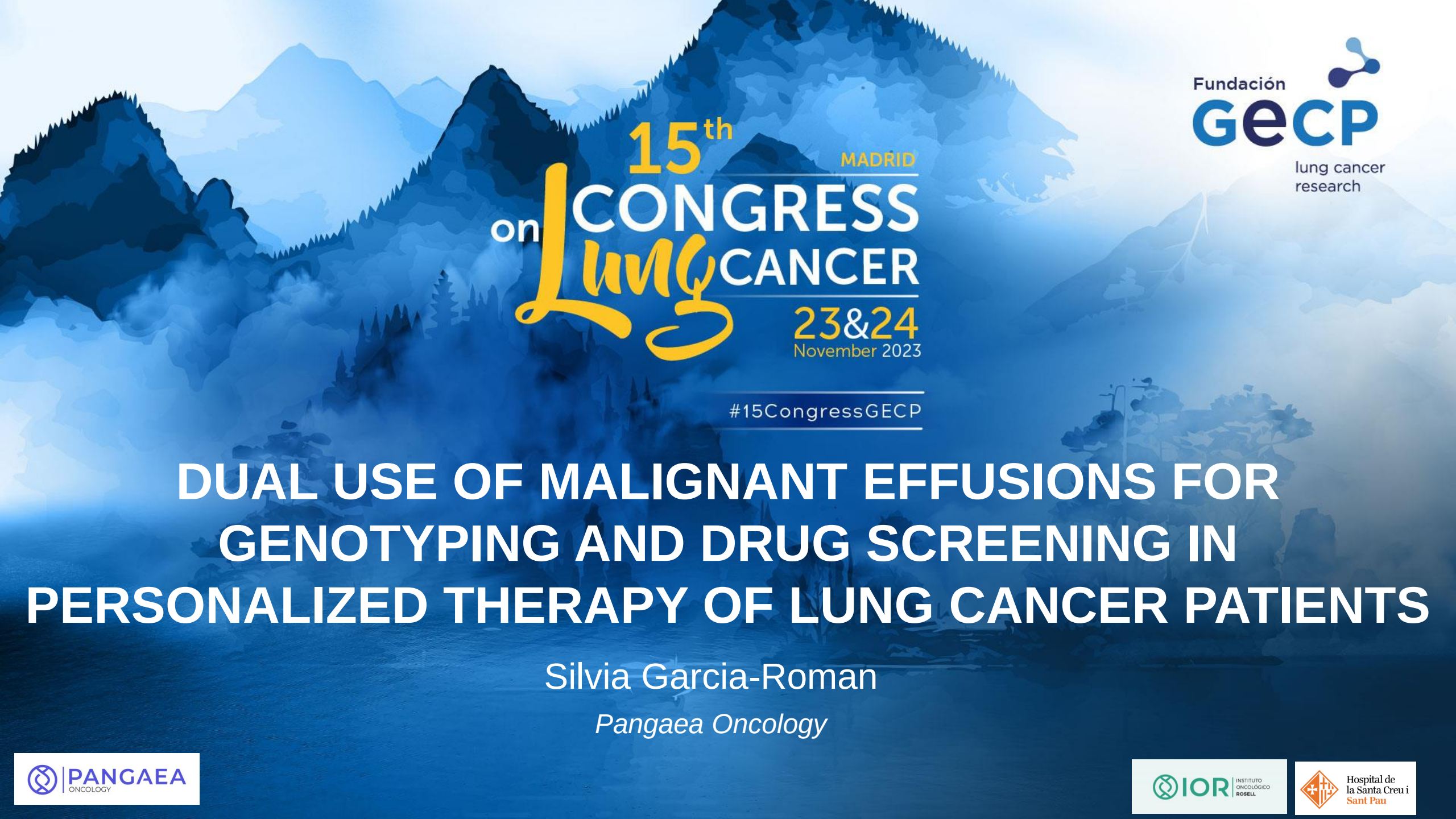

DUAL USE OF MALIGNANT EFFUSIONS FOR GENOTYPING AND DRUG SCREENING IN PERSONALIZED THERAPY OF LUNG CANCER PATIENTS

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DISCLOSURES

I do not have any financial relationships to disclose

BACKGROUND

Malignant effusions (ME's) are a **good source** for **genetic testing** in lung cancer patients

