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Research experience as young respiratory physician

2023 동계 분자폐암연구회 임상연구 워크숍

2023. 02. 11
영남대학교병원 호흡기알레르기 내과
안 준 홍

Contents

- From the first study until now
- Currently in progress
- Future research plan

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연구의 원동력

- 임상적 궁금증
  - 내가 잘하고 있나?
- 함께하는 동료
  - Colleagueship ≥ Authorship
- 위기를 기회로

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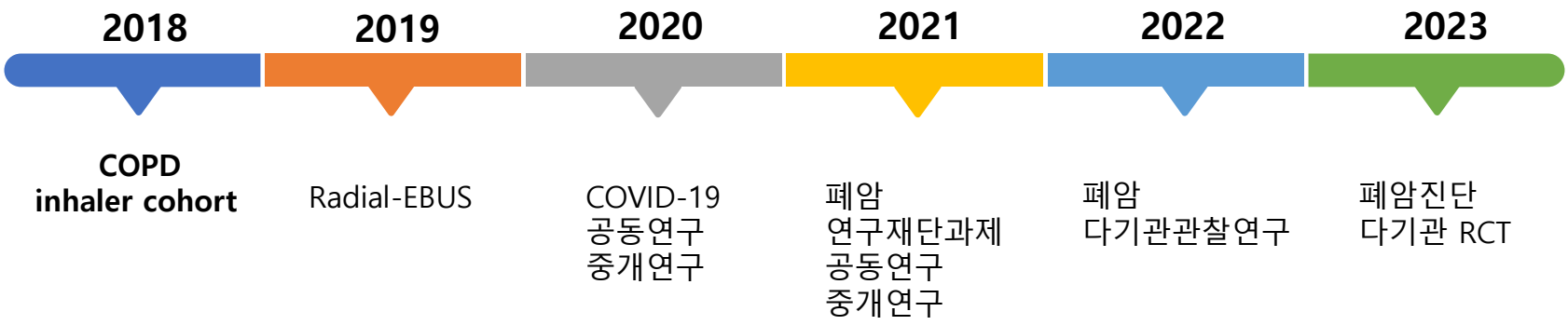
From the first study until now

안준홍

- [진료과] 호흡기·알레르기내과
- [주연구분야] 폐암의 조기진단과 치료, 만성폐쇄성폐질환
- [직위] 교수
- [진료과목] 폐암의 진단과 치료, 폐결절, 만성폐쇄성폐질환

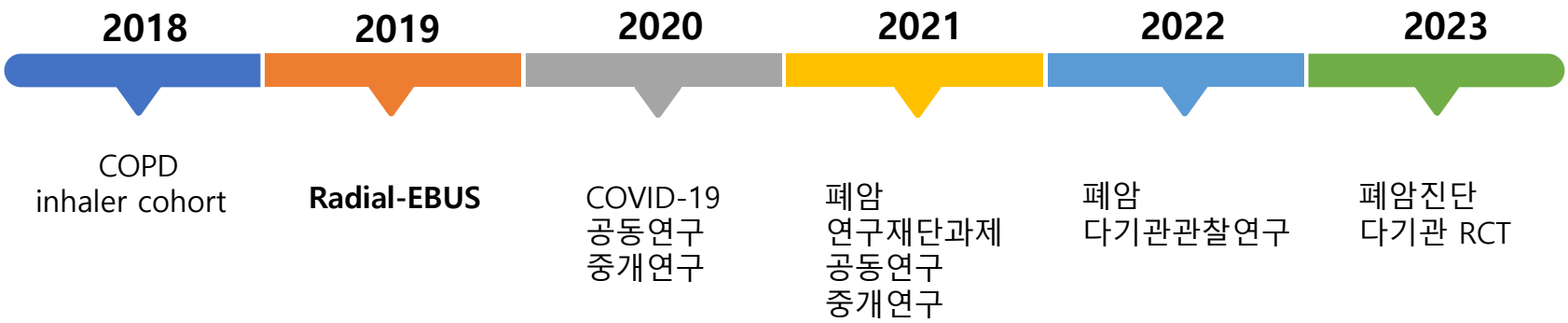
2018	2019	2020	2021	2022	2023
COPD inhaler cohort	Radial-EBUS	COVID-19 공동연구 중개연구	폐암 연구재단과제 공동연구 중개연구	폐암 다기관관찰연구	폐암진단 다기관 RCT

2018 (Y1)



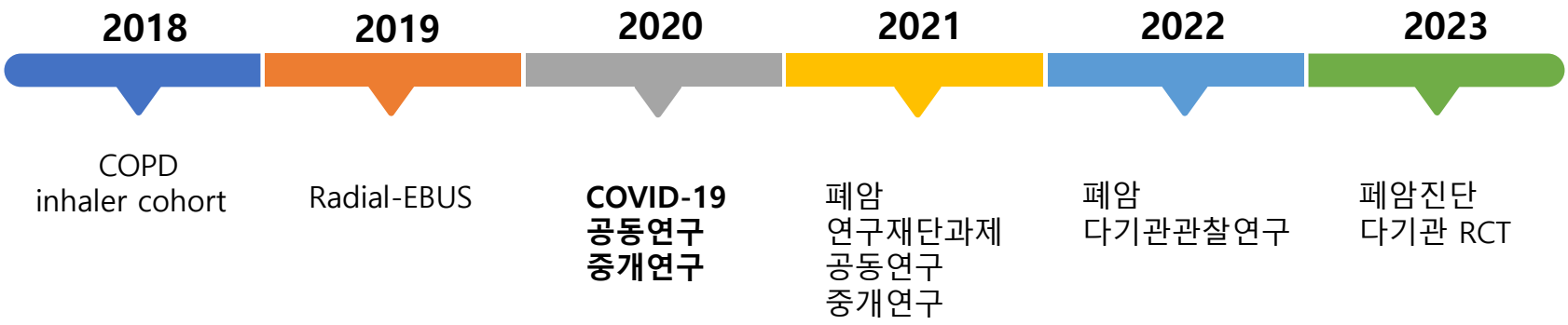
- 부족한 연구비 → 단일 기관 코호트 연구
- 폐암 진료에 대한 경험이 별로 없음 → 연구에 대한 아이디어 부족
- **COPD inhaler cohort study (권역 호흡기 센터, 교육 간호 인력 풍부) (single center prospective interventional study)**
- SCIE #4
  - Critical inhaler error & AE (2019)
  - Educational effect (2020)
  - Comparative study of device technique (2021)
  - Assessment of inhaler satisfaction (2022)

2019 (Y2)



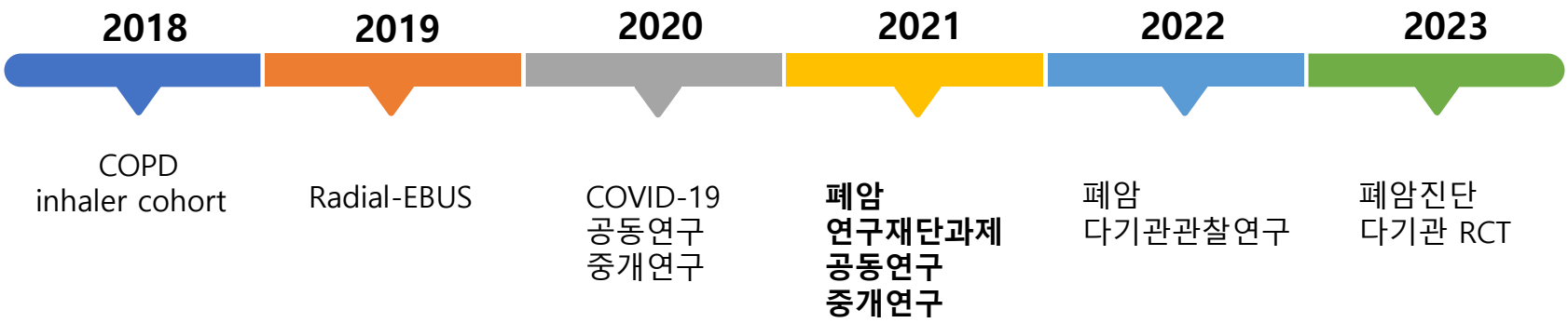
- 부족한 연구비 → 단일 기관 연구
- 부족한 폐암 진료 인력
  → 폐암 진단에 대한 어려움 (영상의학과 의사 부재)
- 말초 폐병변 진단에 대한 기술 습득 (TTNB, Radial-EBUS)
- Radial-EBUS: 2019.01-2021.08: 1000 례
- **Radial-EBUS cohort study**
  (single center retrospective observational study)
- SCIE #4, SCOPUS #1
  - TTNB by pulmonologist (2019)
  - Radial EBUS with GS without fluoroscopy (2021)
  - Radial EBUS in bronchus sign negative PPLs (2021)
  - Radial EBUS in cavitary lesions (2021)
  - EBUS guided re-biopsy after EGFR-TKI resistance (2022)

2020 (Y3)



- 권역 호흡기 전문질환센터 → 단기간에 많은 COVID-19 중환자 진료
- 적은 인력 → 진료 로딩의 증가
- 새로이 발병한 질환 → 연구에 대한 needs 증가
- **COVID-19 study (임상연구, 공동중개연구)**
- SCIE #11, SCOPUS #1 (2020-2021)
    - 공동연구 (본원 임상과, 성균관대학교, DGIST)

2021 (Y4)



- 한국연구재단 연구 책임자
  - 혁신형 의사과학자 공동연구 (2021-2022, 2년)
  - 우수신진연구 (2021-2023, 3년)

- 폐암환자의 조직 검체를 활용한 **폐암 모사 바이오칩** 제작

Preclinical tumor models

- **Platform for mechanistic research, testing new drugs**

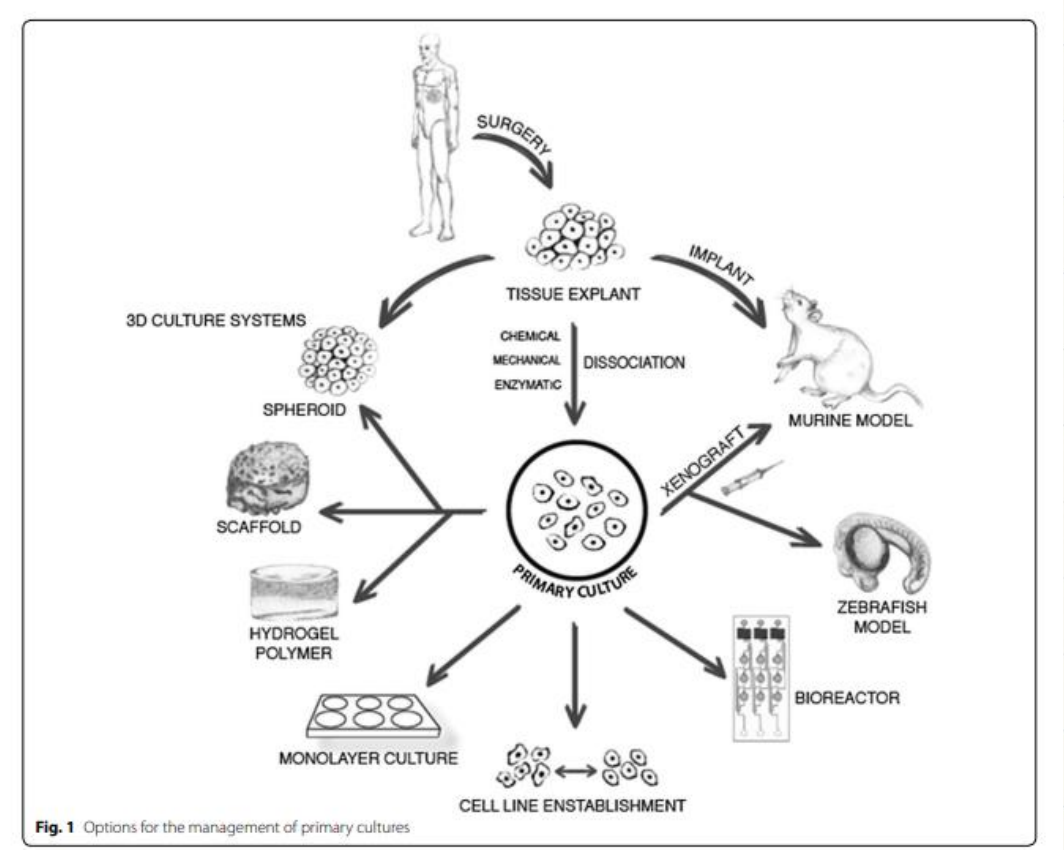


Fig. 1 Options for the management of primary cultures

J Transl Med 2017

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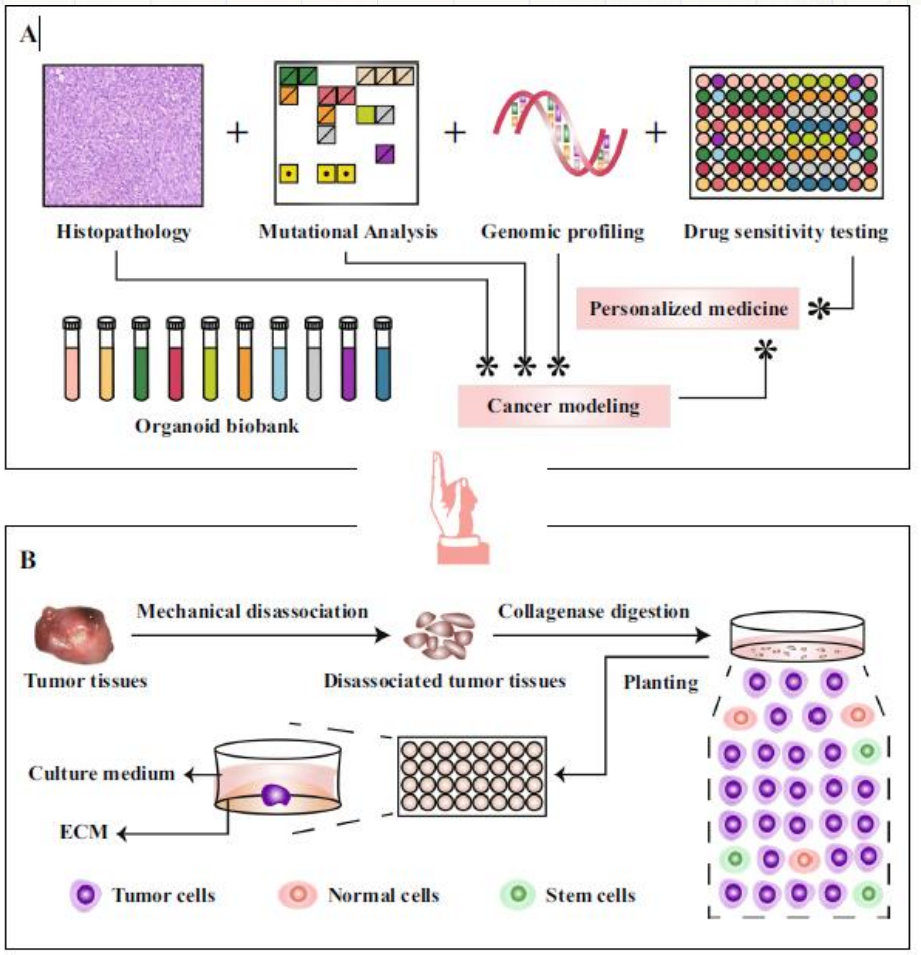
환자 유래 오가노이드 (PDO)

- 환자로부터 제공받은 정상 혹은 질환 조직으로부터 세포를 분리하여 3차원 배양상태에서 만들어진 세포 배양체



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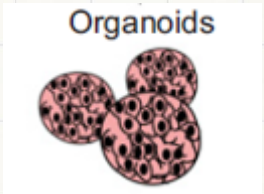
오가노이드 = 환자 아바타 모델

Patient tumor

A Histology
B Mutation
C Genomic

Organoid



A Histology
B Mutation
C Genomic

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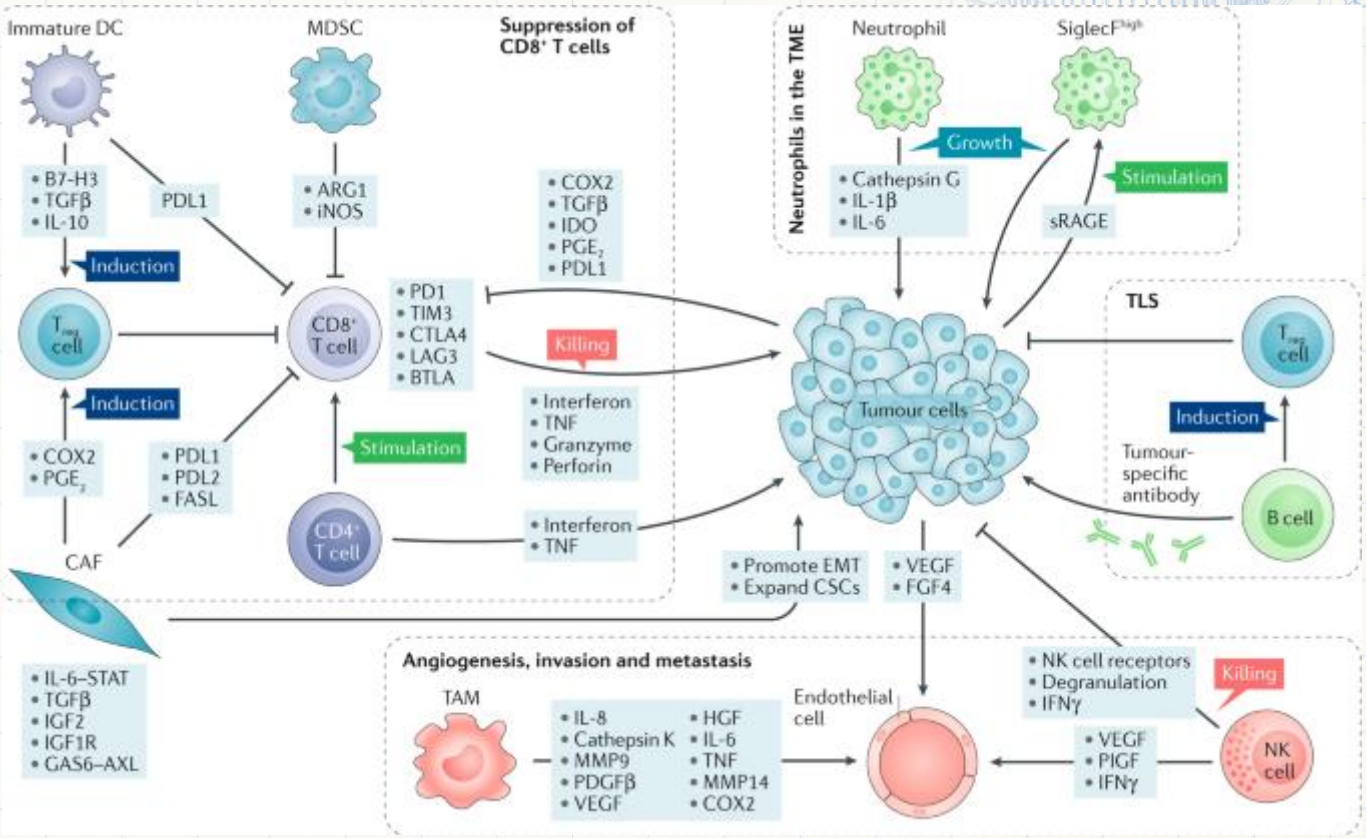
Tumor microenvironment (TME)



