Real-time clinical utility of ctDNA genomic alterations in untreated patients with advanced NSCLC

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BACKGROUND

- The comprehensive genomic profile by next generation sequencing (NGS) circulating tumour DNA (ctDNA) can identify a wide spectrum of genomic alterations in patients with non-small cell lung cancer (NSCLC) leading to targeted therapies in :
  - Routine clinical care
  - Clinical trials
  - Others (expanded access, off label, etc)
- At diagnosis liquid biopsy offers a minimal-invasive & easy alternative to tissue profiling (1,2,3)

OBJECTIVE

We aimed to assess the **real-time** clinical utility of liquid biopsy by InVisionFirst®-Lung for guiding targeted therapies.

PATIENTS AND METHODS

- Prospective study of consecutive patients with newly diagnosed **advanced NSCLC** at Hospital Clinic (Barcelona, Spain) before systemic therapy, enrolled between January - June 2021
- ctDNA liquid biopsy was analyzed using **InVisionFirst® -Lung** *(INIVATA)*. Tissue NGS was performed with ***Oncomine™ Focus*** *Assay.*
- We assessed the **clinical utility** considering:
  - → The rate of detection of any genomic alterations (GAs)
  - → The % of informative results (at least one GA that can guide treatment selection)
  - → The tissue- blood concordance
  - → The turnaround time; from liquid biopsy to report (in tissue since date of request of molecular testing to report).
- We reported the GAs based on the ESMO Scale for Clinical Actionability of Molecular Target (ESCAT), classifying the GAs by ESCAT tiers (3)

Ready for routine use	Investigational	Hypothetical target	Combination development	
Tier I. *EGFR ex19/21 ALK ROS1 BRAF V600E MET ex14*	***Tier II.*** *EGFR ex20 HER2 ex20 KRAS G12C*	***Tier III.*** *HER2 amp MET amp KRAS others BRAF non_V600E FGFR famp*	V: alteration-drug match is associated with objective response, but without clinically meaningful benefit	X: lack of evidence for actionability

Table 1: *ESMO Tiers (4)*

REFERENCES

1. Remon J, Lacroix L, Jovelet C *et al* JCO PO 2019; 2. Mezquita L, Swalduz A, Jovelet C et al JCO PO 2020; 3. Ortiz-Cuaran, Mezquita L, Swalduz A et al, Clin Cancer Res 2021; 4. Mateo J, Chakravarty D, Dientsmann R et al Ann Oncol 2018

RESULTS

Patients characteristics

- A total of 61 patients with advanced NSCLC were enrolled
- Baseline characteristics of the study population is summarized in **Table 2**

Clinical characteristics		N=61 (%)
Age (median, range)		67 (42-80)
Gender	Male	36 (59%)
	Female	25 (41%)
Smoking Status	Non or light smokers	10 (27%)
	Former/Current	51 (73%)
Histology	Squamous	10 (16%)
	Non-squamous	51 (84%)
Stage at diagnosis	IIIB	15 (24%)
	IVA	8 (12%)
	IVB	38 (64%)
Metastatic sites at LB	<2	26 (43%)
	≥2	35 (57%)
Patients with tissue NGS	Yes	43 (61%)
	No	18 (29%)

Table 2: *Baseline characteristics; light smoker: < 10 pack-years*

ctDNA GAs

- The median number of GAs per patient was 2 (range 0-6)

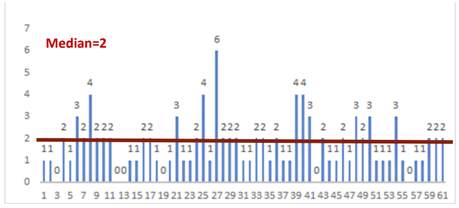
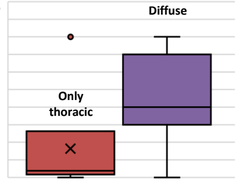


Fig. 1: *Number of pathogenic GAs per sample/patient*

ctDNA ALLELE FREQUENCY (AF)



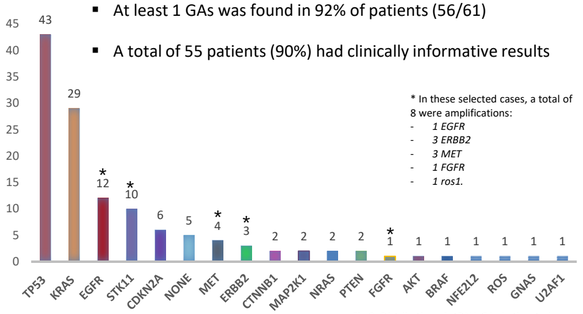
- The median AF in the overall population was 1,8% (range 0-60)
- According to the metastatic involvement:
  - **Diffuse disease**: median AF was 1,9% (0-60)
  - **Only thoracic involvement**: median AF was 0,2 % (0-4)

