EGFR 변이 비소세포폐암에서 면역치료의 역할: 선행요법 시대의 기회와 한계

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EGFRmt NSCLC 에서 면역항암제는...

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2. Palliative setting에서 효과?
3. PD-L1 high 인 경우?
4. 독성 문제?
5. 기전적 근거?

쓸 수도 있다

1. 일부 response 보인 논문

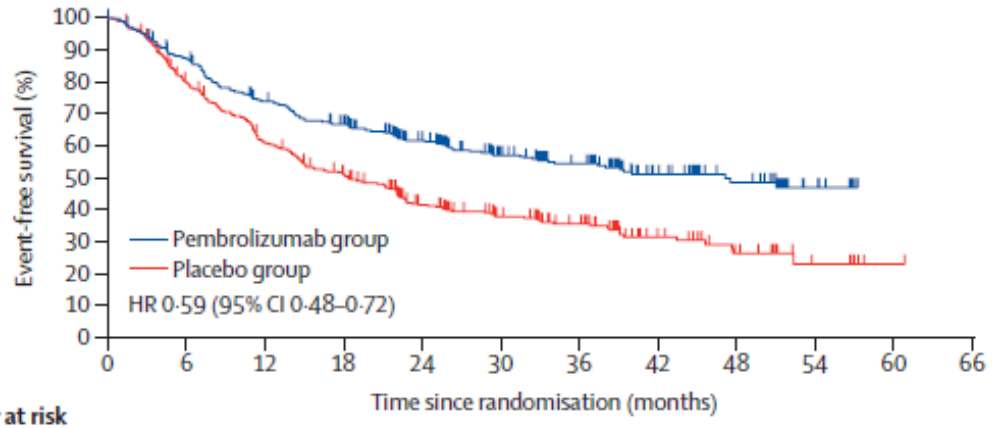
Overview of Perioperative Immunotherapy Trials

Trial	KEYNOTE-671	AEGEAN	CheckMate 77T	RATIONALE-315	CheckMate 816	IMpower010	KEYNOTE-091
Regimen (ICI)	Pembrolizumab (PD-1)	Durvalumab (PD-L1)	Nivolumab (PD-1)	Tislelizumab (PD-1)	Nivolumab (PD-1)	Atezolizumab (PD-L1)	Pembrolizumab (PD-1)
Setting	Perioperative	Perioperative	Perioperative	Perioperative	Neoadjuvant	Adjuvant	Adjuvant
Design (Masking)	Double-blind RCT (vs. placebo)	Double-blind RCT (vs. placebo)	Double-blind RCT (vs. placebo)	Double-blind RCT (vs. placebo)	Open-label RCT	Open-label RCT (vs. BSC)	Double-blind RCT (vs. placebo)
Stage	IIB–IIIB	IIA–IIIB	IIA–IIIB	II–IIIB	IB–IIIA	IB–IIIA	IB–IIIA
Stage II% / III%	~28% II / ~72% III	~19% II / ~81% III	~17% II / ~83% III	~20% II / ~80% III	~15% IB / ~21% II / ~64% IIIA	~23% IB / ~29% II / ~48% IIIA	~17% IB / ~34% II / ~49% IIIA
EGFR/ALK Permitted	Included	Included	Excluded	Excluded	Excluded	Permitted (~12%)	Permitted (~14%)
N (ITT)	786	802	461	453	358	1,005	1,177
Primary Endpoint	EFS & OS (co-primary)	pCR & EFS (co-primary)	EFS (primary)	pCR & EFS (co-primary)	pCR & EFS (co-primary)	DFS (primary; hierarchical)	DFS (overall & PD-L1 TPS≥50%; co-primary)
OS results	**YES: HR 0.72 (95%CI 0.56–0.93), p=0.0052**	Immature: HR 0.89 (95% CI 0.70-1.14)	No: HR 0.85 (97.63 % CI 0.58-1.25)	**YES: HR 0.65 (95% CI 0.45-0.93) p=0.009**	**YES: HR 0.72 (95% CI 0.52-1.00) p=0.048**	No: ITT: HR 0.97 (9 5% CI 0.78-1.22)	Immature
FDA Approval	Yes	Yes	Yes	**No**	Yes	Yes	Yes
MFDS Approval	Yes	Yes	**No**	Yes	Yes	Yes	Yes

선행/수술 전후 면역치료는 절제 가능 비소세포폐암에서 os 개선을 입증하였다.

KEYNOTE-671 (pembrolizumab+chemo): EFS/OS

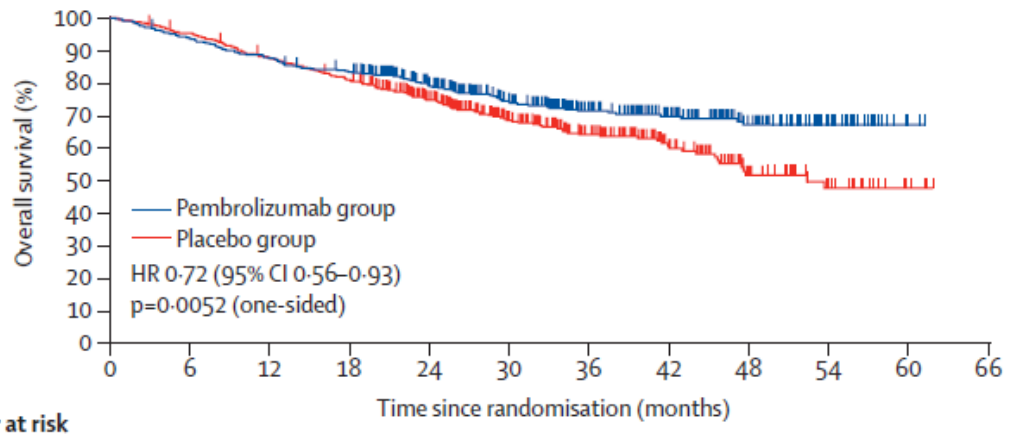
Event free survival



Number at risk (number censored)												
Pembrolizumab group	397	339	282	250	196	142	102	62	37	10	0	0
	(0)	(8)	(13)	(18)	(54)	(95)	(129)	(164)	(187)	(213)	(223)	(223)
Placebo group	400	308	232	189	128	87	66	34	18	6	1	0
	(0)	(13)	(16)	(22)	(50)	(81)	(97)	(123)	(135)	(146)	(151)	(152)

mEFS 47.2 months vs 18.2 months
HR 0.59 (95% CI 0.48-0.72)

Overall survival



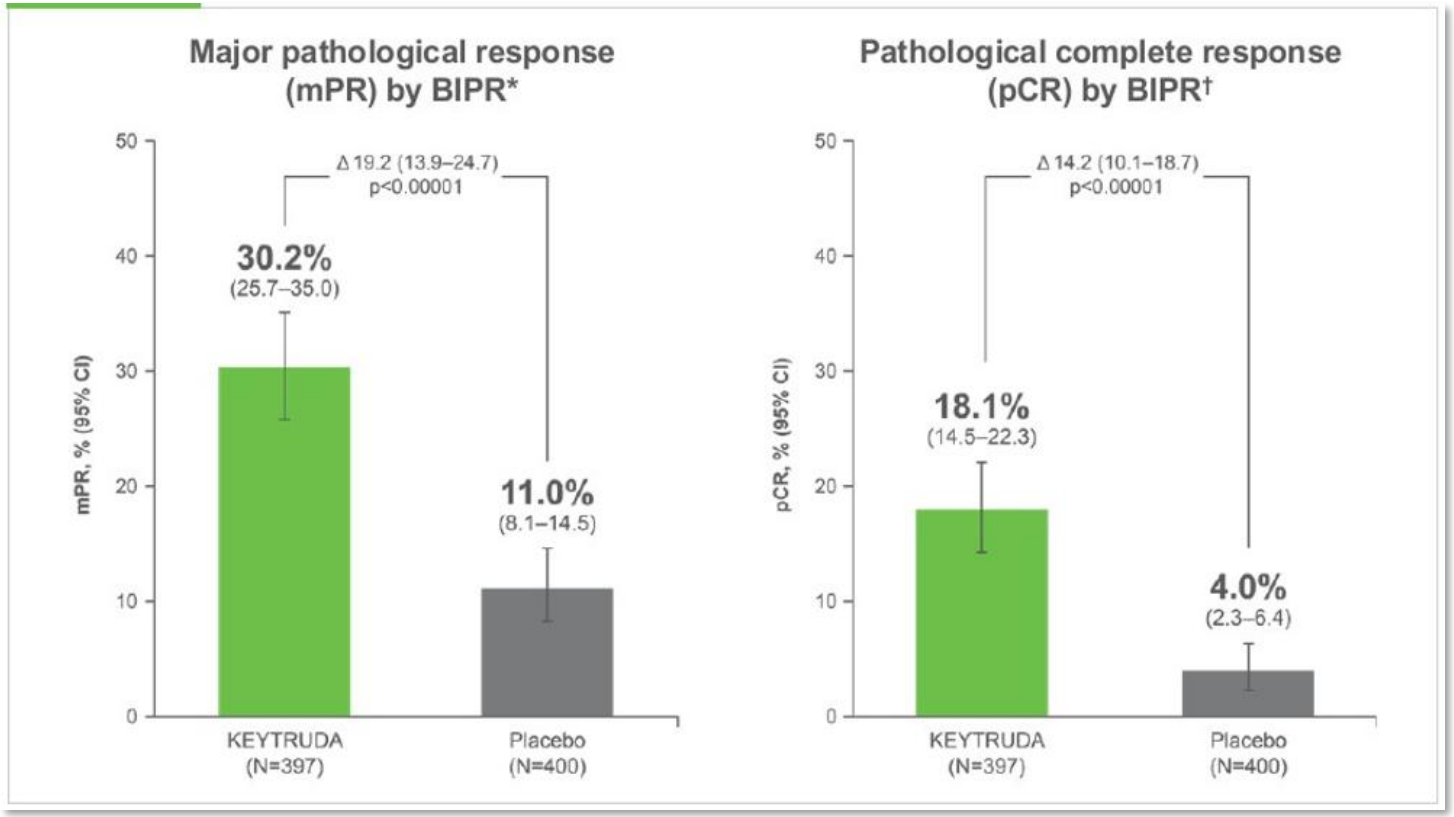
Number at risk (number censored)												
Pembrolizumab group	397	371	347	327	277	205	148	108	69	32	4	0
	(0)	(1)	(1)	(4)	(38)	(95)	(145)	(182)	(218)	(255)	(283)	(287)
Placebo group	400	379	347	319	256	176	125	77	39	20	4	0
	(0)	(2)	(4)	(5)	(45)	(106)	(147)	(190)	(219)	(236)	(252)	(256)

36 months OS 71% vs 64%
mOS NR vs 52.4 months
HR 0.72 (95% CI 0.56-0.93), *P*=0.0052

Pembolizumab+항암제 병용요법은 mEFS 47.2개월, OS 은 5년 f/u에도 아직 달성되지 않았다.