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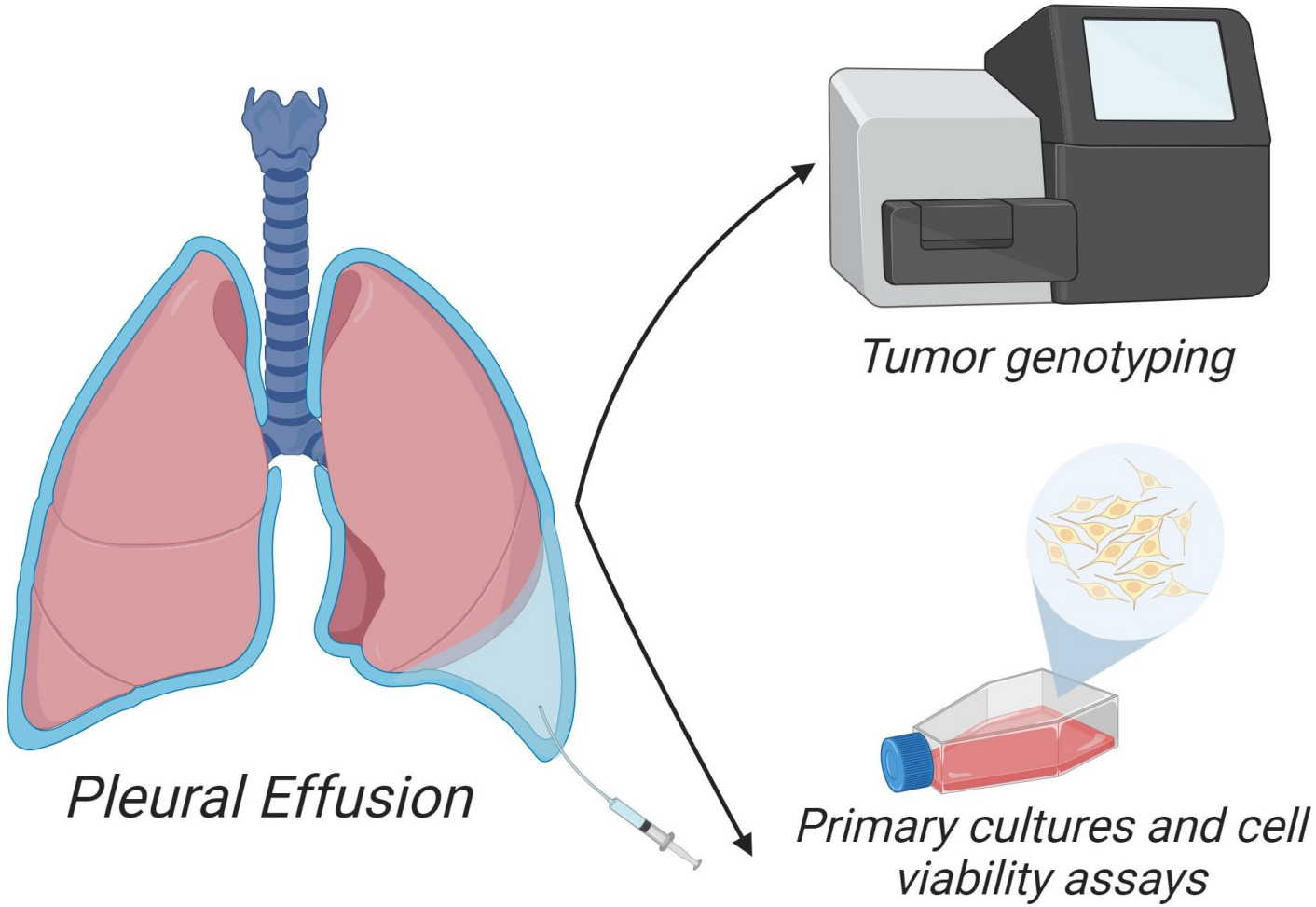
Results from **MEs** could be used for treatment **decision**

