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Clinical utility of ctDNA genomic alterations (GA) based on ESMO scale for clinical actionability of molecular targets (ESCAT) in advanced NSCLC

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DISCLOSURE INFORMATION

Laura Mezquita

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Background

- Guidelines advocate **molecular profiling in advanced NSCLC**; circulating tumor DNA (ctDNA)-based profiling can be an option for patients with insufficient tissue
- **Next generation sequencing** (NGS) **ctDNA** can identify a wide spectrum of genomic alterations (GAs) to support treatment selection
- **ESMO scale** for clinical actionability of molecular targets **(ESCAT)** classified these GAs:

	Ready for routine use	Investigational	Hypothetical target	Combination development	
ESCAT evidence tier	I: Alteration-drug match is associated with improved outcome in clinical trials	II: alteration-drug match is associated with antitumour activity, but magnitude of benefit is unknown	III: alteration-drug match suspected to improve outcome based on clinical trial data in other tumour type(s) or with similar molecular alteration IV: pre-clinical evidence of actionability	V: alteration-drug match is associated with objective response, but without clinically meaningful benefit	X: lack of evidence for actionability

- **AIM: Clinical utility** of ctDNA GAs according to the **ESCAT tiers** in a prospective cohort of advanced NSCLC patients

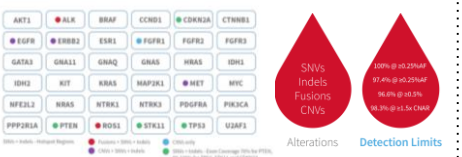
Remon J, JCO PO 2019
Mateo J, Ann Oncol 2018

Methods

319 advanced NSCLC patients prospectively enrolled between Nov. 2015 and May 2019 in the Liquid Biopsy Program* in Gustave Roussy (NCT02666612)

- **Blood collection (n=535 samples)**
  - *Treatment-naive, n=115*
  - *Under therapy, n=211*
  - *At progressive disease (PD), n=209*
- **Clinical data were collected**

- **Amplicon-based InVisionFirst®- Lung**



- We evaluated the **detection & clinical utility of GAs on ctDNA** by **ESCAT tiers**

ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)

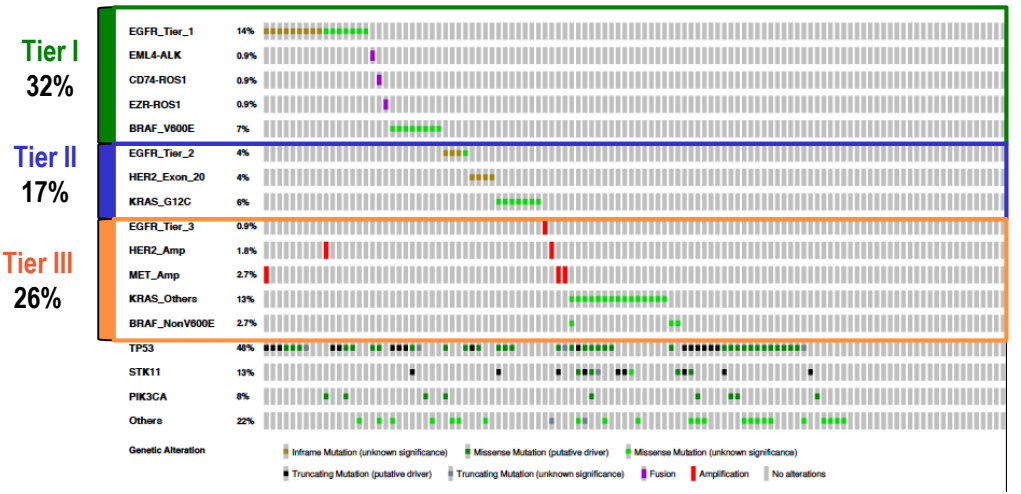
ESCAT evidence tier	Ready for routine use	Investigational	Hypothetical target	Combination development	
	Tier I. *EGFR ex19/21* *ALK* *ROS1* *BRAF^{V600E}* *MET ex14*	***Tier II.*** *EGFR ex20* *HER2ex20* *KRAS^{G12C}*	***Tier III.*** *HER2^{amp}* *MET^{amp}* *KRAS^{others}* *BRAF^{non_V600E}* *FGFR1^{amp}*	V: alteration-drug match is associated with objective response, but without clinically meaningful benefit	X: lack of evidence for actionability

Plagnol V, PLoS ONE 2018
Pritchett, D., JCO PO 2019
Remon J, JCO PO 2019
Mateo J, Ann Oncol 2018

ctDNA: **treatment-naïve** advanced NSCLC

Baseline characteristics, All NSCLC	N=112 (%)
Age, median (range)	67 (39-90)
Sex	
Female	60 (54%)
Male	52 (46%)
Smoking status	
Non-smoker	38 (34%)
Smoker	73 (66%)
Missing	1
Molecular testing (tissue)	
NGS	66 (59%)
Other	20 (28%)
Not specified	16 (14%)

