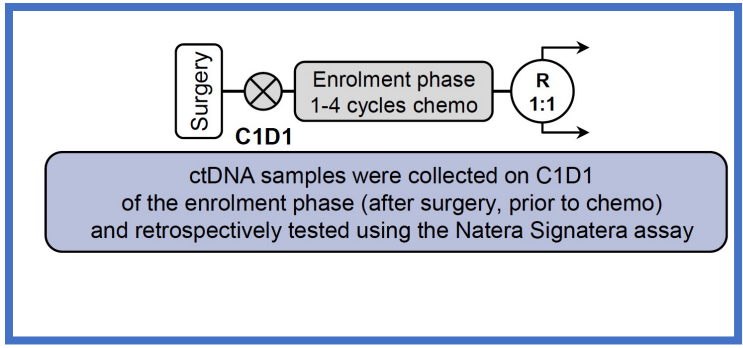
In all ctDNA-evaluable stage II-IIIA patients, mDFS was NR (atezo) vs 31.4 months (BSC), with an HR of 0.69 (95% CI: 0.53, 0.89)



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)	

Plasma collection for ctDNA analysis



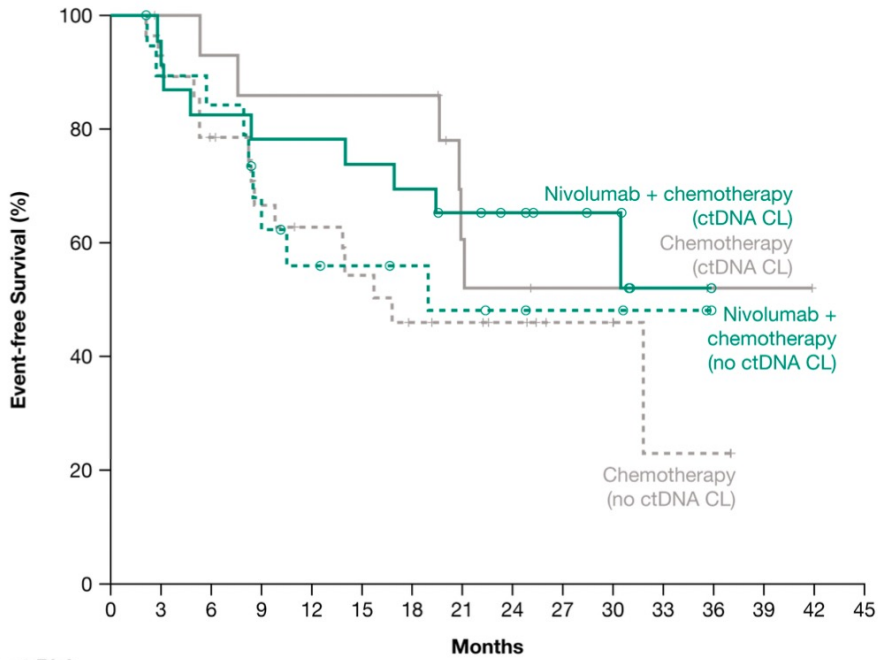
Clinical cutoff: 21 January 2021. Unstratified HRs are shown.

