IX SIMPOSIO · SYMPOSIUM | 2024
BIOPSIA LÍQUIDA · LIQUID BIOPSY

EL CAMINO A LA ONCOLOGÍA DE PRECISIÓN · THE WAY TO PRECISION MEDICINE

25, 26 Y 27 DE ENERO · JANUARY 25th, 26th and 27th

PLASMA-FIRST APPROACH FOR MOLECULAR GENOTYPING IN NON-SMALL CELL LUNG CANCER

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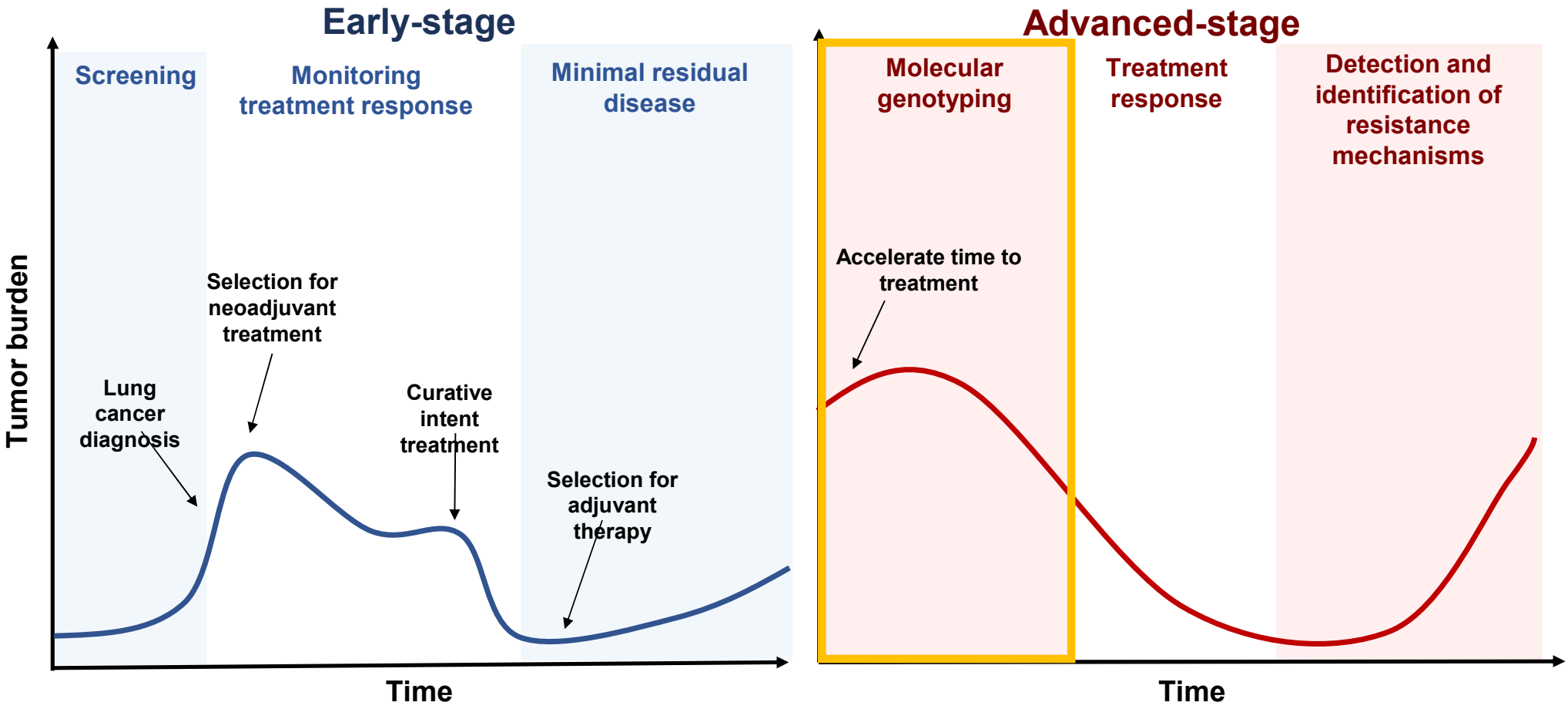
DISCLOSURES