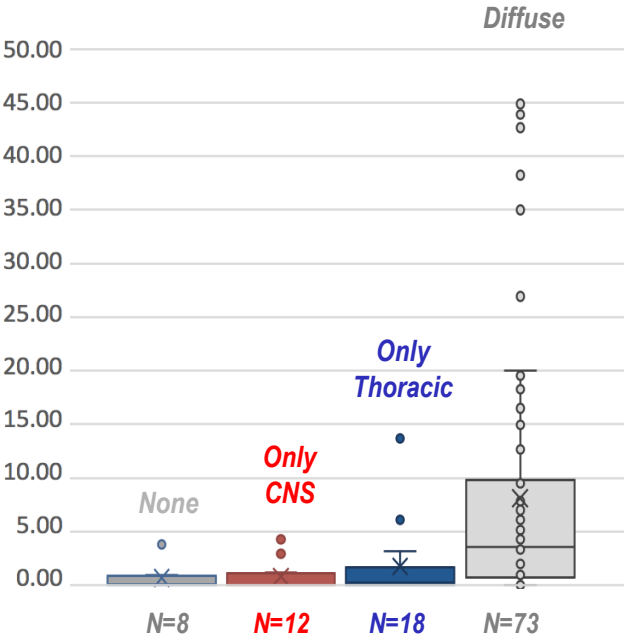
- N= 115 samples in naïve patients (112 analyzed)
- **79%: ≥1 ctDNA GA** (88/112)
- **56%: ctDNA clinically** informative results (63/112)



ctDNA GAs: **metastatic pattern**

- **1.09%**: median ctDNA allele fraction (AF) *(range 0.01% - 44.88%)*

- ***ctDNA AF by metastatic sites:***
  - ✓ None (stage III): **0.06%** (0.01% – 3.78%)
  - ✓ **Only CNS**: **0.01%** (0.01% – 4.3%)
  - ✓ **Only thoracic**: **0.33%** (0.01% – 13.71 %)
  - ✓ **Diffuse***: **3.7%** (0.01% – 44.88%)

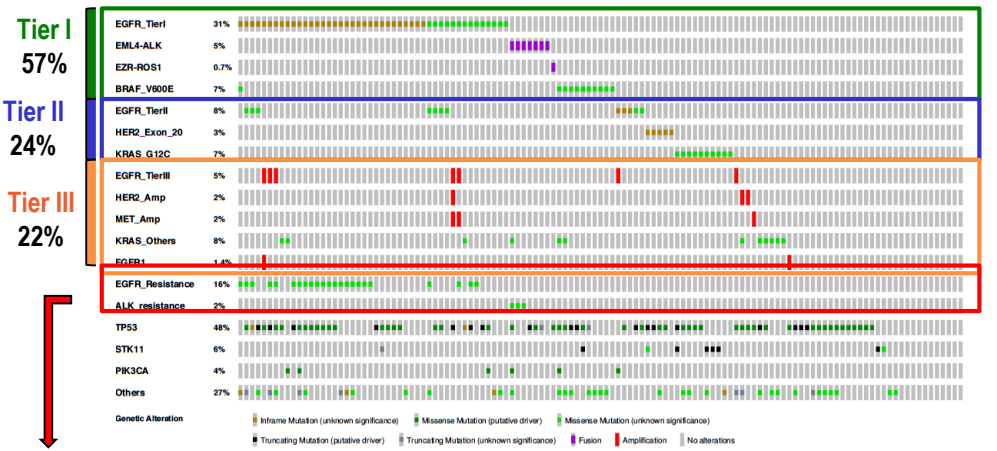


* >2 metastatic sites: diffuse pattern

ctDNA: advanced NSCLC **at PD**

Baseline characteristics	N=147 (%)
Age, median (range)	63 (27-93)
Sex	
Female	88 (60%)
Male	59 (40%)
Smoking status	
Non-smoker	68 (46%)
Smoker	77 (54%)
Missing	2
Molecular testing (tissue)	
NGS	65 (44 %)
Other	21 (14%)
Not specified	61 (42%)

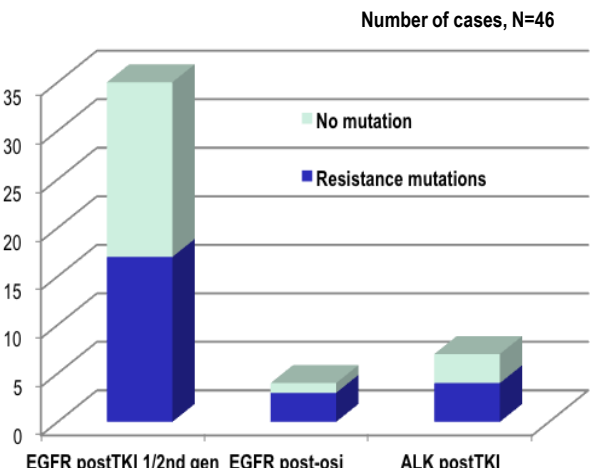
- N= 147 samples from patients at PD
- **76%: ≥1 ctDNA GA** (112/147)
- **64%: ctDNA clinically** informative results (94/147)



Acquired Resistance mutations in previously TKI-pretreated patients

ctDNA: **TKI-failure**

- **Overall TKI pretreated population**
  - ctDNA clinically informative: **52%** (24/46)
- **In EGFR cases**
  - **49% *T790M*** at TKI-failure* (17/35)
  - **75% *C797S*** at osimertinib-failure (3/4)
- **In ALK cases**
  - **57% *ALK* mutations** at TKI-failure (4/7)



* *1st/2nd generation TKI*

TAKE HOME MESSAGES

- NGS-ctDNA demonstrated clinically informative results for **56% in treatment-naïve** advanced NSCLC patients; and for **64% at progressive disease**
- **In treatment-naïve population**, ctDNA detected:
  - ✓ **31% ESCAT tier I,** directing targeted therapies in routine
  - ✓ **17% ESCAT tier II, 26% ESCAT III**, directing investigational targeted therapies in clinical trials
- In ***EGFR/ALK*** **population at time of relapse to TKI**, ctDNA demonstrated:
  - ✓ **52% clinically informative** results assessing resistance
- This study is still ongoing (N=932 samples)

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