



증례를 통해 본 폐암 면역항암치료

*Korea University Medicine
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Contents

- Introduction of immune checkpoint inhibitors
- Case study of Immune Checkpoint Inhibitors
 - 2nd line
 - Front line
 - Inoperable stage III lung ca
 - Neoadjuvant IO-IO or IO-cytotoxic chemotherapy combination therapy
- Summary

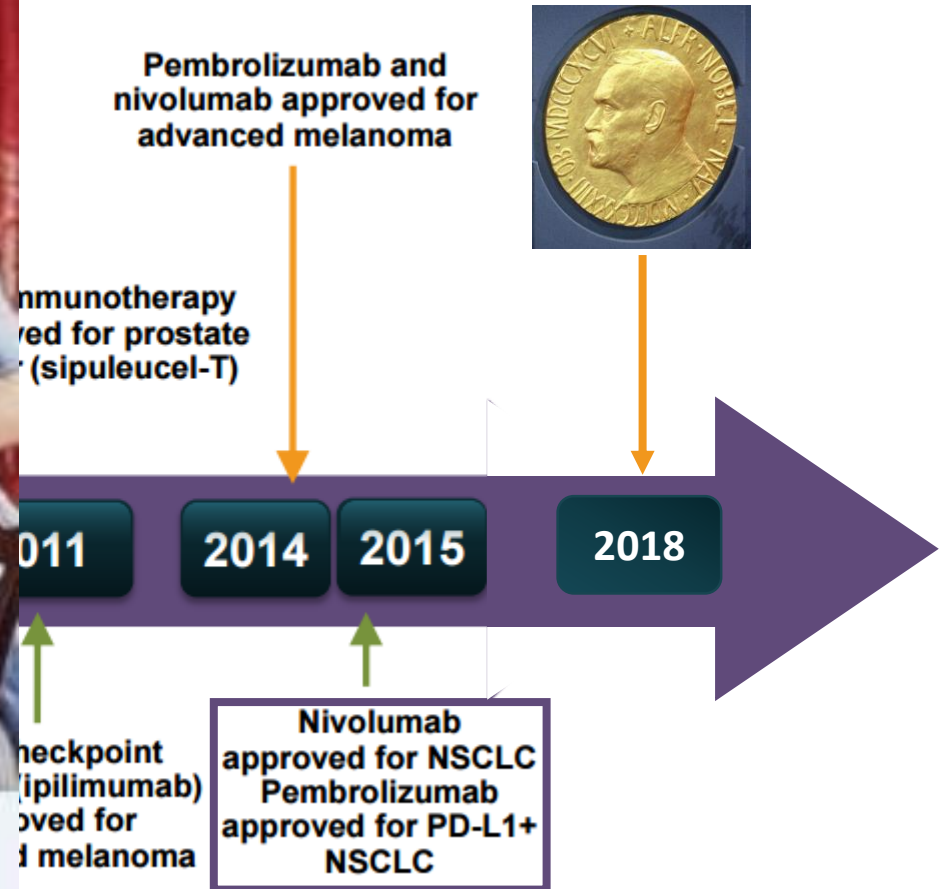


History of Cancer Immunotherapy

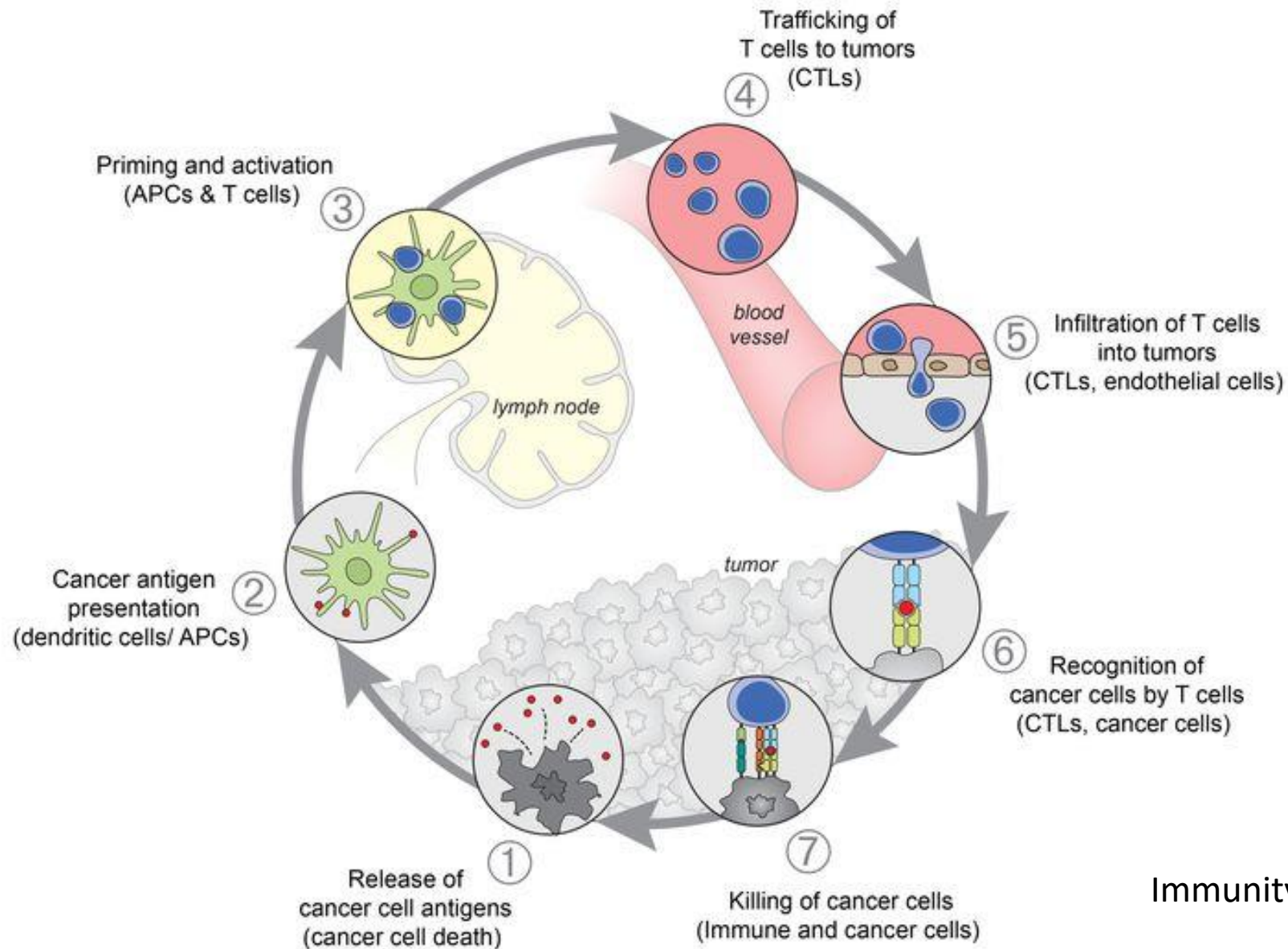
Key Milestones



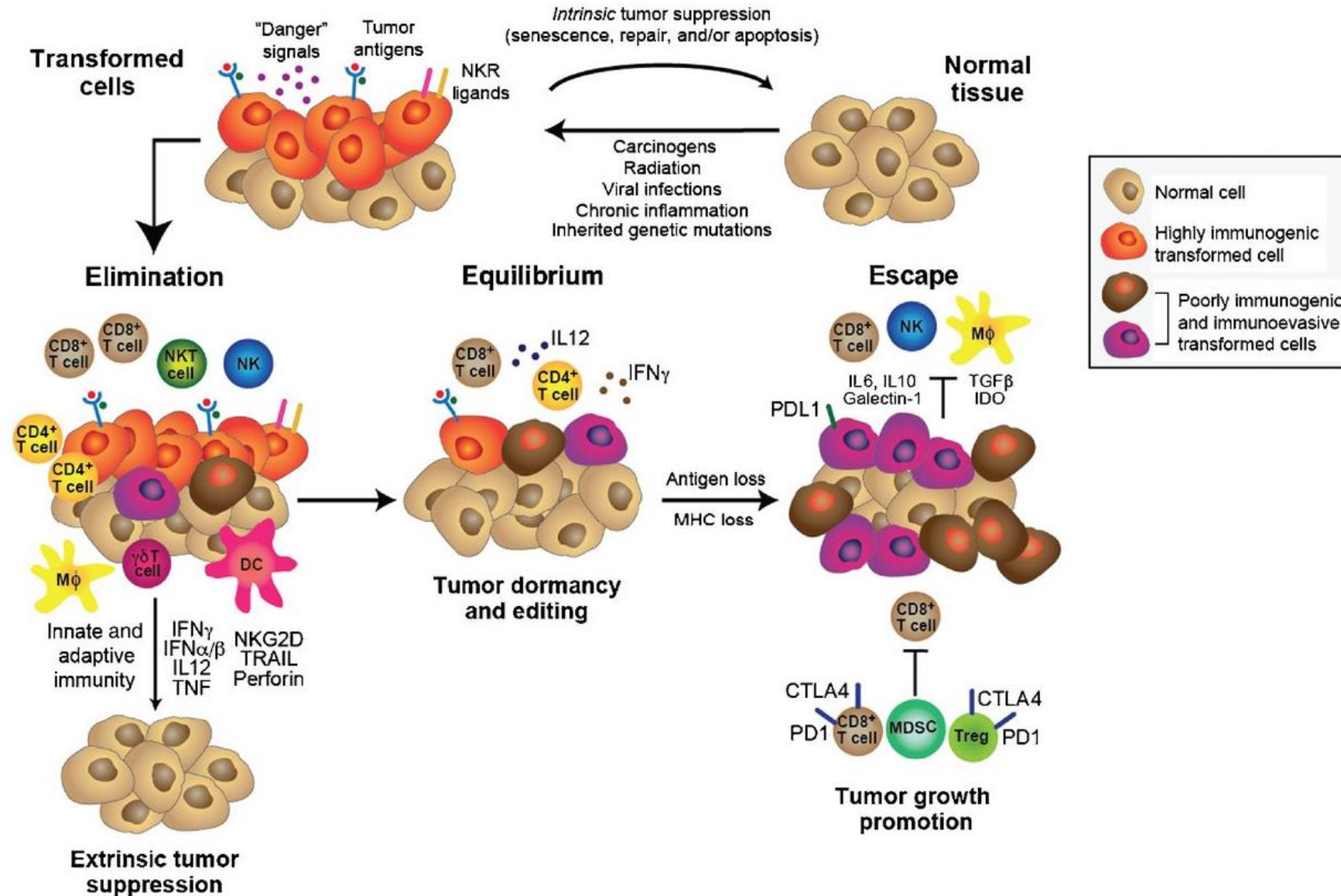
에드워드 제너의 천연두 시술 장면



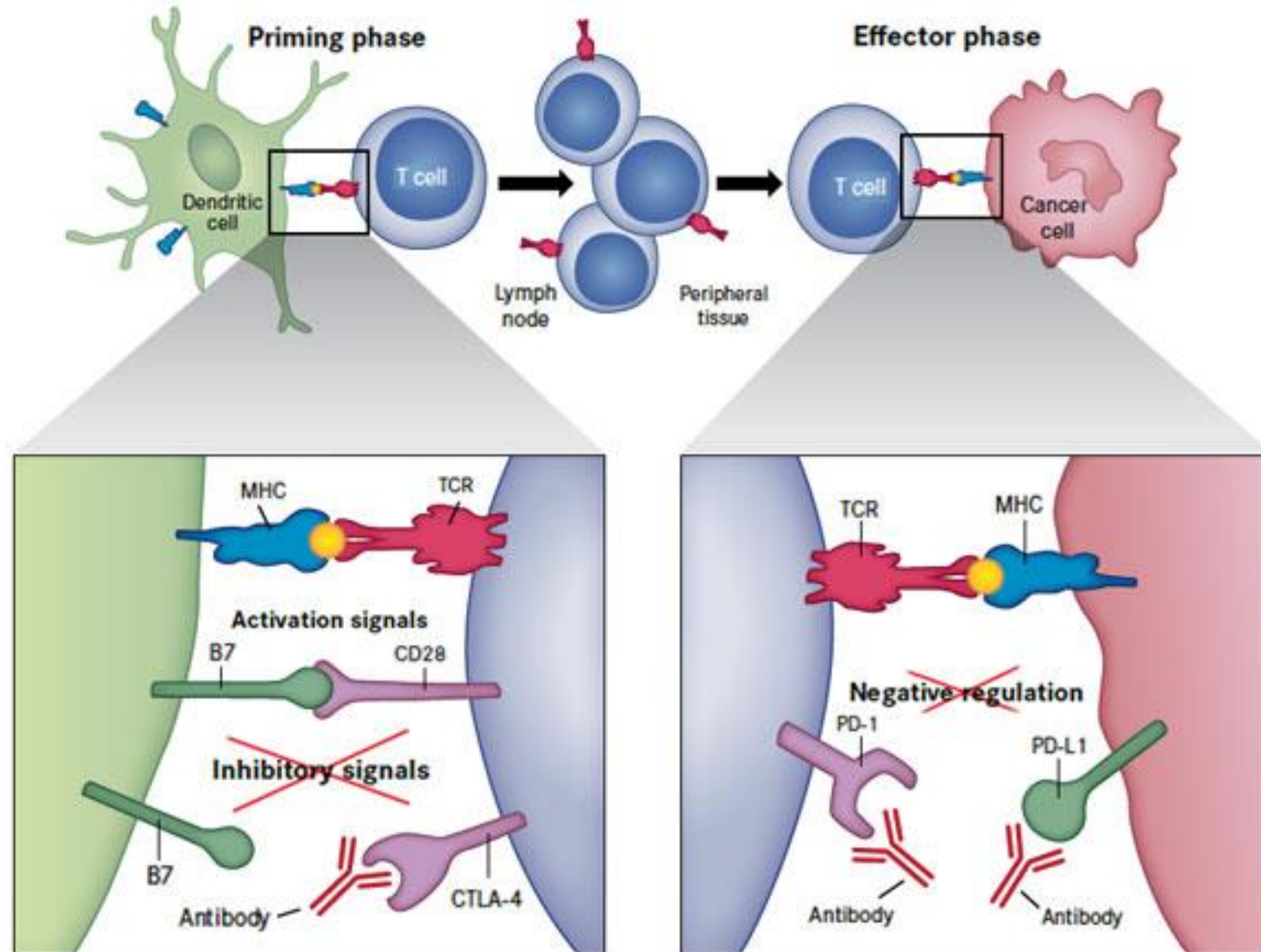