Wakelee H. ASCO 2023; Wakelee H et al. N Engl J Med 2023; Spicer J ESMO 2023; Spicer JD et al. Lancet 2024

KEYNOTE-671 (pembrolizumab+chemo): mPR/pCR



대부분의 환자 는 pCR (82%) 이나 mPR (70%)을 달성하지 못했다

KEYNOTE-671: EGFR mutation status

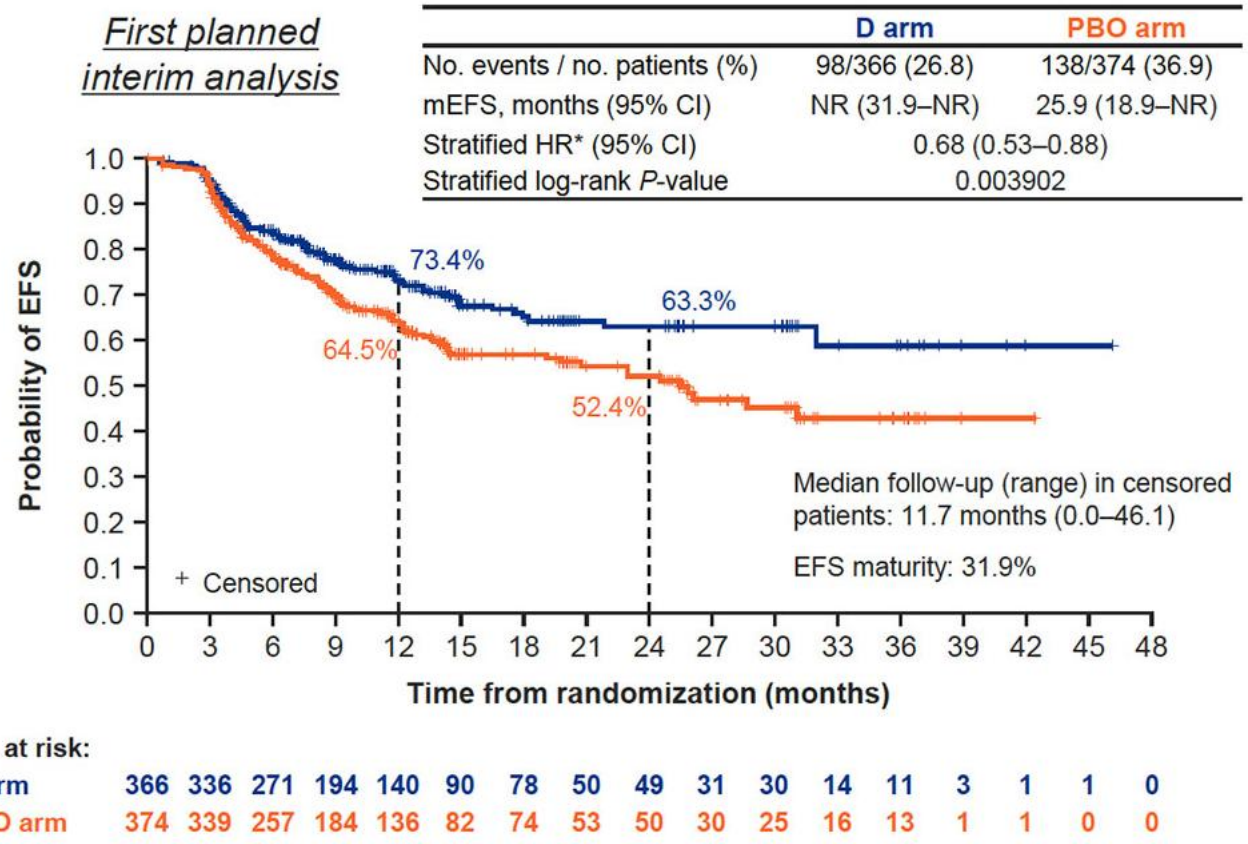
EGFR mutation status — no. (%)		
No	111 (28.0)	127 (31.8)
Yes	14 (3.5)	19 (4.8)
Unknown	272 (68.5)	254 (63.5)
ALK translocation status — no. (%)		
No	104 (26.2)	133 (33.2)
Yes	12 (3.0)	9 (2.2)
Unknown	281 (70.8)	258 (64.5)

* The intention-to-treat population included all the participants who had undergone randomization. Percentages may not total 100 because of rounding. PD-L1 denotes programmed death ligand 1.
† Race and ethnic group were reported by the participant.
‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.

KEYNOTE-671 연구에서는 분자검사가 필수가 아니었다

EGFRmt 환자는 pembro 군 14명 (3.5%), placebo 군 19명 (4.8%) 로 매우 적었다.

AEGEAN: Durvalumab+Chemo



EFS HR: 0.68 (0.53-0.88; p=0.004)

OS immature

- EGFRmt (n=51/740, 6.9%)
- EFS HR 0.86 (0.35-2.19)

- pCR rate:
  EGFR mt 3.8% vs. ITT 17.2%

EGFR 변이 환자는 면역항암제 효과가 상대적으로 제한적일 수 있다

He J, Gao S, Reck M, et al. Neoadjuvant durvalumab + chemotherapy followed by adjuvant durvalumab in resectable *EGFR*-mutated NSCLC (AEGEAN). Presented at: 2023 IASLC World Conference on Lung Cancer; September 9-12, 2023; Singapore, Republic of Singapore. Abstract OA012.06.

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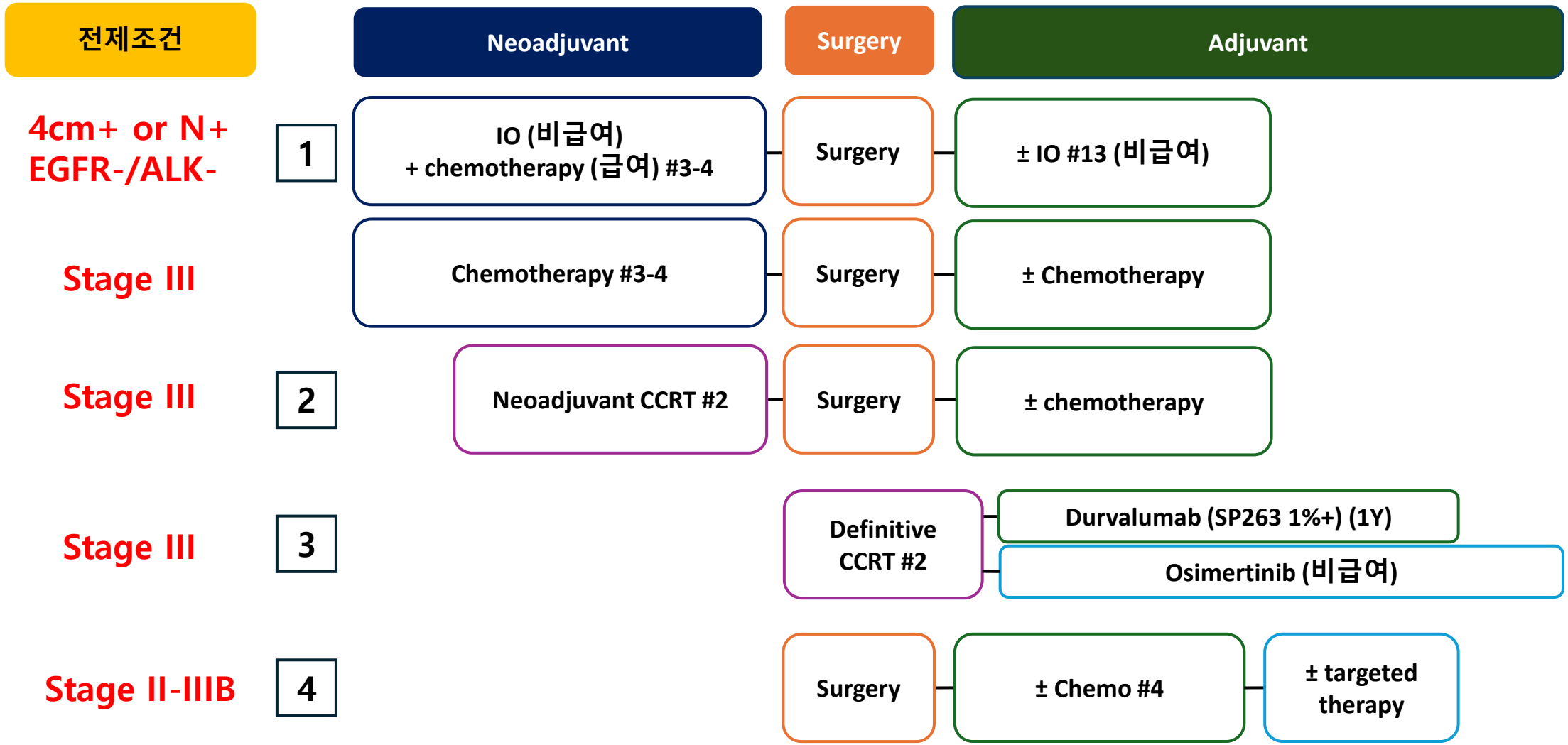
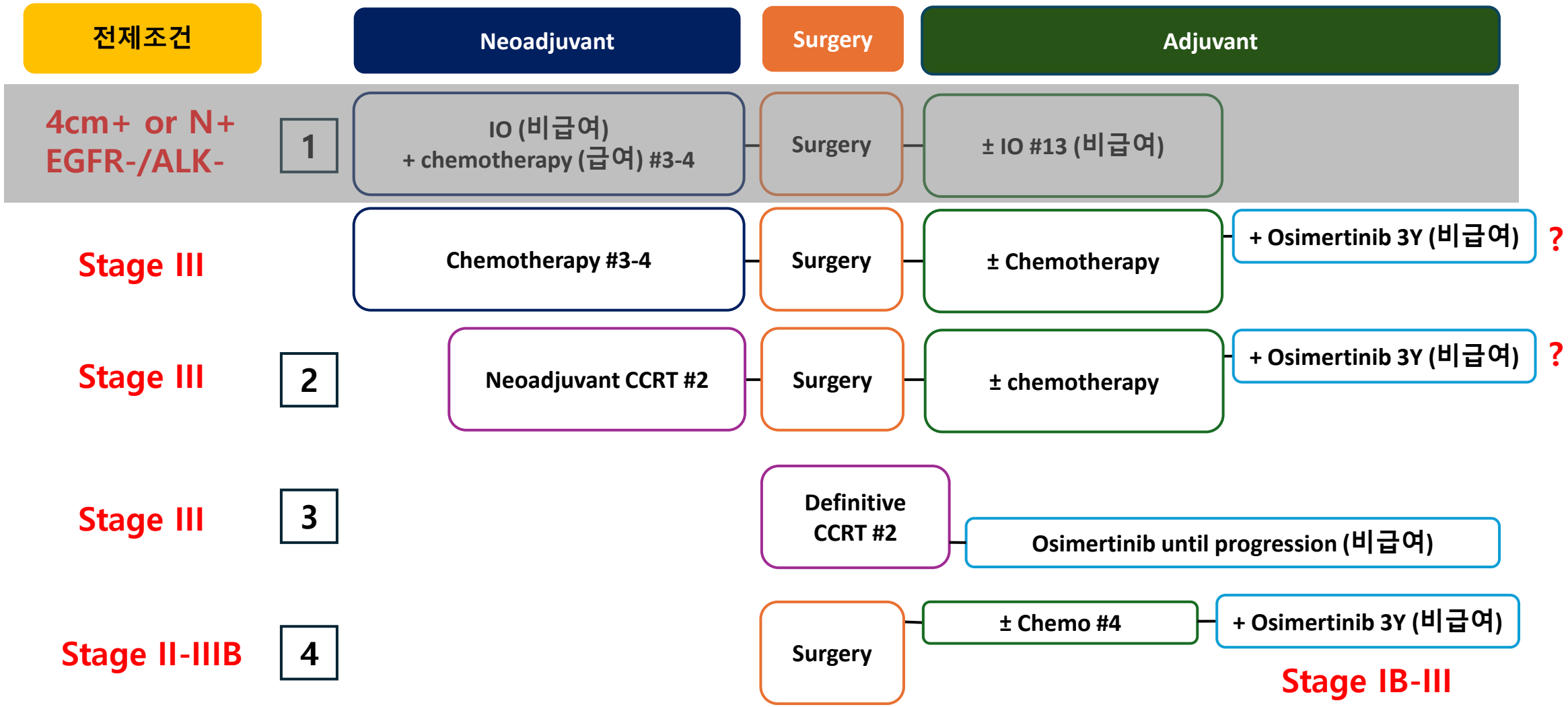
선행/수술 전후 면역치료는 절제 가능 비소세포폐암에서 OS 개선을 입증하였으나, **EGFR 변이 환자는 대부분 제외되었다.**

