

Basics of Medical Treatment Targeted therapy and Immunotherapy

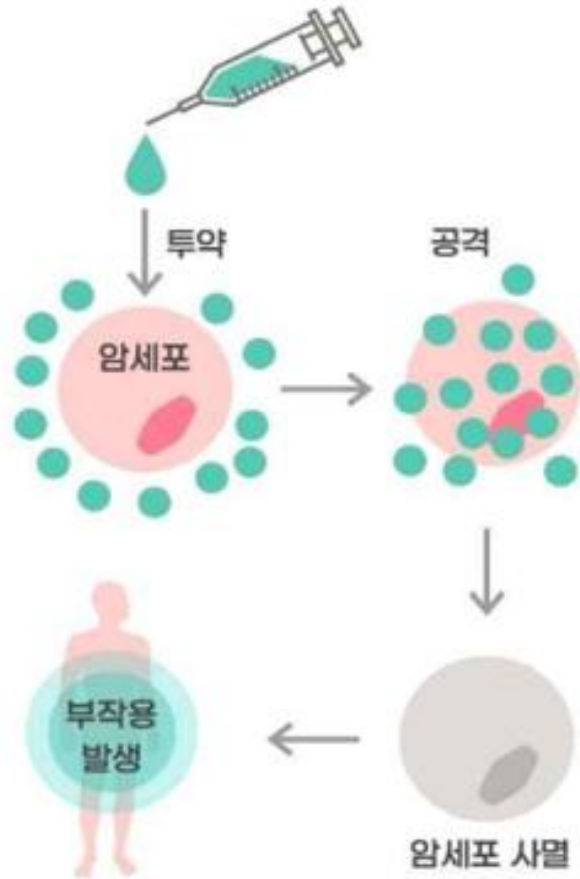
2026년 제9회 Lung Cancer School

일정
장소

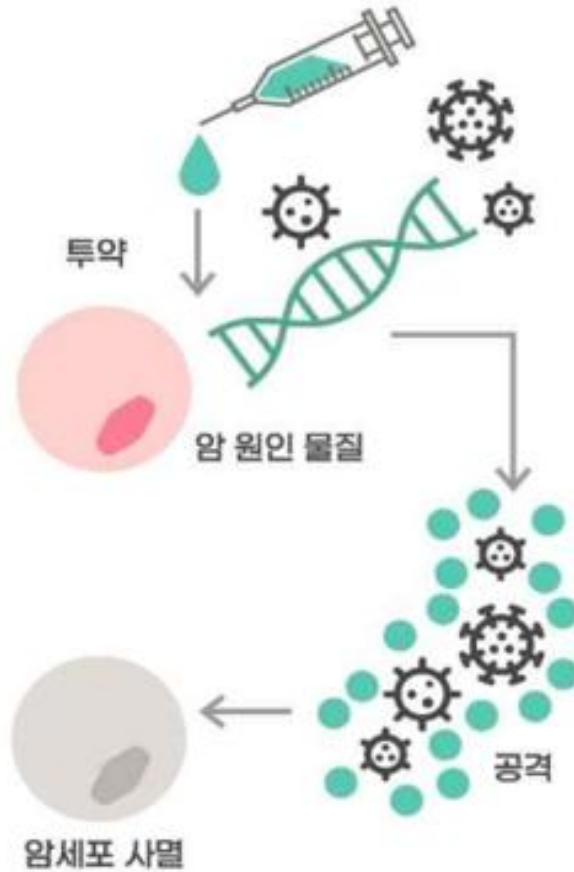
영 남 의 대
안 준 홍

항암제의 작용원리

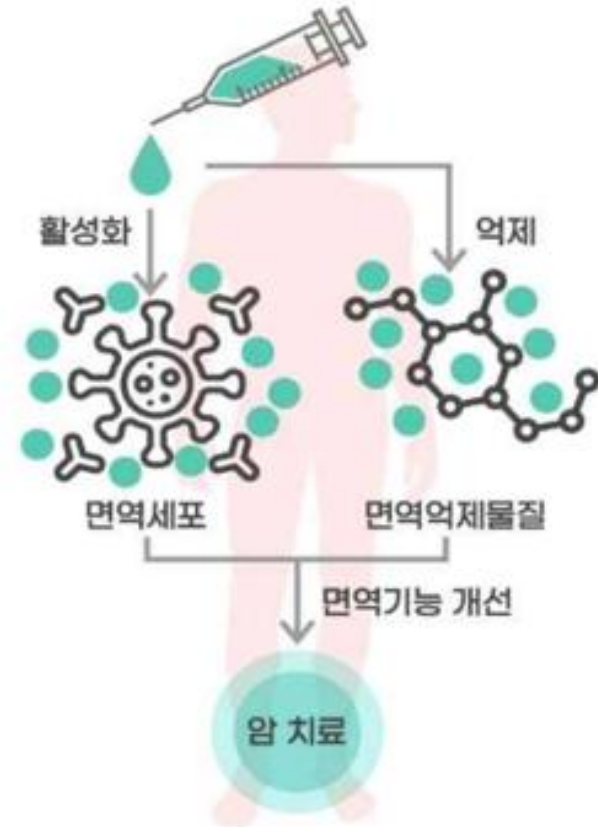
1세대 | 화학항암제



2세대 | 표적항암제

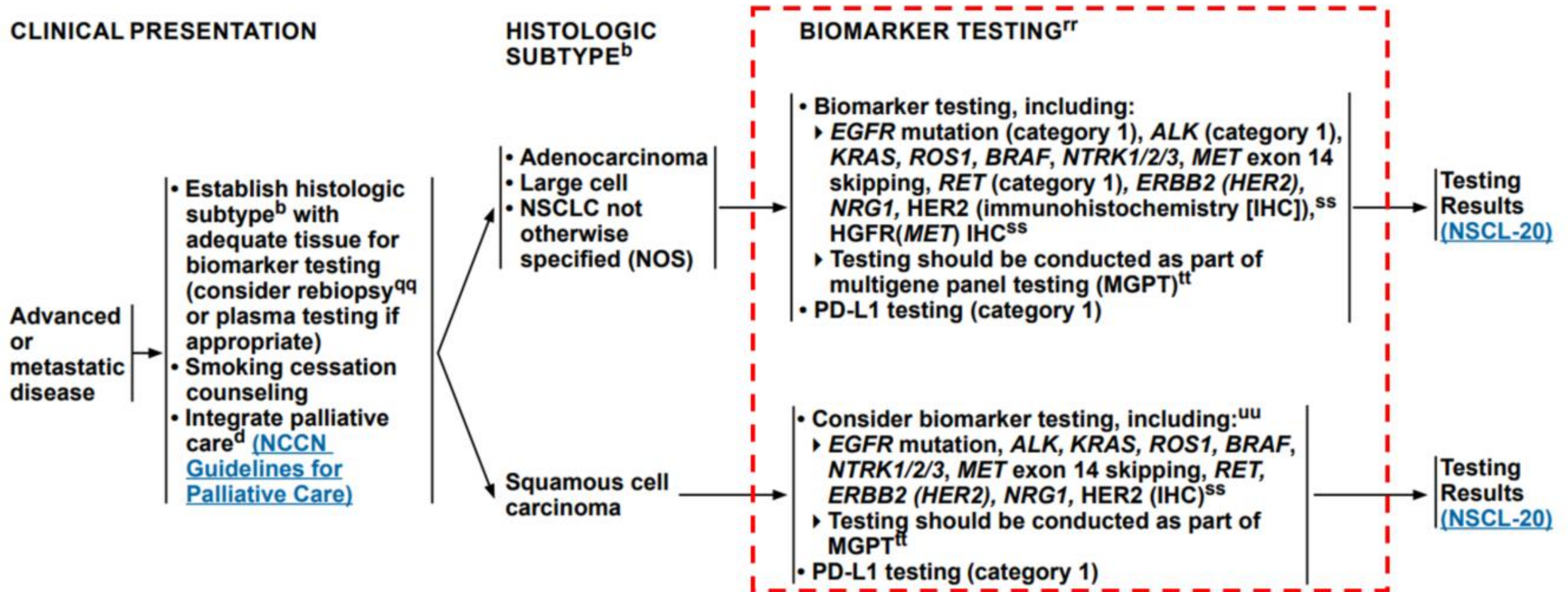


3세대 | 면역항암제

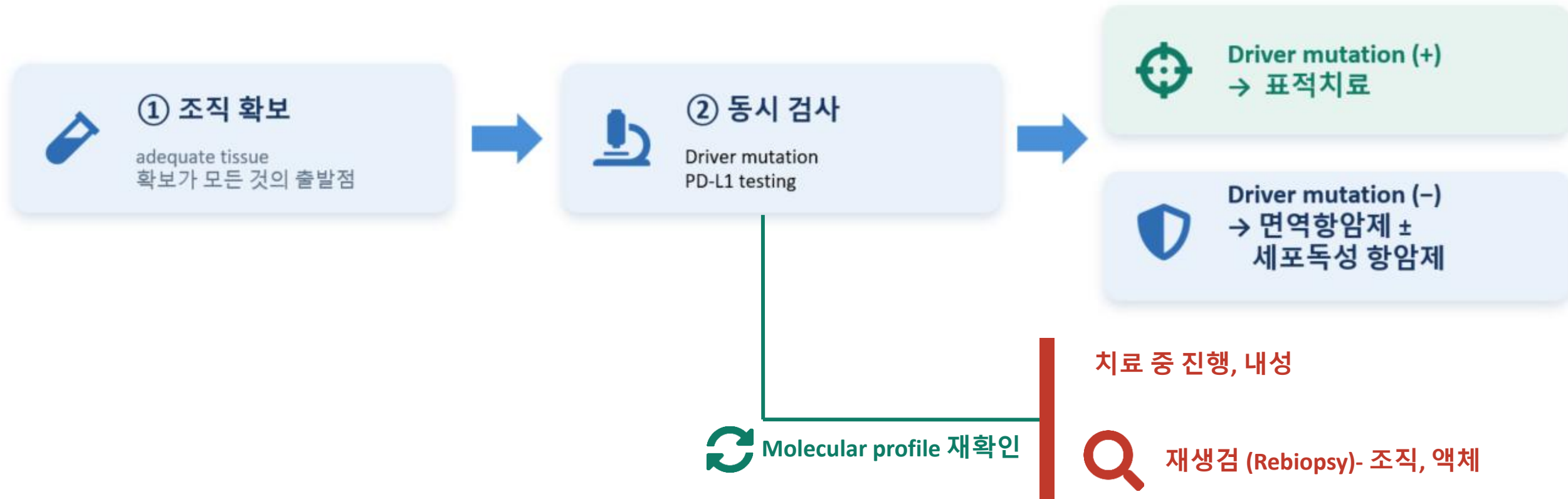


*출처: 안전한 약물사용 가이드 면역항암제 교육자료 (재)병원약학교육연구원, 2020

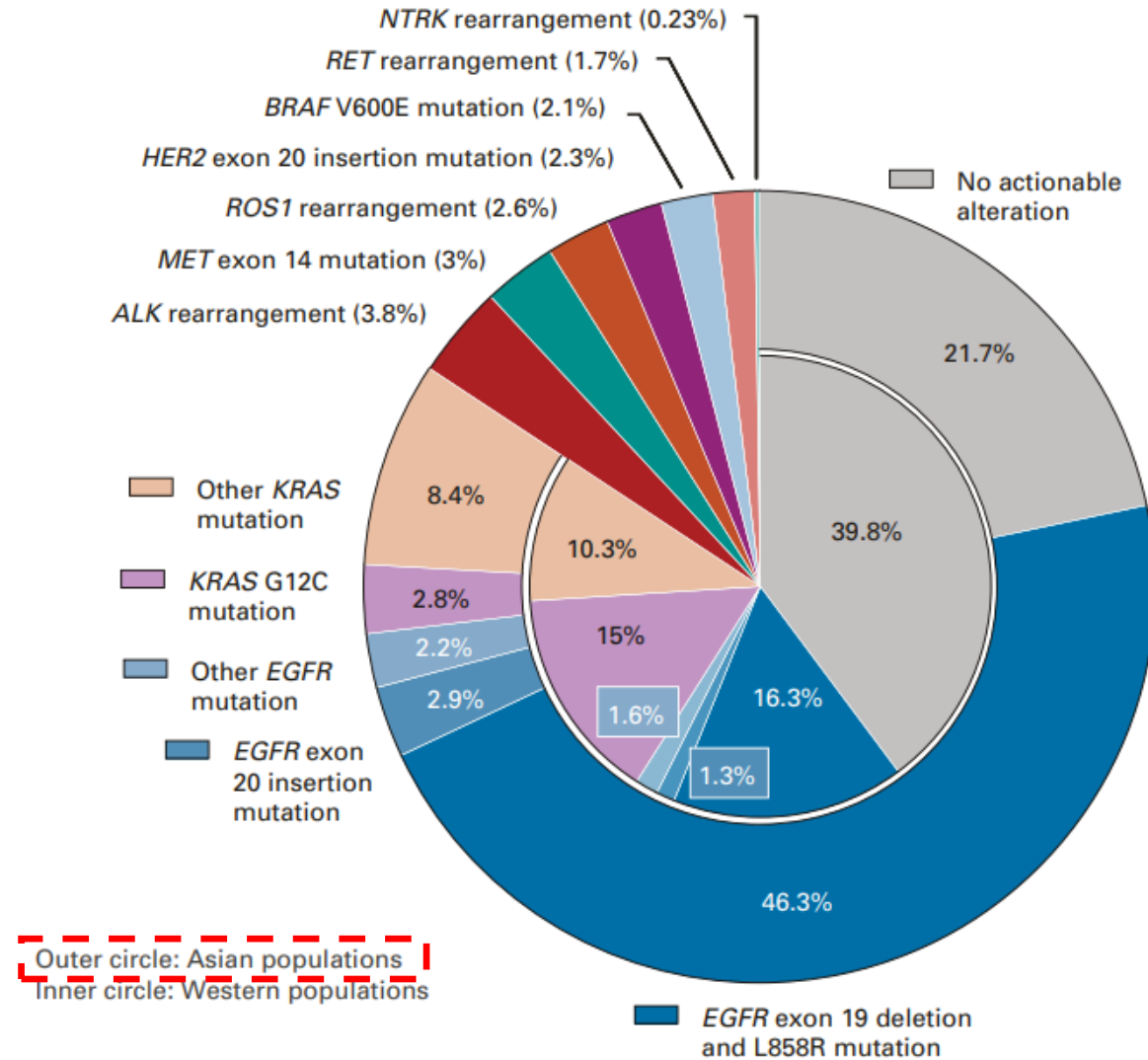
1차 치료의 첫 단추는 '약'이 아니라 '조직과 biomarker'다



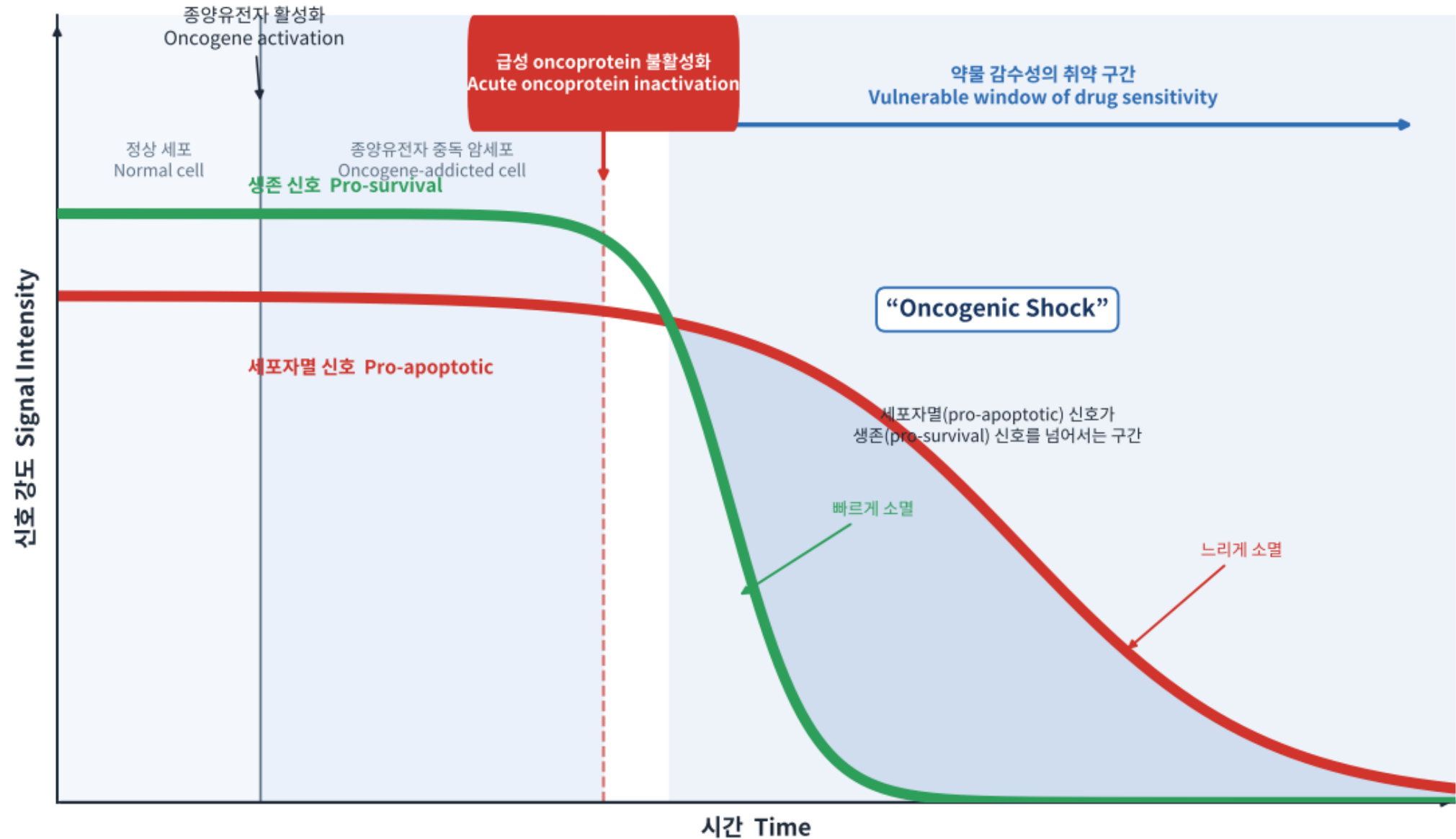
Biomarker 확인이 되어야 최적의 1차 치료가 정해진다



Frequency of oncogenic driver alterations



표적 치료제의 원리



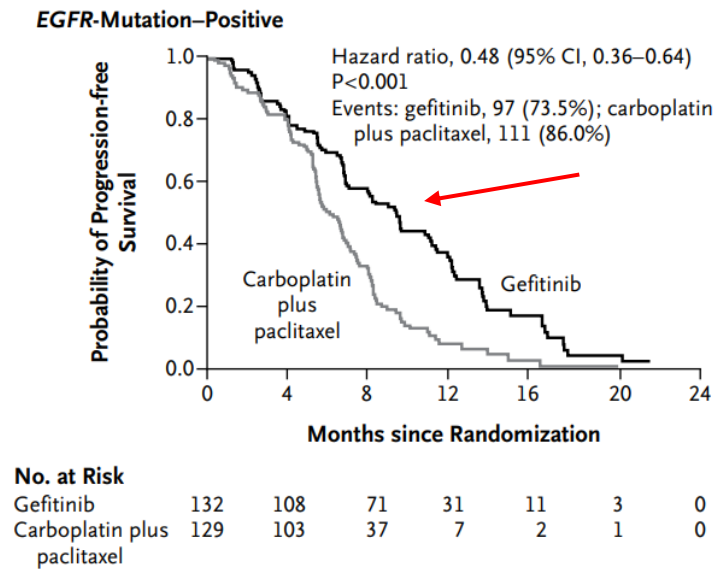
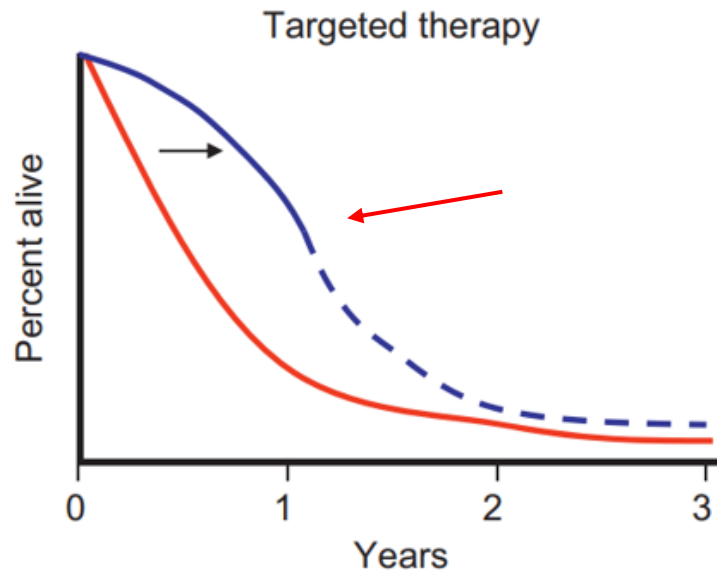
표적 치료제의 특징

