

Clinical Applications of Liquid Biopsy Monitoring in Lung Cancer

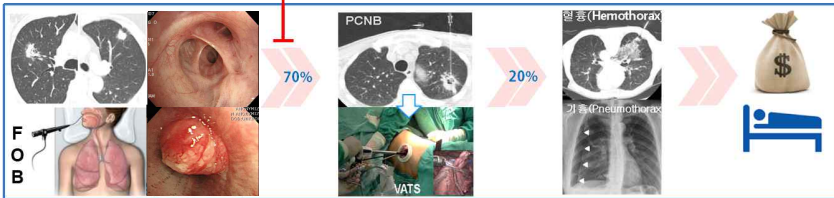
Molecular Response and Minimal Residual Disease

Jun Hyeok Lim
Division of Pulmonology
Department of Internal Medicine
Inha University Hospital

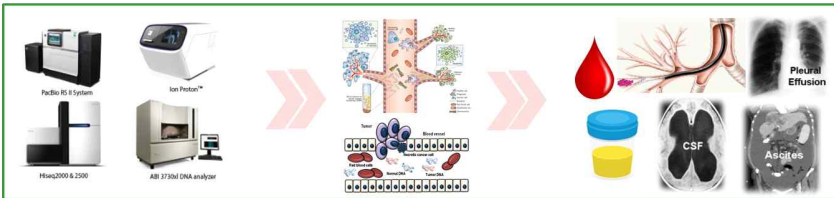
Liquid biopsy: non-invasive



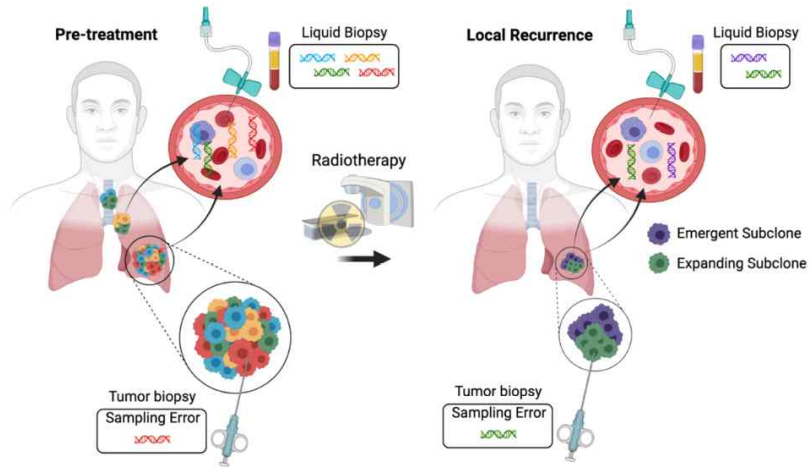
폐결핵 진단



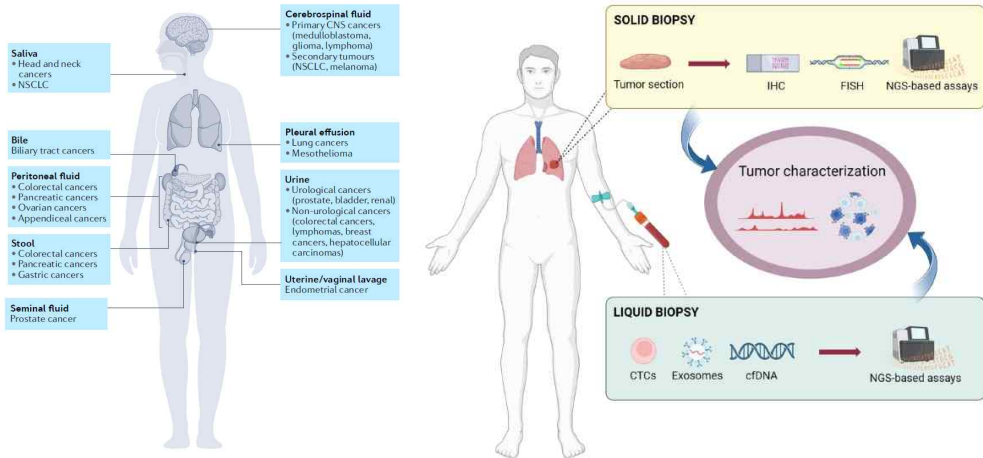
과학기술 발전



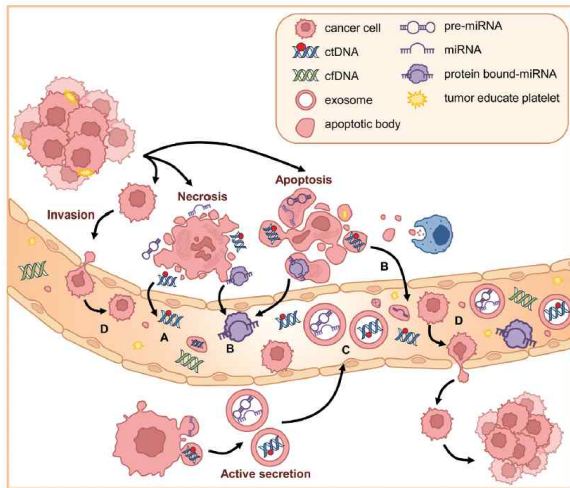
Liquid biopsy: overcome tumor heterogeneity