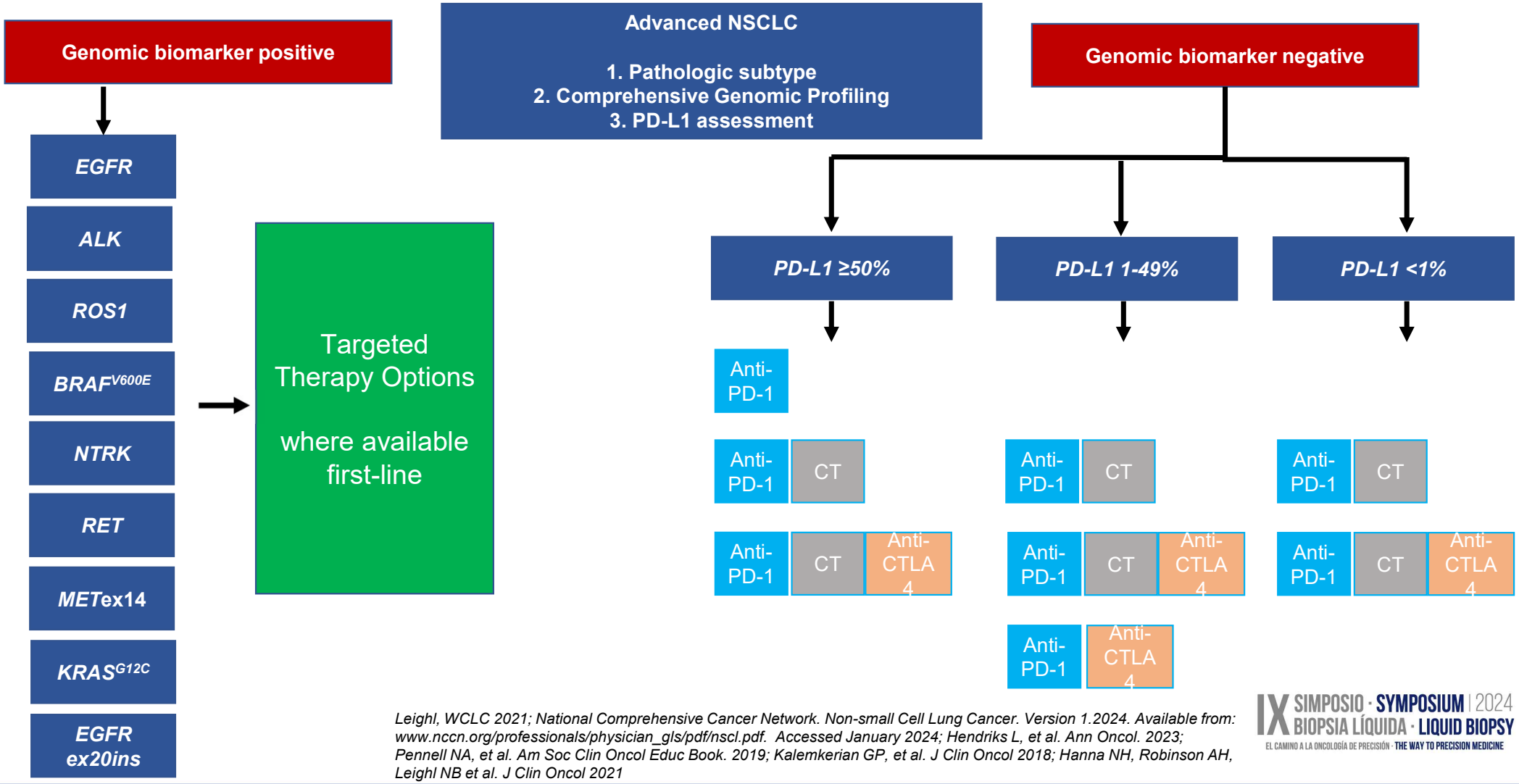
No COIs to disclose

EMERGING INDICATIONS FOR CTDNA TESTING IN NSCLC



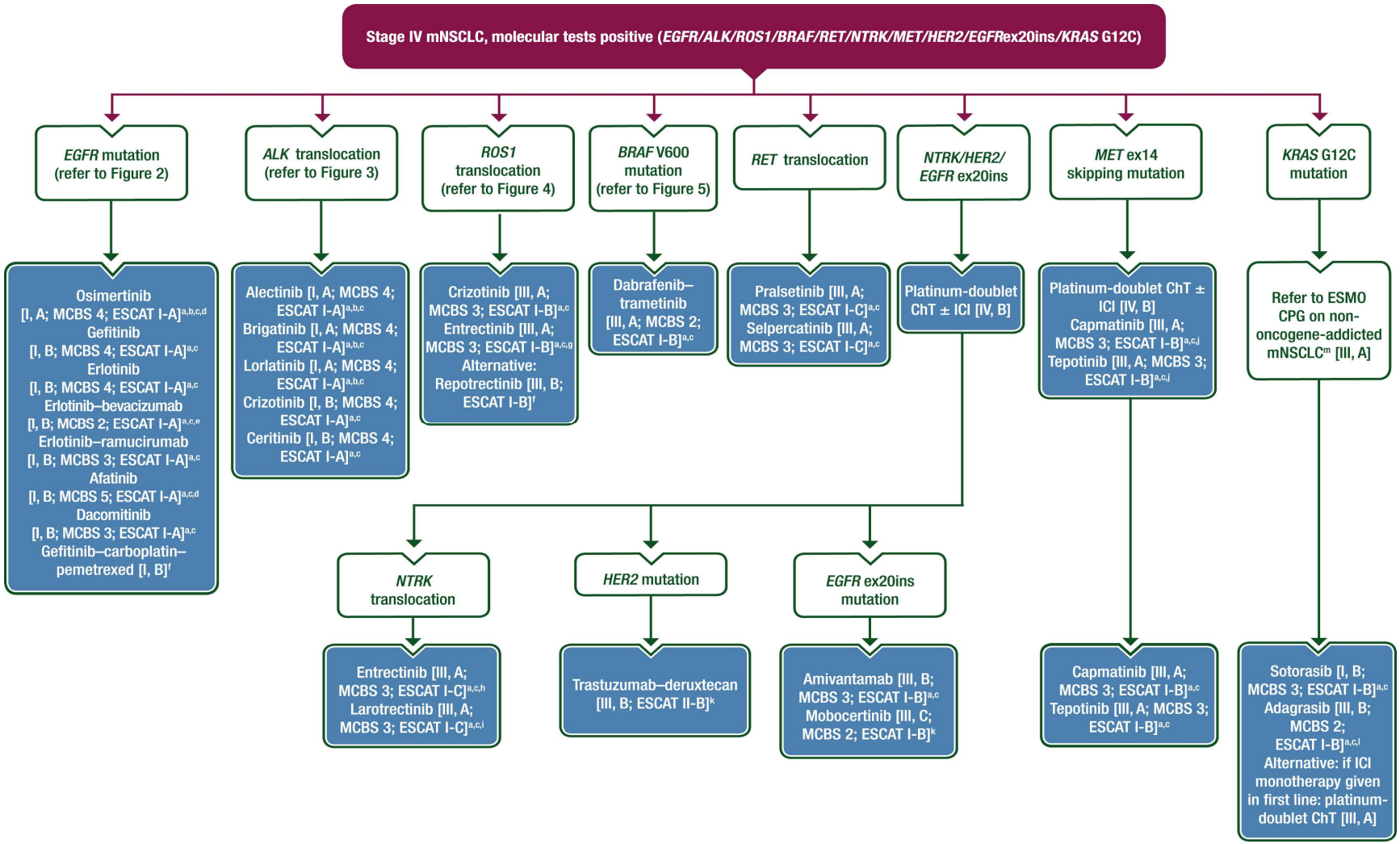
Garcia-Pardo, Makarem, Kelly , Li, Leighl under review

MOLECULAR GENOTYPING IS ESSENTIAL IN NSCLC



Leighl, WCLC 2021; National Comprehensive Cancer Network. Non-small Cell Lung Cancer. Version 1.2024. Available from: www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed January 2024; Hendriks L, et al. Ann Oncol. 2023; Pennell NA, et al. Am Soc Clin Oncol Educ Book. 2019; Kalemkerian GP, et al. J Clin Oncol 2018; Hanna NH, Robinson AH, Leighl NB et al. J Clin Oncol 2021

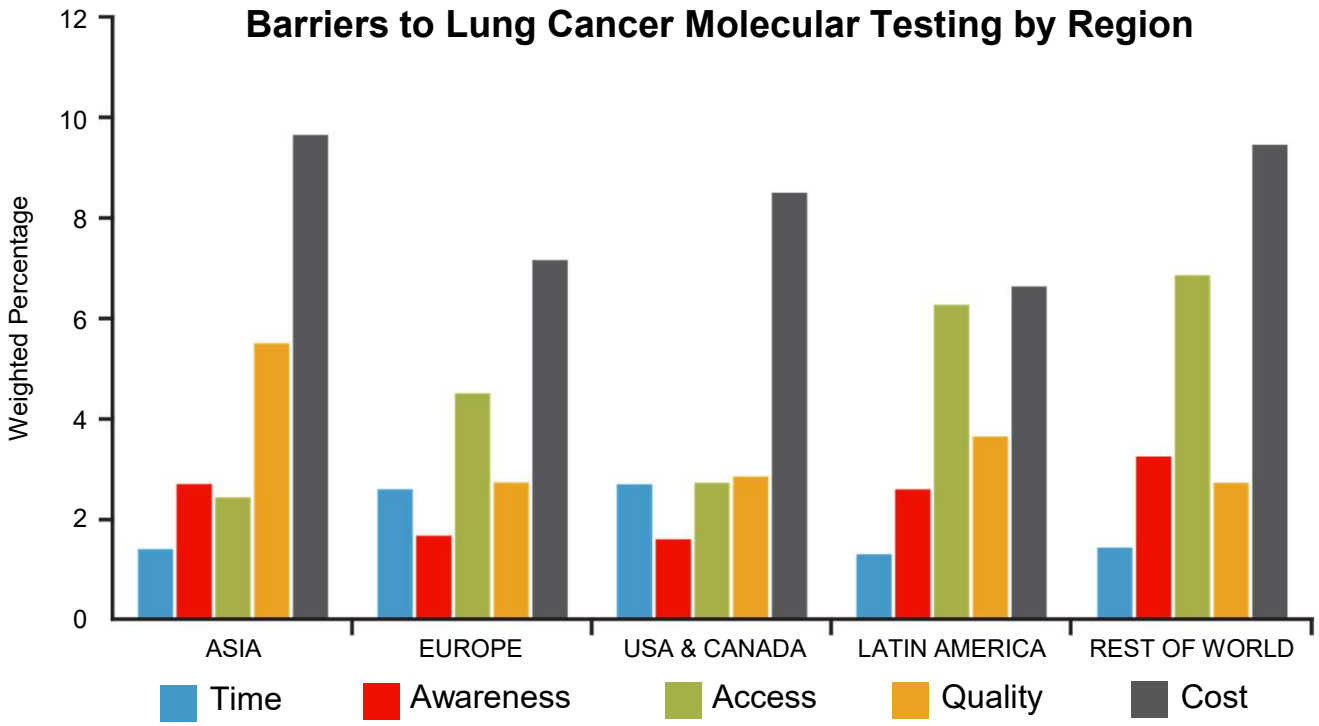
MOLECULAR GENOTYPING IS ESSENTIAL IN NSCLC



Hendricks et al. Annals of Oncology 2023 34339-357DOI: (10.1016/j.annonc .2022.12.009)

