HOW TO INCORPORATE LIQUID BIOPSIES IN PRACTICE

Luis E. Raez MD, FACP

Medical Director and Chief Scientific Officer

Memorial Cancer Institute/Memorial Healthcare System

Co-Director MCIFAU Florida Cancer Center of Excellence

Past-President Florida Society of Clinical Oncology (FLASCO)

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IASLC INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
Conquering Thoracic Cancers Worldwide

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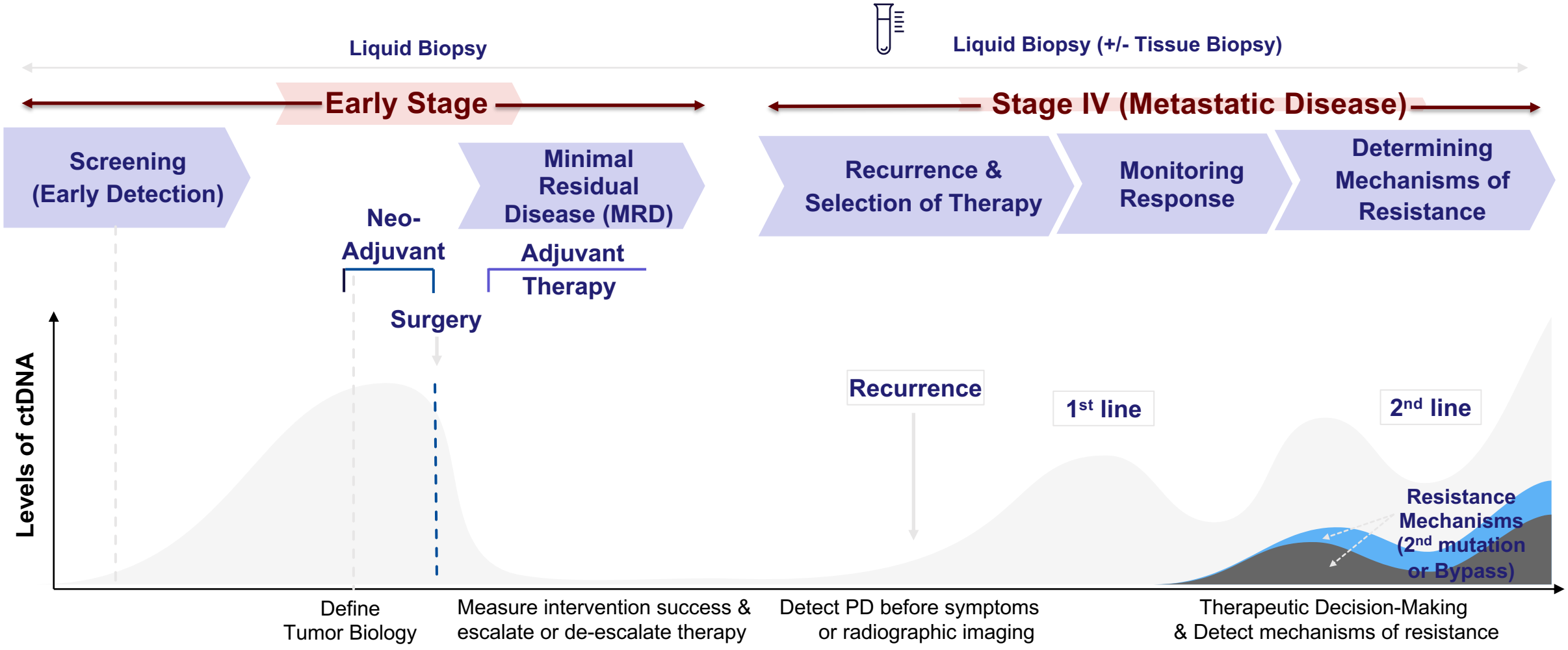
Liquid biopsy Across the Cancer Care Continuum in Individual Patients (Precision Oncology)



Gandara: ISLB Congress 2021 (Adapted from Wan, J.C.M., et al. *Nat Rev Cancer 2017)*