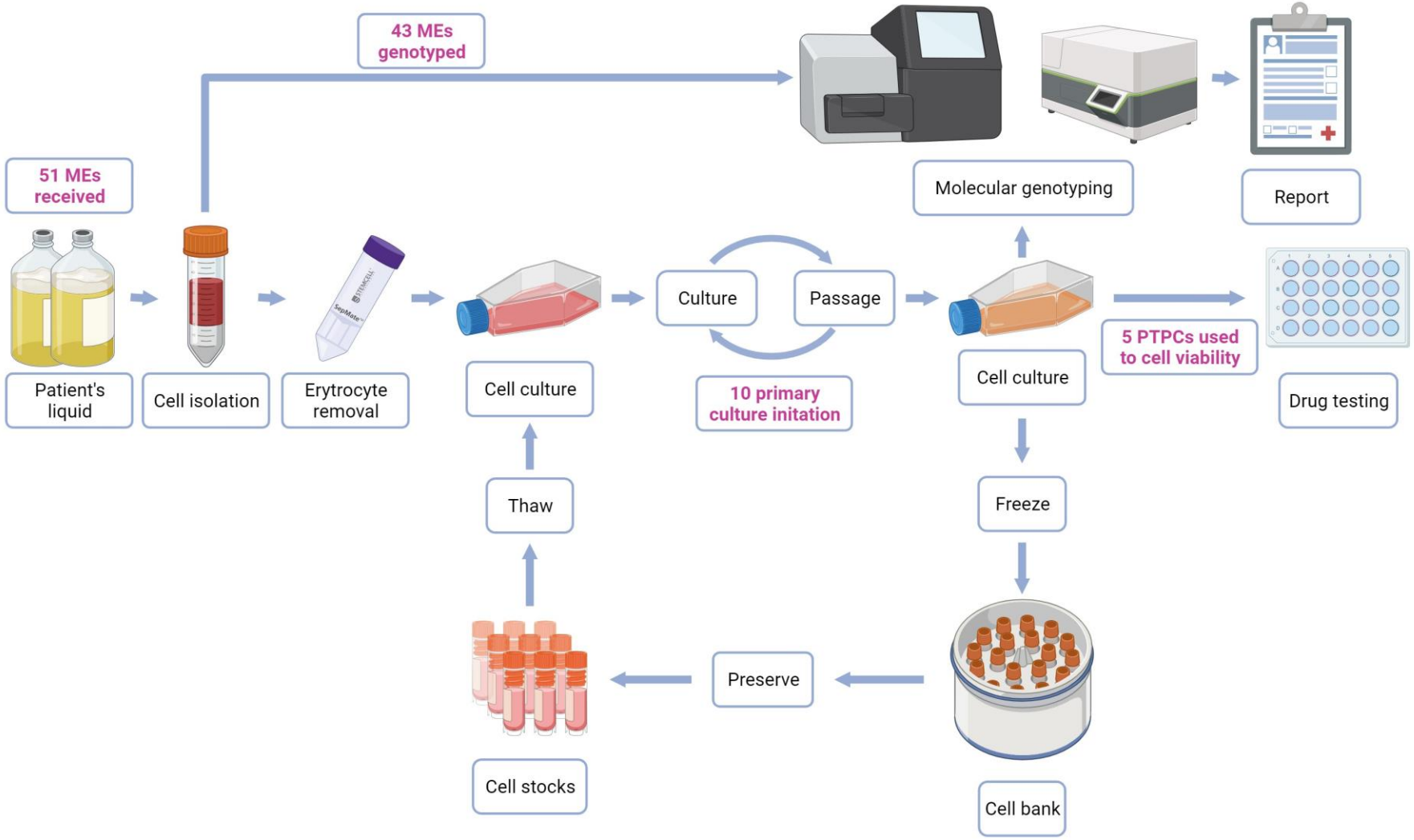


OBJECTIVES

- Incorporate MEs collection into the routine clinical practice for:
  - Determination of relevant genetic alterations
  - Initiation of primary cultures and cell viability assays with anticancer drugs