CHALLENGES IN MOLECULAR DIAGNOSIS IN NSCLC

IASLC survey 2020 (including 2537 respondents from 102 countries)

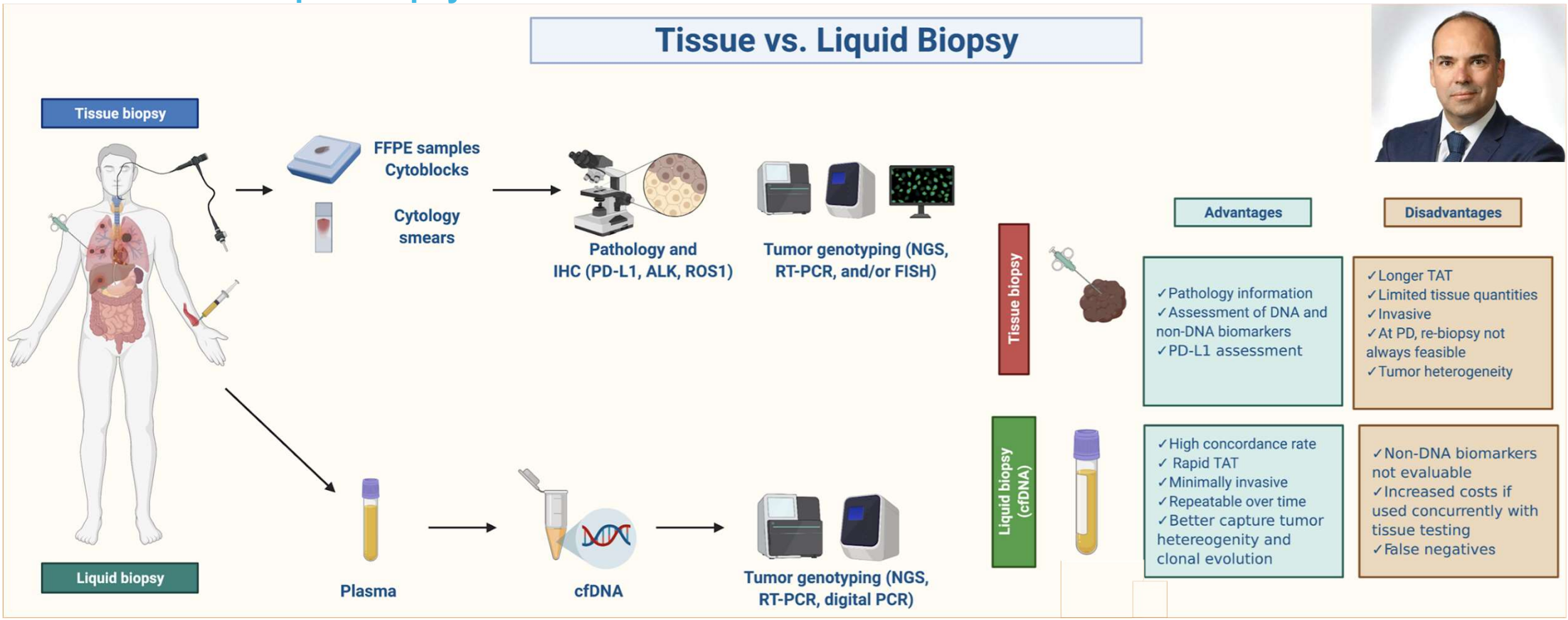


- **Tissue for Profiling**
  - 6-34% of patients have insufficient tissue for complete testing
- **Time to Profiling Result**
  - 23% of US patients start treatment without profiling
  - Only 21% of Canadian patients have profiling results at the initial consultation
- **Access and cost**
  - Funding & reimbursement for NGS testing
  - Validated testing at local laboratories

Smeltzer MP, et al. J Thorac Oncol. 2020; Hao, Leighl WCLC2020; Aggarwal C et al JAMA Oncol 2018; Lim, Leighl Ann Oncol 2015

CTDNA TESTING IN ADVANCED NSCLC

2021 IASLC Liquid Biopsy Consensus Statement



Rolfo C et al.Journal of Thoracic Oncology 2021 161647-1662. DOI: (10.1016/j.jtho.2021.06.017)

CTDNA TESTING IN ADVANCED NSCLC

2021 IASLC Liquid Biopsy Consensus Statement Recommendations

1. ctDNA collection, sample handling and automated processing should be performed using standardized, clinically validated procedures to reduce operator variability and false negative results

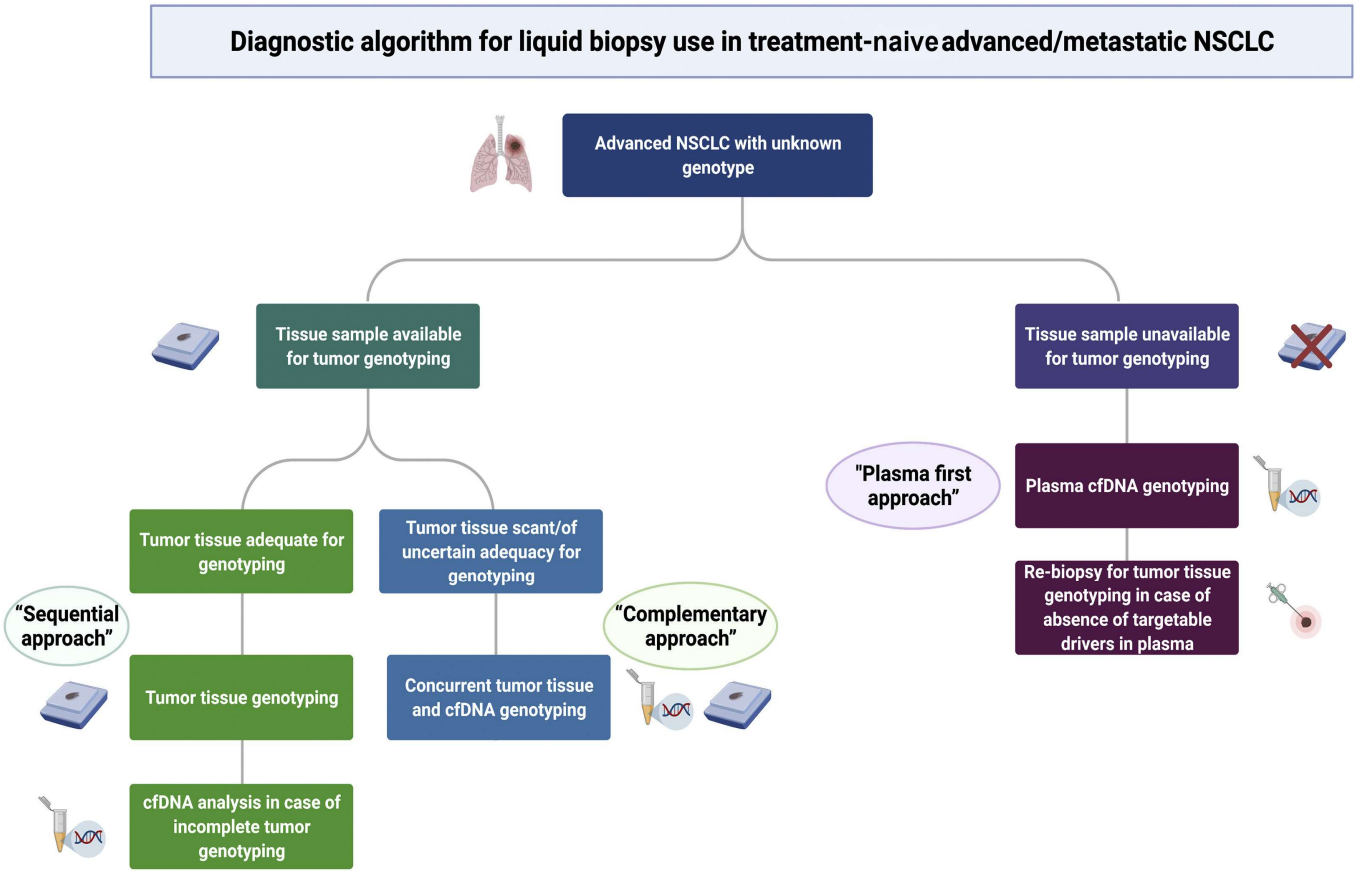
2. Plasma ctDNA testing should be performed using clinically validated NGS platforms rather than single gene PCR-based assays both in treatment-naïve patients and those with acquired resistance to targeted agents.