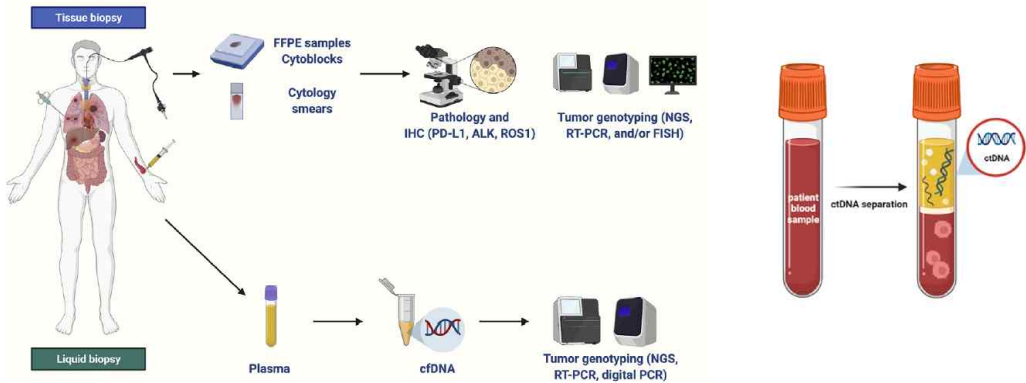
Liquid biopsy



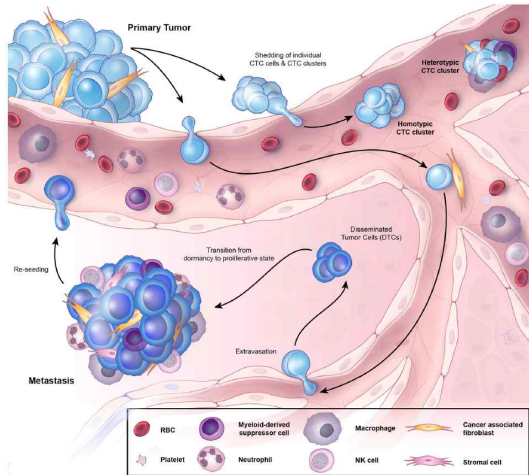
Circulating Tumor DNA



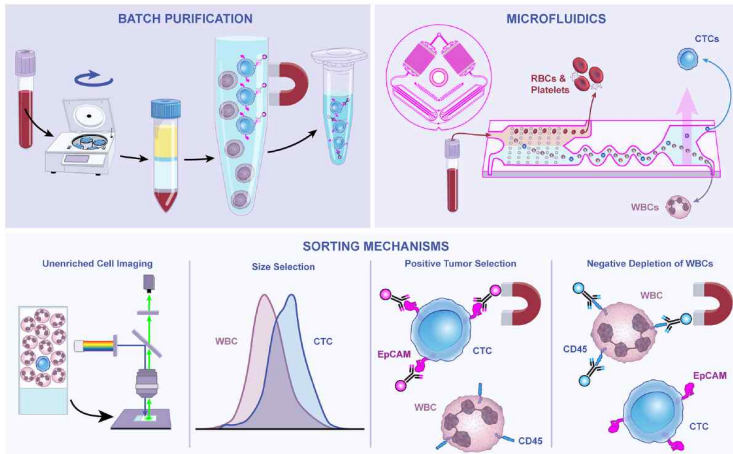
Circulating Tumor DNA



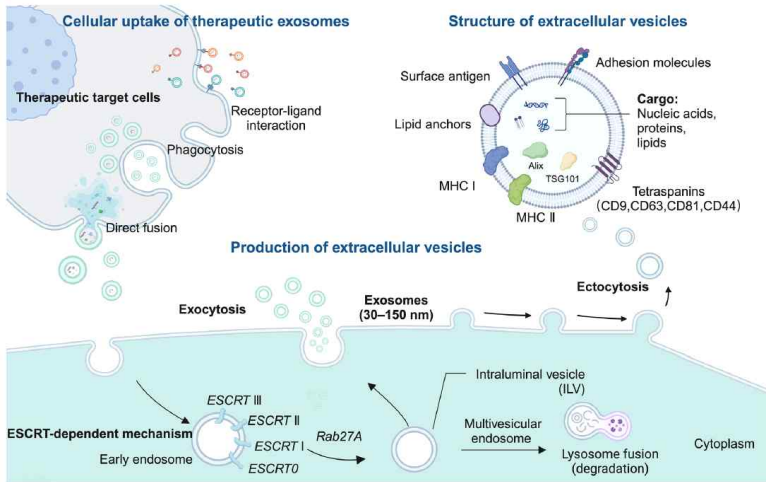
Circulating Tumor Cell



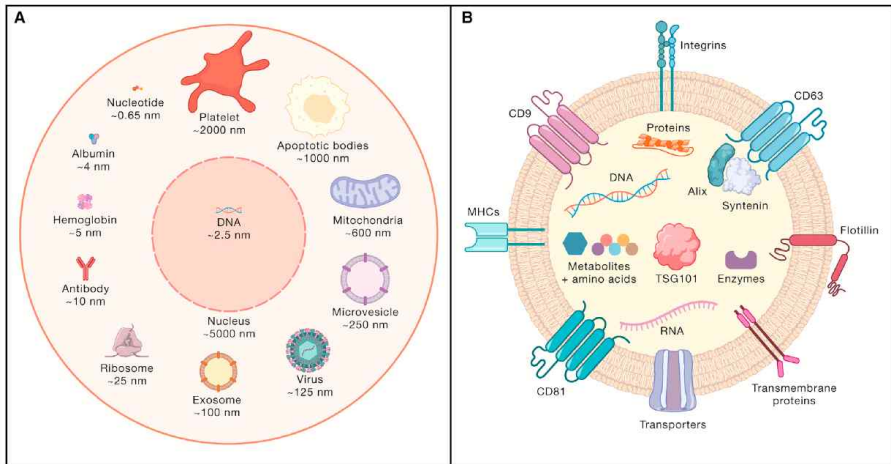
Circulating Tumor Cell



Exosome

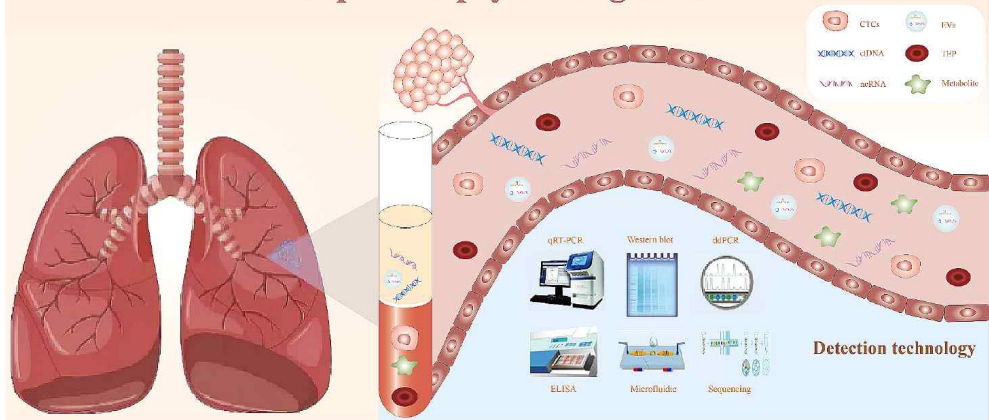


Exosome

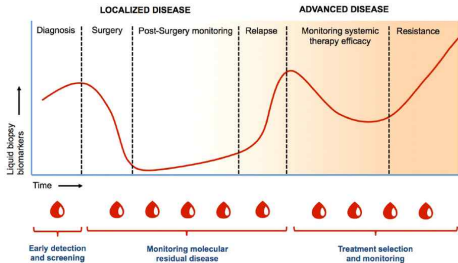


ctDNA? CTC? Exosome?

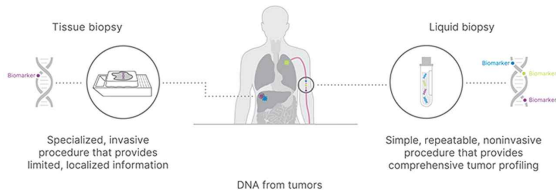
Liquid biopsy of lung cancer



Clinical applications of liquid biopsy



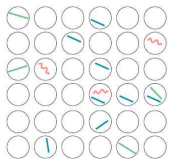
Monitoring



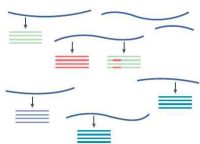
Biomarker Detection

ctDNA: Coverage vs Depth

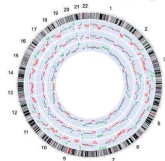
Increasing genomic coverage (and cost) →