METHODS

Volumes of MEs ranged from 5 to 5,000 mL



PTPCs: Pure Tumor Primary Cultures

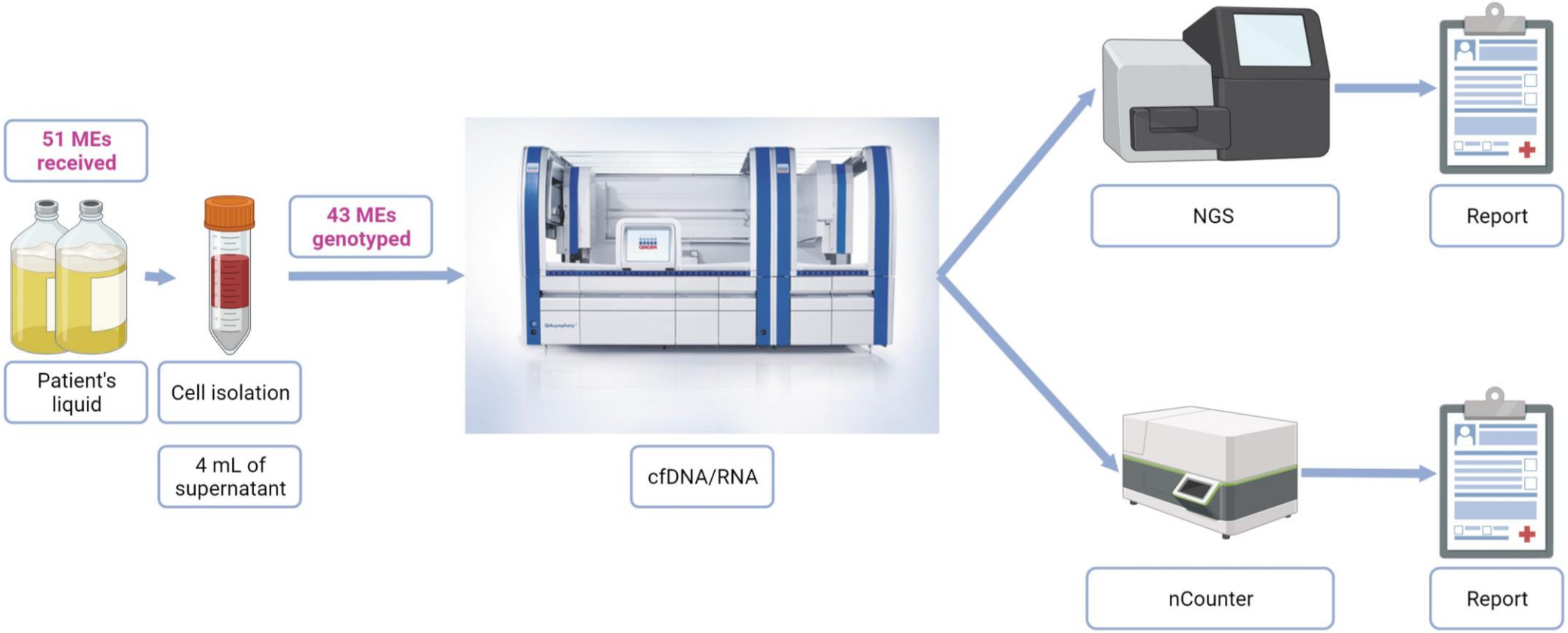
Data cut off May 2023

CHARACTERISTICS OF THE MEs GENOTYPED AND CULTURED

Fluid Characteristics	Total of samples n=43	PTPCs n=10
Type of fluid		
Pleural effusion (MPE)	40 (93 %)	10 (100.0 %)
Ascites	3 (7 %)	0 (0.0 %)
Cytology (presence of tumor cells)		
Positive	6 (14.0 %)	3 (30 %)
Negative	0 (0.0 %)	0 (0.0 %)
ND	37 (86.0%)	7 (70.0 %)
Histology		
Adenocarcinoma	42 (97.7 %)	10 (100.0 %)
Squamous Cell Carcinoma	1 (2.3 %)	0 (0.0 %)
Paired blood or FFPE samples		
Yes	10 (23.3 %)	7 (70.0 %)
No	33 (76.7 %)	3 (30 %)
Collection time		
Baseline	17 (39.5 %)	5 (50.0 %)
Progression	17 (39.5 %)	4 (40.0 %)
ND	9 (20.9 %)	1 (10.0 %)
Clinically relevant alterations		
Detected	38 (88.4 %)	9 (90.0 %)
Not detected	5 (11.6 %)	1 (10.0 %)