- 빠르고 극적인 반응, 높은 반응률
- 약을 끊으면 효과 소실, 지속 투여 필요
- 내성(저항성) 출현
- 대체로 예측 가능 (표적경로관련), 관리 가능한 부작용 (용량감량)

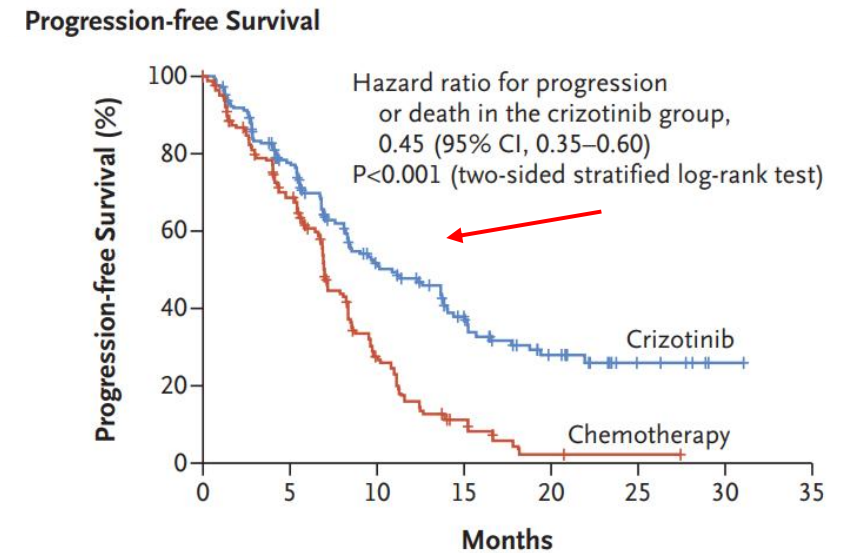
빠르고 극적인 반응, 높은 반응률

Target	Agent	ORR
EGFR	Osimertinib (FLAURA) Lazertinib (LASER 301)	80% (1L) 76% (1L)
ALK	Lorlatinib (CROWN)	76% (1L)
ROS1	Entrectinib (STARTRK-2)	77% (different lines)
RET	Selpercatinib (Libretto-001)	85% (1L)
METex 14 skipping	Capmatinib (GEOMETRY-mono1) Tepotinib (VISION)	68% (1L) 46% (different lines)

Early separation, converging tails

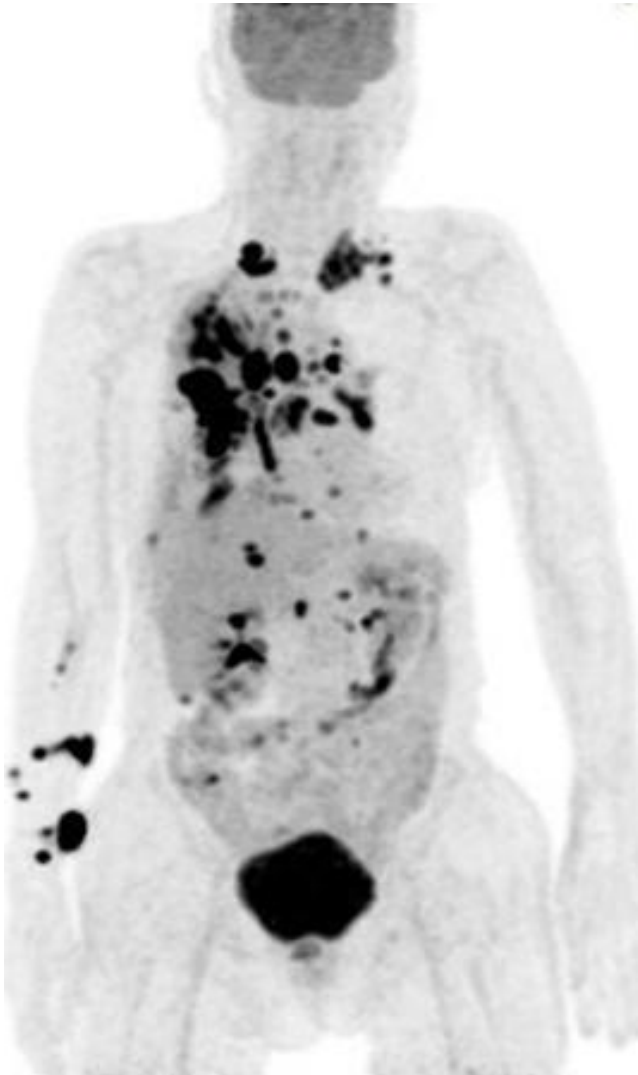


IPASS



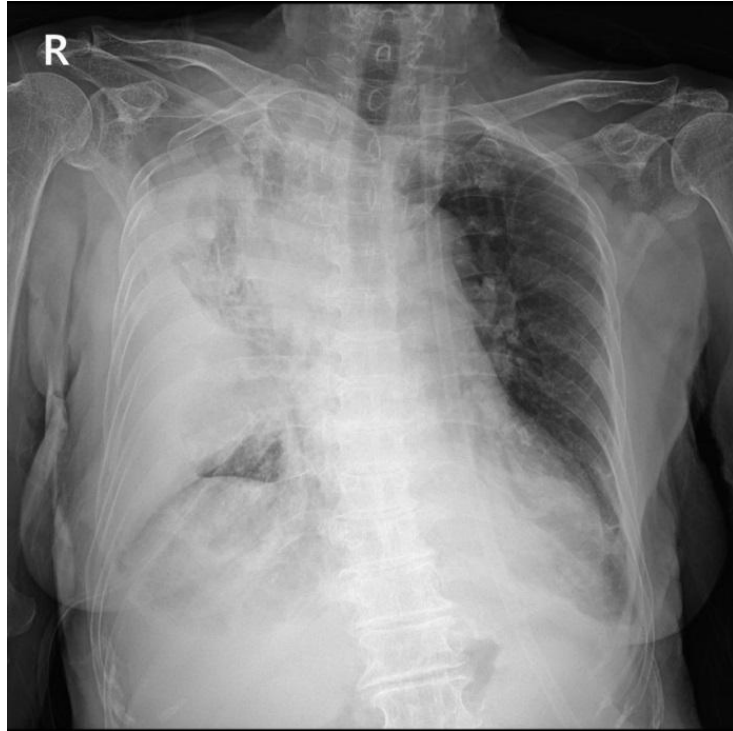
PROFILE 1014

79/F, Never smoker, ADC, RML, cT4N3M1c, (IVB)
M/liver, pleura metastasis, ALK +



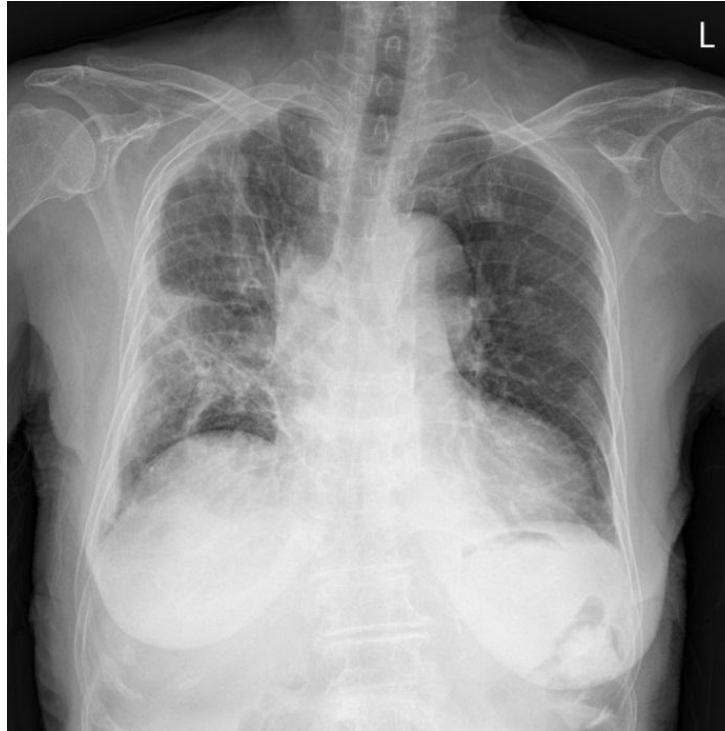
Rapid response to ALK TKI

Baseline



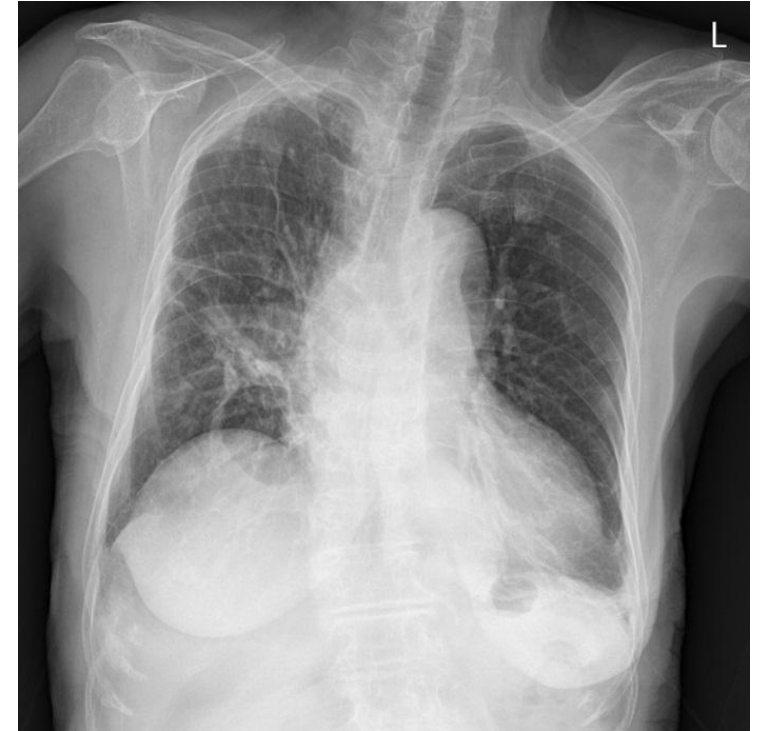
Nasal prong 6L/min

After 9 days



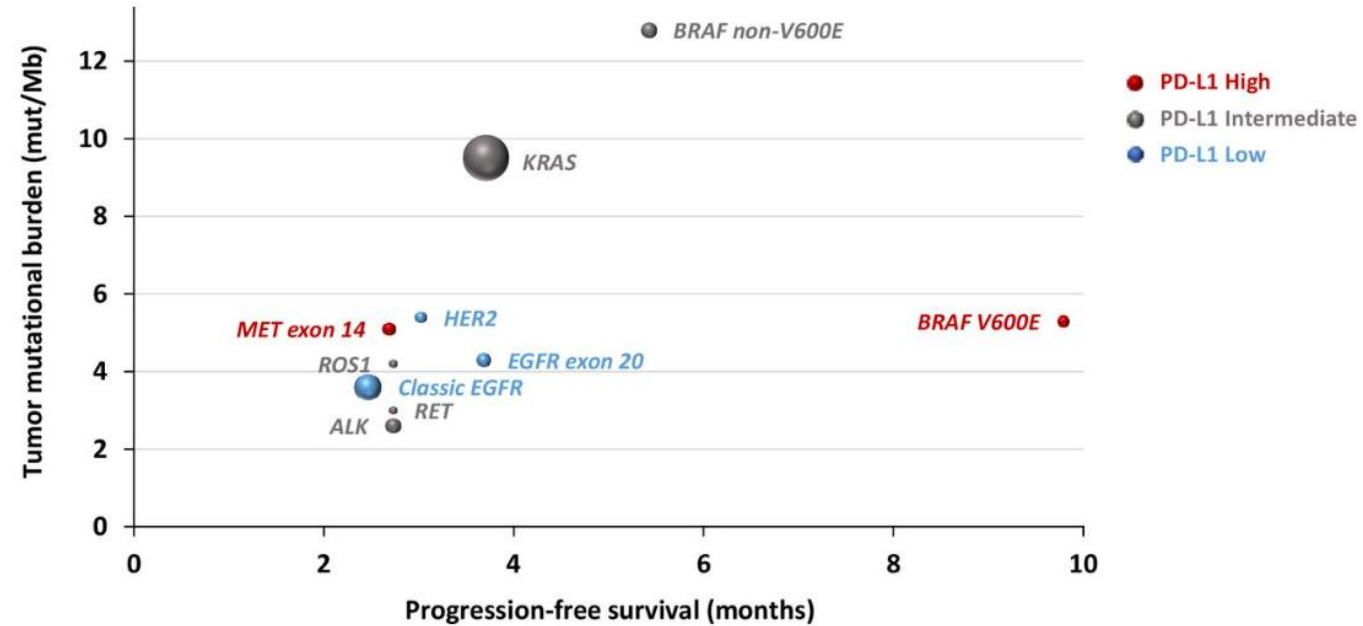
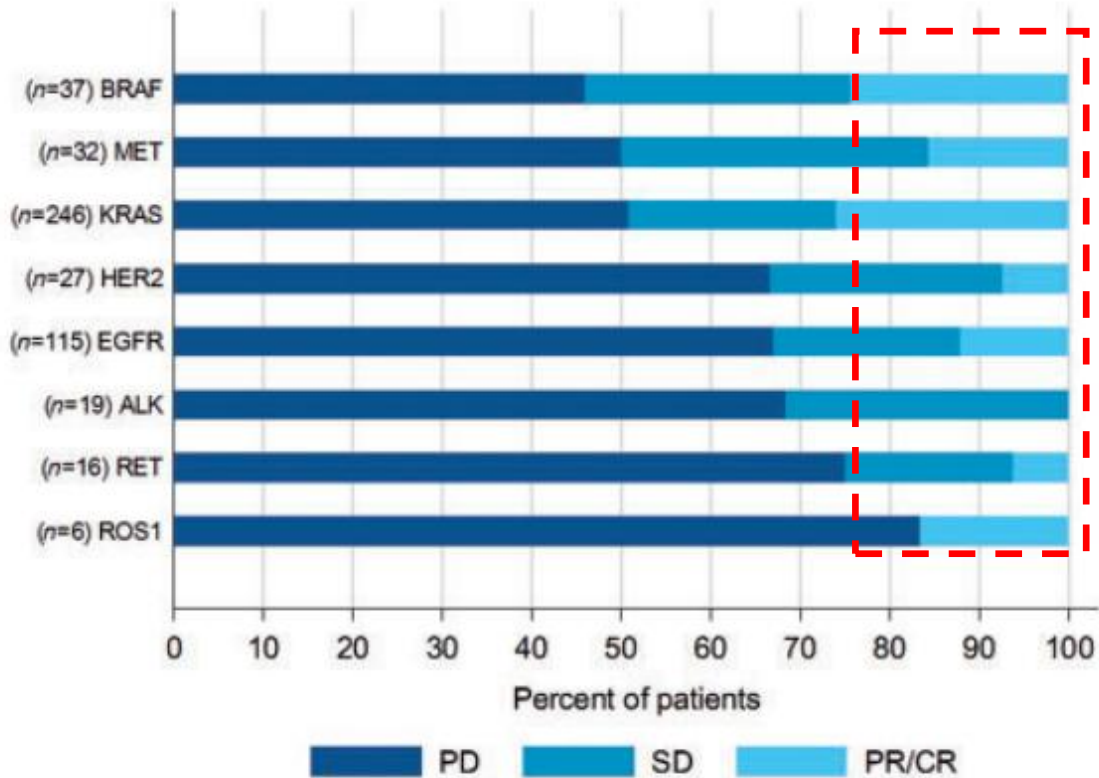
Room air, D/C