Cancer Immunity Cycle



Three phase of cancer immuno-editing

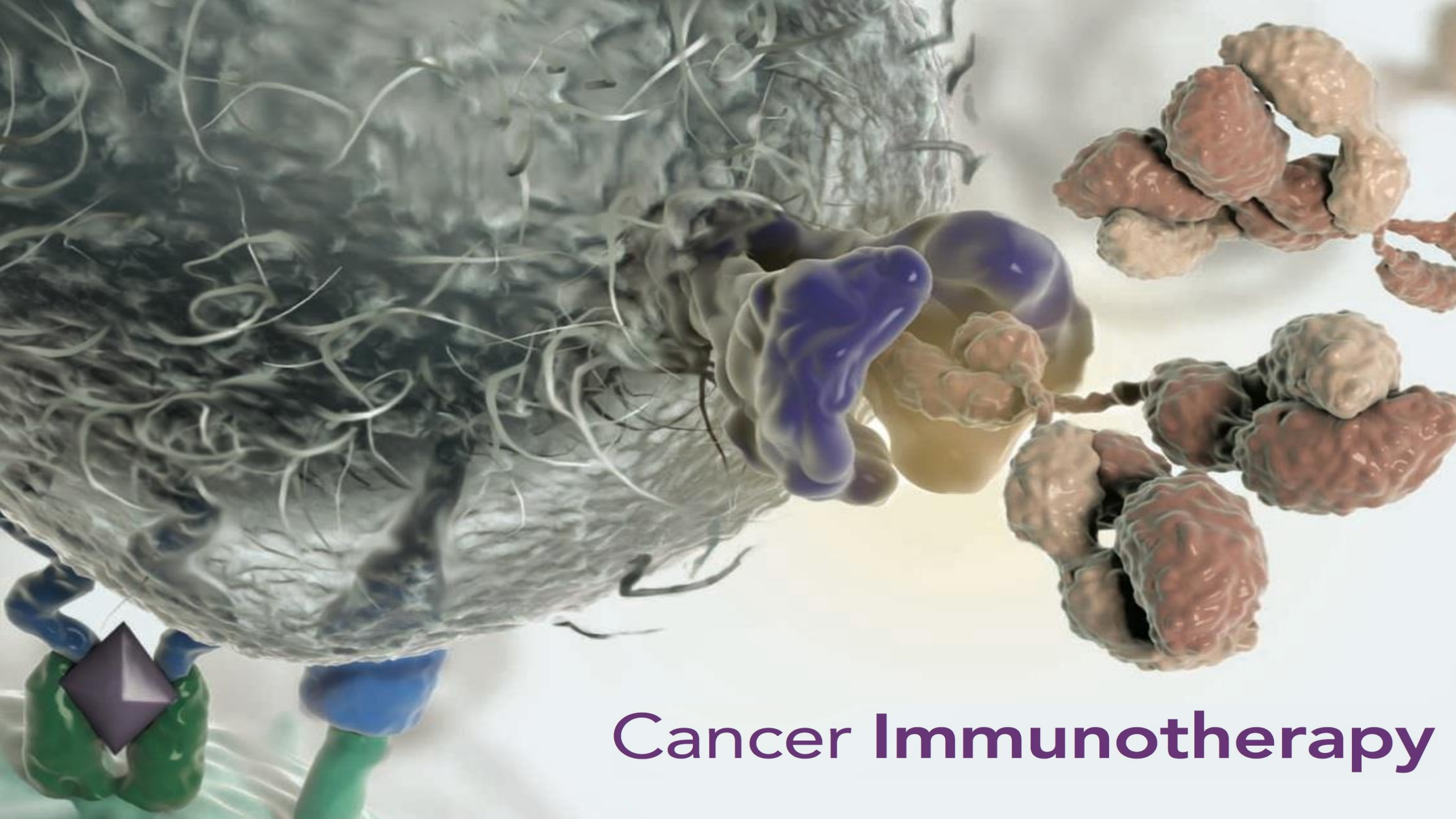


T cell activation and immune checkpoint



Immune Checkpoint Inhibitors

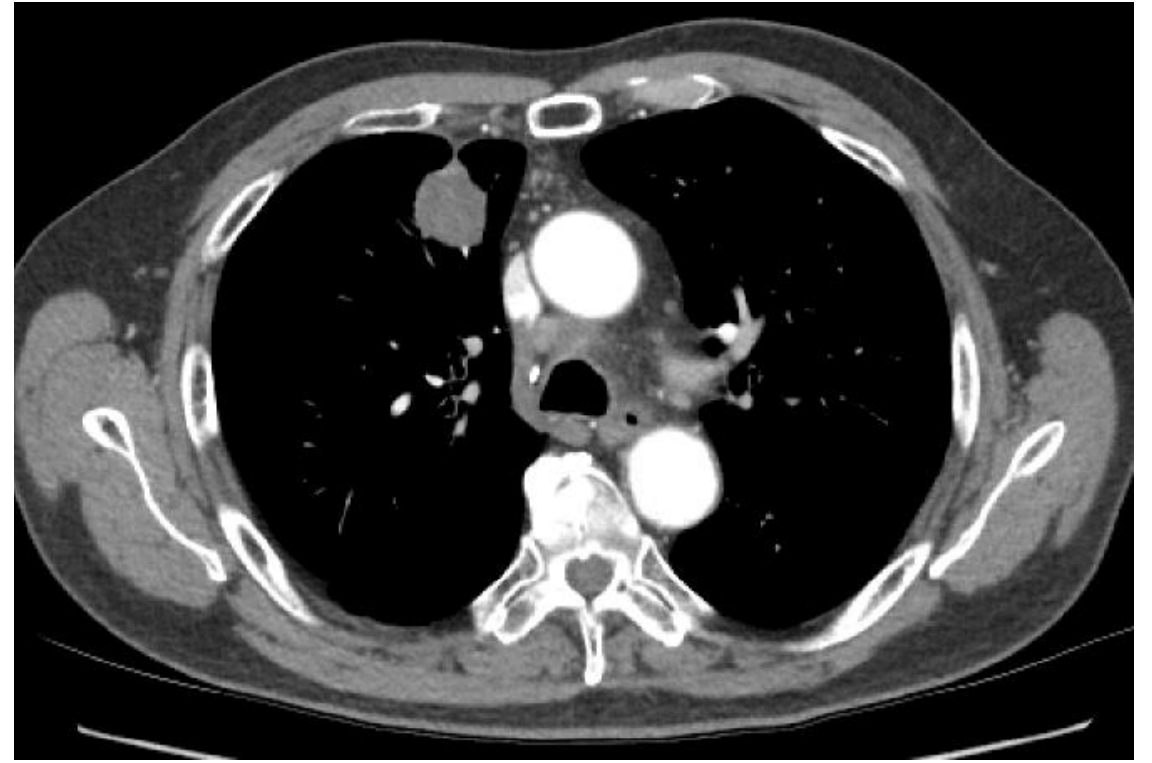
Target	Antibody	Molecule	Company
PD-1	Nivolumab	Fully human IgG4	ONO/ Bristol-Myers Squibb
	Pembrolizumab	Humanized IgG4	MSD
PD-L1	Durvalumab	Engineered human IgG1	Astrazeneca
	Atezolizumab	Engineered human IgG1	Genentech
	Avelumab	Fully human IgG1	Merk/Pfizer
CTLA-4	Iplimumab	fully human IgG1k	BMS
	Tremelimumab	Fully human IgG2	Astrazeneca