Nature reviews cancer 2019

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Organoid vascularization

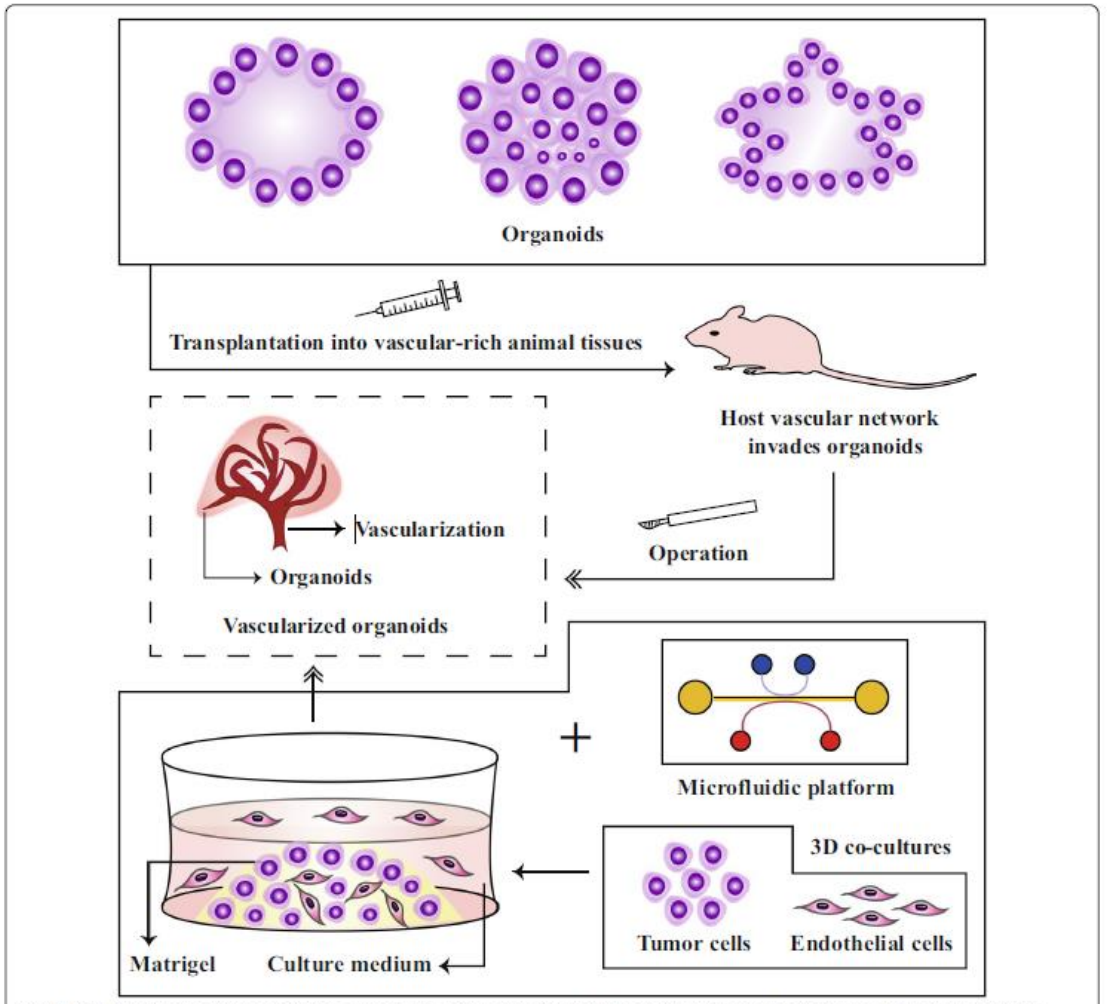

Fig. 2 Workflow of organoid vascularization. Implantation of tumoroids into highly vascularized tissues in animals is an effective approach for organoid vascularization. After organoids are engrafted in vasculature-rich mouse tissue, the host vasculature infiltrates the organoids. Another approach to generate vascularized organoids is combining the coculture of mixed cells or microfluidic platforms

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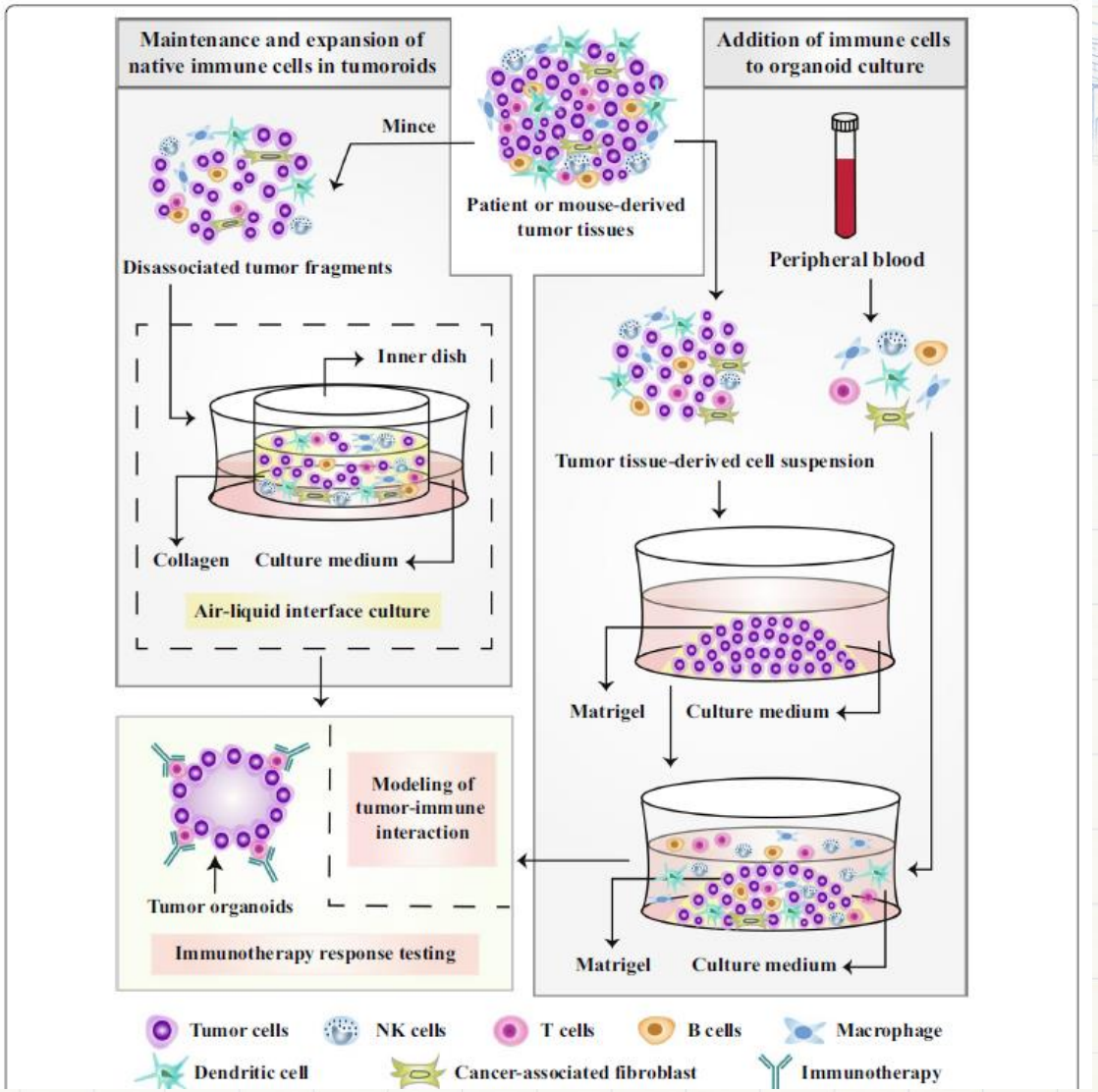
Modeling of TME



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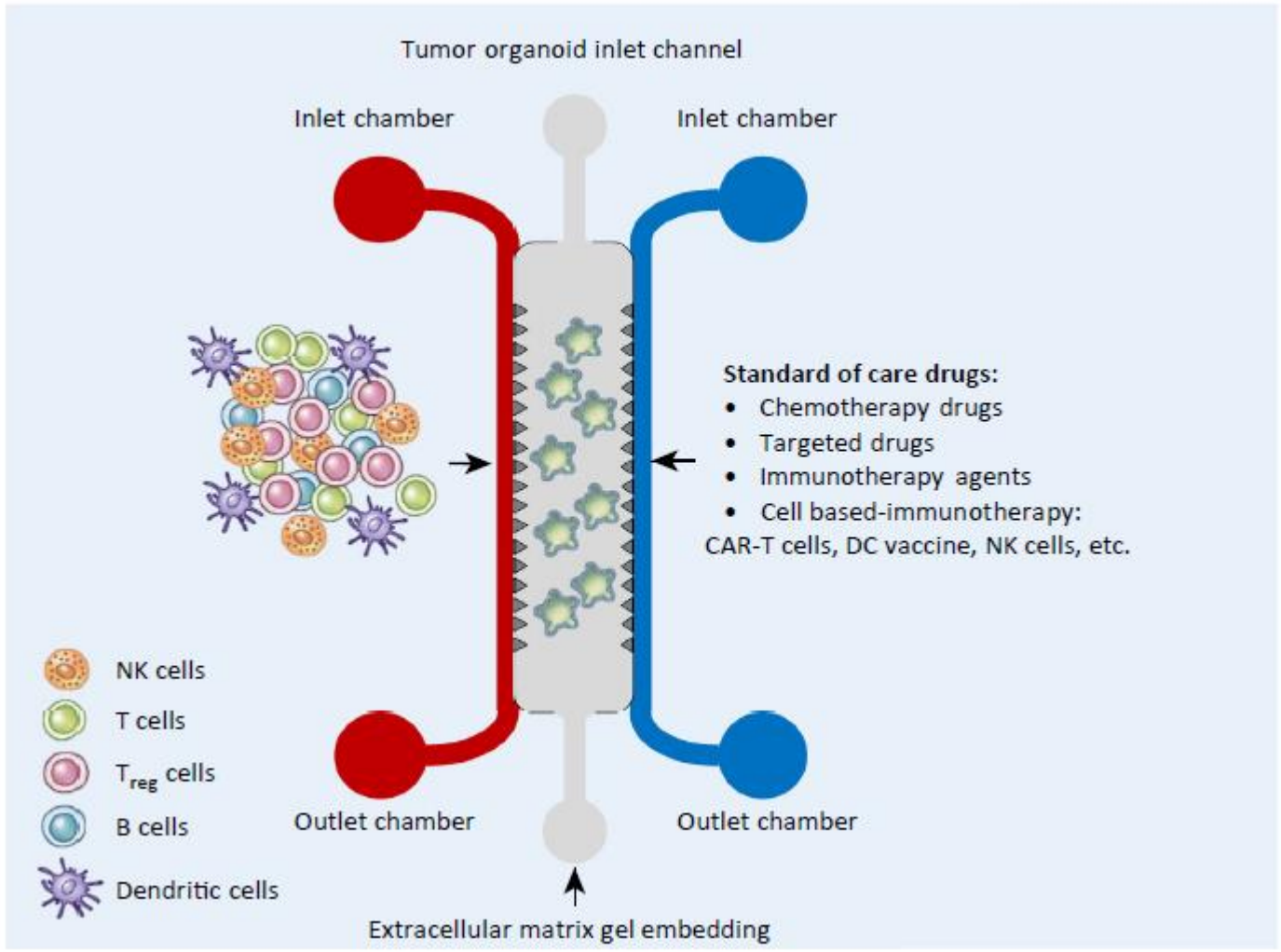
Tumor organoid-on-a chip platform



Trends in Biotechnology 2018

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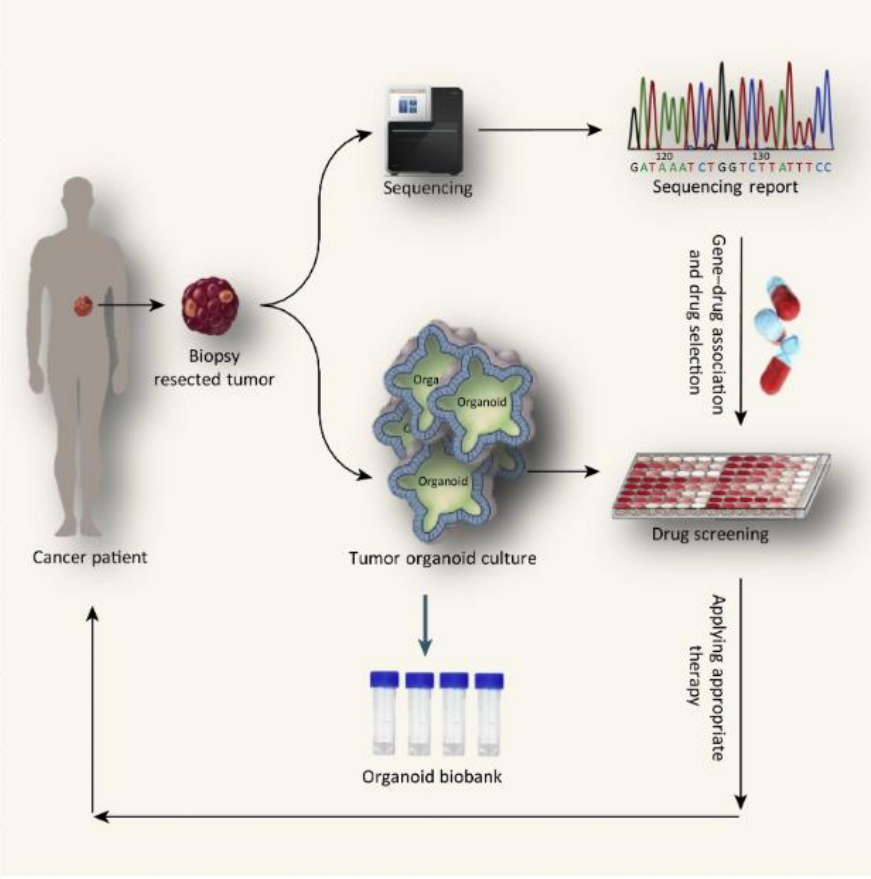
The potential for personalized medicine



- **Predicting the drug response**
- **Exploration of drug resistance-related mechanisms**
- **Exploration of promising combination treatment strategies**
- **Discovery of novel anticancer targets and promising drug candidates**

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Trends in Biotechnology 2018

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PDXs vs. PDOs

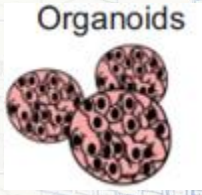

Table 2 Comparison between patient-derived xenografts (PDXs) and patient-derived organoids (PDOs)

	PDXs	PDOs
Ex vivo, in vivo, or in vitro	In vivo	Ex vivo or in vitro
Use of immunodeficient animals	Yes	No
Quantity of cells for establishment	Large	Small
Establishment time	6–8 months	4–6 weeks
Initiation success	Moderate	Moderate
Cost	More expensive	Expensive
Genetic/epigenetic alterations	Similar	Similar
Pathohistological characteristics	Similar	Similar
Response to anticancer drugs	Similar	Similar
Reliability as preclinical models	Yes	Yes
Throughput	Low	Moderate
Standardization	Moderate	Low

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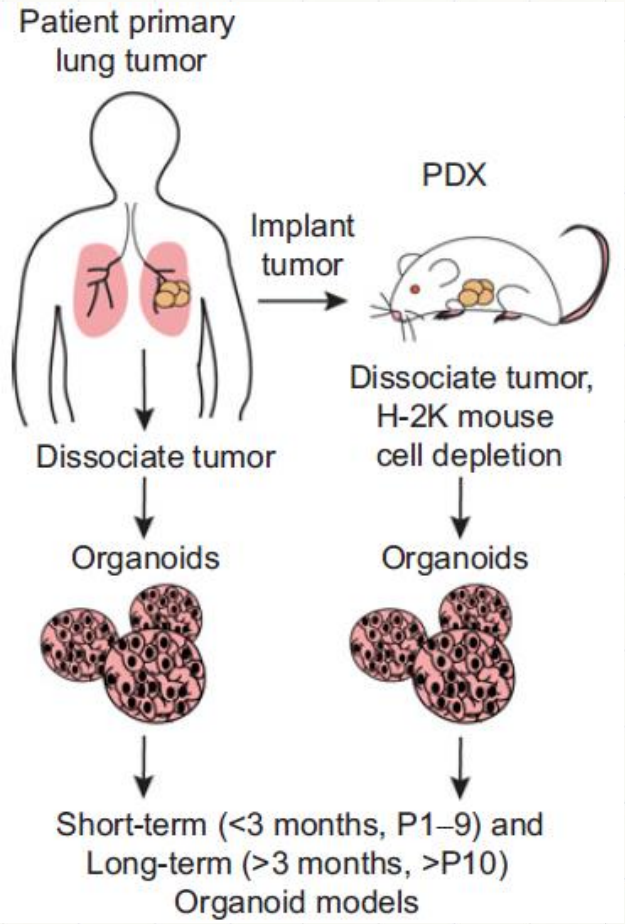
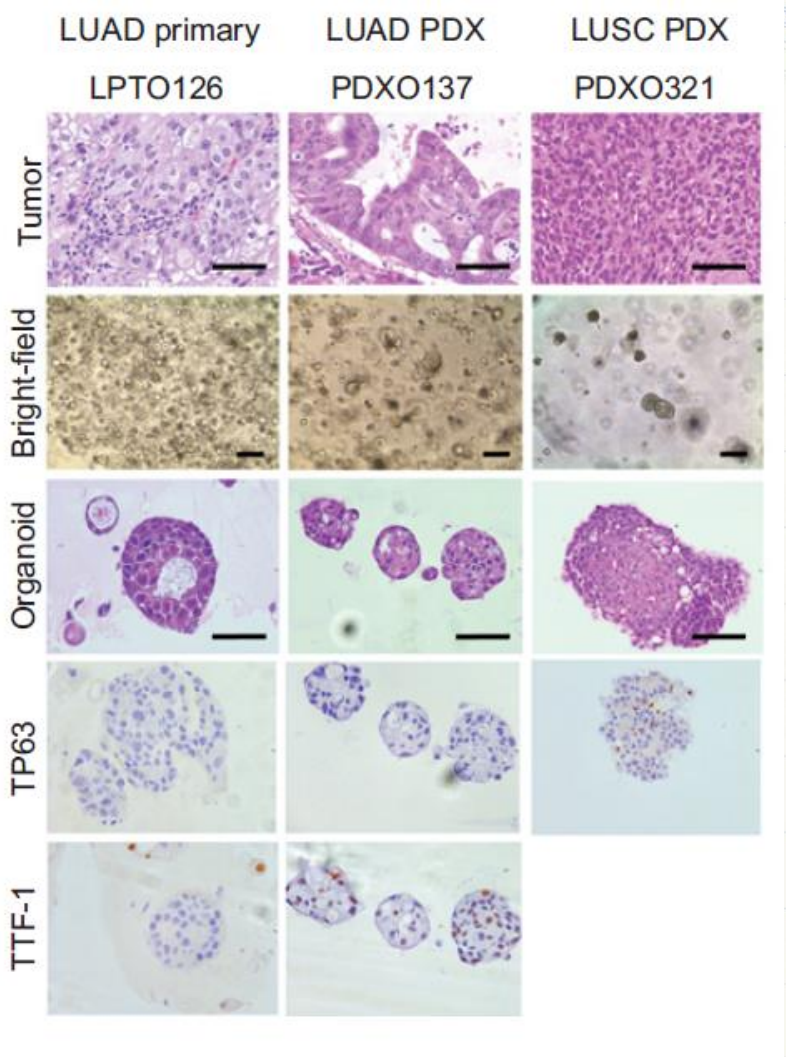
Organoid Cultures as Preclinical Models of Non–Small Cell Lung Cancer