Data cut off May 2023

MEs GENOTYPING



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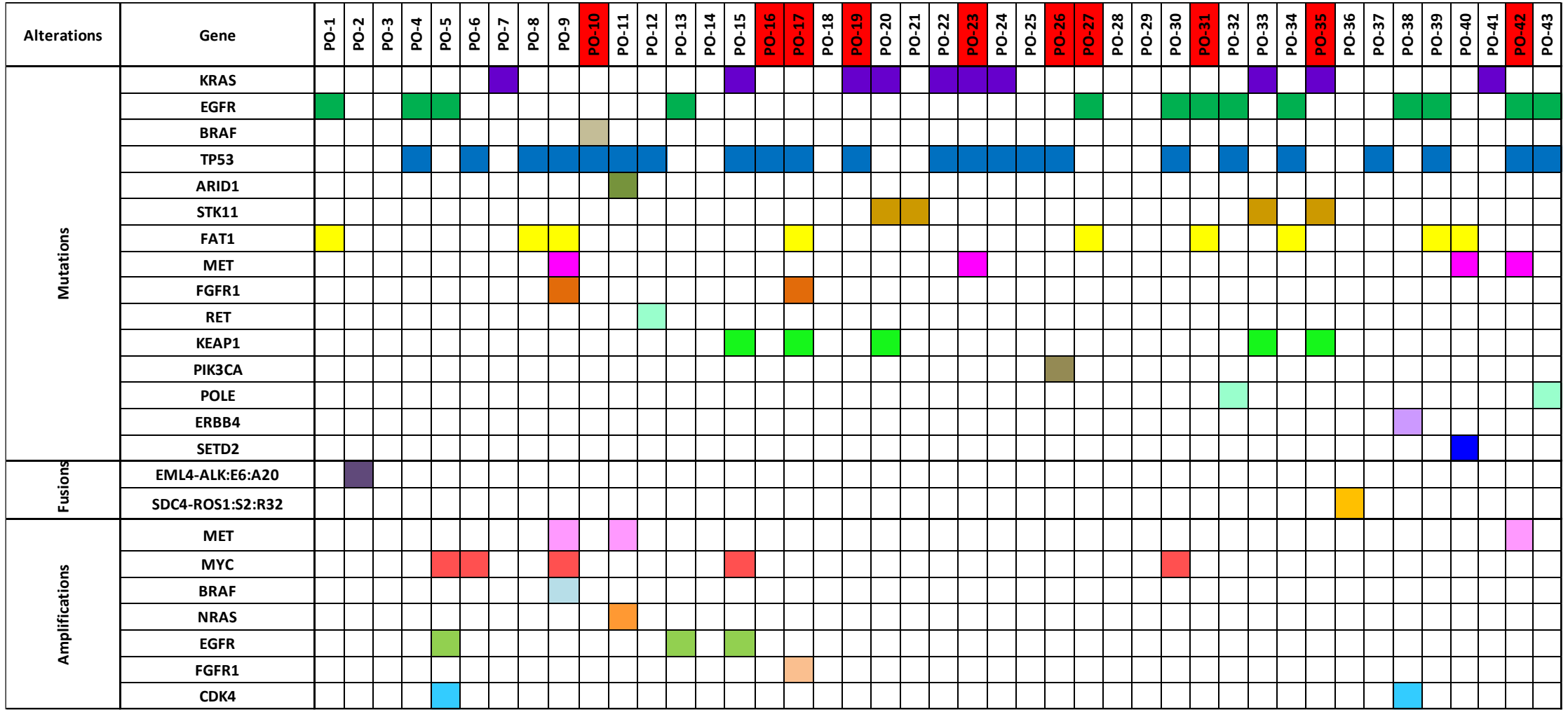
GENOTYPE OF THE MEs (I)

Most common alterations detected, mutations in *TP53* (n=23); *EGFR* (n=13); *KRAS* (n=10)



In red tissue and MEs paired samples

Data cut off May 2023

GENOTYPE OF THE MEs (II)

	Alterations in tissue	Alterations in MEs
PO-10	*BRAF* pV600E; *TP53* c.97-2A>T	*BRAF* pV600E; *TP53* c.97-2A>T
PO-16	TP53 p.G266E	TP53 p.G266E
PO-17	*FAT1 p.D4244E; FGFR1 c.936+86G>C; KEAP1 p.G571V; TP53* p.G266R and p.E68; amp *FGFR1*	*FAT1 p.D4244E; FGFR1 c.936+86G>C; KEAP1 p.G571V; TP53* p.G266R and p.E68; amp *FGFR1*
PO-19	*KRAS* p.G12C; *TP53* p.V157F	*KRAS* p.G12C; *TP53* p.V157F
PO-23	*KRAS* p.G12D; MET p.H1174Y; *TP53* p.G245C	*KRAS* p.G12D; MET p.H1174Y; *TP53* p.G245C
PO-26	*PIK3CA* p.H1047R; *TP53* p.Y163C	*PIK3CA* p.H1047R; *TP53* p.Y163C
PO-27	*EGFR* p.E746_A750del; FAT1 p.G855R; *TP53* p.C176Y	*EGFR* p.E746_A750del; FAT1 p.G855R; *TP53* p.C176Y
PO-31	*EGFR* p.L747_P753delins	*EGFR* p.L747_P753delins
PO-35	*KEAP1 [NM_203500.2:g.10486720_10486721insACTC...]; KRAS* G12A; *STK11* E165*	*KEAP1 [NM_203500.2:g.10486720_10486721insACTC...]; KRAS* G12A; *STK11* E165*
PO-42	*EGFR* p.E746_A750del; MET p.D1228N; *TP53* p.C135Y; amp *MET*	*EGFR* p.E746_A750del; MET p.D1228N; *TP53* p.C135Y; amp *MET*

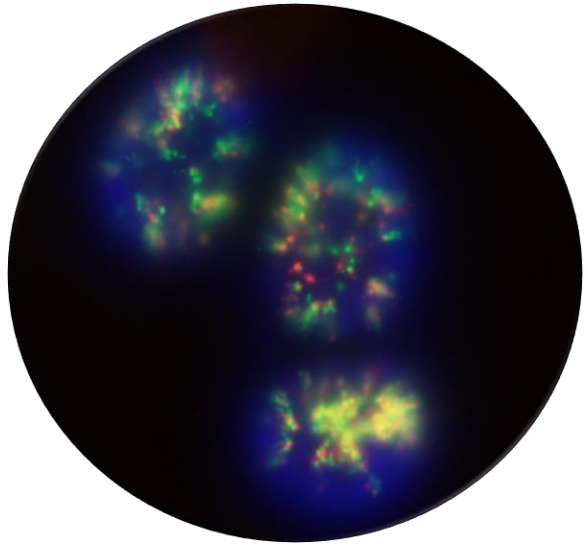
Paired tissue and MEs samples ⟶ 100% concordance

