

P2.196 – ExpandingLUNG: The utility of negative plasma ctDNA results in newly diagnosed advanced NSCLC

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Background

- Plasma circulating tumour DNA (ctDNA) testing is widely used in advanced NSCLC, particularly for detecting actionable genomic alterations (AGA) to guide treatment selection
- If ctDNA testing does not detect AGA, reflex tissue NGS testing must be performed, which delays results and treatment initiation
- Informative negative results** (adequate ctDNA for testing, but no AGA detected) may reliably exclude the need for tissue NGS, enabling earlier treatment decisions based on histology and PD-L1
- Objective:** To investigate the utility of informative negative plasma ctDNA results for selecting optimal treatment and accelerating treatment initiation

Methods

- Pooled analysis of 4 prospective liquid biopsy databases (DISCOVER¹, ACCELERATE-1², ACCELERATE-2³, PM B-FAST⁴) from the Princess Margaret Cancer Centre
- Patients with advanced NSCLC diagnosis and available matched ctDNA and tumour tissue NGS at diagnosis
- Using tissue NGS as the reference, the negative predictive value (NPV), concordance, and factors associated with AGA detection (*BRAF* V600E, *EGFR* sensitizing mutations, *EGFR* ex20 insertions, *ERBB2* mutations, *KRAS* G12C, *MET* ex14 skipping, *MET* amplification, *ALK*, *NRG1*, *RET* and *ROS1* fusions) in ctDNA were assessed
- ctDNA NGS platforms included the TSO500, Canexia, Inivata and Foundation Medicine research assays

Results

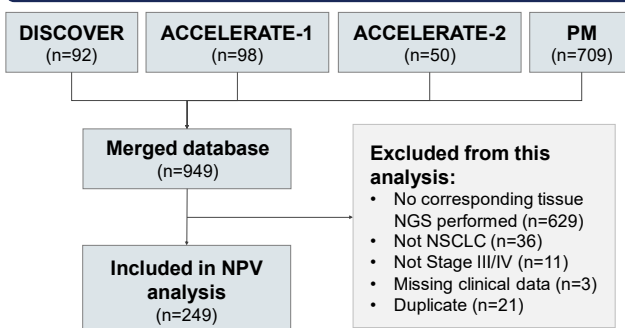


Figure 1. Consort diagram

Table 1. Patient demographics

Characteristic	Total (n=249)
Age, median (range, years)	67 (23-90)
Male, n (%)	119 (48)
Smoking Status	
Current	22 (9)
Former	116 (46)
Never	106 (43)
Unknown	4 (2)
Stage IV, n (%)	228 (92)
Histology, n (%)	
Adenocarcinoma	223 (90)
Adenosquamous	1 (1)
Squamous	6 (2)
Large Cell	3 (1)
Other	15 (6)
Plasma uninformative	107 (43)

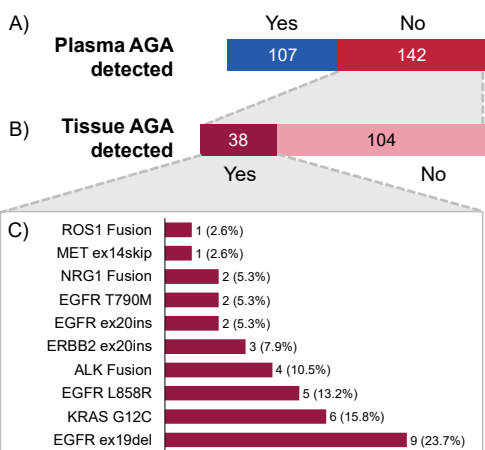


Figure 2. Plasma tissue concordance for AGA informative plasma results. A) Plasma AGA detection. B) Tissue AGA detection among plasma negative patients. C) AGA detected in discordant plasma-negative/tissue-positive cases

Results

Table 2. Negative predictive value (NPV), sensitivity, and concordance of tissue and plasma NGS results for AGA

Mutation	# tested	NPV (%)	Concordance (%)	Sensitivity (%)
ALK Fusion	201	97.93	96.02	50
BRAF V600E	246	100	99.59	100
EGFR Ex18	245	100	100	100
EGFR Ex19del	246	95.73	93.09	75
EGFR Ex20ins	247	99.17	98.79	66.67
EGFR T790M	246	99.18	99.19	50
EGFR L858R	247	97.71	97.17	84.38
ERBB2 Ex20ins	247	98.76	98.38	62.5
KRAS G12C	247	97.44	96.76	64.71
MET Ex14 skip	247	99.59	98.79	66.67
MET Amp	201	99.50	99.50	0
NRG1 Fusion	201	99	99	0
RET Fusion	201	100	100	100
ROS1 Fusion	201	98.99	98.51	33.33

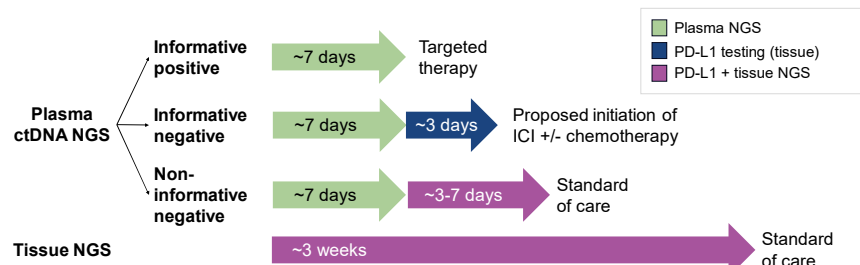


Figure 3. Time to molecular results and proposed treatment pathways based on plasma ctDNA NGS results. ICI, immune checkpoint inhibitor

Conclusions

- Informative negative plasma ctDNA results demonstrated high NPV and strong concordance with tissue NGS across AGAs and ctDNA platforms
- Integrating negative plasma ctDNA results into treatment planning may enable earlier treatment initiation and improve diagnostic efficiency in advanced NSCLC
- Future studies should incorporate tumor fraction and other clinical/molecular factors to further refine the interpretation of negative results and identify patients who may safely avoid tissue NGS testing