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DLL3-based Enrichment Enables Sensitive and Specific Detection of Circulating Tumor Cells During Immunotherapy in Small-Cell Lung Cancer

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Disclosure

- The author declares no conflicts of interest.

Disclosure

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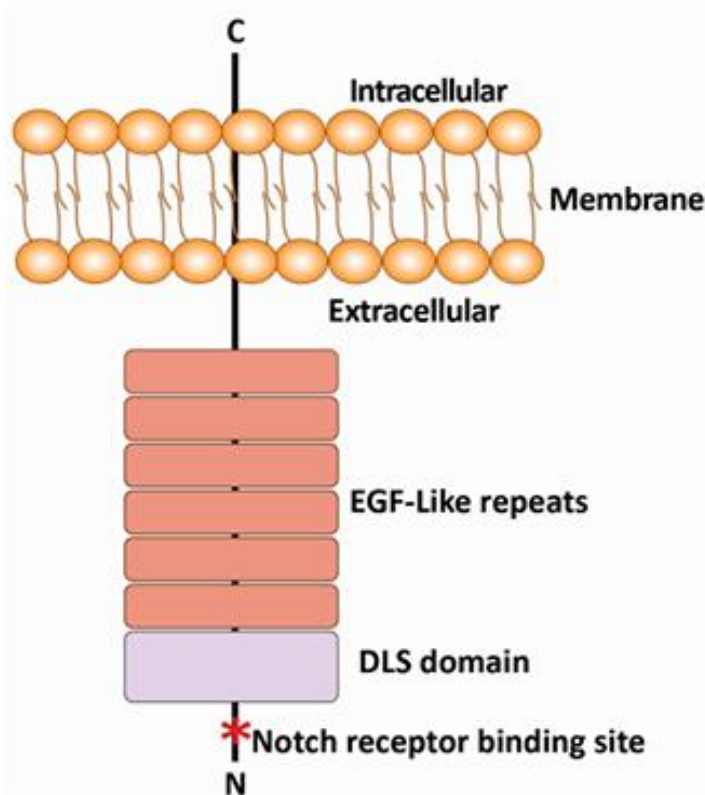
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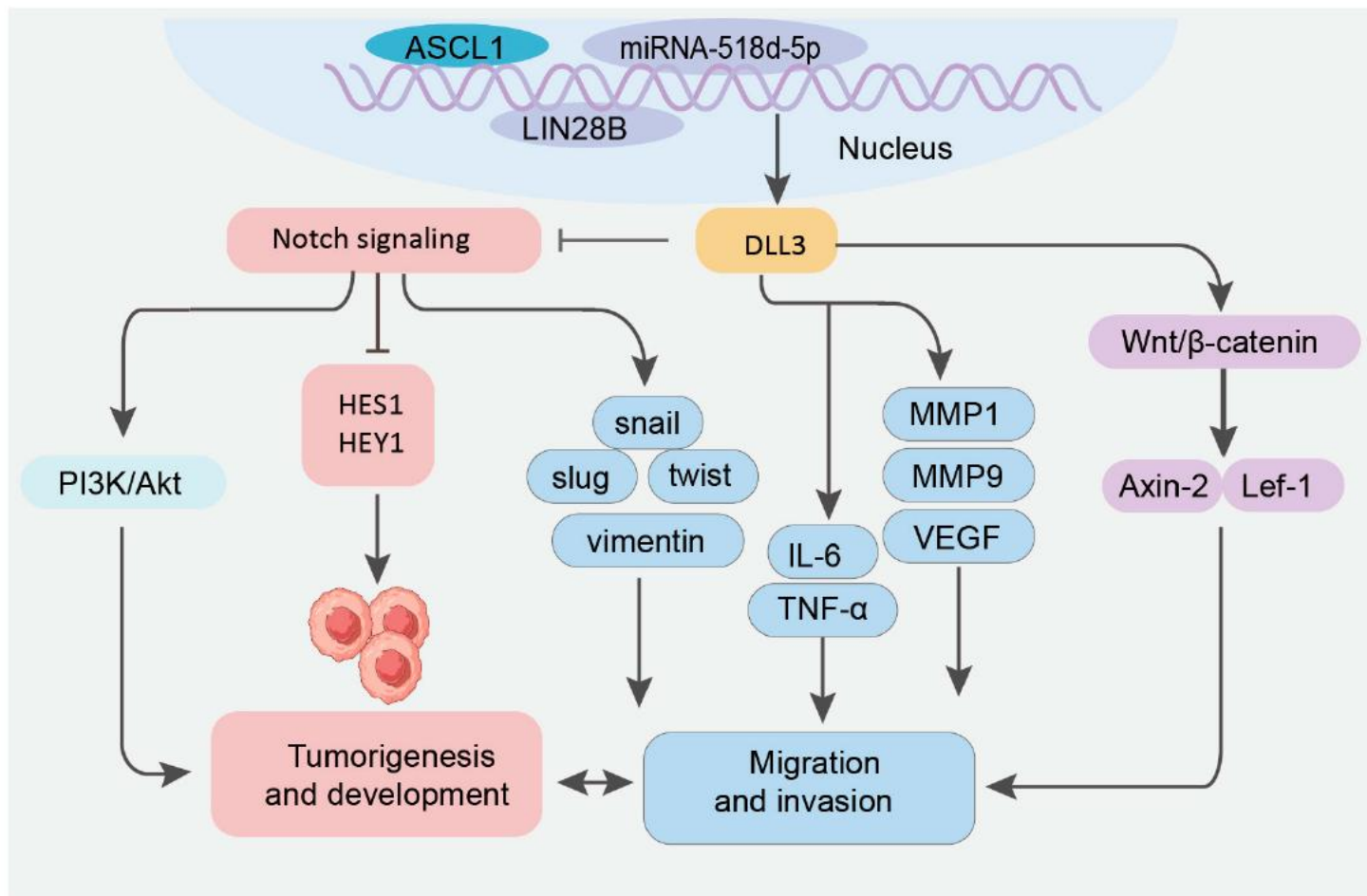
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Introduction

Structure of DLL3

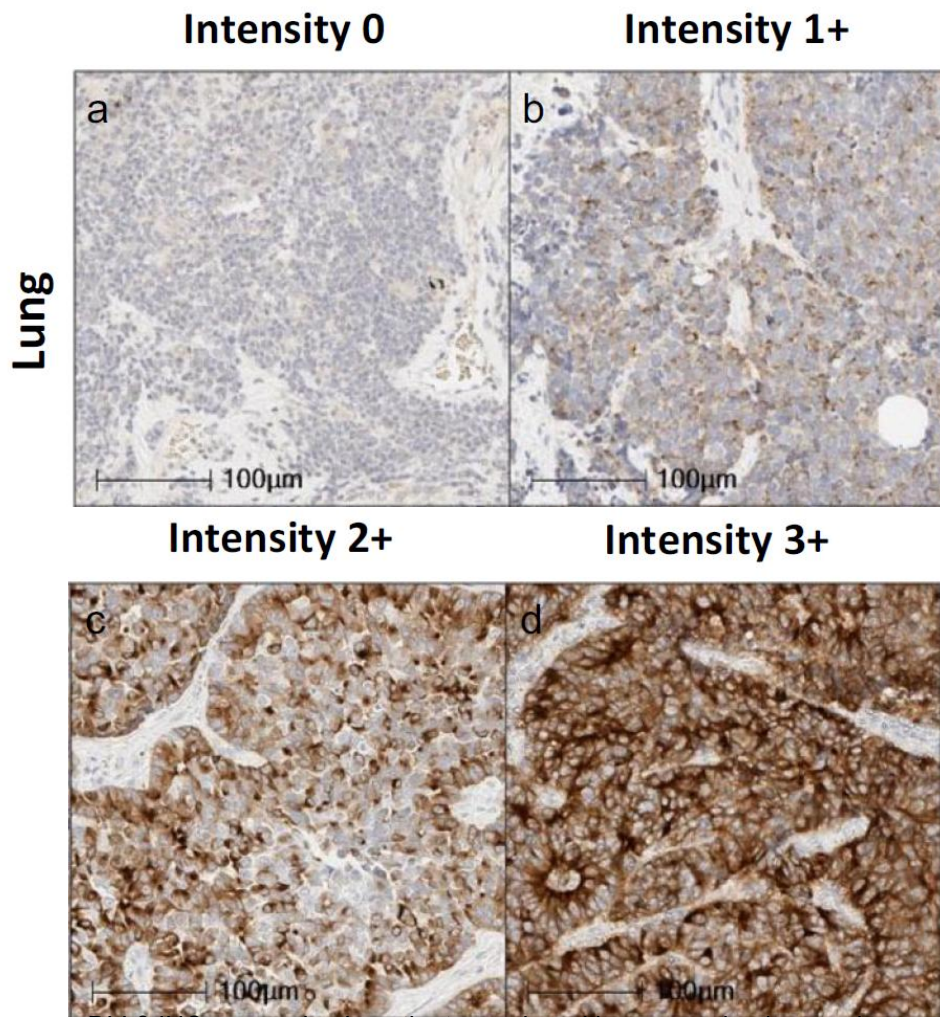


Regulatory network of DLL3 in cellular signaling

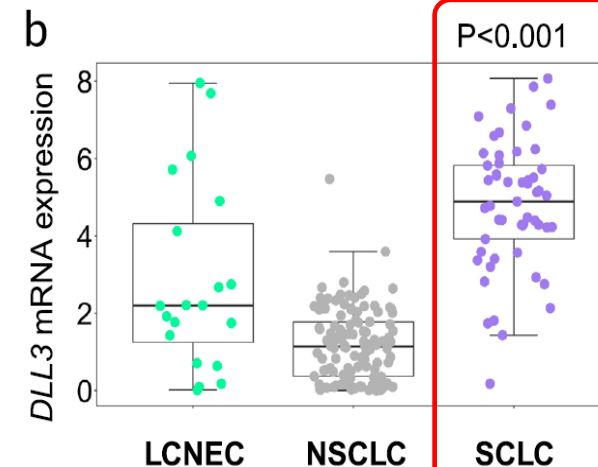
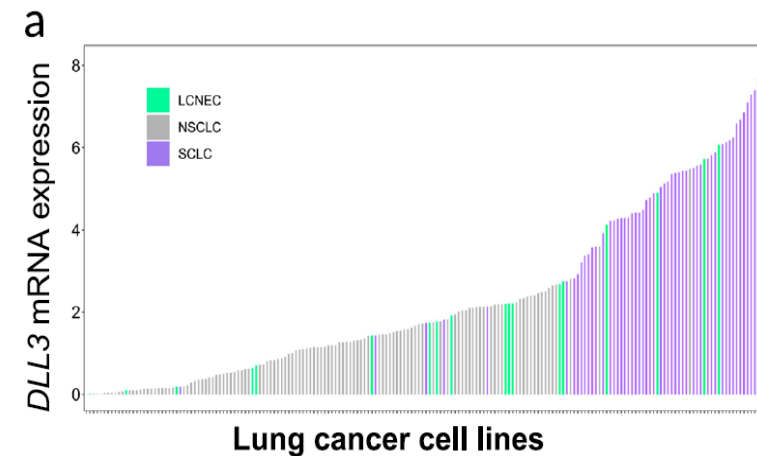