C. Zhou, ESMO 2021

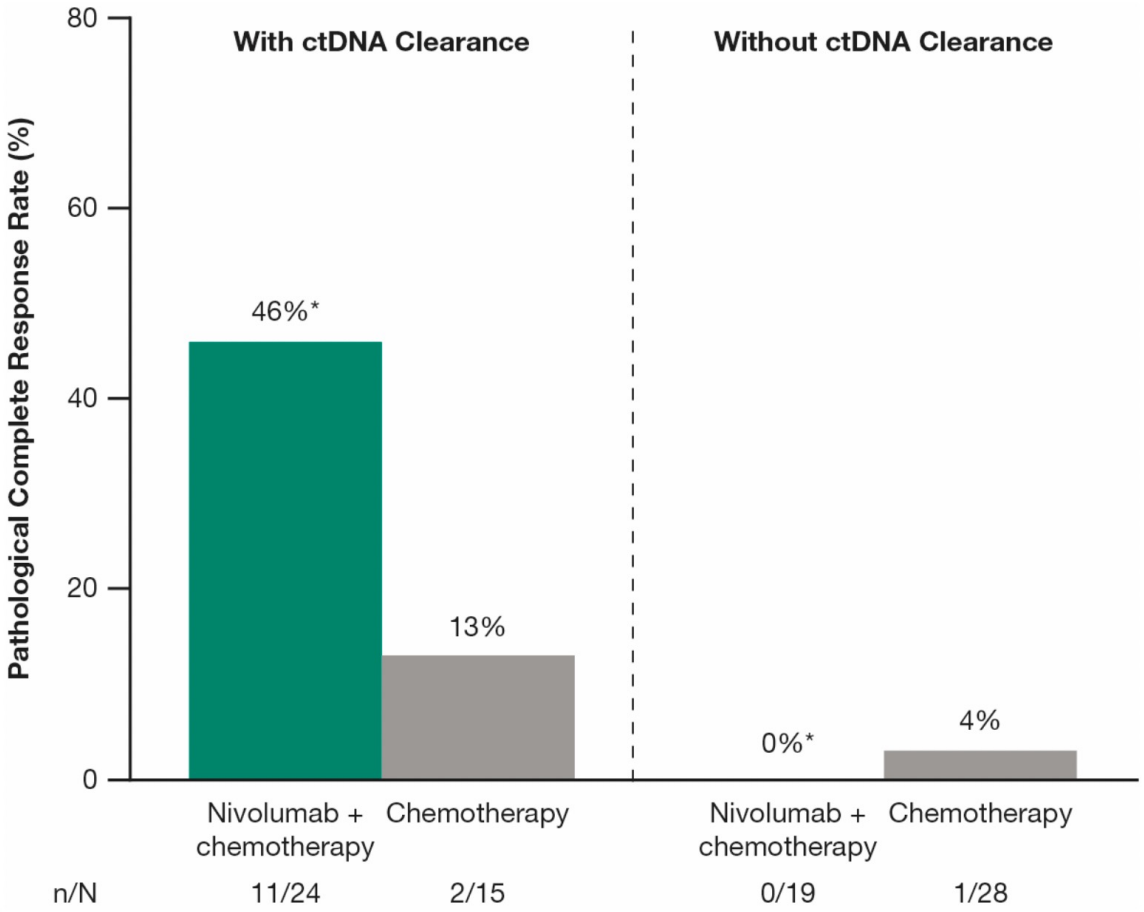
Liquid Biopsy in Neoadjuvant IO + chemo combination

WES ctDNA in 89 pts

	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)	



No. at Risk																
Nivolumab + chemotherapy (ctDNA CL)	24	21	19	18	18	17	16	13	11	8	7	1	0	0	0	0
Chemotherapy (ctDNA CL)	15	14	13	12	12	12	12	7	6	5	5	5	3	1	0	0
Nivolumab + chemotherapy (no ctDNA CL)	19	17	16	12	9	8	7	6	5	3	3	2	0	0	0	0
Chemotherapy (no ctDNA CL)	28	26	21	17	15	13	10	9	7	4	3	1	1	0	0	0