조기 폐암의 치료 (국내 허가/급여 기준)

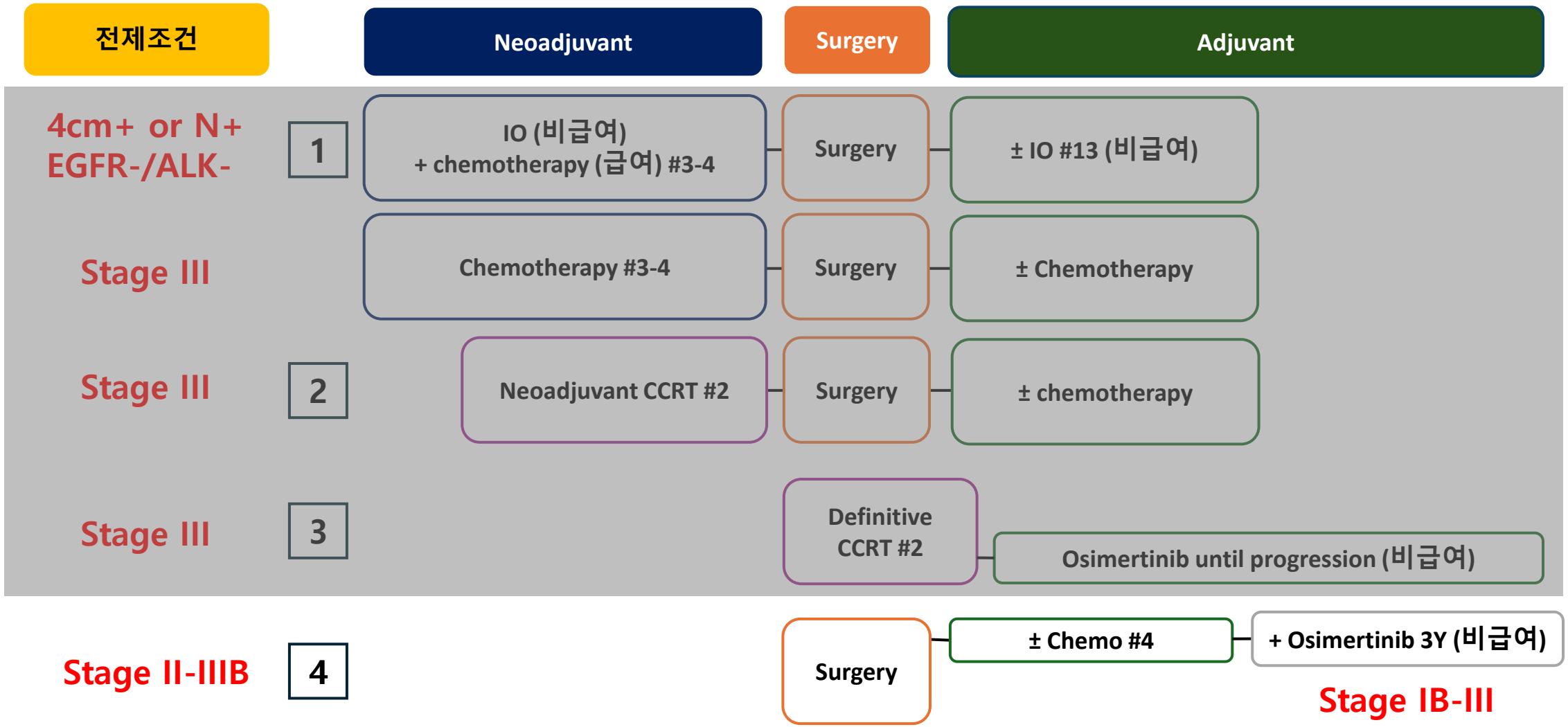


Stage III, EGFR+



Stage III NSCLC 에서 neoadjuvant IO+chemo 요법은 **EGFR/ALK+ 인 경우 불가하다.**

Stage II, EGFR+



Stage II EGFRmt NSCLC 에서는 upfront surgery + adj osimertinib이 권고된다.

NCCN guidelines

Neoadjuvant Systemic Therapy for Patients Who Are Not Candidates for Immune Checkpoint Inhibitors

Targeted Therapy Options

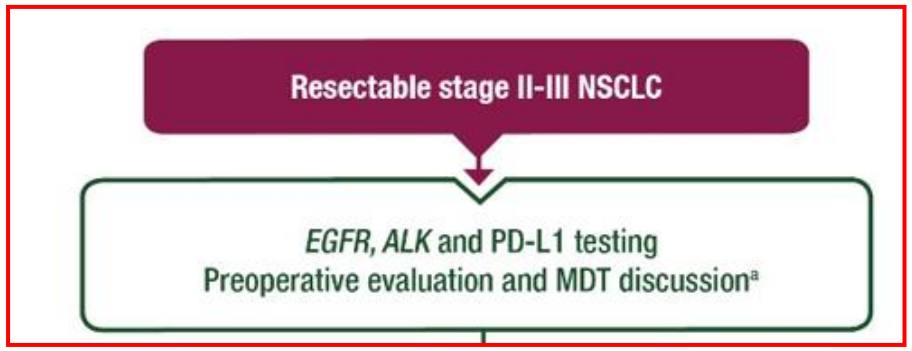
- **After surgical evaluation, consider osimertinib ± chemotherapy, with the option of single-agent osimertinib as adjuvant therapy after surgery, for patients with stage II–IIIA, IIIB (T2–T3, N2b; T4, N2) NSCLC that is positive for *EGFR* exon 19 deletion or L858R mutation;[5] Other Adjuvant Systemic Therapy**