Data cut off May 2023

CONCORDANT RESULTS OF PAIRED ME AND PTPC SAMPLES: CASE PO-6

Patient PO-6: Female, 59 y.o, smoker, diagnosed with stage IIIA. Tumor biopsy was not possible. Pleural effusion was collected. PTPC and supernatant were genotyped by NGS showing in both cases a *TP53* mutation and copy number gain in *MYC* (A, B). Additionally, FISH using ZytoLight® SPEC MYC Dual Color Break Apart Probe was performed in viable tumoral cells, further confirming copy number gain of *MYC* gene (C).

C



A

Biomarker	Alteration	Function	Impact	Case - Quantity
MYC E cT R 2C Pathogenic	amplification	gain	-	57.92 copies
TP53 E cT 2C Pathogenic	c.216delC p.V73fs*50	loss	Frameshift	85% (of 170 reads)

PTPC

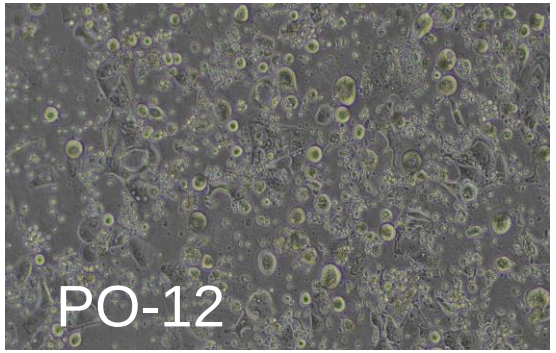
B

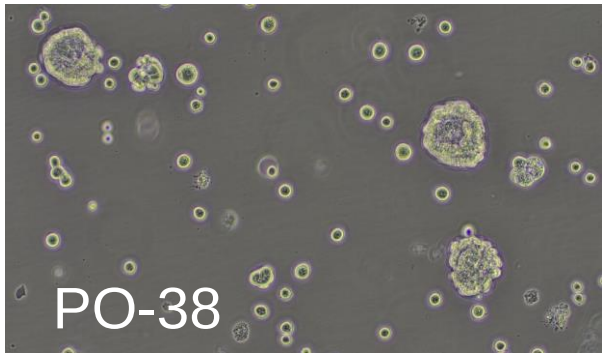
Biomarker	Alteration	Function	Impact	Case - Quantity
MYC E cT R 2C Pathogenic	amplification	gain	-	32.70 copies
TP53 E cT 2C Pathogenic	c.216delC p.V73fs*50	loss	Frameshift	86% (of 1057 reads)

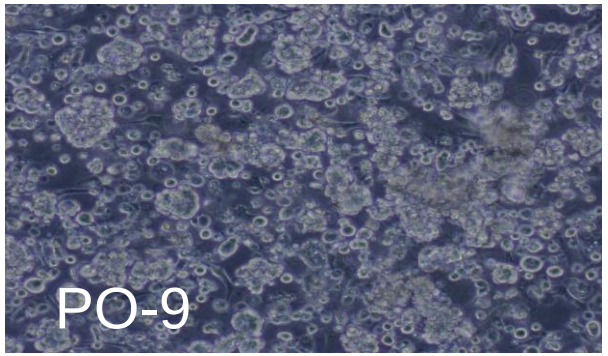
Fluid supernatant

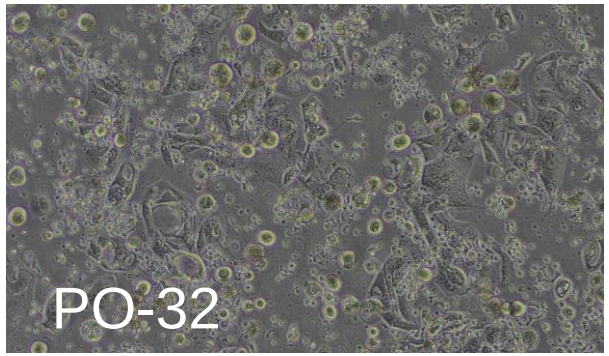
PTPCs

Sample	Fluid	Primary tumor	Basal/Progression	Treatment progression	Alterations
PO-12	Pleural	Lung ADC	Basal		*MET* polisomy
PO-38	Pleural	Lung ADC	Basal		*EGFR* p.S768_D770dup
PO-9	Pleural	Lung ADC	Progression	Tepotinib	*MET* amp *MET* p.D1228N/H and p.Y1230H
PO-11	Pleural	Lung ADC	Progression	Tepotinib	*MET* amp; *NRAS* amp
PO-32	Pleural	Lung ADC	Progression	Osimertinib	*EGFR* p.L858R