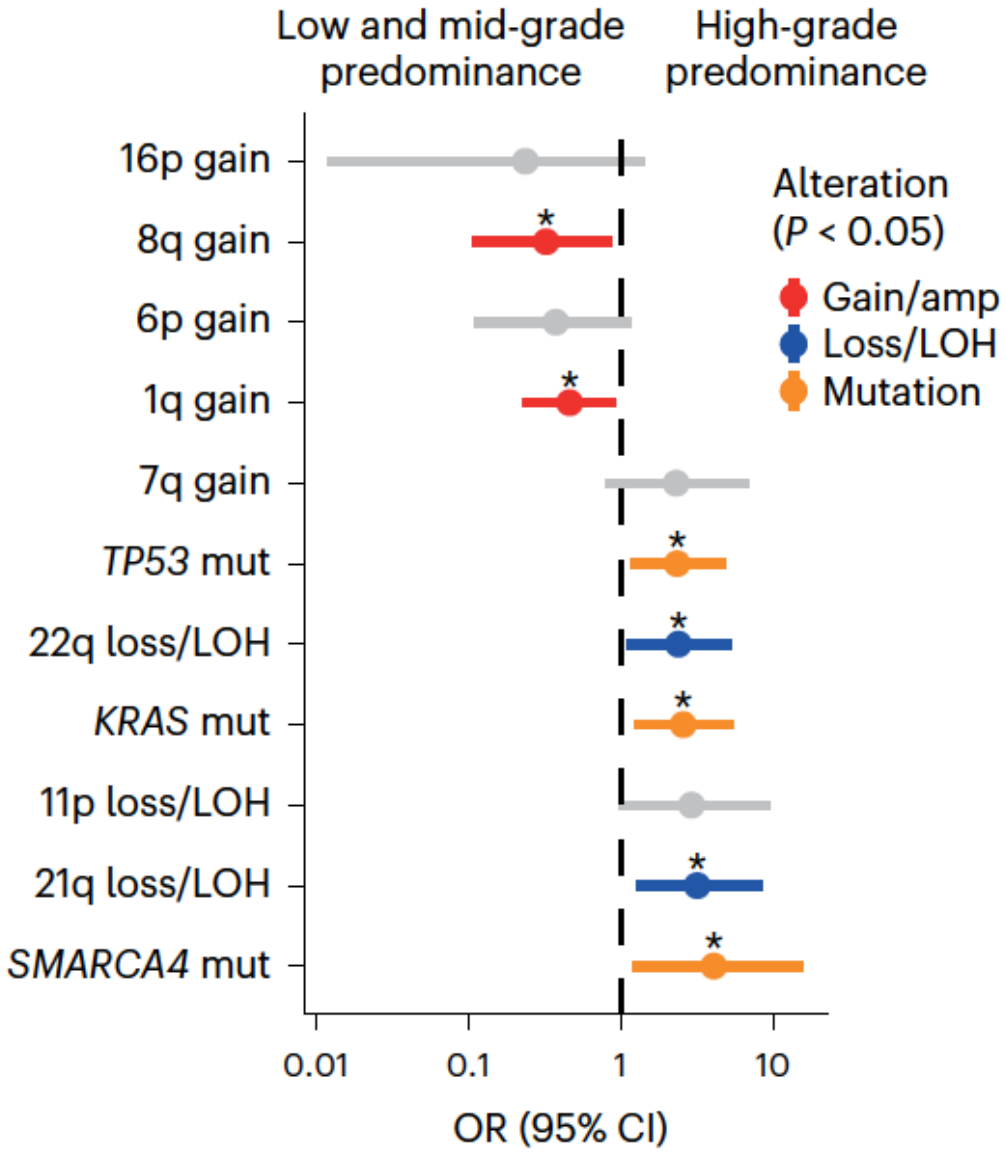


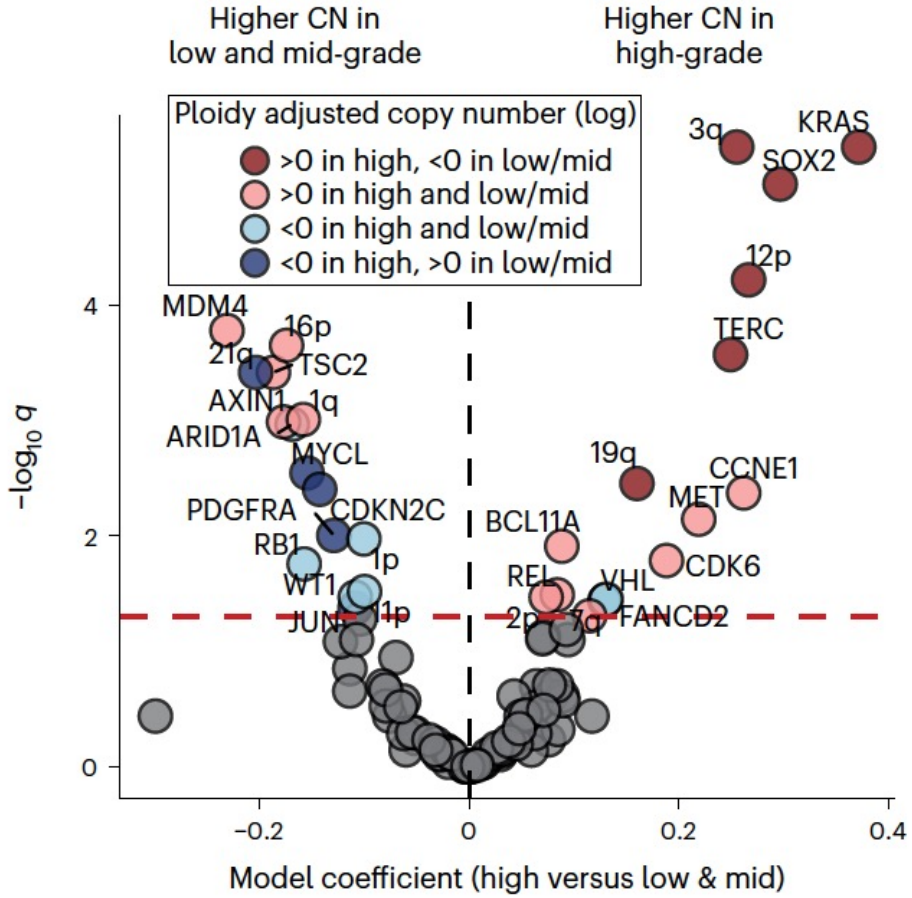
Courtesy Dr. Natasha Leighl

Forde P. et al, NEJM, APR 20

The example of the evolutionary characterization of lung adenocarcinoma morphology in TRACERx