Clin Cancer Res 2020

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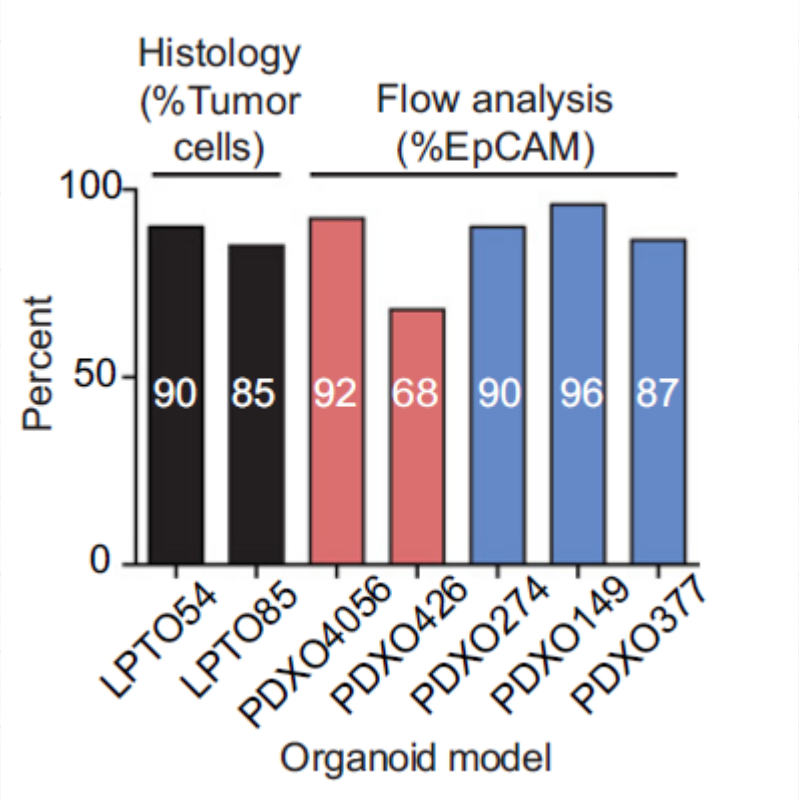
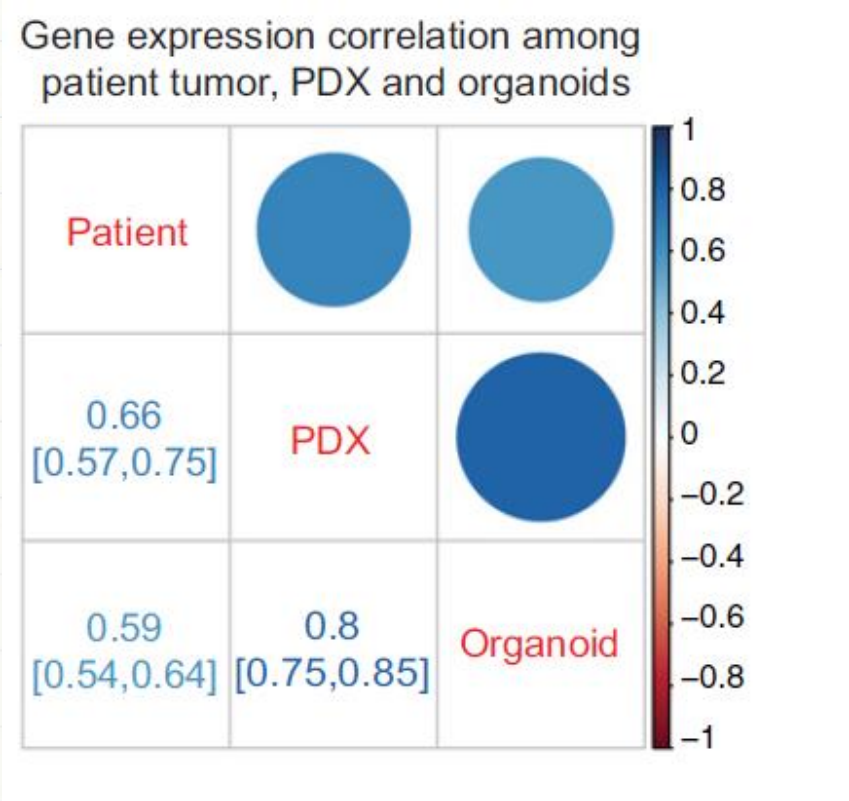
Tumor cell purity & Gene expression correlation

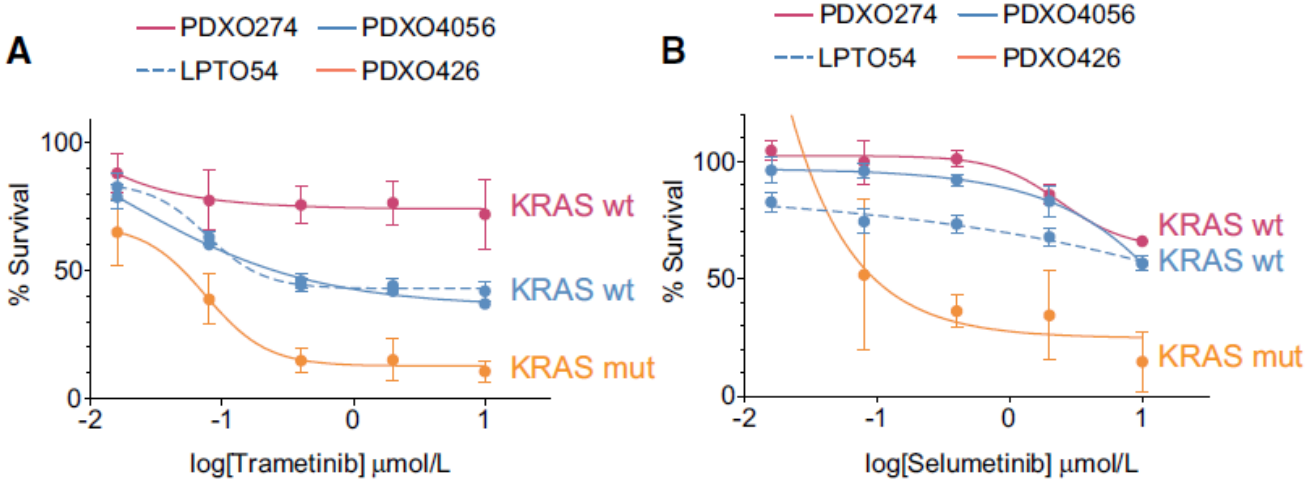




Clin Cancer Res 2020

Yeungnam University

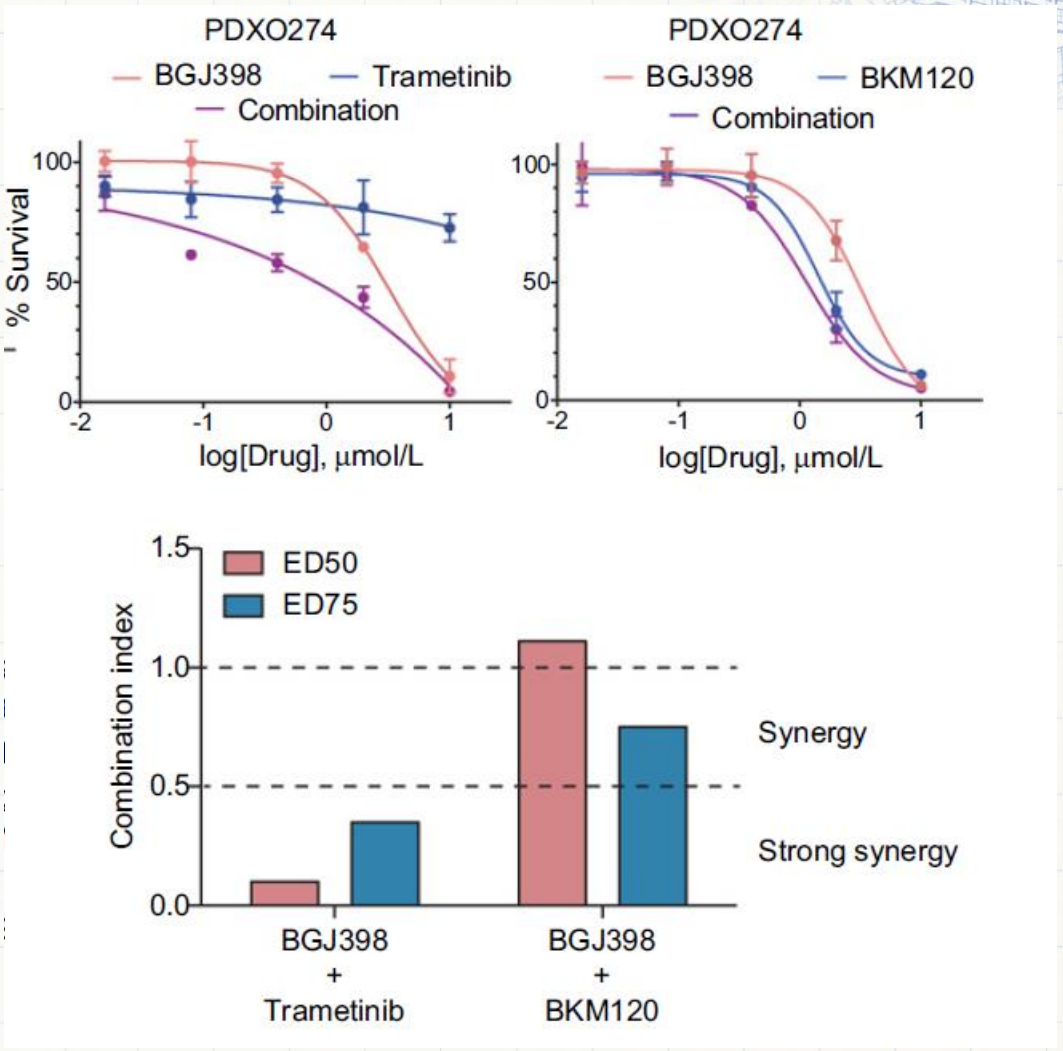
Drug testing in NSCLC organoids



Clin Cancer Res 2020

Yeungnam University

Combination of FGFR1 and MEK inhibitors in LUSC organoid models



Clin Cancer Res 2020

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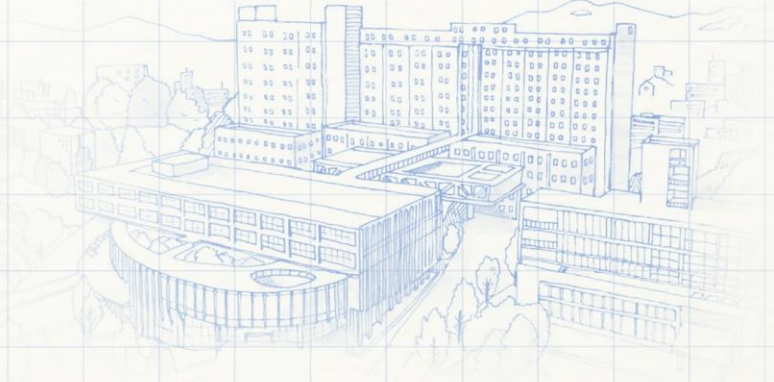
Method



- 2021.03~2022.07
- 영남대병원에서 기관지내시경 및 초음파기관지내시경을 이용해 폐암 환자에서 유래한 small biopsy sample
- Primary culture 후 Organoid 를 제작

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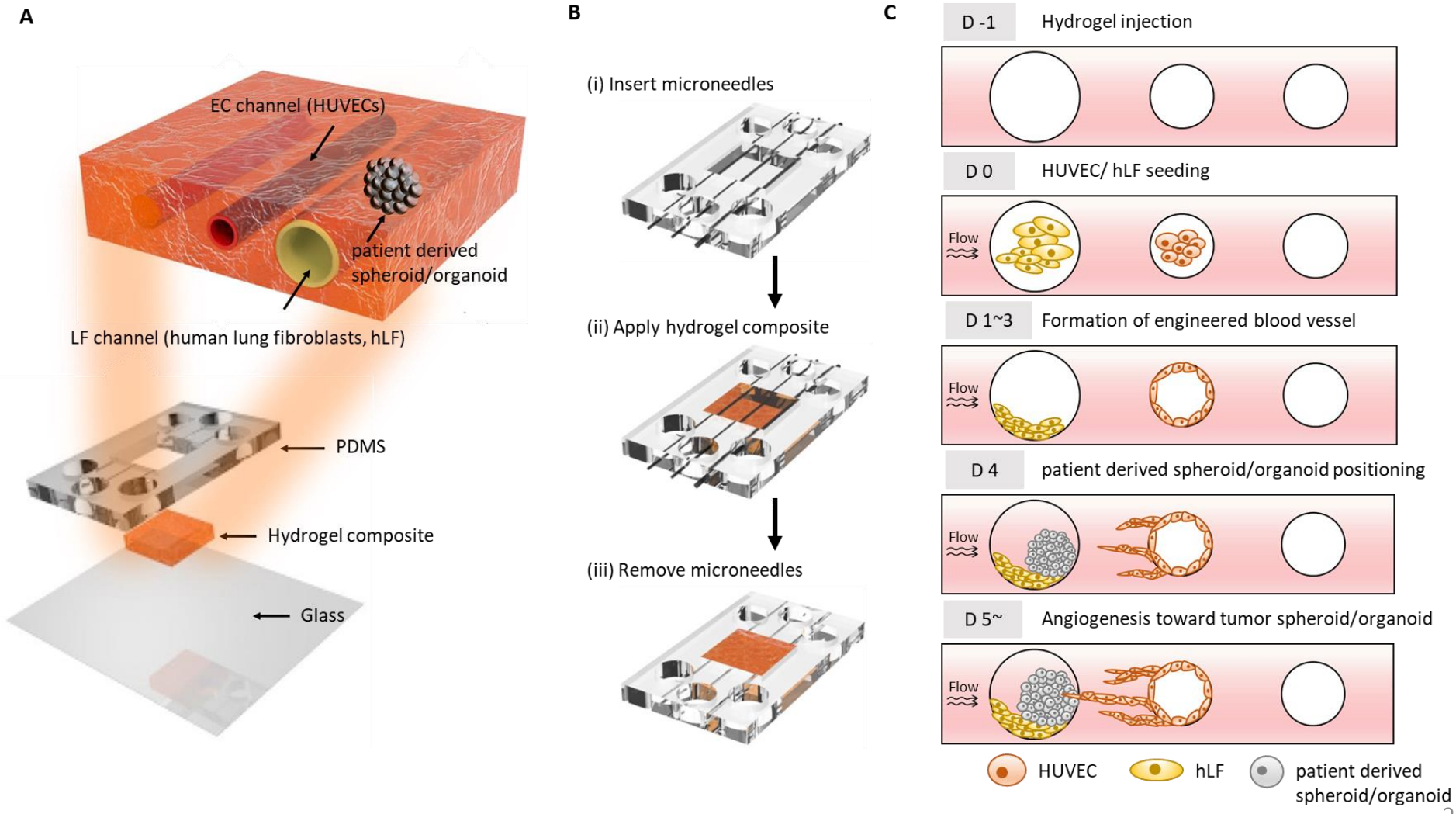
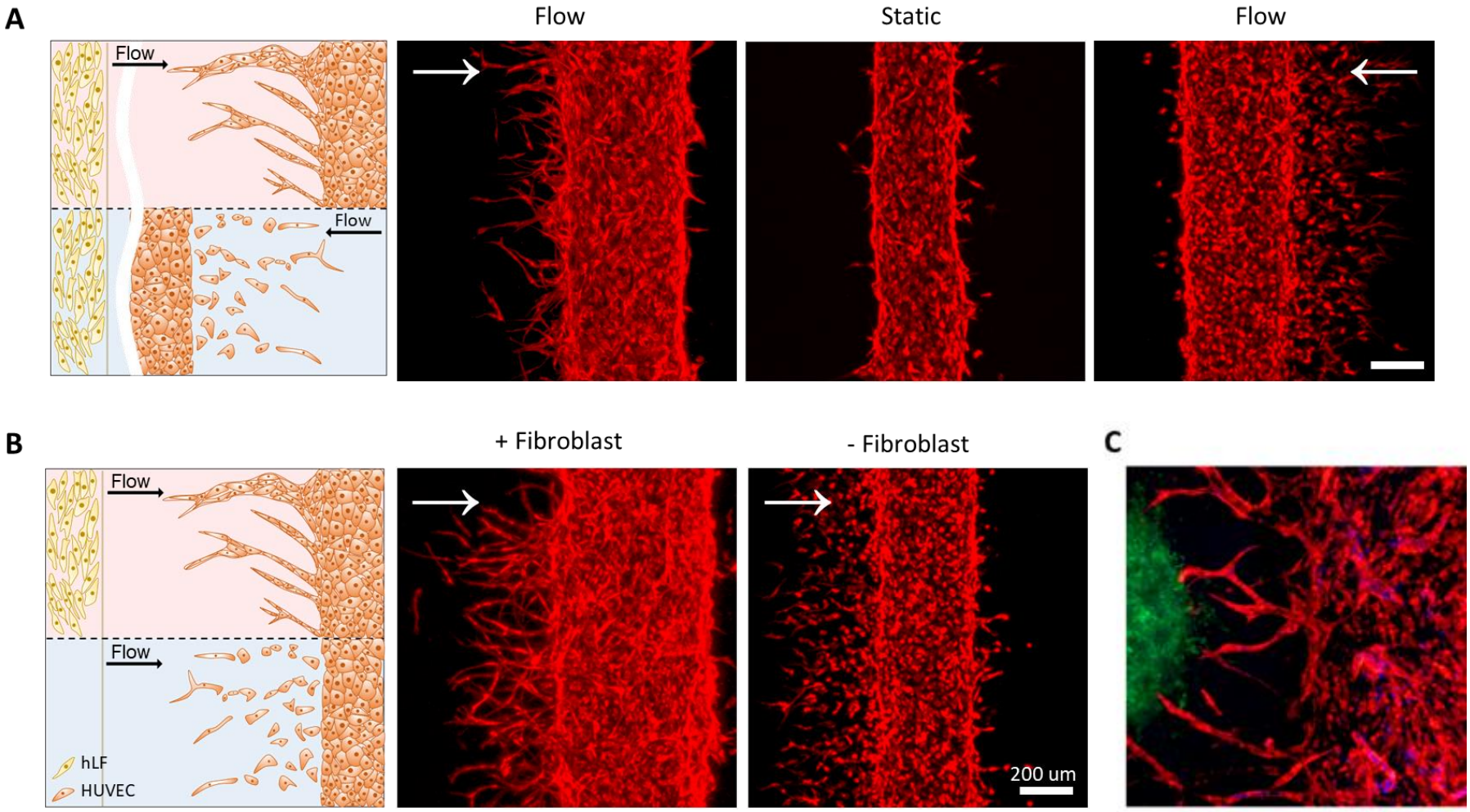
Fabrication of vascularized tumor spheroids/organoid