After 15 days



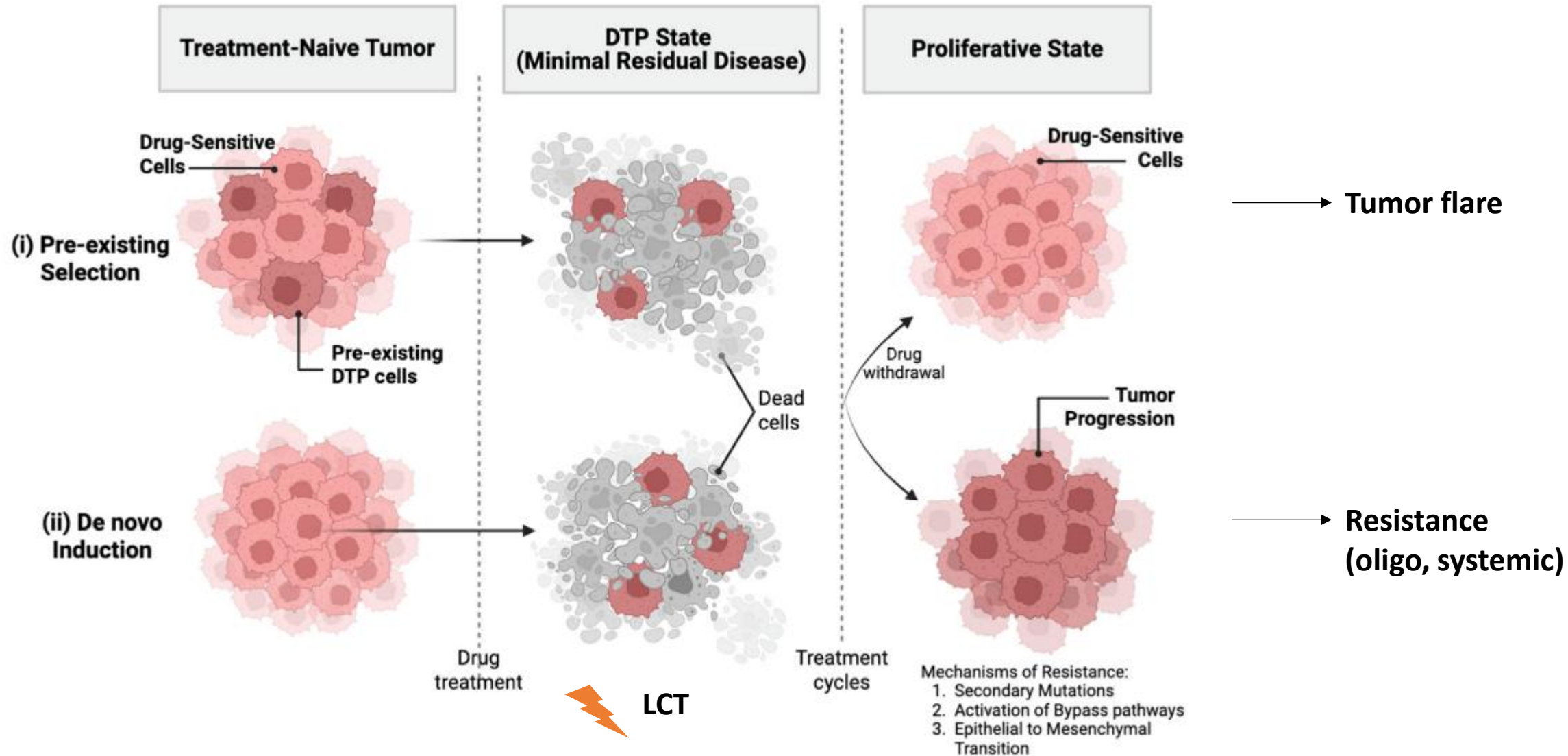
OPD

Lower clinical activity with ICI



Low TMB, Cold tumor, Immunosuppressive microenvironment

Generation of DTP (Drug-Tolerant Persister) cells



Disease Flare after Tyrosine Kinase Inhibitor Discontinuation in Patients with *EGFR*-Mutant Lung Cancer and Acquired Resistance to Erlotinib or Gefitinib: Implications for Clinical Trial Design

Jamie E. Chaft, Geoffrey R. Oxnard, Camelia S. Sima, Mark G. Kris, Vincent A. Miller, and Gregory J. Riely

Abstract

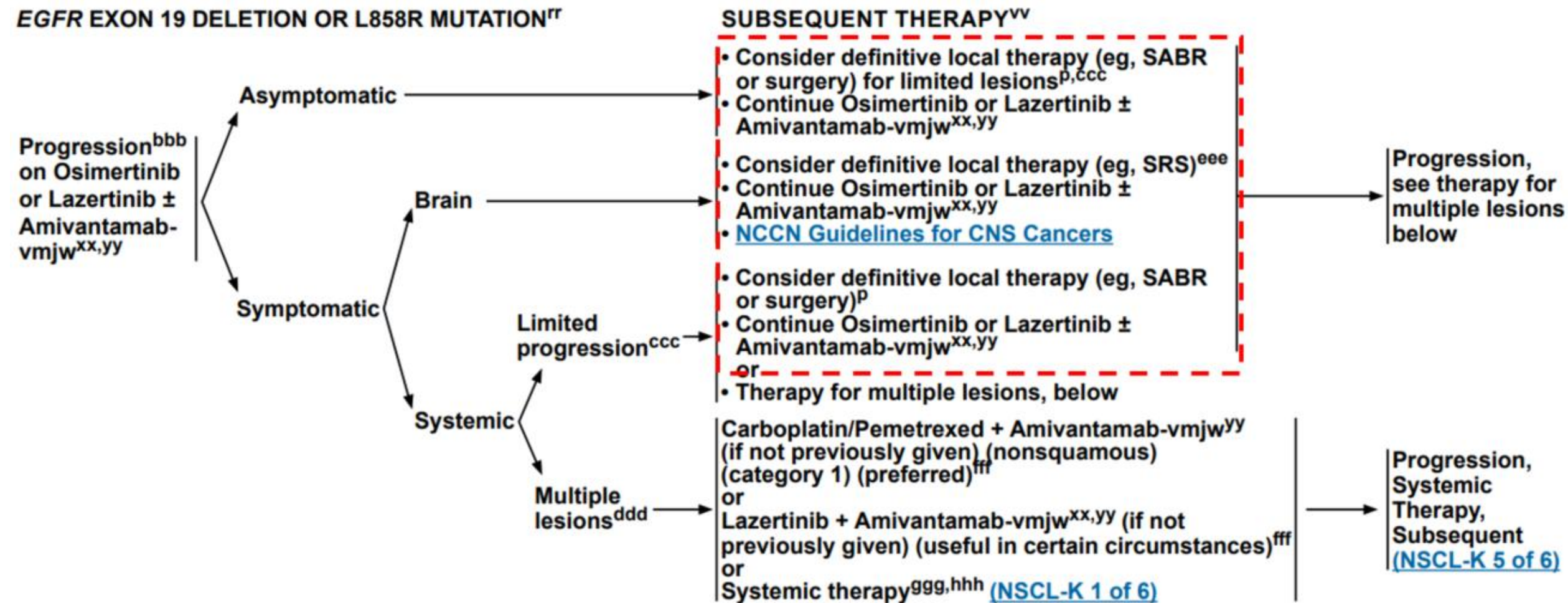
Purpose: Treatment of patients with oncogene-addicted cancers with tyrosine kinase inhibitors (TKI) is biologically and clinically different than with cytotoxic chemotherapy. We have observed that some patients with *EGFR*-mutant lung cancer and acquired resistance to erlotinib or gefitinib (RECIST progression after initial benefit) have accelerated progression of disease after discontinuation of TKI. To examine this observation and define the course of patients following TKI discontinuation, we systematically evaluated patients enrolled on clinical trials of agents to treat acquired resistance to erlotinib or gefitinib.

Methods: We evaluated patients with *EGFR*-mutant lung cancer who participated in trials for patients with acquired resistance that mandated TKI discontinuation before administration of study therapy. Disease flare was defined as hospitalization or death attributable to disease progression during the washout period.

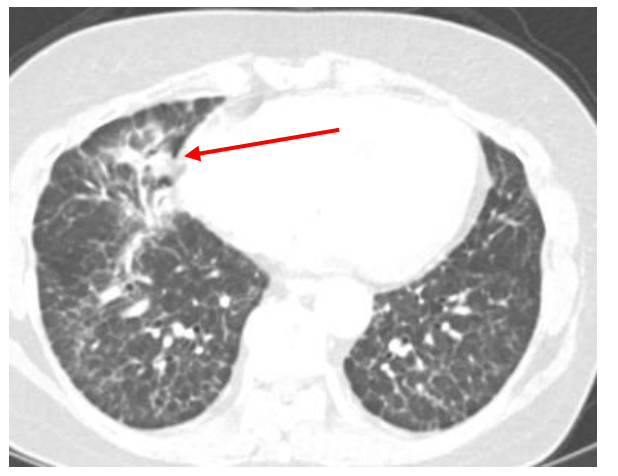
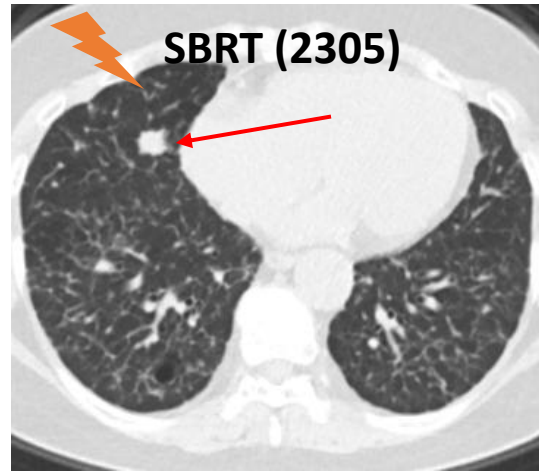
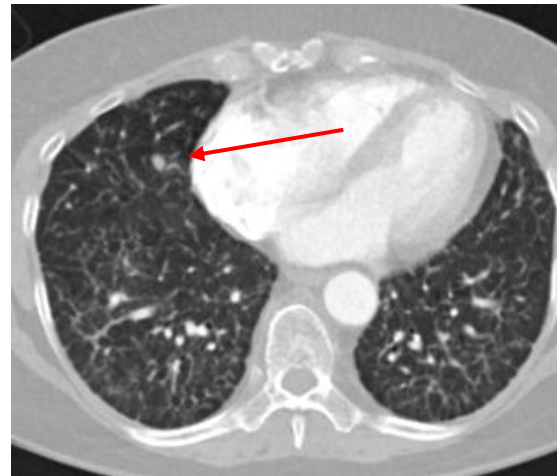
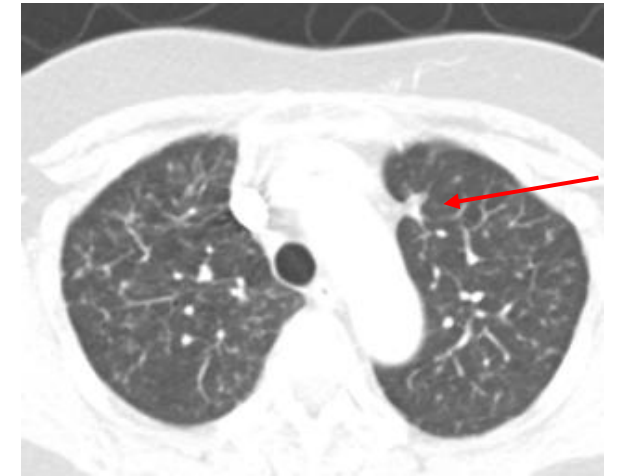
Results: Fourteen of 61 patients (23%; 95% CI: 14–35) experienced a disease flare. The median time to disease flare after TKI discontinuation was 8 days (range 3–21). Factors associated with disease flare included shorter time to progression on initial TKI ($P = 0.002$) and the presence of pleural ($P = 0.03$) or CNS disease ($P = 0.01$). There was no association between disease flare and the presence of T790M at the time of acquired resistance.

Conclusions: In patients with *EGFR*-mutant lung cancer and acquired resistance to epidermal growth factor receptor TKIs, discontinuation of erlotinib or gefitinib before initiation of study treatment is associated with a clinically significant risk of accelerated disease progression. Clinical trials in this patient population must minimize protocol-mandated washout periods. *Clin Cancer Res*; 17(19):6298–303. ©2011 AACR.

Beyond PD: TKI continuation + LAT (Except Multiple Systemic PD)



55/F, Never smoker, ADC, LUL, cT4N3M1c, (IVB)
M/lung to lung, brain metastasis, EGFR (19del)



1912

2110

2303

2312

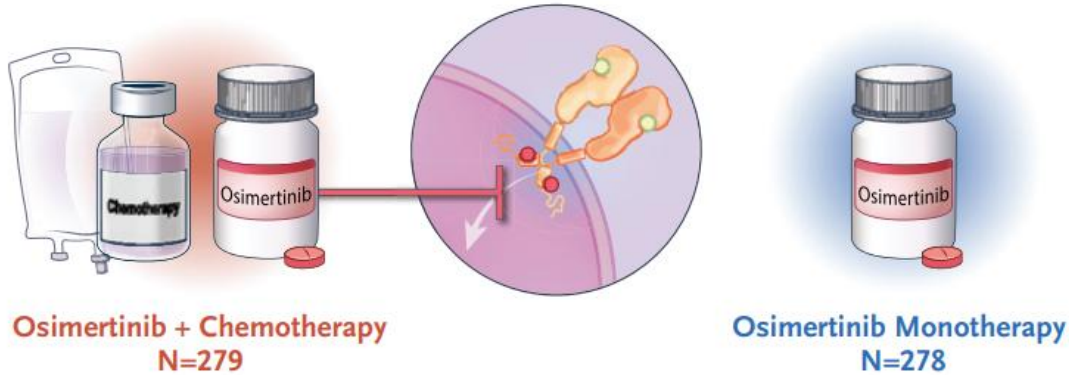
Osimertinib (비급여)

Gefitinib (급여)

Beyond PD, Gefitinib (급여)

Osimertinib with or without Chemotherapy in EGFR-Mutated Advanced NSCLC

Planchard D et al. DOI: 10.1056/NEJMoa2306434



FLAURA2: Overall survival

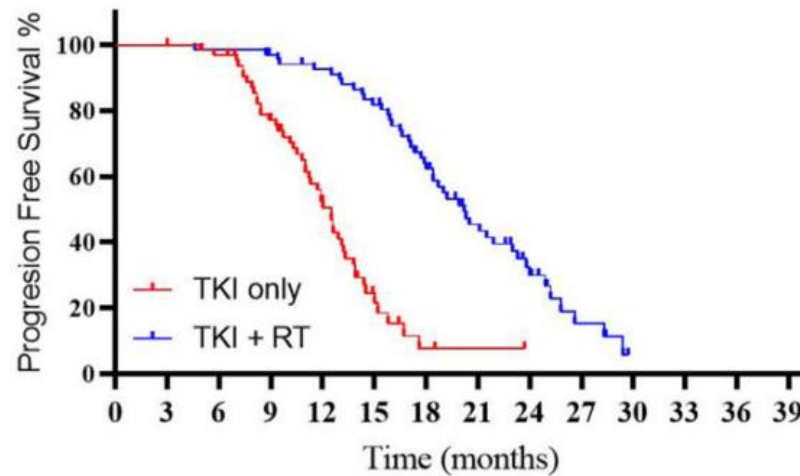
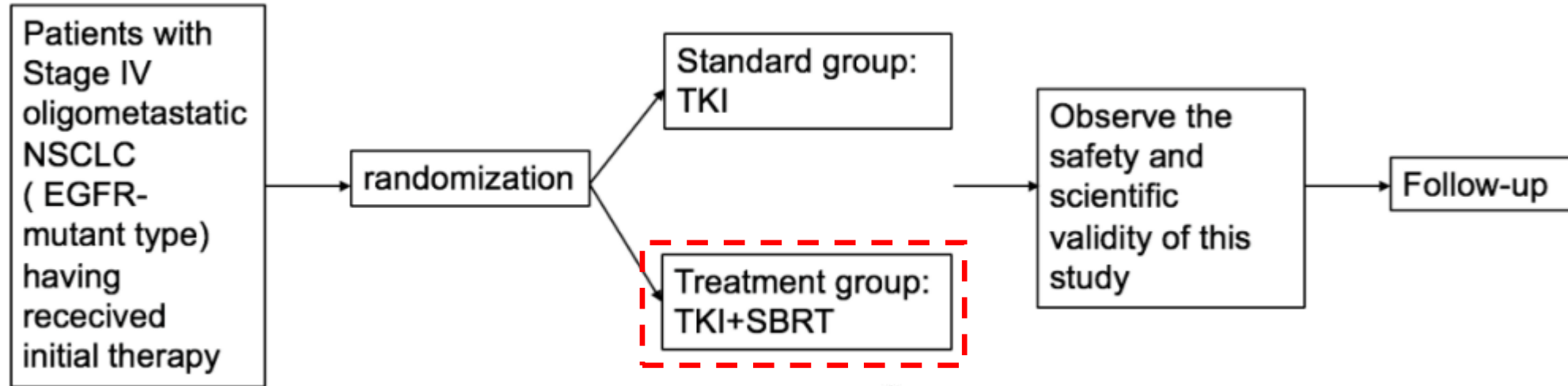
Median OS with osi + CTx was 47.5 months



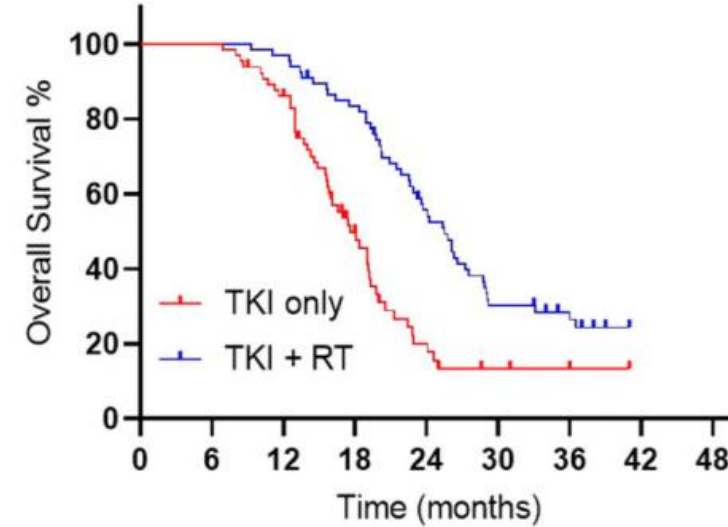
FLAURA2 Strategy (Osi + Chemo)

- **Eradicating DTP Pool:** Adding Platinum-Pemetrexed chemotherapy directly targets and kills non-proliferating/persister cells.
- **Deeper Response:** Achieves a significantly deeper initial response, reducing the total MRD burden.
- **Delaying Resistance:** Depleting the DTP reservoir prevents the subsequent evolution of resistance mechanisms.