Genomic determinants of predominant growth pattern

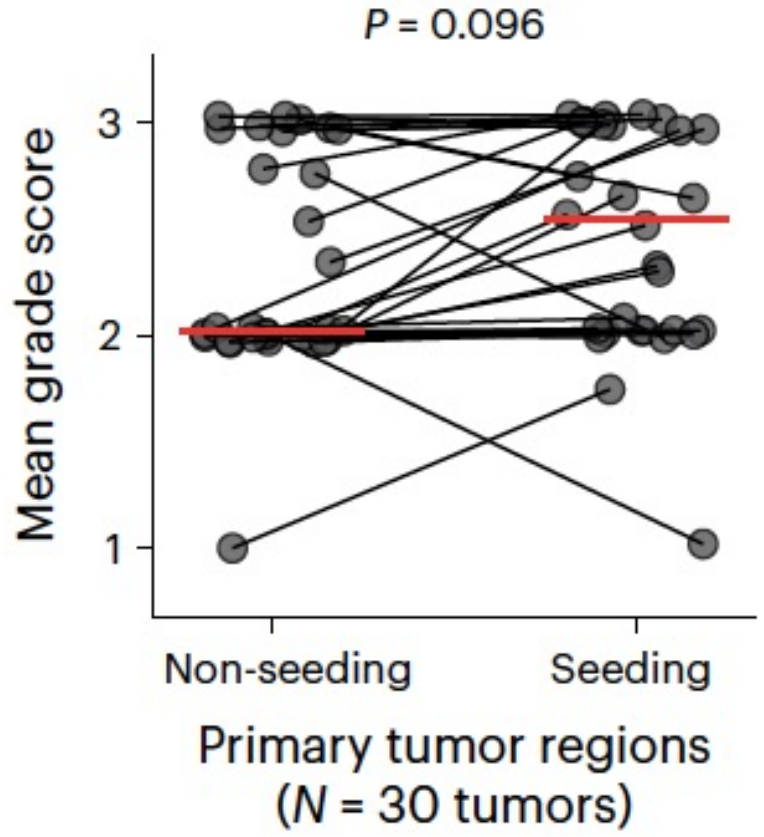




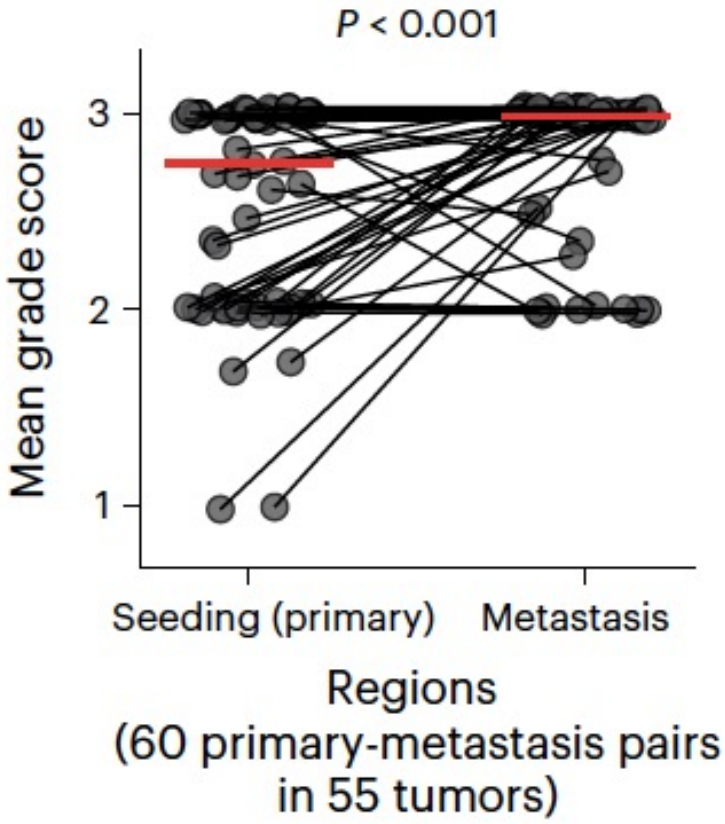
Comparison of ploidy-adjusted mean copy number of chromosomal arm and driver genes between high-grade and low-/mid-grade predominant tumors.