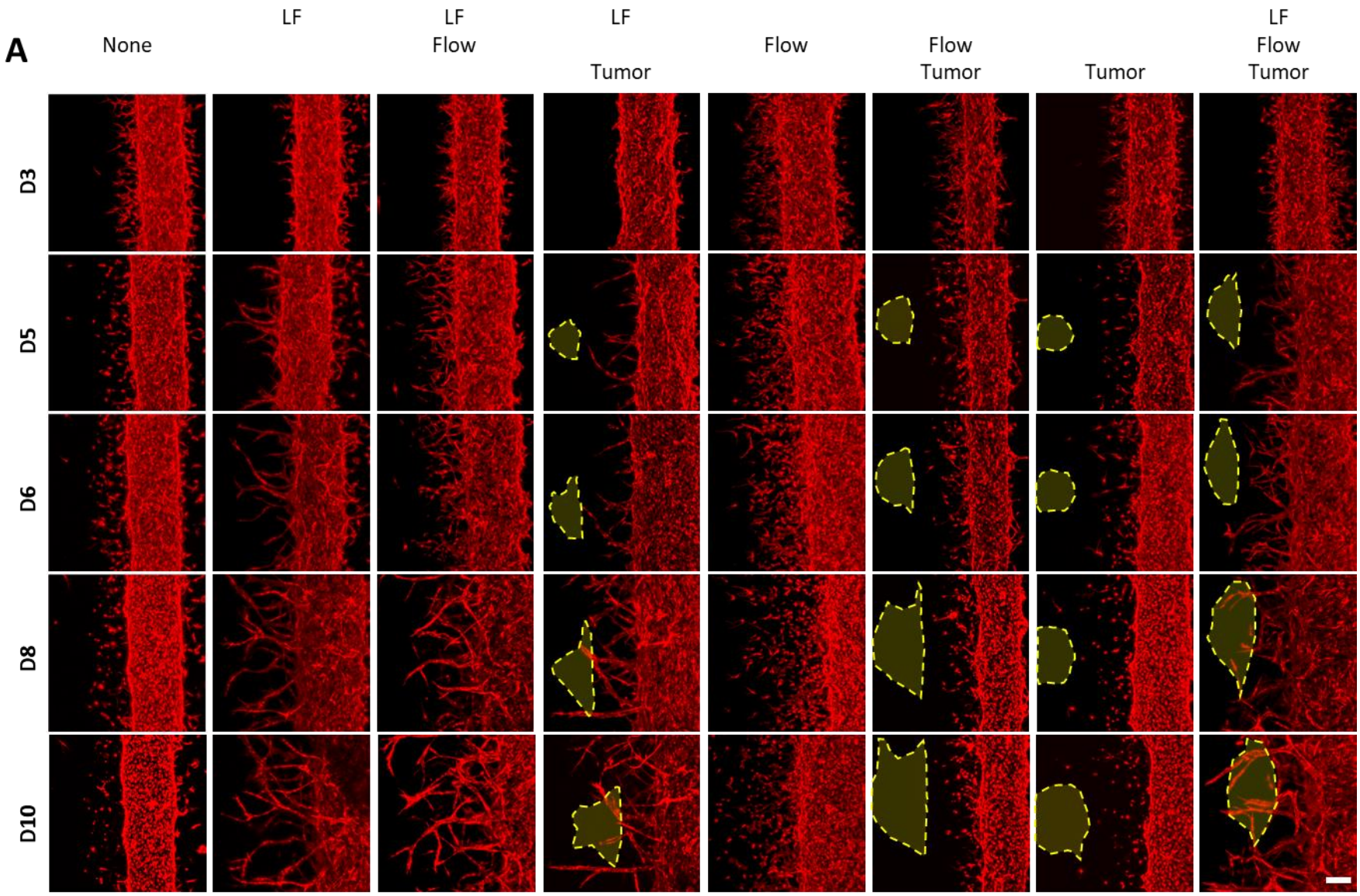
Speaker's data

Combinatorial effects of environmental factors



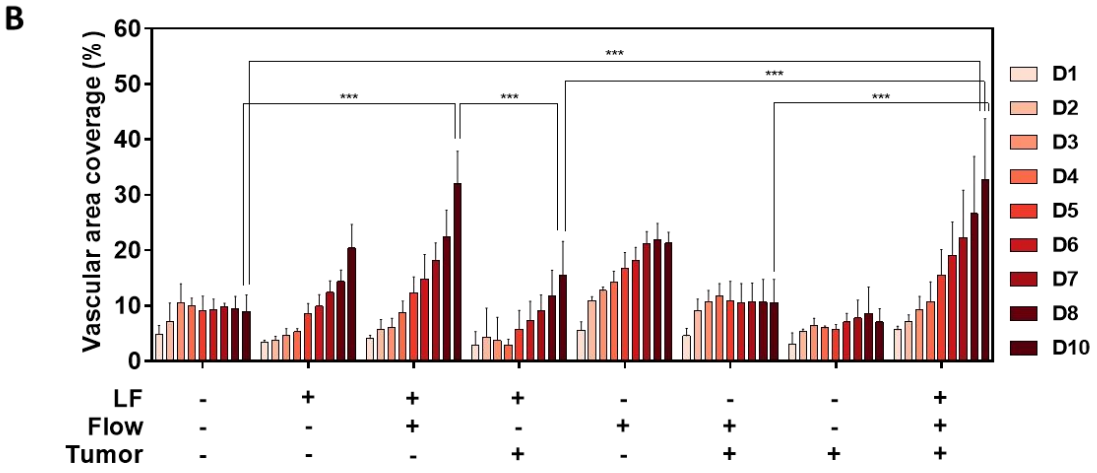
Speaker's data

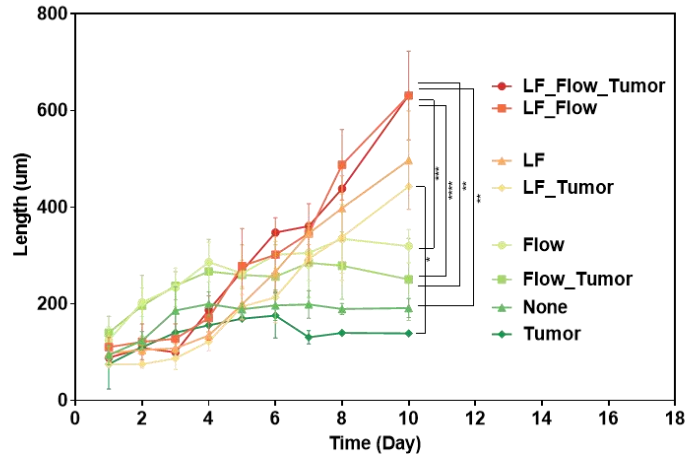
Control of angiogenesis

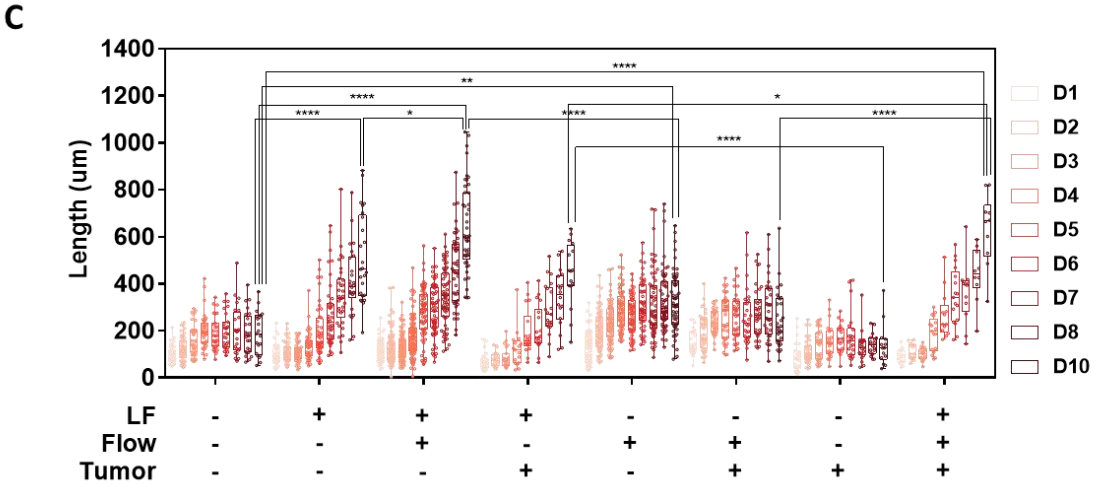


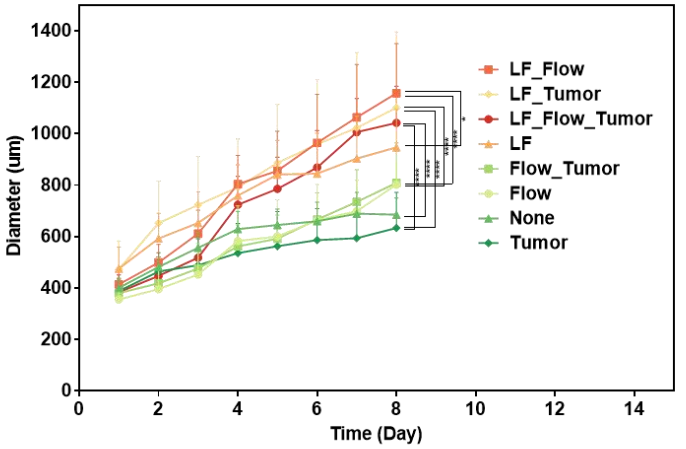
Speaker's data Scale bar: 200 μm

Control of angiogenesis



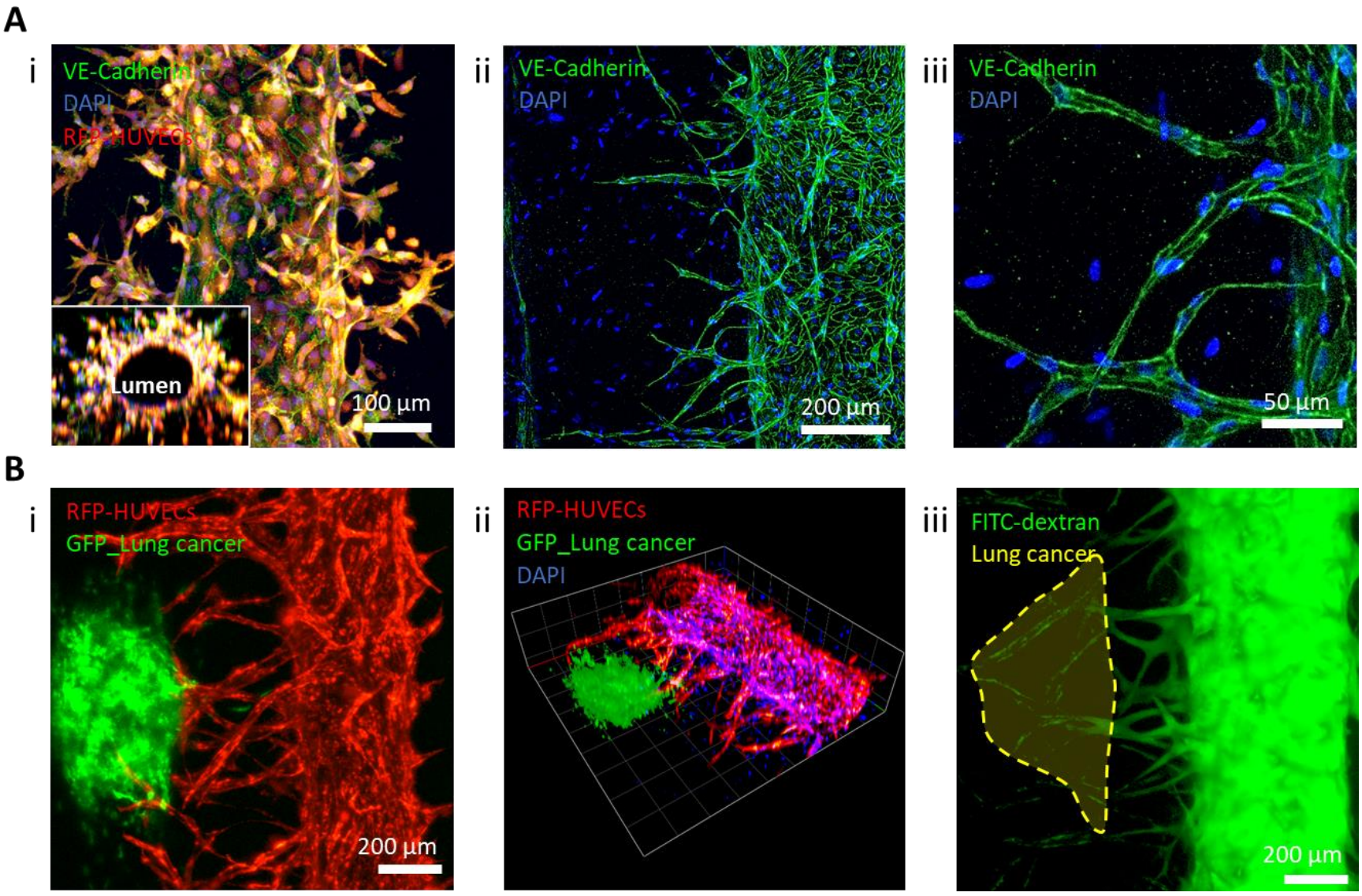






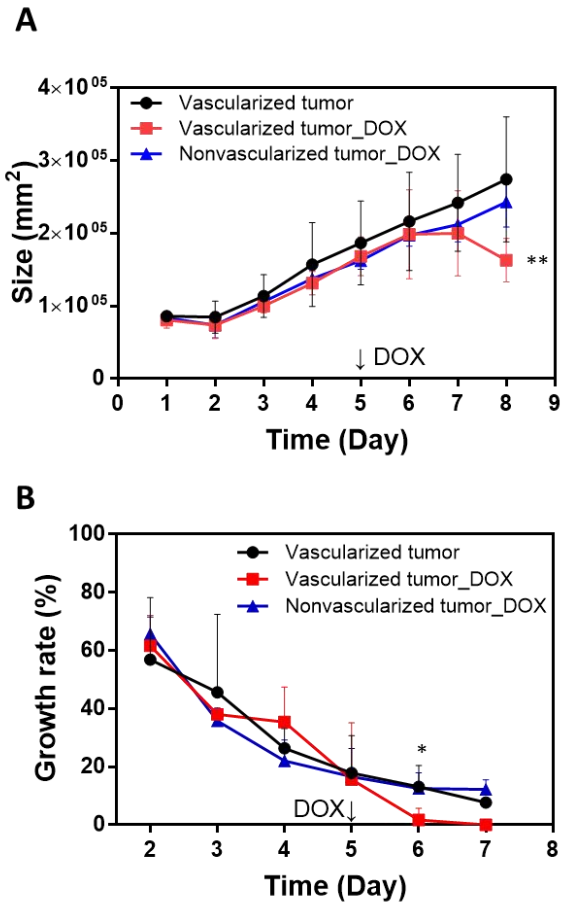
Speaker's data

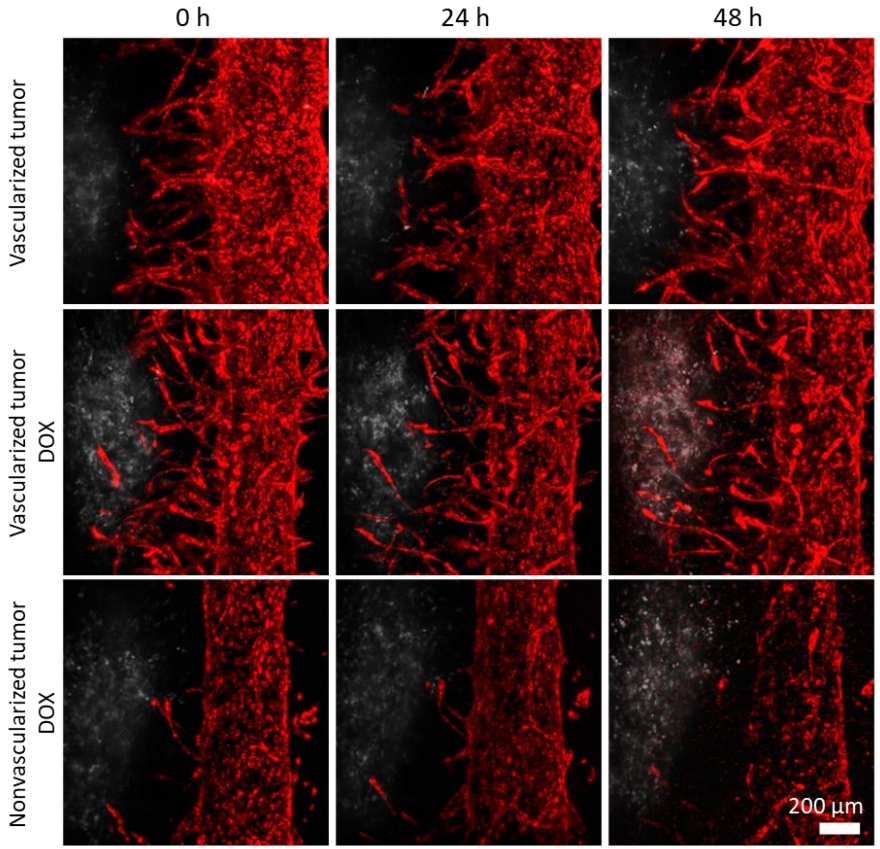
Representative immunofluorescence images