Utility of Liquid Biopsies in Clinical Practice

1. Molecular profiling of metastatic lung cancer tumors as complement of tissue biopsies
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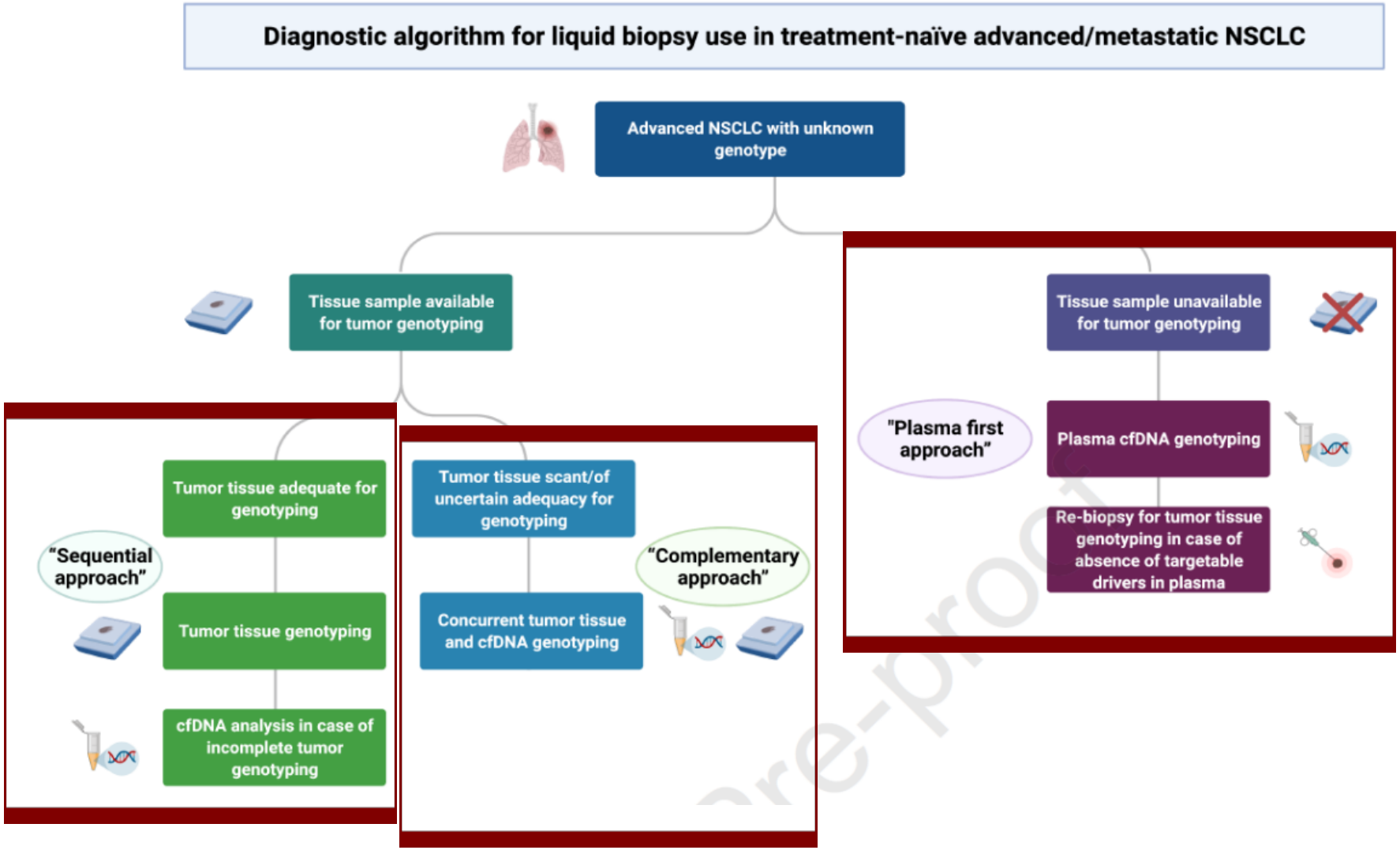
Updated IASLC Consensus Statement on Liquid Biopsy in NSCLC: 2021



Rolfo, Gandara (Raez) et al. JTO 2021

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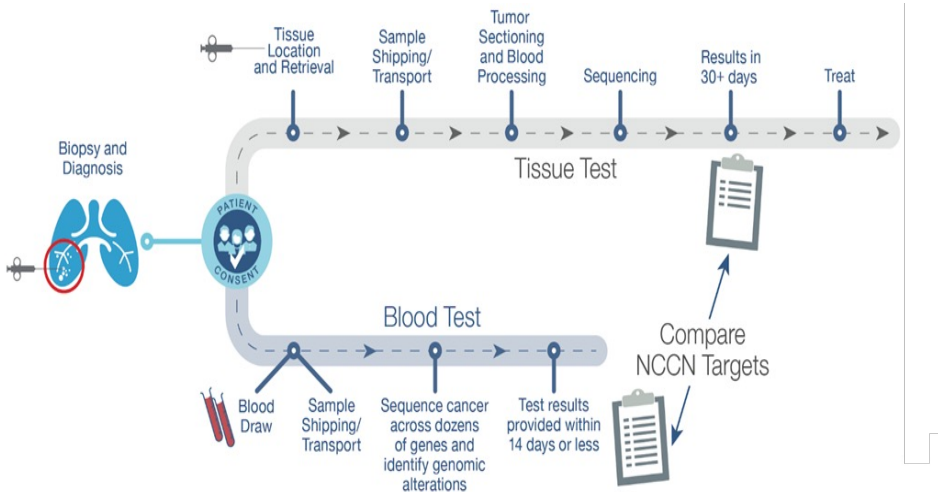
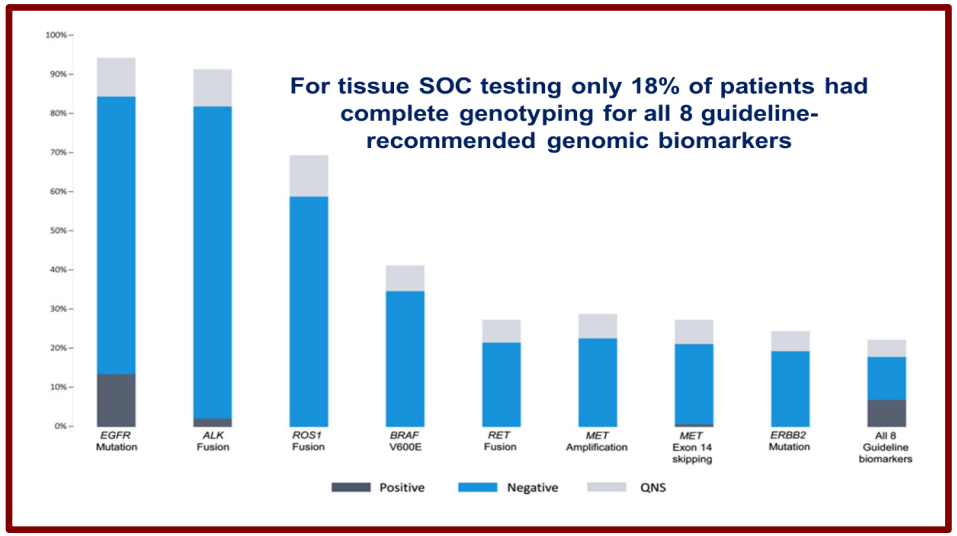
Plasma NGS vs. SOC tissue genotyping: The NILE study