Cancer Immunotherapy

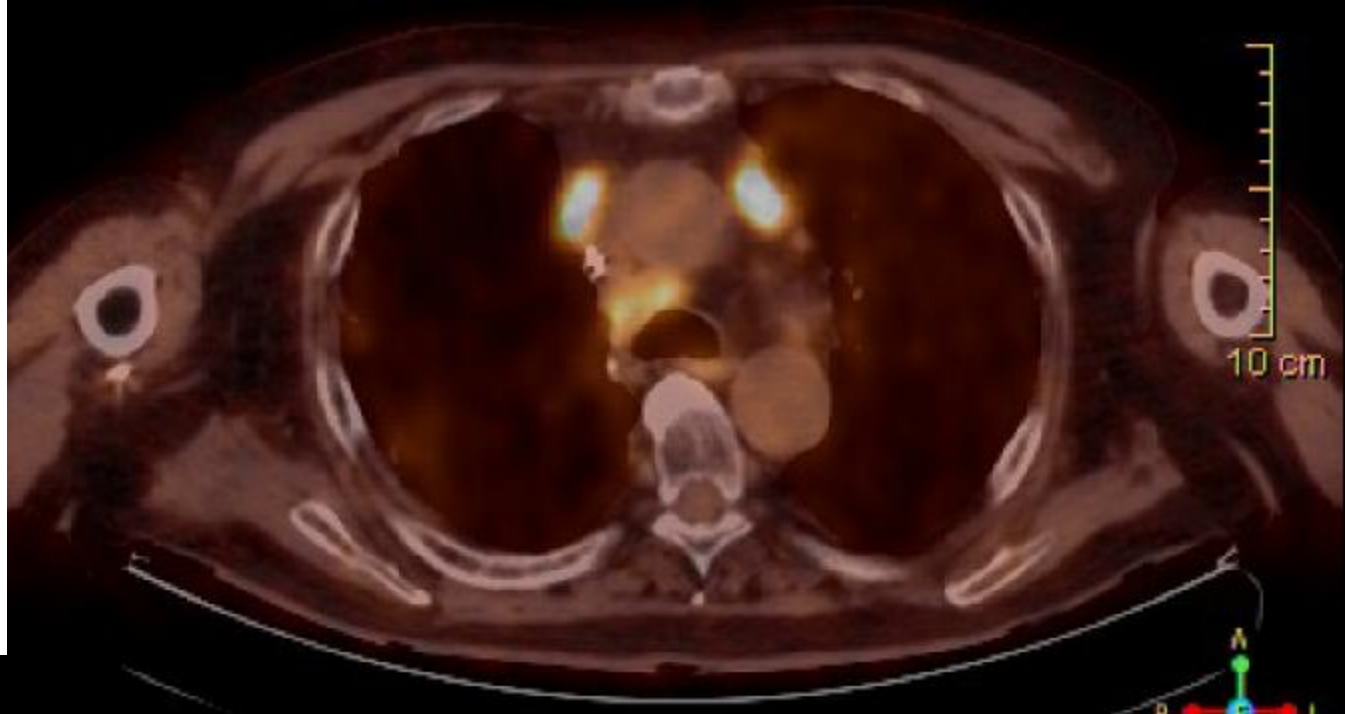
Case 1

- M/68
- RULobectomy sq. cell ca. pT2aN1 18.12/10. SP263/22C3 (60%/50%)
→ adj. taxol-carboplatin 19.1/22-3/20



Case 1

- Recur 19. 4/30



Case 1. 다음 단계 치료는?

M/68, PS 2

RULobectomy sq. cell ca. SP263/22C3 (60%/50%)

Adj. taxol-carbo 19.1/22-3/20

Recur 19.4/30

- 1) 경과 관찰
- 2) Platinum based doublet treatment
- 3) Single cytotoxic chemotherapy (docetaxel, gemcitabine etc.)
- 4) Single IO (pembrolizumab, nivolumab, atezolizumab)
- 5) IO + Cytotoxic chemotherapy

Nivolumab

ORIGINAL ARTICLE

Phase III study (CheckMate 017)

Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer

Julie Brahmer, M.D., Karen L. Reckamp, M.D., Paul Baas, M.D., Lucio Crinò, M.D., Wilfried E.E. Eberhardt, M.D., Elena Poddubskaya, M.D., Scott Antonia, M.D., Ph.D., Adam Pluzanski, M.D., Ph.D., Everett Vokes, M.D., Esther Holgado, M.D., Ph.D., David Waterhouse, M.D., Justin Gainor, M.D., Osvaldo Arén Franco, M.D., Martin Steins, M.D., Marina C. Garassino, M.D., Manuel Domine, M.D., Christine Baudelet, M.D., Brian Lestini, M.D., and Robert J. Gray, M.D.