Introduction

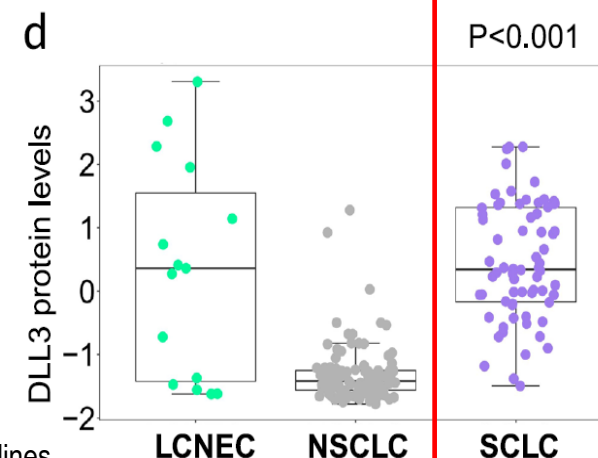
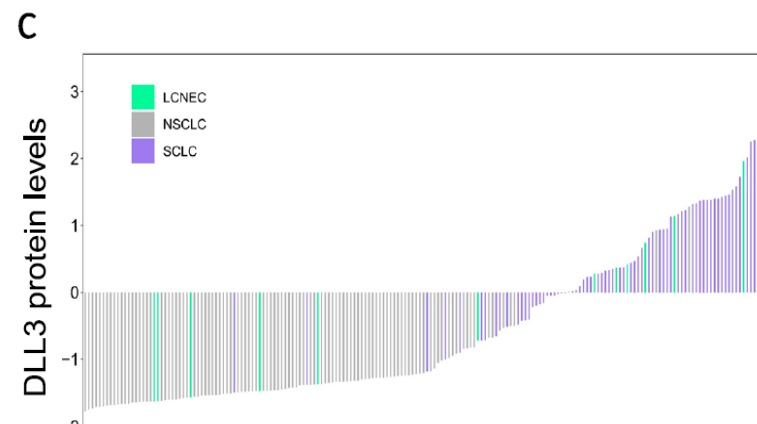
DLL3 expression in lung cancer



DLL3 gene expression in lung cancer cell lines



DLL3 protein expression in lung cancer cell lines

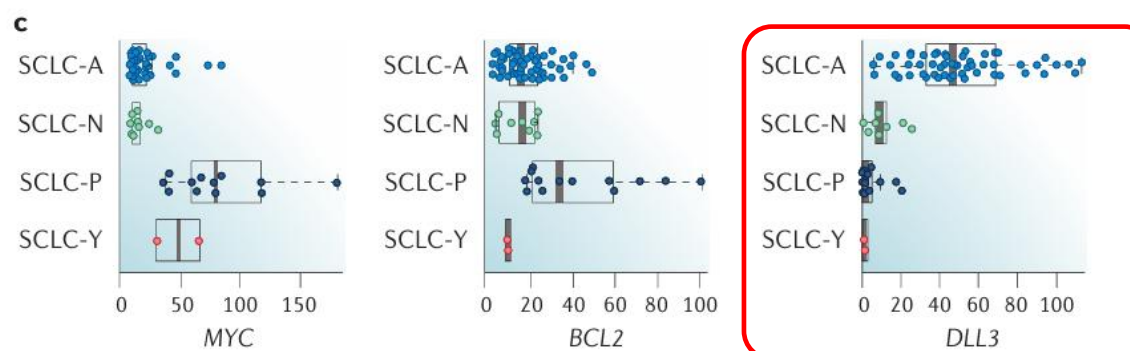
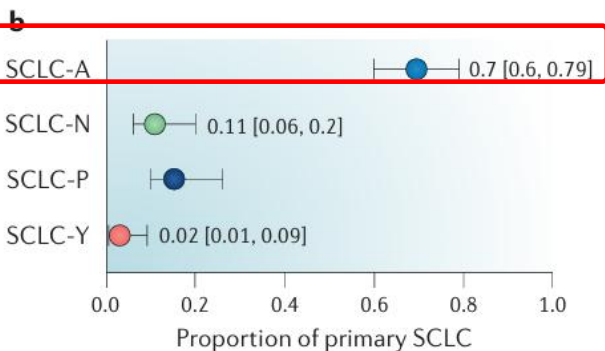
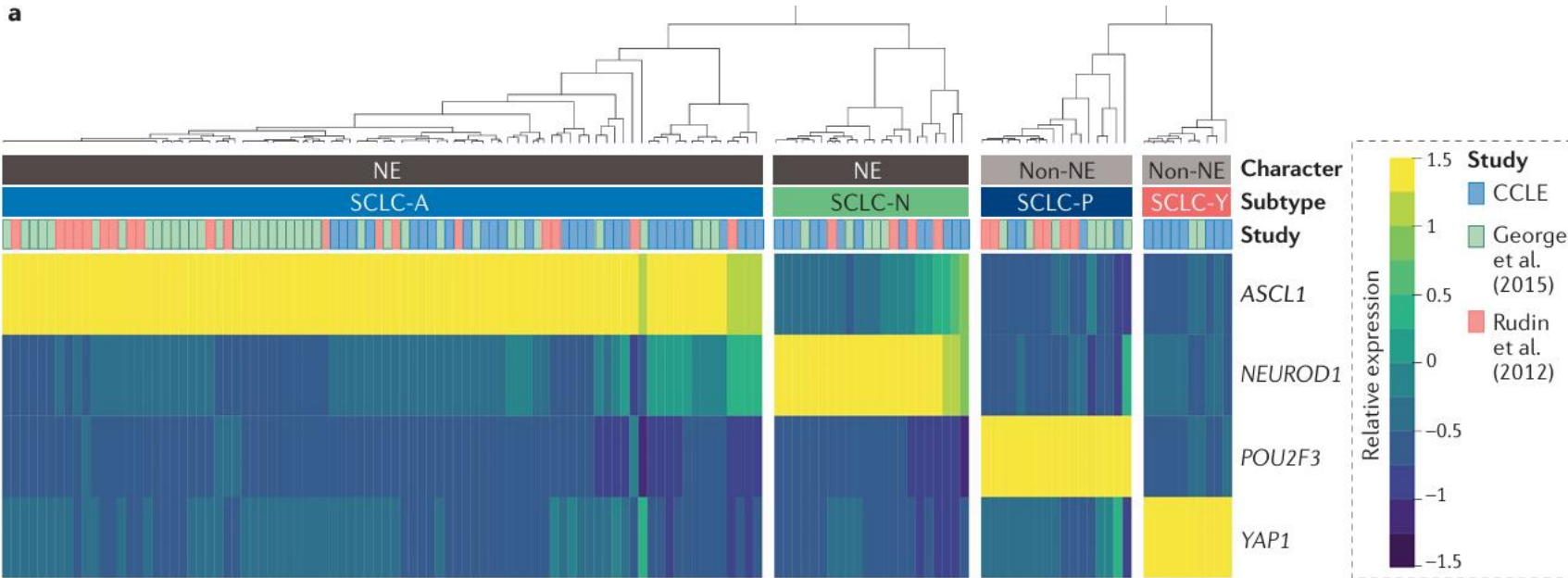


Gene and protein expression patterns of DLL3 in lung cancer cell lines.

DLL3 IHC expression in patient samples with neuroendocrine carcinomas

Introduction

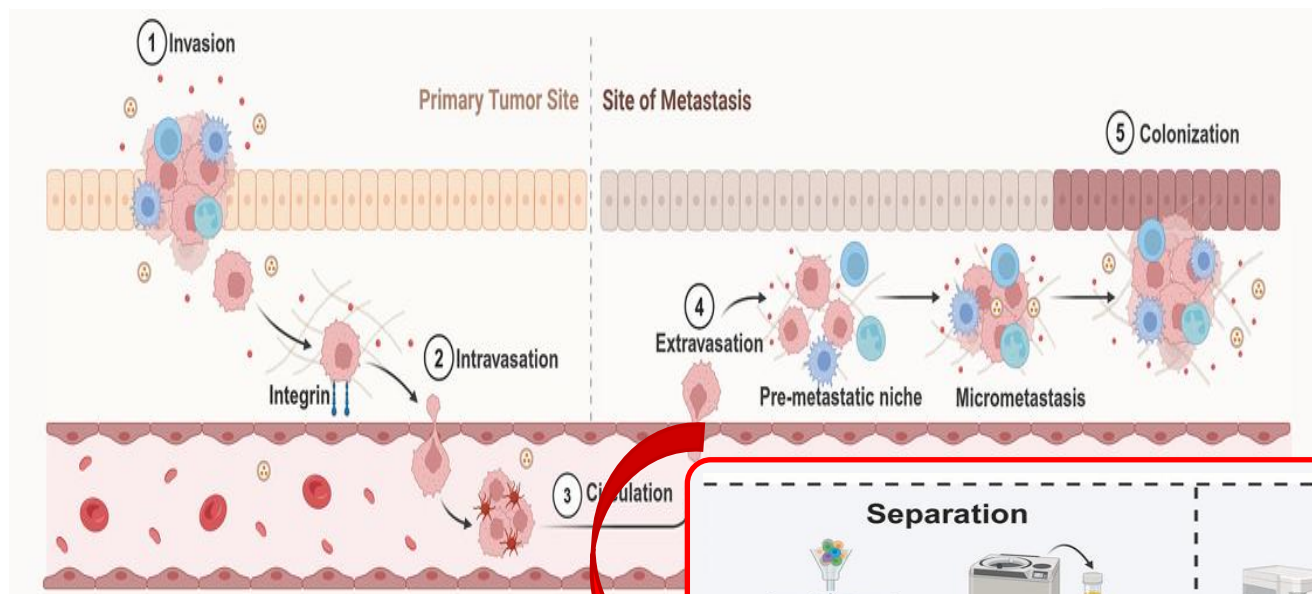
Small cell lung cancer subtypes and DLL3 expression