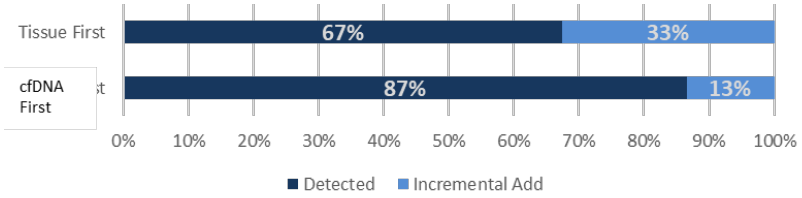
- **Methods: 282 patients with newly diagnosed non-squamous mNSCLC, undergoing physician discretion SOC tissue genotyping were prospectively recruited from 28 North American centers**
- **Patients underwent ctDNA testing utilizing a validated clinically available assay**





- **For tissue-based SOC testing only 18% had complete genotyping for all 8 guideline-recommended biomarkers**
- **If the first genomic testing was ctDNA, 87% had a NCCN biomarker identified vs 67% with SOC tissue testing (p<0.0001)**
- **cfDNA testing had a faster turn-around time (TRT): median 9 days (cfDNA) vs 15 days (SOC tissue testing) p<0.0001**

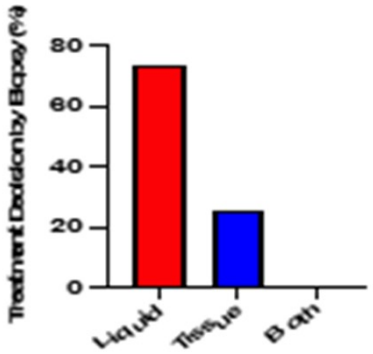
Percentage of Guideline-Recommended Biomarker Positive Patients Identified by Tissue versus cfDNA First



Papadimitrakopoulou, AACR 2019. Leighl et al. CCR 2019.

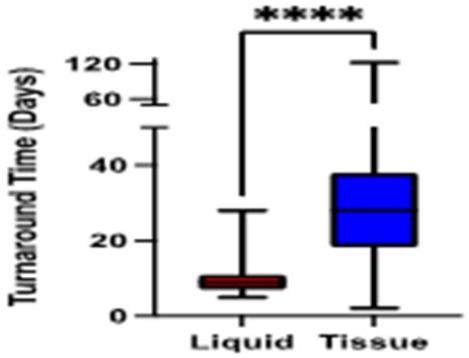
Using Liquid Biopsies First to Make Front Line Treatment Decisions in Patients With Metastatic Non-Small Cell Lung Cancer

- Liquid biopsies (LB) are non-inferior to tissue biopsies (TB) to identify actionable genetic alterations (AGA) in patients with NSCLC
- LB are able to report NGS results significantly faster than TB NGS and overcome the logistical barriers of finding and shipping tissue samples for sequencing.
- 170 patients diagnosed with mNSCLC and treated at Memorial Cancer Institute.



	Liquid Guided	Tissue Guided	Both
Patients	119	42	1

Majority of treatment decisions were based on LB results (74.0%) vs. TB (24.7%).



N=165	Liq	Tissue
TAT Mean	9.6	30.5
TAT Median	9	28
Samples QNS	0	18 (10.6%)

Median TAT for LB was 18 days shorter than TB (9d vs. 28d)

Raez LE, et al. JTO Nov 25, 2022. https://doi.org/10.1016/j.cllc.2022.11.007

Plasma NGS at time of diagnostic tissue biopsy impact on time to treatment: results from a pilot prospective study

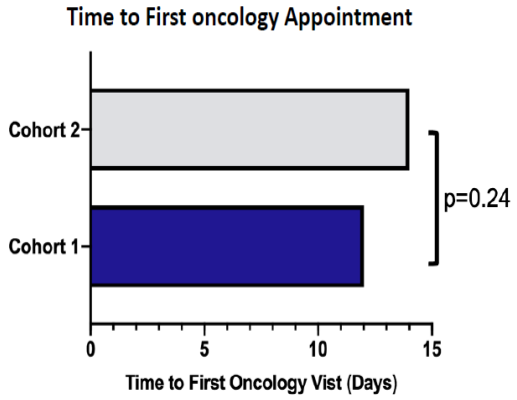
Jeffrey C. Thompson, Charu Aggarwal, Janeline Wong, Vivek Nimgaonkar, Michelle Andronov, David M. DiBardino, Christoph T. Hutchinson, Kevin Ma, Anthony Lanfranco, Edmund Moon, Andrew R. Haas, Anil Vachani, Erica L. Carpenter