3. Implementation of a multidisciplinary molecular tumor board to assist clinicians in treatment decision-making is advised,

Rolfo C et al.Journal of Thoracic Oncology 2021 161647-1662. DOI: (10.1016/j.jtho.2021.06.017)

CTDNA TESTING IN ADVANCED NSCLC

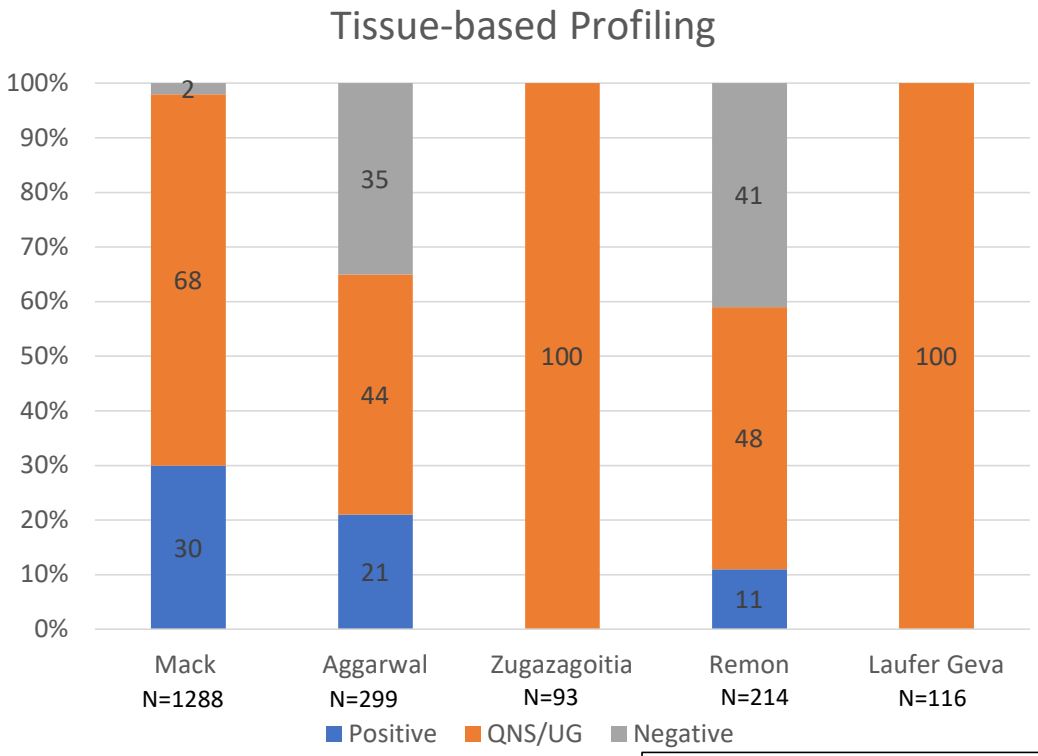
2021 IASLC Diagnostic algorithm for ctDNA

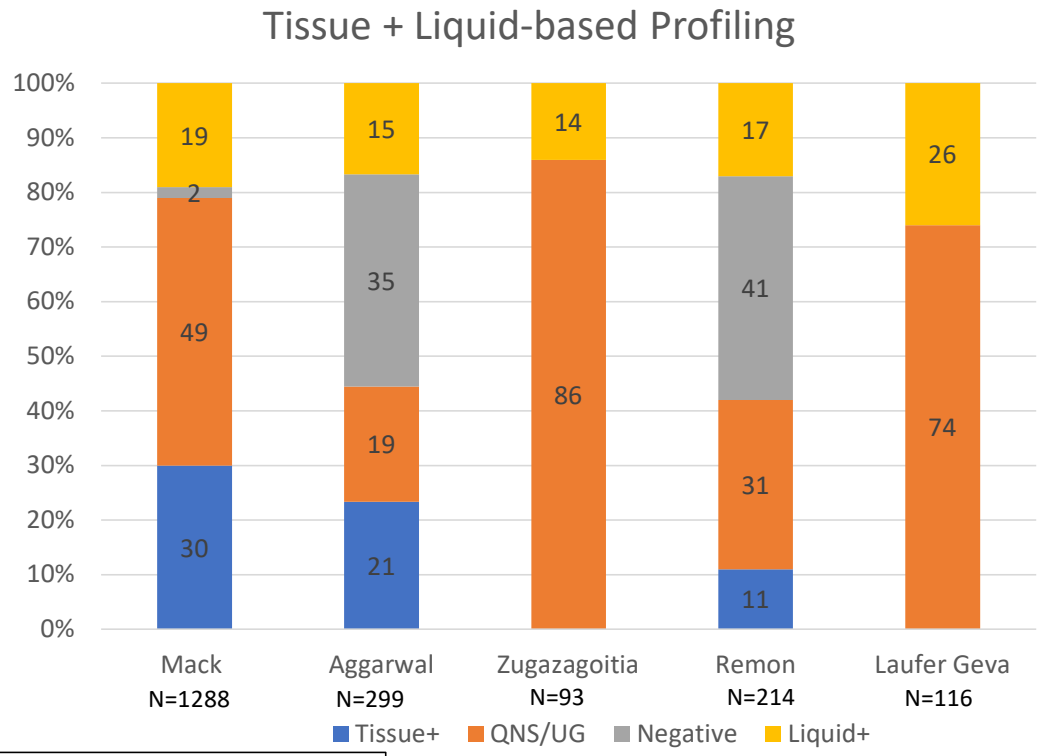


Rolfo C et al.Journal of Thoracic Oncology 2021 161647-1662. DOI: (10.1016/j.jtho.2021.06.017)

SEQUENTIAL / CONCURRENT APPROACH

ctDNA testing enables patients with insufficient or undergenotyped tissue to access precision medicine