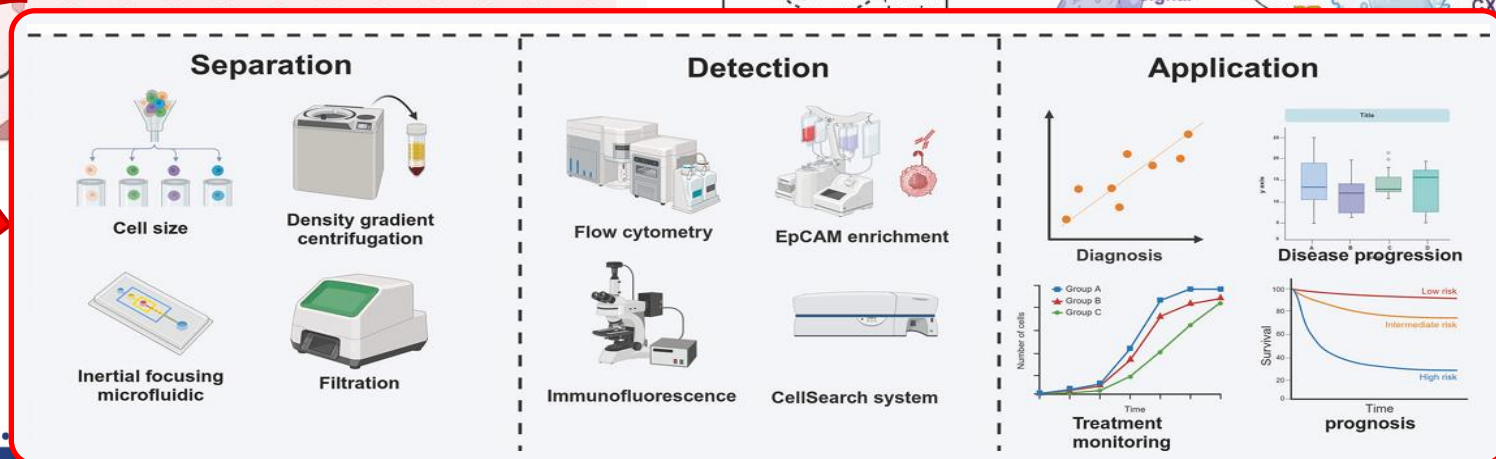
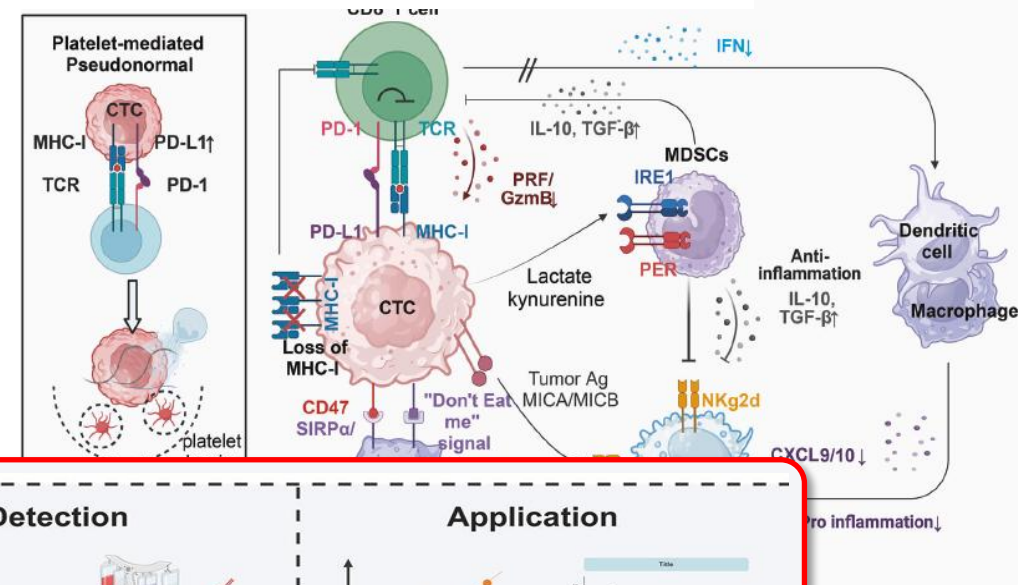
Introduction

Circulating tumor cells (CTCs)

Epithelial-mesenchymal transition (EMT) of tumor cells



Immune-escape mechanisms of CTCs



Introduction

Previous studies on CTC in SCLC

	No patients	Method		Findings
Naito et al. J Thorac Oncol. 2012	N=51 (ED, N=24)	Cellsearch® (VeridexLLC)	EpCAM isolated intact cells Cytokeratin +, CD 45-	Prognostic marker
Hiltermann TJN et al. Ann Oncol. 2012	N=59 (ED, N=38)	Cellsearch®		Predict of response and Survival
Hou JM, et al. Am J Pathol. 2009	N=50 (ED, N=30)	Cellsearch®		Prognostic marker
Tanaka F, et al. Clin Cancer Res. 2009	N=9	Cellsearch®		Marker for distant metastasis

Limitation of Cellsearch

: EpCAM-dependent, positive selection

Naito T et al, *J Thorac Oncol.* 2012 Mar;7(3):512-9.
Hiltermann TJN et al. *Ann Oncol.* 2012 Nov;23(11):2937-2942.
Hou JM, et al. *Am J Pathol.* 2009 Aug;175(2):808-16
Tanaka F, et al. *Clin Cancer Res.* 2009 Nov 15;15(22):6980-6..

Introduction

Purpose of the study

Evaluate the potential of DLL3 as a biomarker for enhancing CTC detection
and monitoring treatment response in patients with SCLC-ES

Methods

Inclusion criteria

Patients diagnosed with extensive stage SCLC scheduled to receive chemo-immunotherapy

Tissue immunohistochemistry

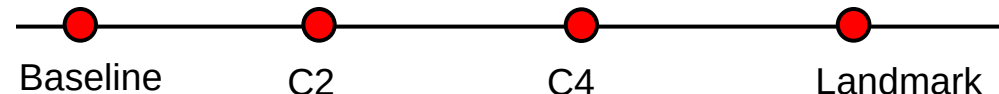
- SCLC subtype (ASCL1, POU2F3, NEUROD1, YAP1)
- CD8, PD-L1(sp263) expression