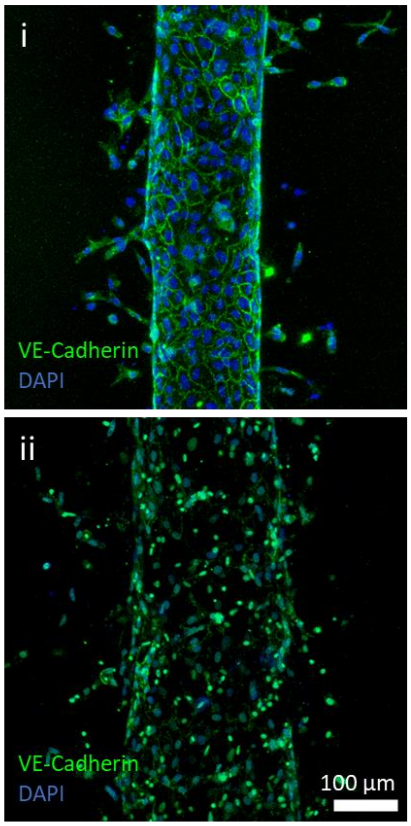


Speaker's data

Effect of vascularization: anticancer drug delivery

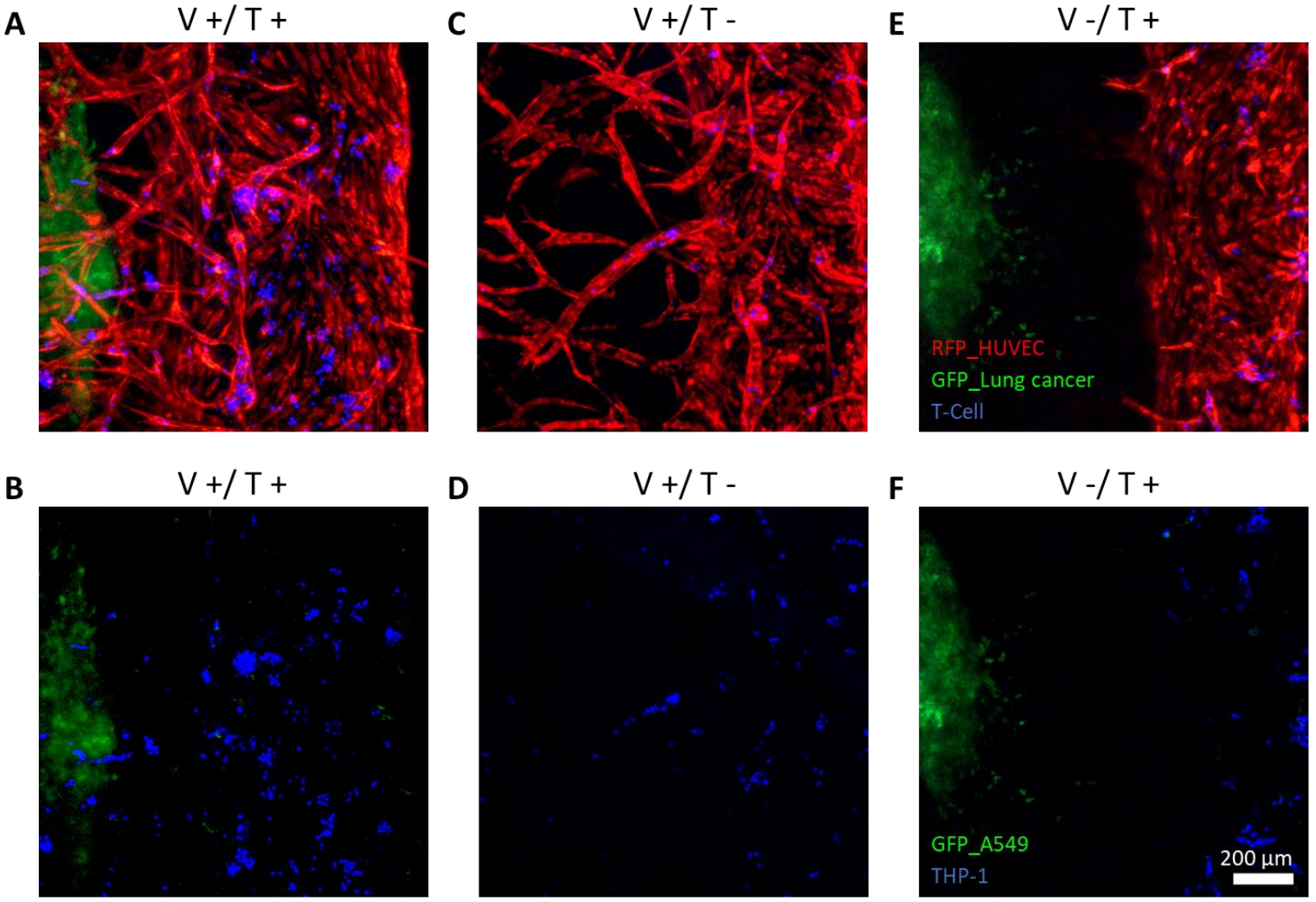






Speaker's data

Effect of vascularization: immune cell transport



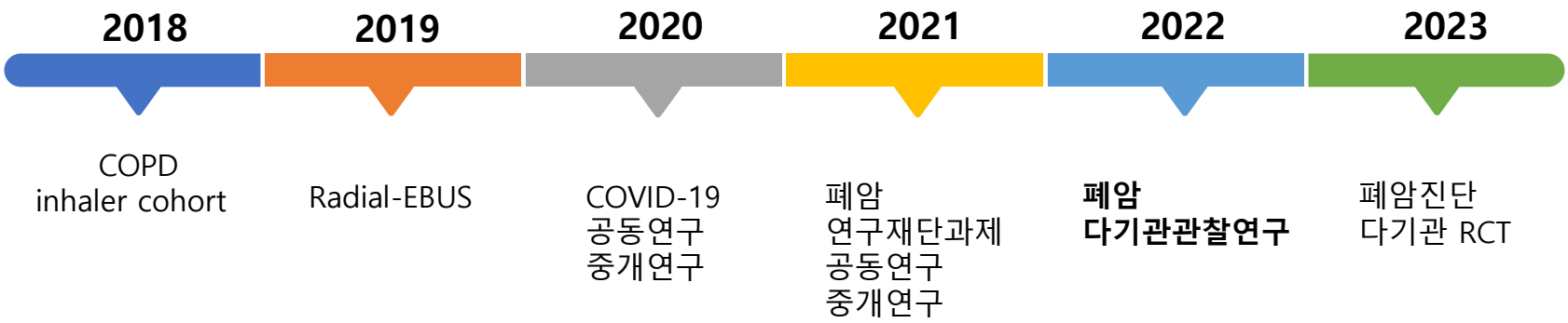
V : VEGF
T : engineered T-cell

Speaker's data

앞으로..

- TME 를 모사하기 위해 하이드로겔 합성물, 미세혈관구조를 포함하는 3D 미세유체 칩을 설계하여 폐암 세포에 대한 신생혈관의 생성을 확인
- 화합물로 항암 효능 평가를 위해 약제를 투여하여 종양세포와 신생혈관생성을 막는 효과를 확인
- 면역세포를 포함한 세포외환경을 잘 반영할 수 있는 표준화된 오가노이드 배양
- 약제 내성 기전에 대한 연구
- 다양한 전이 모델 재현 및 약제 반응성 평가
  - ex) brain metastasis

2022 (Y5)



- 폐암 진료 비중에 대한 증가 → 임상적 궁금증, 관심
- 단일 기관 연구를 하기에 연구의 파워가 약하다
- 다른 기관의 practice 를 반영한 **일반화된 연구가 필요**
- **Real-world multicenter study of durvalumab for stage III NSCLC after CCRT**

Real-world multicenter study of durvalumab for stage III NSCLC after CCRT

연구기관명 및 연구기관별 책임 연구자

- 영남대학교병원/ 안준홍 (PI)
- 경북대학교병원/ 박지은
- 계명대학교동산병원/ 권용식
- 고신대학교복음병원/ 김제훈
- 대구가톨릭대학교병원/ 최금주
- 동아대학교병원/ 김인수
- 부산대학교병원/ 엄중섭
- 인제대학교 해운대백병원/ 박진한
- 양산부산대학교병원/ 설희윤
- 칠곡 경북대학교병원/ 최선하

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Treatment Characteristics and Real-World Progression-Free Survival in Patients With Unresectable Stage III NSCLC Who Received Durvalumab After Chemoradiotherapy: Findings From the PACIFIC-R Study

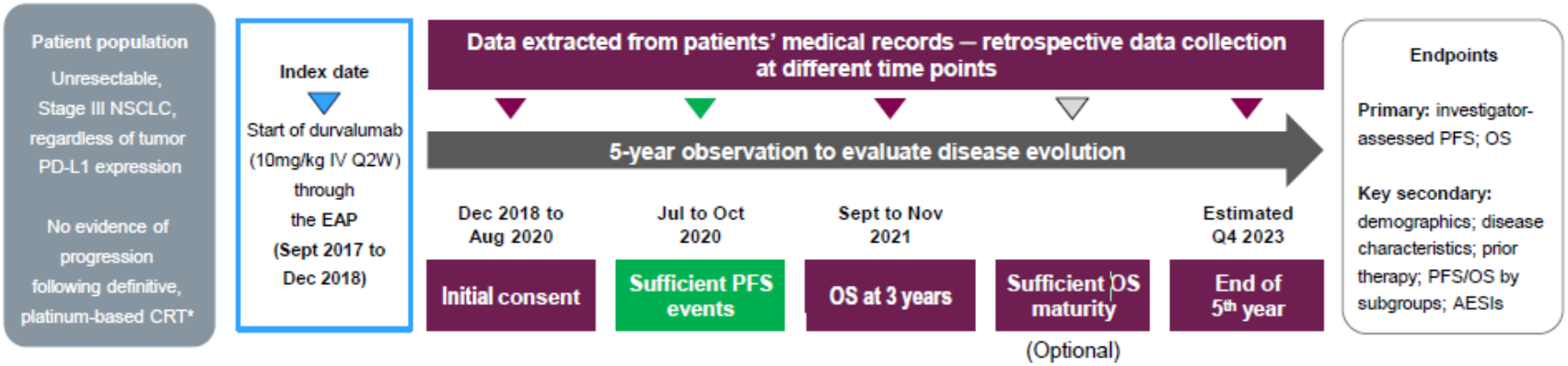

Figure 1. PACIFIC-R study design. The current analysis is based on the second data extraction of PACIFIC-R (highlighted in green), which was timed to allow sufficient PFS maturity. *Patients had completed platinum-based chemotherapy concurrent or sequential to radiotherapy within the previous 12 weeks without evidence of disease progression. AESIs, adverse events of special interest; CRT, chemoradiotherapy; EAP, early access program; IV, intravenously; OS, overall survival; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; Q, quarter; Q2W, every 2 weeks.

JTO 2022

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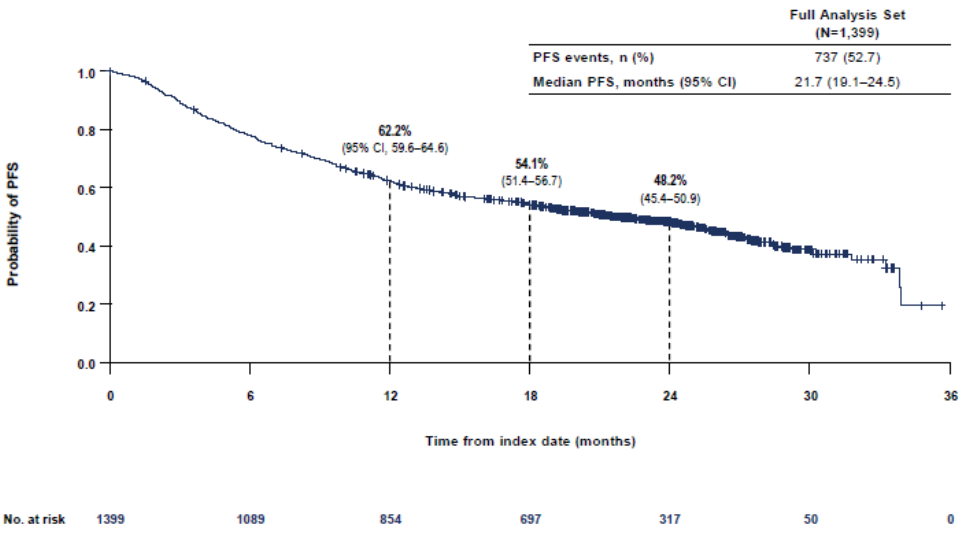
Table 1. Patient Demographics and Disease Characteristics

Characteristics	Full Analysis Set (N = 1399)
Median age at EAP inclusion, y (range)	66.0 (26-88)
Age category at EAP inclusion, n (%)	
<70 y	958 (68.5)
70-75 y	296 (21.2)
>75 y	145 (10.4)
Sex, n (%)	
Male	944 (67.5)
Female	455 (32.5)
Smoking status at EAP inclusion, n (%)	
Never	111 (7.9)
Current	456 (32.6)
Former	832 (59.5)
ECOG or WHO PS at EAP inclusion, n (%)	n = 951[a]
0	489 (51.4)
1	443 (46.6)
2 or 3	19 (2.0)
Disease stage at initial NSCLC diagnosis, n (%)	n = 1392[b]
IA to IIB	74 (5.3)
IIIA	604 (43.4)
IIIB or IIIC	714 (51.3)
Histologic subtype at stage III diagnosis, n (%)	n = 1378[c]
Squamous	496 (36.0)
Nonsquamous	882 (64.0)
PD-L1 status, n (%)	n = 967[d]
≥1%	700 (72.4)
<1%	174 (18.0)
Inconsistent	93 (9.6)
EGFR status, n (%)	n = 582[e]
Mutated	46 (7.9)
Wild type	517 (88.8)
Inconclusive or unknown	19 (3.3)



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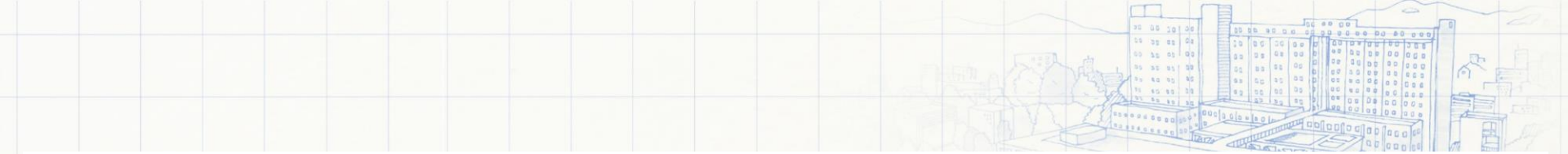
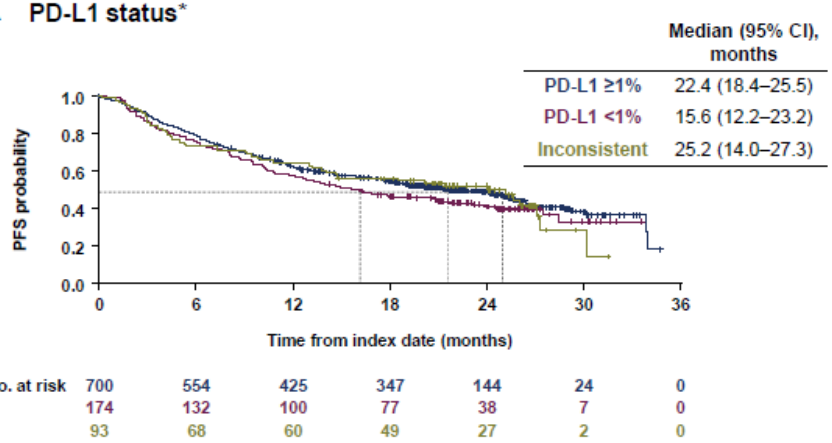


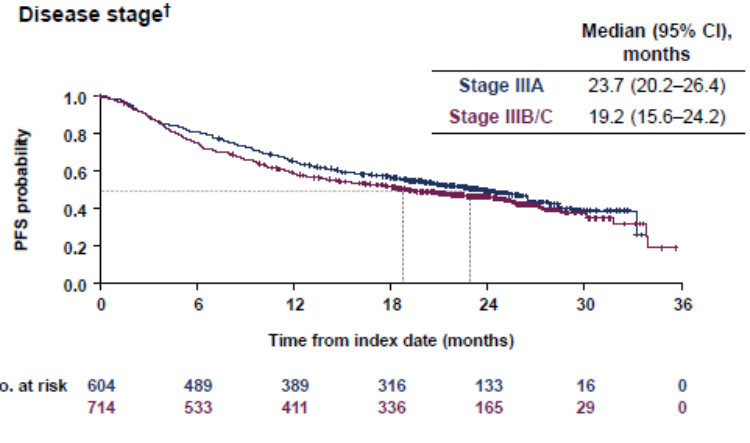
A PD-L1 status*



	Median (95% CI), months
PD-L1 ≥1%	22.4 (18.4–25.5)
PD-L1 <1%	15.6 (12.2–23.2)
Inconsistent	25.2 (14.0–27.3)

No. at risk							
PD-L1 ≥1%	700	554	425	347	144	24	0
PD-L1 <1%	174	132	100	77	38	7	0
Inconsistent	93	68	60	49	27	2	0

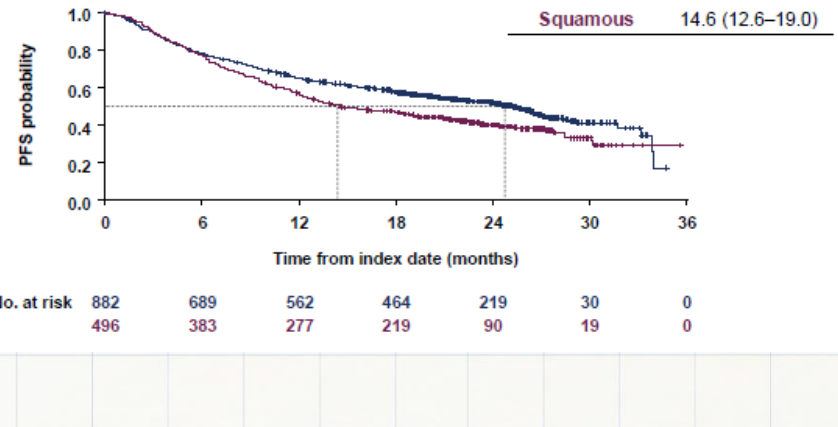
B Disease stage†



	Median (95% CI), months
Stage IIIA	23.7 (20.2–26.4)
Stage IIIB/C	19.2 (15.6–24.2)