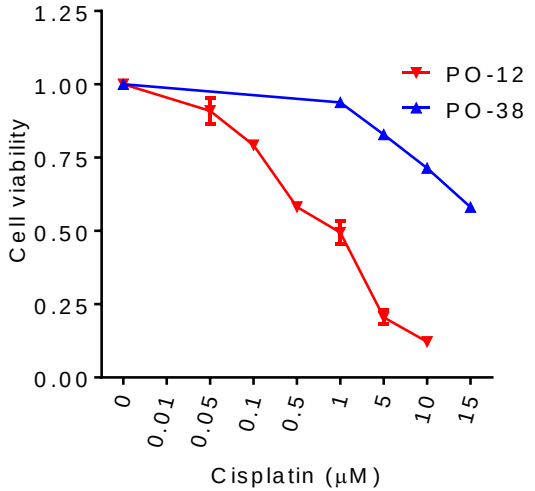


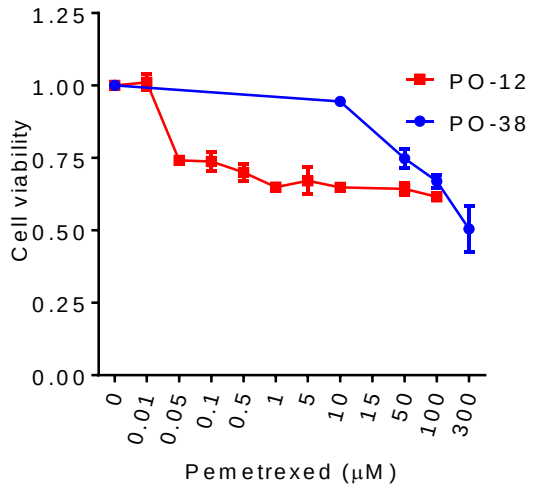


RESPONSE TO ANTITUMOR DRUGS OF PTPCs

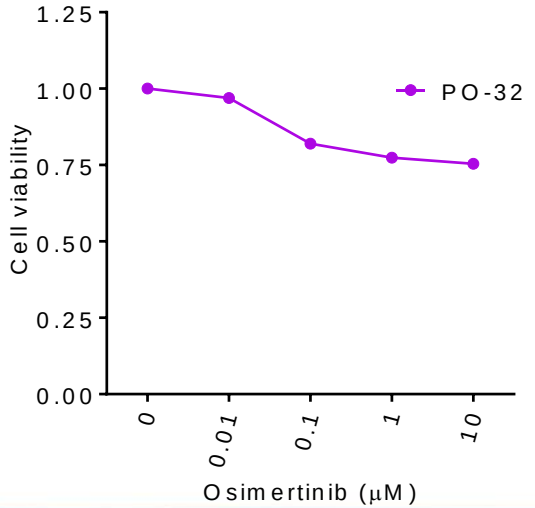
Sample	IC_{50} (µM)	Maximum plasmatic concentration (µM)
PO-12	0.8 (cisplatin) > 300.0 (pemetrexed)	14.4 306.0
PO-38	15.0 (cisplatin) 300.0 (pemetrexed)	14.4 306.0
PO-9	4.7 (tepotinib)	0.9
PO-11	4.5 (tepotinib)	0.9
PO-32	> 10 (osimertinib)	0.2

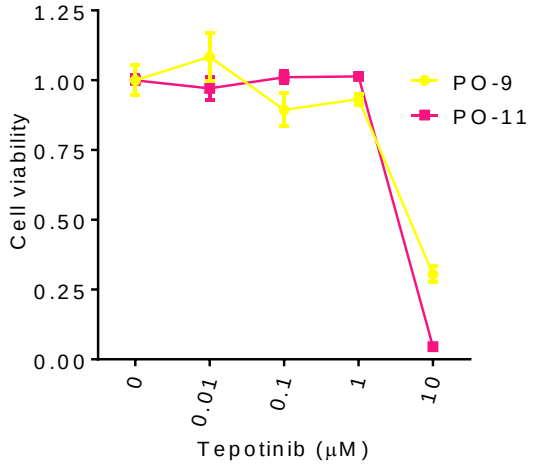
Baseline PTPCs treated with chemotherapeutic agents