Blood sample process

Whole body 6ml, collected at each cycle

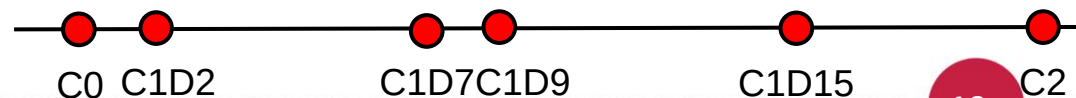
1st line

Chemo-I/O treatment



2nd line

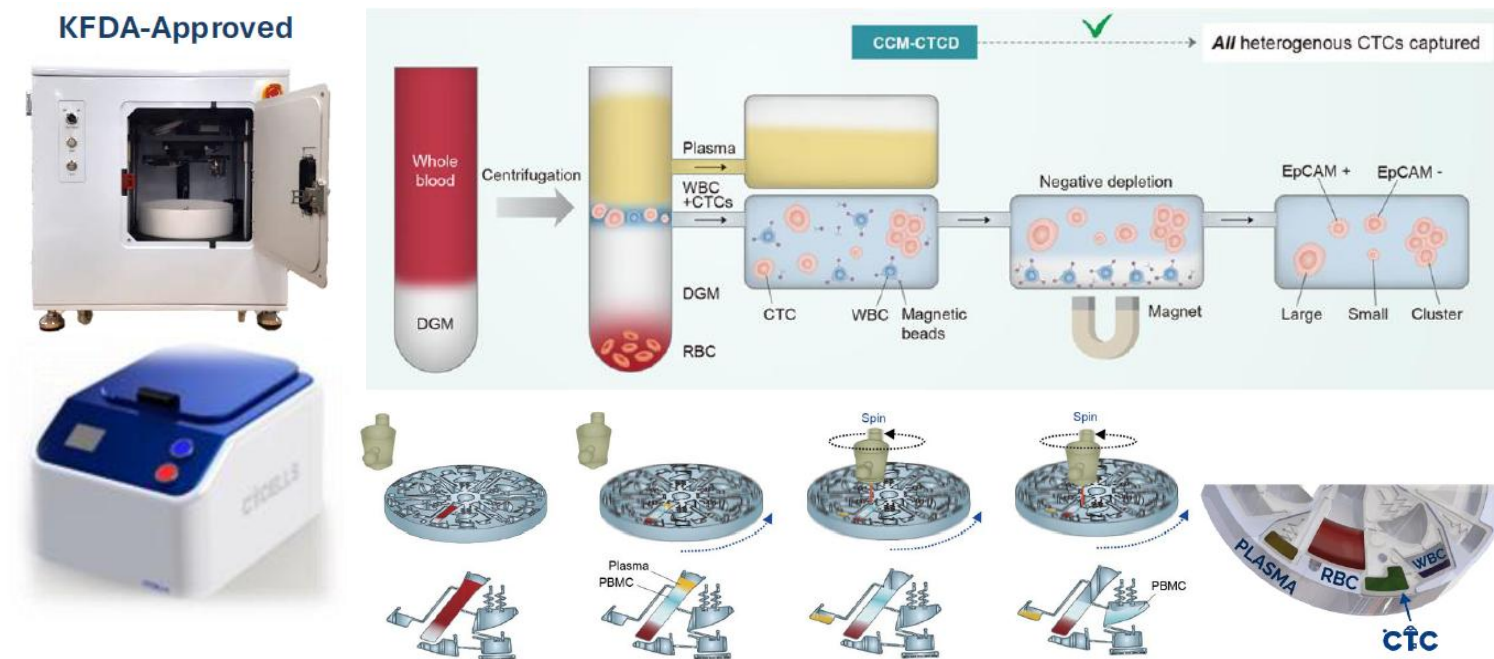
Tarlatamab treatment



Methods

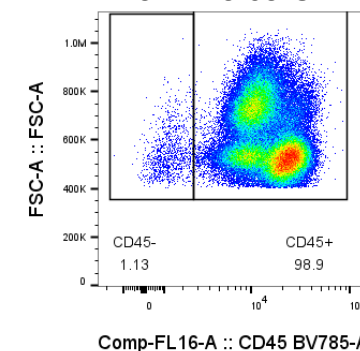
CTC enrichment

CTCeptor™ - TRACE platform for CTC isolation



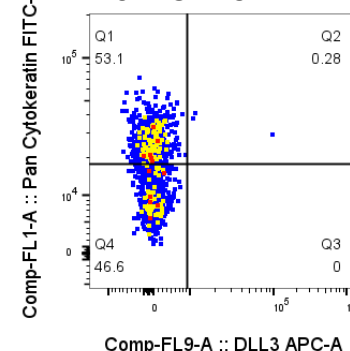
Before enrichment

From live cells

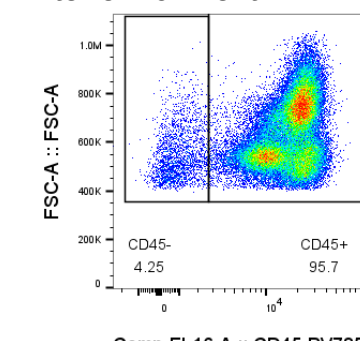


Comp-FL1-A :: Pan Cytokeratin FITC-A

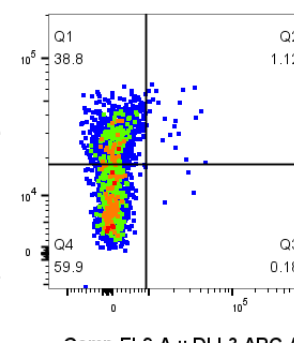
From CD45-



After enrichment



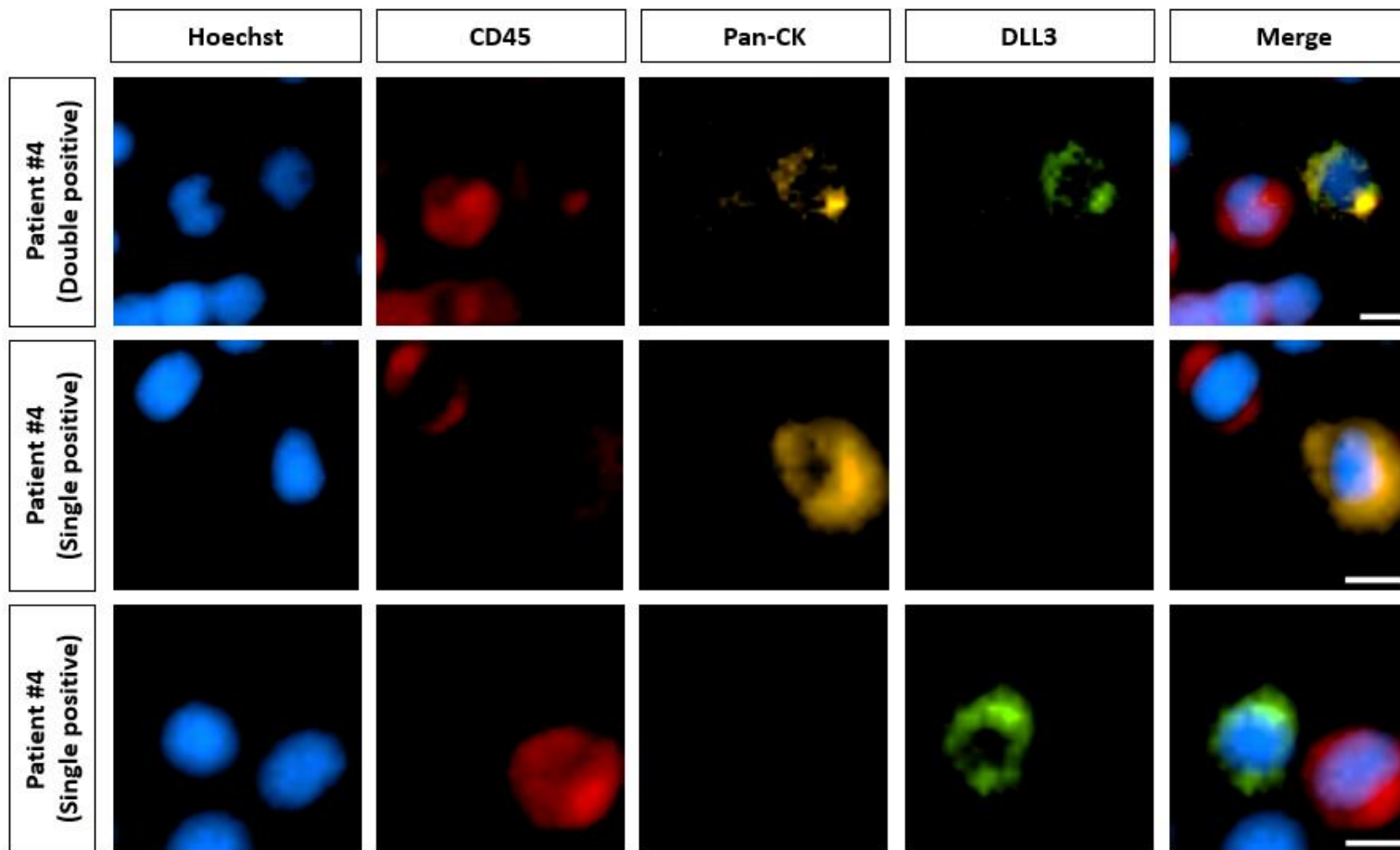
Comp-FL1-A :: Pan Cytokeratin FITC-A



- CTCELLS developed Continuous Centrifugal Microfluidics device to isolate CTCs via negative isolation
- Label-free** and **Cell size-free** isolation system