Fig. 2: *AF according to the metastatic involvement*

ctDNA Genomic alterations (GAs)

DISTRIBUTION OF ctDNA GAs

- At least 1 GAs was found in 92% of patients (56/61)
- A total of 55 patients (90%) had clinically informative results



* In these selected cases, a total of 8 were amplifications:
- *1 EGFR*
- *3 ERBB2*
- *3 MET*
- *1 FGFR*
- *1 ros1.*

Fig 3*: Distribution of* ctDNA GAs in the study population

INSUFFICIENT TISSUE

- In 18 patients (29%) tissue was insufficient for molecular assessment
- In 9 patients (50%), liquid biopsy provided clinically informative results (**Fig. 4**)

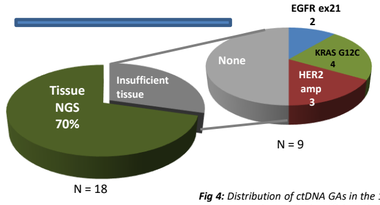


Fig 4: *Distribution of ctDNA GAs in the 18 patients with insufficient tissue*

DISTRIBUTION of ctDNA GAs BY ESCAT TIERs

- A total of **20 patients (33%)** had at least 1 GAs included in ESCAT tier I & tier II

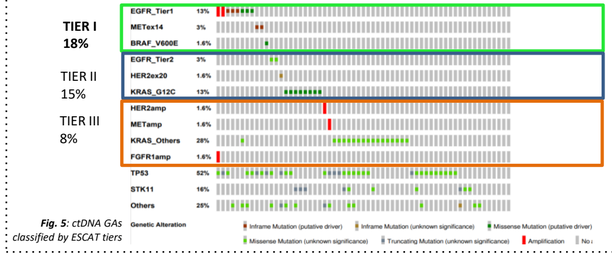


Fig. 5*: ctDNA GAs classified by ESCAT tiers*

Clinical utility

TURNAROUND TIME

- The median **turnaround time** of liquid biopsy was 10 calendar days (range 6-14) from blood draw to report delivery (5 days from lab receipt to report)
- The median time of tissue molecular report was 13 days (9-21), since day of test request to report

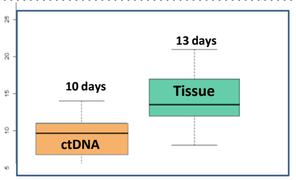


Fig. 6: *Turnaround time of ctDNA & tissue molecular result*

TISSUE-BLOOD CONCORDANCE

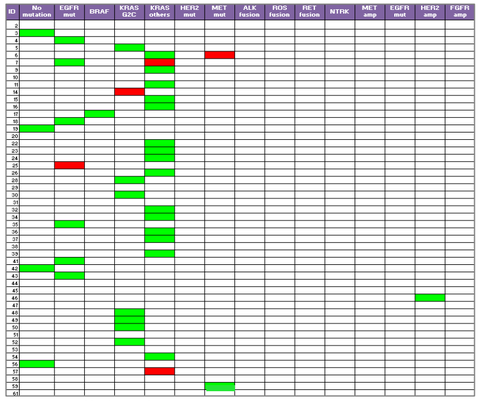


Fig. 7: *Tissue-blood concordance*

- The **concordance** between tissue/liquid biopsy NGS was assessed in 54 cases

→ Regarding the main GAs, the tissue/liquid concordance was:

- ***EGFR***: 86% (6/7)
- ***MET***: 67% (2/3)
- ***BRAFV600E***: 100% (1/1)
- ***KRAS G12C***: 86% (7/8)
- ***KRAS non-G12C***: 88% (15/17)

Concordant

Not-concordant

* Tissue-blood concordance is calculated in patients with tissue NGS and just for the genes detected with both Oncomine™ and InVisionFirst® - Lung

** For patient 25, *EGFR* was only detected in liquid bioppsy Patient 14, *KRAS* G12C was detected in blood and G13C in tissue

ctDNA GAs FOR GUIDING TREATMENT SELECTION IN 1st LINE

- A total of **10 patients (15%)** were treated with targeted therapy
- The median time from report to treatment beginning was 3 days (range 2-17)

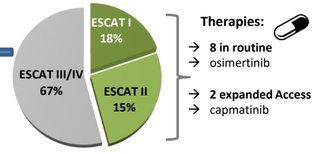


Fig. 8: *Prescription of targeted terapies by ESCAT tiers*

CONCLUSIONS

- **Real-time ctDNA NGS is feasible for routine clinical care in unselected patients with newly diagnosed advanced non-small cell lung cancer**
- **In our cohort, ctDNA NGS could guide treatment selections in 33% of the cases *(ESCAT tier I-II)* in clinical routine and/or clinical trials.**