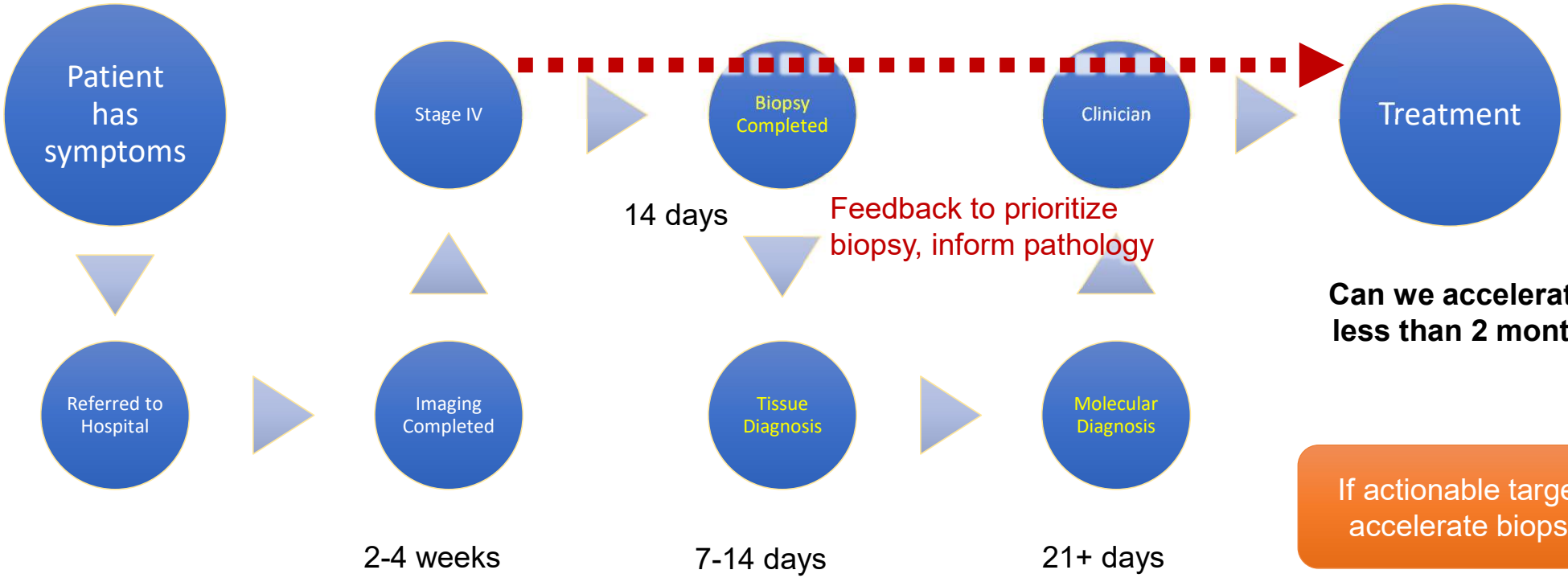


Positive: biomarker+; QNS/UG: insufficient tissue or undergenotyped

Leighl WCLC Liquid Biopsy Meeting 2020; Mack et al Cancer 2020; Aggarwal et al JAMA Oncol 2018; Zugazagoitia Ann Oncol 2019; Remon; Laufer Geva et al J Thorac Oncol 2018

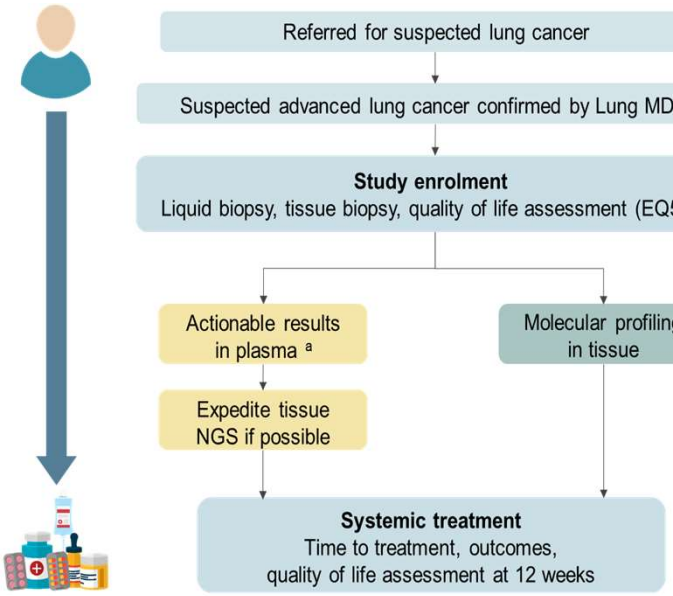
PLASMA-FIRST APPROACH

Can ctDNA testing ***before*** tissue diagnosis accelerate the time to treatment?



PLASMA-FIRST APPROACH

Accelerating time to treatment



Study	N	Time (days) to molecular results plasma vs tissue	TTT (days) plasma vs tissue	TTT if actionable alteration	% NSCLC among all evaluable patients	% non-squamous among NSCLC
Cheng et al, Dana Farber	20 hospitalized	**3 vs 35.5**	**NA**	**NA**	68%	NA
Cui et al, Royal Marsden	49	**9 vs 33**	**NA**	**NA**	63%	NA
Thompson et al, University of Penn	65 (55 control cohort)	**8 vs 26**	**12 v 20** **P = 0.003**	**10 v 19** **P = 0.001**	85%	74%
García-Pardo et al, Princess Margaret	20 light/never smokers (41 control cohort)	**17.8 vs 23.6**	**33 vs 62** **P <0.001**	**29 v 49** **P< 0.001**	85%	94%
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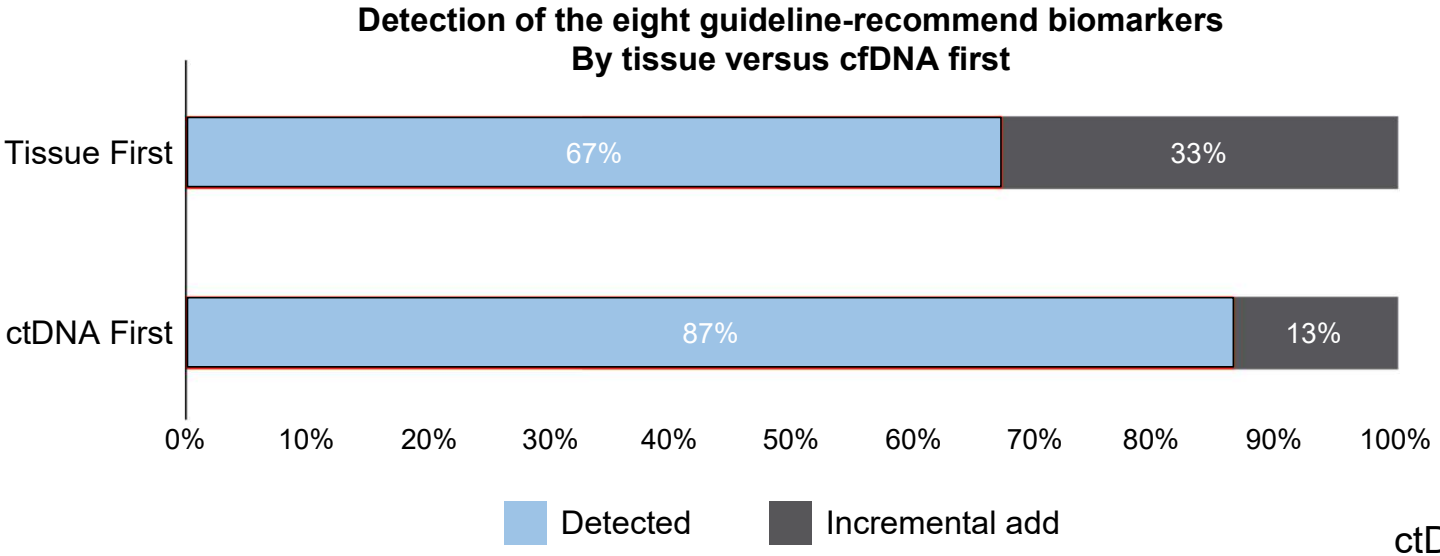
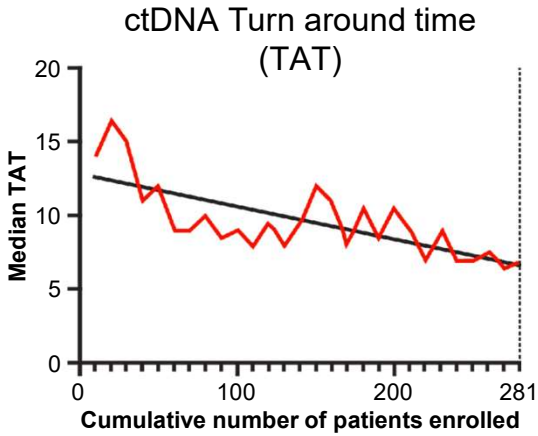
Swalduz et al, multicenter randomized trial in France	161 (158 control arm)	**17.9 vs 25.6**	**29 v 33.2** **P<0.001**	**21 v 37.4** **P<0.001**	67.7%	80%

Garcia-Pardo M, Leighl NB. Journal of Liquid Biopsy 2023

PLASMA-FIRST / CONCURRENT APPROACH – NILE STUDY

Higher detection of actionable alterations and higher odds of availability of results before 1L therapy





