Convergence of Liquid Biopsy and Precision Oncology in the management of NSCLC

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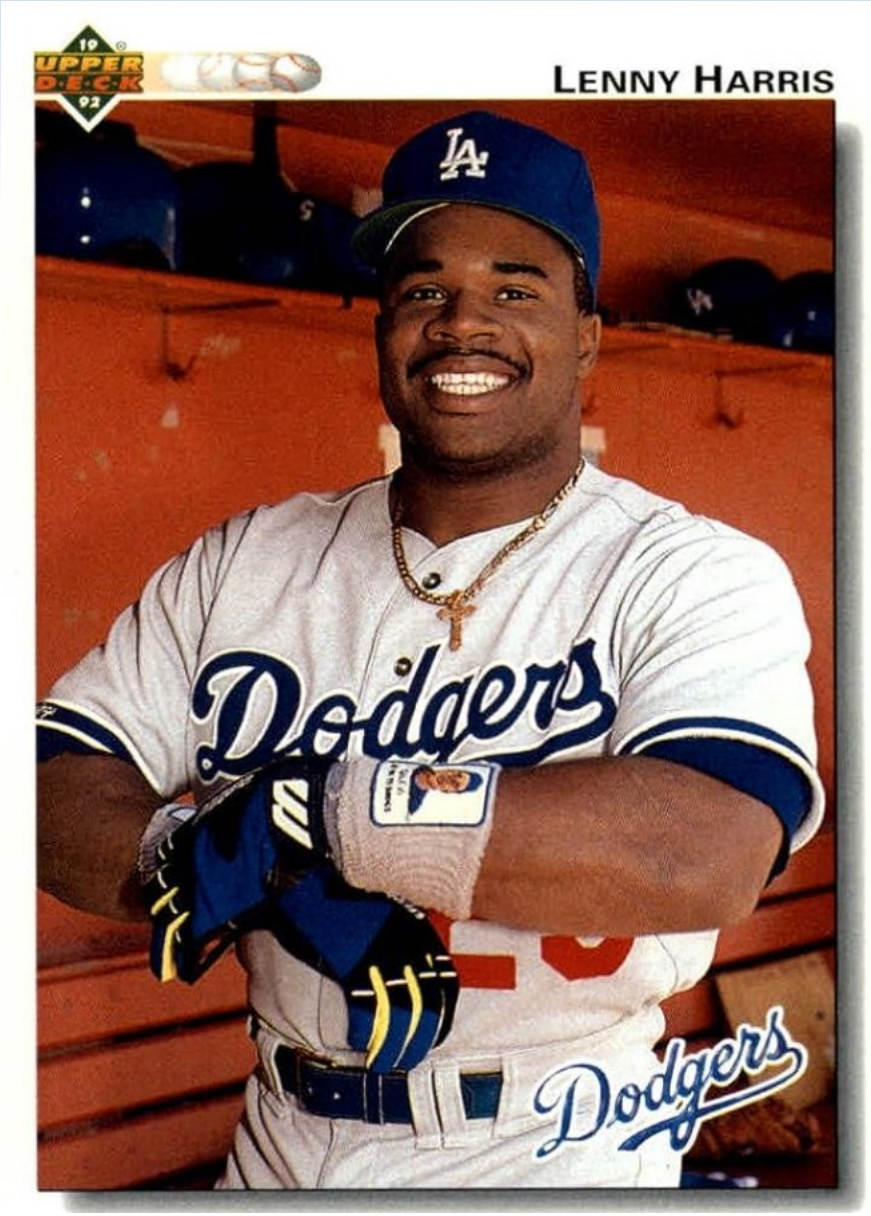
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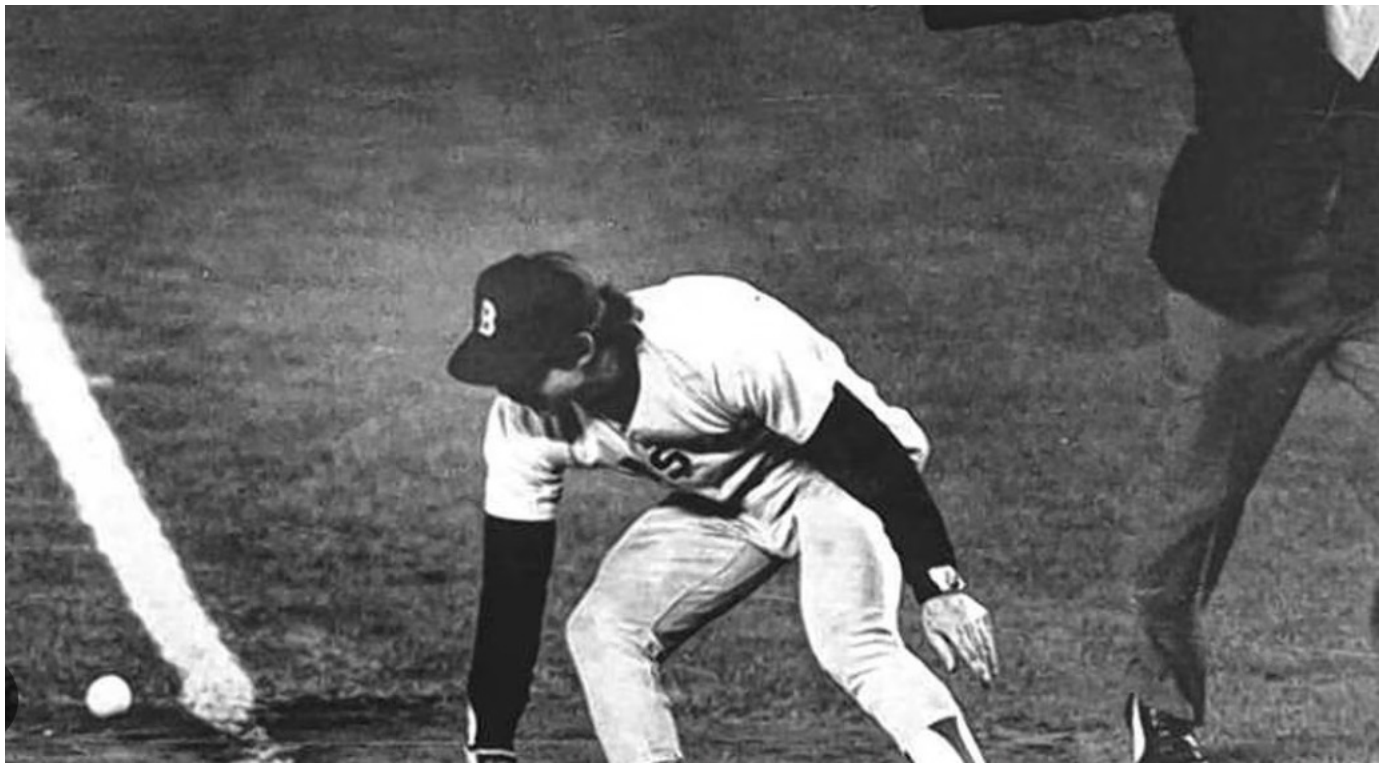
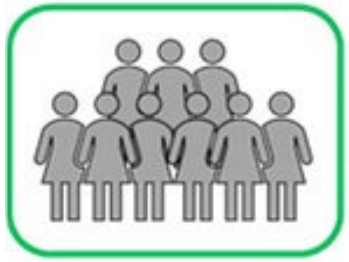


From Empiric Treatment Decision-Making → Precision Oncology (Personalized Therapy)

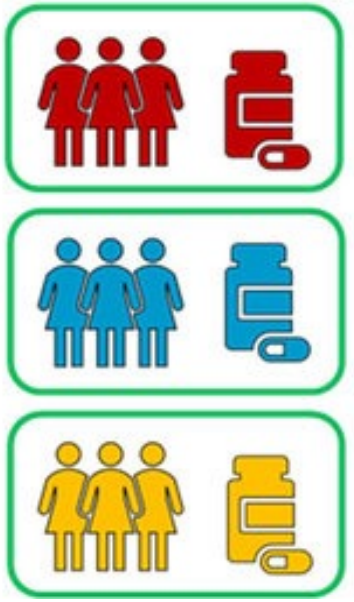
Empiric Therapy



All patients in this category are the same. They can all be treated the same way

- Clinical Variables
- Tumor or liquid biopsy
- Tumor Omics Profiling
- Host Omics Profiling

Personalized Therapy

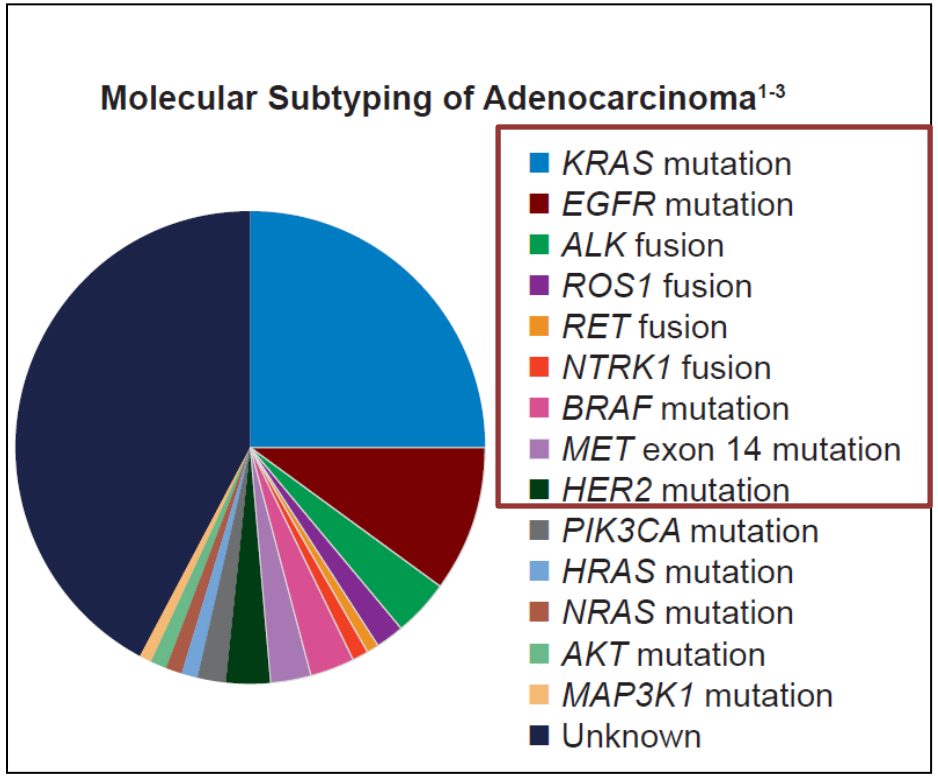


Each patient in this category is an individual & should be treated as such

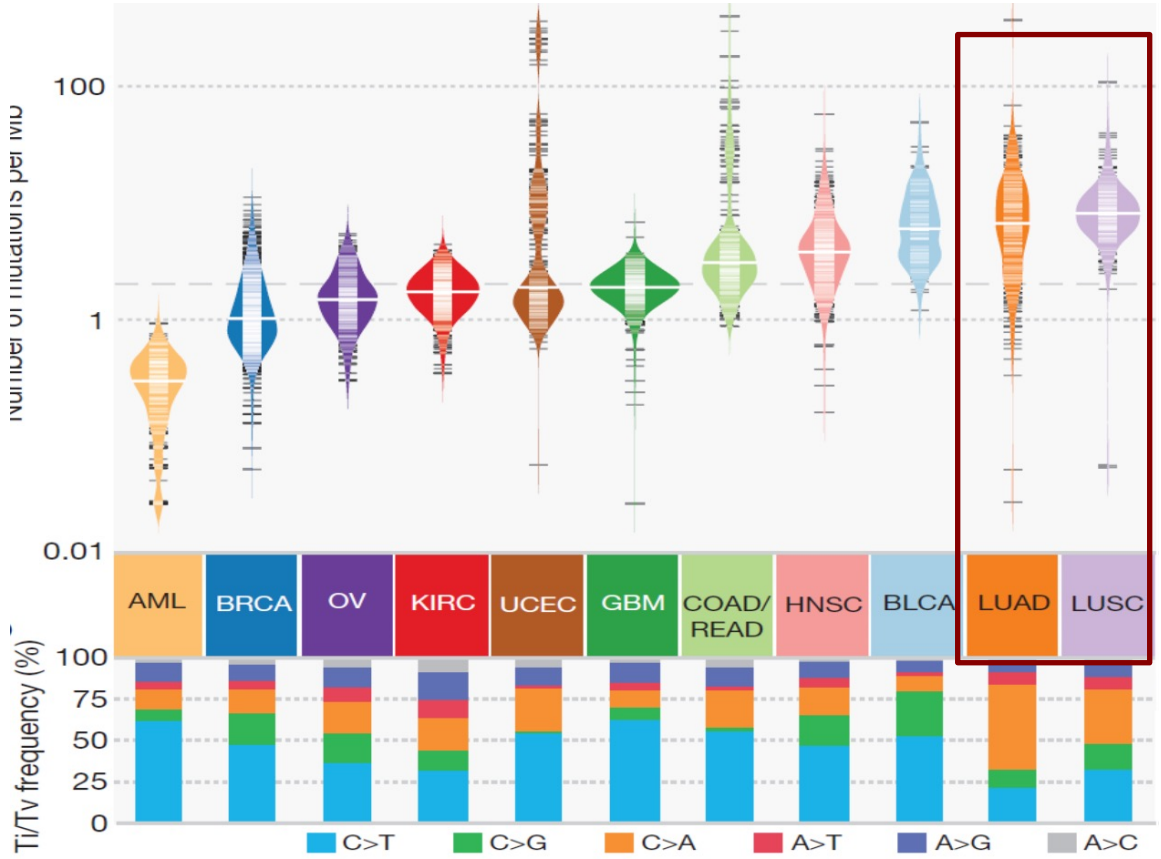
Liquid Biopsy is uniquely suited to fulfill this role

NSCLC is Genomically & Immunologically Complex

- **Genomically complex cancers** with a multitude of potential oncogenes known to drive tumor growth
- **Quantitatively & Qualitatively well suited** for biomarker-driven **checkpoint immunotherapy**
- Improving the biomarker selection process in individual patients and **individualizing therapy** is now possible
- Newer technologies **(Next Gen Sequencing/NGS)** now in the clinic for both tissue & blood-based assays