No. at risk							
Stage IIIA	604	489	389	316	133	16	0
Stage IIIB/C	714	533	411	336	165	29	0

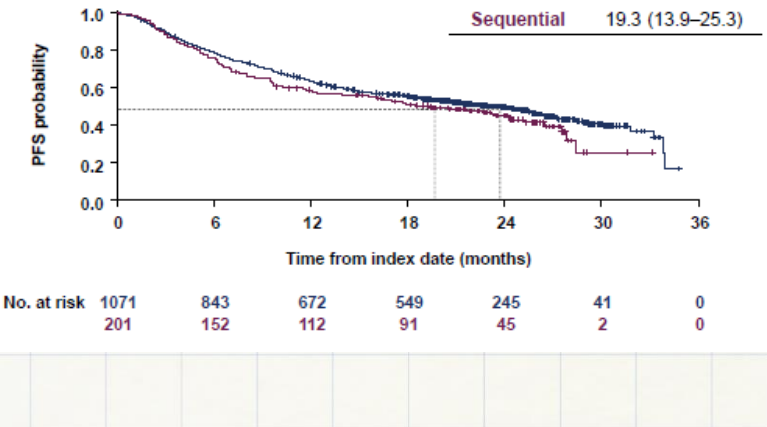
C Tumor histologic type‡



	Median (95% CI), months
Nonsquamous	25.3 (22.0–26.9)
Squamous	14.6 (12.6–19.0)

No. at risk							
Nonsquamous	882	689	562	464	219	30	0
Squamous	496	383	277	219	90	19	0

D Prior CRT type



	Median (95% CI), months
Concurrent	23.7 (20.1–25.8)
Sequential	19.3 (13.9–25.3)

No. at risk							
Concurrent	1071	843	672	549	245	41	0
Sequential	201	152	112	91	45	2	0

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Table 2. Reasons for and Timing of Durvalumab Treatment Discontinuation

	Full Analysis Set (N = 1399)	
Reason[a]	n (%)	Median Time to Discontinuation, mo (Range)[b]
Completed treatment[c]	659 (47.1)	11.9 (5.5-28.5)[d]
Disease progression	377 (26.9)	4.9 (0.0-30.2)[d]
Adverse event	233 (16.7)	2.8 (0.0-19.6)
Death	21 (1.5)	1.9 (0.0-13.6)
Patient decision	20 (1.4)	6.0 (0.0-19.5)
Other	68 (4.9)	5.9 (0.0-28.2)[d]

Table 3. AESIs Leading to Interruption and Permanent Discontinuation of Durvalumab

	Full Analysis Set (N = 1399)	
AESI Category	Temporary Interruption, n (%)	Permanent Discontinuation, n (%)
Any	156 (11.2)	231 (16.5)
Pneumonitis or ILD	73 (5.2)	133 (9.5)
Diarrhea or colitis and intestinal perforation	16 (1.1)	15 (1.1)
Hepatitis or transaminase increases	10 (0.7)	17 (1.2)
Endocrinopathies	18 (1.3)	10 (0.7)
Other[a]	33 (2.4)	51 (3.6)

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Study design

- 2016년 8월 1일부터 2022년 9월 30일까지의 의무기록 분석 중, 첫 진단 혹은 재발 이후 수술적 절제 불가능한 비소세포폐암 3기를 진단받고, CCRT 후에 면역항암제인 durvalumab 으로 한번이라도 치료받은 적이 있는 폐암환자

- 데이터 수집: 2022.10.01-2023.02.28
- 데이터 분석: 2023.02.28-2023.06.30
- 예상 데이터 결과 도출일: 2023.06.30-2023.08.31
- 예상 연구 결과 보고일: 2023.10.

- DCO date: 2022.09.30
- Primary endpoint: rwPFS

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Patient demographic and clinical characteristics

Characteristic	N=178
Patients	
Age, years	68.0 (63.0–72.3)
Sex	
Male	150 (84.3)
Smoking status	
Never smoker	28 (15.7)
Ex-smoker	85 (47.8)
Current smoker	63 (35.4)
Unknown	2 (1.1)
ECOG	
0	34 (19.1)
1	130 (73.0)
2	14 (7.9)

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Characteristic	n=178
Comorbidities	
COPD	75 (42.1)
IPF	9 (5.1)
Diagnosis	
First diagnosis	153 (86.0)
Recurred	25 (14.0)
Histology	
Adenocarcinoma	57 (32.0)
Squamous cell carcinoma	96 (53.9)
NSCLC, NOS	22 (12.4)
Others	3 (1.7)
Stage	
IIIA	71 (39.9)
IIIB	80 (44.9)
IIIC	27 (15.2)

Characteristic	n=178
PD-L1 status (SP 263)	
<1%	6 (3.4)
≥1%	172 (96.6)
Driver oncogenic variation	
EGFR	24 (13.5)
ALK	11 (6.2)
Others	3 (1.7)
Induction chemotherapy	8 (4.5)
Chemotherapy interval	
Q 1wk	165 (92.7)
Q 3wk	13 (7.3)

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Characteristic	n=178
Chemotherapy regimen	
Paclitaxel/Cisplatin	104 (58.4)
Paclitaxel/Carboplatin	64 (36.0)
Pemetrexed/Cisplatin	3 (1.7)
Pemetrexed/Carboplatin	1 (0.6)
Etoposide/Cisplatin	1 (0.6)
Etoposide/Carboplatin	1 (0.6)
Others	4 (2.2)
Radiation dose, Gy	66.0 (60.0-66.0)
Follow-up, days	272 (138.5-516.5)

Durvalumab treatment hx.

Treatment history	N=178
1년 사용 후 종결	60 (33.7)
PD 로 중단	37 (20.8)
Durvalumab AE 로 중단	23 (12.9)
다른 이유로 중단	23 (12.9) (f/u loss, RT esophagitis, pneumonia 등)
Ongoing (PD 없이 사용 중)	35 (19.7)
Radiation pneumonitis 로 중단	0 (0)

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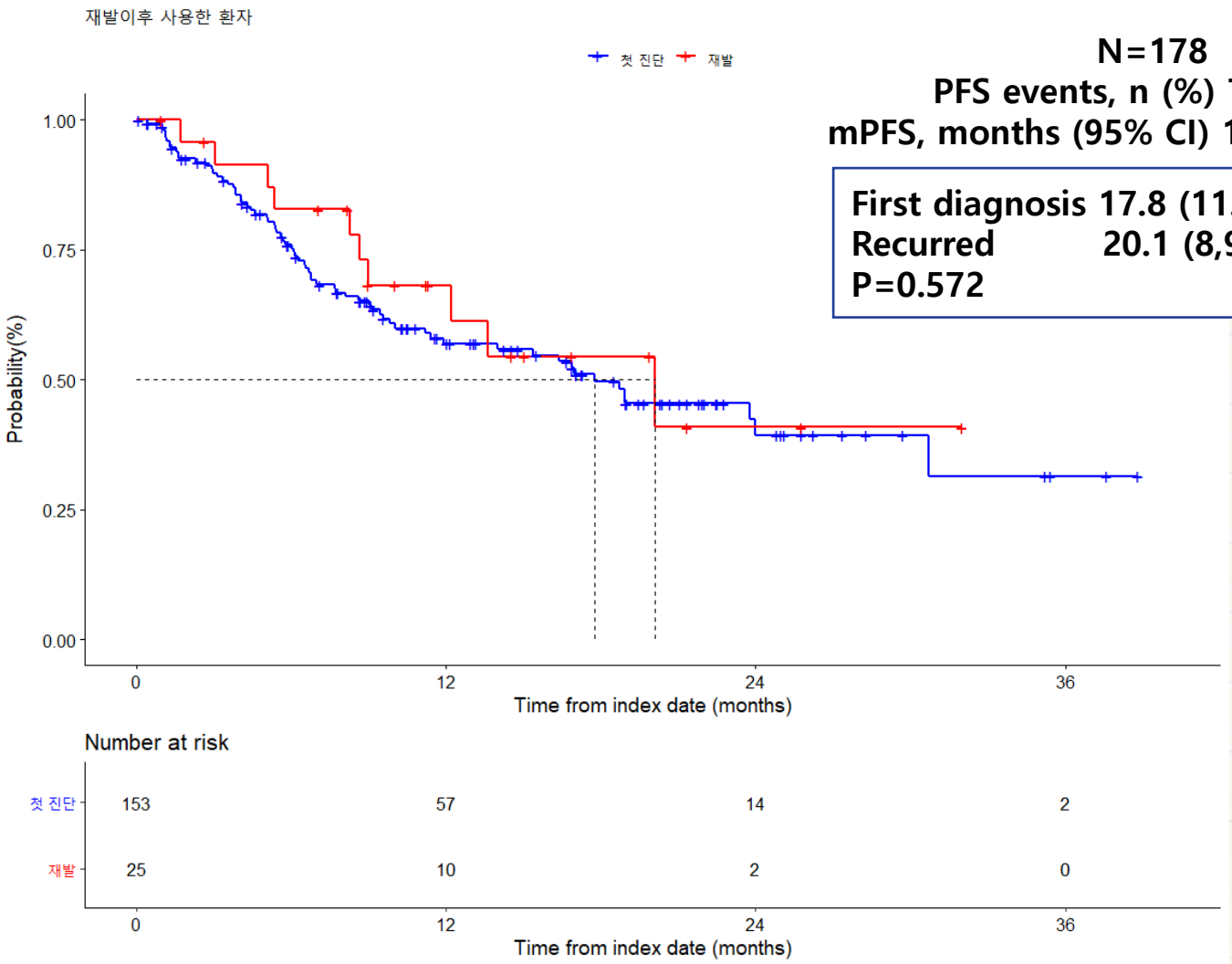
rwPFS in the interim analysis



N=178
PFS events, n (%) 79 (44.4)
mPFS, months (95% CI) 19.7 (12.3-25.2)

First diagnosis 17.8 (11.0-24.5)
Recurred 20.1 (8,9-31.3)
P=0.572

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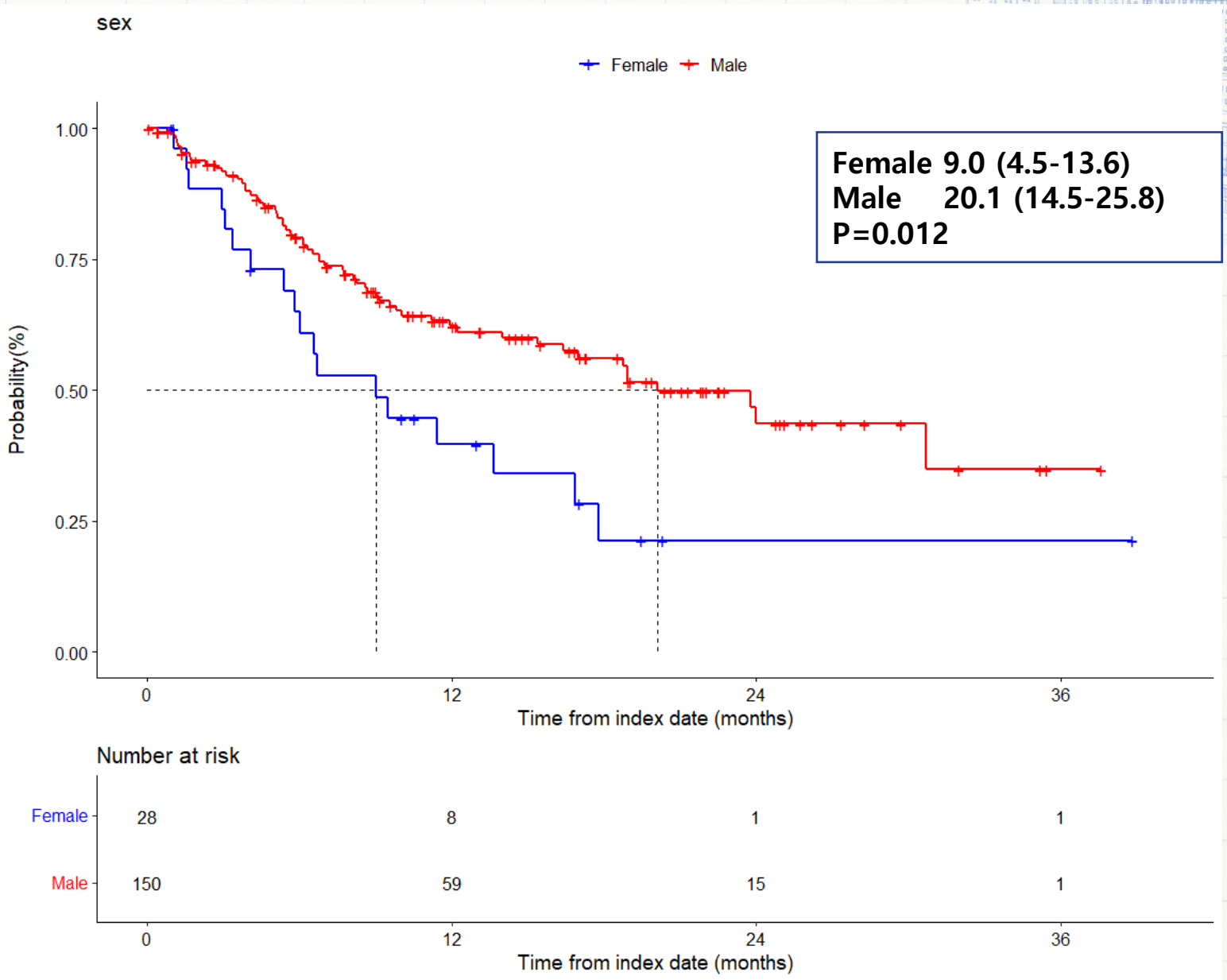

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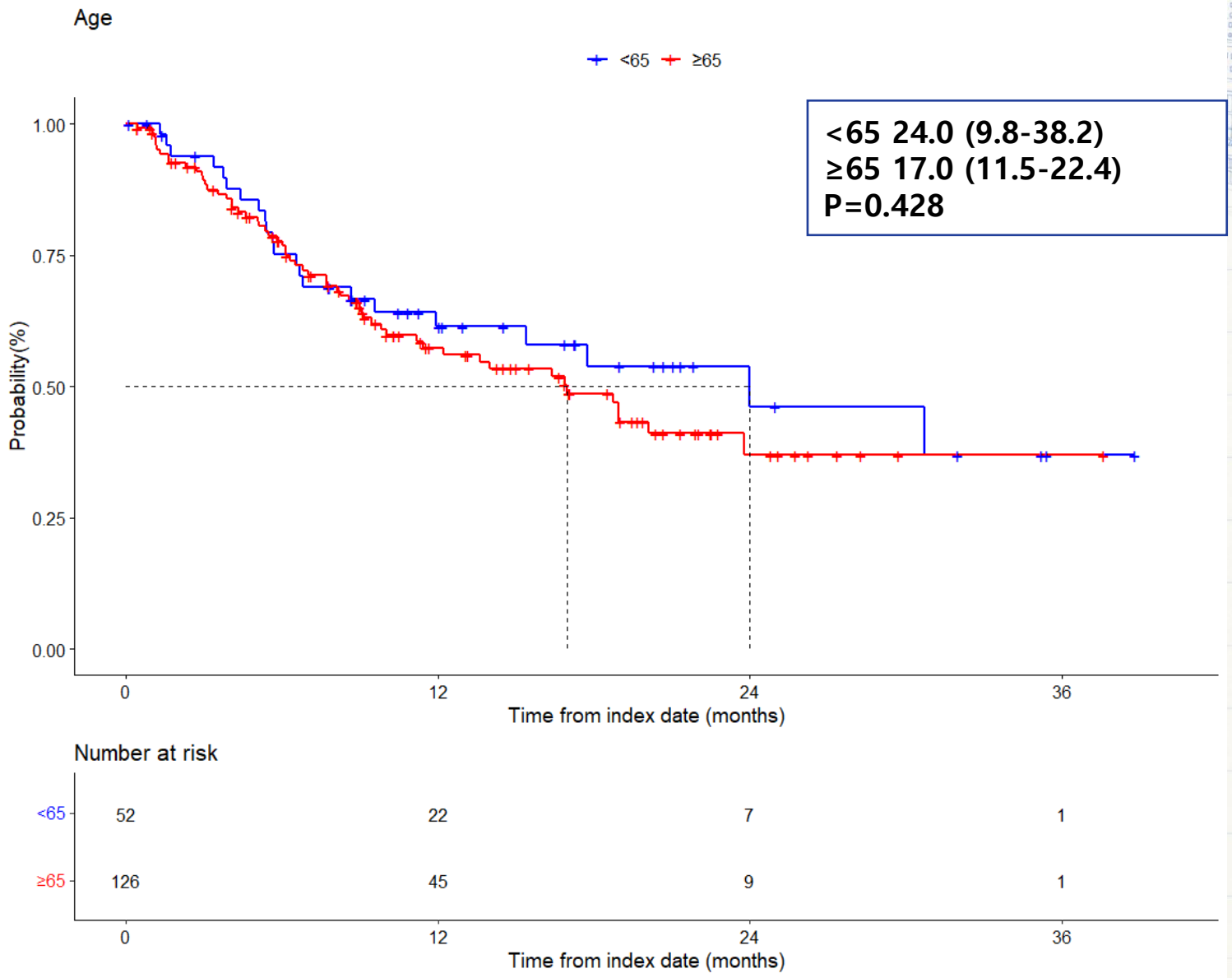