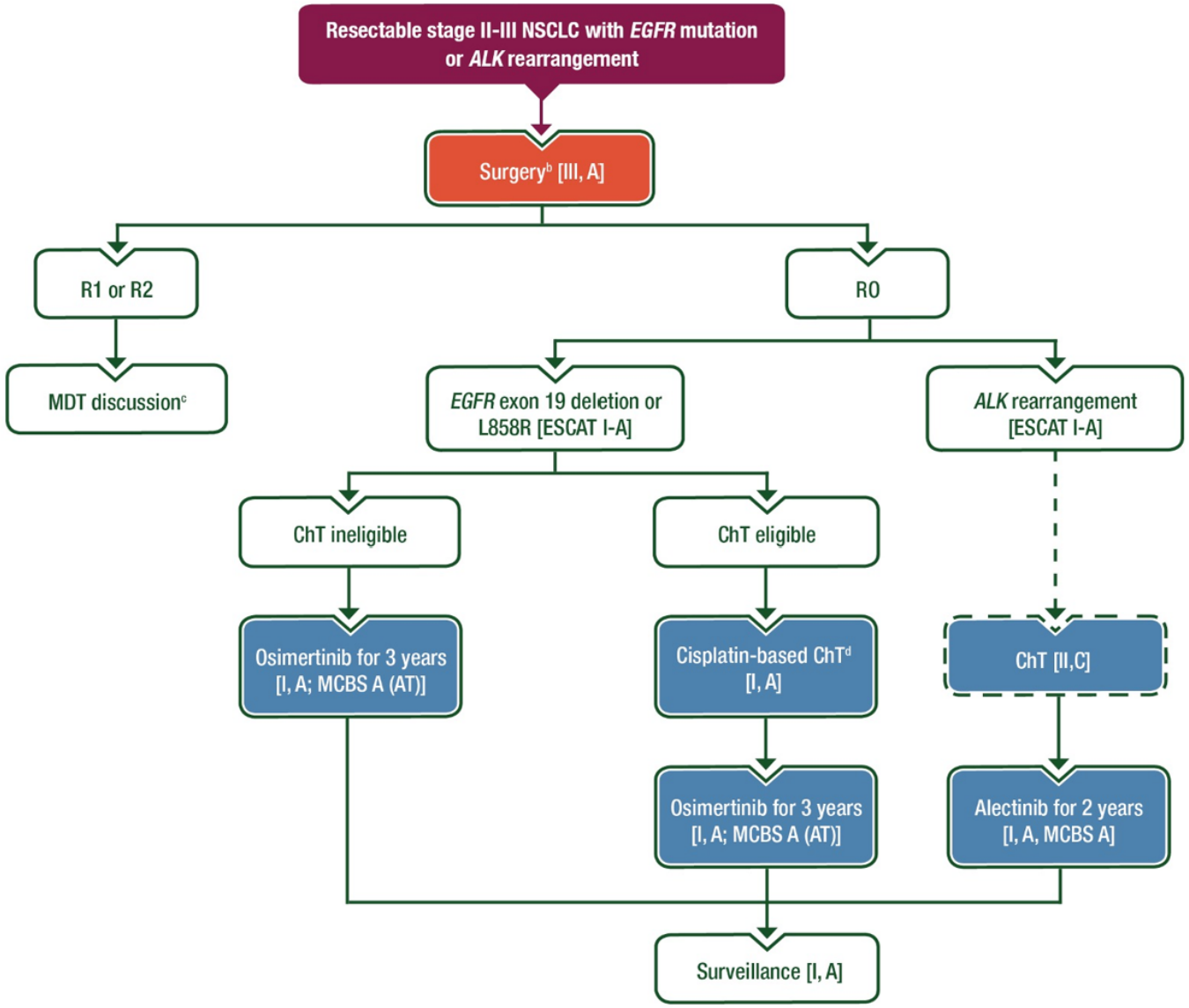
  Chemotherapy options with osimertinib include:

  - **Cisplatin/Pemetrexed (nonsquamous)**
  - **Carboplatin/Pemetrexed (nonsquamous)**

NCCN Guideline: stage II-IIIB EGFRmt NSCLC에서는 **NeoADAURA를 권고함.**

ESMO guideline for early stage NSCLC (2026)

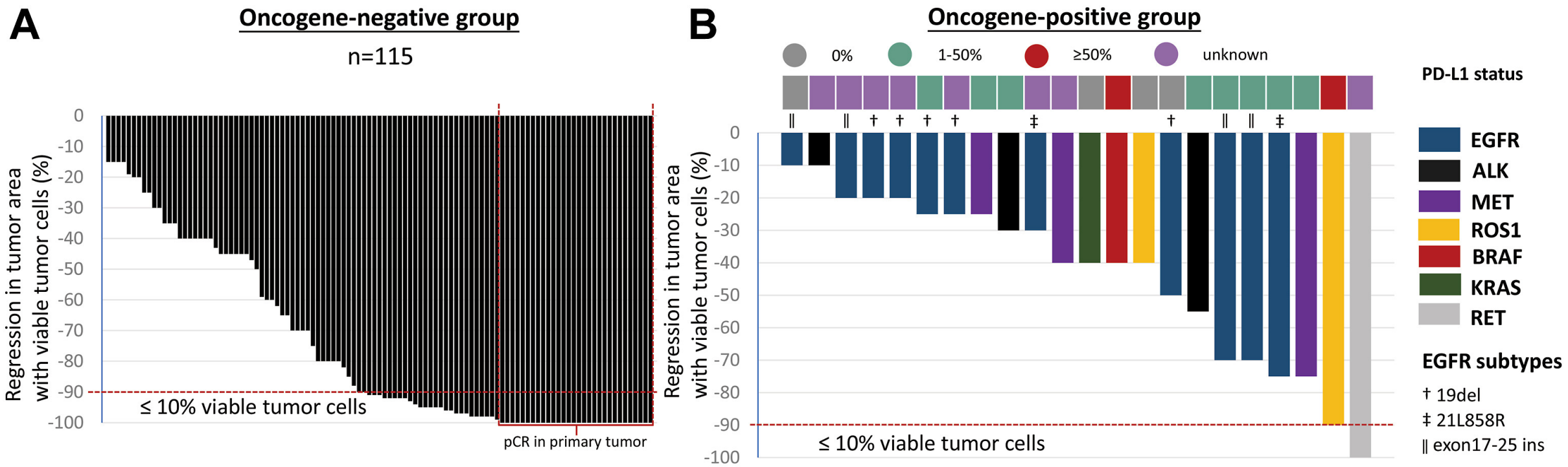




2026 ESMO guideline:

- **Resectable stage II-III에서 EGFR 검사를 우선 권고함.**
- **Stage II-III 에서 R0 resection 후 adjuvant osimertinib (3Y) 를 권고함.**

Retrospective data (1) Neoadj IO+CTx in AGA+ NSCLC: mPR



MPR: oncogene+ **9%** (2/22) vs. oncogene-: **56.5%** (p<0.001).

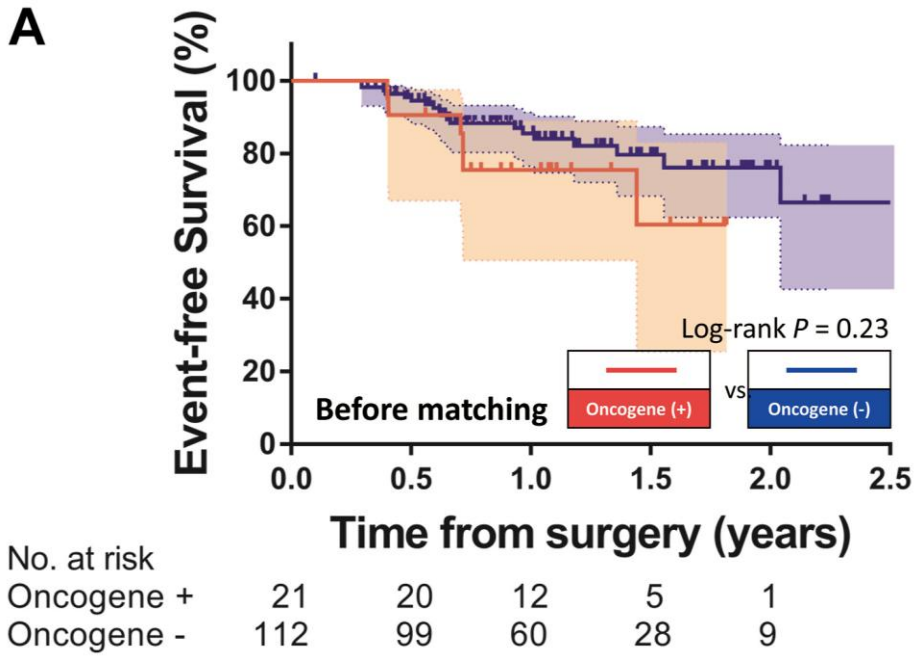
EGFRmt는 oncogene+ 환자 중 50% (11/22), **MPR 달성은 0%**

Oncogene+는 MPR의 음성 예측인자로 확인됨 (OR 0.13, 95% CI 0.03-0.64)

Zhao ZR, et al. Ann Thorac Surg. 2023 Oct;116(4):703-710. PMID: 36521526.

Retrospective data (1) Neoadj IO+CTx in AGA+ NSCLC: EFS

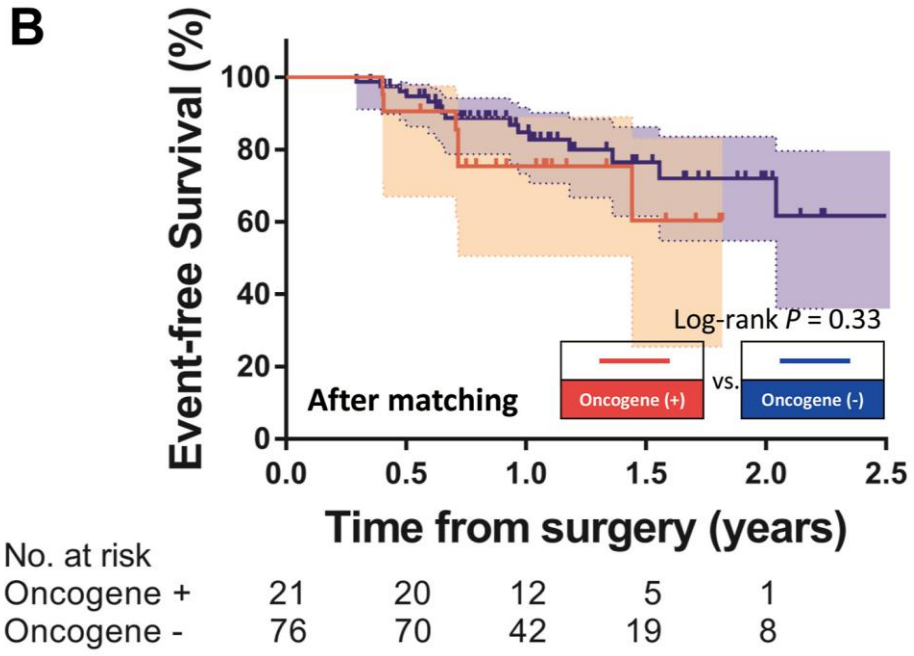
EFS before propensity score matching



No. at risk

Oncogene +	21	20	12	5	1
Oncogene -	112	99	60	28	9

EFS after propensity score matching



No. at risk

Oncogene +	21	20	12	5	1
Oncogene -	76	70	42	19	8

1Y EFS는 유의한 차이가 없었으나 (oncogene+ 75.4% vs. oncogene- 85.5%, p=0.23),
수가 적어 유의한 분석이 어렵다 (oncogene+ n=22).