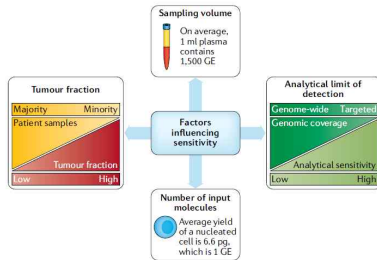
Single-locus assays



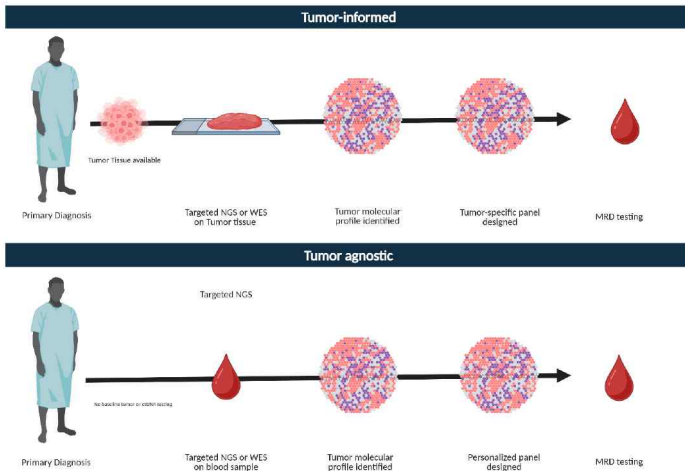
Targeted sequencing



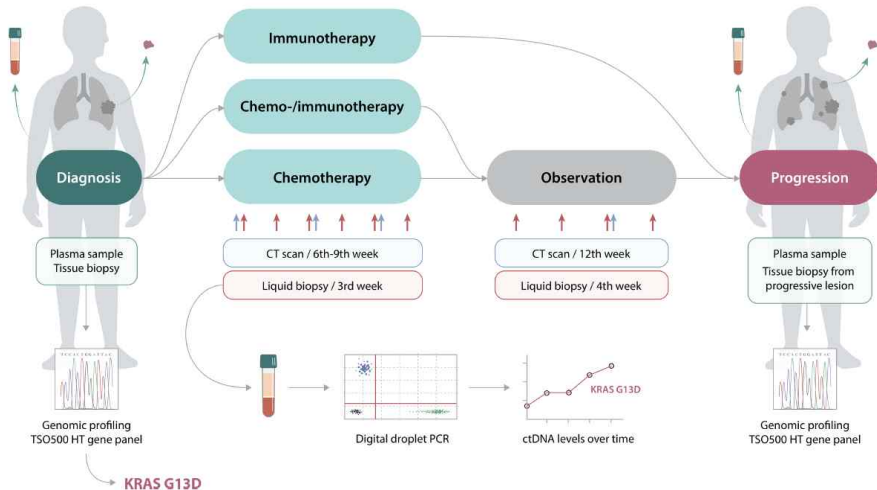
Whole-genome sequencing



MRD: Tumor-informed vs. Tumor-agnostic



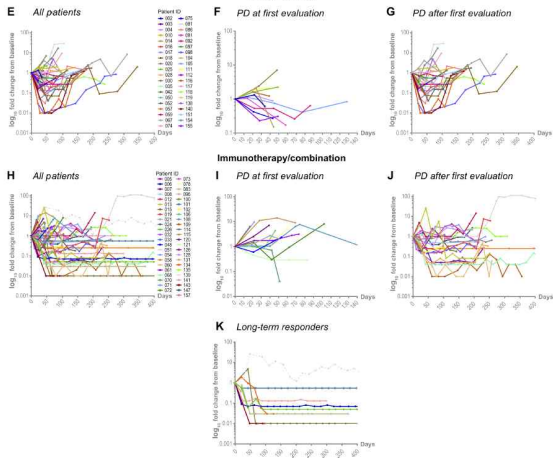
1. ctDNA monitoring reveals molecular PD before radiologic PD



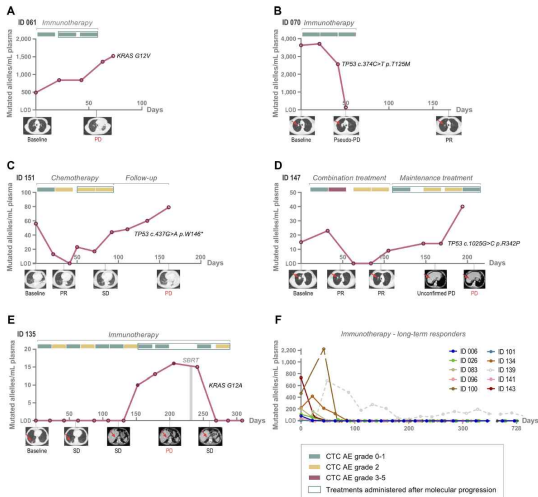
1. ctDNA monitoring reveals molecular PD before radiologic PD

Longitudinal ctDNA measurements

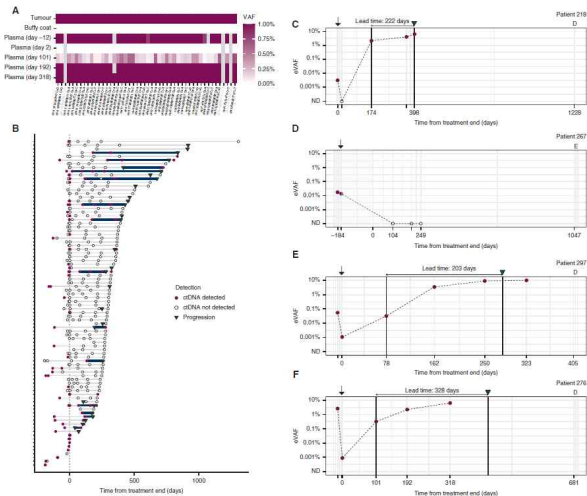
Chemotherapy



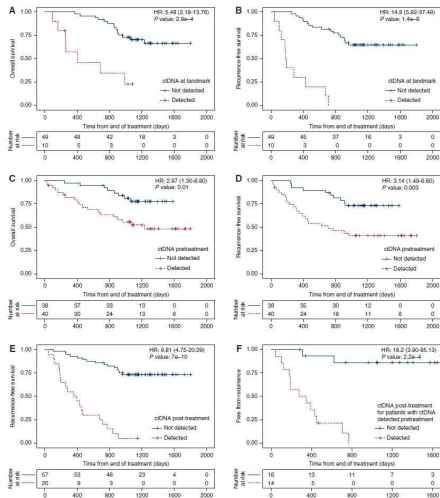
1. ctDNA monitoring reveals molecular PD before radiologic PD



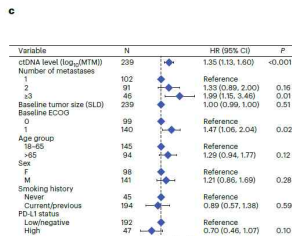
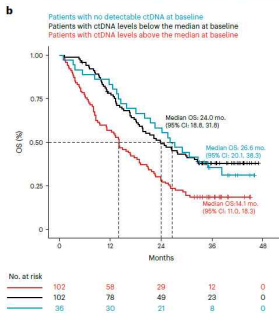
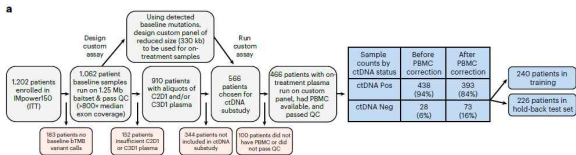
2. Residual ctDNA after treatment predicts early relapse



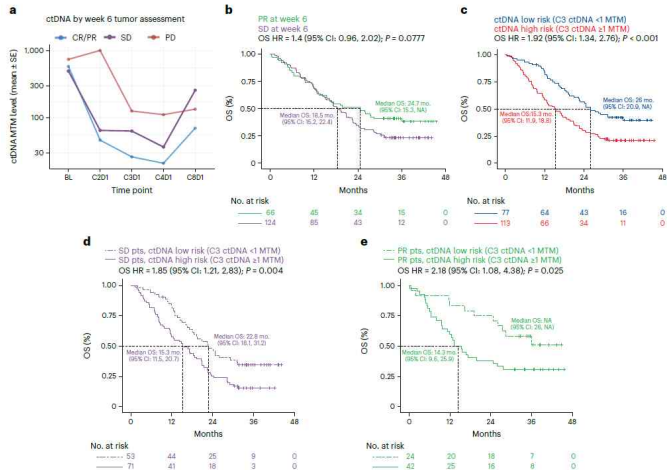
2. Residual ctDNA after treatment predicts early relapse