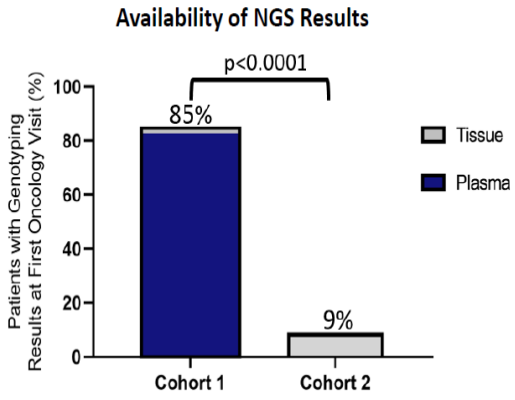
University of Pennsylvania
Abramson Cancer Center
Philadelphia, PA, USA

RESULTS

- Median time to first medical oncology visit did not differ between cohorts (12 vs. 14 days, p=0.24)
- Turnaround time for plasma NGS was shorter compared to tissue (8 vs. 22 days, p<0.0001)

- A significantly higher percentage of patients in cohort 1 had NGS results available at the first medical oncology visit.
- This was mostly driven by the availability of plasma NGS results

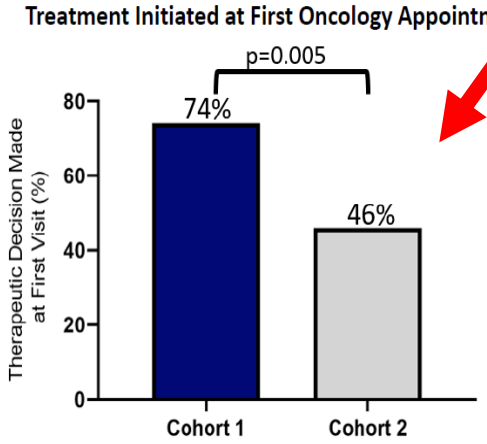


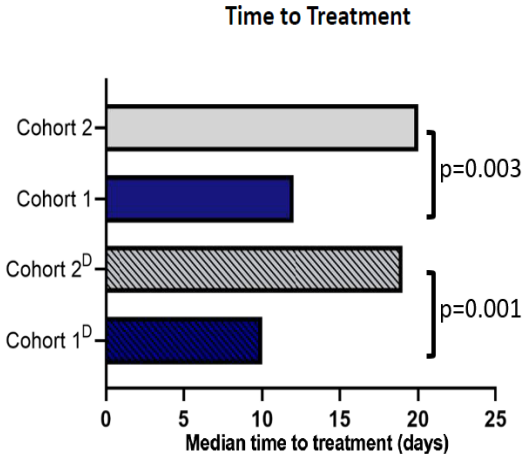


IMPACT ON TIME TO TREATMENT

- More NSCLC patients with plasma genotyping performed at the time of initial diagnostic biopsy received a specific treatment recommendation during the first oncology visit

- Time to first-line therapy was significantly shorter in patients with plasma genotyping at diagnostic biopsy, with an event shorter time to treatment in patients with an oncogenic driver mutation identified





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Assessing Resistant to Therapy and Choosing the Best Next Therapy

Table 9-1. ROS1 Inhibitors (Approved and in Development)

TKI	Phase (Clinical Study)	N	ORR (%)	mPFS (months)	mOS (months)
Crizotinib	1 and 2 (Profile 1001)	53	72	19	51
	1 and 2 (AcSé)	36	47	6	17
	2 (EUCROSS)	34	70	20	NR
	2 (METROS)	26	65	23	NR
Ceritinib	2	32	62	19	24
Entrectinib	2 (STARTRK 1/2, ALKA 372)	172	69	18	NR
Lorlatinib	1 and 2	69	62[a]	21	NA
			35[b]	9	NA
Cabozantinib	2	6	33	NA	NA
Taletrectinib	2	40	90[c]	NA	NA
		21	47[d]	NA	NA
Repotrectinib	2	55	86	30.9	NA
Ensartinib	2	59	27	NA	NA
TQ-B3101	2	111	78	15	NA

IC_{50} (nmol/L)	Crizotinib	Entrectinib	Lorlatinib	Repotrectinib	Cabozantinib	Ceritinib	Brigatinib	Taletrectinib	Alectinib
Parental	840.5	1,801.0	>3,000	1,218.0	>3,000	1,117.0	>3,000	>3,000	1,207.0
Nonmutant	5.4	2.7	0.7	2.0	2.8	16.4	9.4	2.6	995.4
G2032R	609.6	436.3	196.6	23.1	17.5	346.4	472.7	53.3	1,091.0
L2000V	37.1	25.9	2.5	10.1	7.6	124.9	78.9	29.8	985.0
L2086F	536.8	440.0	>3,000	587.9	3.6	226.9	159.3	1,265.0	672.5
S1986F/L2000V	159.4	36.1	2.4	7.2	5.1	86.9	62.5	20.3	1,080.0
S1986F/L2086F	469.7	344.2	>3,000	241.2	1.3	154.8	48.5	662.6	919.9
G2032R/L2086F	498.6	335.4	>3,000	248.9	5.0	573.9	450.9	744.2	1,254.0
S1986F/G2032R	594.4	718.5	990.6	65.1	70.1	614.7	717.0	105.4	1,137.0
S1986F/G2032R/L2086F	562.8	1,111.0	2,131.0	1,178.0	9.4	1,116.0	1,341.0	2,432.0	1,150.0

$IC_{50} \leq 50$ nmol/L

50 nmol/L < IC_{50} <200 nmol/L

$IC_{50} \geq 200$ nmol/L

Santejoul S, Raez LE, et al. IASLC Atlas of Molecular Testing 2023.