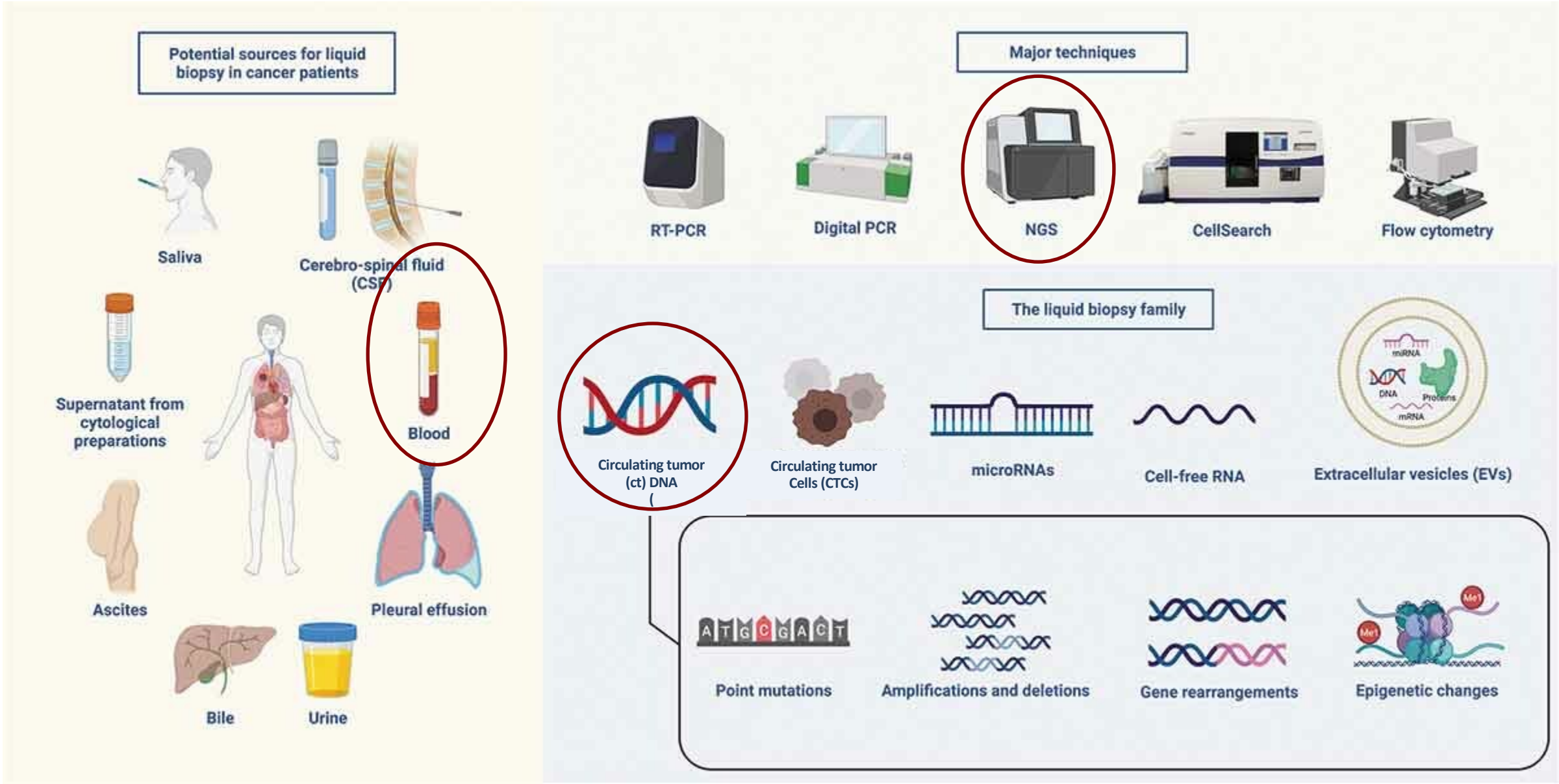


Adapted from Kalemkerian et al. J Clin Oncol. 2018



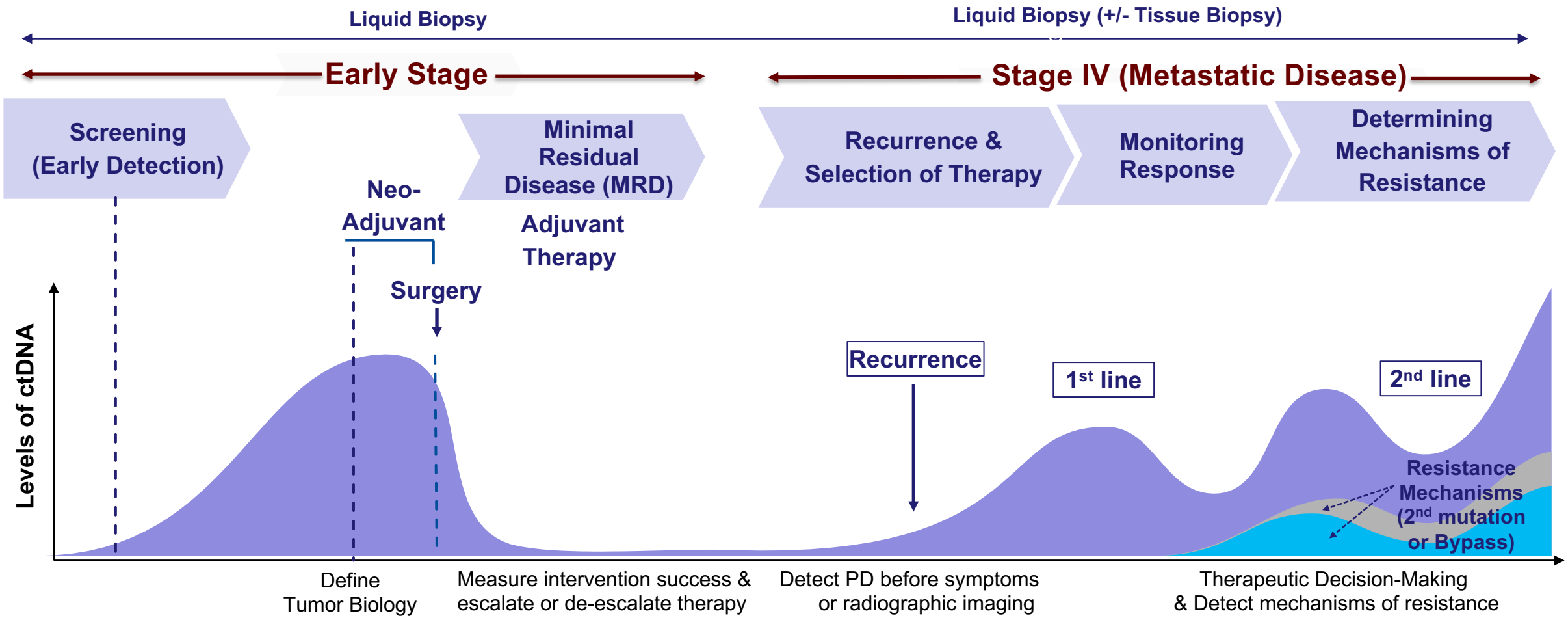
Adapted from Kandoth et al *Nature* 2013

Liquid Biopsy as a Path to Precision Oncology



Malapelle, Gandara, Rolfo et al. Exp Rev Mol Diagnostics, 2021

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



Strategies for the successful implementation of plasma-based NSCLC genotyping in clinical practice

Charu Aggarwal, Christian D. Rolfo, Geoffrey R. Oxnard, Jhanelle E. Gray, Lynette M. Sholl and David R. Gandara

Table 1 | **Differences between tumour tissue genotyping and plasma ctDNA genotyping**

Feature	Tumour tissue genotyping	Plasma ctDNA genotyping
Convenience	Inconvenient if tissue is not immediately available or is inadequate	Highly convenient with widespread availability of commonly used tube types (such as EDTA and Streck tubes)
Speed	Usually slower, particularly if tissue must first be requested from elsewhere or if a new biopsy sample is required	Usually faster, facilitated by the ease of collection and shipping
Sensitivity	Sensitivity is excellent as all specimens undergo review such that genotyping is limited to specimens deemed adequate for analysis	Sensitivity is lower because there is no adequacy review, such that ctDNA may not be detectable, particularly in samples with limited ctDNA shedding
Specificity	Specificity is excellent except that germline variants can sometimes be reported as somatic	Specificity is excellent for targetable driver mutations but false positives can emerge for certain genes (especially at low allelic fractions) owing to clonal haematopoiesis
Cost	Variable, increased by the potential need for repeat biopsy sampling to obtain a tissue specimen	Variable, increased by the potential need for subsequent tumour tissue genotyping if plasma ctDNA analysis is negative

√ Plasma

√ Plasma

√ Plasma

√ Tissue

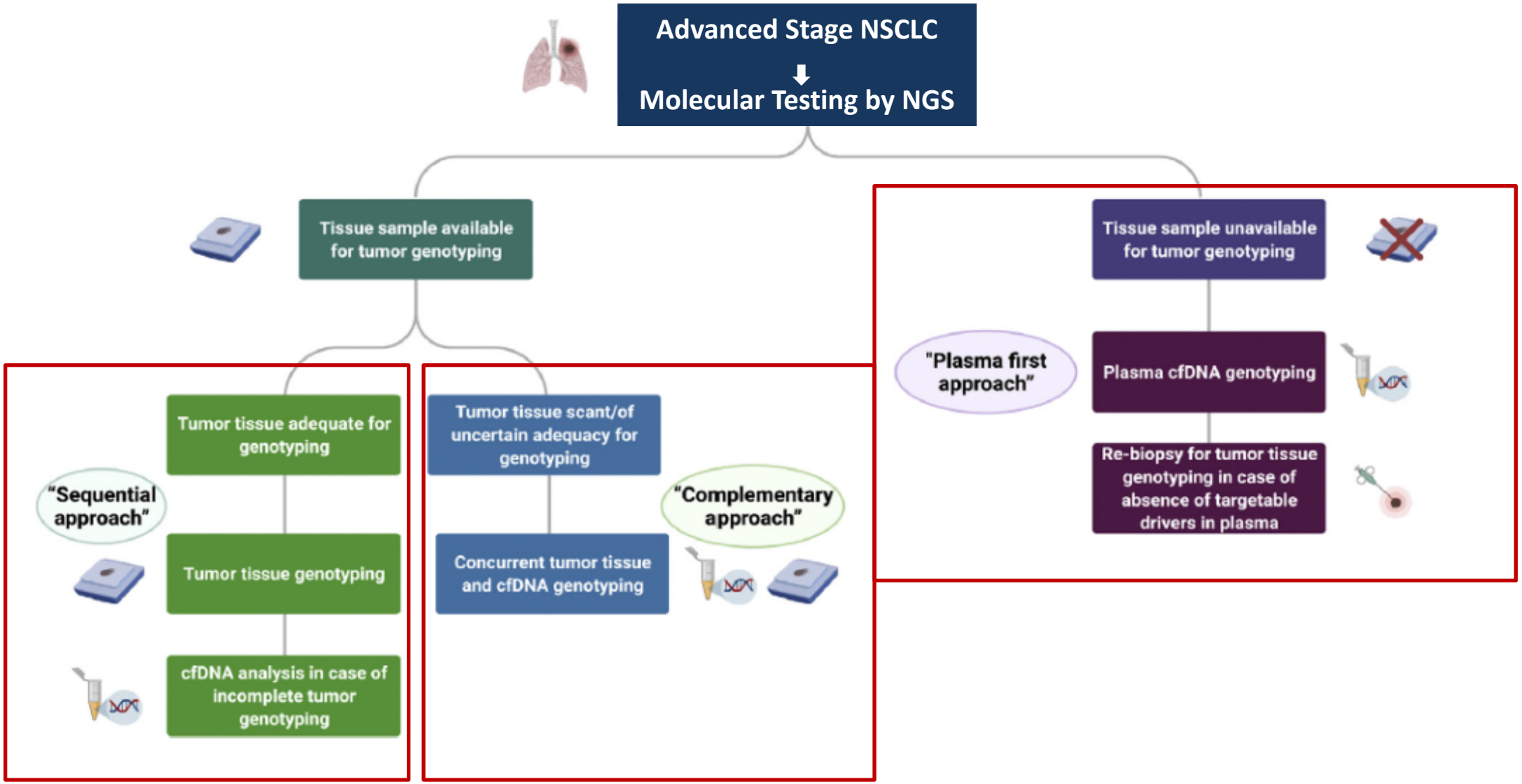
√ Plasma (if factor in re-biopsy costs)

Recommended: simultaneous testing for actionable oncogene targets, NGS preferred.

Similar recommendations from IASLC, NCCN, ESMO, ASCO, ISLB

Aggarwal, Rolfo, Gandara et al, Nature Reviews Clin Oncol 2020

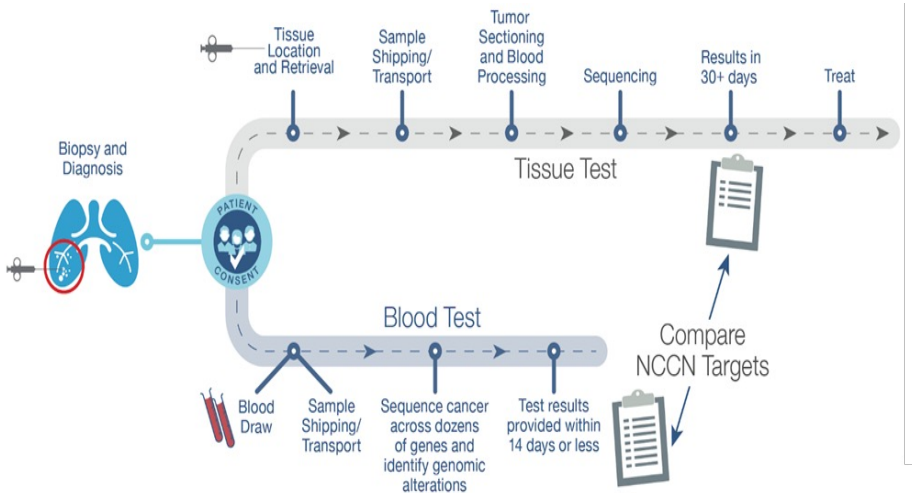
IASLC Consensus Statement on Liquid Biopsy in NSCLC

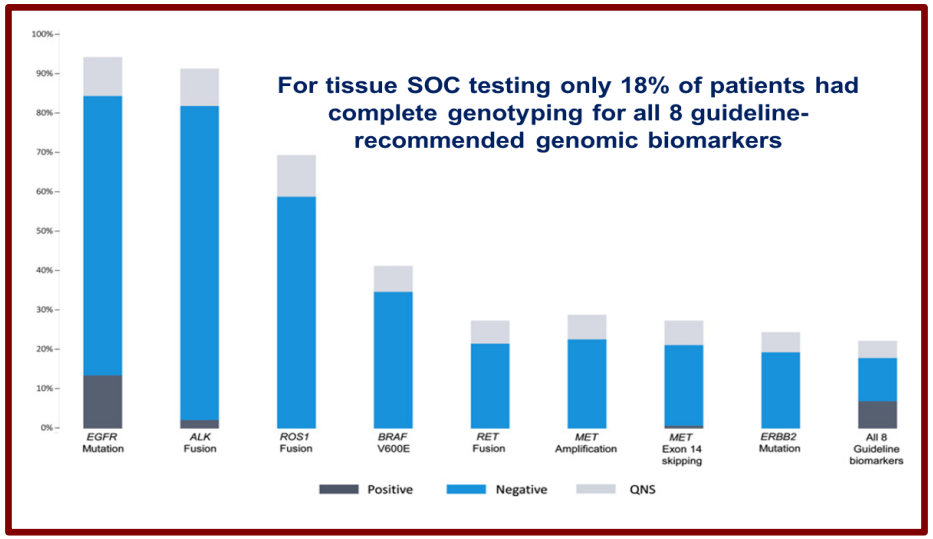


Rolfo, Gandara et al. JTO 2021

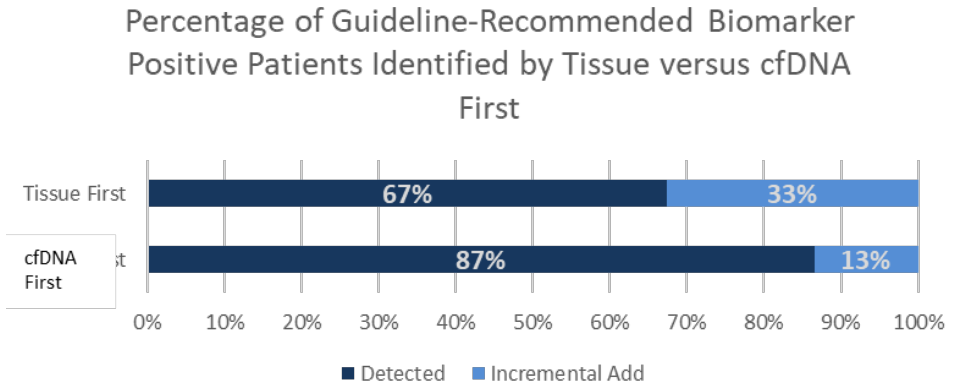
Plasma NGS vs. SOC tissue genotyping: The NILE study

- Methods: 89 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



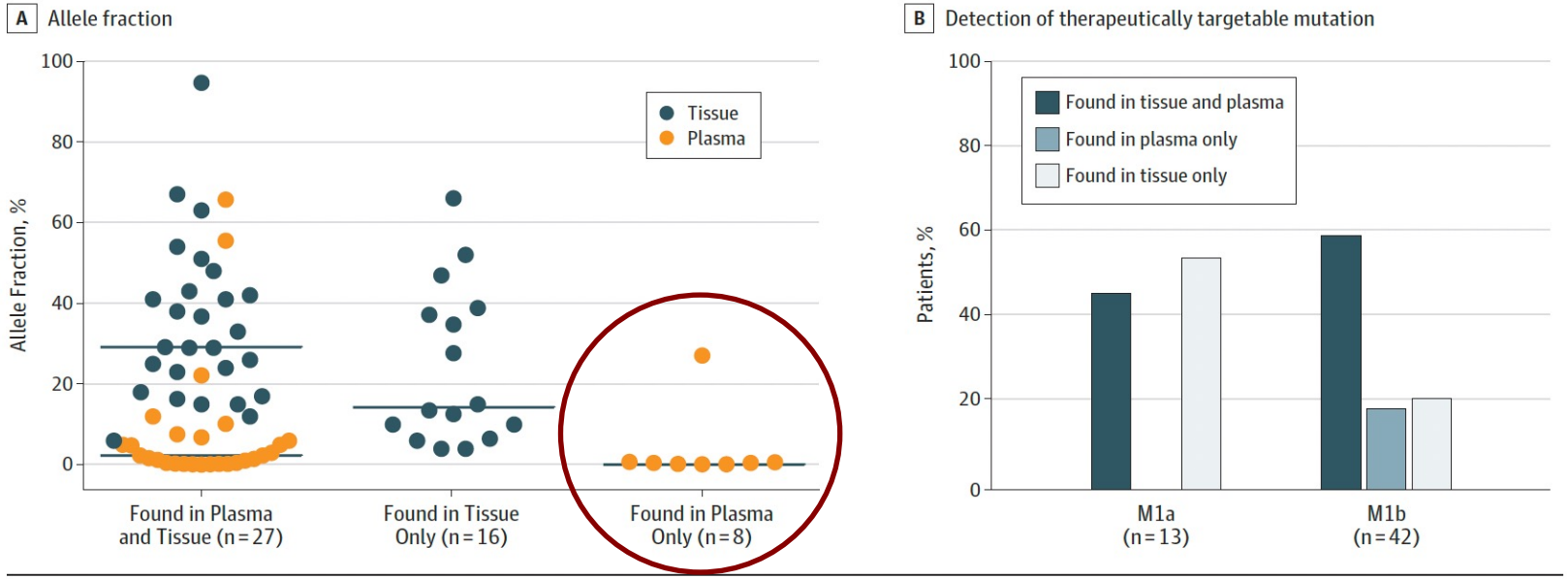


- For tissue-based SOC testing only 18% had complete genotyping for all 8 guideline-recommended biomarkers
- If the first genomic testing was ctDNA, 87% had a NCCN biomarker identified vs 67% with SOC tissue testing (p<0.0001)
- cfDNA testing had a faster turn-around time (TRT): median 9 days (cfDNA)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



Leighl et al. CCR 2019.