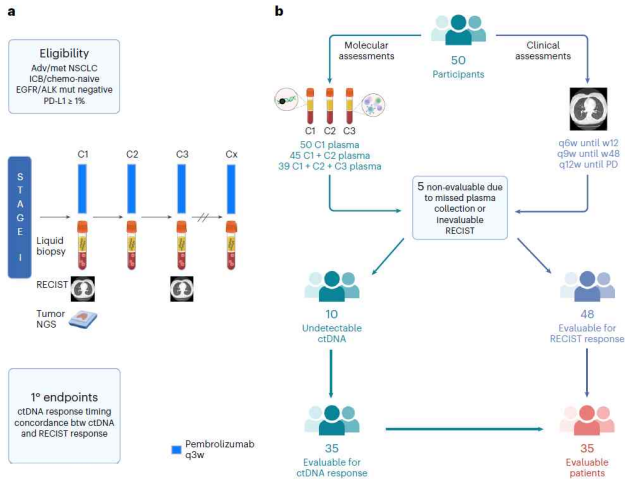
3. A longitudinal ctDNA-based model



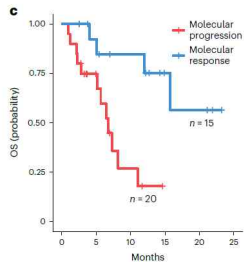
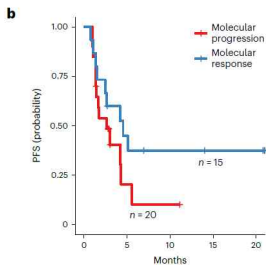
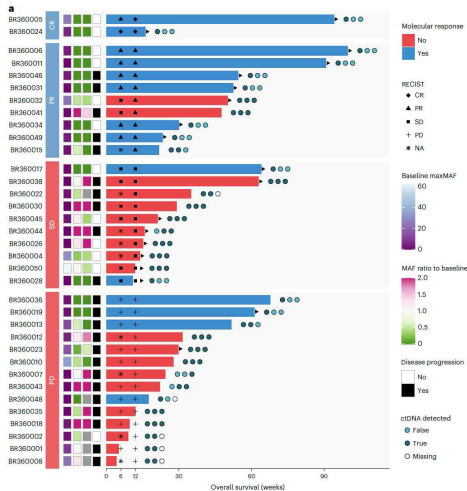
3. A longitudinal ctDNA-based model



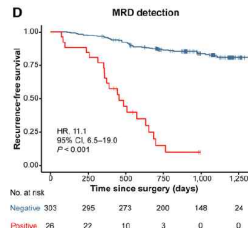
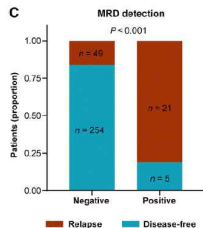
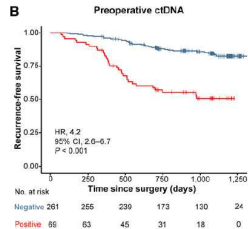
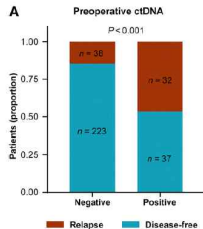
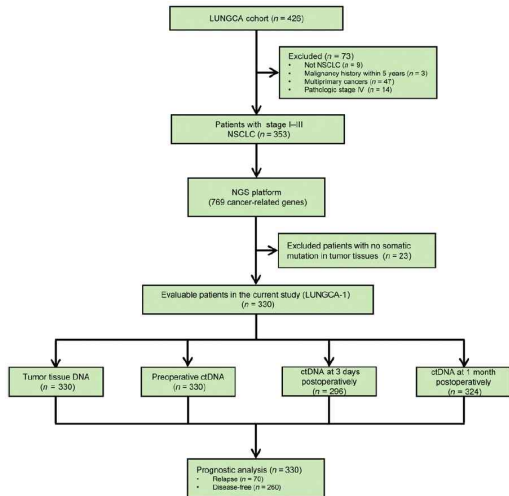
4. ctDNA response after pembrolizumab



4. ctDNA response after pembrolizumab



5. Perioperative ctDNA-Based MRD detection



6. Neoadjuvant Nivolumab plus Chemotherapy

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AUGUST 21/28, 2025

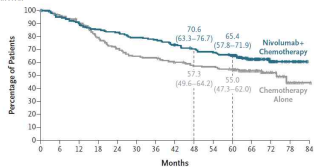
VOL. 393 NO. 8

Overall Survival with Neoadjuvant Nivolumab plus Chemotherapy in Lung Cancer

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Tetsuya Mitsudomi, M.D., Ph.D.,⁴ Mark M. Awad, M.D., Ph.D.,⁵ Changli Wang, M.D.,⁶ Shun Lu, M.D., Ph.D.,⁷
Enriqueta Felip, M.D., Ph.D.,⁸ Scott J. Swanson, M.D.,⁹ Julie R. Brahmer, M.D.,¹⁰ Keith Kerr, M.B., Ch.B.,¹¹
Janis M. Taube, M.D.,¹² Tudor-Eliade Ciuleanu, M.D., Ph.D.,¹³ Fumihiko Tanaka, M.D., Ph.D.,¹⁴
Gene B. Saylor, M.D.,¹⁵ Ke-Neng Chen, M.D., Ph.D.,¹⁶ Hiroyuki Ito, M.D., Ph.D.,¹⁷ Moishe Liberman, M.D., Ph.D.,¹⁸
Claudio Martin, M.D.,¹⁹ Stephen Broderick, M.D.,¹⁹ Lily Wang, M.D.,²⁰ Junliang Cai, M.D.,²⁰ Quyen Duong, Ph.D.,²⁰
Stephanie Meadows-Shropshire, Ph.D.,²⁰ Joseph Fiore, Pharm.D.,²⁰ Sumeena Bhatia, Ph.D.,²⁰ and
Nicolas Girard, M.D., Ph.D.,²¹ for the CheckMate 816 Investigators*

6. Neoadjuvant Nivolumab plus Chemotherapy

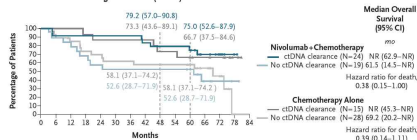
A Overall Survival



Nivolumab+Chemotherapy (N=179)
Chemotherapy Alone (N=179)
 Hazard ratio for death, 0.72 (95% CI, 0.523-0.998)
 P=0.048

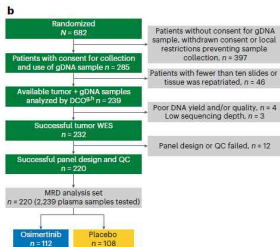
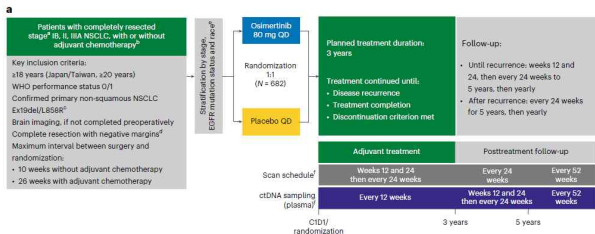
No. at Risk	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84
Nivolumab+chemo-therapy	179	168	159	151	147	140	137	129	122	117	111	67	29	9	0
Chemotherapy alone	179	170	159	139	124	114	112	104	98	97	91	58	29	6	1

B Overall Survival in Patients with or without Circulating Tumor DNA (ctDNA) Clearance