Emerging role of LCT

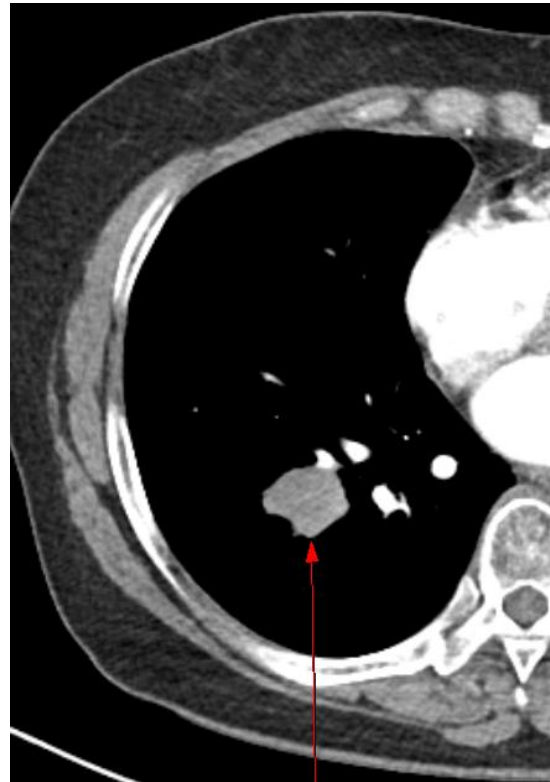
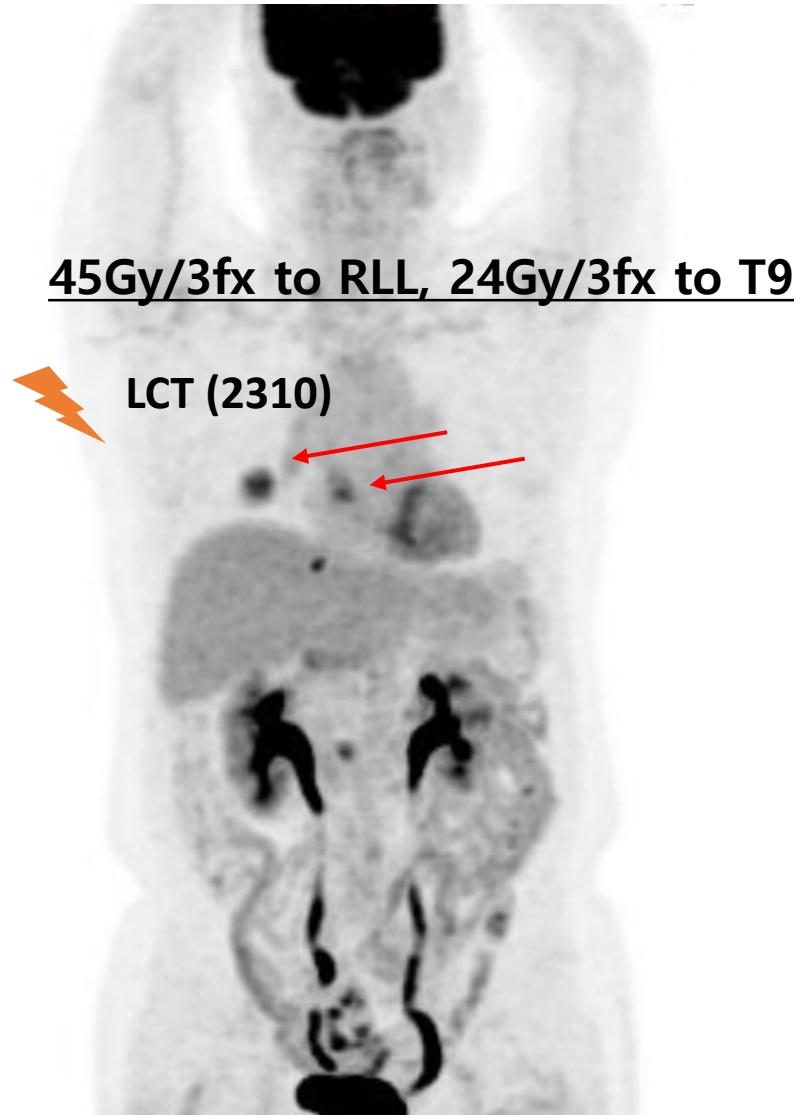


TKI only	65	65	62	48	28	8	3	2	1	0	0
TKI + RT	68	67	67	65	60	51	37	22	12	5	1

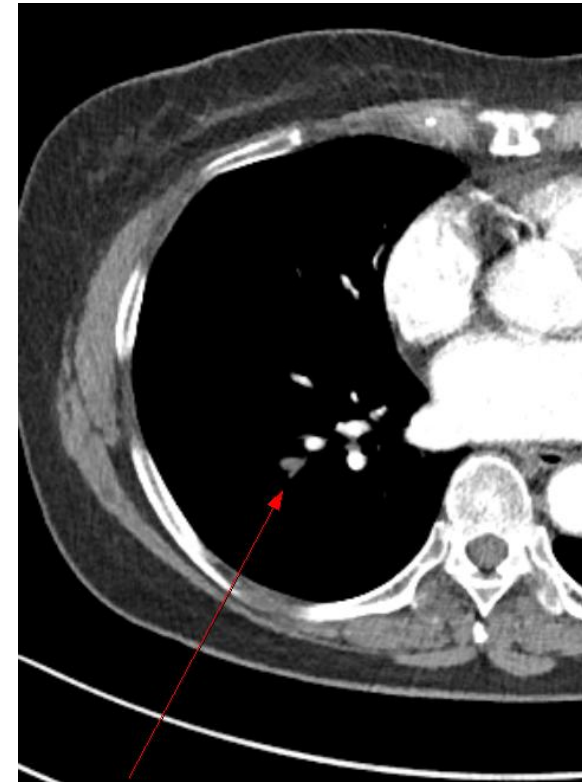


TKI only	65	65	55	26	9	5	3	2
TKI + RT	68	68	66	56	36	20	14	9

70/F, ADC, RLL, cT1cN0M1a, IVA (ALK+), Brigatinib (2307)

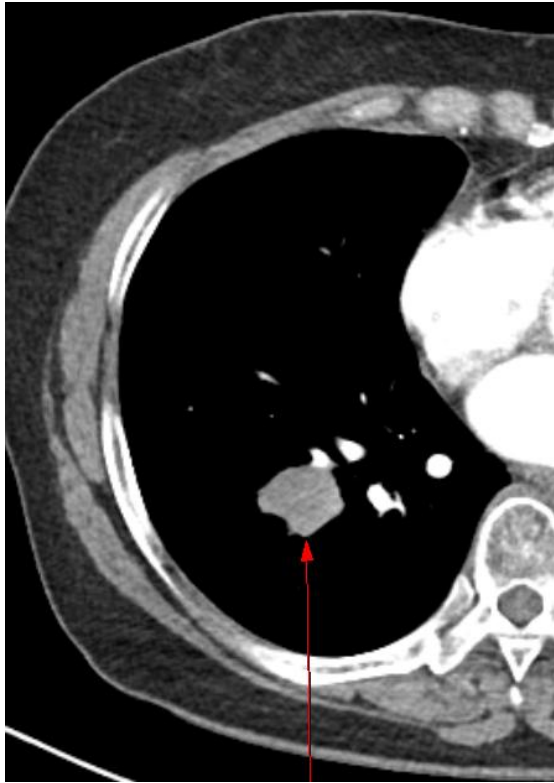


2307

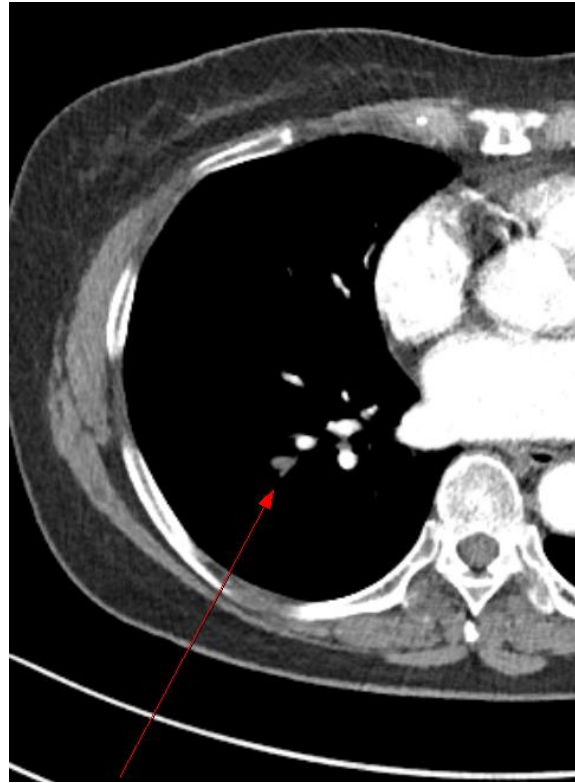


2309

70/F, ADC, RLL, cT1cN0M1a, IVA (ALK+), Brigatinib (2307)



2307



2309



2404



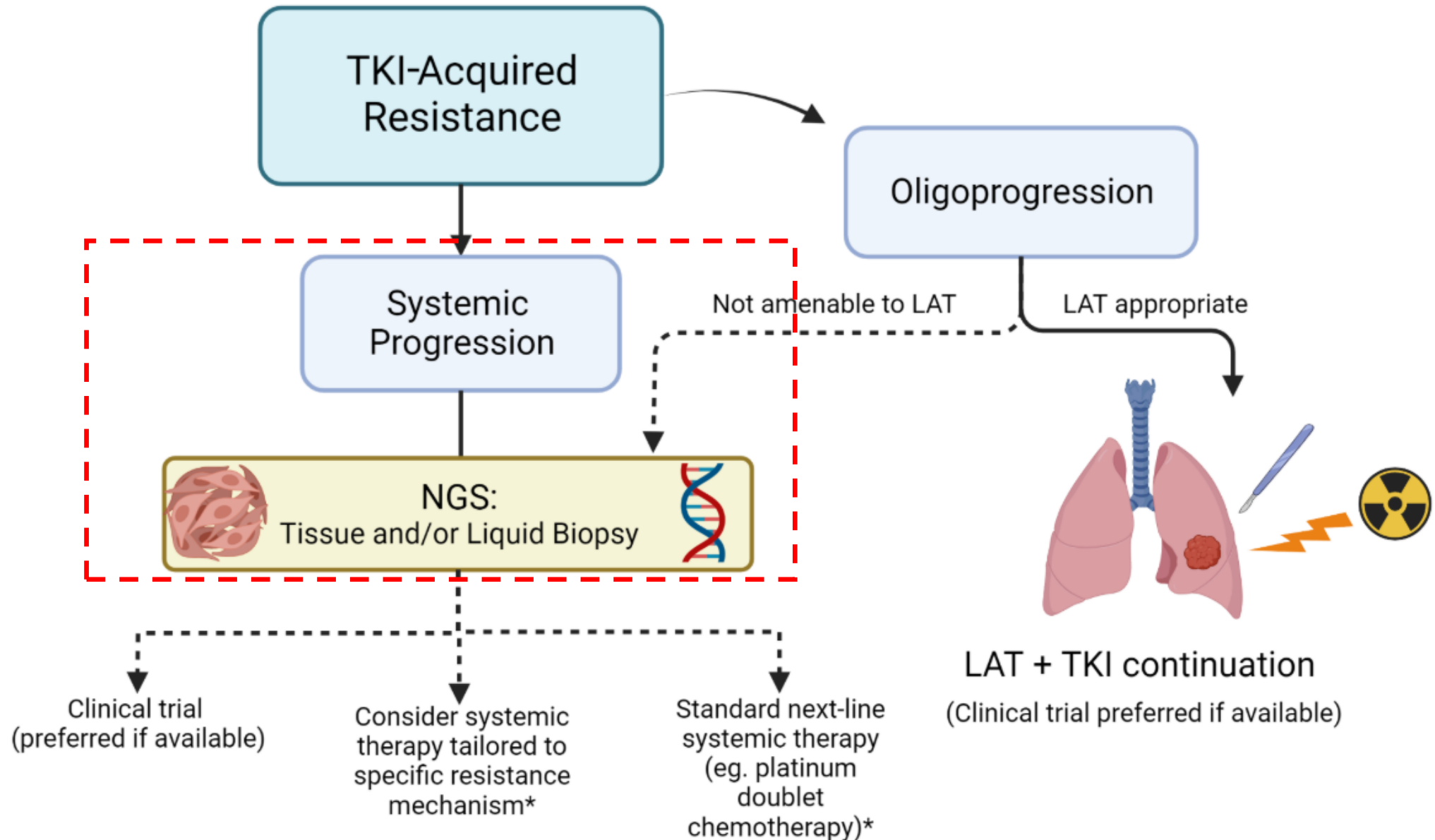
2606

Brigatinib ongoing

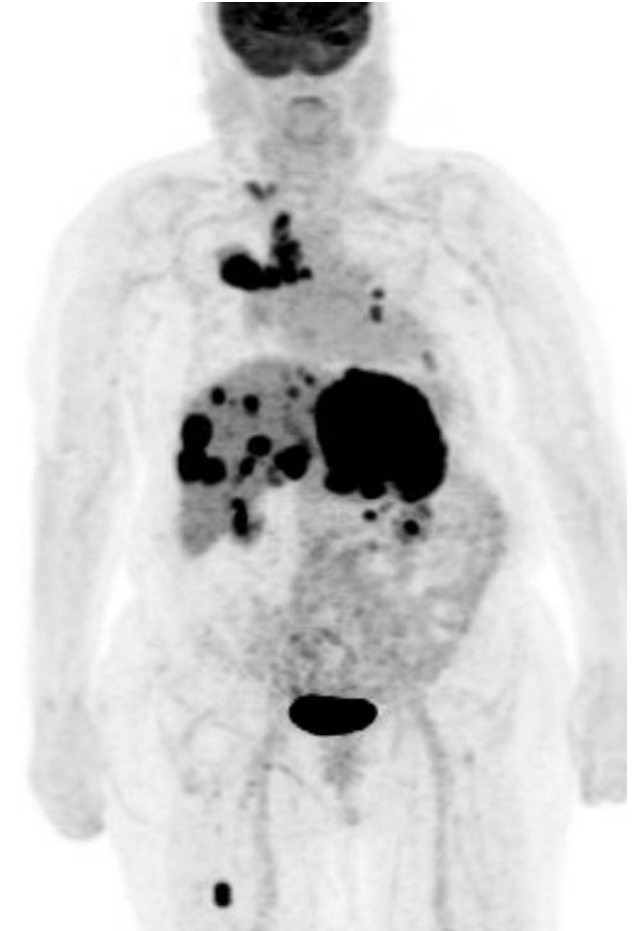
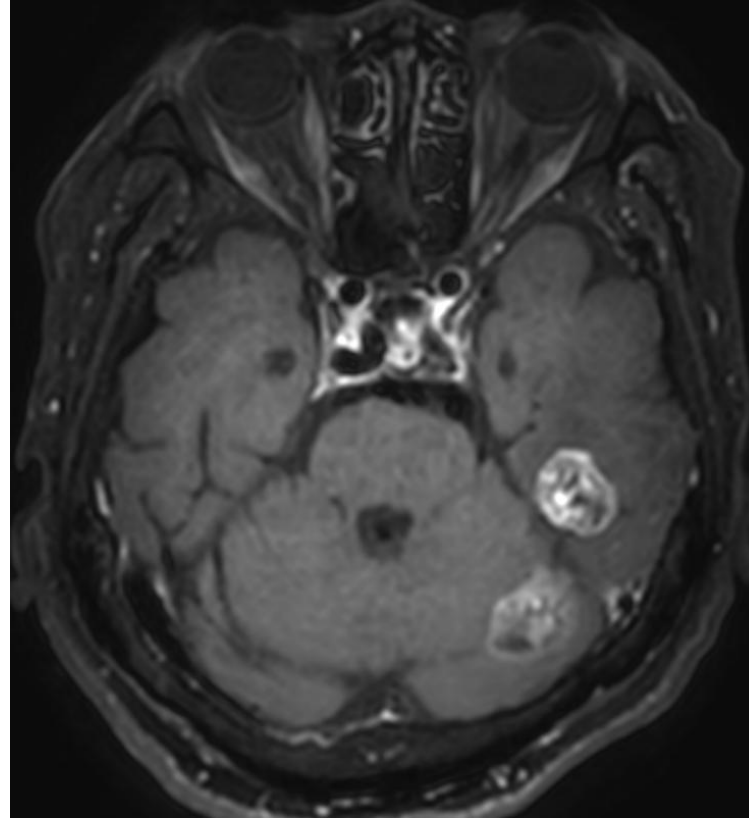


LCT (2310)

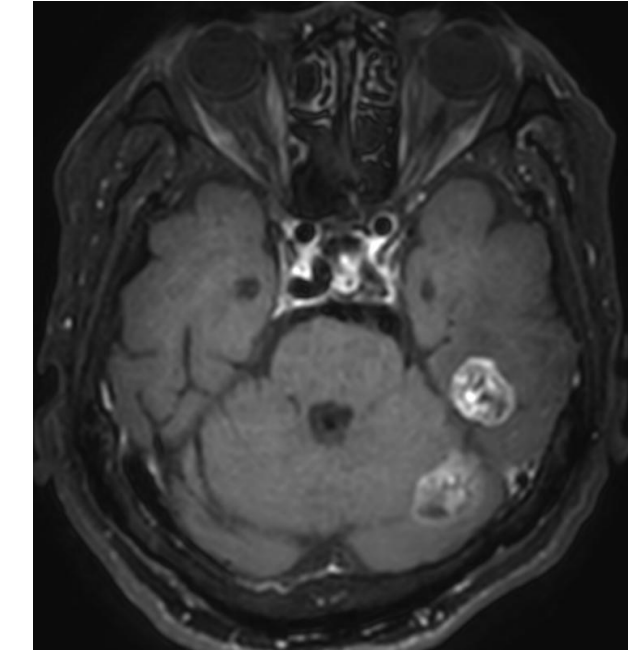
Strategies for managing acquired resistance