Figure 2. Analysis of Mutation Detection by Type of Test and Disease Stage

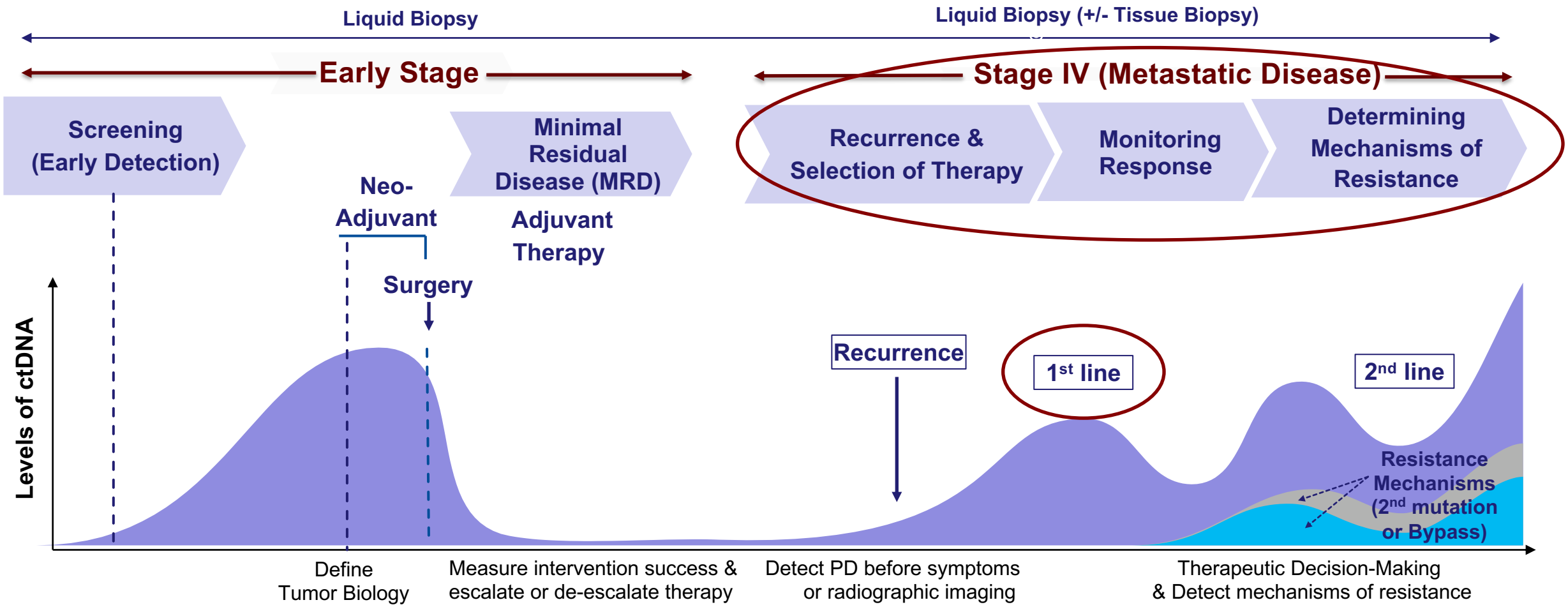


A, Fifty-five patients had concurrent plasma and tissue next-generation sequencing (NGS) with a therapeutically targetable mutation detected. This subset included 4 patients with outside hospital testing for whom no allele fraction (AF) was reported. For the remaining 51 patients, a comparison of the AFs of therapeutically targetable mutations is shown. The horizontal black line indicates median AF for each group. For the 27 patients who had the mutation AF reported for plasma and tissue, the upper horizontal line corresponds to the median for the tissue AFs, and the lower horizontal line corresponds to the median for the plasma AFs. B, To assess the effect of disease location on detection of therapeutically targetable mutations in plasma and tissue, plasma and tissue testing results were compared for 55 patients with concurrent testing. Included are 13 with disease limited to the thoracic cavity (M1a) and 42 with extrathoracic metastases (M1b) as determined by imaging.

Among the 128 patients with concurrent plasma and tissue NGS testing, 8 had a therapeutically targetable mutation detected in plasma for which the tissue test result was wild-type,with plasma testing thus increasing mutation detection from 36.7% (47 of 128 patients) to 43.0% (55 of 128 patients).

C. Aggarwal et al. JAMA Onc 2018.

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



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

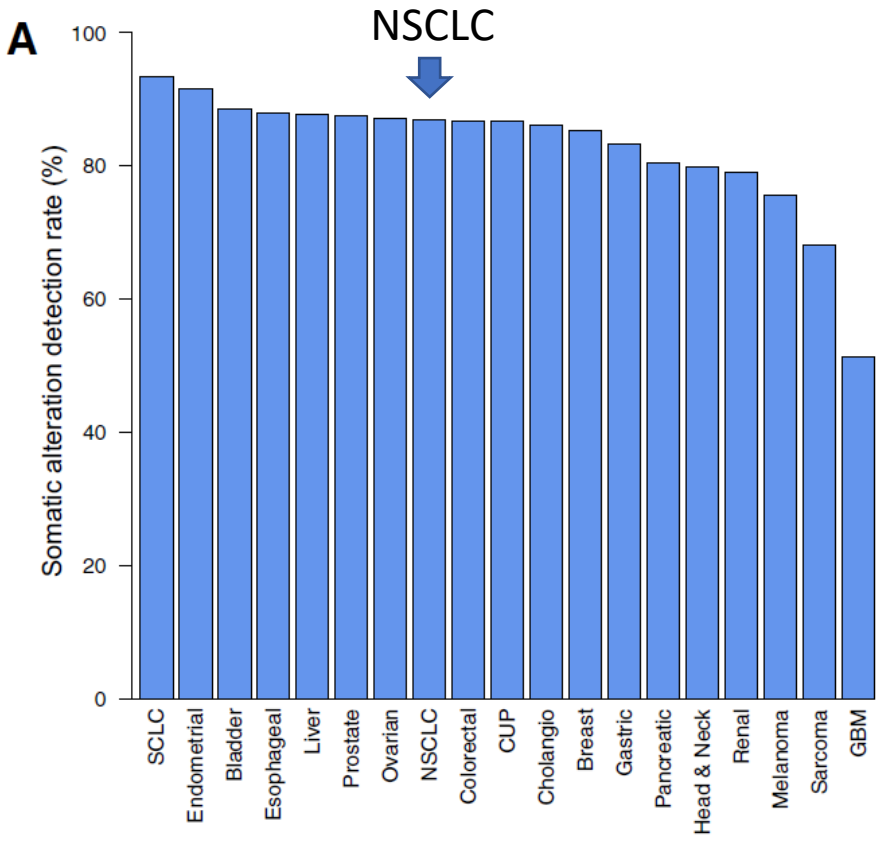
Evolution & Expanding List of Guideline Recommendations for Genomic Testing in Advanced Stage NSCLC

"The NCCN NSCLC Guidelines Panel strongly endorses **broader molecular profiling** with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. **Broad molecular profiling** is a key component of the improvement of care of patients with NSCLC)."

Genomic Alteration (i.e. driver event)KKR	Available targeted agents with activity against driver event in NSCLC
***EGFR* mutations**	osimertinib, erlotinib, gefitinib, afatinib, dacomitinib
***ALK* rearrangements**	crizotinib, alectinib, brigatinib, ceritinib, lorlatinib
***ROS1* rearrangements**	crizotinib, ceritinib, entrectinib, lorlatinib
***BRAF* V600E mutations**	dabrafenib + trametinib, vemurafenib
***HER2* mutations (emerging)**	ado-trastuzumab emtansine, afatinib
***MET* mutation/amplification (emerging)**	crizotinib, capmatinib, tepotinib
***RET* rearrangements (emerging)**	cabozantinib, vandetanib, selpercatinib, pralsetinib
***NTRK* rearrangements (emerging)**	entrectinib, larotrectinib,
EGFR Ex20ins	amivantamab, mobocertinib
KRAS G12C	sotorasib, adagrasib

Gandara: ASCO PER 2023 (Adapted from NCCN Clinical Practice Guidelines. NSCLC)

High Circulating Tumor (ct)DNA Detection Rate across Multiple Cancer Types (N=21,807)

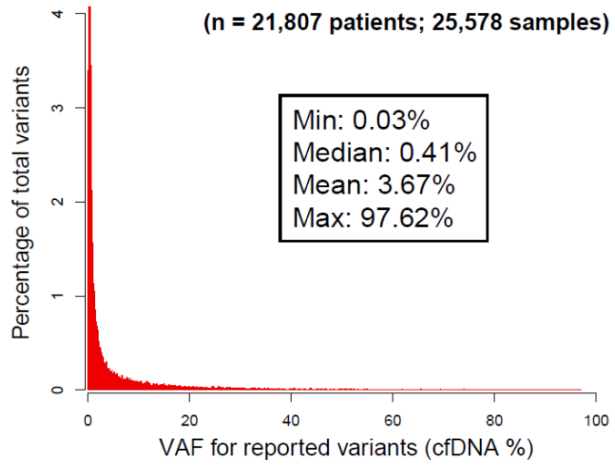


Guardant360 plasma NGS assay for detection of somatic alterations in 21,807 cancer patients

85% detection rate across all cancers

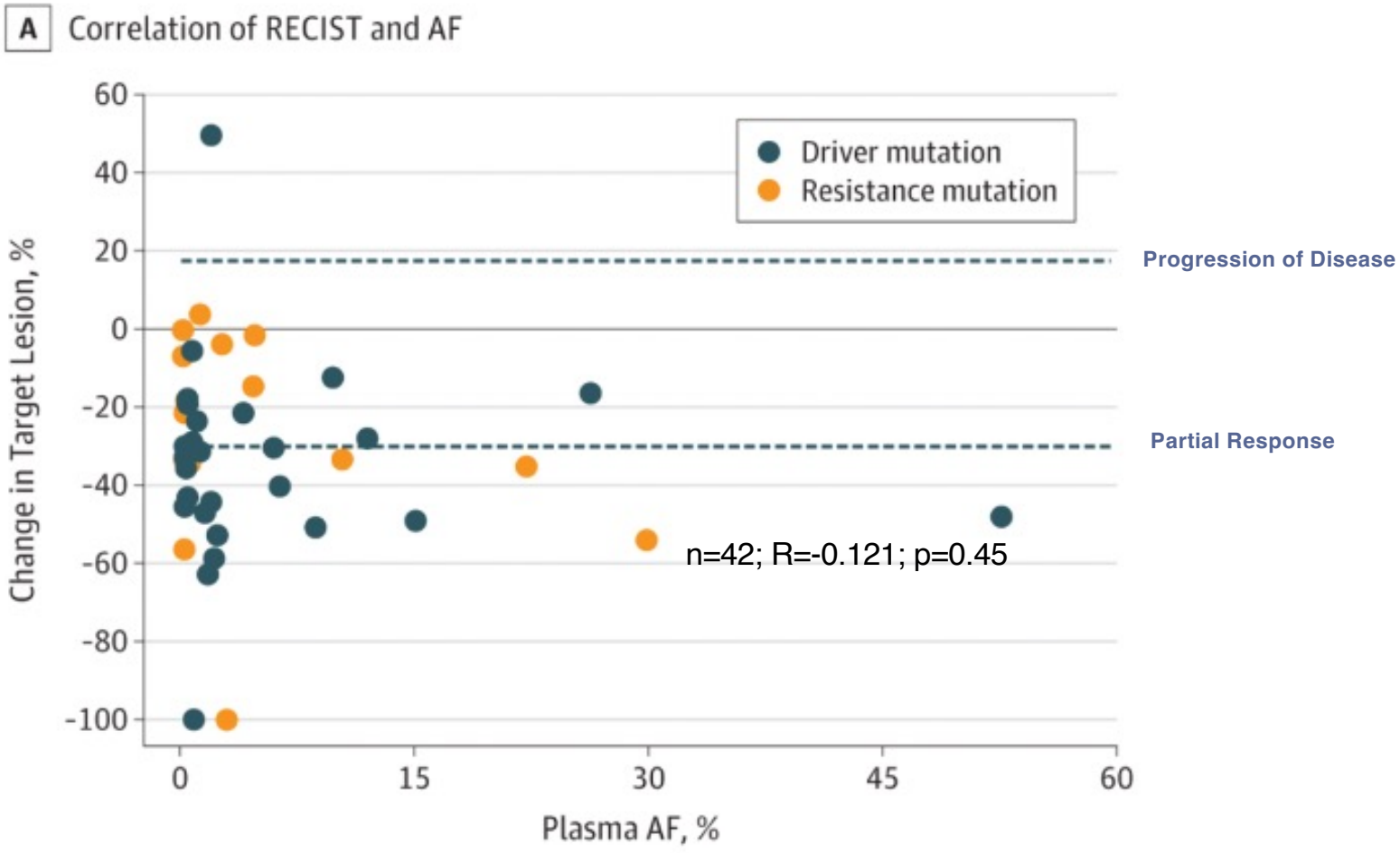
- **93% SCLC**
- **87% NSCLC**

Median VAF: 0.41% (range 0.03-97.6)



Zill, Mack, Gandara, Landman et al, CCR 2018

PENN2 Study: Response to Targeted Therapy is Independent of Plasma Mutation Allelic Fraction



Aggarwal et al: JAMA Oncol 2018

Immune Phenotype as potential Predictive Biomarkers for benefit from Checkpoint Immunotherapy (Detection in Liquid Biopsy)

Tumor Neo-antigenicity

- Biomarkers indicative of hypermutation & neoantigens

Examples:

–TMB, MSI-high, Neoantigen load

Tumor Immune Suppression/Evasion

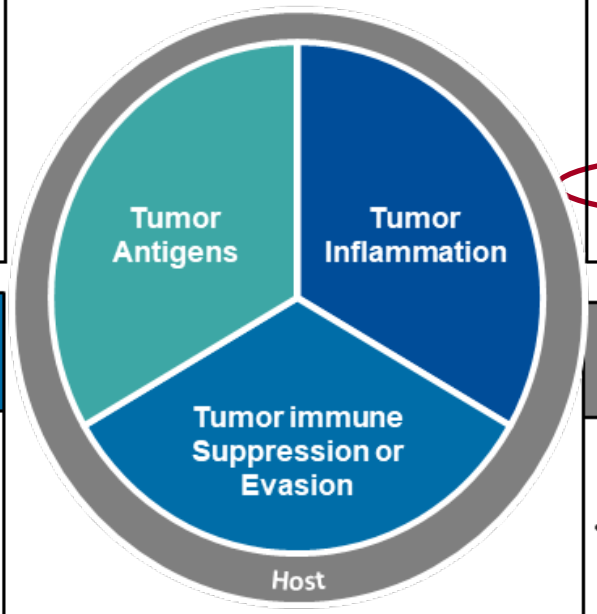
- Biomarkers that identify tumor immune system suppression or evasion beyond PD-1/CTLA-4

Examples:

–Tregs, MDSCs, IDO, LAG-3

–STK11 and KEAP1

–-ARID1A



Tumor Microenvironment (TIME)

- Biomarkers (intra- or peri-tumoral) indicative of an immuno-sensitive phenotype

Examples:

–PD-L1, inflammatory signatures

–PROphet: proteomic signature

Host Environment (e.g. Microbiome)

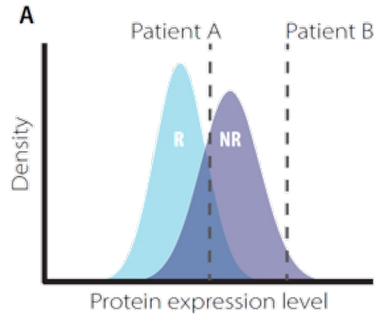
- Biomarkers that characterize the host environment, beyond tumor microenvironment

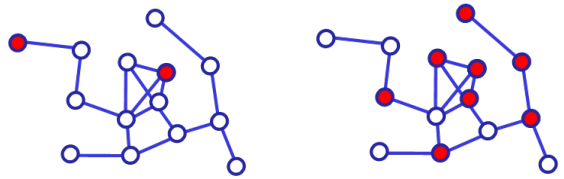
Examples:

–Microbiome, germline genetics

PROphet®

Differentially expressed proteins:





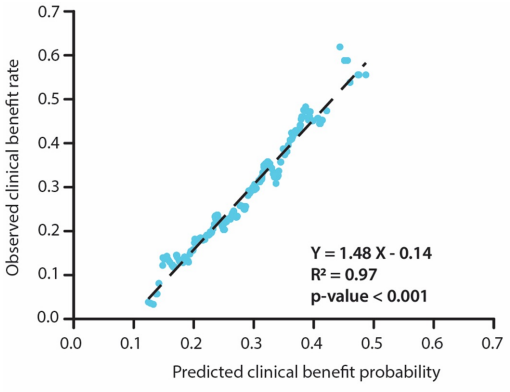
Patient A
-High probability of efficacy

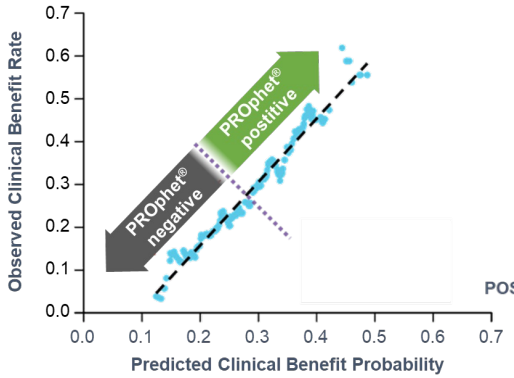
Patient B
-Low probability of efficacy

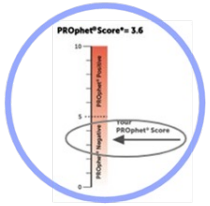
Proteogenomic patterns with AI detection to predict patient response

Adapted from Blank CU, et al. *Science.* 2016;352:658-660.