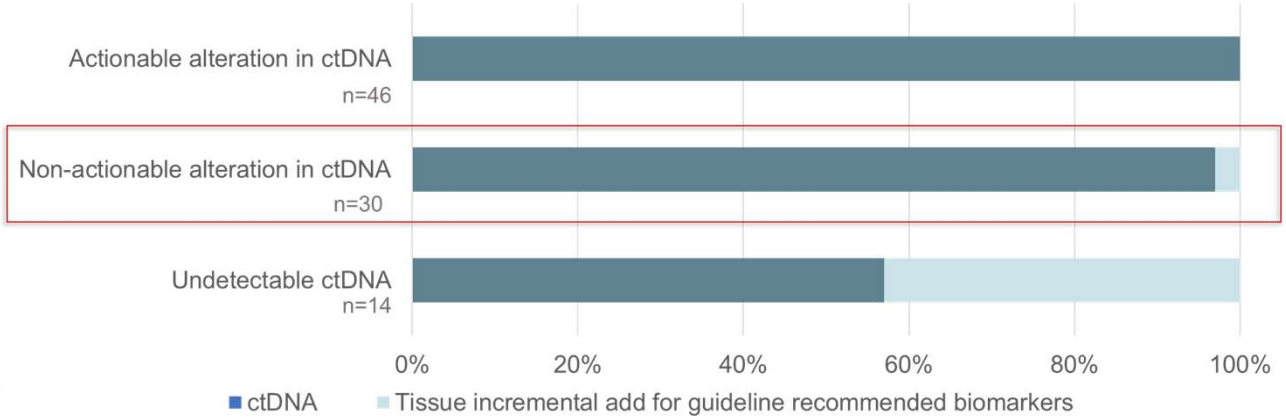
ctDNA results median TAT faster than tissue at 9 days versus 15 ($p<0.0001$)

Leighl NB, et al. *Clin Cancer Res*. 2019;25:4691-4700.

PLASMA-FIRST: ACCELERATE STUDY

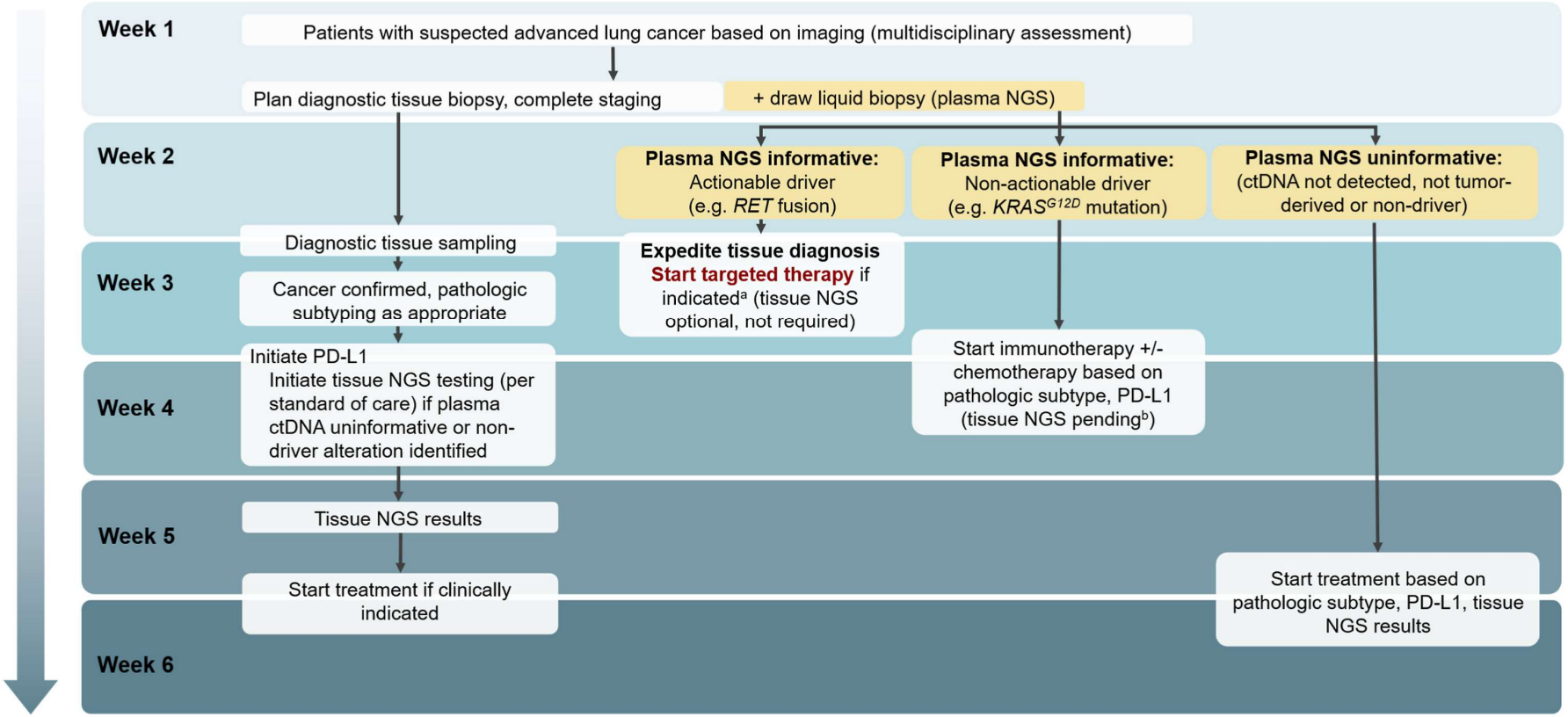
High NPV value

Molecular alteration	ctDNA	Tissue +	Tissue -	Tissue NA[b]	Total	NPV excluding undetectable ctDNA
EGFR ex19del/L858R/ atypical[a] (n=29)	ctDNA+	18	3	4	25	100%
	ctDNA-	0	48	3	51	
	ctDNA not detected	4	10	0	14	
	Total	22	61	7	90	
EGFR ex20ins (n=3)	ctDNA+	3	0	0	3	100%
	ctDNA-	0	66	7	73	
	ctDNA not detected	0	14	0	14	
	Total	3	80	7	90	
ALK fusion (n=5)	ctDNA+	1	0	1	2	98.5%
	ctDNA-	1[c]	67	6	74	
	ctDNA not detected	2	12	0	14	
	Total	4	79	7	90	
ROS1 fusion (n=1)	ctDNA+	1	0	0	1	100%
	ctDNA-	0	68	7	75	
	ctDNA not detected	0	14	0	14	
	Total	1	82	7	90	
MET ex14 skip (n=2)	ctDNA+	1	1	0	2	100%
	ctDNA-	0	58	16	74	
	ctDNA not detected	0	14	0	14	
	Total	1	73	16	90	
ERBB2 ex20ins (n=4)	ctDNA+	4	0	0	4	100%
	ctDNA-	0	56	16	72	
	ctDNA not detected	0	14	0	14	
	Total	4	70	16	90	
BRAF V600E (n=1)	ctDNA+	1	0	0	1	100%
	ctDNA-	0	59	16	75	
	ctDNA not detected	0	14	0	14	
	Total	1	73	16	90	
KRAS G12C (n=8)	ctDNA+	6	1	1	8	100%
	ctDNA-	0	53	15	68	
	ctDNA not detected	0	14	0	14	
	Total	6	68	16	90	



- Excluding cases with undetectable ctDNA, the NPV of plasma testing was 96.7% (29/30)
- Tissue genotyping remains essential, especially following undetectable or uninformative ctDNA results - both assays are complementary