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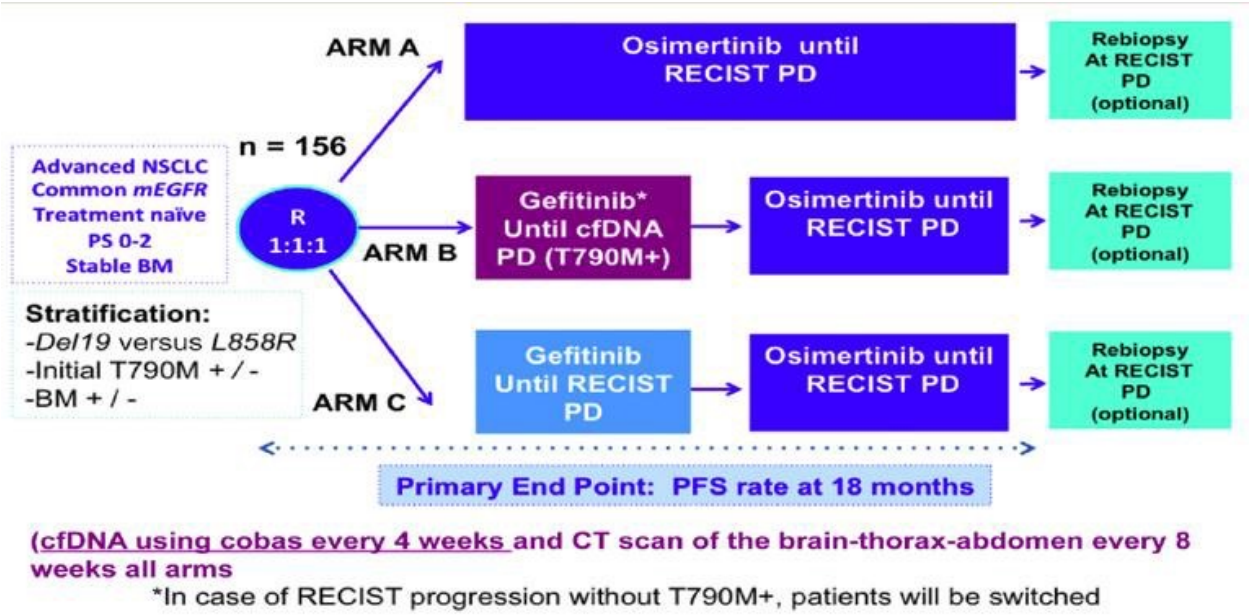
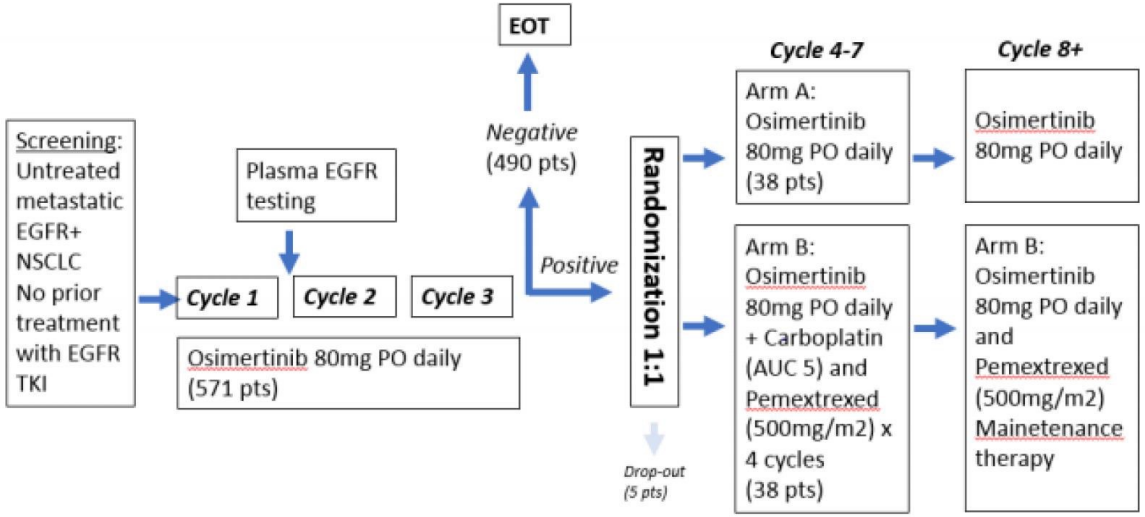
Demonstrating Clinical Utility of Plasma ctDNA Monitoring