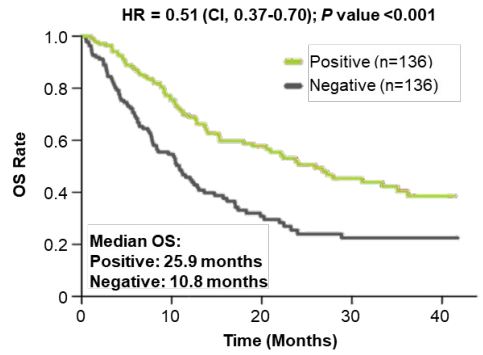
Analytical & Clinical Validation of PROphet Assay



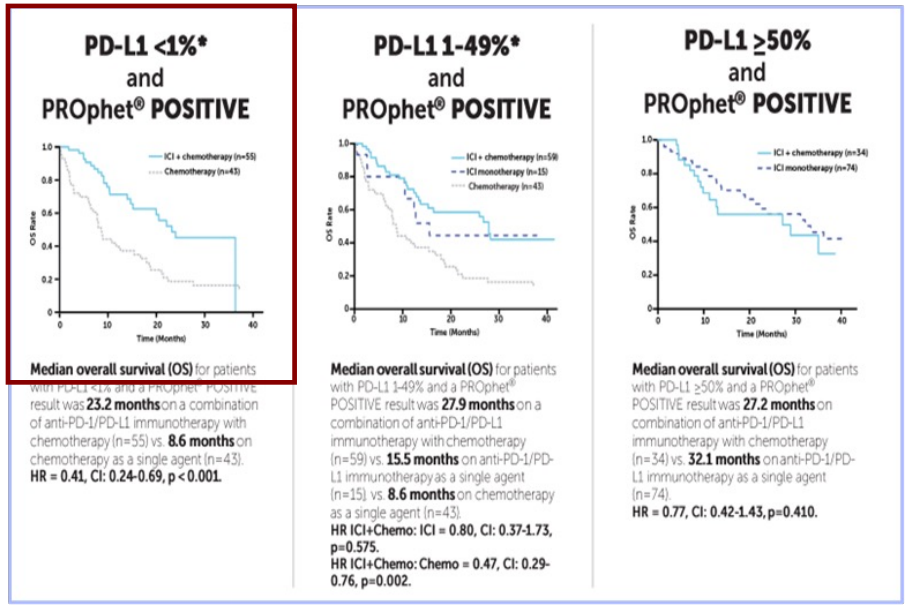




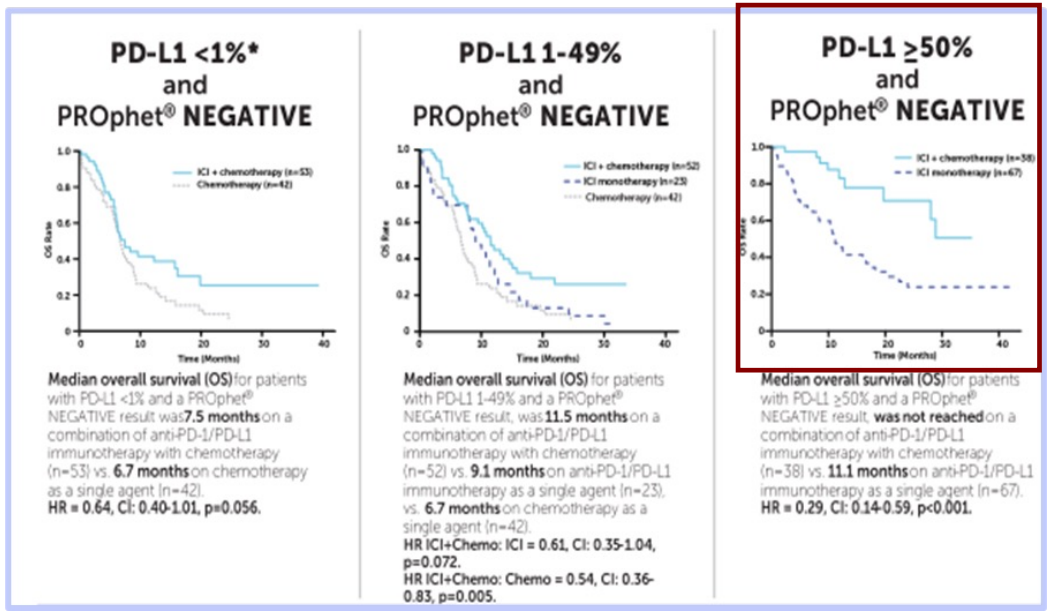
PROphet Score
POSITIVE (5-10) or NEGATIVE (<5)



PROhet Positive vs PD-L1



PROhet Negative vs PD-L1



. Christopoulus P, et al. medRxiv 2022. **doi:** https://doi.org/10.1101/2022.12.01.22282769.

Trials evaluating blood TMB

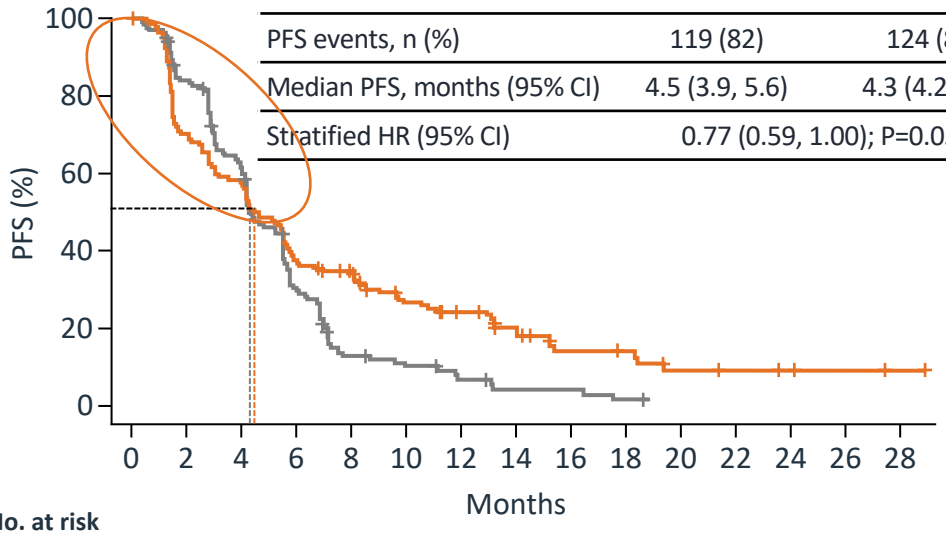
Table 1 Summary of studies evaluating blood TMB as a predictive biomarker for response to immune checkpoint blockade

Study	Analysis	Approach	NGS assay	Panel size	Cohort size	Tumor type	Disease stage	Trial ID	Treatment	TMB cut-off
Gandara *et al*, 2018[60]	Retrospective	Targeted NGS	Custom NGS assay (bait set version T7, Integrated DNA Technology, >300 genes)	1.1 Mb	n=259	NSCLC	Advanced/metastatic	POPLAR (NCT01903993); OAK (NCT02008227)	Atezolizumab vs docetaxel	16 Muta
Wang *et al*, 2019[146]	Retrospective	Targeted NGS	Custom assay (NCC-GP150, 150 genes)	Not reported	n=48 cohort 1; n=50 cohort 2	NSCLC	Advanced/metastatic	N/A	Anti-PD-1/PD-L1	6 Mutati
Si *et al*, 2021[63]	Retrospective	Targeted NGS	Guardant OMNI (500 genes)	2 Mb	n=1001	NSCLC	Metastatic	MYSTIC (NCT02453282)	Durvalumab and tremelimumab vs chemotherapy	20 Muta
de Castro Jr *et al*, 2022[65]	Prospective	Targeted NGS	Guardant OMNI (500 genes)	2 Mb	n=512	NSCLC	Metastatic	NEPTUNE (NCT02542293)	Durvalumab and tremelimumab versus chemotherapy	20 Muta
Kim *et al*, 2022[66]	Prospective	Targeted NGS	Foundation Medicine (>300 genes)	1.1 Mb	n=152	NSCLC	Locally advanced/ metastatic	B-F1RST (NCT02848651)	Atezolizumab	16 Muta
Peters *et al*, 2022[68]	Prospective	Targeted NGS	Foundation Medicine (>300 genes)	1.1 Mb	n=472	NSCLC	Advanced/metastatic	BFAST (NCT03178552)	Atezolizumab versus chemotherapy	16 Muta
He *et al*, 2022[69]; Schenker *et al*, 2022[70]	Prospective	Targeted NGS	Foundation Medicine (>300 genes)	1.1 Mb	n=212	Pan-cancer	Advanced/metastatic	CheckMate 848 (NCT03668119)	Nivolumab+ipilimumab vs nivolumab monotherapy	10 Muta

BFAST, Blood First Assay Screening Trial; bTMB, blood tumor mutation burden; N/A, not available; NGS, next-generation sequencing; NSCLC, Non-small cell lung cancer; VUS, variants of unknown significance

Adapted from Sivapalan et al. JITC 2023

Phase III BFAST Trial: Atezolizumab vs Platinum Chemotherapy in bTMB high (≥16)



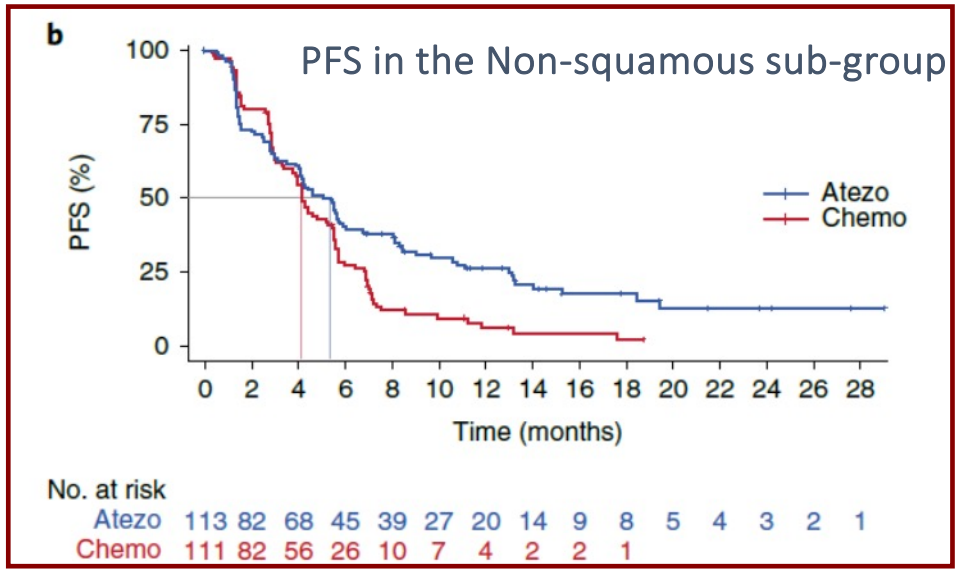
	Atezolizumab	Chemotherapy
PFS events, n (%)	119 (82)	124 (85)
Median PFS, months (95% CI)	4.5 (3.9, 5.6)	4.3 (4.2, 5.5)
Stratified HR (95% CI)	0.77 (0.59, 1.00); P=0.053	

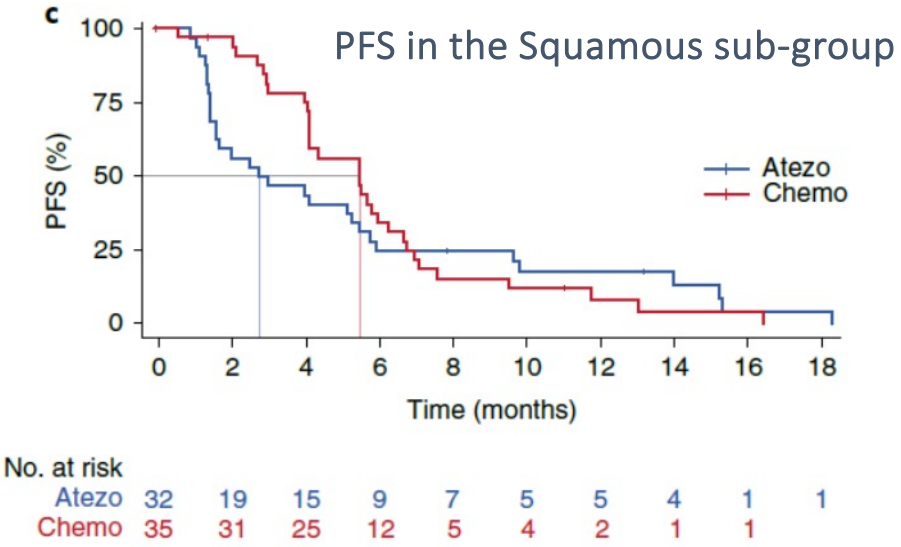
No. at risk

Atezo	145	101	83	54	46	32	25	18	10	9	5	4	3	2	1
Chemo	146	113	81	38	15	11	6	3	3	1	0	0	0	0	0

Initial PFS "KM Gap" as seen in prior IO monotherapy trials.
Although progression rates were initially greater in the atezolizumab vs chemotherapy arm, PFS benefit was seen with atezolizumab after 4 months.

Confirmed ORR for bTMB ≥16 was 25.5% (95% CI: 18.7, 33.4) for atezolizumab vs 17.8% (95% CI: 12.0, 25.0) for chemotherapy
OS: median 13.3 mos for ≥ bTMB 16 (6.6-18.4) and 10.3 mos (8.5-13.8) for bTMB low.





