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PROSPECTIVE COMPARISON OF LIQUID BIOPSY TO STANDARD OF CARE TISSUE TESTING IN METASTATIC, NON-SQUAMOUS, NSCLC PATIENTS
SPANISH LUNG LIQUID VS. INVASIVE BIOPSY PROGRAM
THE SLLIP STUDY

Ramon Palmero[1], Alvaro Taus[2], Margarita Majem[3], Santiago Viteri[4], Enric Carcereny[5], Javier Garde[6,7], Enriqueta Felip[8], Crystal Cassidy[9], Daniel Dix[9], Niki Karachaliou[4,10], Rafael Rosell[5,4,10]

[1]Catalan Institute of Oncology, Hospitalet, Spain; [2]del Mar Hospital, Barcelona, Spain; [3]Santa Creu i Sant Pau Hospital, Barcelona, Spain; [4]Institute of Oncology Rosell (IOR), Dexeus University Hospital Quiron Salud Group, Barcelona, Spain; [5]Catalan Institute of Oncology, Germans Trias i Pujol Health Sciences Institute and Hospital, Badalona, Spain; [6]Arnau de Vilanova University Hospital, Valencia, Spain; [7]Medica Scientia Innovation Research – MEDSIR, Barcelona, Spain; [8]Vall d'Hebrón University Hospital, Barcelona, Spain; [9]Guardant Health Inc., Redwood City, USA; [10]Pangaea Oncology, Dexeus University Hospital Quiron Salud Group, Barcelona, Spain.

BACKGROUND

Targeted therapy improves clinical outcomes in patients with advanced NSCLC harboring specific genetic alterations[1].

Guidelines recommend tissue-based assessment of biomarkers[2]. This approach may be sometimes difficult due to insufficient or low quality tissue[2]. An alternative approach is to assess somatic mutations in circulating cell-free tumor DNA (cfDNA)[3, 4].

The aim of this study is to demonstrate that cfDNA has performance comparable to that of tissue-based genotyping for the task of detecting clinically actionable tumor biomarkers in patients with newly diagnosed metastatic non-squamous NSCLC.

OBJECTIVES

Primary objective:

- To investigate cfDNA-based versus tissue based genotyping as it pertains to the detection of clinically actionable biomarkers in first line, treatment naïve, metastatic non-squamous NSCLC.

Secondary objectives:

- To estimate the following parameters:

1. *Turn Around Time* for both cfDNA and tissue methods.
2. *Time to treatment initiation.*
3. *Quantity not sufficient rate* (QNS) of tissue for clinically-actionable biomarker testing, and liquid biopsy rescue rate of QNS tissue samples.
4. *Tumor Not Detected (TND) rate* of cfDNA in blood.
5. *Sensitivity, specificity and diagnostic accuracy* of all other identified biomarkers on the Guardant360 panel.
6. *Rate of response* for patients who are actionable biomarker positive (either in cfDNA or tissue) and are treated with targeted therapies according investigator criteria.
7. *Discovery rate* of genomic-mediated, acquired resistance to targeted therapies in the biomarker-positive subsets.

Fig. 1: SLIPP study overview and calendar scheme

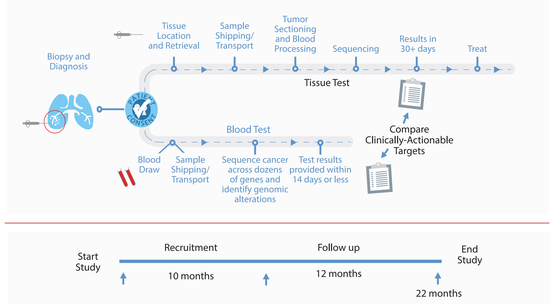

Fig. 2: Genomic alterations covered by Guardant360

Point Mutations - 73 Genes

AKT1	ALK	**APC**	**AR**	ARAF	ARID1A	ATM	**BRAF**	**BRCA1**	**BRCA2**
CCND1	CCND2	CCNE1	CDH1	CDK4	CDK6	CDKN2A	CTNNB1	DDR2	**EGFR**
ERBB2 (HER2)	ESR1	EZH2	FBXW7	FGFR1	FGFR2	FGFR3	GATA3	GNA11	GNAQ
GNAS	HNF1A	HRAS	IDH1	IDH2	JAK2	JAK3	**KIT**	**KRAS**	MAP2K1 (MEK1)
MAP2K2 (MEK2)	**MAPK1 (ERK2)**	**MAPK3 (ERK1)**	**MET**	MLH1	MPL	MTOR	**MYC**	NF1	NFE2L2
NOTCH1	NPM1	**NRAS**	NTRK1	NTRK3	PDGFRA	**PIK3CA**	PTEN	PTPN11	RAF1
RB1	RET	RHEB	RHOA	RIT1	ROS1	SMAD4	SMO	**STK11**	TERT**
TP53	TSC1	VHL							

**Includes TERT promoter region

Indels - 23 Genes

ATM	APC	ARID1A	BRCA1	BRCA2	CDH1	CDKN2A	EGFR	ERBB2	GATA3
KIT	MET ex14	MLH1	MTOR	NF1	PDGFRA	PTEN	RB1	SMAD4	STK11
TP53	TSC1	VHL							

Amplifications - 18 Genes

AR	BRAF	CCND1	CCND2	CCNE1	CDK4	CDK6	EGFR	ERBB2
FGFR1	FGFR2	KIT	KRAS	MET	MYC	PDGFRA	PIK3CA	RAF1

Fusions - 6 Genes

ALK	FGFR2	FGFR3	RET	ROS1	NTRK1

TRIAL DESIGN

Table 1: Eligibility criteria

Inclusion Criteria:	Exclusion Criteria:
1. Patients with biopsy-proven, metastatic, previously untreated, nonsquamous NSCLC. Patients may have received adjuvant cytotoxic chemotherapy, but not targeted neo-adjuvant or adjuvant therapy.	1. Any concurrent, non-cutaneous, malignancy (with the exception of early stage non-invasive cervical cancer). Any prior cancer must have occurred more than 5 years prior with no evidence of currently active disease.
2. Age ≥ 18 years.	2. Pregnancy
3. Ability to provide written informed consent.	
4. Willingness to provide blood sample at three time points.	
5. Standard-of-care tissue genotyping ordered.	

- This is a Spanish multi-center, prospective, single-cohort study.
- Peripheral blood (20 mL) is collected in Streck™ cell preservation tubes for cfDNA sequencing prior to treatment initiation.
- Additional blood is collected two weeks after treatment initiation and at disease progression (or at 12 months if no progression).
- cfDNA sequencing is performed using Guardant360, Guardant Health Inc., Redwood City USA.
- Tumor tissue testing for genetic alterations is performed according to local standard of care.
- Treatment decisions are made according to local standard of care.
- Archived pre-treatment tissue samples (if available) are sent to an external central laboratory (Pangaea Oncology S.A.).
- Tumor response is assessed centrally per RECIST v1.1

STATISTICAL DESIGN

The sample size for the study is 182 patients. This number gives a 65% probability (under reasonable hypotheses) that the observed detection rate (sensitivity x prevalence) for the liquid assay will be no more than 2% lower than the corresponding detection rate for the tissue test.

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