ORIGINAL ARTICLE

Phase III study(CheckMate 057)

Nivolumab versus Docetaxel in Advanced Non–Small-Cell Lung Cancer

D.R. Spigel, M. Steins, N.E. Ready, L.Q. Chow, M. Barlesi, M. Kohlhäufel, O. Arrieta, M.A. Burgio, D.E. Gerber, S.N. Gettinger, C.M. Rudin, J. Schein, Jr., S.J. Antonia, C. Dorange, M. Mackenstein, and J.R. Brahmer



Second Line



NEJM 2015 OCT

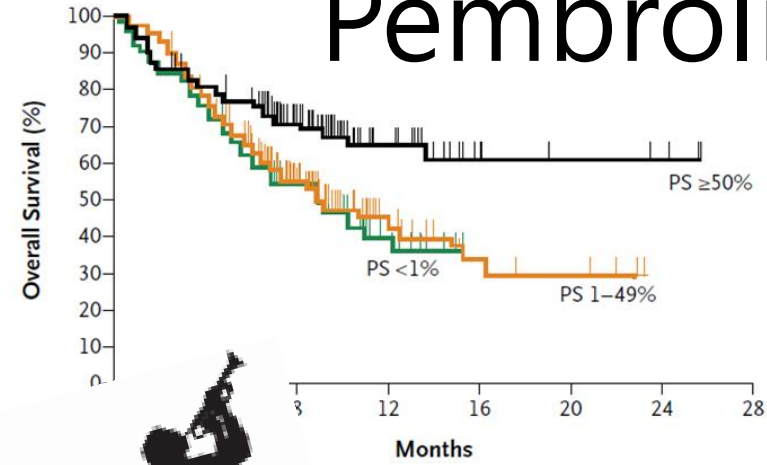


Pembrolizumab for the Treatment of Non-Small-Cell Lung Cancer

Edward B. Garon, M.D., Naiyer A. Rizvi, M.D., Rina Hui, M.B., B.S.,
 Natasha Leighl, M.D., Ani S. Balmanoukian, M.D., Joseph Paul Eder, M.D.,
 Amita Patnaik, M.D., Charu Aggarwal, M.D., Matthew Gubens, M.D.,
 Leora Horn, M.D., Enric Carcereny, M.D., Myung-Ju Ahn, M.D.,
 Enriqueta Felip, M.D., Jong-Seok Lee, M.D., Matthew D. Hellmann, M.D.,
 Omid Hamid, M.D., Jonathan W. Goldman, M.D., Jean-Charles Soria, M.D.,
 Marisa Dolled-Filhart, Ph.D., Ruth Z. Rutledge, M.B.A., Jin Zhang, Ph.D.,
 Jared K. Luceford, Ph.D., Reshma Rangwala, M.D., Gregory M. Lubiniecki, M.D.,
 Charlotte Roach, B.S., Kenneth Emancipator, M.D.,
 and Leena Gandhi, M.D., for the KEYNOTE-001 Investigators