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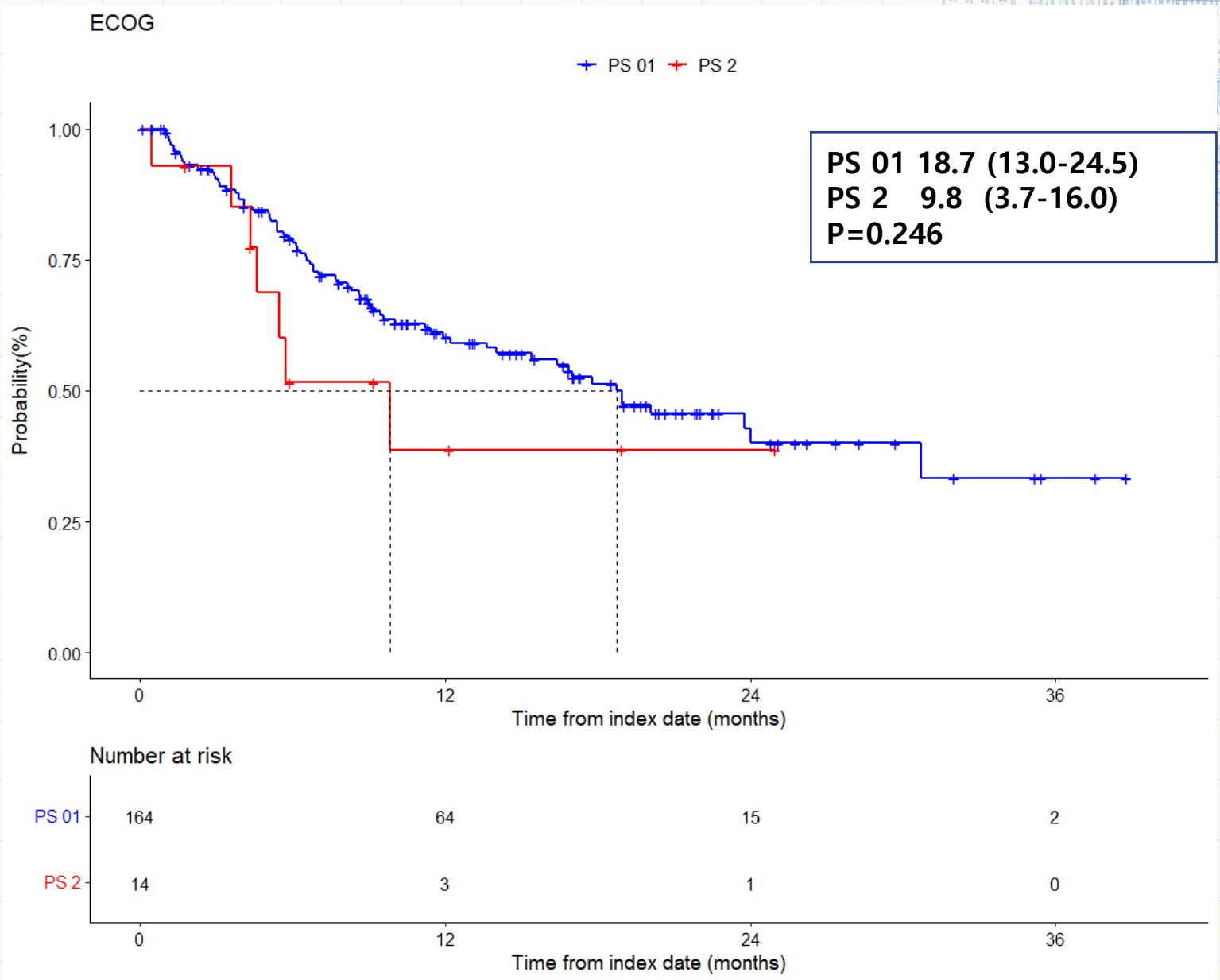

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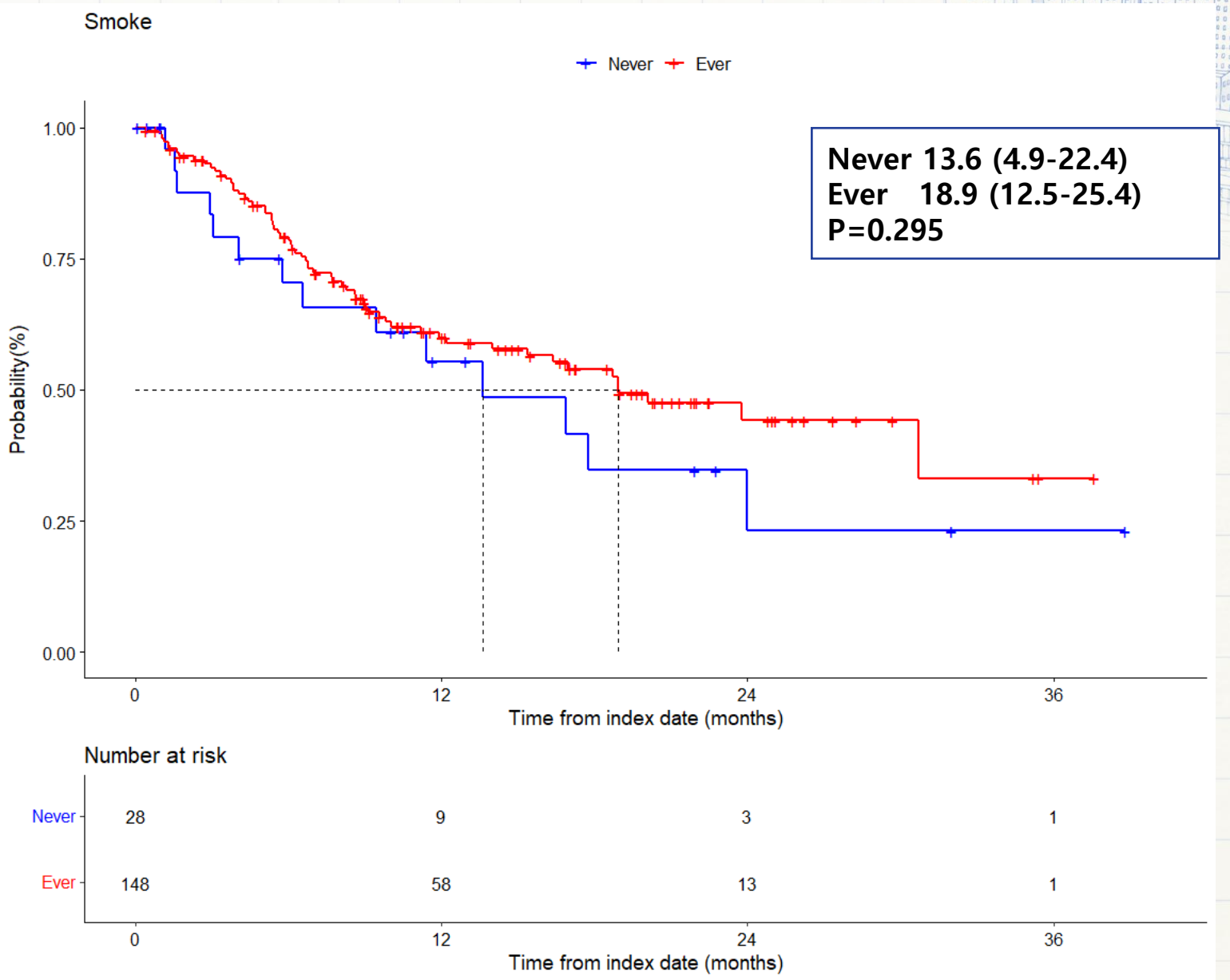

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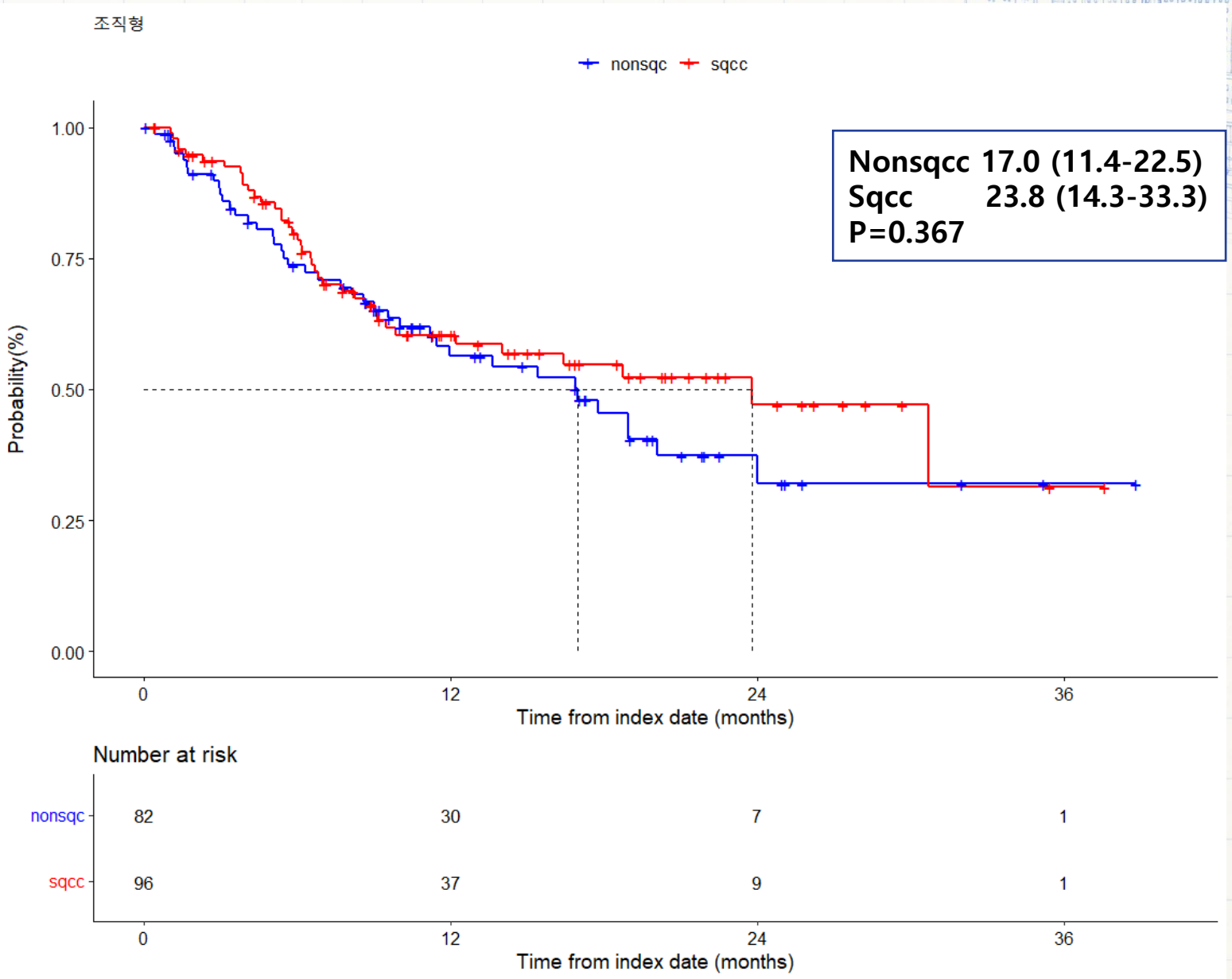

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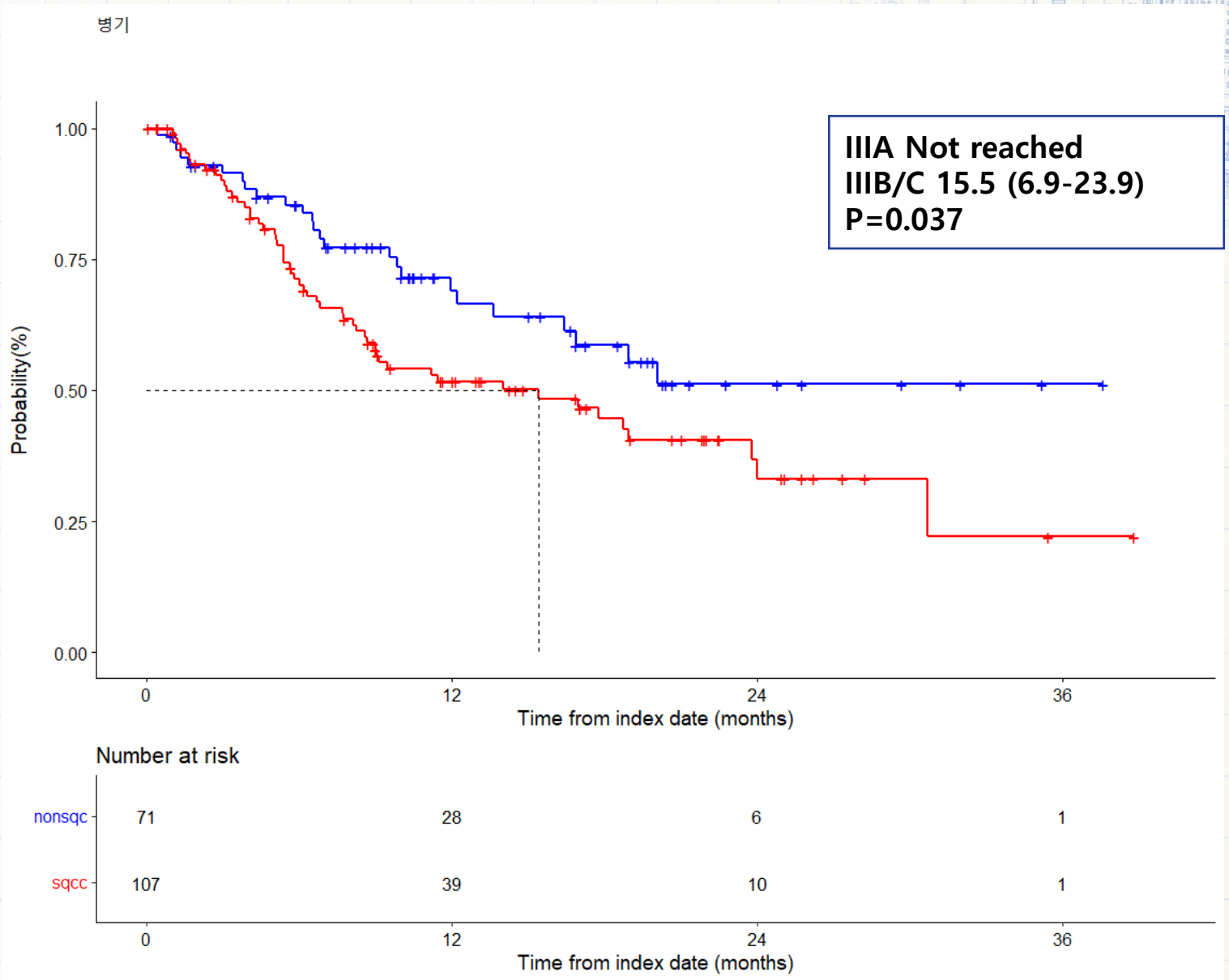

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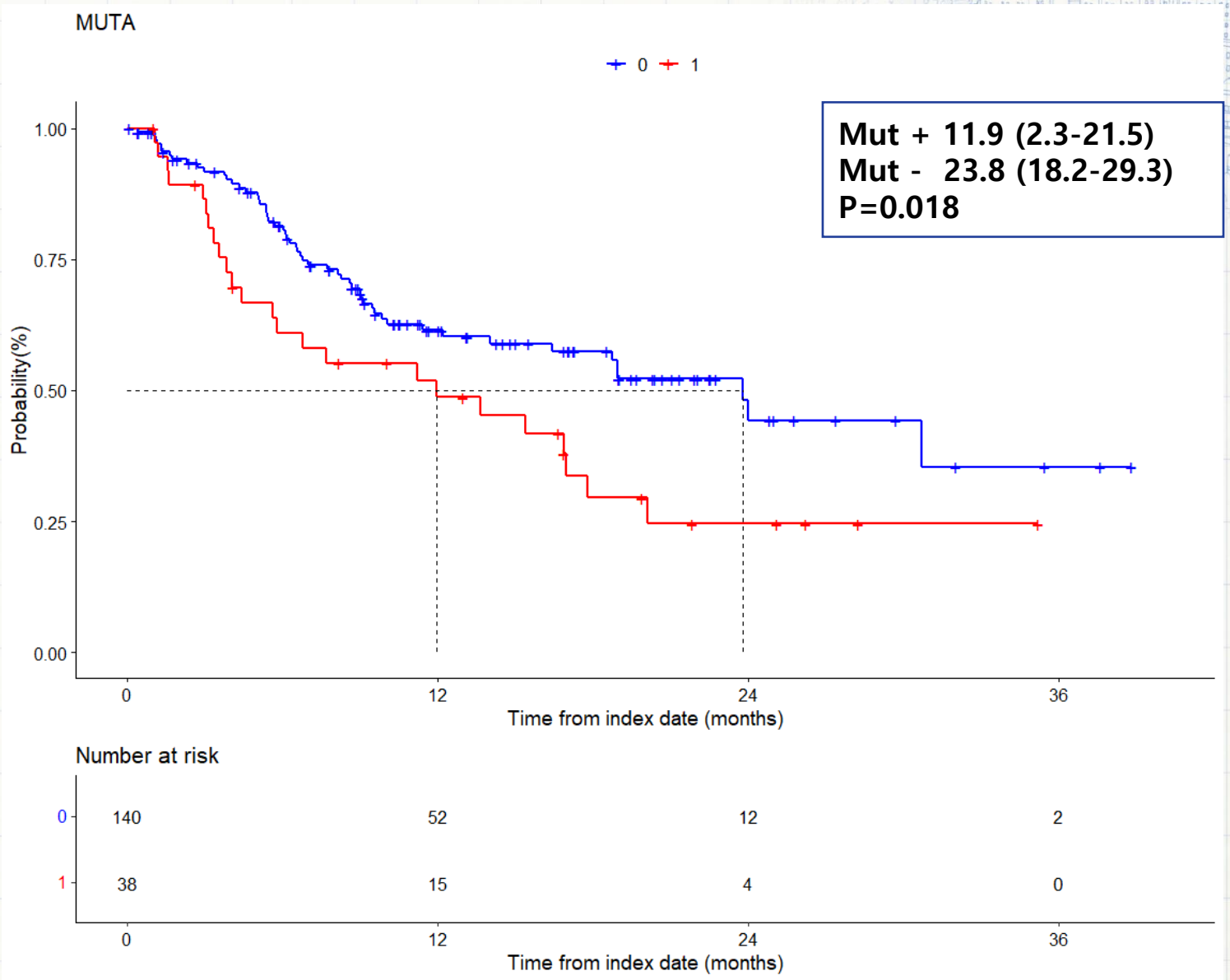