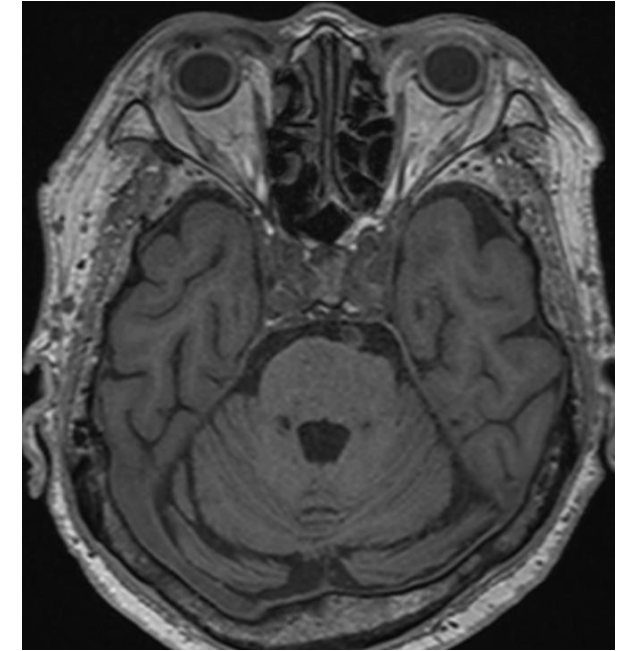
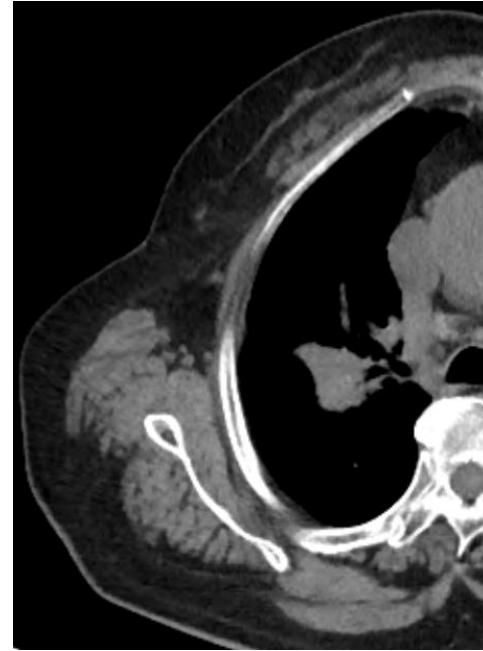
85/F, ADC, RUL, cT4N3M1c2, IVB (L858R)



85/F, ADC, RUL, cT4N3M1c2, IVB (L858R), Osimertinib (2410-)



2410



2601

연고지 포항으로 전원

85/F, ADC, RUL, cT4N3M1c2, IVB (L858R), Osimertinib (2410-)

Gene	RefSeq	Exon	NT Change	AA Change	VAF*
EGFR	NM_005228.5	21	c.2573T>G	p.Leu858Arg	95.03

N

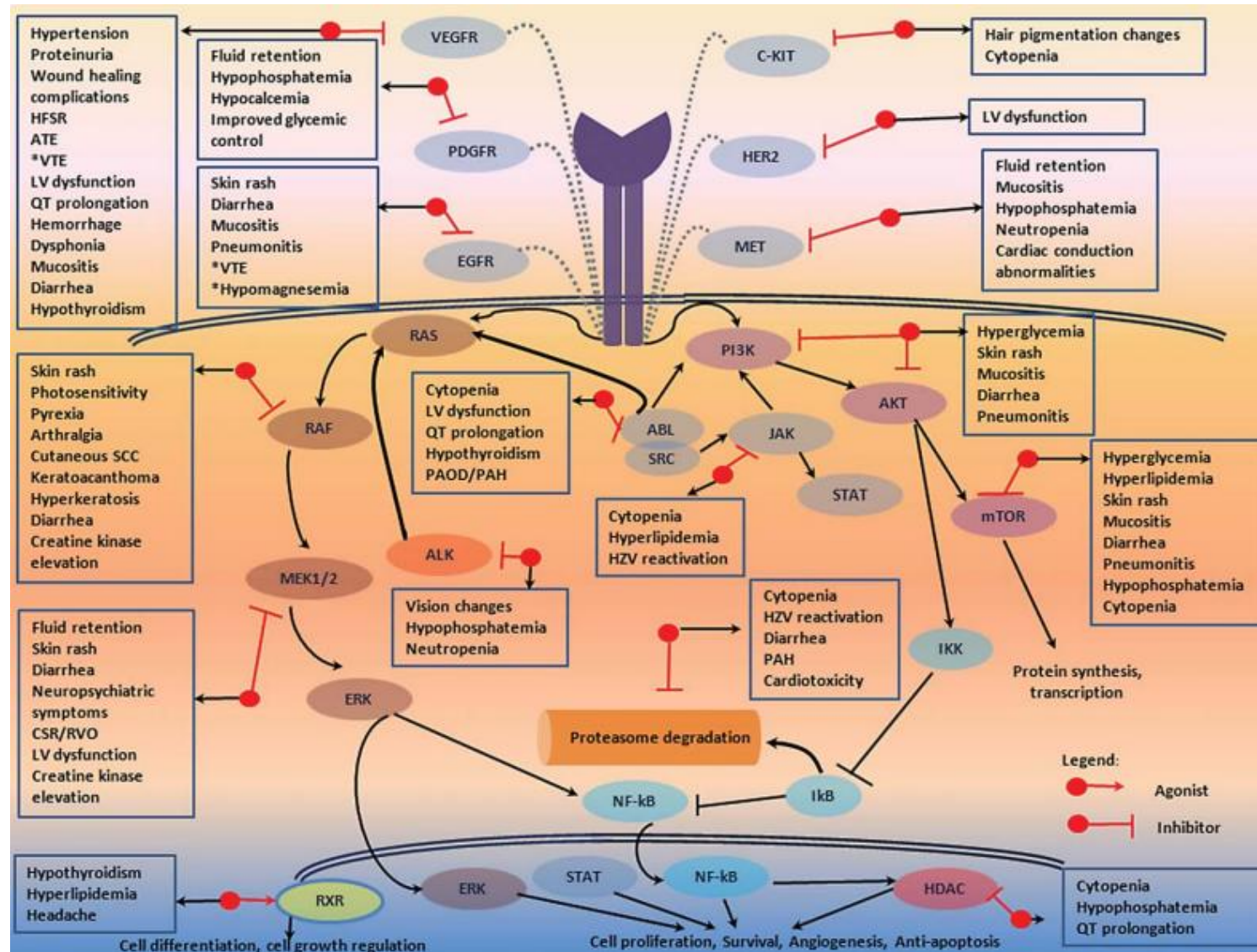
Gene	Locus	DNA Copy Number**	Variant Type
EGFR	7p11.2	31.285	Amplification
MET	7q31.2	17.644	Amplification
CCNE1	19q12	9.945	Amplification
KRAS	12p12.1	18.072	Amplification

Liquid NGS (AlphaLiquid® 100)

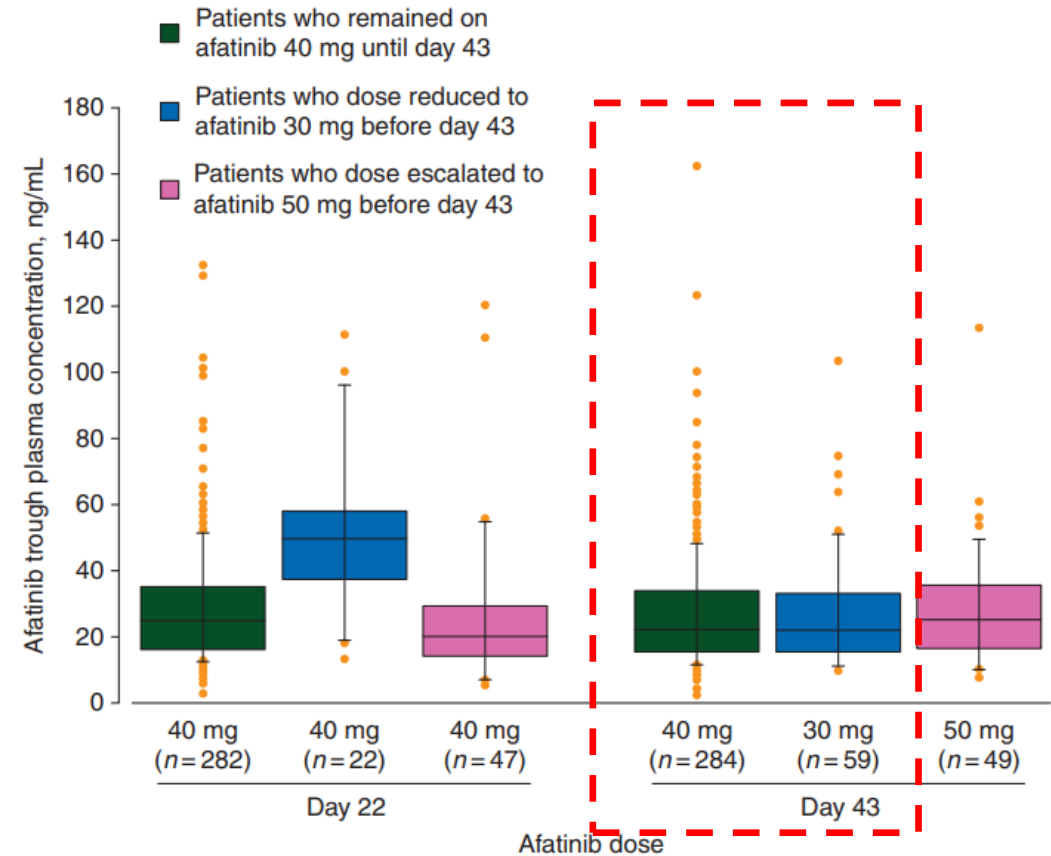
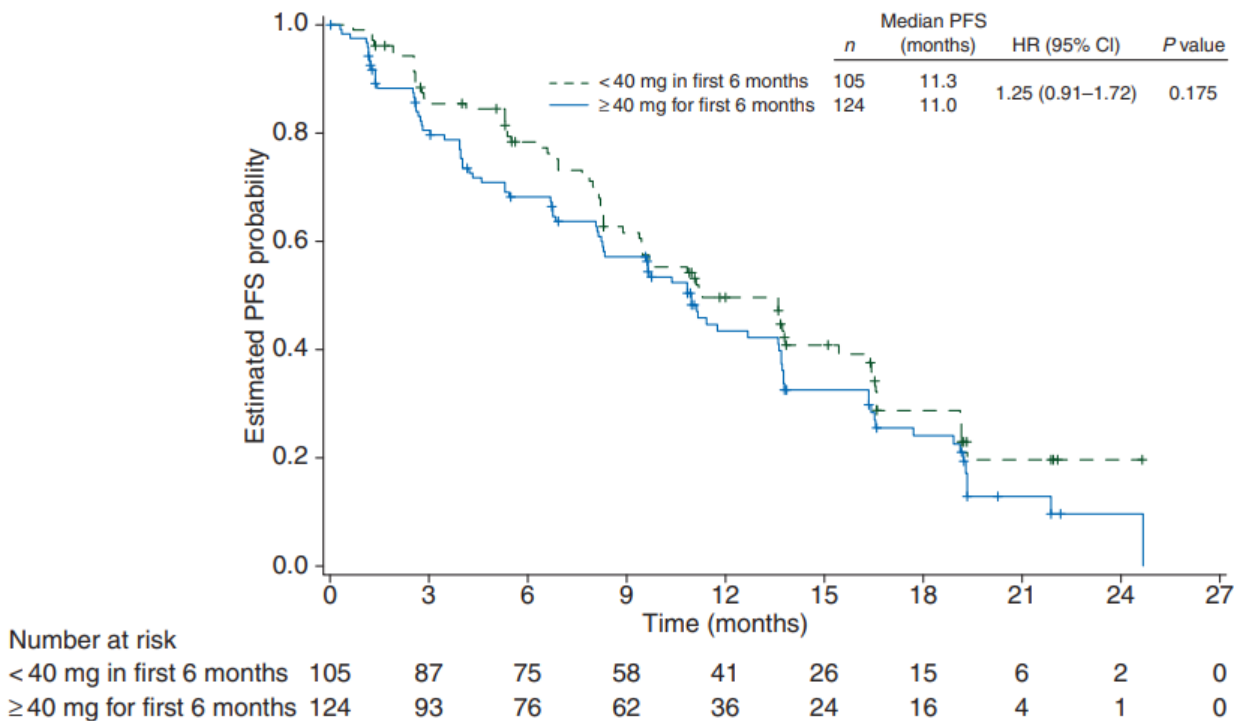
2410

2601

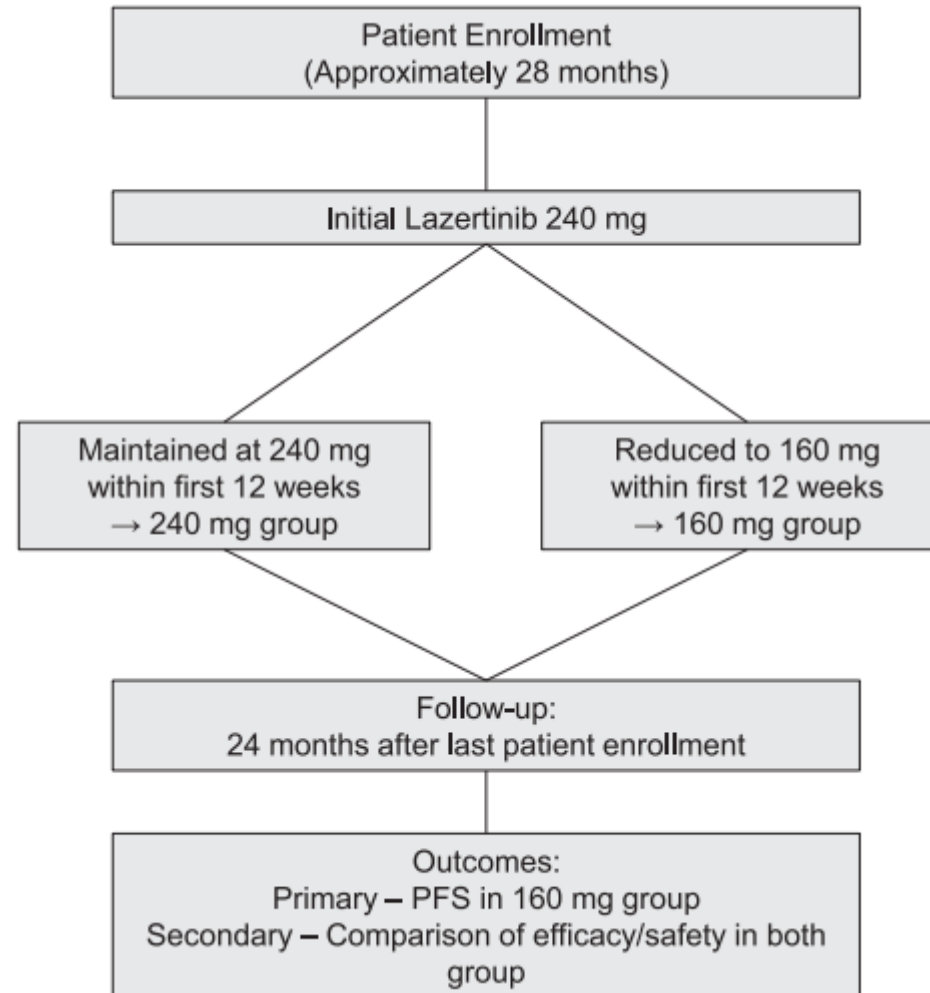
Toxicity Follows the Target



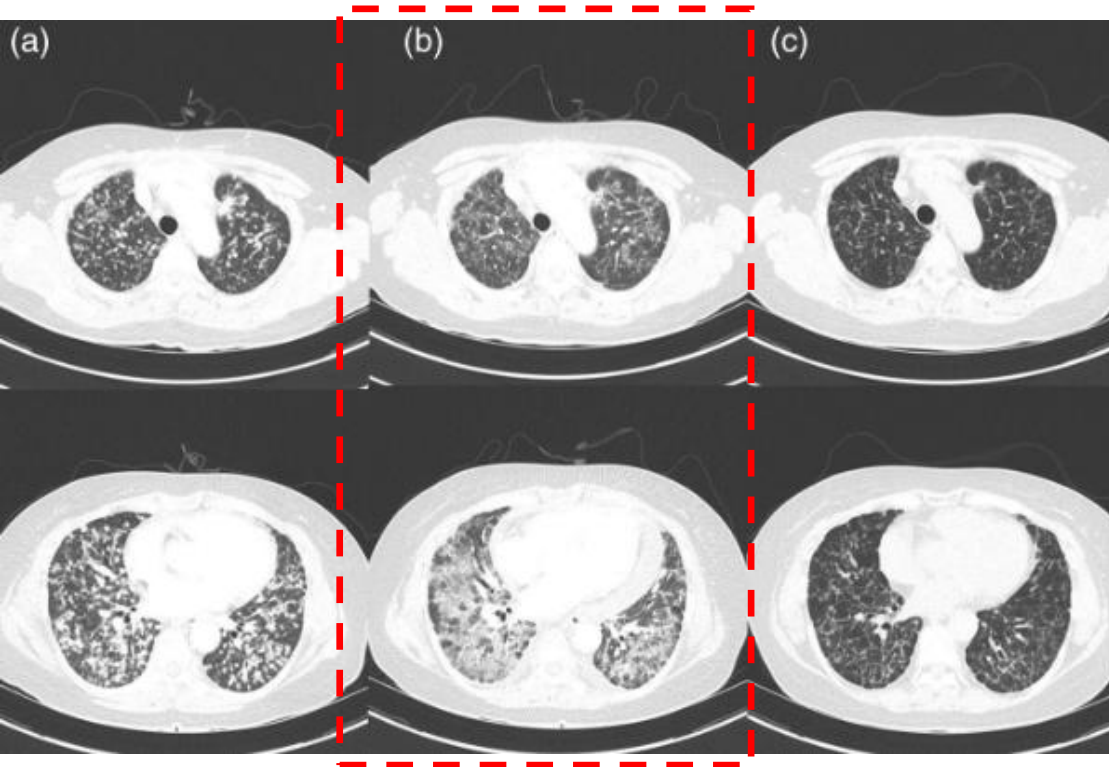
Effect of dose adjustment on the safety and efficacy of afatinib for *EGFR* mutation-positive lung adenocarcinoma: *post hoc* analyses of the randomized LUX-Lung 3 and 6 trials



Impact of Modifying Lazertinib Doses on Effectiveness and Safety in Patients With EGFR-Positive Advanced Lung Cancer: A Multicenter, Prospective Observational Cohort Study