Frankell AM, et al. Nature 2023 Apr;616(7957):525-533

Growth pattern evolution from primary tumor to metastasis



Comparison of mean grade scores between seeding and non-seeding regions in primary tumors.

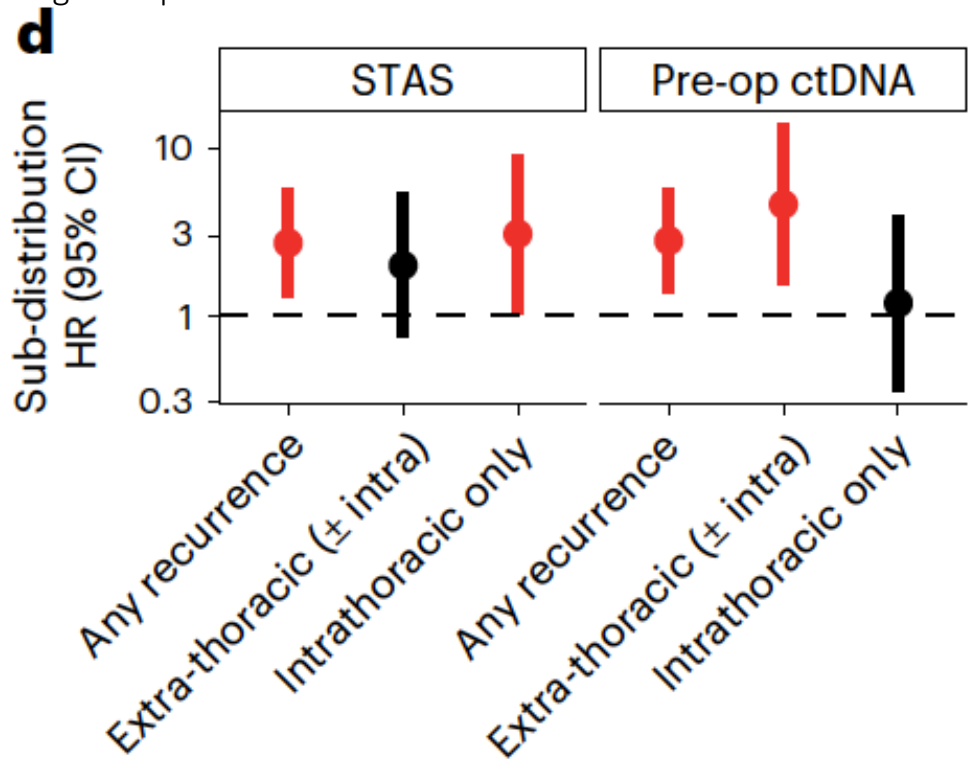


Comparison of growth pattern between metastasis and the primary tumor seeding regions.

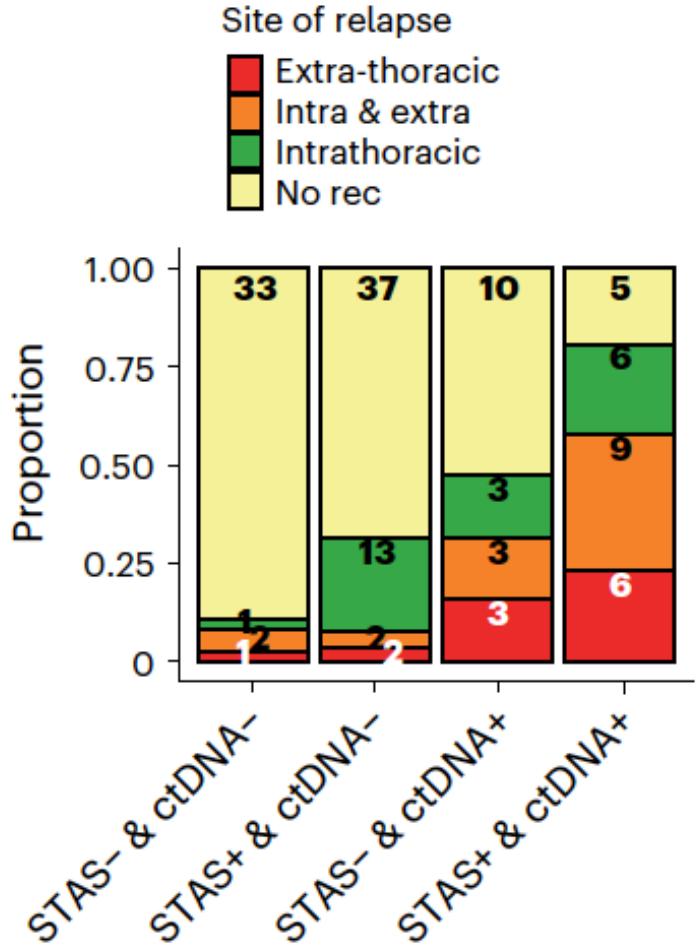
Frankell AM, et al. Nature 2023 Apr;616(7957):525-533