Methods

CTC identification



CD45-
/CK+/DLL3+

CD45-
/CK+/DLL3-

CD45-/CK-
/DLL3+

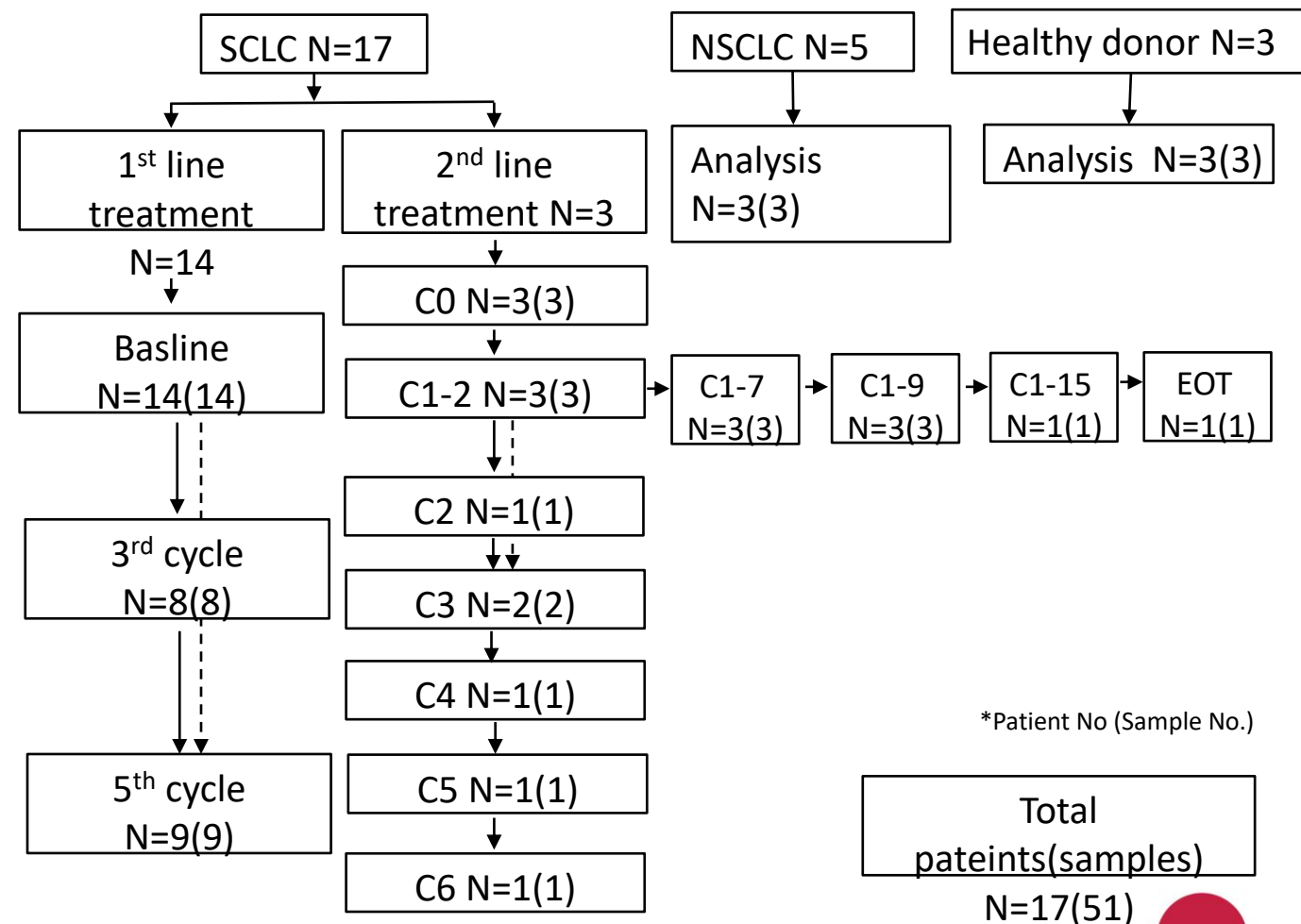
Scale bar : 5um

Results

1. SCLC patients characteristics

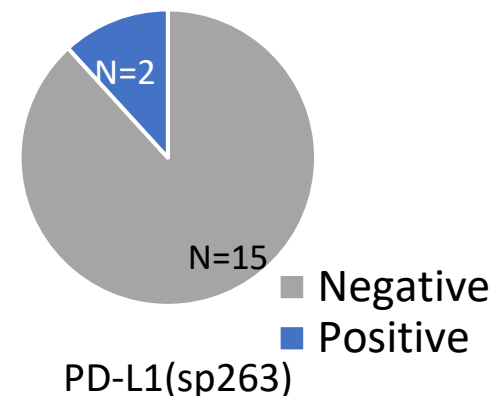
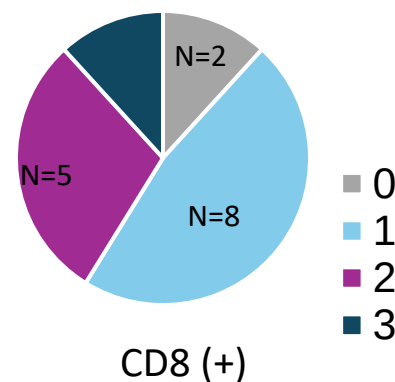
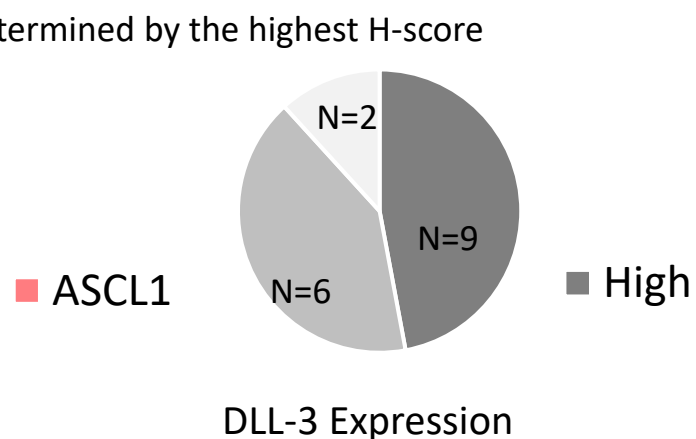
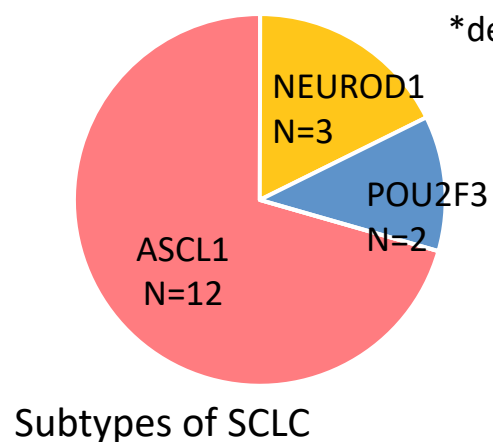
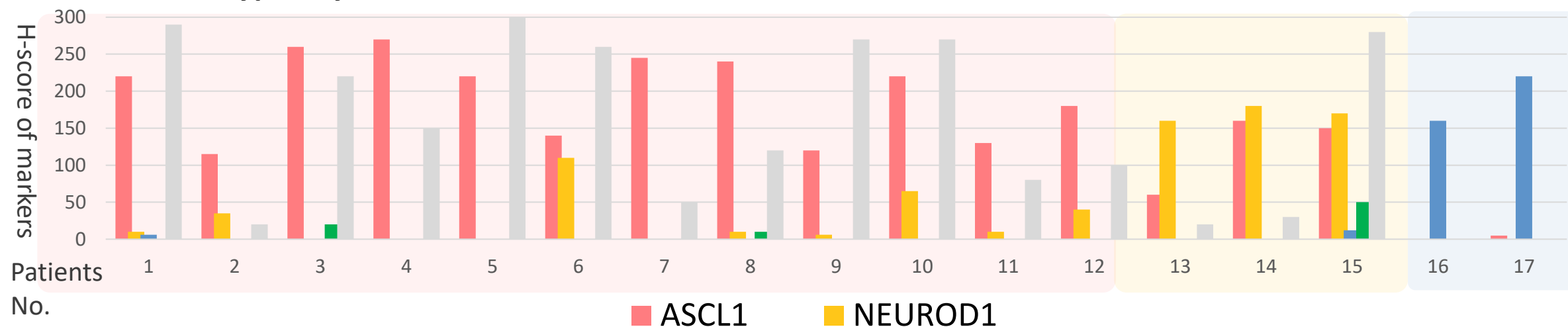
	N=17
Age (median)	71.6 ± 7.4
Sex, N(%)	
Mae	14 (82.3)
Female	3 (17.6)
ECOG PS, n(%)	
0	2 (11.7)
1	8 (47.0)
2	6 (35.3)
3	1 (5.8)
Smoking, PYS (median, IQR)	40 (32.5-40.0)
proGRP (median, IQR)	3,081 (135-3830.0)
Stage IVA, n(%)	5 (29.4)
IVB	13 (76.4)

2. Flowchart of sample analysis



Results

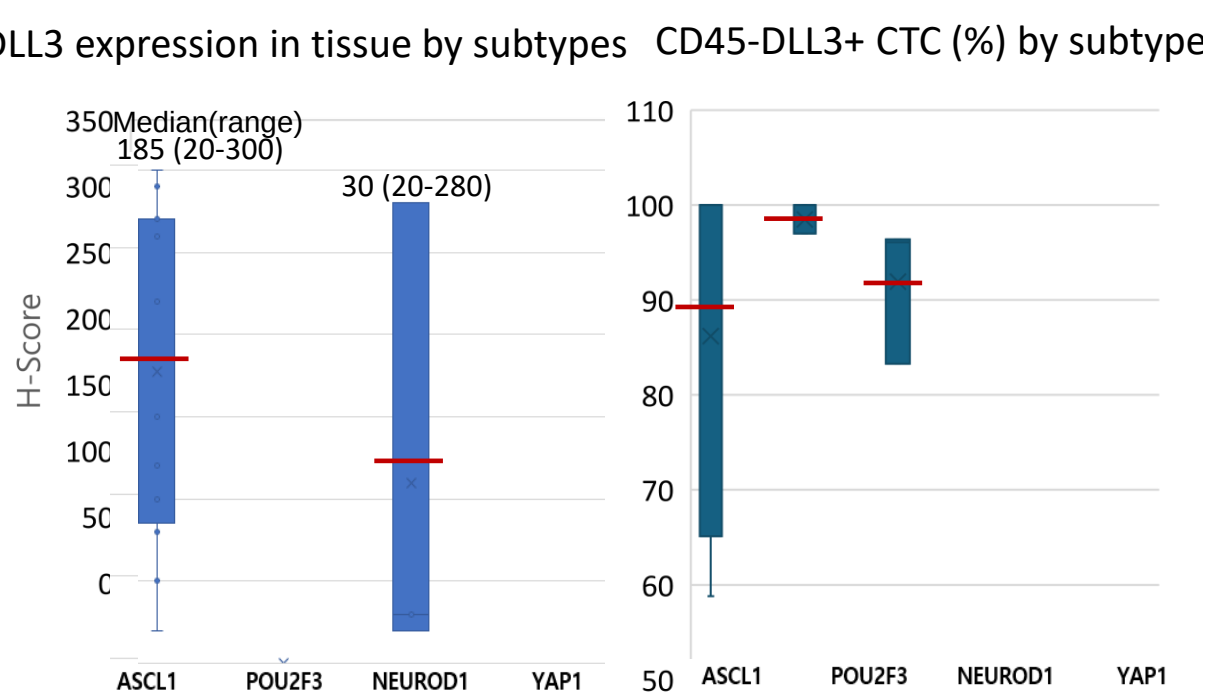
Molecular subtypes by IHC markers in tumor tissue