Pembrolizumab

A All Patients

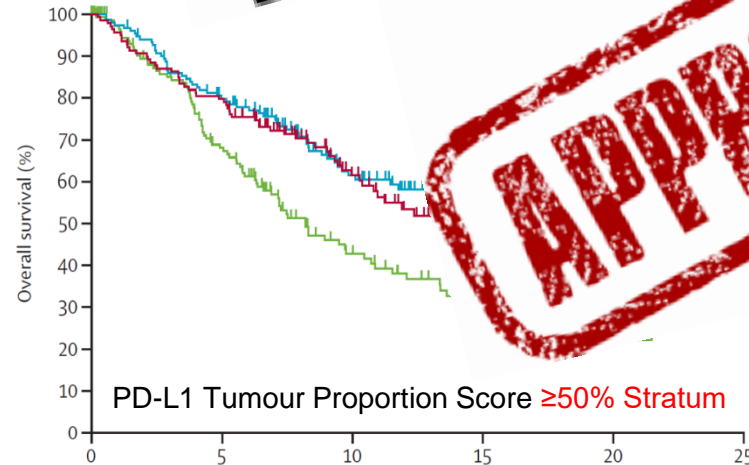


22	5	4	3	0
15	6	4	0	0
8	0	0	0	0

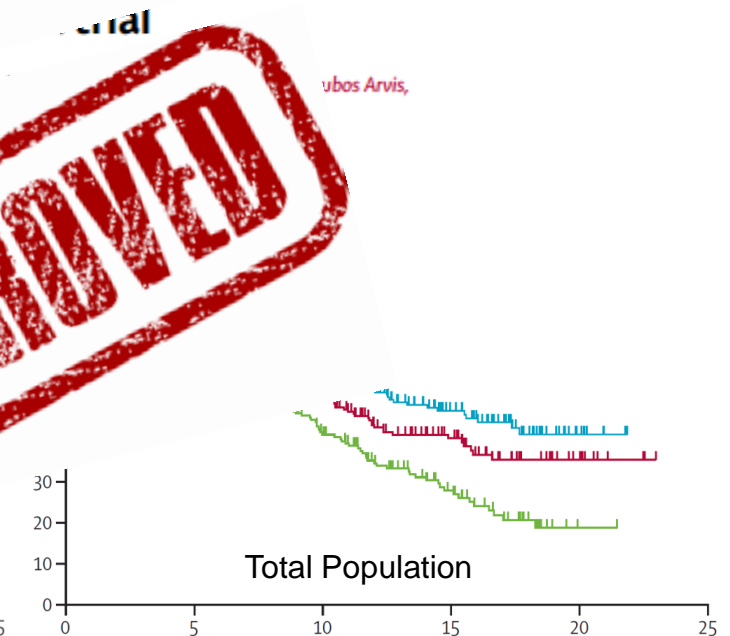


Pembrolizumab
 PD-L1
 (KEYNOTE-001)

Roy S Herbst, Paul
 Myung-Ju Ahn, Ma
 Marisa Dolled-Filhar.



Second Line



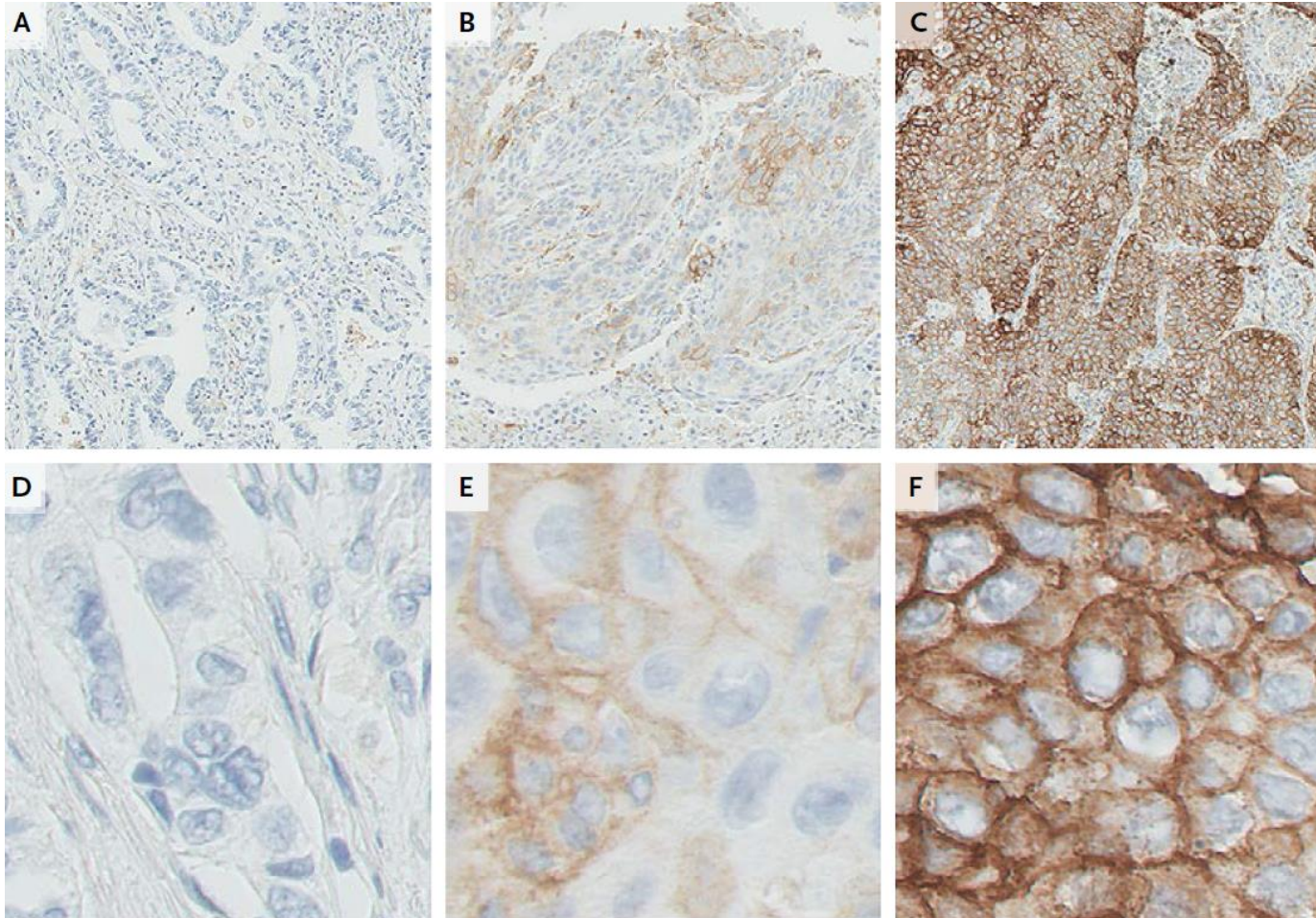
건강보험심사평가원 급여 기준(2차 이상)

Target	Drug name	급여고시	세부 인정 기준
PD-1	Nivolumab	2017년 8월	<ul style="list-style-type: none"> PD-L1 발현 양성 IHC 28-8 pharmDx/VENTANA PD-L1(SP263)($\geq 10\%$) And 이전 백금기반 화학요법에 실패한 stage IIIB 이상
	Pembrolizumab	2017년 8월	<ul style="list-style-type: none"> PD-L1 발현 양성 IHC 22C3 pharmDx ($\geq 50\%$) And 이전 백금기반 화학요법에 실패한 stage IIIB 이상
PD-L1	Atezolizumab	2019년 7월	