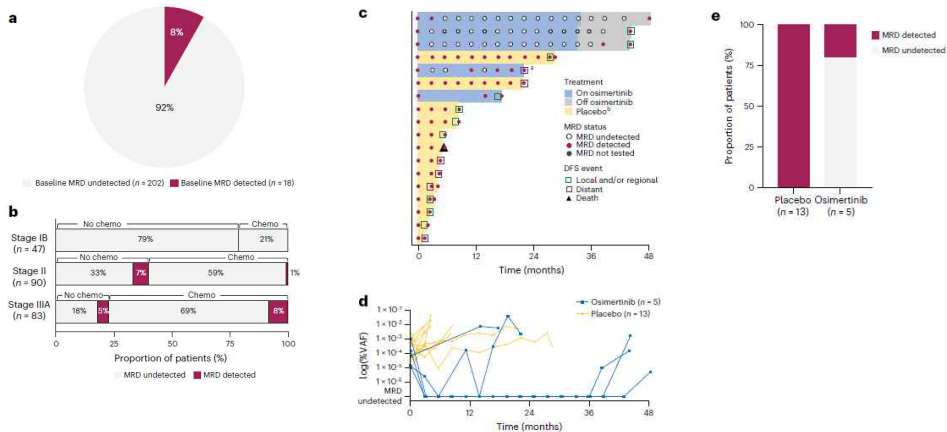


No. at Risk	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84
ctDNA clearance															
Nivolumab+chemotherapy	24	22	22	22	22	22	20	19	19	18	11	6	1	0	
Chemotherapy alone	15	15	15	14	13	13	13	11	11	9	8	7	2	0	
No ctDNA clearance															
Nivolumab+chemotherapy	19	17	16	13	11	10	10	10	10	9	4	2	1	0	
Chemotherapy alone	28	24	22	19	18	16	16	15	15	15	14	9	5	0	

7. Molecular residual disease analysis of adjuvant osimertinib

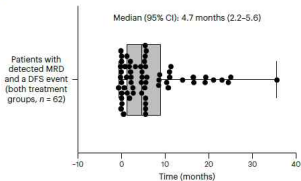


7. Molecular residual disease analysis of adjuvant osimertinib

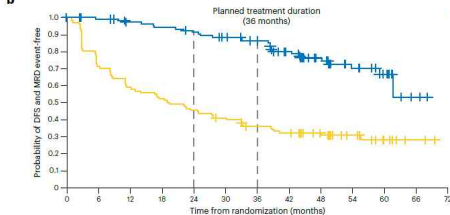


7. Molecular residual disease analysis of adjuvant osimertinib

a



b



No. at risk	0	6	12	18	24	30	36	42	48	54	60	66	72
Osimertinib (n = 112)	112	107	101	98	94	89	84	67	47	28	16	2	0
Placebo (n = 108)	108	76	63	56	49	43	36	32	23	14	7	2	0

Percent (95% CI)	DFS and MRD event-free rate	
	24 months	36 months
Osimertinib (n = 112)	91 (84-95)	86 (78-92)
Placebo (n = 108)	46 (36-55)	36 (27-45)
HR (95% CI) 0.23 (0.15-0.36)		
Median follow-up time, months (95% CI): osimertinib: 44.2 (42.4-49.1), placebo: 19.1 (11.1-28.3)		

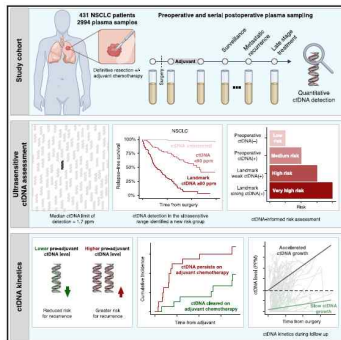
8. Longitudinal ultrasensitive ctDNA monitoring

Cell

Article

Longitudinal ultrasensitive ctDNA monitoring for high-resolution lung cancer risk prediction

Graphical abstract



Authors

James R.M. Black, Takahiro Karasaki, Charles W. Abbott, ..., Sean M. Boyle, Richard O. Chen, Charles Swanton

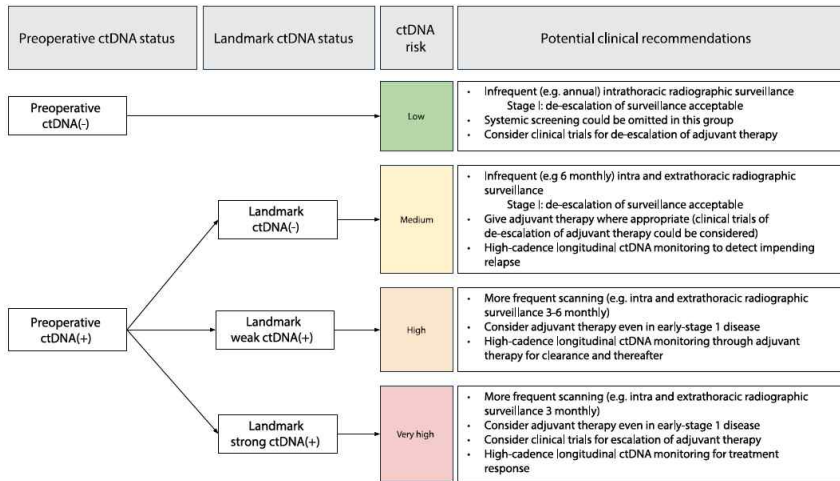
Correspondence

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In brief

Longitudinal ultrasensitive ctDNA detection improves disease stratification accuracy, demonstrates clinical utility for adjuvant therapy, and reveals insights into characteristic features of relapse in patients with non-small cell lung cancer.

8. Longitudinal ultrasensitive ctDNA monitoring



CANCER RESEARCH

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**Volume 85, Issue
8_Supplement_1**
15 April 2025



POSTER PRESENTATIONS - PROFFERED ABSTRACTS | APRIL 21 2025

Abstract 7138: Whole genome sequencing-based detection of minimal residual disease using individual-specific features FREE

Jun Hyeok Lim; Jeong-Seon Ryu; Ji Won Byun; Jongsuk Chung; Hyun-Tae Shin

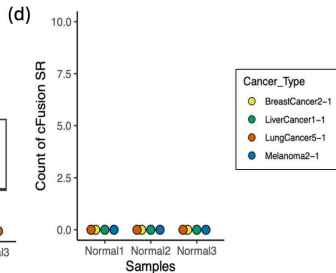
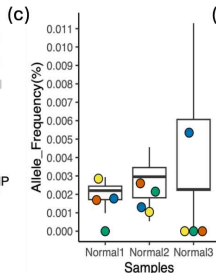
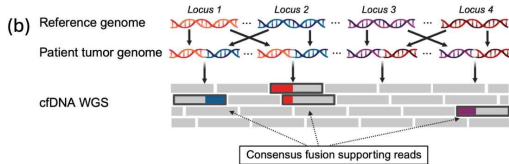
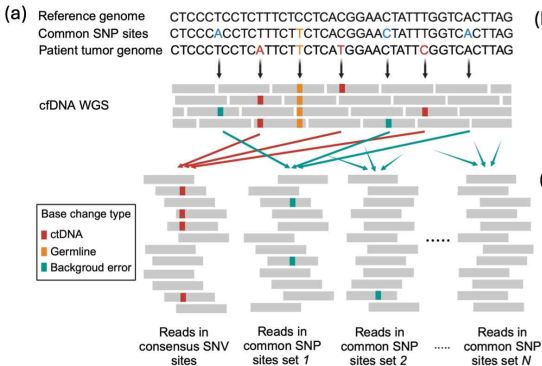


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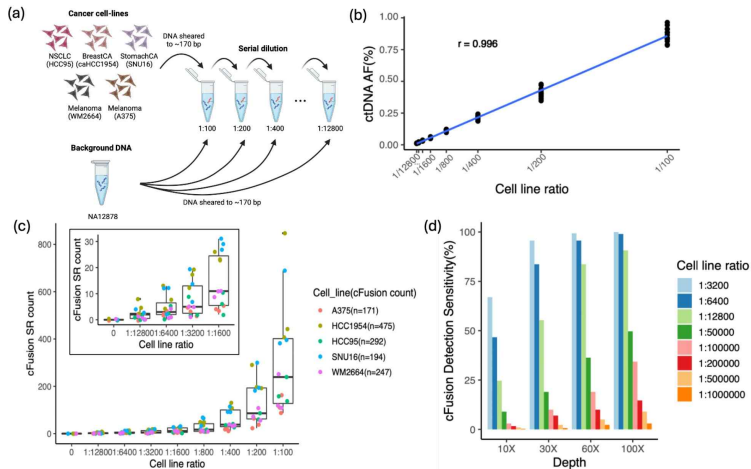
Cancer Res (2025) 85 (8_Supplement_1): 7138.