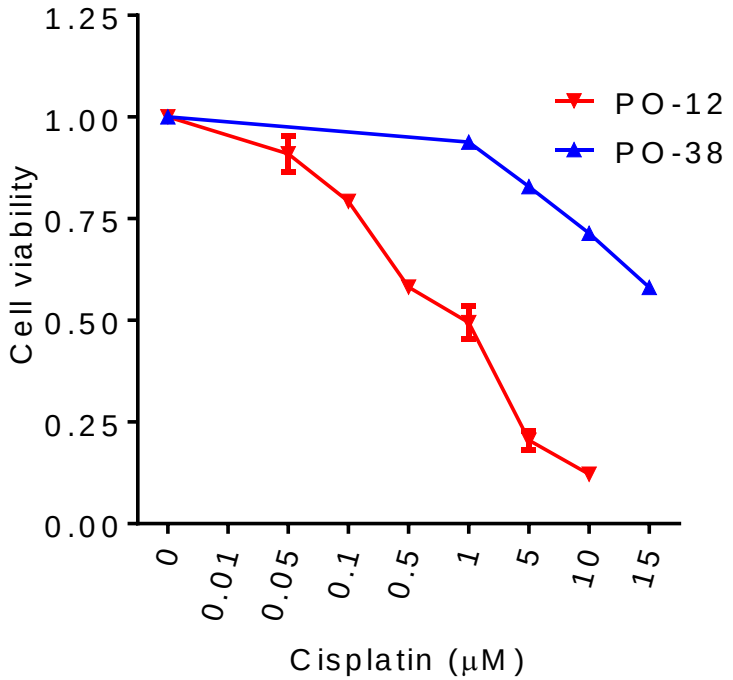


PTPCs at progression treated with targeted therapies





PTPCs AS A POSSIBLE TOOL IN TREATMENT SELECTION (I)

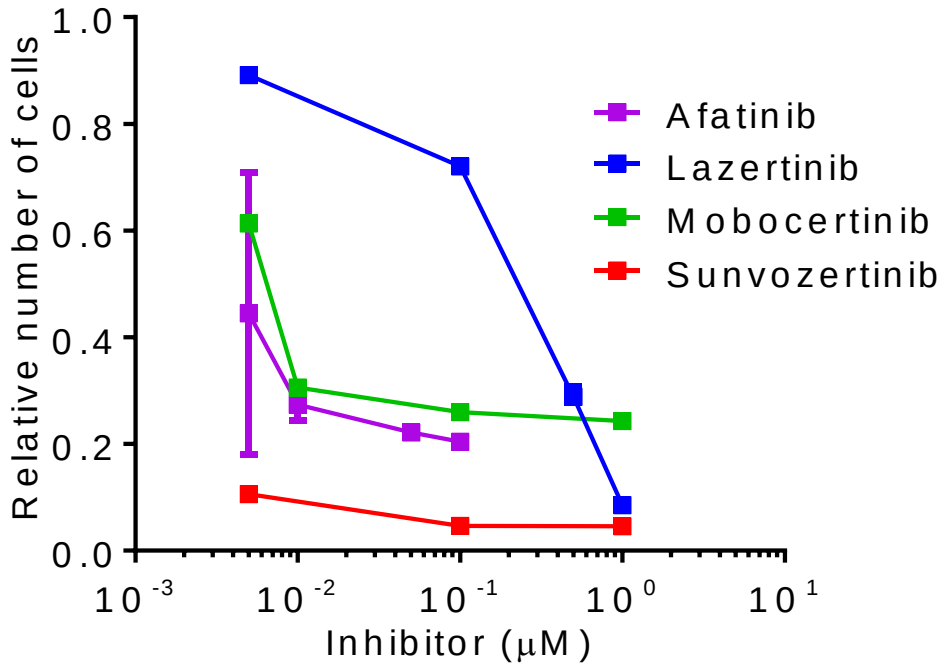


Patient PO-12, partial response to platin-based chemotherapy

Patient PO-38, stable disease to platin-based chemotherapy

PTPCs AS A POSSIBLE TOOL IN TREATMENT SELECTION (II)

Patient PO-38: Female, 67 y/o, non-smoker, diagnosed with stage IV NSCLC. Pleural effusion was genotyped and cultured showing *EGFR* p.S768_D770dup and CDK4 amplification.



	IC_{50} (μM)
Afatinib	< 0.005
Lazertinib	0.300
Mobocertinib	0.007
Sunvozertinib	< 0.005

CONCLUSIONS

MEs can be prospective collected in the clinical setting and used for a **dual purpose:**

- **Genotyping**
- **Culturing** and cell viability assays

Drug testing in primary cultures could be of help in **treatment selection**

15th CONGRESS on Lung CANCER

MADRID

23&24 November 2023

#15CongressGECP

Fundación GECP lung cancer research

Muchas Gracias

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