EORTC APPLE Trial
(NCT02856893)
PI: Dr. Rafal Dziadziusko



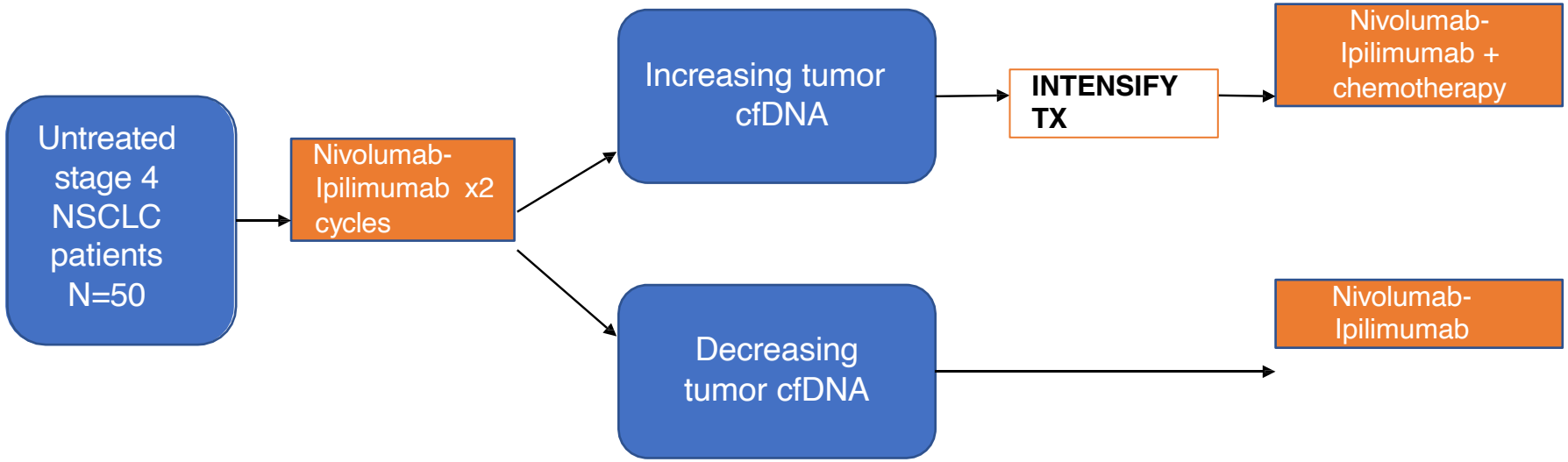
Will address whether switching TKIs based on plasma ctDNA levels is superior to switching based on progression by RECIST

Osimertinib +/- Chemotherapy
(NCT04410796)
PI: Dr. Helena Yu



Will address whether failure of early ctDNA clearance identifies patients that require additional treatment (adding chemotherapy)

ATLAS: Beyond Chemotherapy: Using Plasma ctDNA to Intensify Therapy PI: Dr. Adrian Sacher, Princess Margaret Cancer Centre (NCT04966676)



1º endpoint

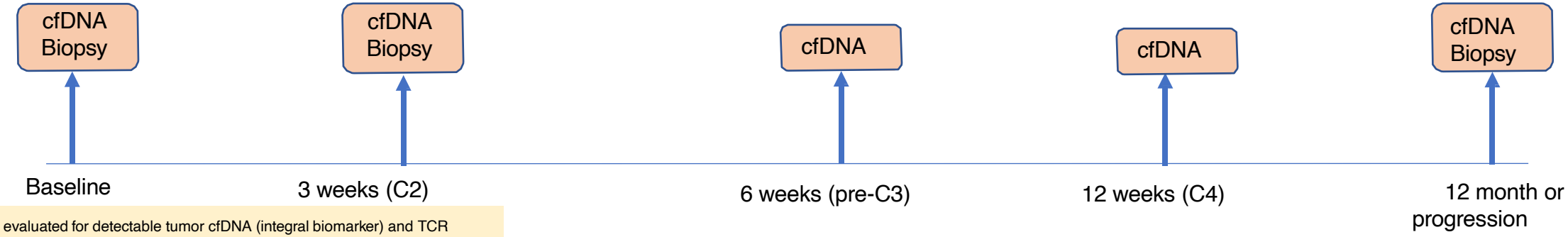
PFS compared to historic controls

2º endpoint

ORR, toxicity, OS

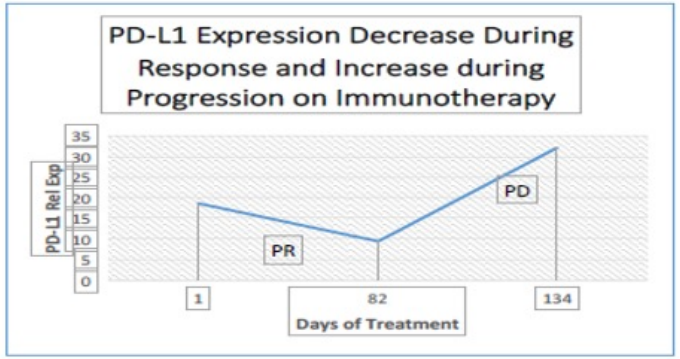
Exploratory endpoints

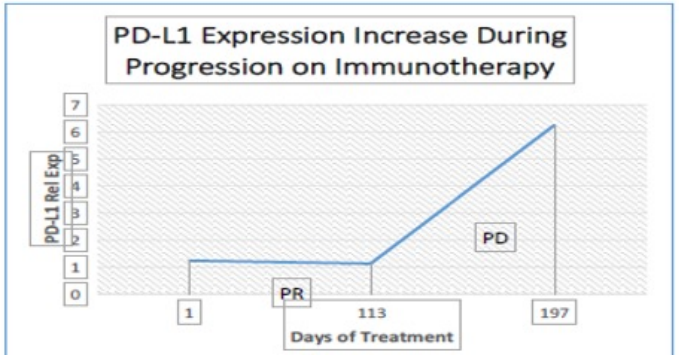
cfDNA response
TCR clonality and clonal tracking
Serial biopsy for TIME profiling by CITEseq