Peters, Gandara et al. Nat Med 2022

MYSTIC: Durvalumab +/- Tremelimumab vs Platinum Chemotherapy in 1st line Advanced NSCLC

- Stage IV NSCLC
- All-comers population (i.e. irrespective of PD-L1 status)
- *EGFR–/ALK–*
- ECOG PS 0/1
- Immunotherapy- and CT-naïve

N=1118 randomized

1:1:1 R

Stratified by PD-L1 TC (<25% vs ≥25%*) and histology

Durvalumab (n=374)
20 mg/kg q4w until disease progression

Durvalumab + tremelimumab (n=372)
D 20 mg/kg q4w until disease progression + T 1 mg/kg q4w for up to 4 doses

Platinum-based CT (n=372)
- Paclitaxel + carboplatin OR
- Gemcitabine + cisplatin/carboplatin (squamous) OR
- Pemetrexed + cisplatin/carboplatin (non-squamous)† for up to 6 cycles

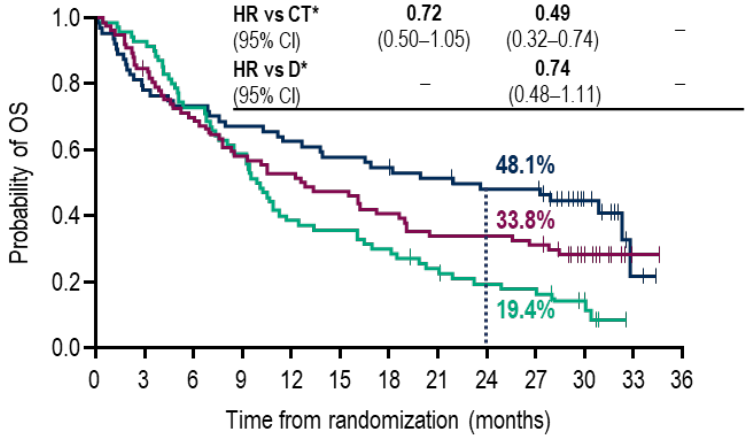
Primary endpoints (PD-L1 TC ≥25%*)
- OS (D vs CT)
- OS (D+T vs CT)
- PFS (D+T vs CT)

Key exploratory endpoints
- OS by bTMB and tTMB

OS by bTMB ≥20 mut/Mb vs <20 mut/Mb

bTMB ≥20 mut/Mb

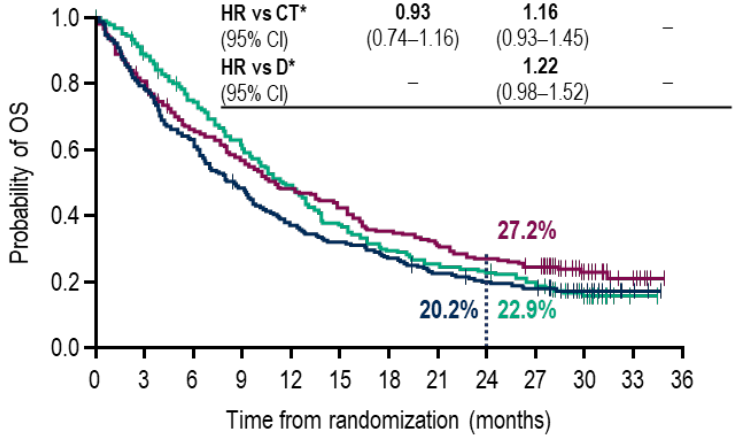
	D (n=77)	D+T (n=64)	CT (n=70)
mOS, months (95% CI)	12.6 (7.8–18.6)	21.9 (11.4–32.8)	10.0 (8.1–11.7)
HR vs CT* (95% CI)	0.72 (0.50–1.05)	0.49 (0.32–0.74)	–
HR vs D* (95% CI)	–	0.74 (0.48–1.11)	–



77	64	53	44	39	35	30	25	25	23	10	1	0
64	50	47	43	40	37	35	32	29	29	14	2	0
70	65	51	41	27	25	21	16	12	11	6	0	0

bTMB <20 mut/Mb

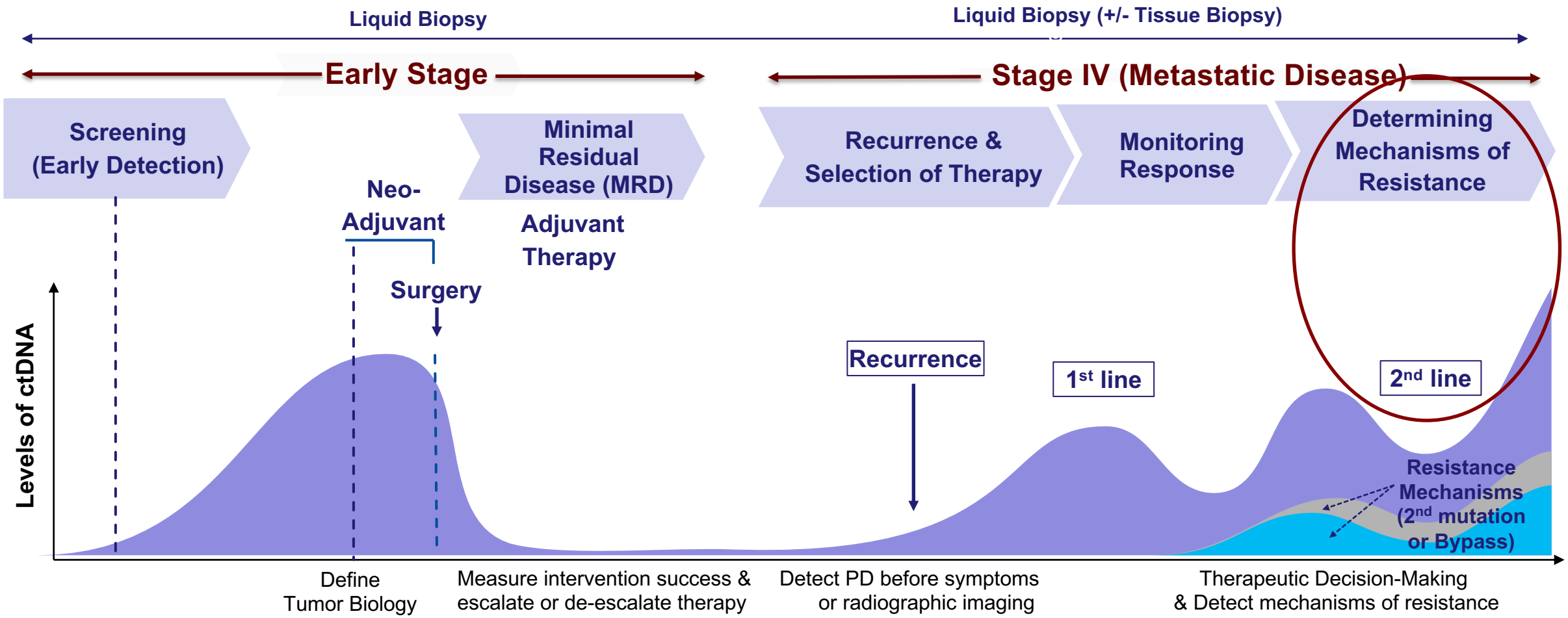
	D (n=209)	D+T (n=204)	CT (n=185)
mOS, months (95% CI)	11.0 (8.9–14.9)	8.5 (6.7–9.8)	11.6 (9.6–13.1)
HR vs CT* (95% CI)	0.93 (0.74–1.16)	1.16 (0.93–1.45)	–
HR vs D* (95% CI)	–	1.22 (0.98–1.52)	–



209	167	134	114	98	86	72	63	55	49	21	8	0
204	161	129	98	75	65	55	45	39	35	18	4	0
185	162	135	110	89	68	53	45	41	34	17	1	0

Peters et al. AACR 2019.

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



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

Despite initial response development of Acquired Resistance to Targeted TKIs in Oncogene-driven NSCLC is almost universal

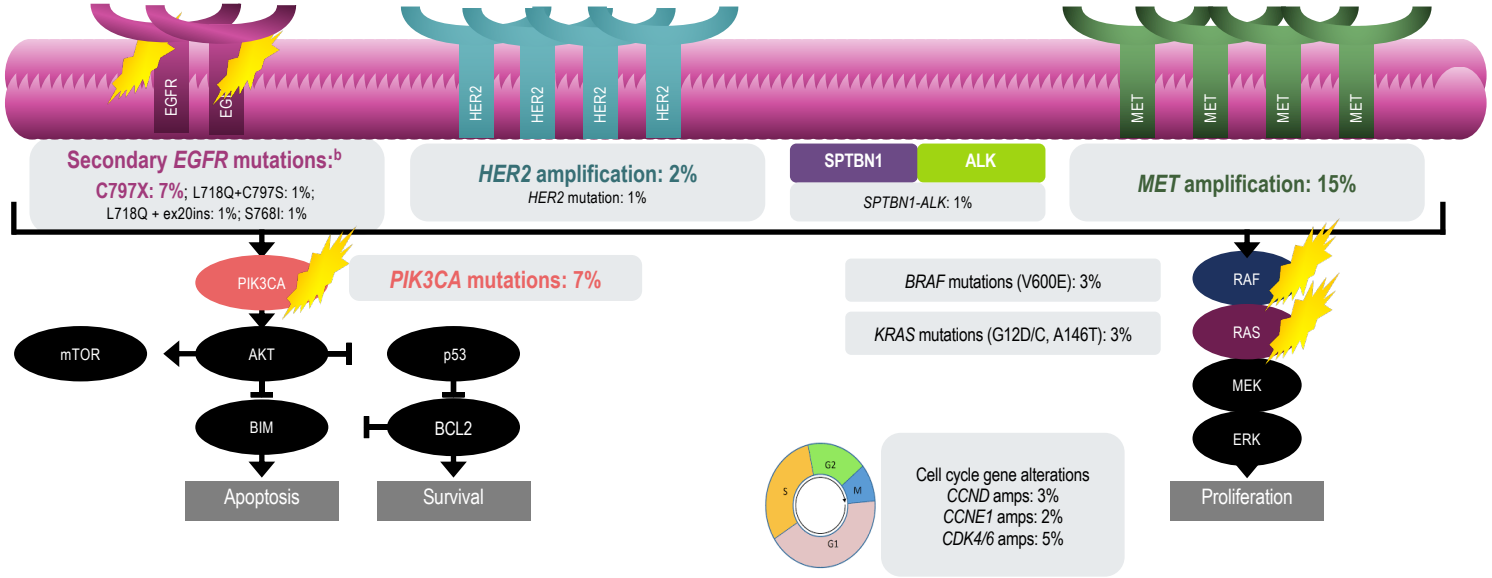
Target	Prevalence	Drug	Response Rate
EGFR	15%-60%	Osimertinib	70%
ALK	5%-10%	Alectinib, Brigatinib	70%
ROS1	1%-2%	Crizotinib, Entrectinib	72%
BRAF V600E	1%-2%	Vemurafenib Dabrafenib	42% 33%
MET exon 14 mutations	3%	Capmatinib, Crizotinib[1]	44-67%
High *MET* amplification	3%-4%	Crizotinib[2]	66%
HER2	1.7%	Afatinib[3] TDM1[4] TDX-d	100% 44% 62%
RET	1%-2%	Selpercatinib (LOXO-292)[5] Pralsetinib (BLU-667)[6]	80% 58%
NTRK1/2/3	3%	Entrectinib, Larotrectinib	80%

- Despite these high response rates, essentially no patients are cured
- All patients develop acquired resistance, either secondary resistance mutations or Bypass mechanisms

1. Drilon AE et al. *J Clin Oncol*. 2016;34(suppl 15):108. 2. Camidge et al. *J Clin Oncol*. 2014;32(suppl 15):8001. 3. Mazières J et al. *J Clin Oncol*. 2013;31:1997-2003. 4. Li et al. *J Clin Oncol*. 2018;36:2532. 5. Drilon AE et al. *J Clin Oncol*. 2015;33(suppl 15):8007. 6. Gainor J et al. ASCO 2019. Abstract 9008.

FLAURA: Acquired Resistance Mechanisms after Osimertinib 1st-line therapy (n=91)[a]

- No cases of acquired *EGFR* T790M
- The most common resistance mechanisms were ***MET* amplification** (15%) and ***EGFR* C797X mutation** (10%)
  - Other mechanisms included HER2 amplification/mutation (3%), *PIK3CA(7%), RAS/RAF* mutations and ALK transformation



Treatable Bypass Mechanisms of Resistance after EGFR TKIs:

- MET amplification/mutation
- Her -2 amplification/mutation
- BRAF mutation
- ALK translocation

Ramalingam et al: ESMO 2019

Progressive Disease (PD) after 1st line TKI Therapy in Oncogene-driven Advanced NSCLC (EGFR, ALK, etc)

Progressive Disease after 1st line TKI

Empiric Approach:
Choice of next line of therapy empirically:
-Next TKI
-Chemotherapy
-Immunotherapy

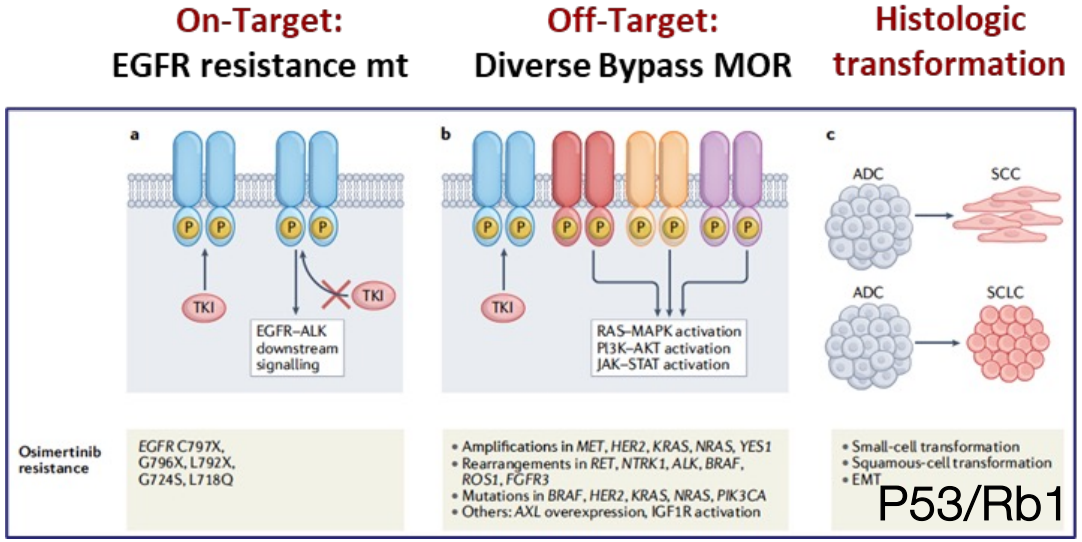
Precision Medicine Approach:
Choice of next line of therapy based on repeat biopsy or plasma ctDNA

On-Target MOR
(Resistance Mutations)

Off-Target MOR
(Bypass Mechanisms Or Histologic Transformation)

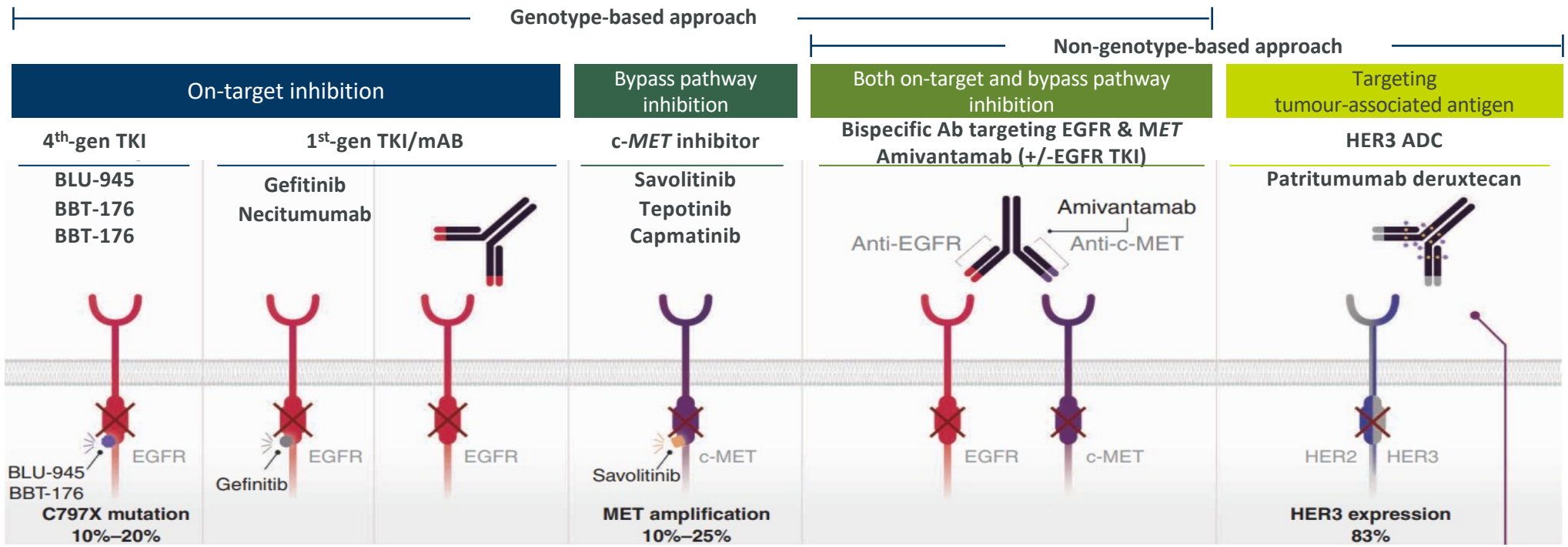
Adapted from Melosky, Popat, Gandara. Clin Lung Cancer. 2017