AACR 2025

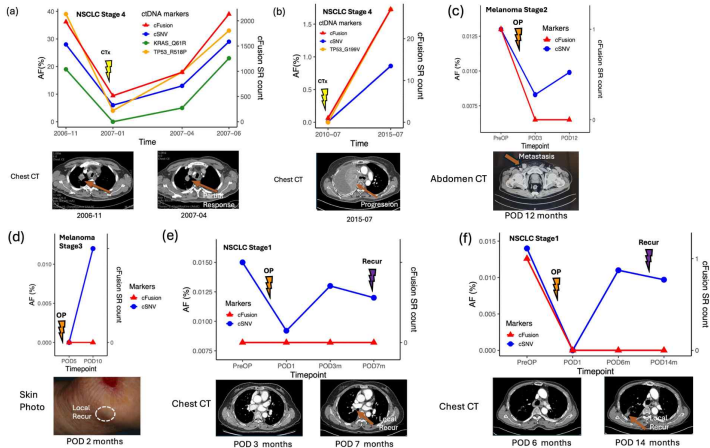
WGS based detection of MRD



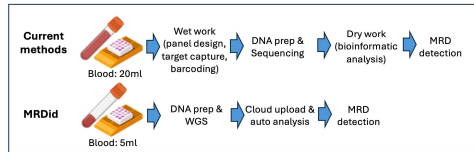
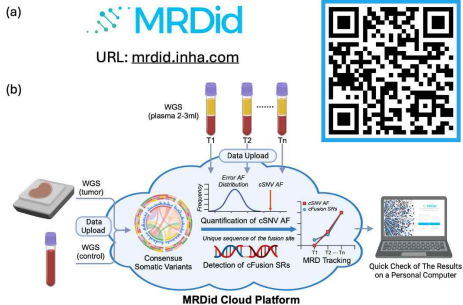
WGS based detection of MRD



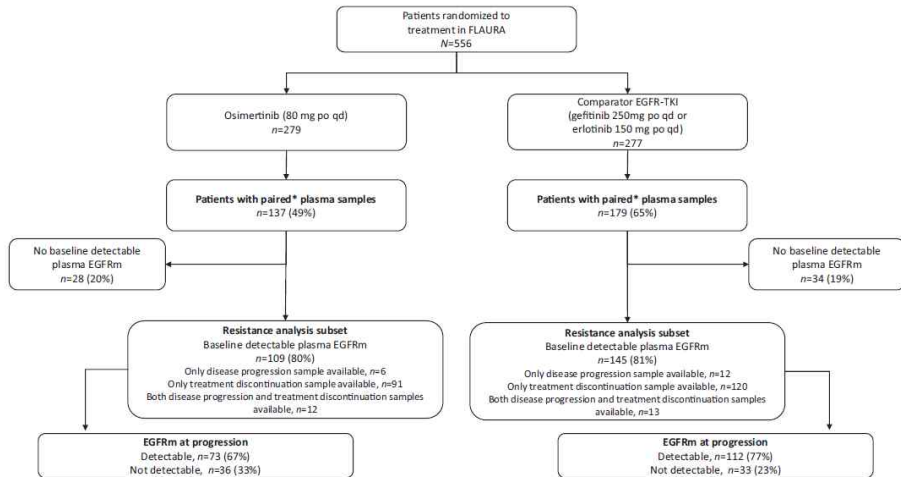
WGS based detection of MRD



WGS based detection of MRD

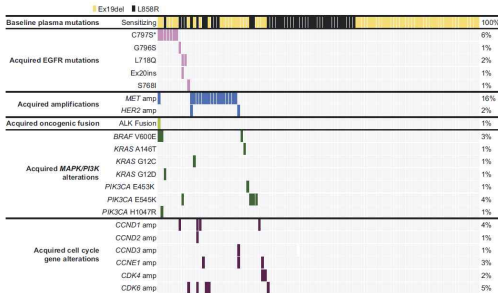


Acquired resistance to first-line osimertinib



Acquired resistance to first-line osimertinib

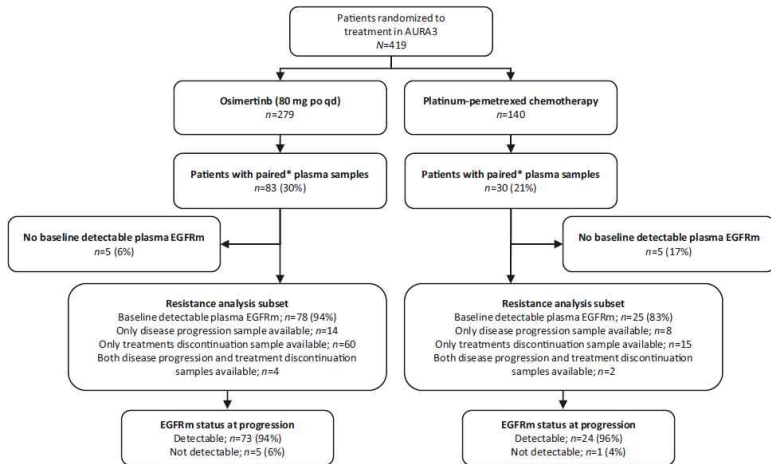
Osimertinib



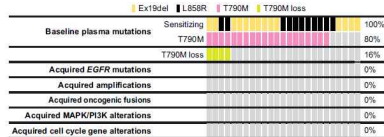
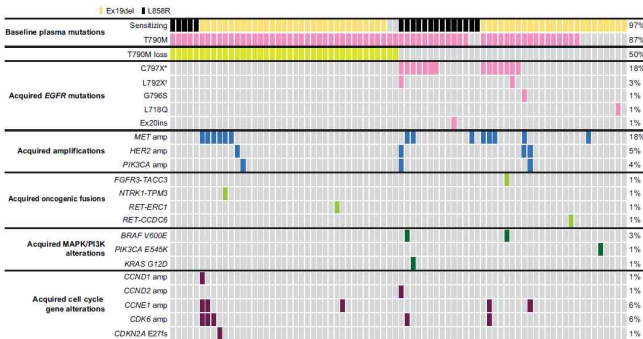
Comparator EGFR-TKI



Acquired resistance to second-line osimertinib

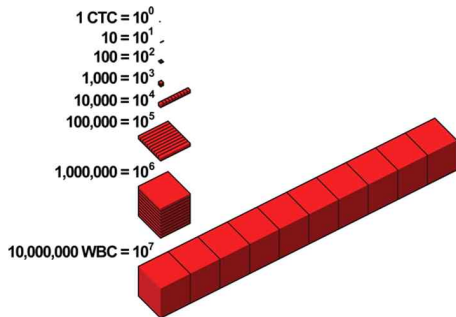


Acquired resistance to second-line osimertinib



Limitation of CTC-based Liquid Biopsy

CTCs are extremely rare



If 1 CTCs in 1 mL of human blood...