Zhao ZR, et al. Ann Thorac Surg. 2023 Oct;116(4):703-710. PMID: 36521526.

Retrospective data (2) Neoadj IO+CTx in EGFR/ALK+ NSCLC: pCR

Response to Neoadjuvant Chemoimmunotherapy in EGFR or ALK-Mutated Non-Small Cell Lung Cancer

Giorgio Caturegli MD, Ebony Jernigan MD, Maureen Canavan PhD, Abigail Lynch BS, Jayaditya Patil MBBS, Benjamin J. Resio MD, Daniel J. Boffa MD MBA
Division of Thoracic Surgery, Department of Surgery, Yale School of Medicine, New Haven, CT

Background

- Role for immunotherapy in EGFR or ALK-mutated non-small cell lung cancer (NSCLC) is limited, and such patients are excluded from most chemoimmunotherapy trials
- Not all mutations are targetable, and some patients may respond to immunotherapy

Methods

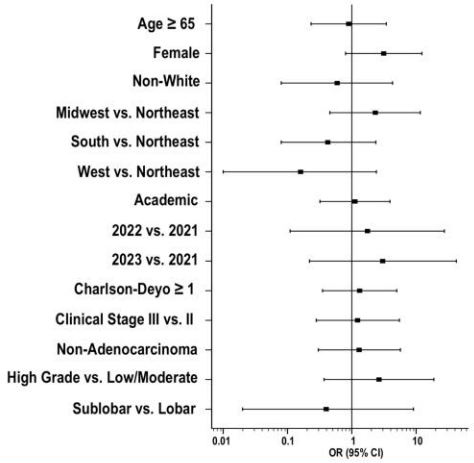
- **Source:** National Cancer Database
- **Study Period**: 2021-2023
- **Inclusion**: Clinical Stage I-III NSCLC, neoadjuvant chemoimmunotherapy followed by definitive surgery
- **Exclusions**: unknown EGFR or ALK mutation status or pathologic staging
- **Outcomes**
  - Nodal downstaging (pN < cN)
  - Pathologic complete response (pCR, ypT0N0)
- **Analysis**
  - Multivariable logistic regressions adjusted for: year of diagnosis, age, sex, race/ethnicity, Charlson-Deyo, insurance, region, facility type, histology, clinical stage, grade, extent of resection

Results

- **Testing rate**: 1,284 / 2,966 (43.3%)
- **Mutation rate:** 132 / 1,284 (10.3%)
  - 105 (77.2%) EGFR & 33 (24.2%) ALK mutations

	EGFR or ALK Mutation Status		
	Wild-type	Mutated	p
Nodal downstaging (cN1-3 only)	482/650 (74.2%)	50/87 (57.4%)	**<0.001**
pCR	356/1152 (30.9%)	22/132 (16.7%)	**<0.001**

Logistic Regression of pCR in EGFR or ALK-Mutated Patients



Future Directions

- Identification of EGFR or ALK-mutated patients benefiting from neoadjuvant immunotherapy
- Contact: giorgio.caturegli@yale.edu

A sizable subset of EGFR or ALK-mutated NSCLC exhibits impressive response (57% nodal downstaging and 17% pCR) to neoadjuvant chemoimmunotherapy.

EGFR/ALK 변이 환자에서 선행 항암면역화학요법의 pCR율은 16.7%로,
변이 음성군(30.9%)에 비해 현저히 낮았다.

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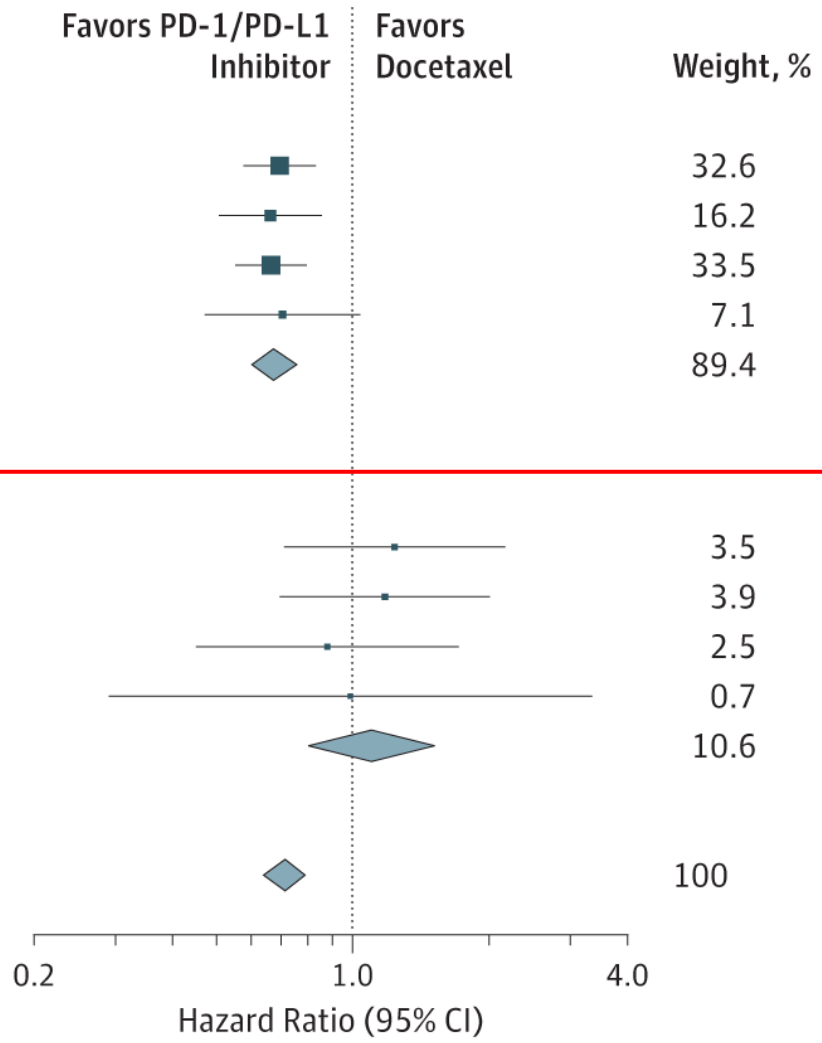
쓸 수도 있다

1. 일부 response 보인 논문

Meta-analyses: 2L IO vs. docetaxel

A *EGFR* wild-type and mutated subgroups

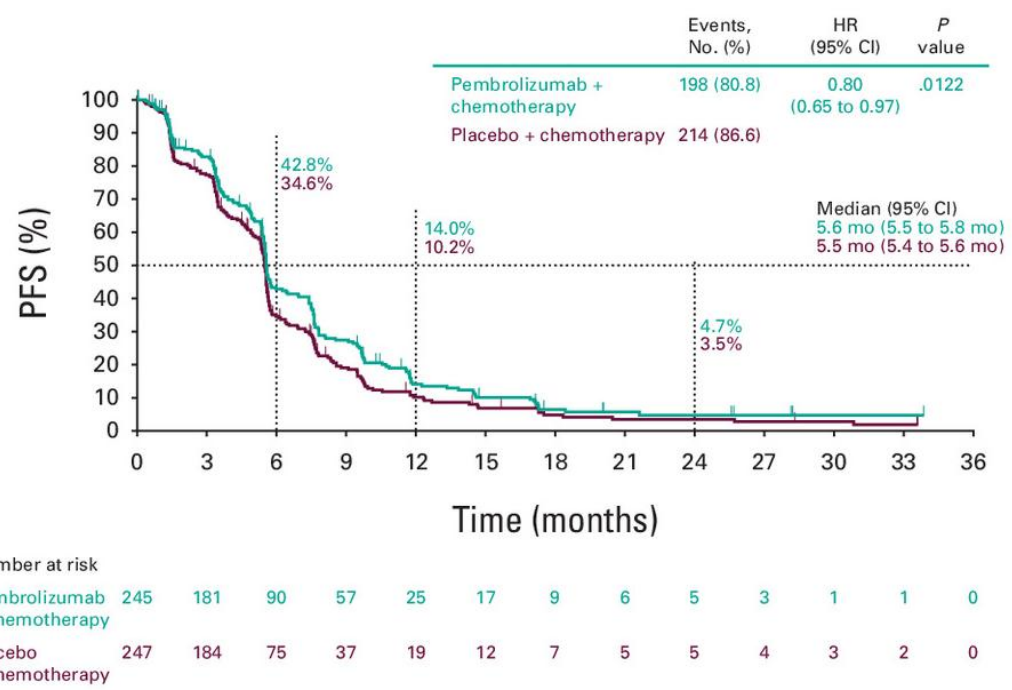
Trial	Hazard Ratio (95% CI)	Weight, %
EGFR wild-type		
OAK	0.69 (0.57-0.83)	32.6
CheckMate 057	0.66 (0.51-0.85)	16.2
Keynote 010	0.66 (0.55-0.79)	33.5
POPLAR	0.70 (0.47-1.04)	7.1
Subtotal	0.67 (0.60-0.75)	89.4
Heterogeneity: $\chi^2_3 = 0.18$, $P = .98$; $I^2 = 0\%$		
Test for overall effect: $z = 6.94$ ($P < .001$)		
EGFR mutated		
OAK	1.24 (0.71-2.18)	3.5
CheckMate 057	1.18 (0.69-2.02)	3.9
Keynote 010	0.88 (0.45-1.72)	2.5
POPLAR	0.99 (0.29-3.40)	0.7
Subtotal	1.11 (0.80-1.53)	10.6
Heterogeneity: $\chi^2_3 = 0.69$, $P = .88$; $I^2 = 0\%$		
Test for overall effect: $z = 0.61$ ($P = .54$)		
Total	0.71 (0.64-0.79)	100
Heterogeneity: $\chi^2_7 = 8.90$, $P = .26$; $I^2 = 21\%$		
Test for overall effect: $z = 6.37$ ($P < .001$)		
Test for subgroup differences: $\chi^2 = 8.03$, $P = .005$; $I^2 = 87.6\%$		



Lee CK, et al. JAMA Oncol. 2018 Feb 1;4(2):210-216. PMID: 29270615; PMCID: PMC5838598.