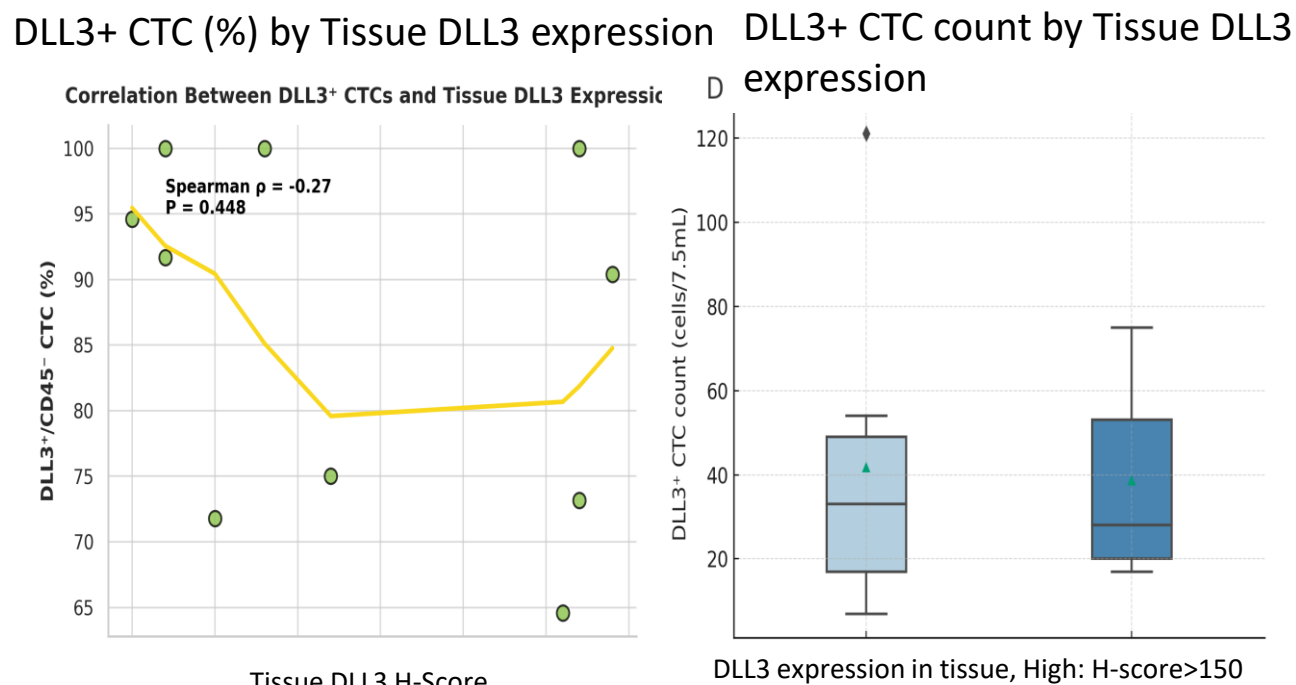
Results

Molecular subtypes by IHC markers in tumor tissue

Tissue DLL3 IHC and DLL3+ CTC by subtypes

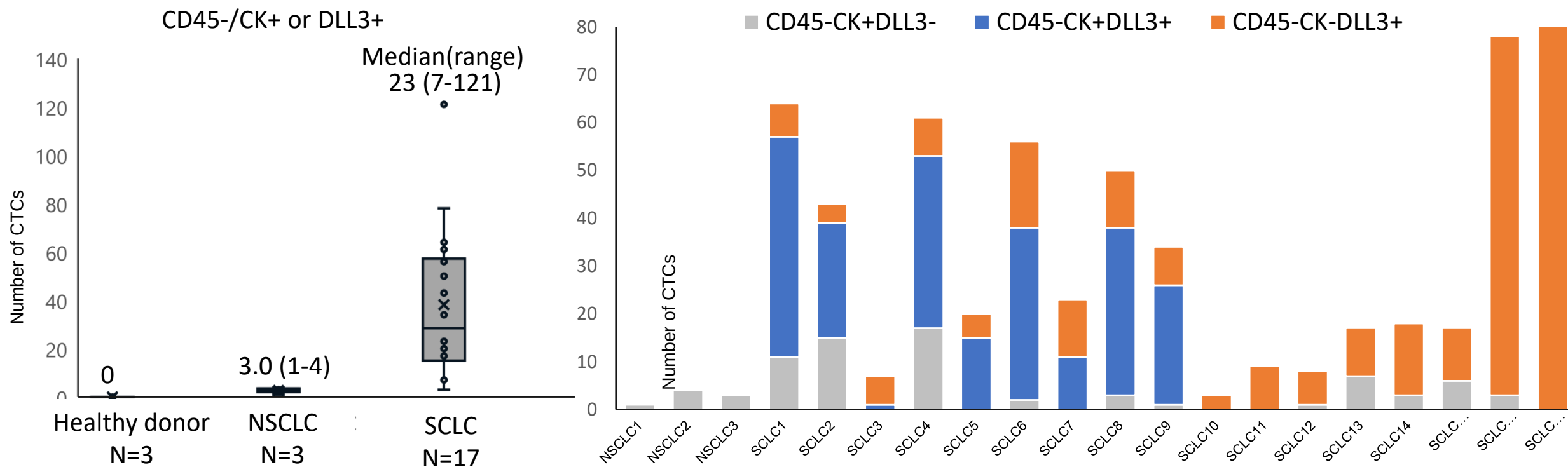


Correlation between tissue DLL3 IHC and DLL3+ CTC



Results

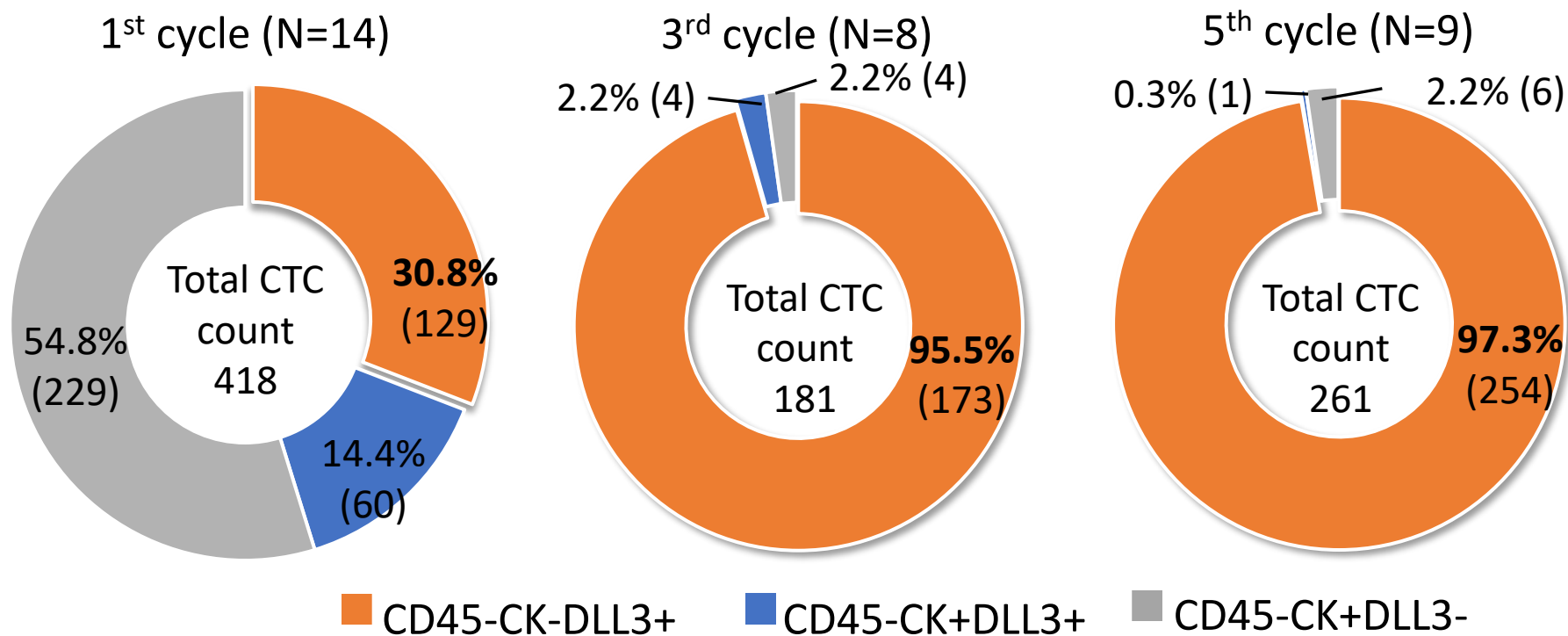
Baseline CTC counts in enrolled patients



Results

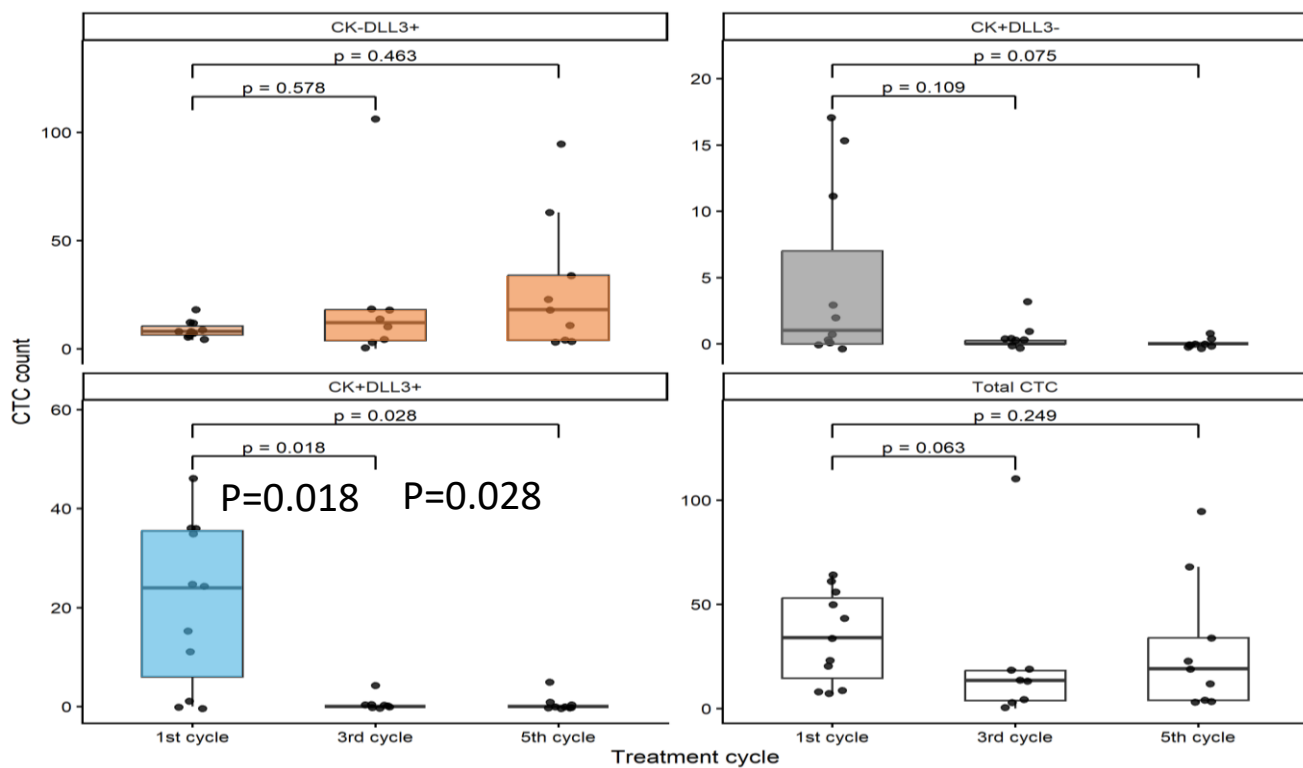
CTC dynamics by CTC subtypes and therapeutic response in Chemo-immunotherapy(first-line)