Impact of tumor morphology upon site and risk of recurrence

STAS: spread through air spaces



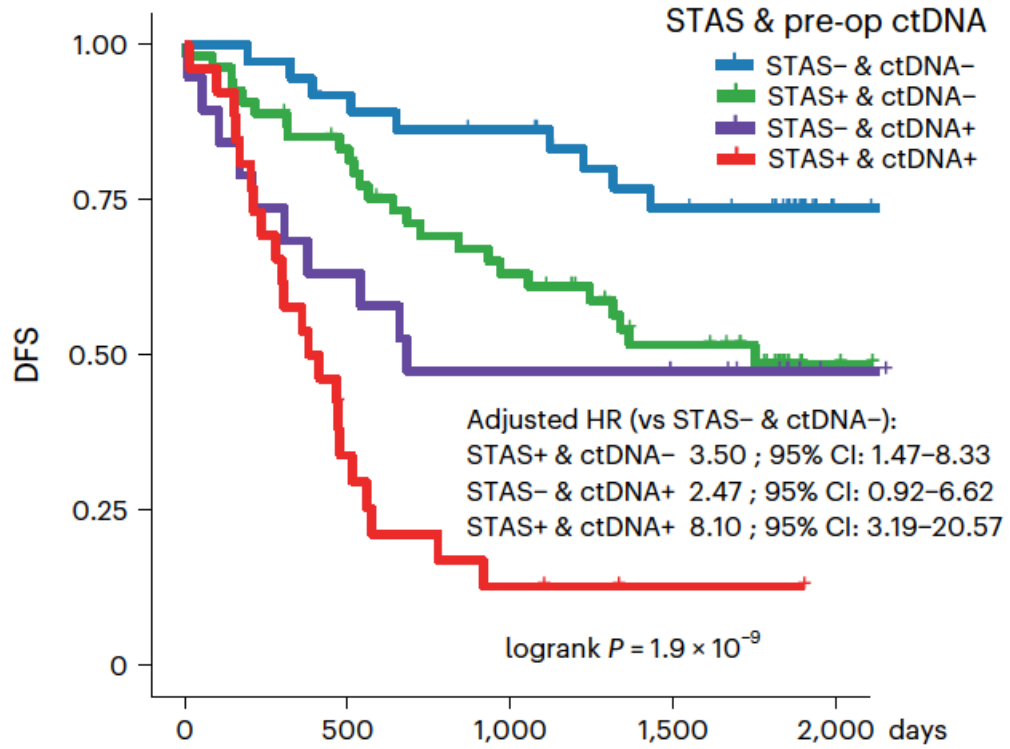
Relapse-site-specific HR for the presence of the positivity of STAS and preoperative ctDNA detection.



Frequency of the site of relapse stratified by the positivity of STAS and preoperative ctDNA detection.

Frankell AM, et al. Nature 2023 Apr;616(7957):525-533

Kaplan–Meier curves of DFS and summary of the findings related to high-grade patterns, pathological and genomic features, and relapse site.



High-grade patterns	**Micropapillary**	**Solid/cribriform**
Pathological features	**STAS+**	**Necrosis+** High Ki-67
Genomic features	High clonal diversity (lack of large recent clonal expansion)	**Pre-op ctDNA+** High CIN Low clonal diversity (presence of large recent clonal expansion)
Relapse site	Intra-thoracic	Extra-thoracic

Frankell AM, et al. Nature 2023 Apr;616(7957):525-533

Take home message

- Liquid and tissue biopsy have a high concordance
- Liquid Biopsy is a great tool for real time monitoring in advance disease
- Liquid Biopsy is a perfect tool for MRD
- Tissue informed approach advantage , but also limitations
- Integrating liquid biopsy in clinical trials is a necessity

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Save the Date
19-21, November 2023