KEYNOTE-789: IO after TKI

A



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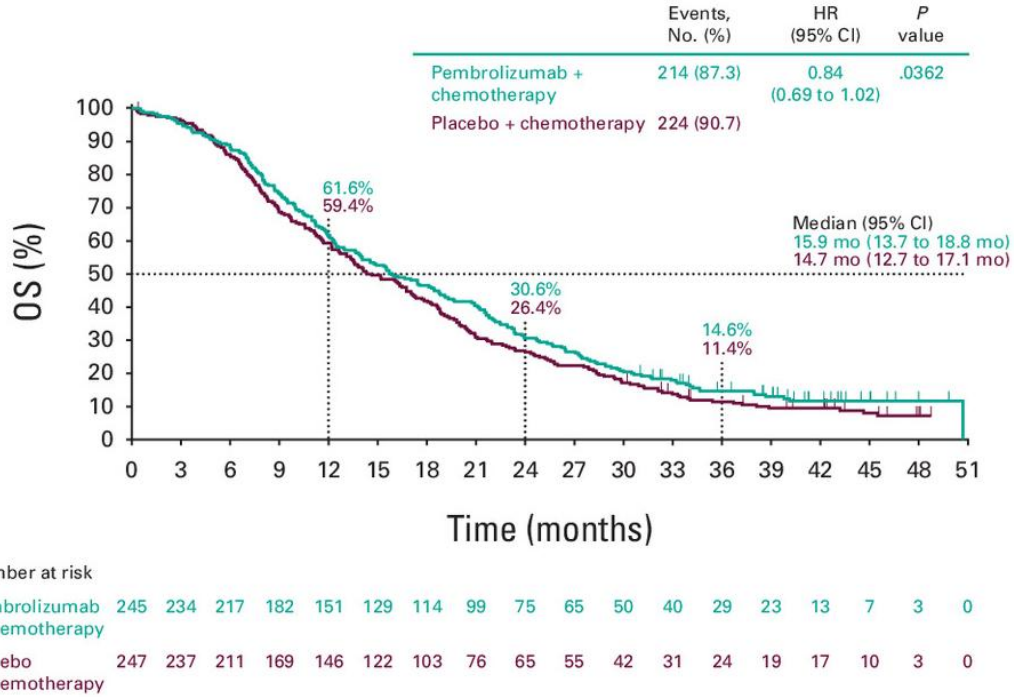

EGFR TKI 후 IO+Chemo 는 Chemo 단독에 비해 PFS, OS의 차이가 없었다.

Yang JC, et al. J Clin Oncol. 2024 Dec;42(34):4029-4039. PMID: 39173098; PMCID: PMC11608596.

Clinical trials of palliative 1L settings

Trial	Regimen	EGFR 포함 여부	비고
KEYNOTE-189	pembro+pemetrexed+platinum (비편평)	**제외**	가장 많이 쓰이는 기준
KEYNOTE-407	pembro+carbo+paclitaxel/nab-P (편평)	제외	편평은 EGFR 드물어 실질적 영향 적음
IMpower150	atezo+bev+carbo+paclitaxel	**포함 허용**	EGFR/ROS1 mut 허용 — TKI 기치료 후 진행
IMpower130	atezo+carbo+nab-P	**제외**	
POSEIDON	durva±treme+chemo	**제외**	
CheckMate 9LA	nivo+ipi+chemo (2cy)	**제외**	

- VEGF 억제가 TME를 개선하여 IO benefit을 살릴 수 있다고 가정함
- 탐색적으로 PFS, OS HR 0.6
- 소규모이고 통계적 검정력 부족
- Osimertinib 기치료 후 환자는 당시 거의 포함 안 됨

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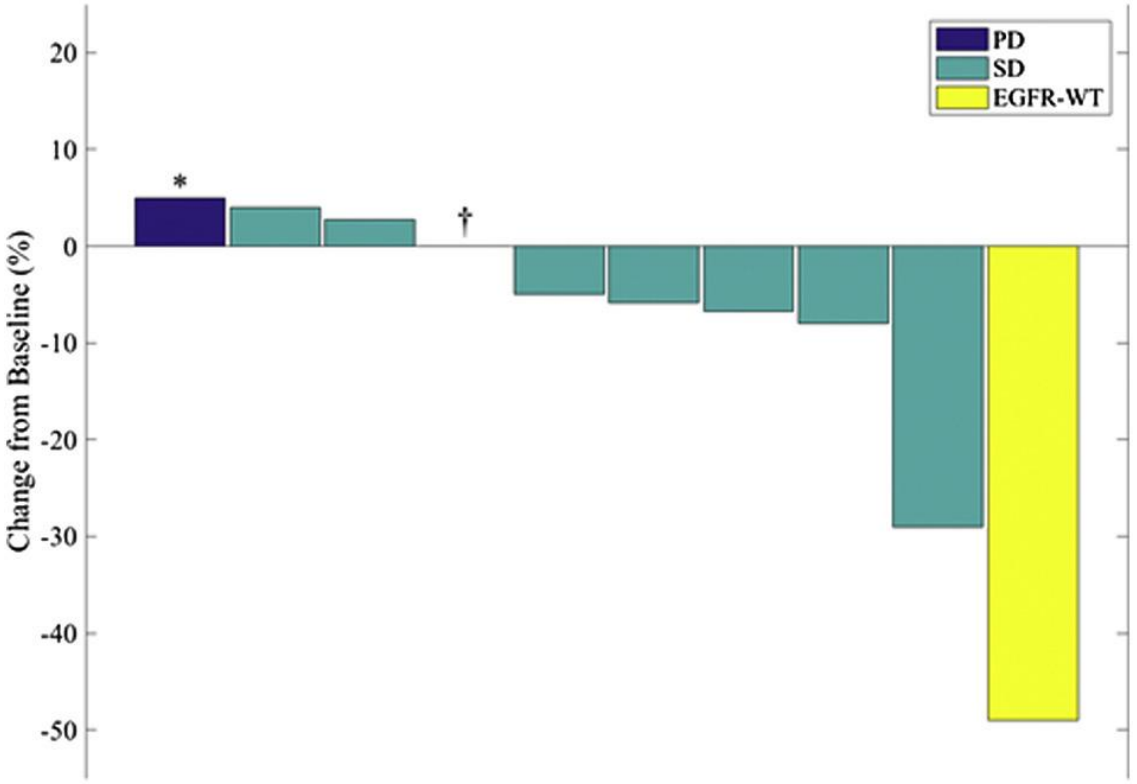
1. 일부 response 보인 논문

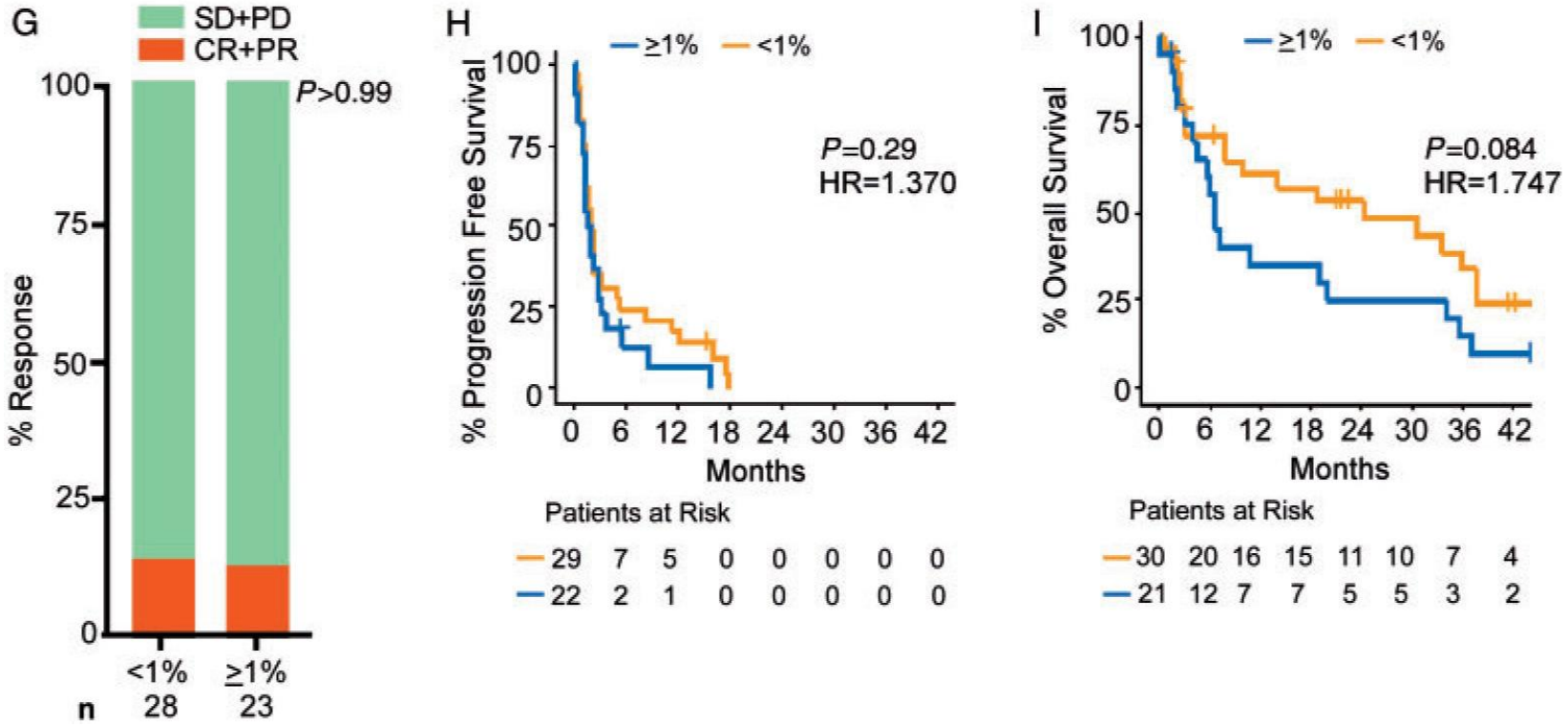
IO in EGFR+, PD-L1 ≥50%



- Lisberg et al. Phase II (JTO 2018)
- EGFRmt, PD-L1 양성, TKI-naïve 환자 25명 계획 중 11명만 등록 후 efficacy 부재로 **조기종료되었다**.
- 73%가 PD-L1 ≥50%였음에도 ORR은 9%
- 유일한 반응자는 추후 EGFR mutation이 오류로 확인되었다.
- 즉, **EGFR mutant에서의 ORR은 0%.**

Lisberg A, et al. J Thorac Oncol. 2018 Aug;13(8):1138-1145. PMID: 29874546; PMCID: PMC6063769.