EGFR TKI resistance mechanisms



Cooper AS, et al, Nat Rev Clin Oncol 2022

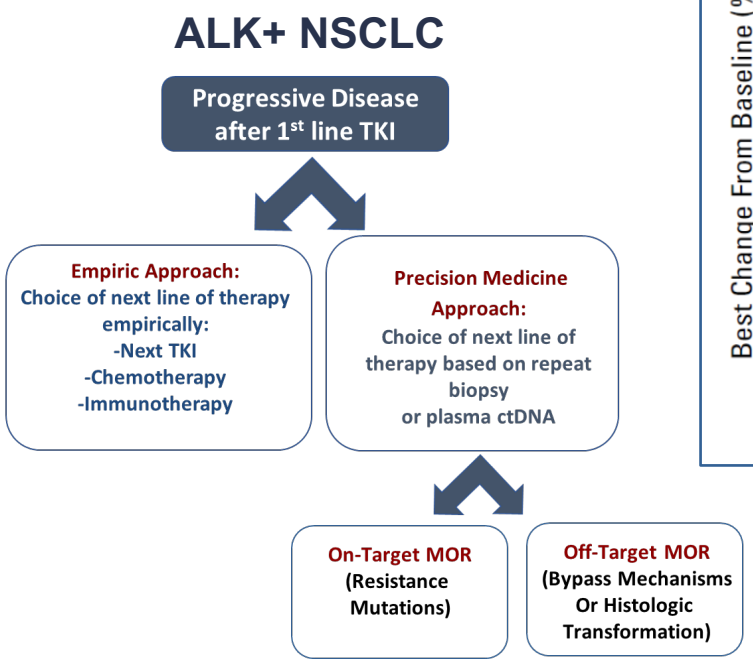
Treatment Strategies for EGFR-mutated NSCLC with progressive disease after 1st-line Osimertinib

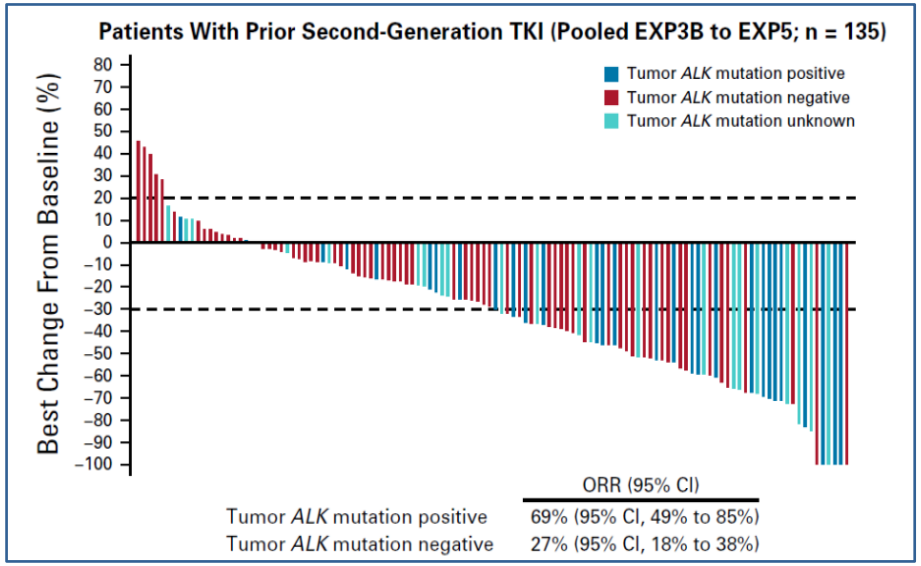


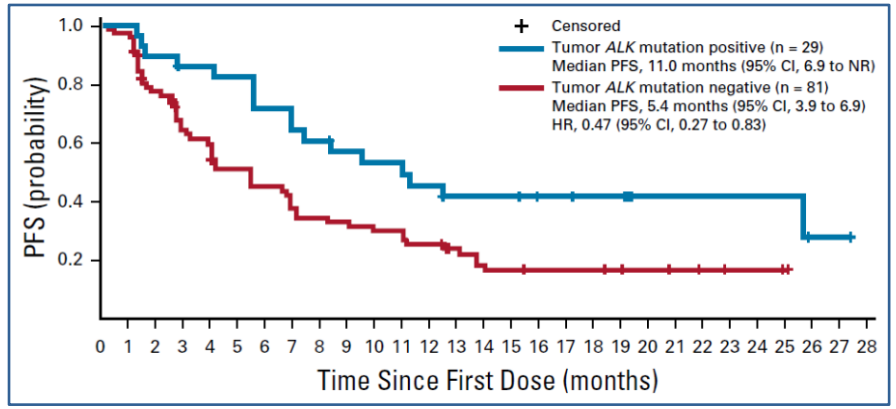
Liquid Biopsy (ctDNA) plays a major role in determining these mechanisms of resistance

adapted from Lim SM, et al. Cancer Disc 2022

Mechanism of Resistance (2nd ALK mutation vs Bypass) affects Lorlatinib Activity in ALK+ NSCLC pre-treated with 2nd Generation ALK Inhibitors





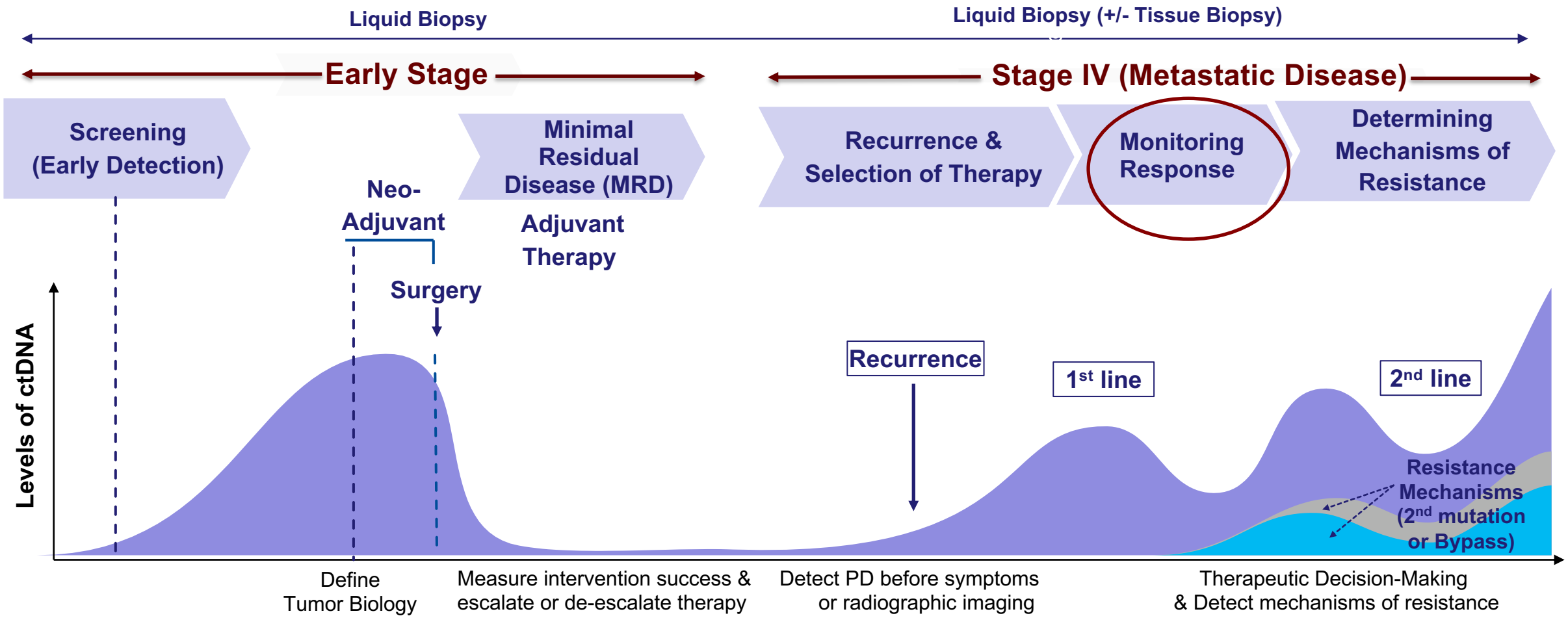


Lorlatinib:

- More active in patients with ALK-resistance mutations than in patients with a Bypass MOR
  - **ORR:** 69% vs 27%
  - **mPFS:** 11 mos vs 5.4 mos
- Worthwhile to re-biopsy or use ctDNA to determine next line of therapy rather than using an Empiric approach

Shaw et al. J Clin Oncol 2019

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



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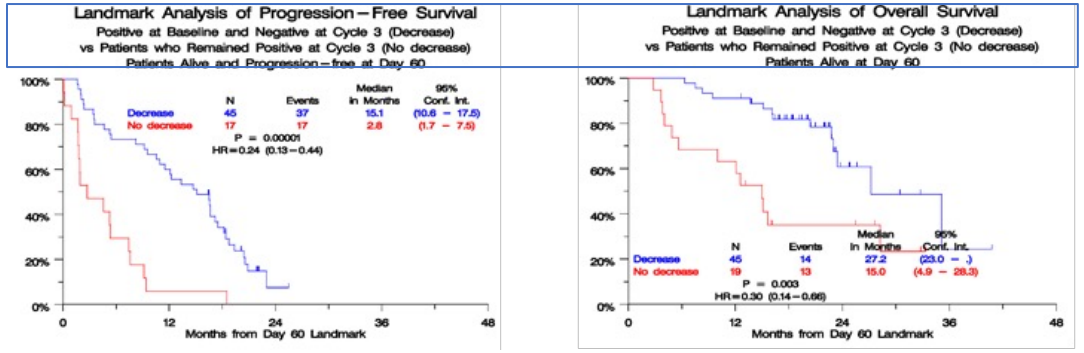
Gandara: ISLB Congress 2021 (Adapted from Wan, J.C.M., et al. *Nat Rev Cancer 2017)*

ctDNA in Advanced Stage NSCLC Response Monitoring: Oncogene driver, Checkpoint Immunotherapy & Chemotherapy

Oncogene Driver

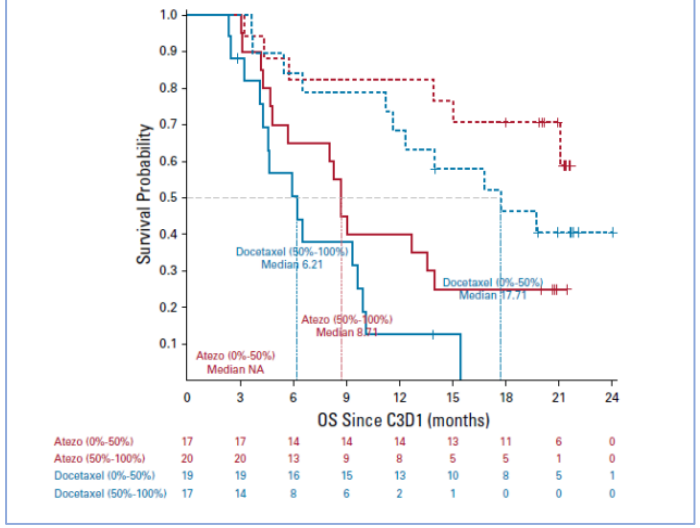
Clearance of ctDNA after Afatinib-Cetuximab (S1403)



Mack, Goldberg, Herbst, Hirsch, Politi, Kelly, Gandara et al. IASLC WCLC20

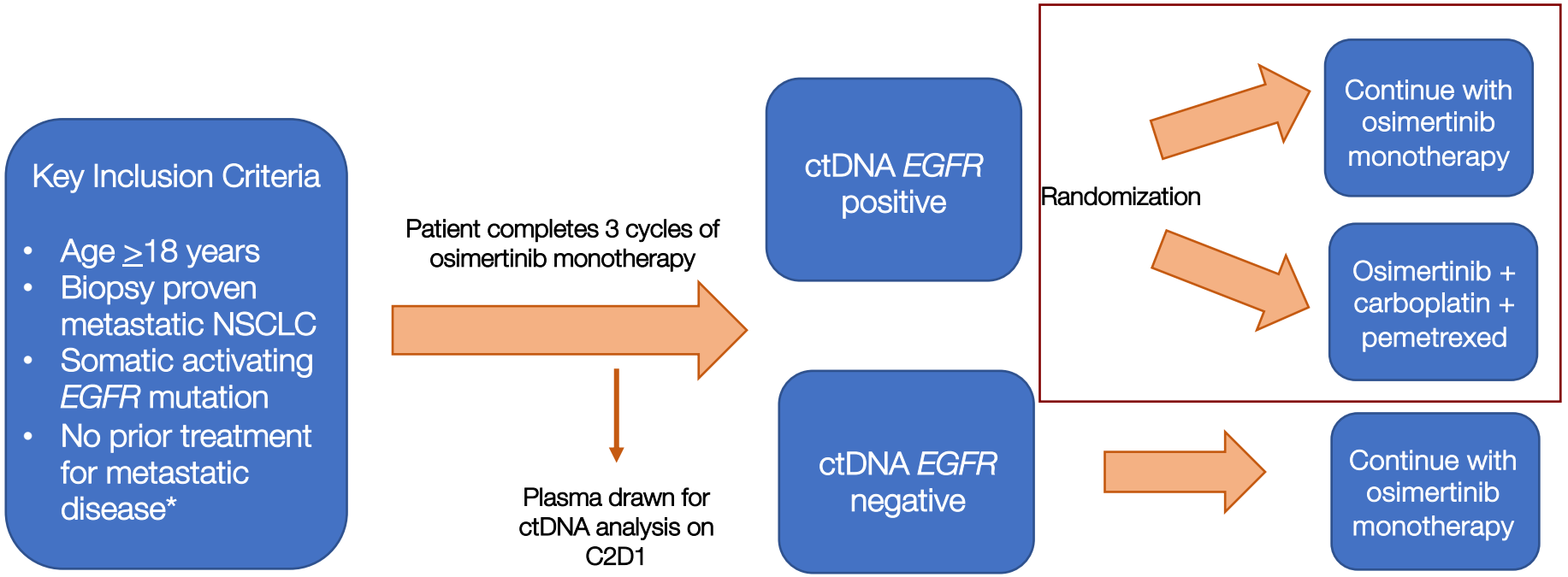
Immunotherapy & Chemotherapy

Metrics of ctDNA after Atezolizumab or Docetaxel



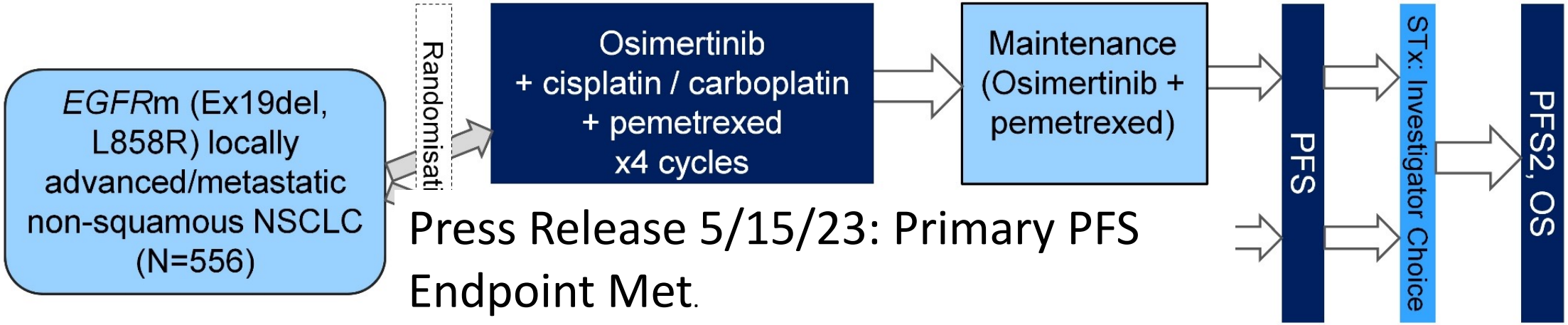
Zou, Gandara, Patel et al. JCO Precis Onc 2021

Clinical Trial Design evaluating "Biomarker Switch Therapy": EGFR-mutated NSCLC treated with Osimertinib