Shifts in CTC subtypes following CIO

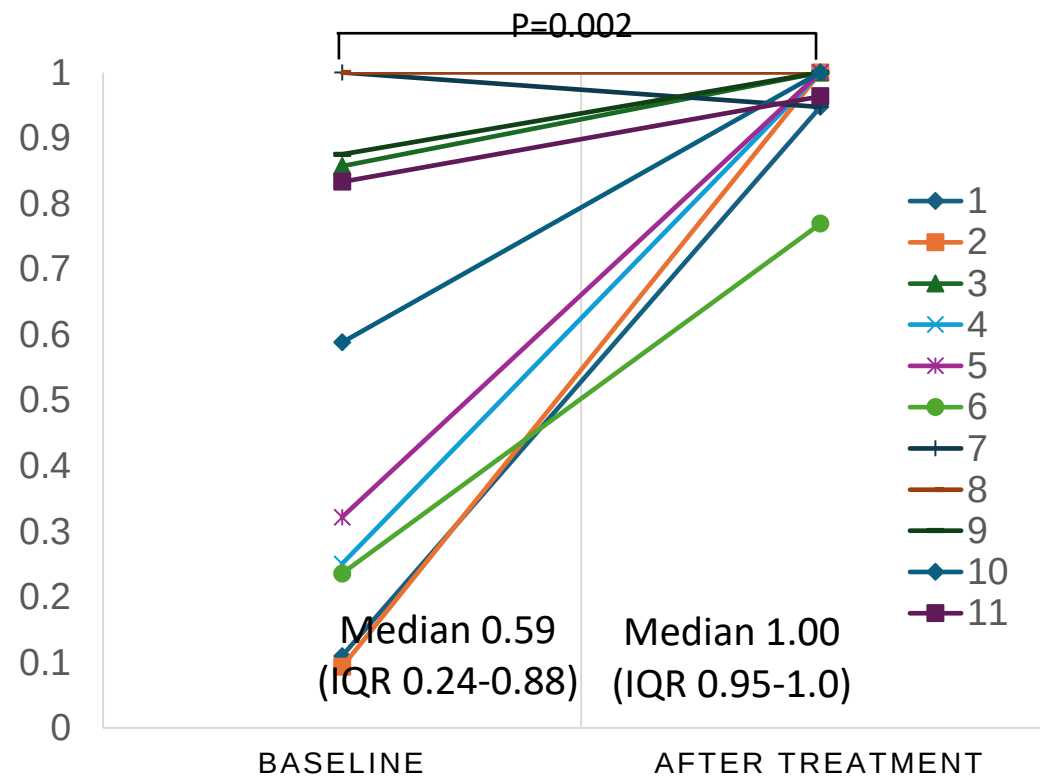


Results

Shifts by CTC subtypes

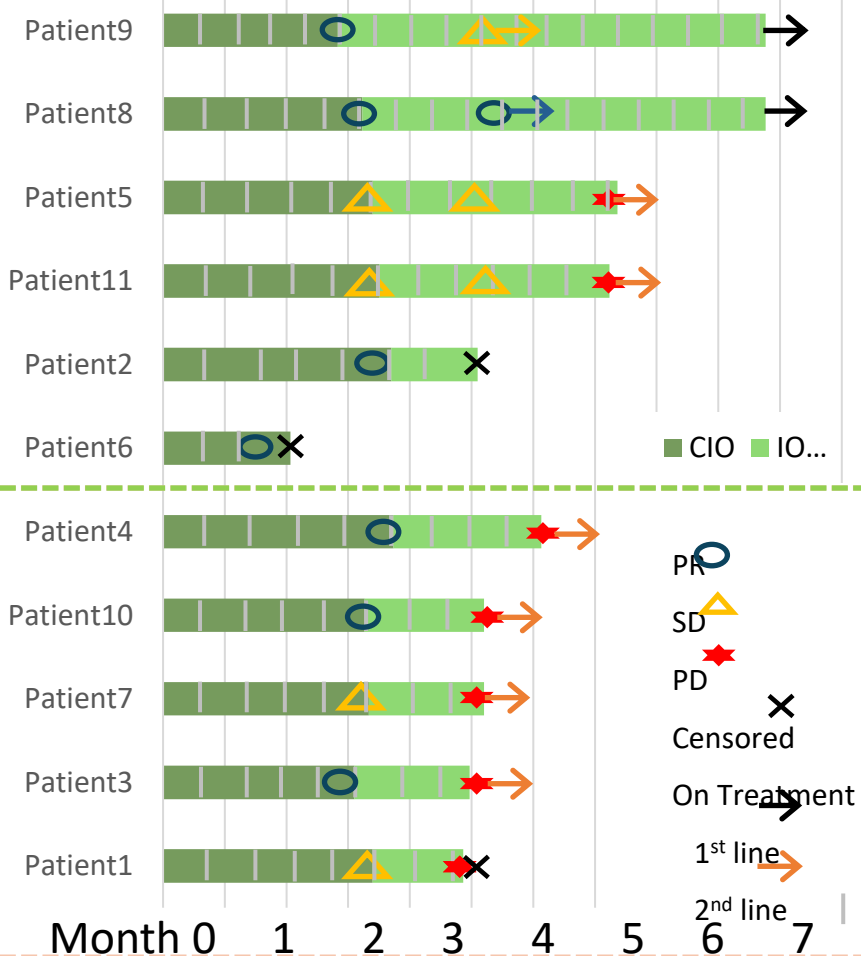


Proportional shift of CK-/DLL3+ CTC



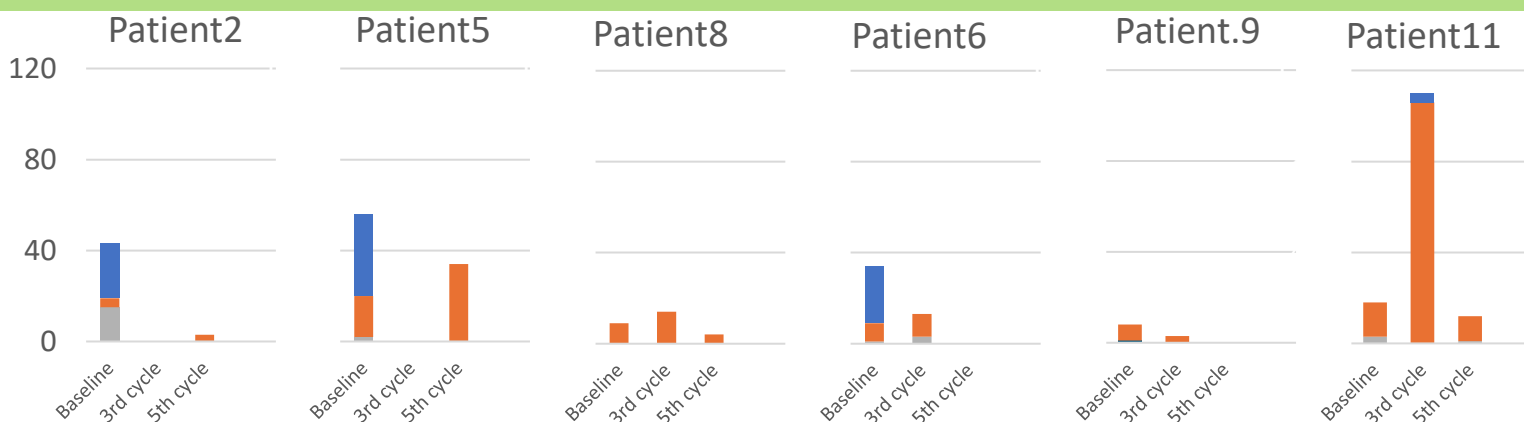
Results

Clinical course and outcomes

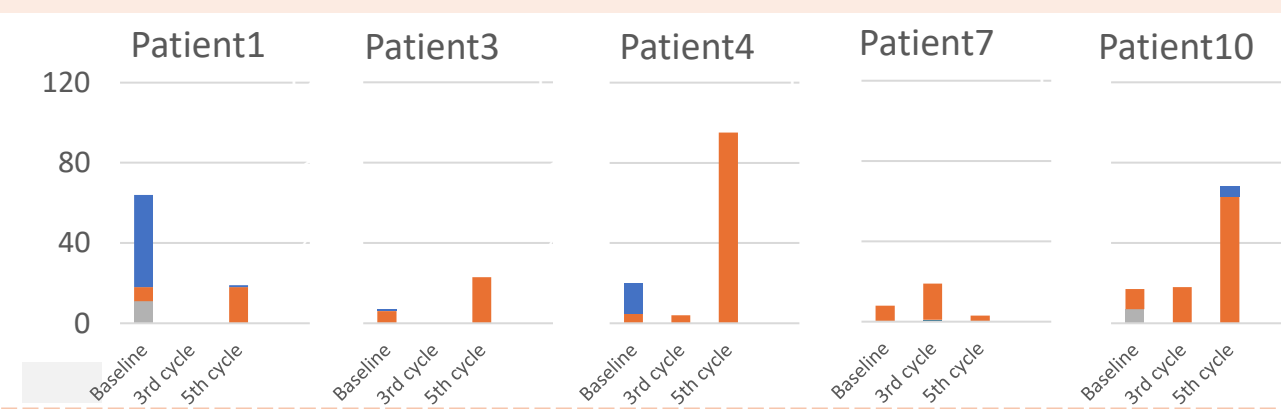


CTC count of individual patients

Progression after the first three cycles of I/O maintenance therapy

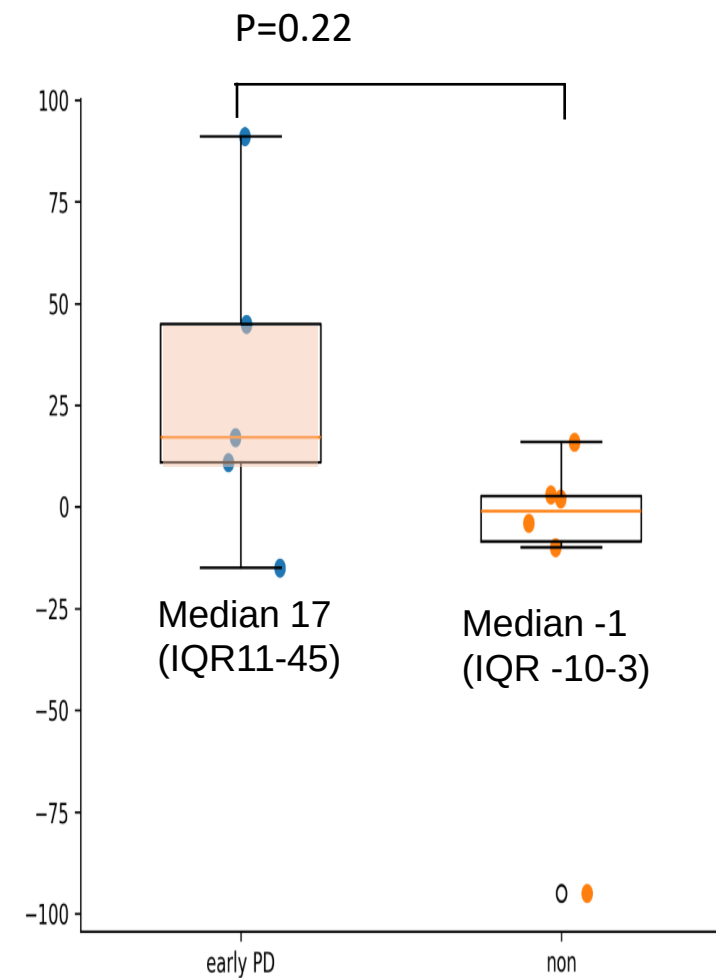
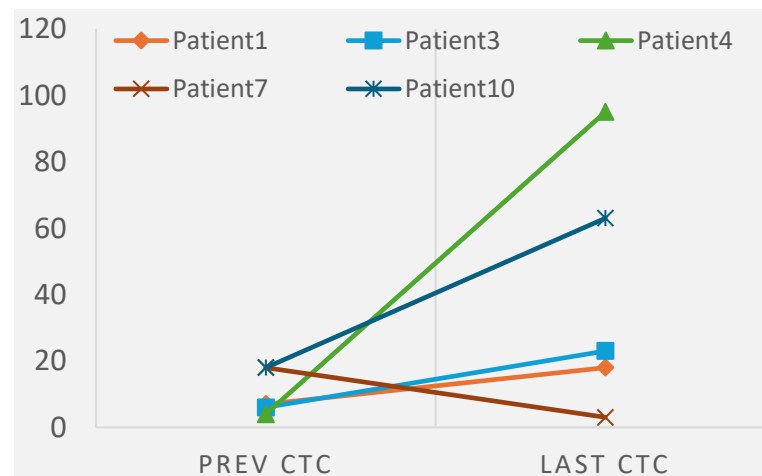
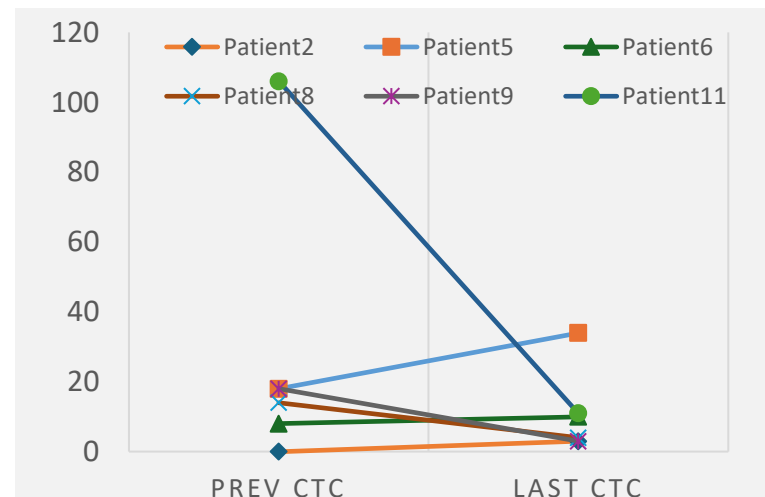


Progression within the first three cycles of I/O maintenance therapy



Results

Difference(Δ) in CK-/DLL3+ CTC count



Results

CTC dynamics in Tarlatamab-treated patients (second-line)

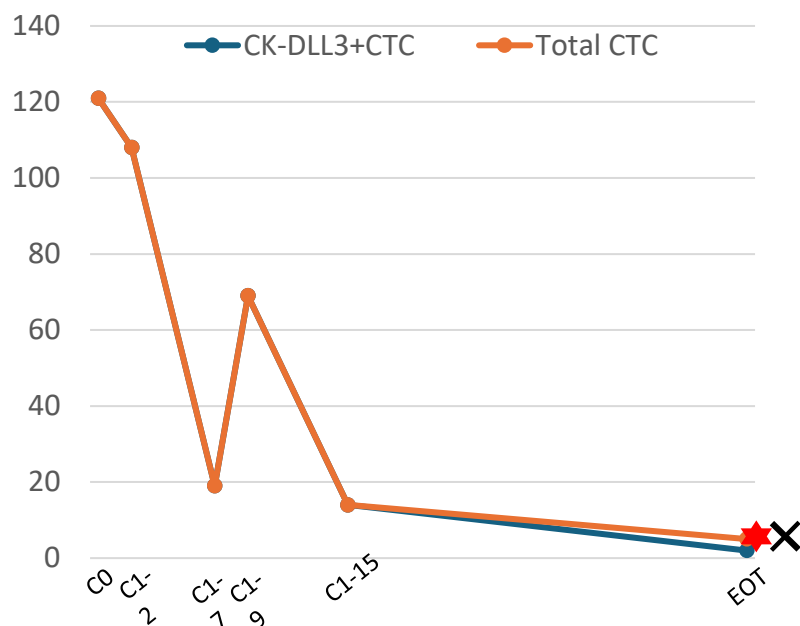
Patient16 69/M

SCLC, RUL (25.4.14), ED

(cT3N3M1c : Both lungs&pleura, liver, sacrum, Lt. ischium, r,