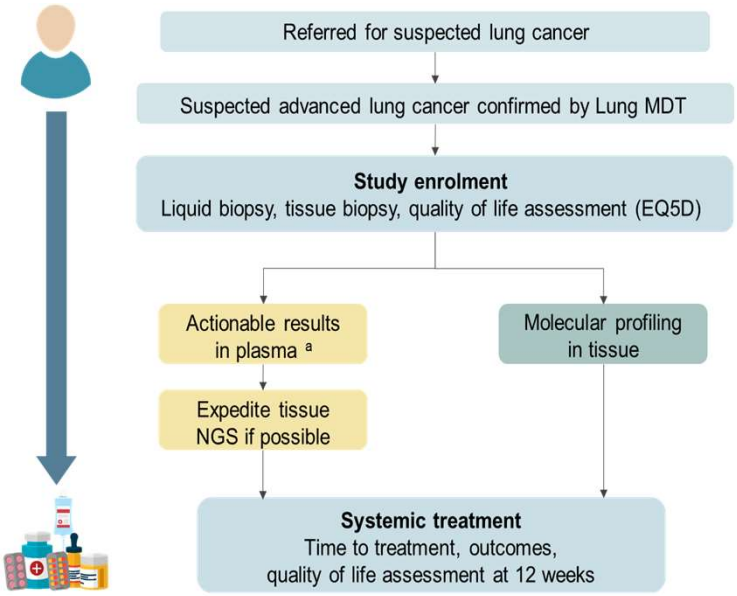
PLASMA-FIRST PROPOSED ALGORITHM



[a]Prioritize tissue sampling (required), pathologic diagnosis and subtyping (if possible) prior to treatment initiation based on ctDNA results; [b]Some may consider tissue NGS testing optional in this scenario as the frequency of actionable co-alterations is uncommon in the presence of another driver alteration.

Garcia-Pardo M et al, JAMA Network Open 2023

PLASMA-FIRST APPROACH: CHALLENGES AND LIMITATIONS



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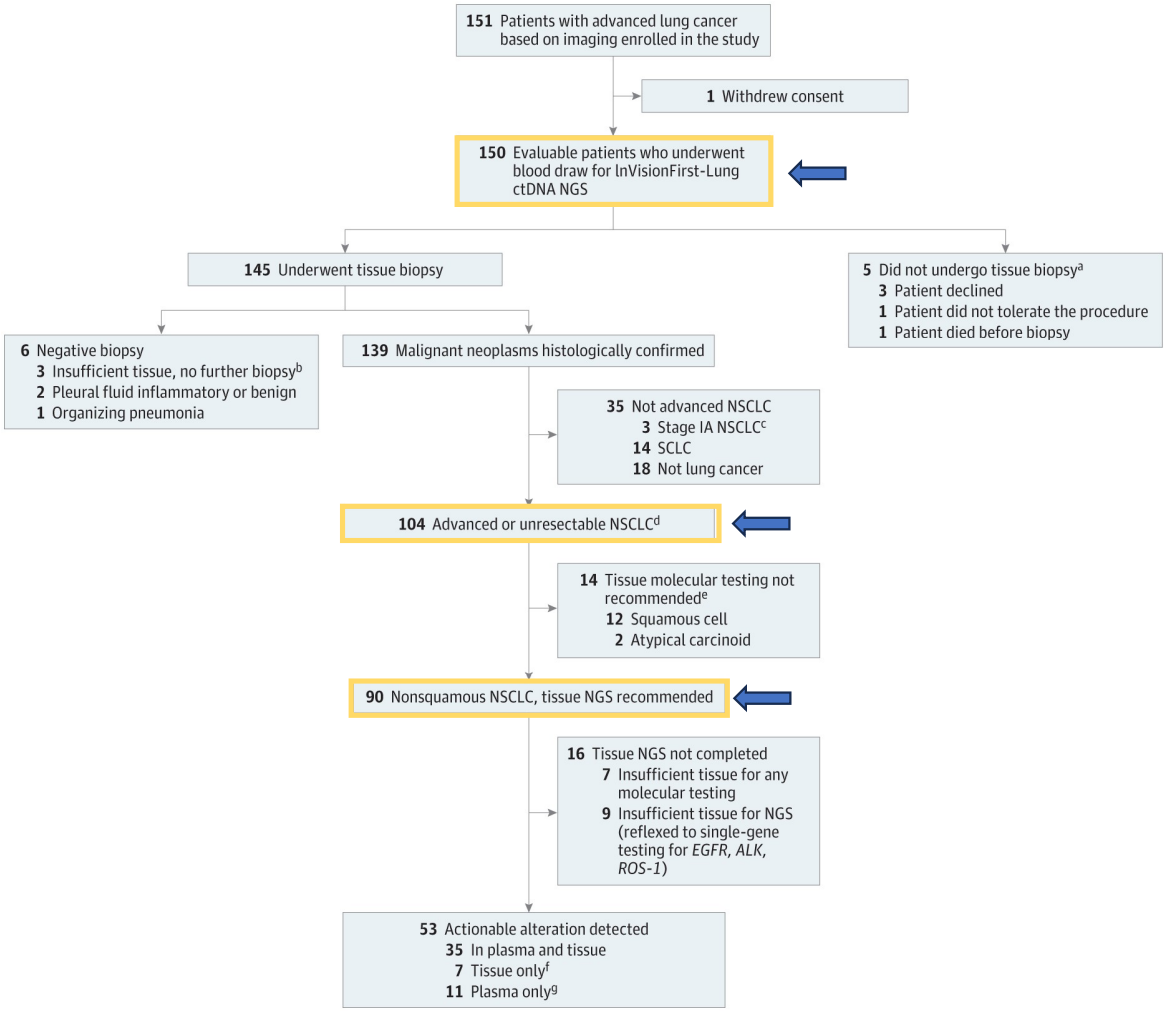
Garcia-Pardo M, Leighl NB. Journal of Liquid Biopsy 2023