NCT04410796

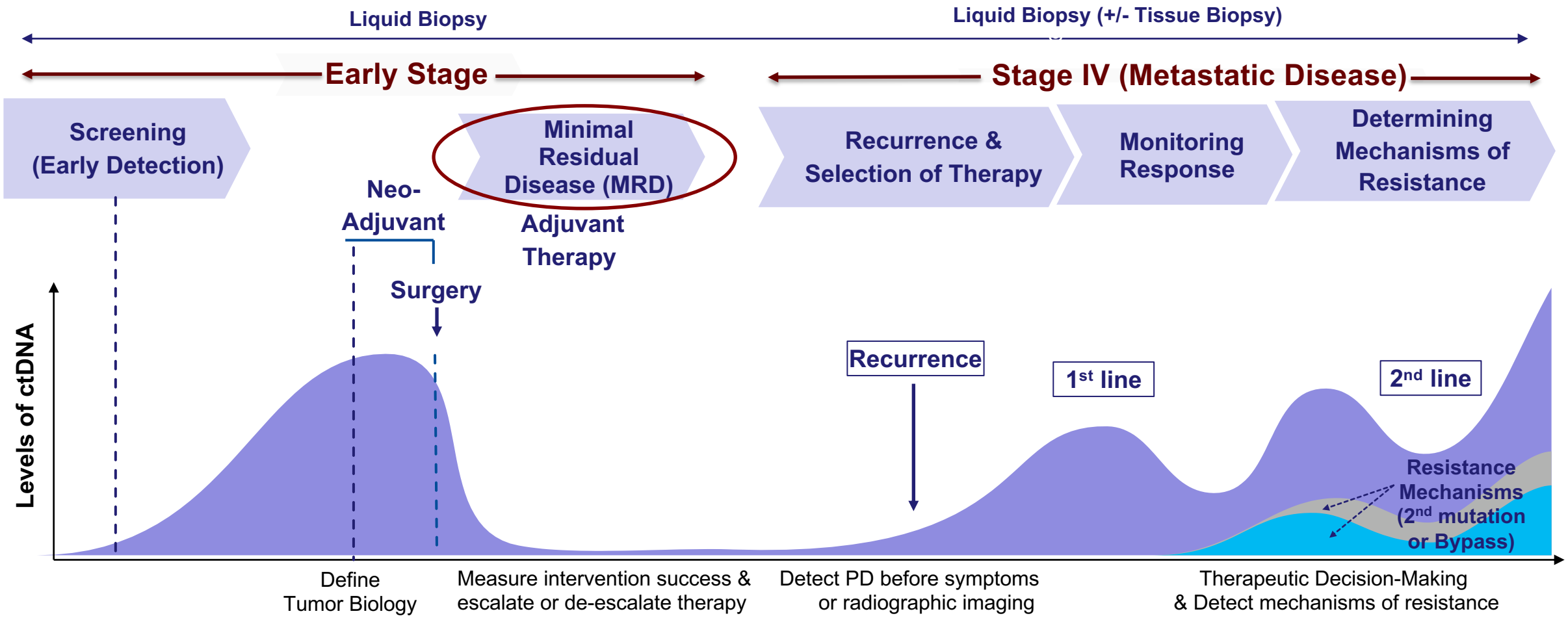
FLAURA2



Press Release 5/15/23: Primary PFS Endpoint Met.

- **Primary Endpoint: PFS**
- Osimertinib given at a dose of 80 mg QD during induction and maintenance
- The osimertinib dose can be reduced to 40 mg QD for management of AEs; chemotherapy dose interruption/reduction is to be prioritised over reduction/interruption of osimertinib
- Randomisation will be stratified by race, WHO PS (0 vs 1), and tissue *EGFR* mutation test at enrolment
- Planned to involve approximately 248 sites in 27 countries

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



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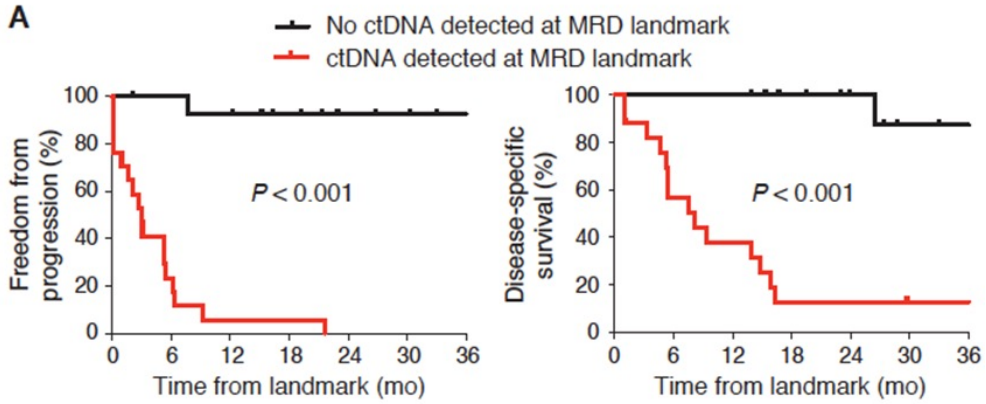
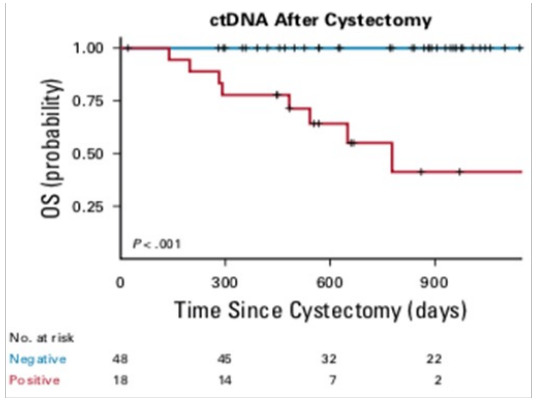
Gandara: ISLB Congress 2021 (Adapted from Wan, J.C.M., et al. *Nat Rev Cancer 2017)*

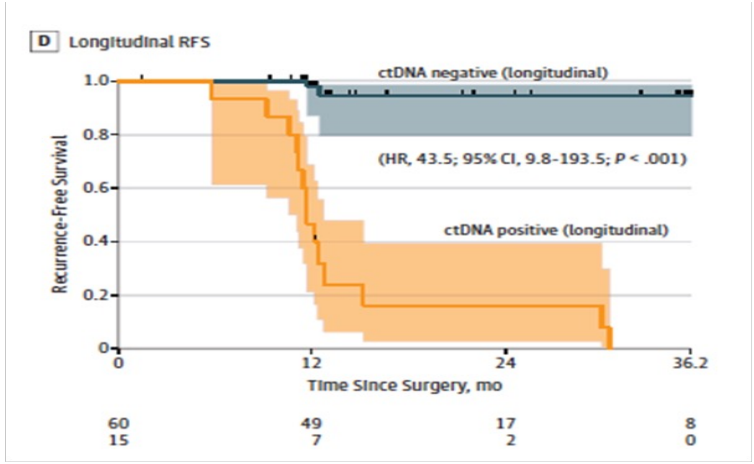
MRD detection post-surgery confers a Poor Prognosis in a pan-cancer fashion



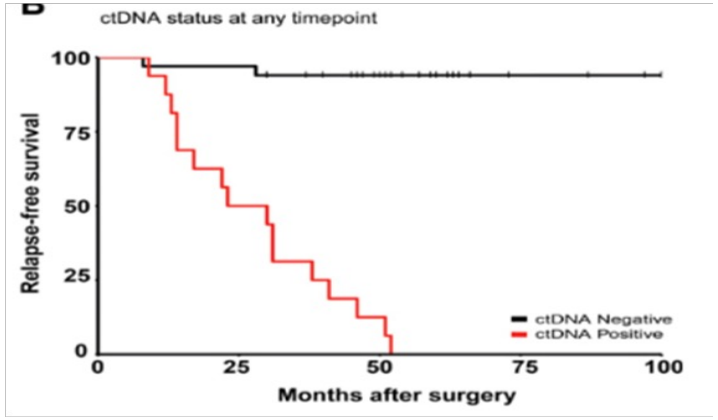
NSCLC (Chaudhuri et al., Cancer Discov, 2017)



Bladder ca (Chirsitensen, JCO, 2019)



Colorectal (Reinert et al., JAMA oncol, 2019)

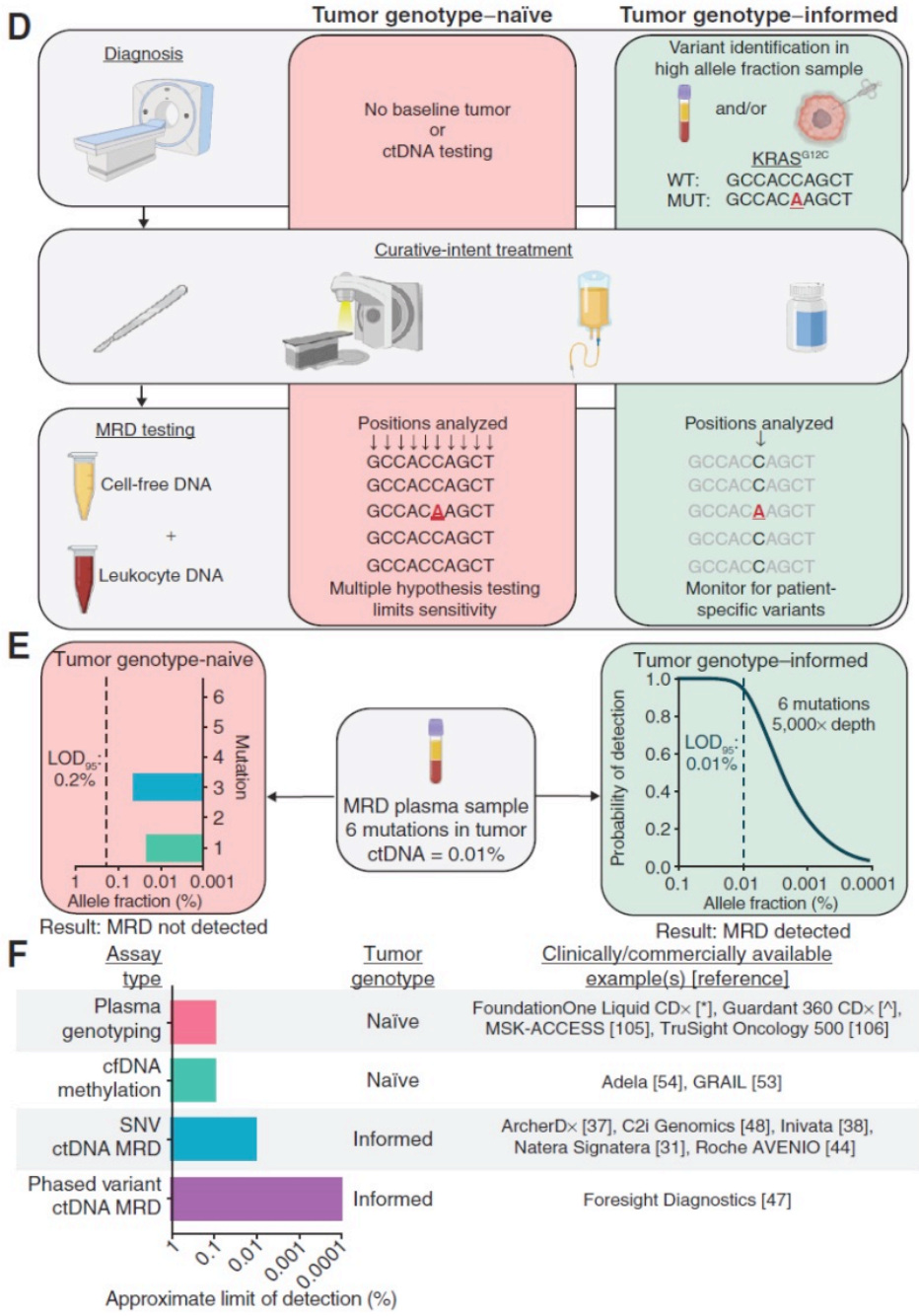


Breast ca (Coombes CCR, 2019)

Courtesy of T. Mitsudomi. IASLC LiqBx Workshop 10-2020

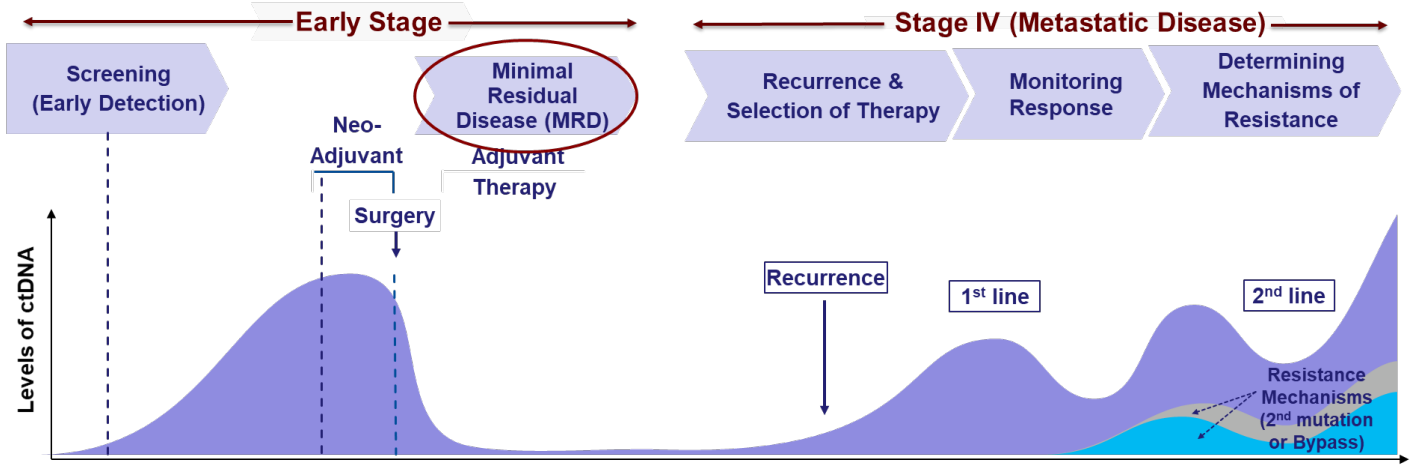
Liquid Biopsy Approaches to MRD

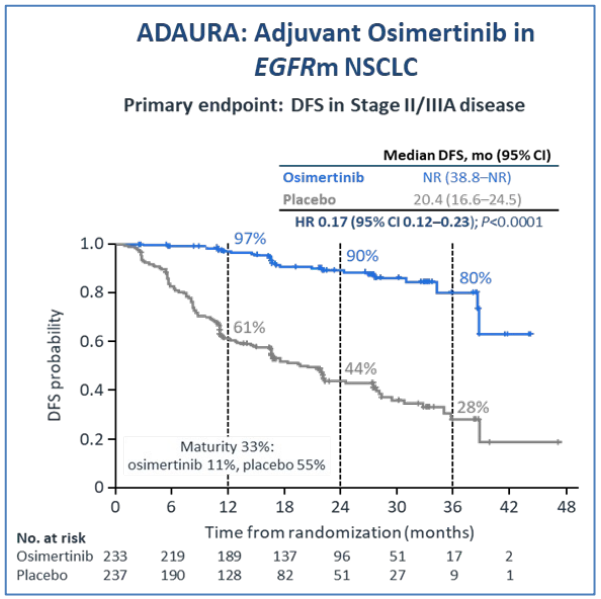
Parameter	Tissue-naive	Tissue-informed
Adequacy of Tumor Tissue Sample	Not required	Practical limitation
Sensitivity	MRD-specific assays improve	Lower LOD
Specificity	CHIP requires filtering algorithm; Improved by baseline ctDNA	Tumor specific
Emergent Variants	Detects	Unable to assess
Resistance Variants	Detects	Unable to assess
Turn Around Time	Much shorter	Longer

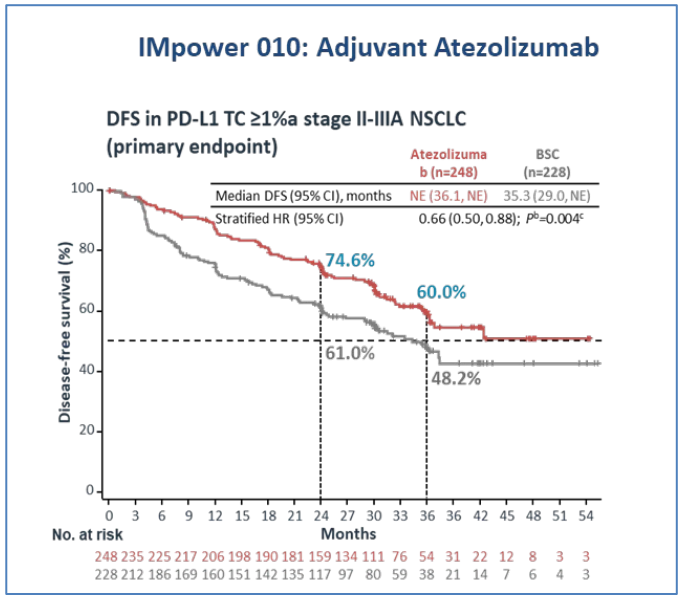


Molding (Diehn) Cancer Discov 2021; Pellini et al. JCO 2022

Two landmark trials in the adjuvant NSCLC space ADAURA & IMpower010: Can plasma ctDNA analysis for MRD define who benefits and who does not?