1/5,000,000

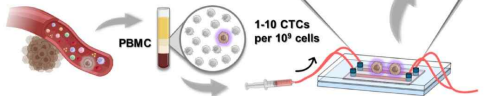
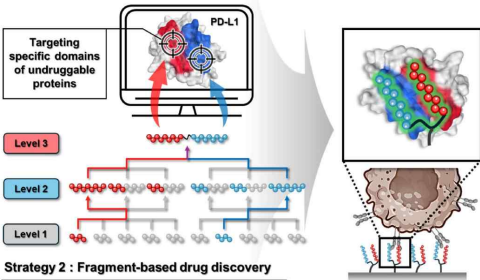
Death due to thunderbolt



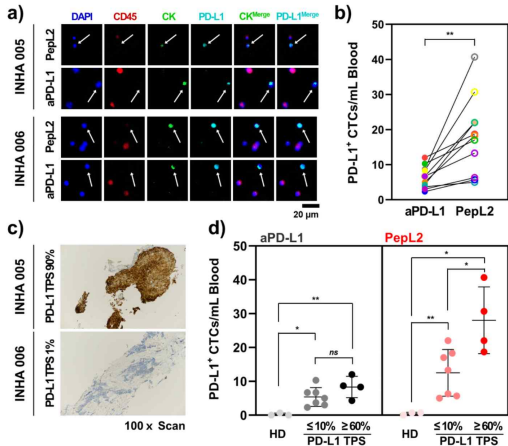
1/4,280,000

Capture of PD-L1+ CTC

Strategy 1 : In silico peptide library screening



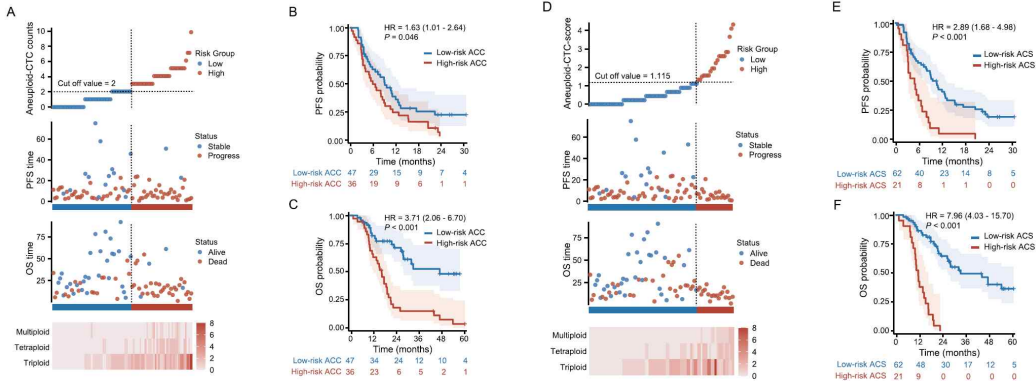
Circulating tumor cell (CTC) detection from blood samples of cancer patients



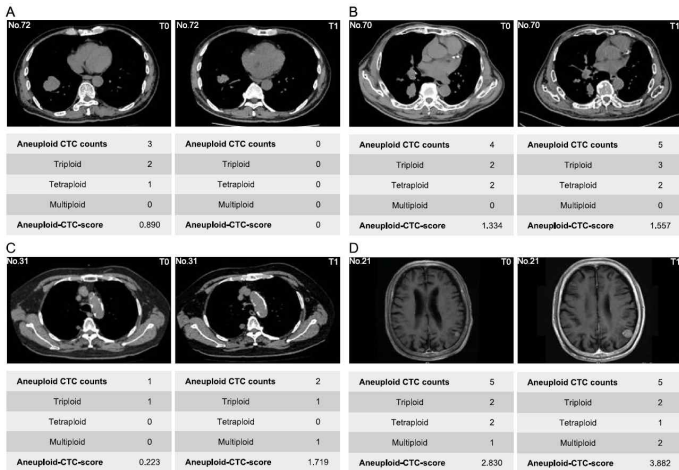
Chem Eng J, 2025

Speaker's Data

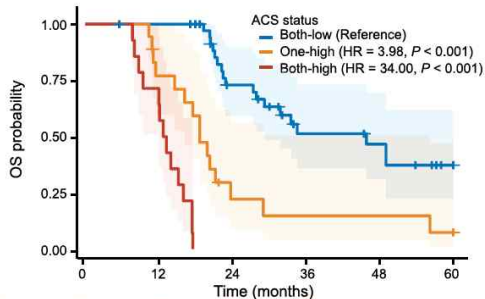
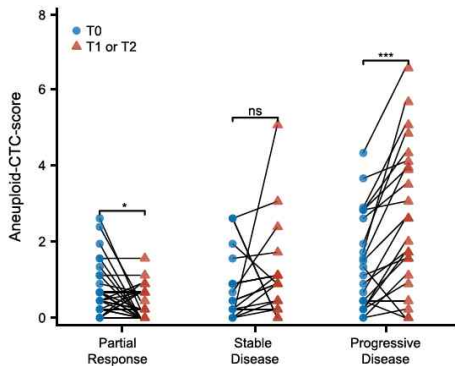
CTC with increasing aneuploidy predict prognosis in SCLC



CTC with increasing aneuploidy predict prognosis in SCLC

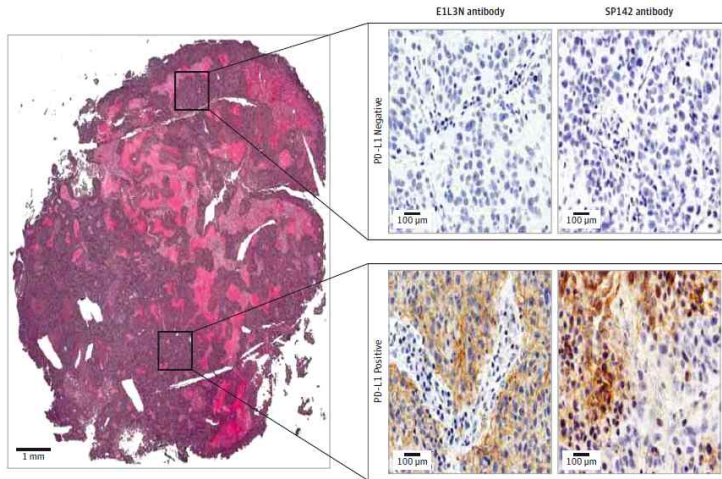


CTC with increasing aneuploidy predict prognosis in SCLC

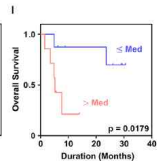
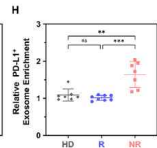
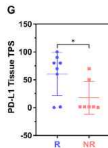
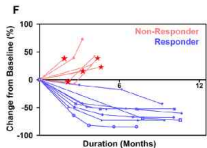
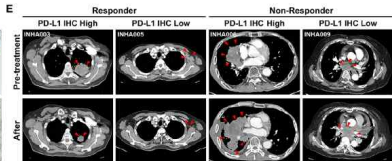
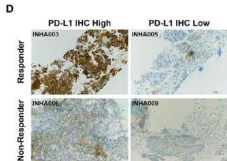
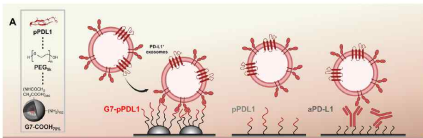


Both-low	38	37	23	12	8	3
One-high	18	13	3	2	2	0
Both-high	14	8	0	0	0	0

Heterogeneity of PD-L1 expression

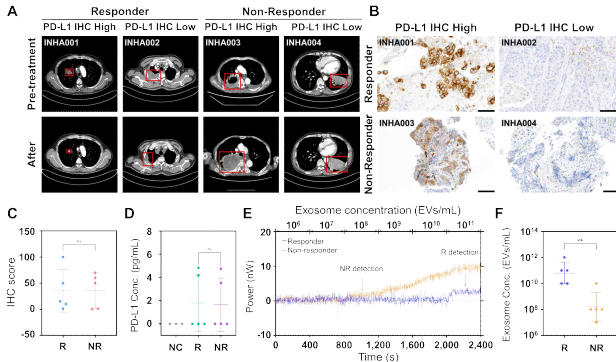
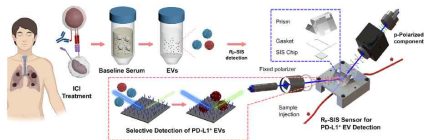