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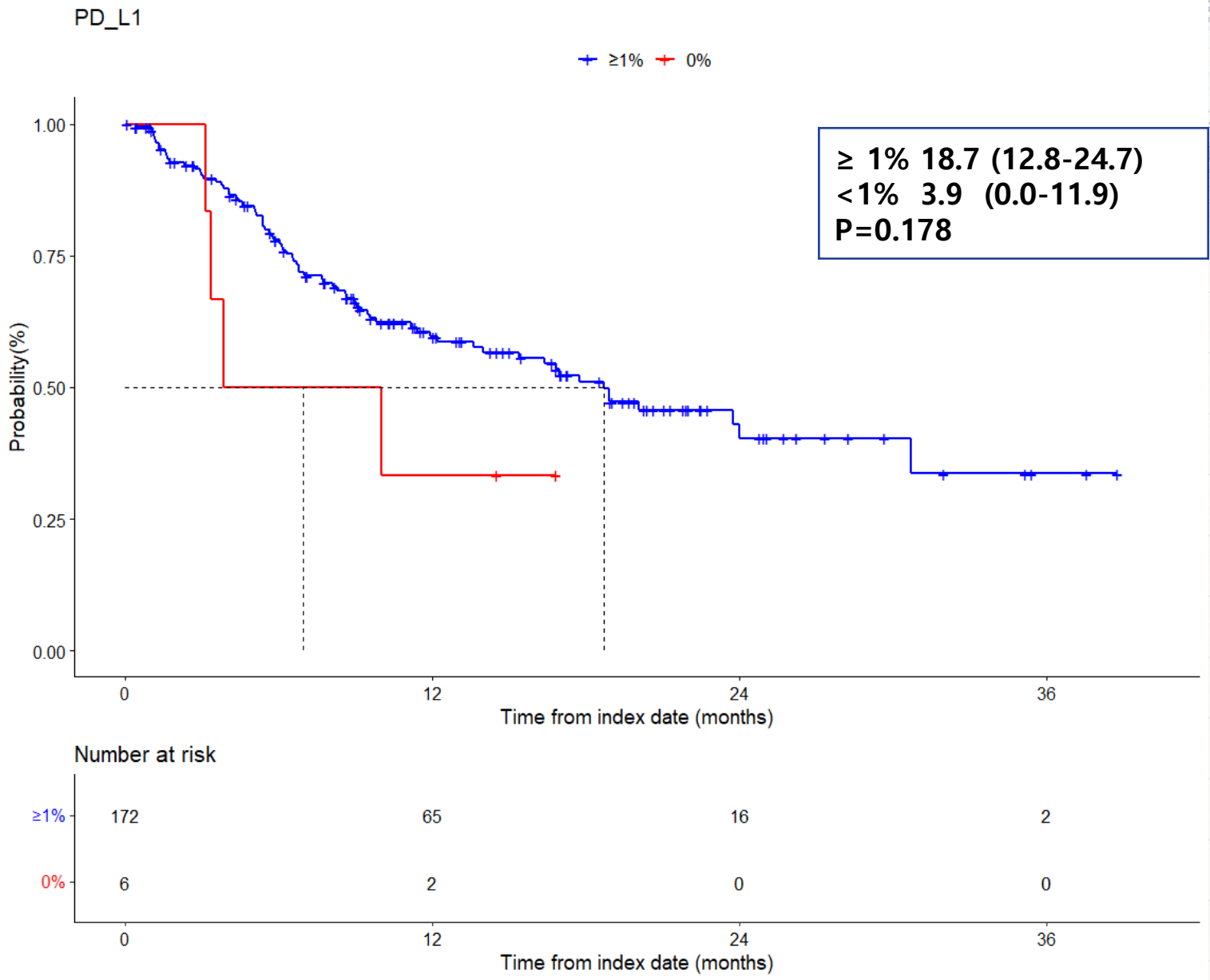

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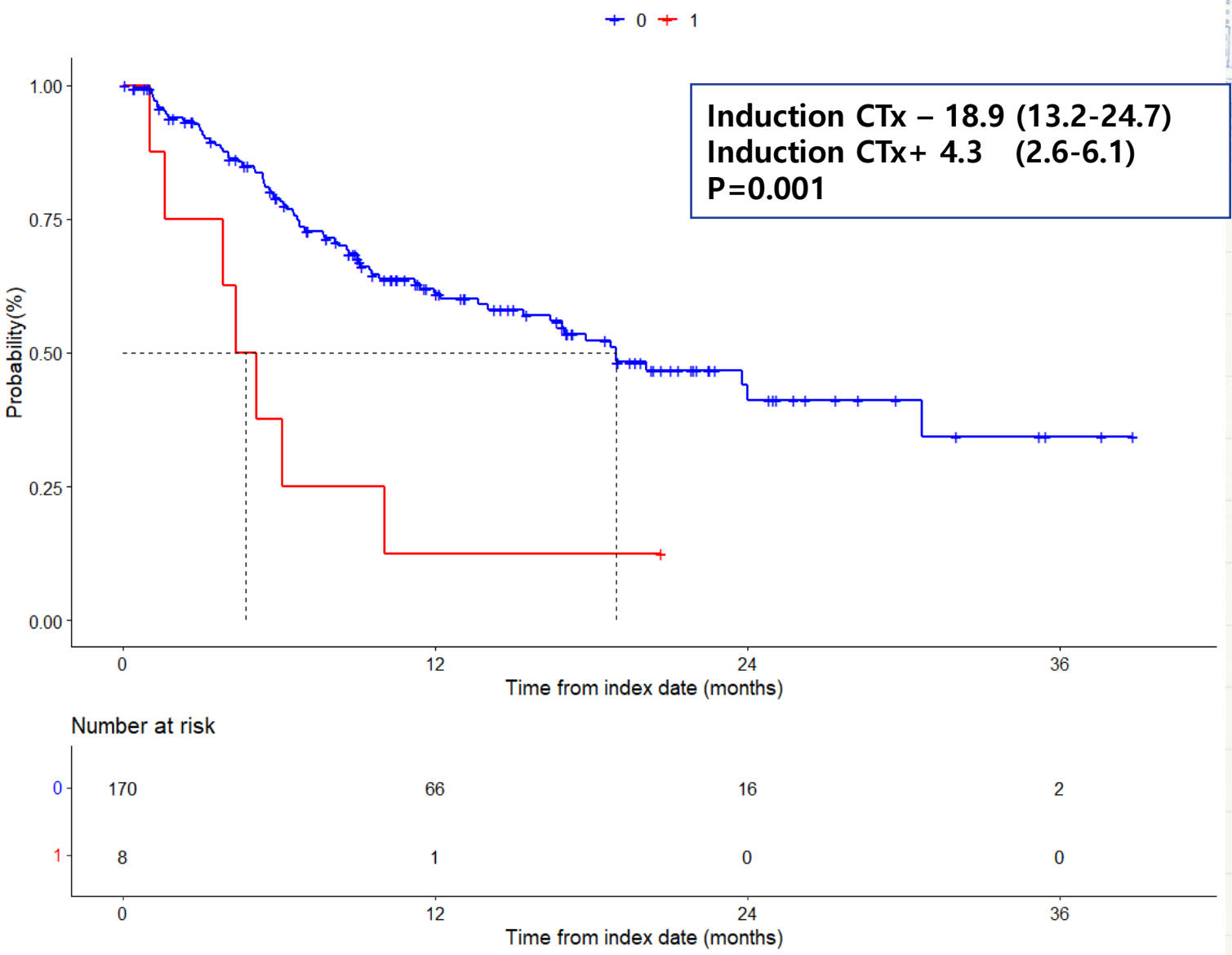
CCRT 형태



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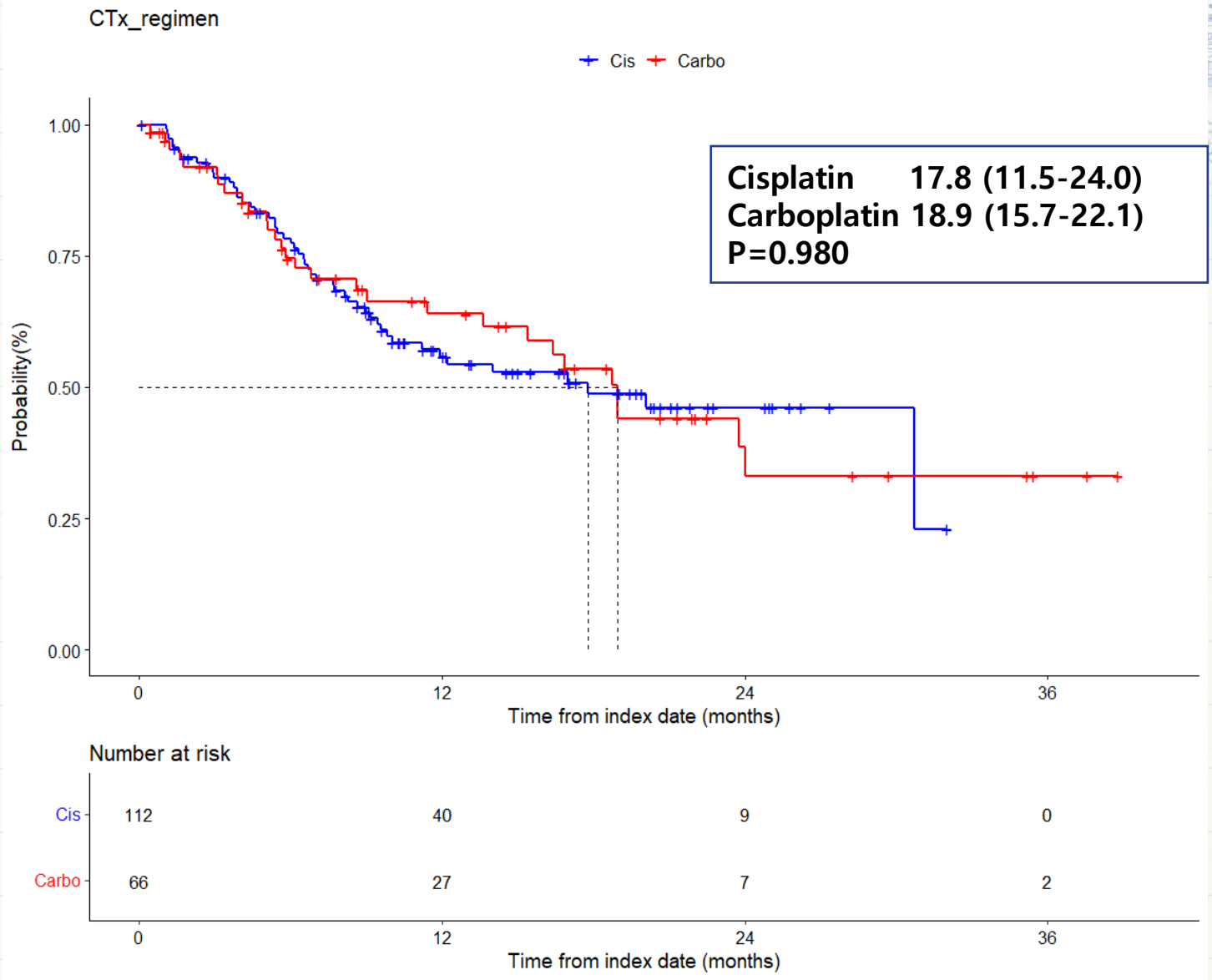

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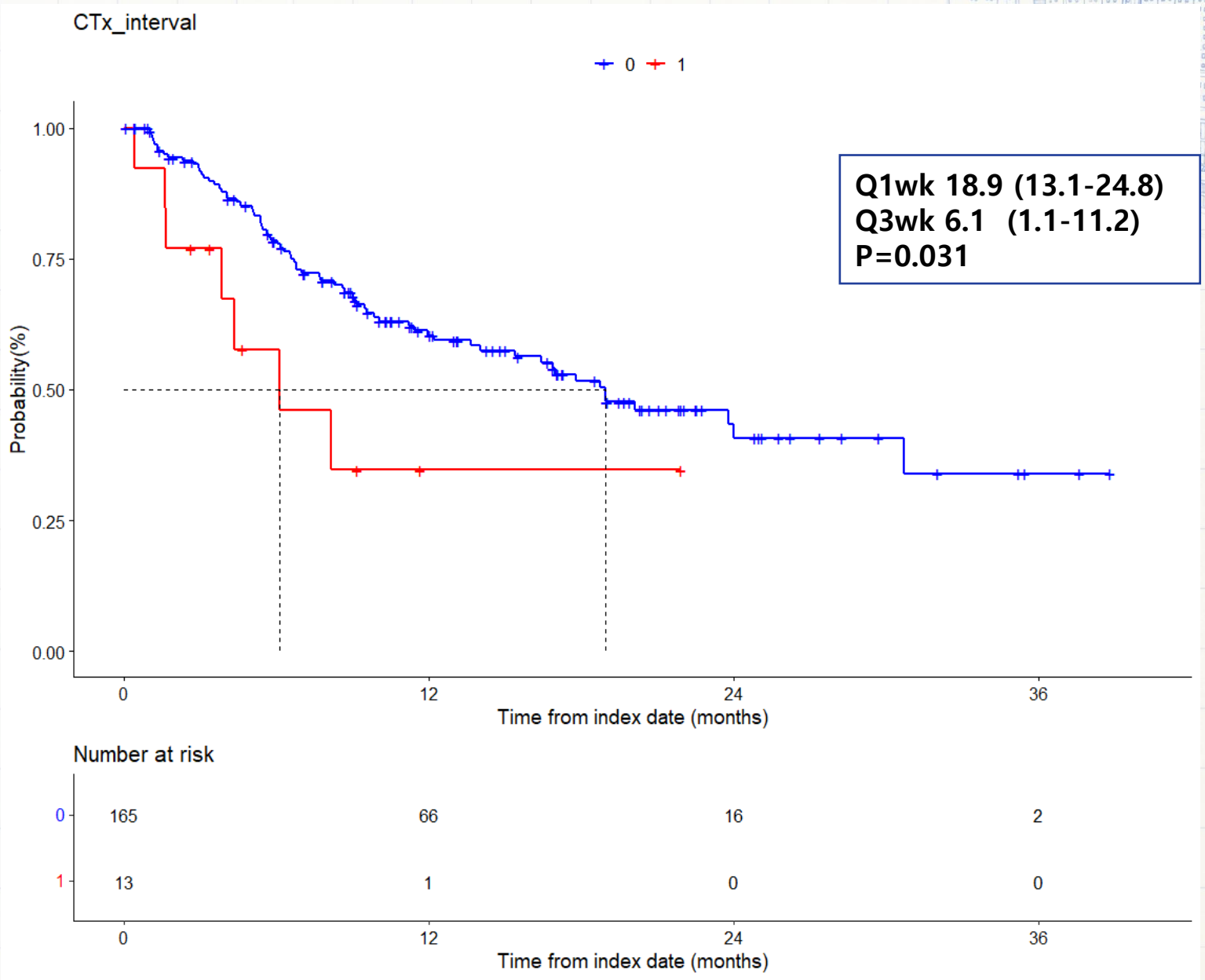

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Multivariable cox regression analysis

방정식의 변수

	B	표준오차	Wald	자유도	TPL 유의확률	Exp(B)	95.0% Exp(B)의 CI 하한	상한
relapse_p	0.142	0.386	0.135	1	0.713	1.152	0.541	2.456
sex	-1.159	0.409	8.009	1	0.005	0.314	0.141	0.700
age_65	0.402	0.279	2.079	1	0.149	1.495	0.865	2.583
ECOG	0.858	0.447	3.683	1	0.055	2.358	0.982	5.664
smoke	0.532	0.481	1.224	1	0.268	1.702	0.664	4.365
COPD	0.078	0.281	0.078	1	0.780	1.081	0.624	1.876
IPF	0.385	0.557	0.477	1	0.490	1.469	0.493	4.375
tissue	0.001	0.283	0.000	1	0.997	1.001	0.575	1.743
stage	0.670	0.280	5.724	1	0.017	1.954	1.129	3.381
MUTA	1.041	0.658	2.501	1	0.114	2.832	0.779	10.293
EGFR_1			0.622	2	0.733			
EGFR_1(1)	-0.397	0.703	0.319	1	0.572	0.672	0.170	2.667
EGFR_1(2)	-0.367	0.638	0.331	1	0.565	0.693	0.198	2.420
ALK_1			0.485	2	0.785			
ALK_1(1)	-0.512	0.762	0.452	1	0.501	0.599	0.135	2.666
ALK_1(2)	-0.115	0.561	0.042	1	0.838	0.892	0.297	2.679
PD_L1	-0.064	0.612	0.011	1	0.916	0.938	0.282	3.113
CCRT	1.386	0.539	6.600	1	0.010	3.999	1.389	11.511
CTx_regimen	0.036	0.265	0.019	1	0.891	1.037	0.617	1.743
CTx_interval	0.591	0.514	1.320	1	0.251	1.805	0.659	4.944

- Favorable factors for rwPFS
  - Male
  - Stage IIIA vs. IIIB/C
  - No induction CTx.

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Recur pattern and FSS treatment

Recurred pattern	N=52
Primary tumor regrowth	11 (21.2)
Intrathoracic (M1a)	13 (25)
Extrathoracic (M1b,M1c)	29 (55.8)

FSS	N=52
Radiation therapy	6 (11.5)
Cytotoxic CTx	28 (53.8)
Immunotherapy	0 (0)
TKI	11 (21.2)
BSC	7 (13.5)

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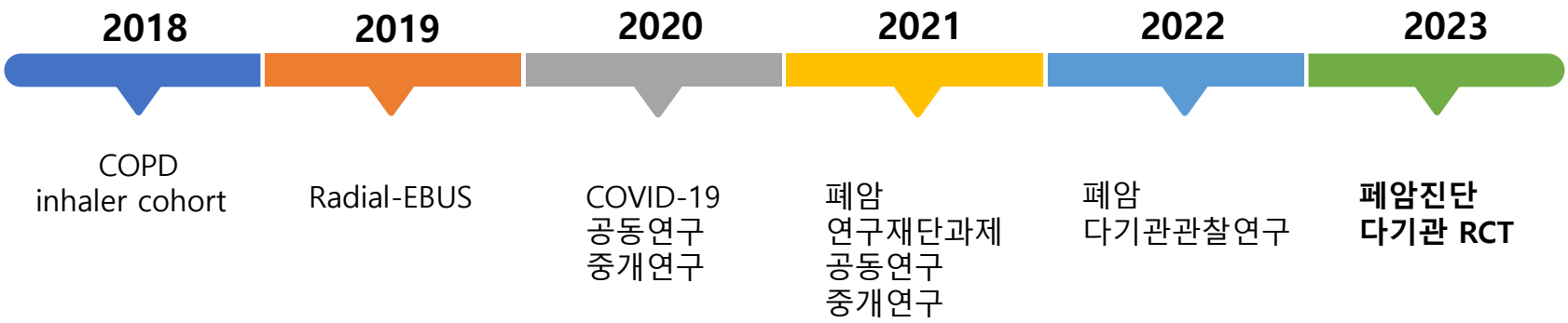
Radiation pneumonitis

CTCAE grade	N=119/178 (66.9%)
1	44 (37.0)
2	60 (50.4)
3	12 (10.1)
4	1 (0.8)
5	1 (0.8)

Durvalumab AE

	Temporary discontinuation (3.4%)	Permanent Discontinuation (8.9%)	Death (5.6%)
Pulmonary (n=28, 15.7%)	3 (1.7)	11 (6.2)	10 (5.6)
Endocrine (n=13, 7.3%)	1 (0.6)	1 (0.6)	0
Dermatologic (n=2, 1.1%)	0	0	0
GI (n=4, 2.2%)	0	2 (1.1)	0
Hepatitis (n=1, 0.6%)	0	0	0
Hematologic (n=2, 1.1%)	1 (0.6)	1 (0.6)	0
Fatigue (n=8, 4.5%)	1 (0.6)	0	0
Bursitis (n=1, 0.6%)	0	1 (0.6)	0

2023 (Y6)~



- **다기관 rwSTUDY**
- **다기관 RCT (호흡기 내과만의 강점인 진단, 시술)**


경청해 주셔서 감사합니다