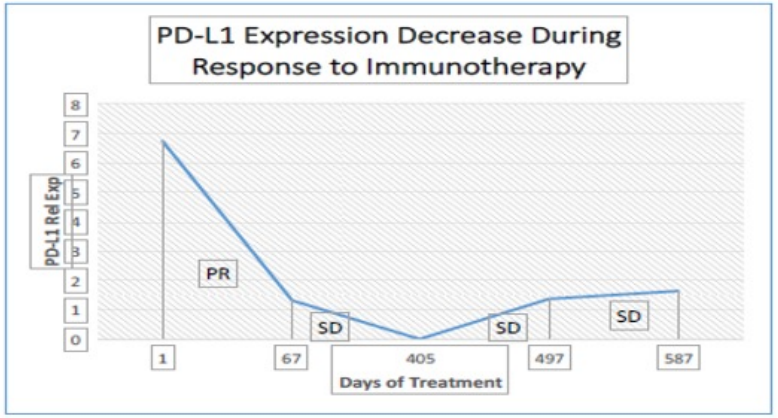
Serial cfDNA will be evaluated for detectable tumor cfDNA (integral biomarker) and TCR clonality/clonal tracking. Serial tumor biopsy will undergo evaluation of evolving tumor immune microenvironment by CITEseq +/- imaging mass cytometry (IMC).

Assessing Lung Cancer Immunotherapy Responses by cfRNA





Examples of the dynamics of PD-L1 expression during individual treatment of NSCLC patients with immunotherapy vs outcome*.



Raez LE, A, et al. J Clin Oncol 37, 2019 (suppl; abstr e14567)

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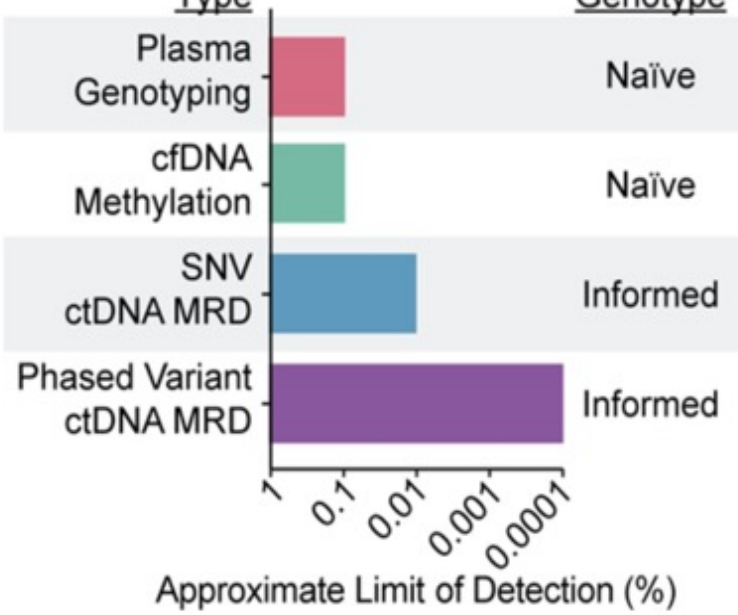
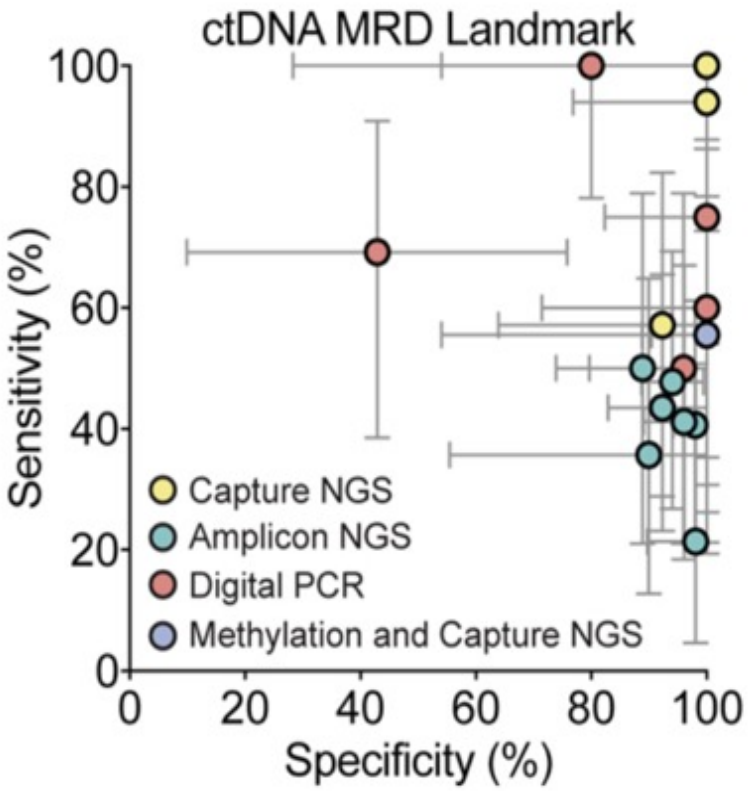
Detecting MRD in Solid Tumors after Curative-Intent Treatment





Modig et al. Cancer Discovery. 2021;11(12):2968-86.