- 1-ACE4# (25.4.24 ~ 7.17) : PR -> PD (RUL, LAPs, both lungs,

- 2Tarlatamab: 2025.9.2~9.23



Patient 17 73/M

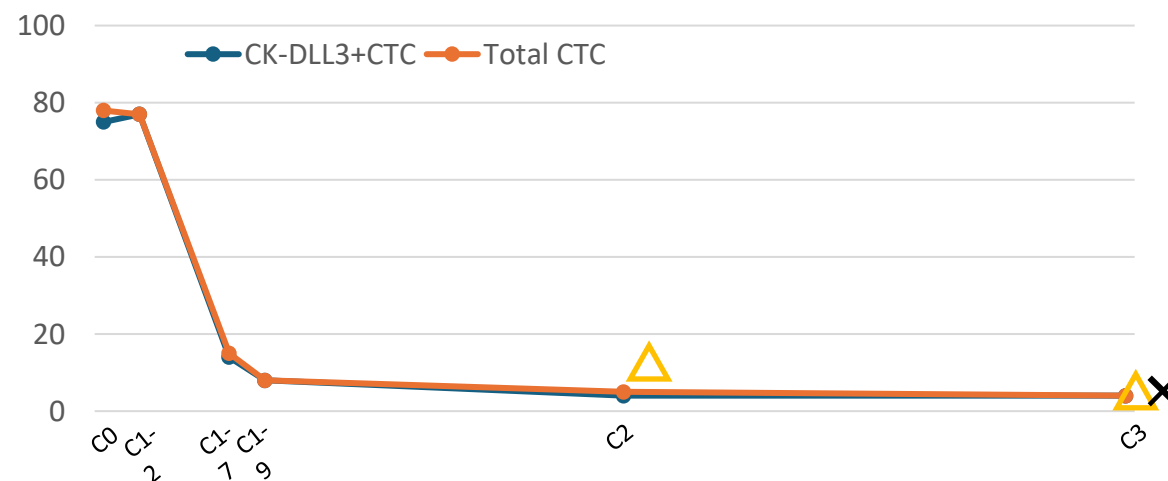
SCLC, RLL (25.2.25, CNUH PD), ED

(cT4N3M1c : T10, L2, sacrum, Lt.1st rib, brain(multiple))

- 1-ACE4# (25.3.5 ~ 5.9) : PR -> SD

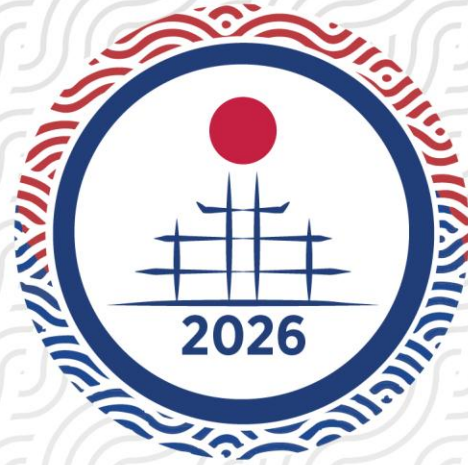
- mATZ7# (25.5.27 ~ 7.8) : PD (LAPs, Rt.pleura, brain(multiple))

- 2Tarlatamab: 2025.8.19~11.11



Conclusions

- DLL3 is more commonly expressed in CTCs than in tumor tissue, and DLL3+ CTCs can be efficiently and exclusively detected in ES-SCLC patients using CTCeceptor™, serving as a complementary marker to CK for CTC identification and a SCLC marker.
- The dynamic shift in DLL3+ CTC phenotypes mirrored therapeutic response and resistance throughout treatment, supporting its potential as a liquid biopsy biomarker for real-time CTC-based monitoring of ES-SCLC heterogeneity and ICI efficacy.



Thank You.