EGFRmt NSCLC 에서 PD-L1 에 따른 1L IO+CTx 효과



EGFR+ NSCLC에서 PD-L1 <1% 와 1% 이상인 그룹은 ORR, PFS, OS 차이없음.

Hastings K, et al. Ann Oncol. 2019 Aug 1;30(8):1311-1320. PMID: 31086949; PMCID: PMC6683857.

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EGFRmt NSCLC 에서 면역항암제는...

쓰지 말아야 한다

1. Neoadjuvant setting에서 **근거 없음.**
2. Palliative setting에서 **효과 없음.**
3. PD-L1 high 인 경우 **효과 없음.**
4. **독성 문제?**
5. 기전적 근거?

쓸 수도 있다

1. 일부 response 보인 논문

ICI + EGFR TKI?

TKI	Erlotinib	Erlotinib	Gefitinib	Erlotinib/Gefitinib	Osimertinib
ICI	**Atezolizumab**	**Nivolumab**	**Durvalumab**	**Pembrolizumab**	**Durvalumab**
Trial phase	Ib	I	I	I/II	Ib
Line of treatment	First or second	First or second	First	First	First or second
No. of patients	28	20	56	19	44
ORR	75%	Second line: 15%	63%	41.7%	First line: 70% Second line: T790M-positive: 67% Second line: T790M-negative: 21%
PFS, months	15.4		10.1		
Halted	No	No	No	No	Yes
Grade 3–5 toxicity	43%	25%	70%	71.4% (gefitinib arm)	38%
Main toxicity	ALT increase, pyrexia, rash, diarrhea	Liver enzyme, diarrhea, weight loss	ALT/AST increase; > 50% treatment-emergent adverse events leading to discontinuation	Liver toxicity, rash	Interstitial lung disease
Reference	8	9	10	11	12

Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase; ICI, immune checkpoint inhibitor; ORR, objective response rate; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

ICI 와 EGFR TKI 병용요법은 pneumonitis, hepatotoxicity 로 제한적이다.

TATTON (Ib)

Table 4. Most common all-causality adverse events, reported in ≥20% of patients in the osimertinib plus durvalumab arm

	Durvalumab			
	3 mg/kg q2w ($n = 10$)		10 mg/kg q2w ($n = 13$)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Patients with any AE	10 (100.0)	6 (60.0)	13 (100.0)	5 (38.5)
Rash[a]	5 (50.0)	1 (10.0)	6 (46.2)	0
Vomiting	7 (70.0)	1 (10.0)	3 (23.1)	0
Diarrhea	3 (30.0)	0	6 (46.2)	0
Nausea	4 (40.0)	0	4 (30.8)	0
Decreased appetite	3 (30.0)	1 (10.0)	4 (30.8)	0
Dry skin[a]	3 (30.0)	0	4 (30.8)	0
Anemia	4 (40.0)	0	2 (15.4)	1 (7.7)
Constipation	3 (30.0)	0	3 (23.1)	0
Fatigue	3 (30.0)	0	3 (23.1)	0
ILD[a]	2 (20.0)	1 (10.0)	3 (23.1)	1 (7.7)
Pyrexia	2 (20.0)	0	3 (23.1)	1 (7.7)

TATTON (phase IB) trial 에서 Osimertinib + Durvalumab 시 ILD 발생률이 38% 였다.

CAURAL (phase III)는 위 safety signal로 조기종료 되었다.

Oxnard GR, et al. Ann Oncol. 2020 Apr;31(4):507-516. PMID: 32139298.

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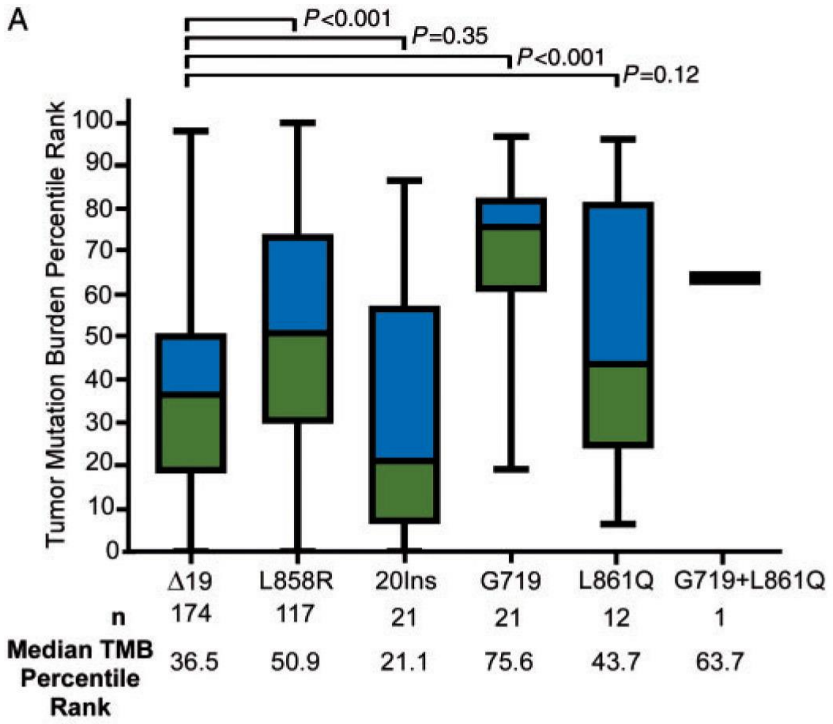
4. 독성 문제 – **ILD, hepatotoxicity**
5. **기전적 근거?**

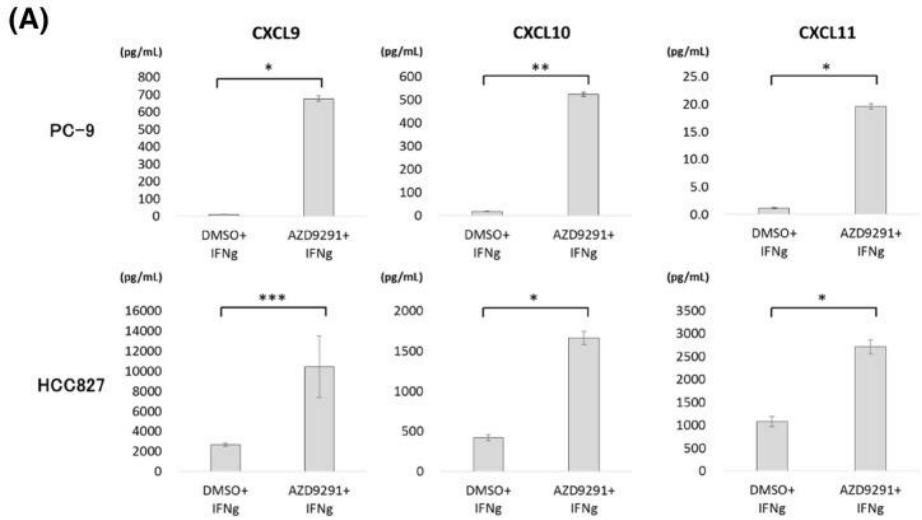
쓸 수도 있다

1. 일부 response 보인 논문

EGFRmt NSCLC에서 IO는 왜 효과가 떨어지는가? "cold" tumor microenvironment



	EGFR-mutant (*N* = 62)
PD-L1 positive	
PD-L1$^+$ (≥50%)	7 (11%)
PD-L1$^+$ (≥5%)	10 (16%)
CD8$^+$ TILs (IHC)[a]	
0	17 (35%)
1+	29 (60%)
2+	2 (4.2%)
3+	0 (0%)
CD8$^+$ TILs (image-based)[b] per mm^2	
Median	185.1
(Range)	(6.1–1,161.9)
Concurrent PD-L1 expression & CD8$^+$ TILs (IHC)	
PD-L1$^+$ (≥50%) & high CD8$^+$ TILs (grade 2–3)	1/48 (2.1%)
PD-L1$^+$ (≥5%) & high CD8$^+$ TILs (grade 2–3)	1/48 (2.1%)
Concurrent PD-L1 expression & CD8$^+$ TILs (image-based)	
PD-L1$^+$ (≥50%) & high[c] CD8$^+$ TILs per mm^2	2/46 (4.3%)
PD-L1$^+$ (≥5%) & high[c] CD8$^+$ TILs per mm^2	2/46 (4.3%)