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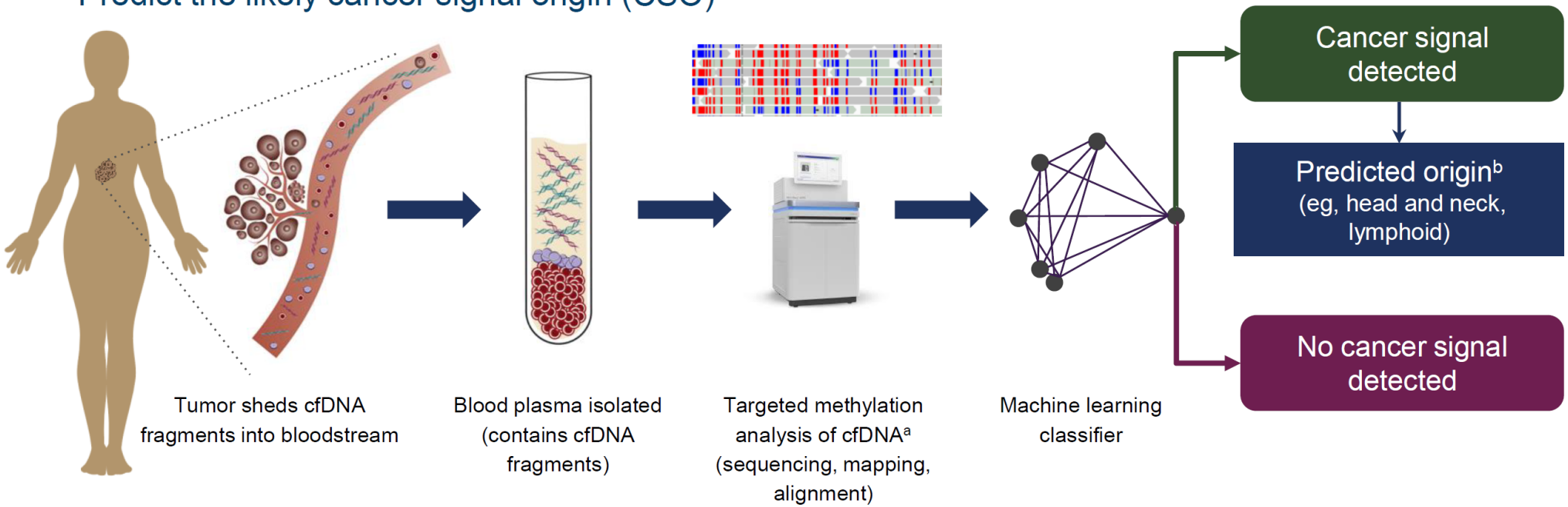
Background: Multi-Cancer Early Detection (MCED) Blood Assays

MCED testing uses a targeted methylation, next-generation sequencing (NGS)-based assay to:

- Detect and analyze cfDNA in the bloodstream
- Deploy machine learning to detect a cancer signal
- Predict the likely cancer signal origin (CSO)



cfDNA, cell-free DNA. [a]Bisulfite treatment; targeted probes pull out fragments matching regions of interest. [b]For a detected signal, the MCED test predicts 1-2 cancer signal origins (CSO) that can be either an anatomic site (eg, colorectal) or a cellular lineage (eg, lymphoid). Adapted from Liu MC, et al. *Ann Oncol*. 2020;31(6):745-759. PMID: 33506766

PARIS 2022 ESMO congress

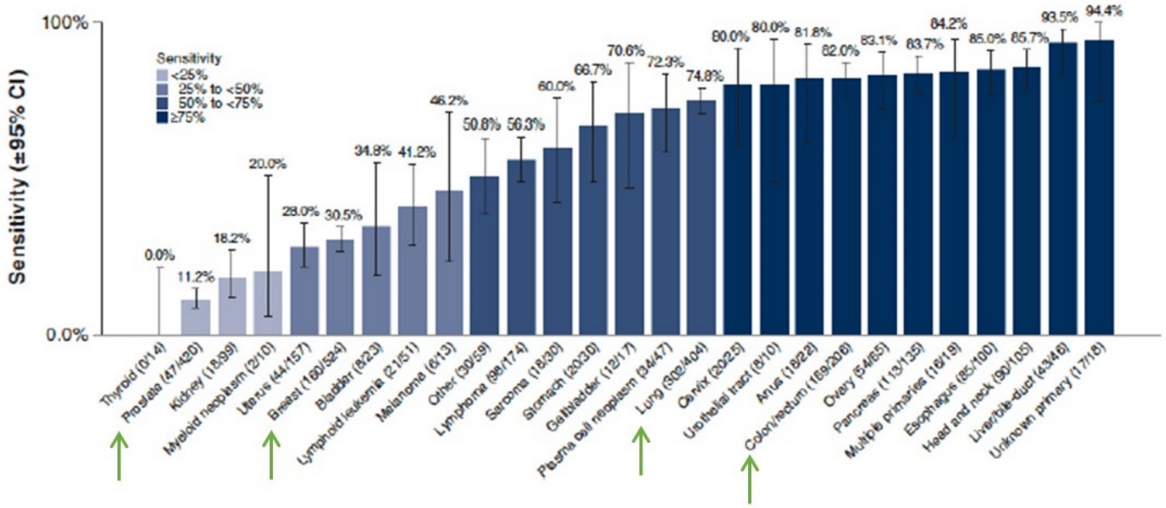
Deb Schrag, MD, MPH

ctDNA methylation for early cancer detection

	Cancer	Non-cancer	Total
	2823	1254	4077
Test positive	1453	6	1459
Test negative	1370	1248	2618
	Sensitivity = 1453/2823 51.5% (49.6%-53.3%)	Specificity = 1248/1254 99.5% (99.0%-99.8%)	

Two-sided 95% Wilson confidence intervals were calculated.

Targeted methylation assay
Tumor-naïve
(GRAIL Galleri)



Sensitivity varies with **cancer** type, **histology**, and **stage**

Klein EA et al. *Ann Oncol*. 2021

PRESENTED BY:
Bruna Pellini, MD
Assistant Member, Department of Thoracic Oncology, Moffitt Cancer Center

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