Potentially fatal toxicities



ICU care & recovery

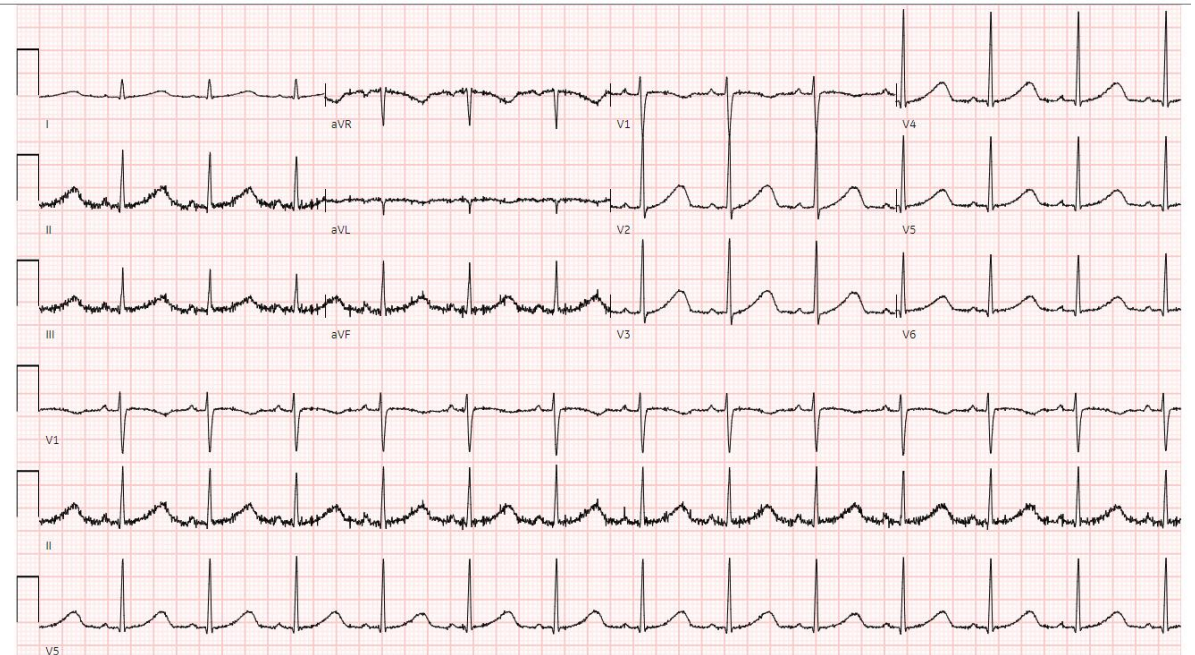
≥Gr 3 AE pneumonitis

Osimertinib (1.1%), Lazertinib (0.8%)

Brigatinib (3.0%), Alectinib (0.7%)

Vent. rate: 79 BPM
PR interval: 154 ms
QRS duration: 72 ms
QT/QTcB: 492 / 564 ms
QTc-TdP: 74 / 74 / 69

Normal sinus rhythm
Prolonged QT
Abnormal ECG



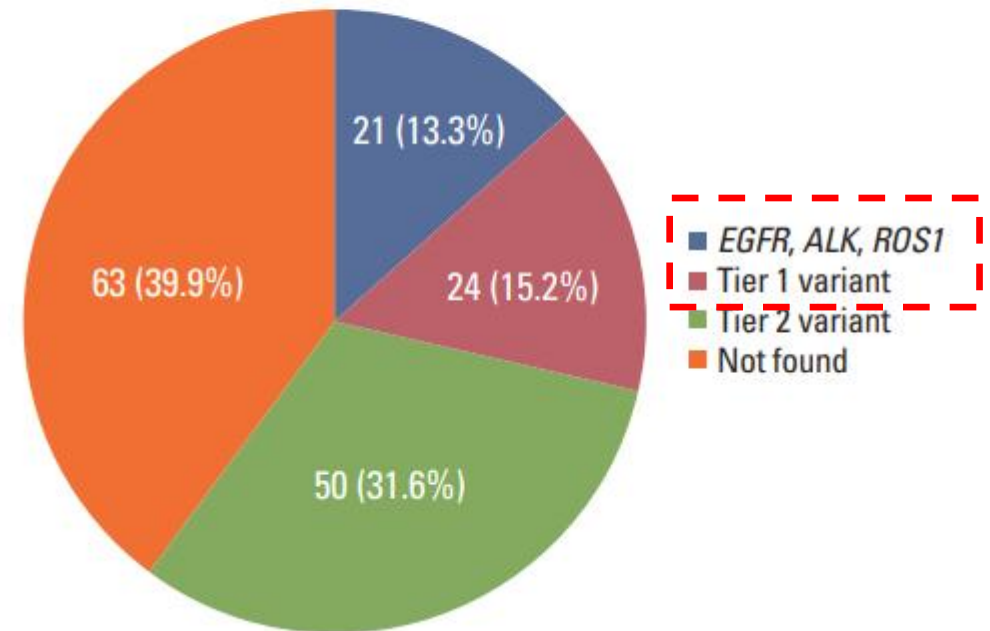
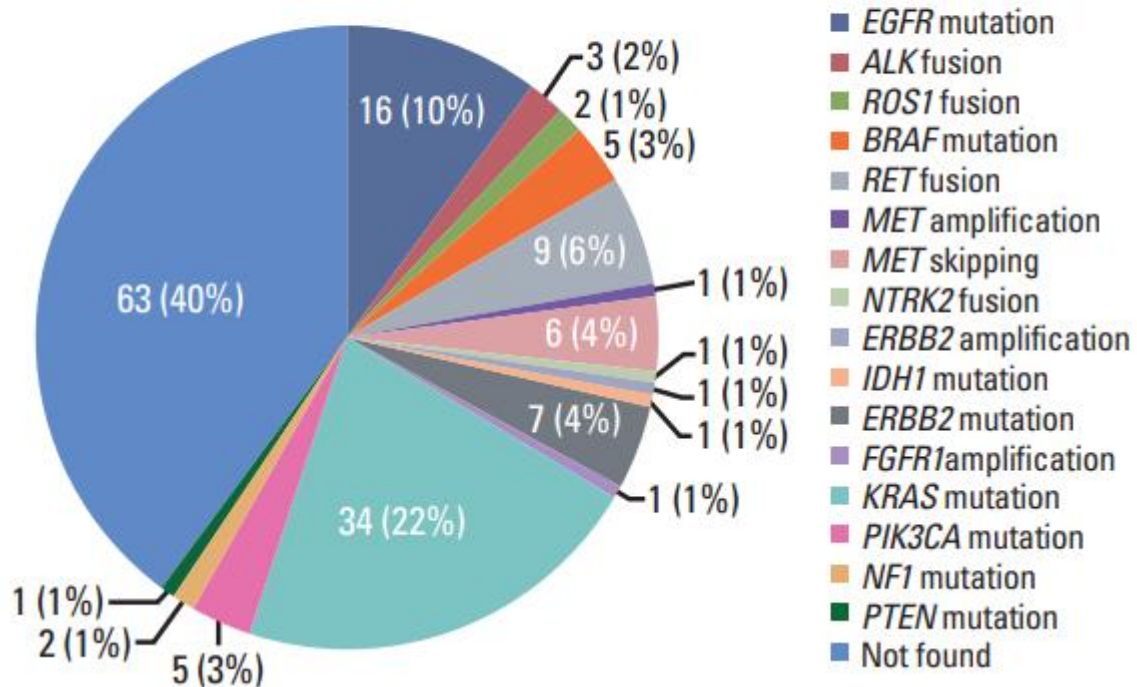
Cardiac arrest due to TdP

≥Gr 3 QTc prolongation (QTc > 500 ms)

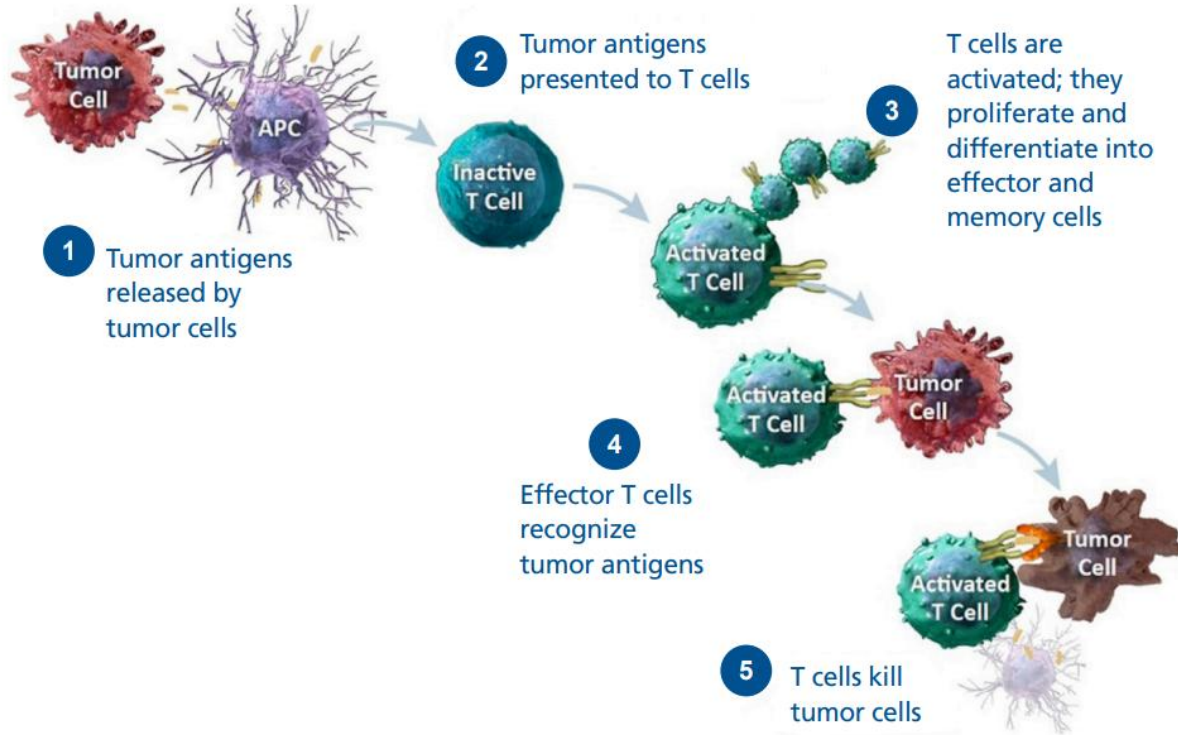
Selpercatinib (4.0%), Osimertinib (0.5%), Crizotinib (1.1%)

NGS in Driver-Negative NSCLC

158 WT patients → 95 (60.1%) actionable alterations → 32.6% (31/95) received matched target therapy



면역항암제의 원리

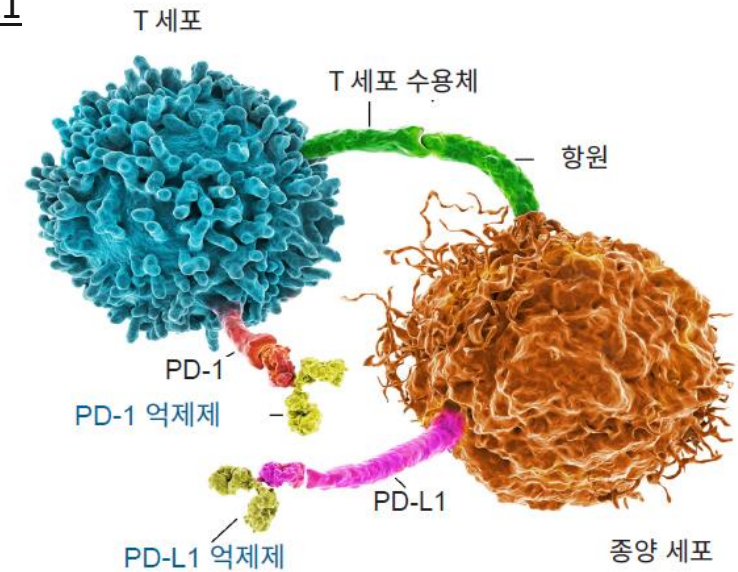


면역관문: 면역 반응을 방지하거나 늦추는 “브레이크”
신체의 건강한 세포를 보호
T 세포의 면역관문 2가지: CTLA-4, PD-1

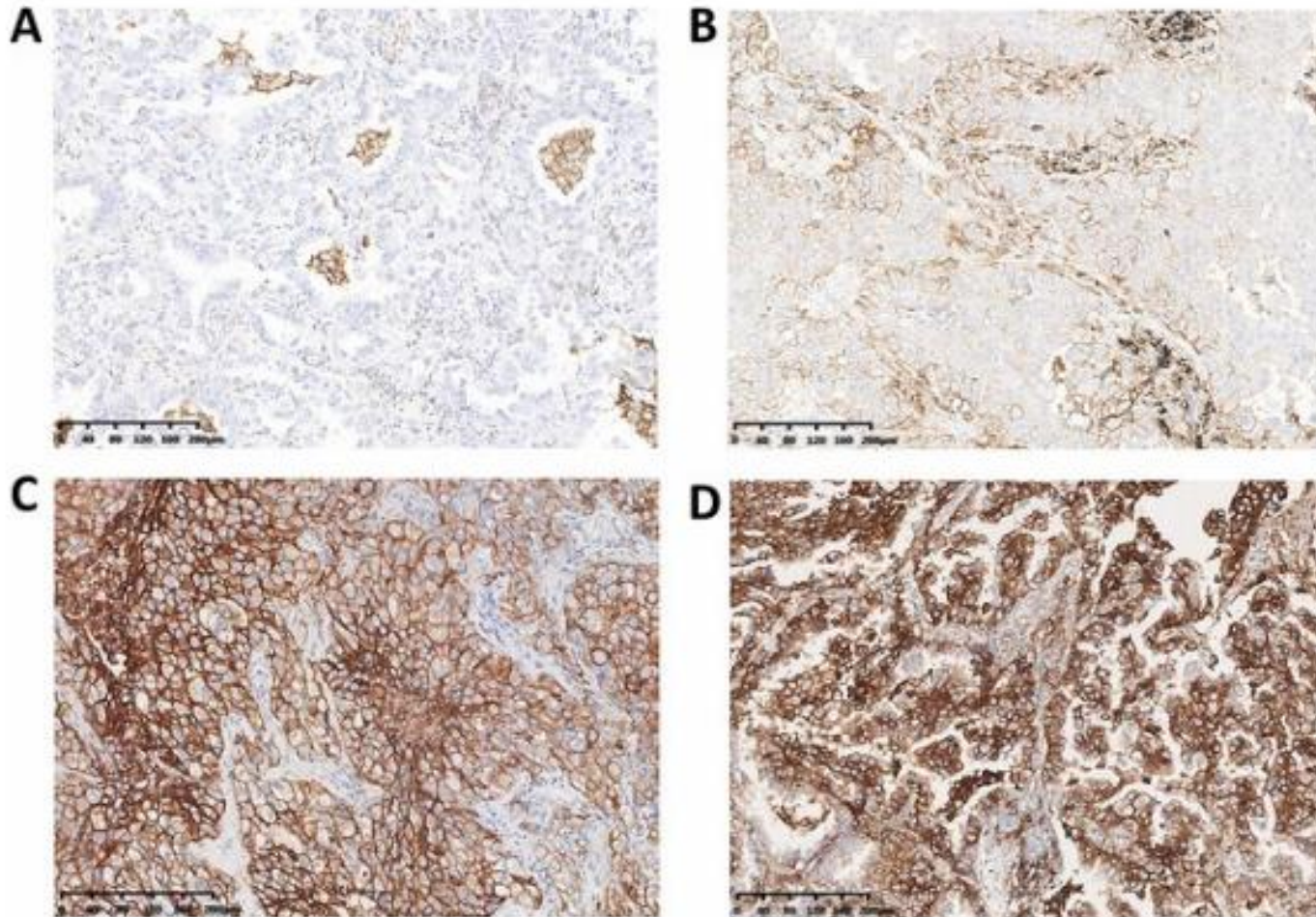
암세포의 면역 회피: PD-L1

면역 요법

일부 폐암은 표면에 PD-L1이 있는 세포로 구성됩니다. PD-L1은 T 세포의 PD-1에 부착되어 T 세포가 암세포를 죽이는 것을 막을 수 있습니다. 면역 요법은 PD-L1이 부착되는 것을 막습니다. 결과적으로 T 세포는 암세포를 공격할 수 있습니다. 면역 요법에는 두 가지 유형이 있습니다. PD-1 억제제는 T 세포에 부착됩니다. PD-L1 억제제는 암세포에 부착됩니다.



PD-L1 expression, TPS (tumor proportion score)

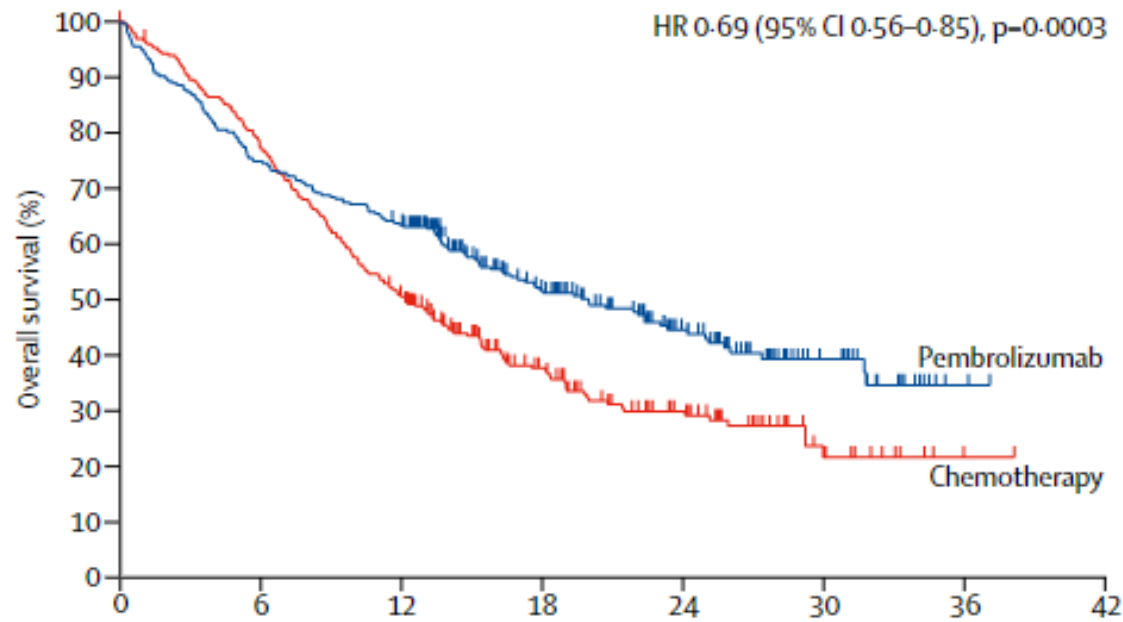


A: TPS <1%
B: TPS 1-49%
C: TPS >50%
D: TPS >50%

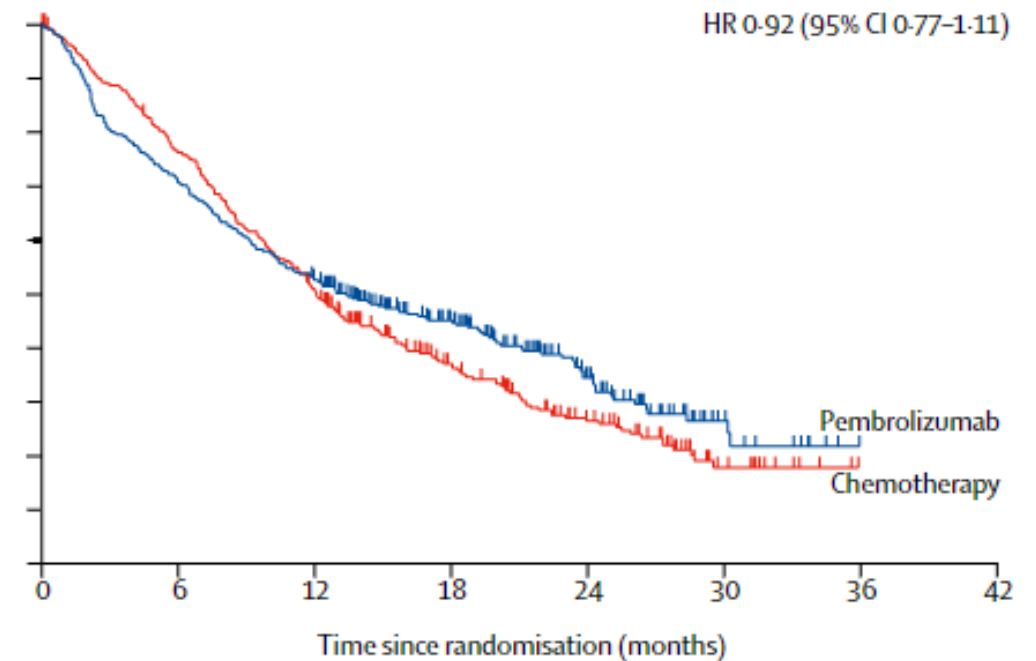
면역항암제의 특징

- PD-L1 expression ↑ TMB ↑, driver mutation (-): good response
- 일부환자에서 장기간 효과 지속, 장기 생존 가능
- 약을 중단하여도 memory T cell 기반의 지속적 항종양 면역
- 차별화된 반응 평가
- 낮은 부작용, 면역 반응과 관련된 부작용, 용량 감량 하지 않음

Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial



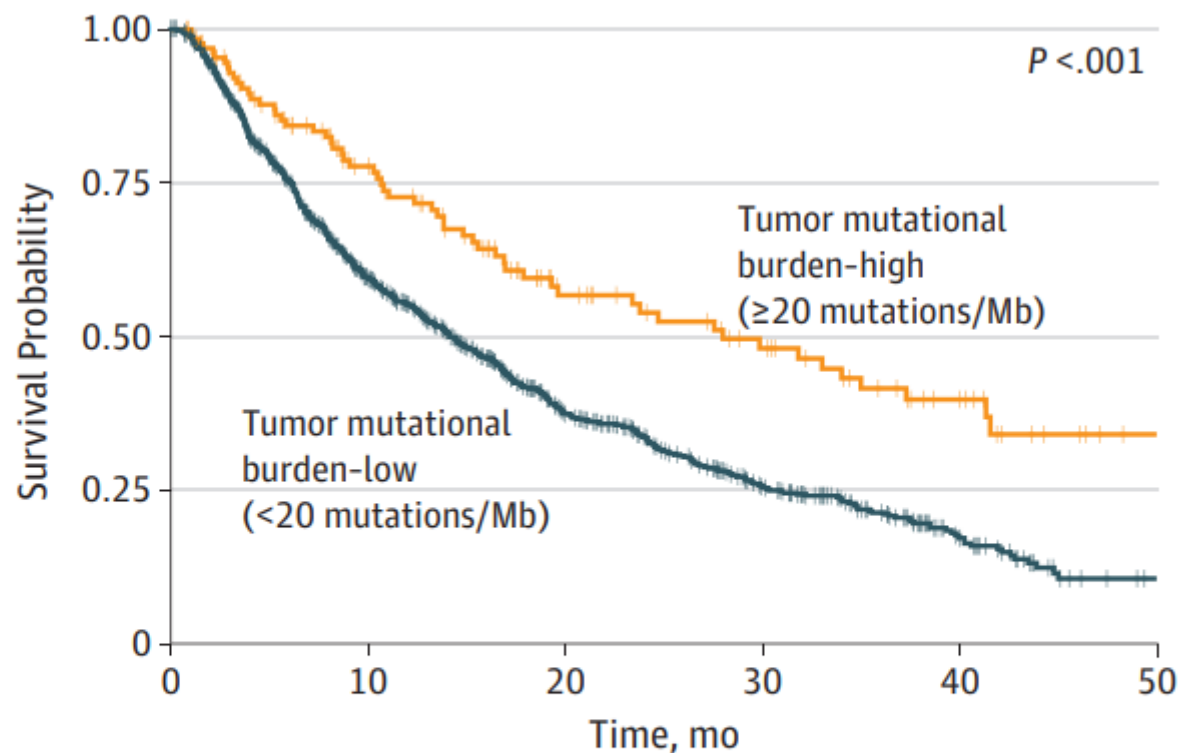
TPS ≥ 50%



TPS ≥ 1-49%

TMB-High → ↑Neoantigens → Better ICI Response

Tumor mutational burden status



No. at risk

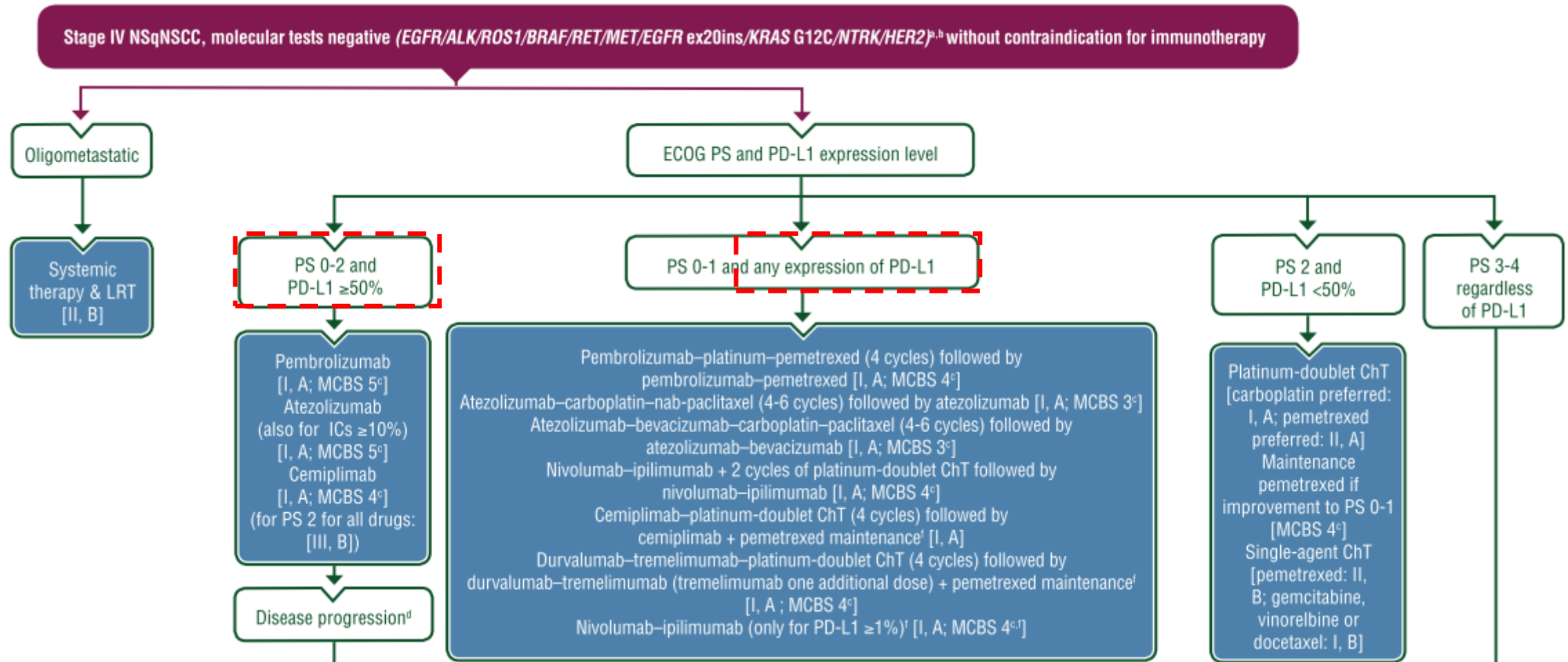
Tumor mutational burden-low (<20 mutations/Mb)

768 461 230 123 41 5

Tumor mutational burden-high (≥20 mutations/Mb)

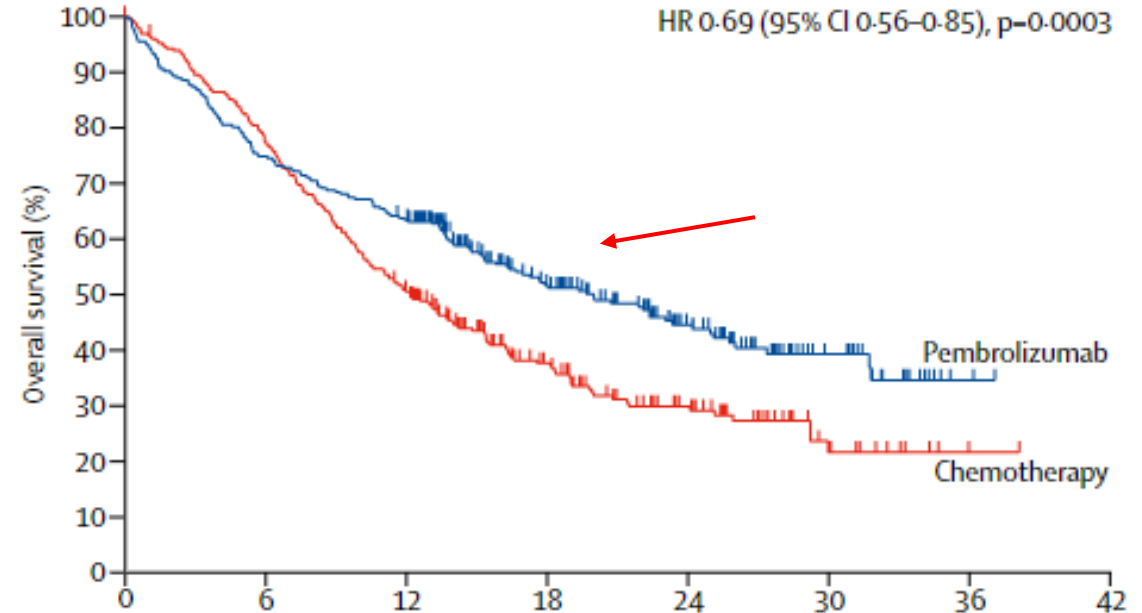
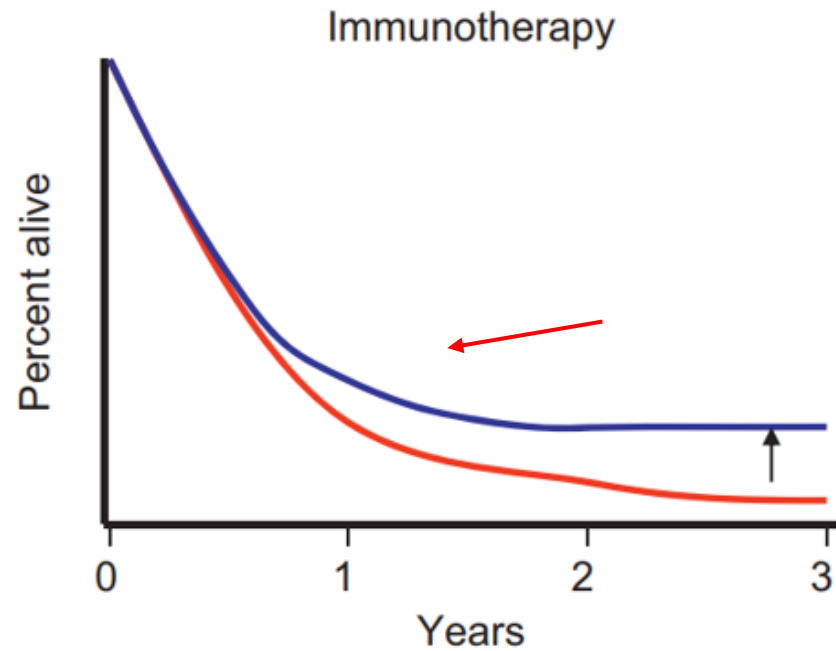
122 79 40 31 17 4

ESMO guideline



Delayed separation, early crossing, long tail

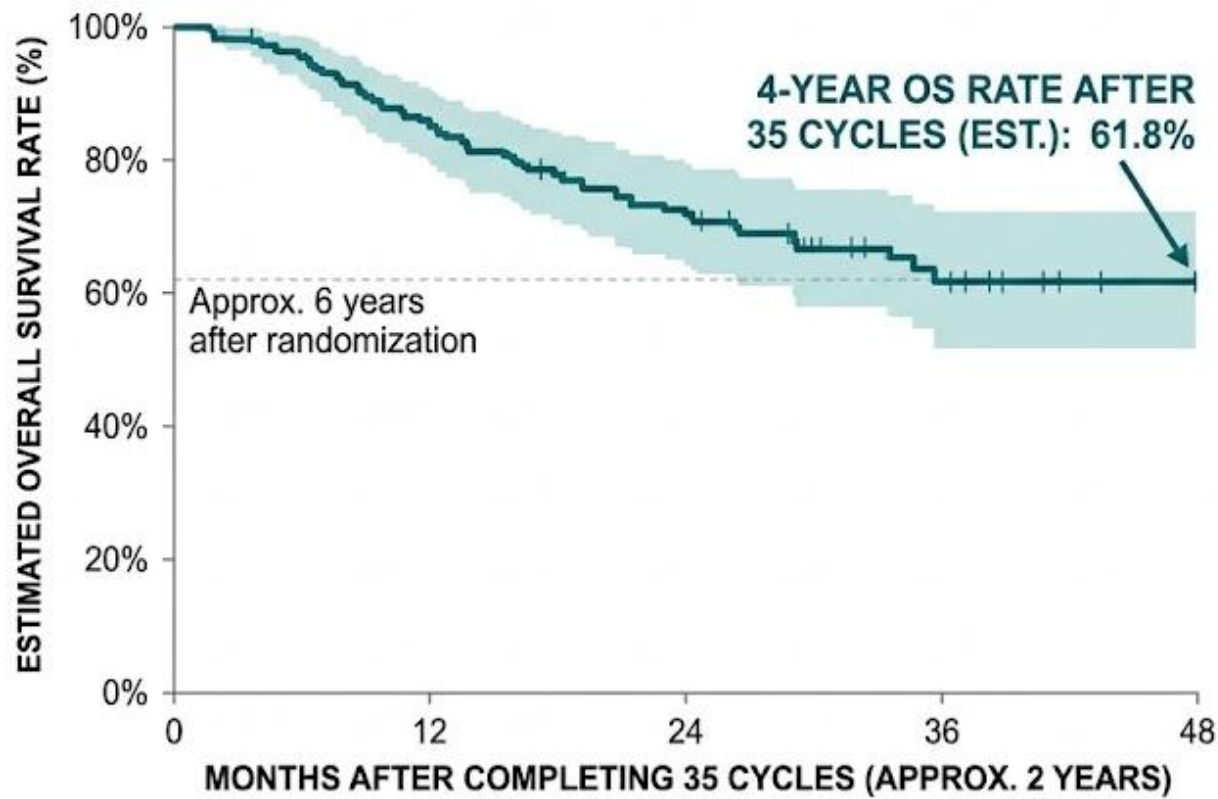
	PD-L1 $\geq$ 50%	PD-L1 $\geq$ 20%	PD-L1 $\geq$ 1%
ORR	39.1%	33.2%	27.3%



KEYNOTE 042 (PD-L1 $\geq$ 50%)

Immune Memory: Sustained Survival After ICI Stop

LONG-TERM SURVIVAL OUTCOMES IN PATIENTS COMPLETING 35 CYCLES OF PEMBROLIZUMAB (KEYNOTE-042)



PATIENT COHORT:

 Completed 35 Cycles: **n=102**
(16.0% of PD-L1 TPS $\geq 1\%$ group)

RESPONSE:

 Objective Response Rate (ORR): **84.3%**

SURVIVAL SUMMARY (at data cutoff)

 Total Deaths: **34 / 102 (33.3%)**

 Median OS (from completion): **NOT REACHED (NR)**

POST-TREATMENT SUCCESS

 Alive without PD or subsequent therapy: **41 patients (40.2% of completers)**

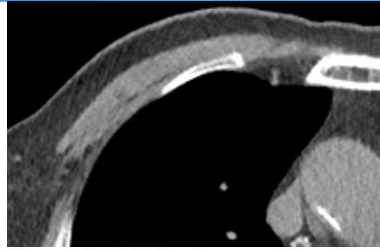
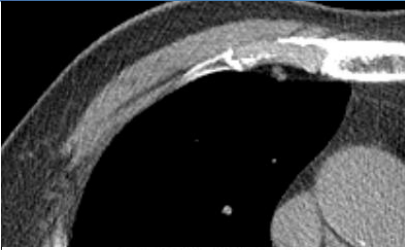
80/M, Never smoker, ADC, RUL, Stage IIIB

Driver mutation (-), PD-L1: 100%



1903

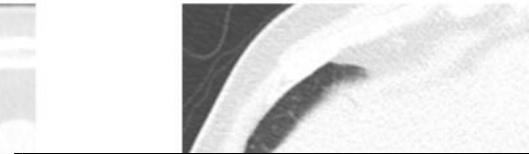
After 2 cyc



COVID-19 pandemic: 2.6Y drug holiday

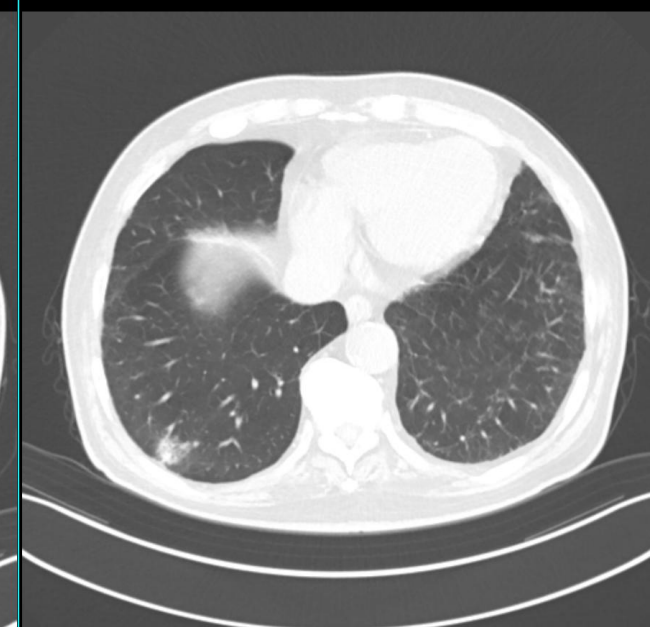


Drug holiday (2.6Y)