Exosome based prediction of ICI response (1)



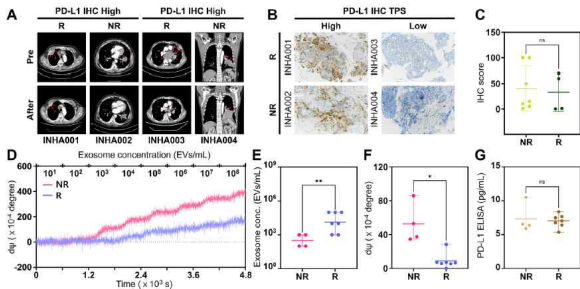
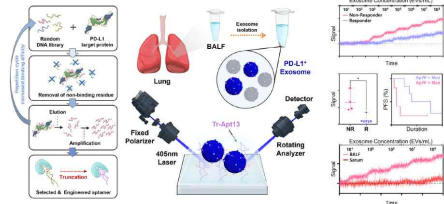
Advanced Science, 2025

Exosome based prediction of ICI response (2)



Small, 2025

Exosome based prediction of ICI response (3)



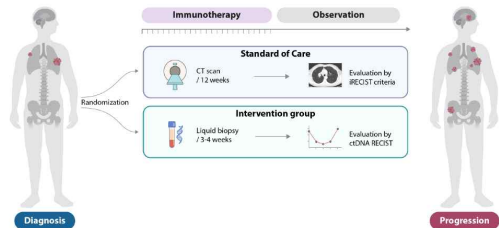
Advanced Science, 2026

BMJ Open ctDNA guided immunotherapy in patients with advanced non-small cell lung cancer: a nationwide Danish, randomised, intervention study (PRELUCA – PRediction in LUnG CAncer Treatment) – study protocol

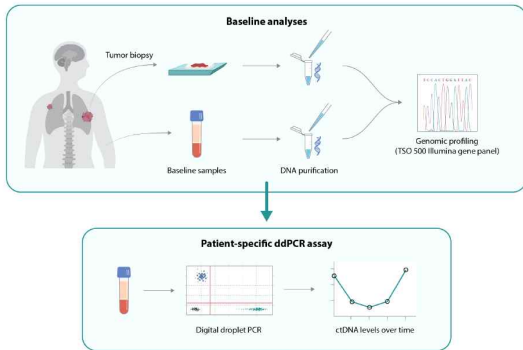
Michael Elmkvist Andersen ^{1,2} Christa Haugaard Nyhus,³
Weronika Maria Szejniuk,^{4,5} Stine Wahlstrøm,⁶ Signe Timm ^{7,8}
Niels Pallisgaard,^{9,10} Malene Green Madsen,⁹ Maria Dalgaard Mikkelsen,⁹
Lise Barlebo Ahlborn,¹¹ Julie Gehl ^{1,2} Malene Støchkel Frank^{1,2}

Future directions – ctDNA guided immunotherapy

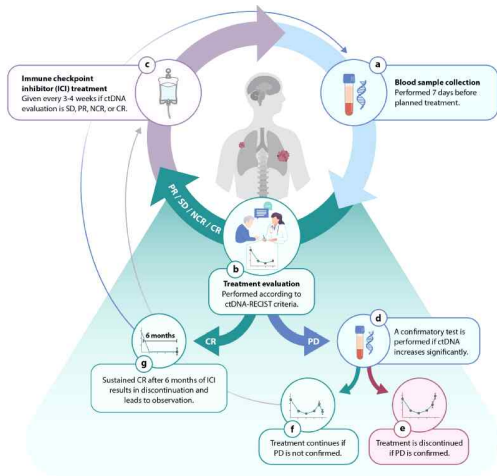
A



B

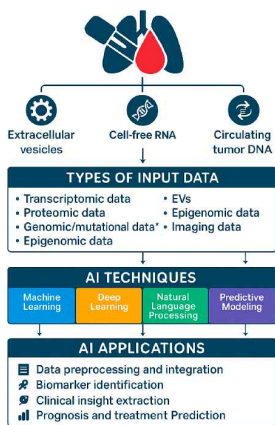


Future directions – ctDNA guided immunotherapy

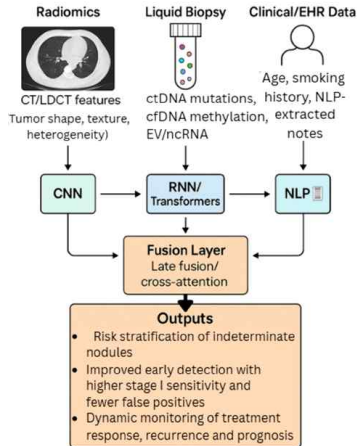


Future directions – Liquid biopsy + Radiomics with AI

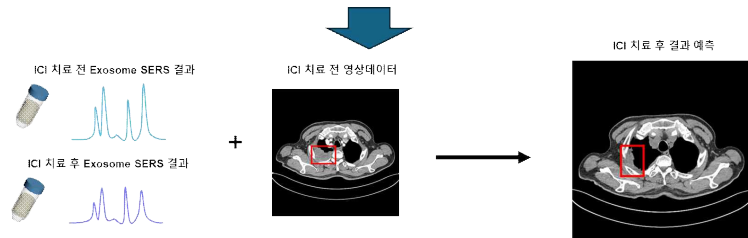
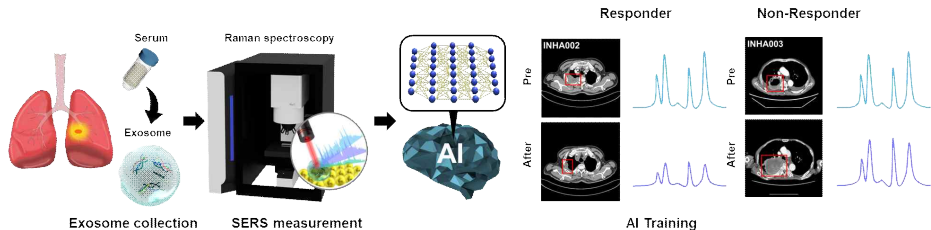
AI-Driven Liquid Biopsy Workflow



AI-driven multimodal integration framework



Future directions – Liquid biopsy + Radiomics with AI



Summary

- **Limitations of Tissue Biopsy**

- Invasive procedure with potential complications
- Rebiopsy often limited by tumor location and patient condition
- Limited representation of tumor heterogeneity

- **Advantages of Liquid Biopsy**

- Minimally invasive and repeatable sampling
- Enables longitudinal monitoring
- Better captures spatial and temporal tumor heterogeneity

Summary

- **Key Liquid Biopsy Components**

- Circulating tumor DNA (ctDNA)
- Circulating tumor cells (CTC)
- Extracellular vesicles (EV) / exosomes

- **Strengths and Limitations**

- ctDNA: High sensitivity for genomic alterations. Limited phenotypic information,
- CTCs: Provide cellular and protein-level insights. Technically challenging due to rarity.
- Exosomes: Abundant and stable. Currently less standardized for clinical use.

Summary

- **Clinical Applications**

- Early detection
- Therapeutic applications

- **Applications in Treatment Setting**

- Real-time treatment monitoring
- Detection of minimal residual disease (MRD)
- Identification of acquired resistance mechanisms
- More sensitive detection of actionable biomarkers at diagnosis



Thank you for your attention