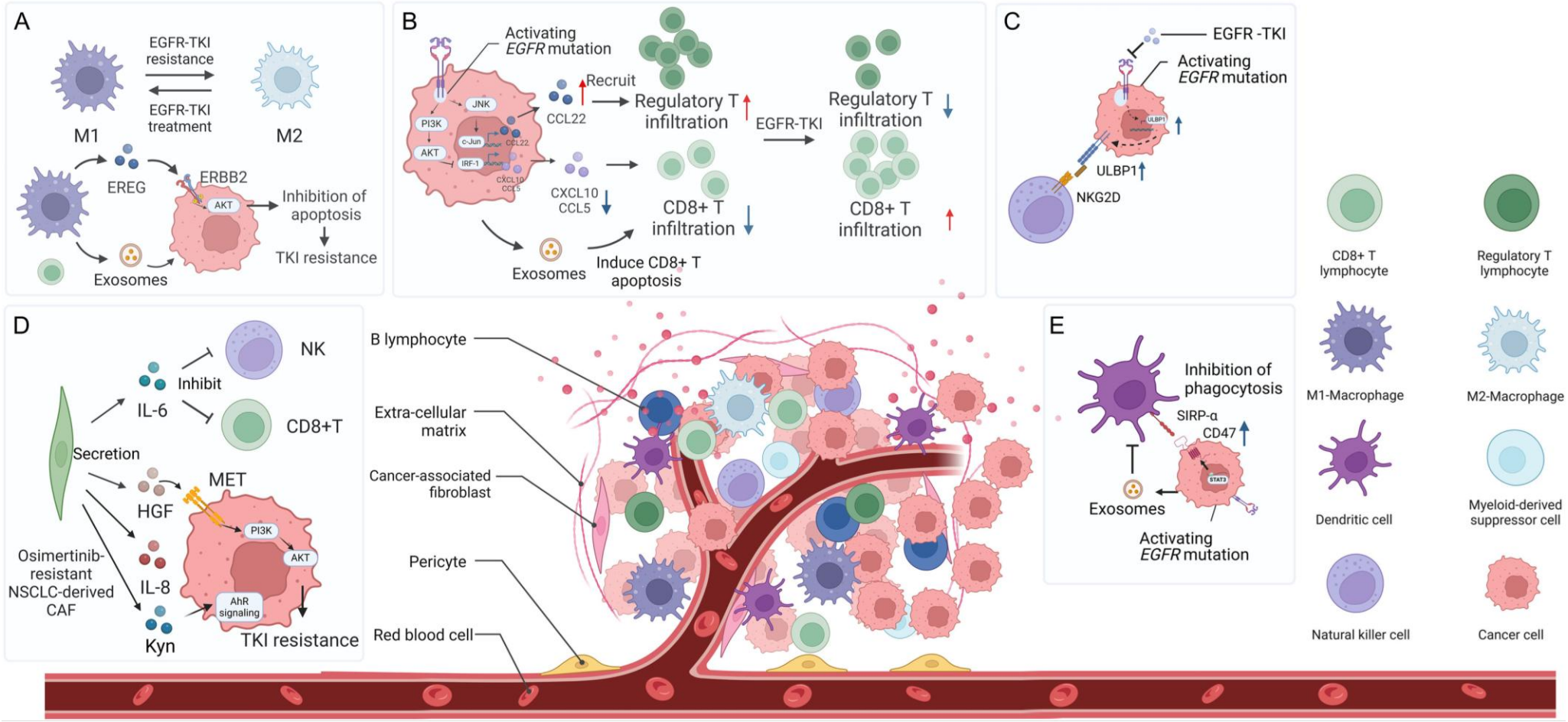
Low TMB

Low CD8$^+$ TILs

CXCL10 등 T cell-attracting chemokine 억제

Hastings K, et al. Ann Oncol. 2019 Aug 1;30(8):1311-1320. PMID: 31086949; PMCID: PMC6683857.
Gainor JF, et al. Clin Cancer Res. 2016 Sep 15;22(18):4585-93. PMID: 27225694; PMCID: PMC5026567.

EGFRmt NSCLC에서 IO는 왜 효과가 떨어지는가? "cold" tumor microenvironment



PD-L1 upregulation, CXCL9/10/11 등 T cell-attracting chemokine 억제, TIL/CD8+ T cell 억제, Treg 유도, Tumor-Associated Macrophage의 M2 polarization, Myeloid-Derived Suppressor Cells 증가, NK세포 및 중성구 기능 저하

Zhang J, et al. Chin Med J Pulm Crit Care Med. 2024 Sep 16;2(3):151-161. PMID: 39403414; PMCID: PMC11471126.

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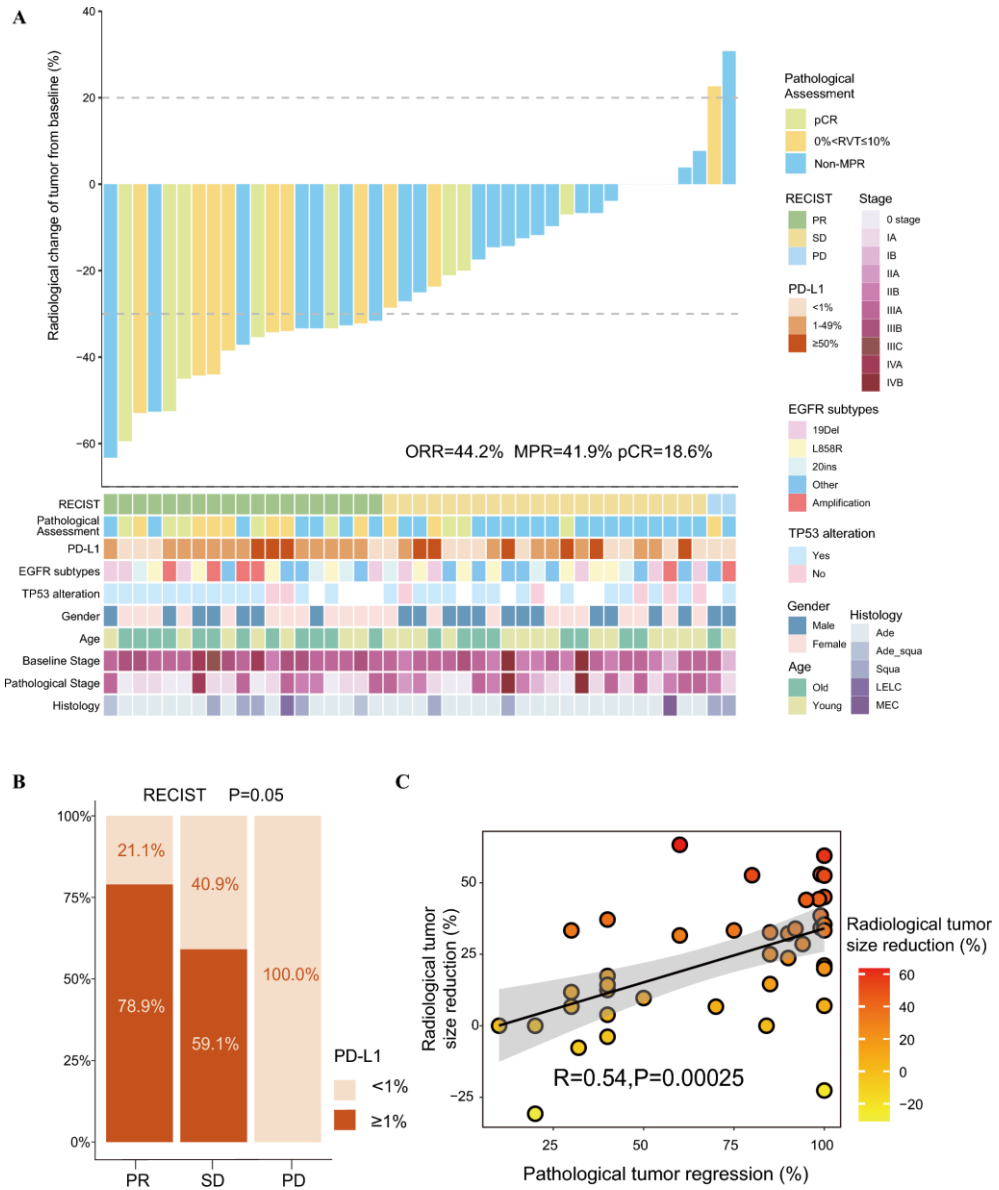
4. 독성 문제 – **ILD, hepatotoxicity**
5. 기전적 근거 – **cold TME**

쓸 수도 있다

1. **일부 response 보인 논문**

Qi et al. Ann Surg Oncol 2026



- EGFRmt neoadj IO+Chemo (N=43)
- ORR 44.2%, MPR 41.9%, pCR 18.6%
- PD-L1 ≥1% 환자에서 PR 비율 더 높음 (78.9% vs. 59.1%)

- 단, N=43, 후향적,
- uncommon mutation 포함,
- control arm 없음
- TKI 없이 IO+chemo만 받은 선택된 환자군이어서 selection bias 불가피

Qi YF, et al. Ann Surg Oncol. 2026 May 27. PMID: 42201492.

Summary

- 대부분의 **perioperative IO trial은 EGFR mutant를 제외**했으며,
  포함된 경우(KEYNOTE-671, AEGEAN)에도 EGFR mutant 에서 **benefit이 확인되지 않았다.**
  (AEGEAN EGFR subgroup EFS HR 0.86, 95% CI 0.35–2.19).
- **Palliative setting의 RCT에서도 일관되게 실패했다** — KEYNOTE-789, CheckMate 722 모두 TKI 내성 EGFR mutant에서 IO+chemo vs. chemo 간 PFS/OS 차이 없음.
- **PD-L1 high여도 IO는 잘 안듣는다** — PD-L1 ≥50%인 TKI-naïve EGFR mutant 환자에서 pembrolizumab 단독 ORR은 실제 0%였다 (Lisberg 2018, phase II 조기종료).
- **IO 와 EGFR-TKI의 병용은 독성 문제로 제한된다** — TATTON에서 osimertinib+durvalumab 조합 시 ILD 38%, CAURAL은 이 signal로 조기종료되었다. Neoadjuvant 세팅에서는 수술 전 폐 기능 손상 위험이 더욱 심각하다.
- **기전적으로** EGFR mutation 자체가 **dominant immunosuppressive driver**다 —
  CCL22↑/CXCL10↓에 의한 T celll 배제, CD47 과발현, TAM M2 polarization, TGF-β↑ 등 복합적 기전이 작동하며, 이는 smoking history나 PD-L1 발현으로 override되지 않는다.