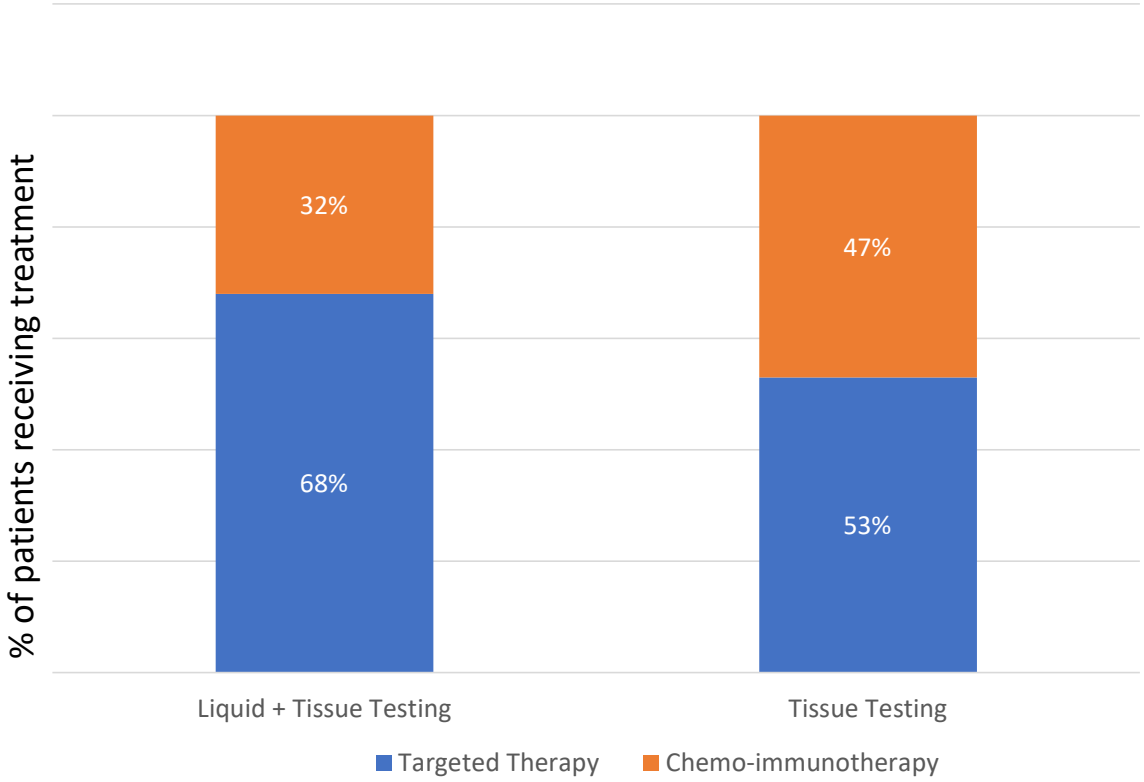
PLASMA-FIRST APPROACH - ACCELERATE

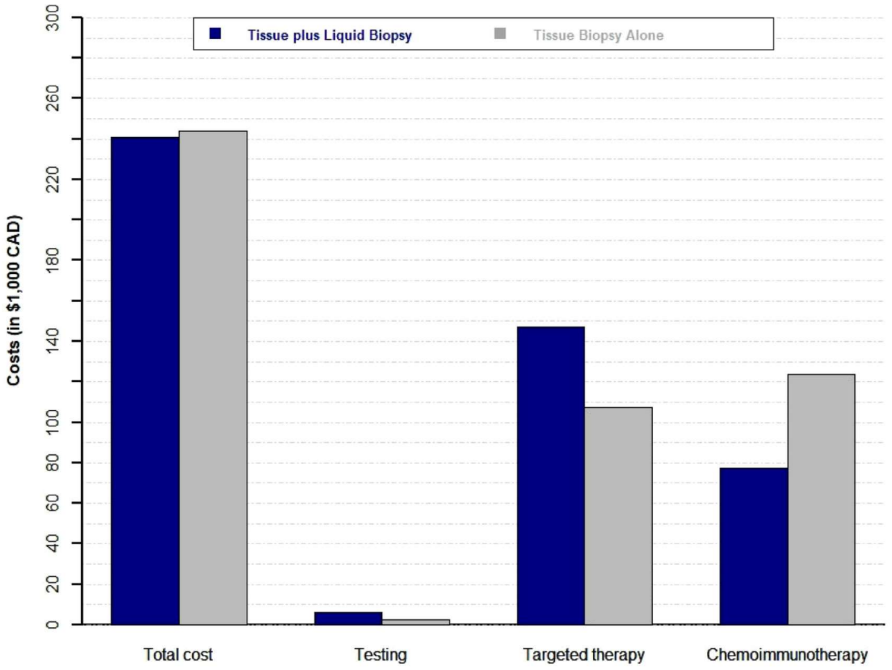
High % of not advanced NSCLC



PLASMA-FIRST: COST-EFFECTIVE?

Canadian VALUE study (NCT03576937) in non-squamous NSCLC and ⩽10 pack-year





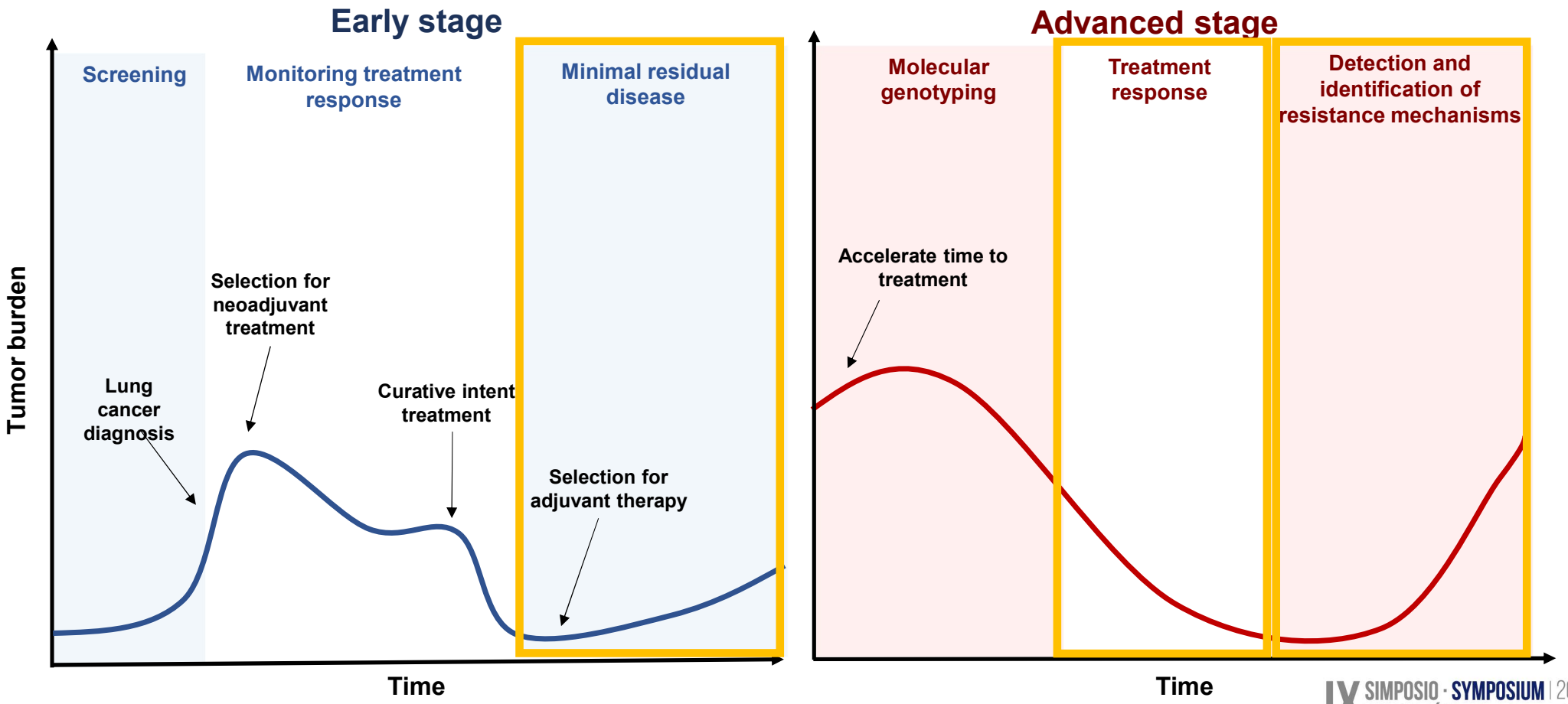
Ezeife et al. Therapeutic Advances in Medical Oncology 2022

TISSUE IS STILL AN ISSUE

Plasma-first does not mean plasma only

- Genomic data are not always independent of histology (e.g. small cell or squamous transformation in 5-20% EGFR mutant cancers)
- Tissue analysis still important for epigenetic, post transcriptional/translational modifications and larger signatures (although cfDNA platforms now reporting MSI, TMB, HRRD…
- Tumor microenvironment increasingly relevant (TILs, stroma) although emerging liquid markers of immune activation (e.g. TCR, others)
- Non-shedders, liquid biopsy failures (disease burden, “sanctuary” sites), clonal hematopoiesis

EMERGING INDICATIONS FOR CTDNA TESTING IN NSCLC AND OTHER CANCERS



Garcia-Pardo, Makarem, Kelly, Li, Leighl *under review*

TAKE HOME MESSAGES

- Plasma ctDNA testing has emerged as a complement to tumor tissue genotyping for advanced NSCLC, especially when tissue or time is limited.
- The optimal way to integrate ctDNA testing into the diagnostic algorithm for patients with newly diagnosed NSCLC remains unclear.
- A “plasma-first” approach, using ctDNA genotyping for patients with suspected or confirmed advanced NSCLC before tissue genotyping, may shorten time to treatment and yield a higher rate of detection of actionable genomic alterations
- Future applications: MRD detection, treatment monitoring

¡GRACIAS!

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