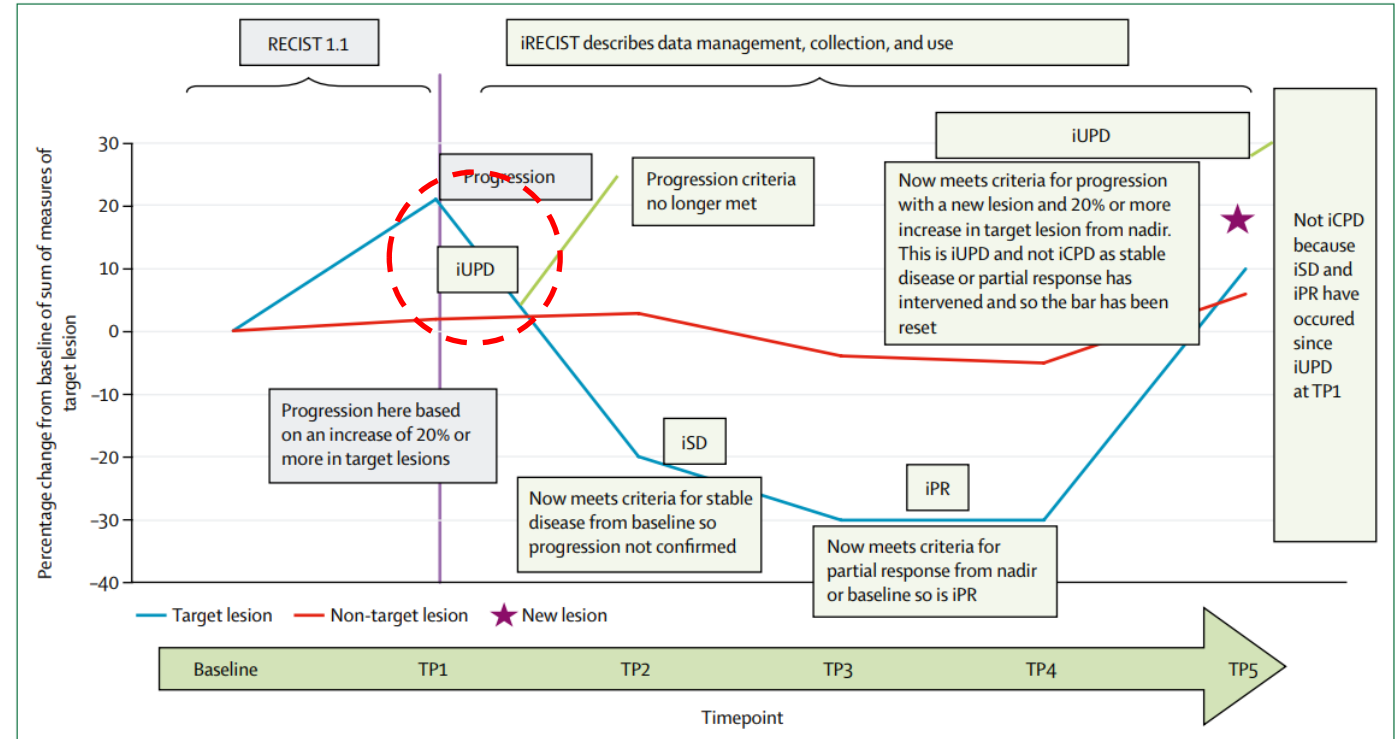
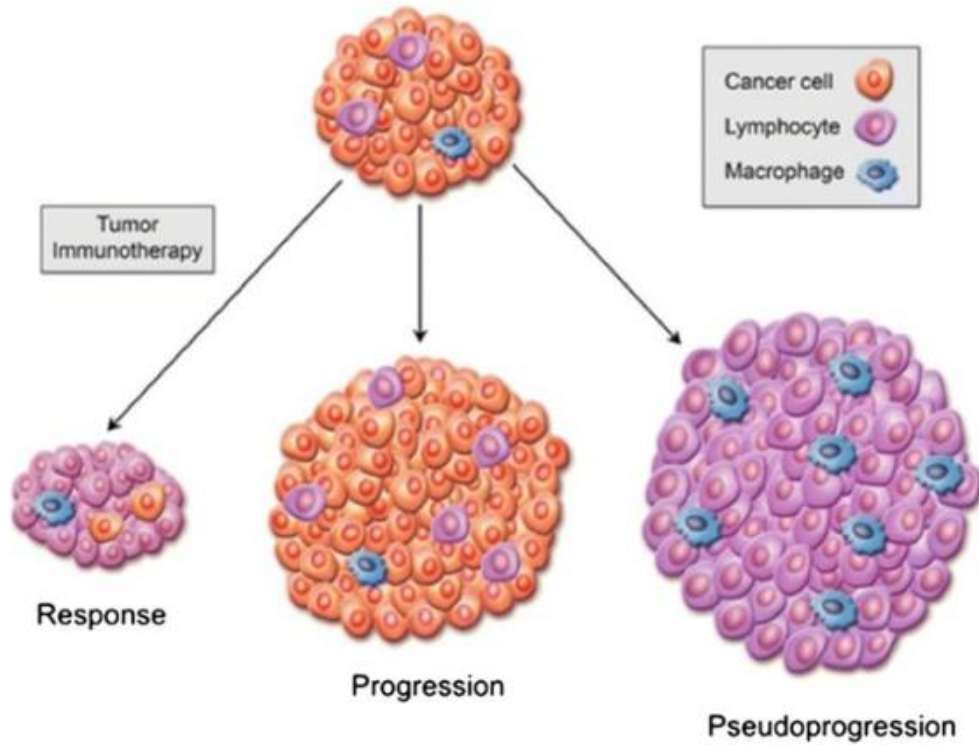
2209

Pembrolizumab maintain



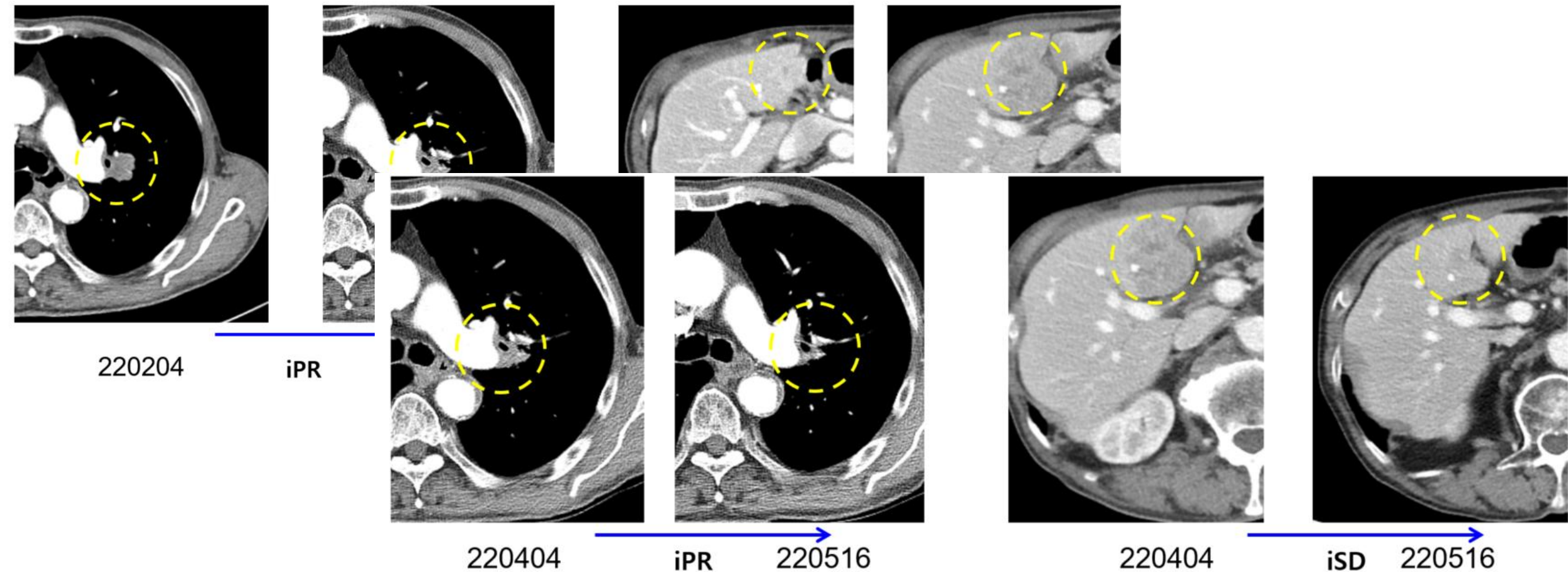
2409

반응평가

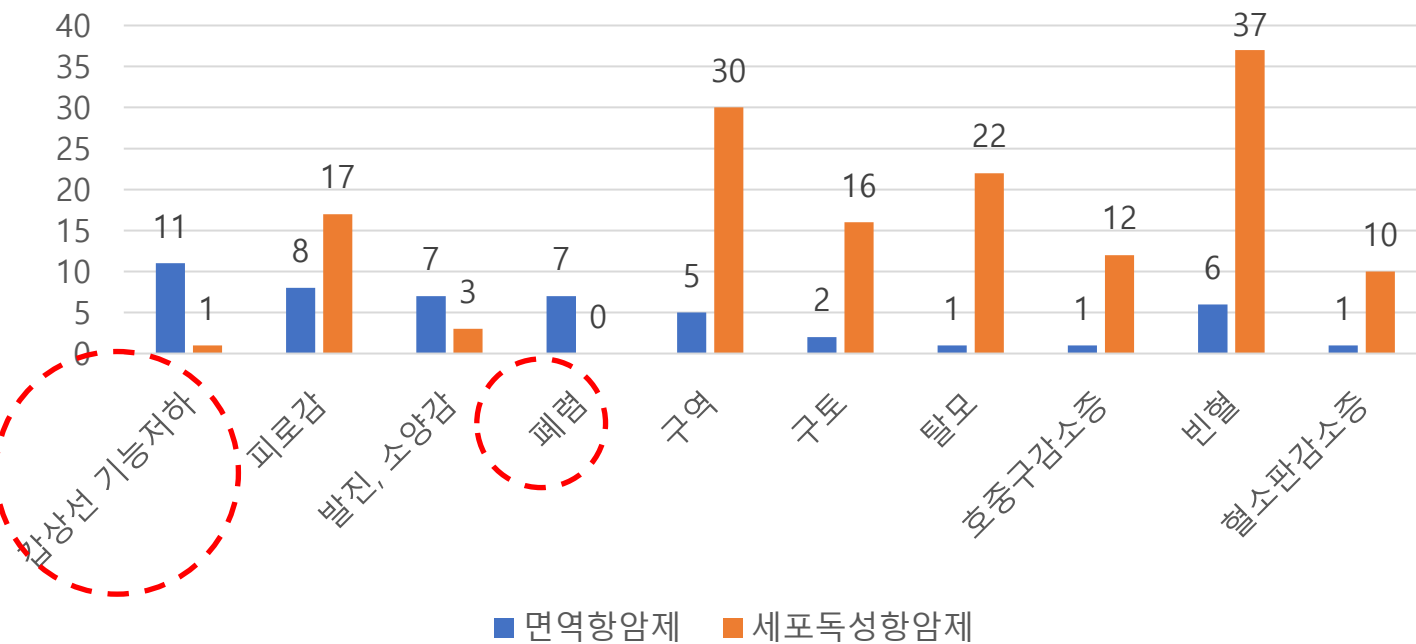


SqCC, LUL, cT3N1M1b, IVA, PD-L1: 50% (SP263), Liver metz

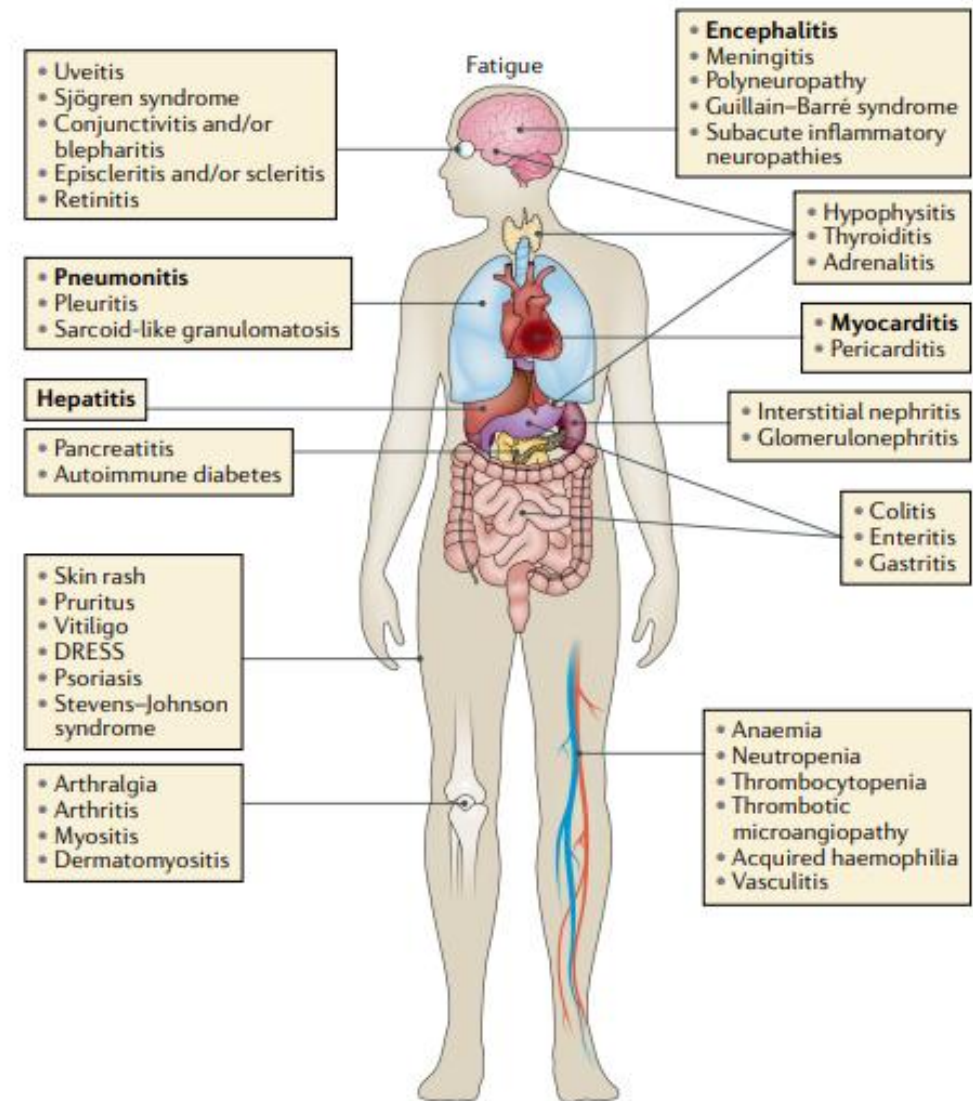
- 1L: Paclitaxel/cisplatin
- 2L: Pembrolizumab (220228-)



AEs of ICI (irAE)



KEYNOTE 042



General management of AEs of ICIs

ASCO 가이드라인 · CTCAE v5.0 기반 · 장기별 세부는 원문 Tables 1-11 참조

공통 원칙 (등급 무관)

교육 — 치료 전 · 중 · 후 환자 · 보호자에게 면역치료 · irAE 교육

높은 의심 — 새 증상은 치료 관련일 수 있다는 높은 의심

재투여 — ≤ G1 회복 시 고려 (조기발생 irAE는 주의) · 용량조정 없음

등급	ICPi 조치	스테로이드 · 추가 처치
G1	지속 + 밀착 관찰 (일부 신경 · 혈액 · 심장 독성은 예외 → 중단)	대개 스테로이드 불필요
G2	대부분 일시 중단, ≤G1 회복 시 재개	프레드니솔론 0.5-1 mg/kg/일 (또는 등가) 고려
G3	중단	고용량 스테로이드 1-2 mg/kg/일 · 최소 4-6 주 감량 48-72 시간 내 무반응 → infliximab 등 고려
G4	영구 중단 (호르몬 보충으로 조절되는 내분비병증은 예외)	고용량 스테로이드 + 면역억제

※ 일반 원칙 요약 — 실제 처치는 장기별 세부 (Tables 1-11) 와 최신 가이드라인에 따름. CTLA-4 병용 독성 후 회복 시 PD-1/PD-L1 단독 재투여를 고려할 수 있음.

Summary

구분	🎯 표적항암제 (Targeted Therapy)	🛡️ 면역항암제 (Immunotherapy)
작용 기전	암세포의 특정 Driver Mutation 및 단백질 불활성화 Oncogenic Shock 암세포 사멸 유도	T세포 면역관문(PD-1/PD-L1) 차단 환자 자신의 면역체계를 재활성화하여 암 공격
주요 바이오마커	유전자 변이 검사 (NGS / Tissue / Liquid) EGFR, ALK, ROS1, RET, MET, KRAS G12C 등	PD-L1 발현율 (TPS) TPS 50% 이상, 1~49%, 1% 미만 및 TMB 평가
반응 양상	빠르고 극적인 반응 (ORR 70~85% 이상) 초기 효과 우수하나 지속 투여 필요 (Early Separation)	느리지만 장기 지속 (Long-Tail) 면역기억(Memory T cell) 기반 반응 및 장기 생존 가능
내성 및 진행 관리	- DTP(Drug-Tolerant) 세포 및 획득 내성 발생 - 국소 진행(Oligo PD): TKI 유지 + 국소치료(SBRT/LAT) - 전신 진행(Systemic PD): NGS 재검사로 내성 기전 확인	- 가성 진행 (Pseudoprogression) 가능 → iRECIST 평가 - 약제 중단(Drug Holiday) 후에도 면역 반응 유효 - Driver Mutation(+) 환자에서는 상대적 효과 저하
독성 및 부작용	- 표적 경로 관련 부작용 (피부발진, 설사, 간독성, QTc 연장 등) - 간질성 폐질환(Pneumonitis) 발생 주의 - 용량 감량(Dose Reduction)을 통해 부작용 관리	- 면역관련 부작용 (irAE) (폐렴, 내분비 장애, 대장염 등) - CTCAE 등급에 따른 스테로이드 및 면역억제제 처리 - 용량 감량 하지 않음 (일시 중단 또는 영구 중단)