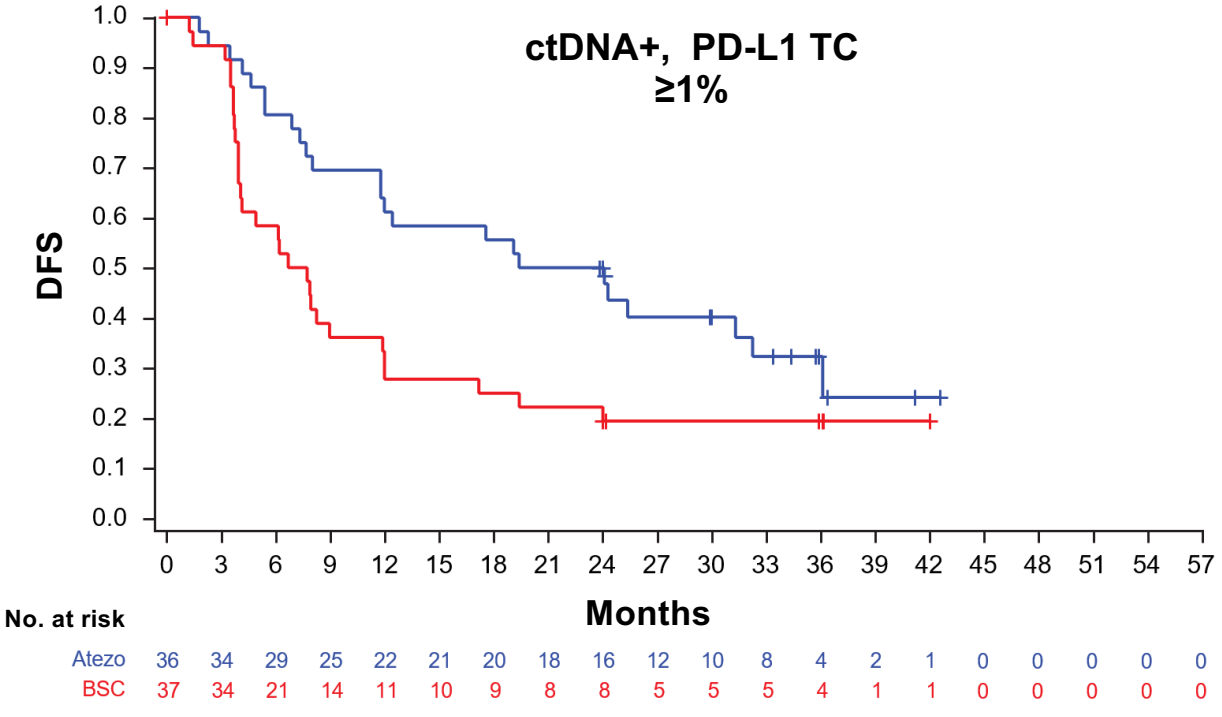


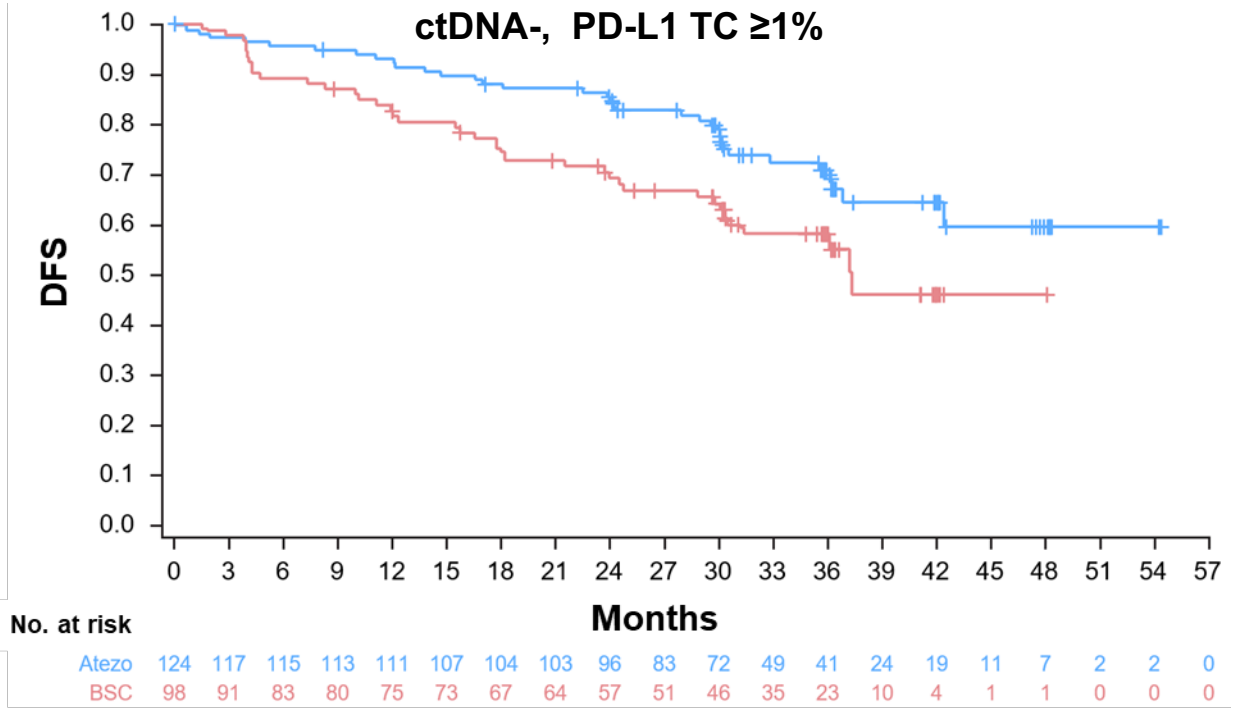


- Is MRD detection by plasma ctDNA only prognostic in these trials? (poor outcome regardless of therapeutic intervention)
- Is MRD detection by plasma ctDNA predictive for outcome with therapeutic intervention?
  - Do only patients with positive MRD after surgery benefit from these therapies?

Wu et al. N Engl J Med 2020; . Felip et al. Lancet 2021.

Impower 010: DFS in Stage II-IIIA ctDNA+ vs ctDNA- populations (PD-L1 TC ≥1%)



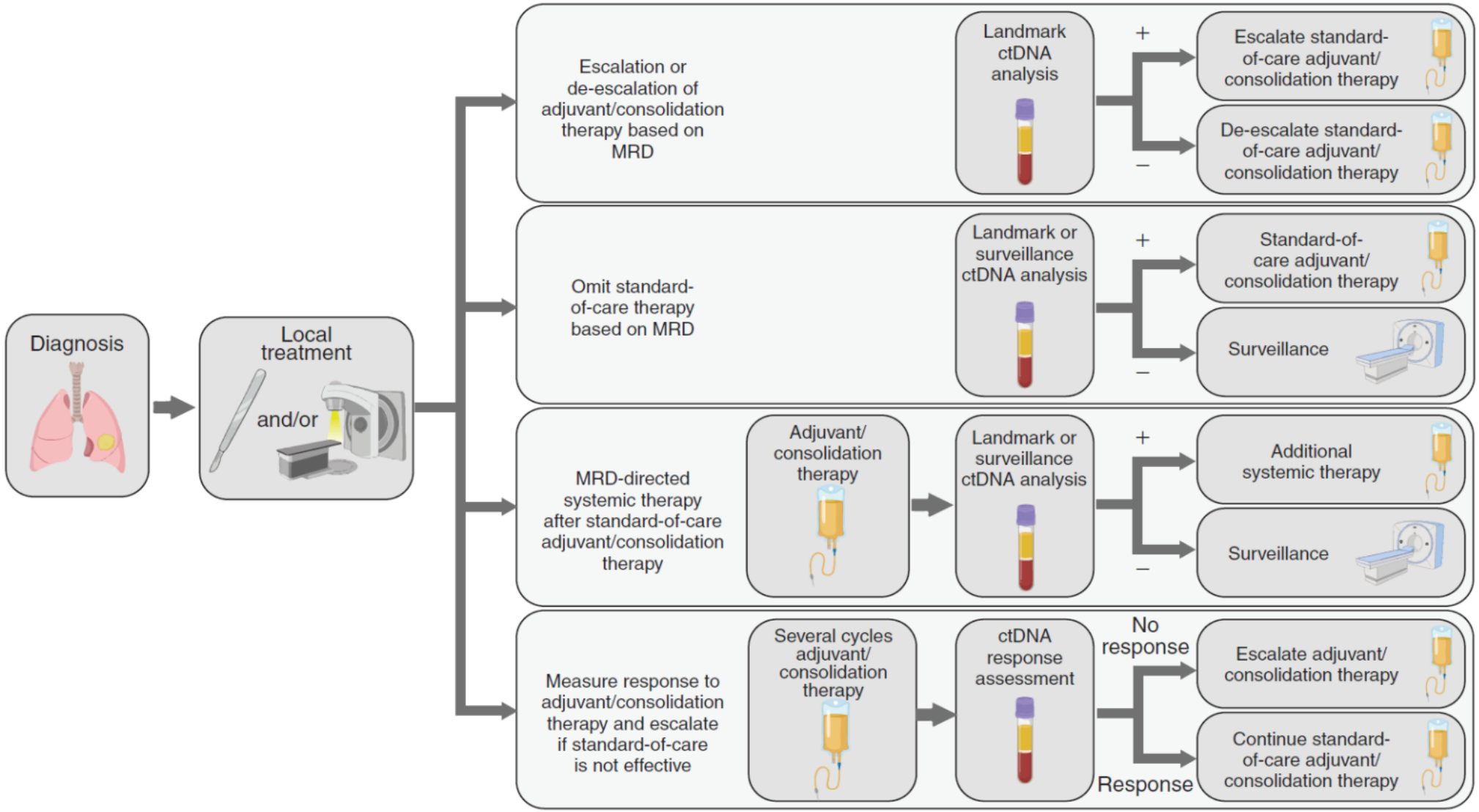


ctDNA+	PD-L1 TC ≥1%	
	Atezo (n=36)	BSC (n=37)
mDFS, mo	21.8	7.2
HR (95% CI)	0.54 (0.31, 0.93)	

ctDNA–	PD-L1 TC ≥1%	
	Atezo (n=124)	BSC (n=98)
mDFS, mo	NR	37.3
HR (95% CI)	0.57 (0.36, 0.90)	

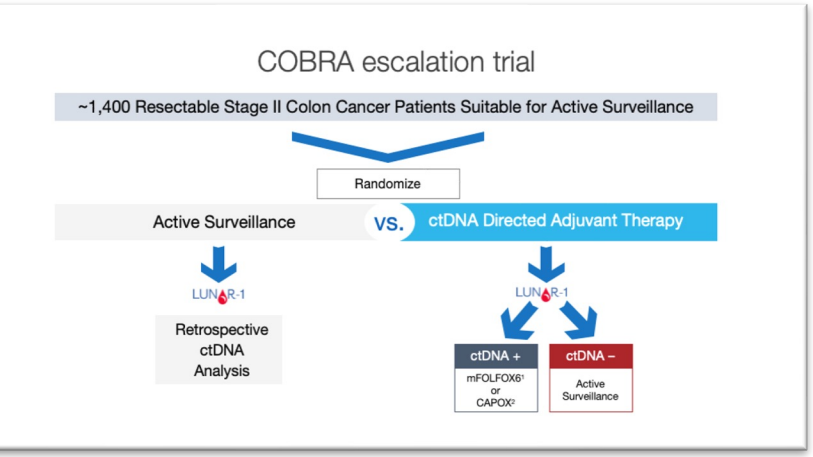
Zhou et al. ESMO 2021

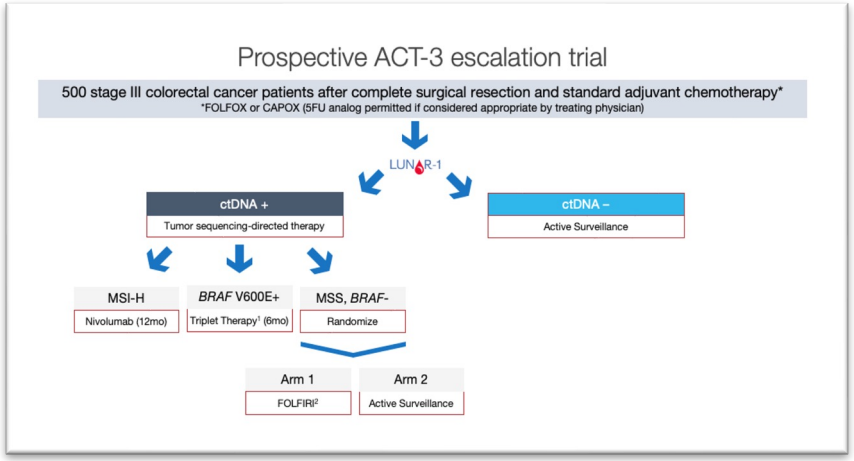
MRD-related Prospective Clinical Trial Designs

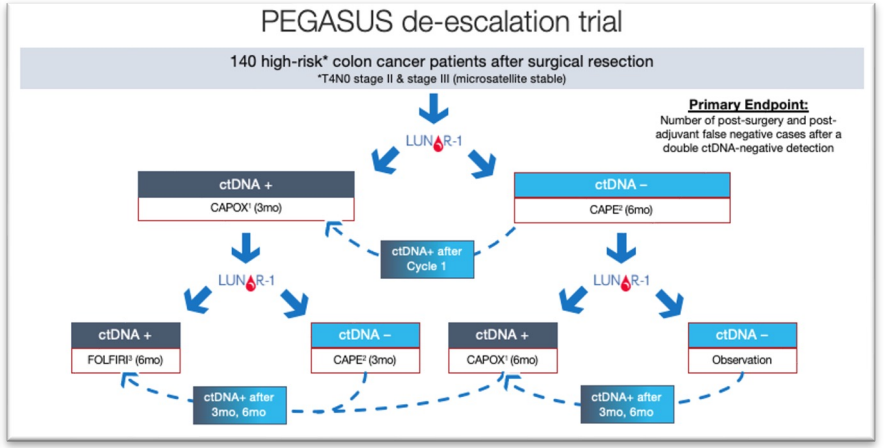


Pellini (Chaudhuri). JCO 2022

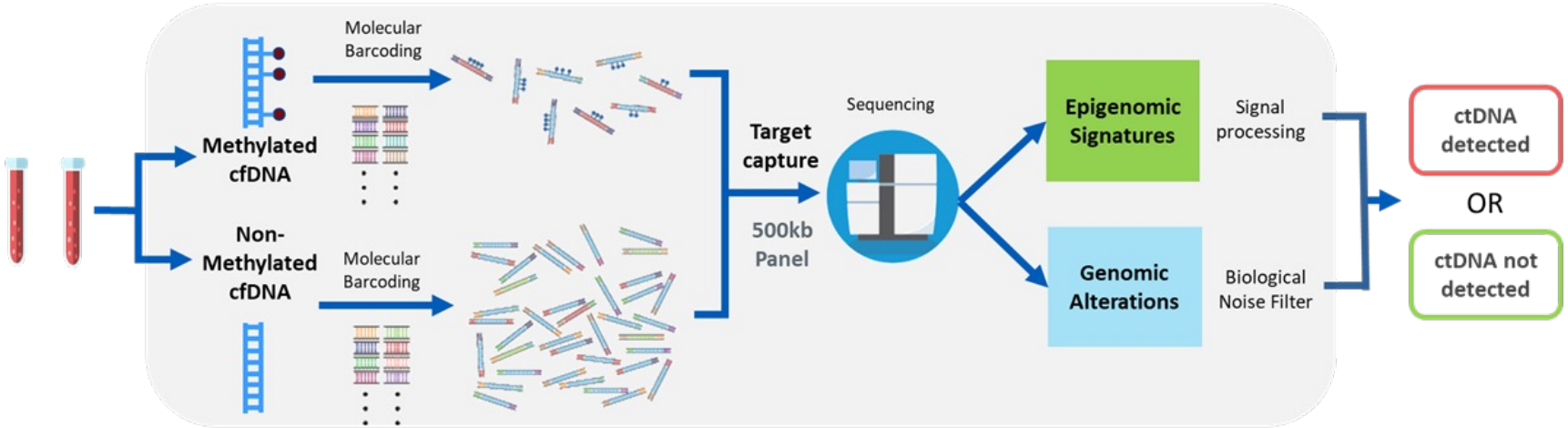
MRD detection by ctDNA to escalate or de-escalate post-operative adjuvant therapy in stage II and stage III Colorectal Cancer







Guardant REVEAL: MRD assay integrating genomic & epigenomic analysis



NCT04068103, NCT03803553, NCT04259944

International Society of Liquid Biopsy (ISLB) Annual Congress
Madrid, November 19-21, 2023