급여 인정 기간

- 1년까지(단, 질병진행시 중단) 급여 인정하되, 1년내에 최적의 투여기간에 대한 임상결과 미발표시 자동 연장하여 최대 2년까지 인정.

anti-PD-L1 antibody clone 22C3



less than 1%

1 to 49%

at least 50%

Immunotherapy	IHC assay	FDA Dx. status
Nivolumab	28-8(Dako), SP263(Ventana)	Complementary
Pembrolizumab	22C3(Dako), SP263(Ventana)	Companion
Atezolizumab	SP142(Ventana)	Complementary
Durvalumab	SP263(Ventana)	Unknown

PD-L1 Expression in Non-Small-Cell Lung Cancers

Case 1. 다음 단계 치료는?

M/68, PS 2

RULobectomy sq. cell ca. SP263/22C3 (60%/50%)

Adj. taxol-carbo 19.1/22-3/20

Recur 19.4/30

- 1) 경과 관찰
- 2) Platinum based doublet treatment
- 3) Single cytotoxic chemotherapy (docetaxel, gemcitabine etc.)
- 4) Single IO (pembrolizumab, nivolumab, atezolizumab)
- 5) IO + Cytotoxic chemotherapy

Case 2

- M/75 PS 1~2
- Adenocarcinoma RUL T3N3M1a , pleura



Case 2.

m/75, PS 1~2

Adenocarcinoma. RUL T3N3M1a , pleura

치료 방침을 결정하기 위해 확인해야 할 검사는?

Case 2. 적절한 치료는?

m/75, PS 1~2

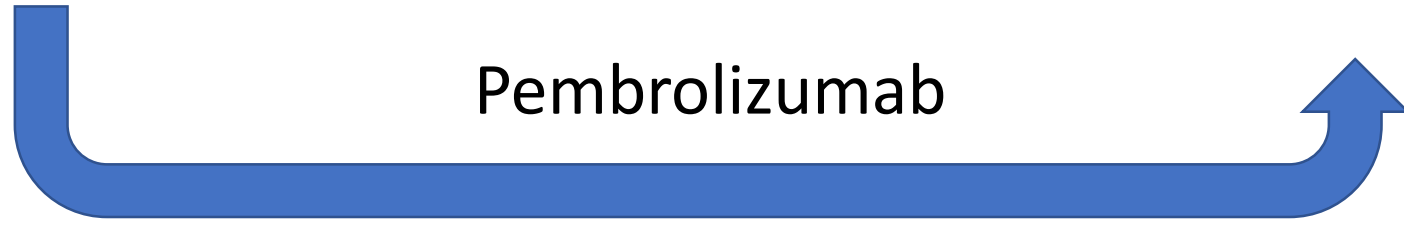
Adenocarcinoma. RUL T3N3M1a , pleura
SP263(>90%), SP142(tu 20%/immune 3%)

- 1) 경과 관찰
- 2) Pemetrexed + cisplatin
- 3) Single cytotoxic chemotherapy (gemcitabine, vinorelbine etc.)
- 4) IO (Pembrolizumab)
- 5) IO + Cytotoxic chemotherapy

Case 2

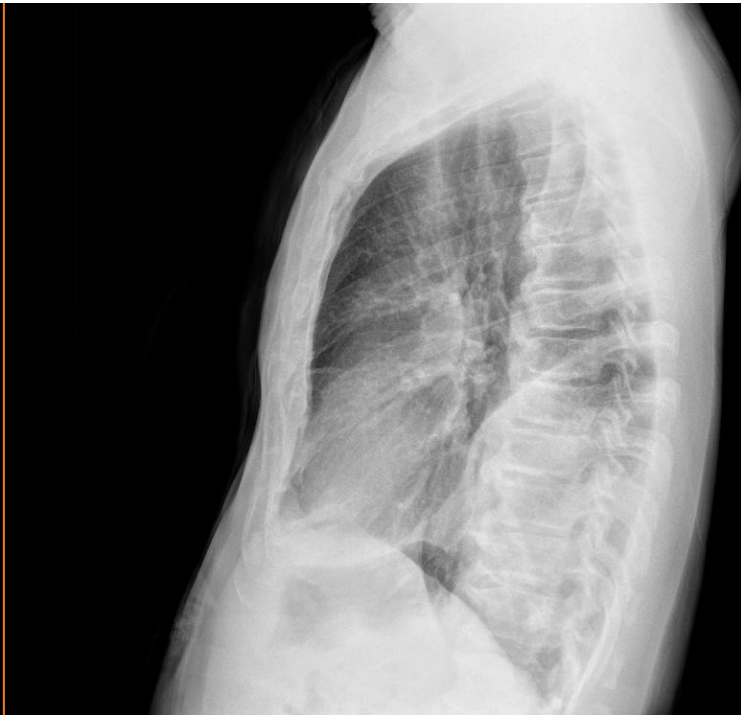


Pembrolizumab



Case 3

- M/59
- sq. cell ca. LLL T3N2M1a, pleura



Case 3

m/59, PS 1

Squamous. T3N2M1a , pleura.

치료 방침을 결정하기 위해 확인해야 할 검사는?

Case 3. 적절한 치료는?

m/59, PS 1

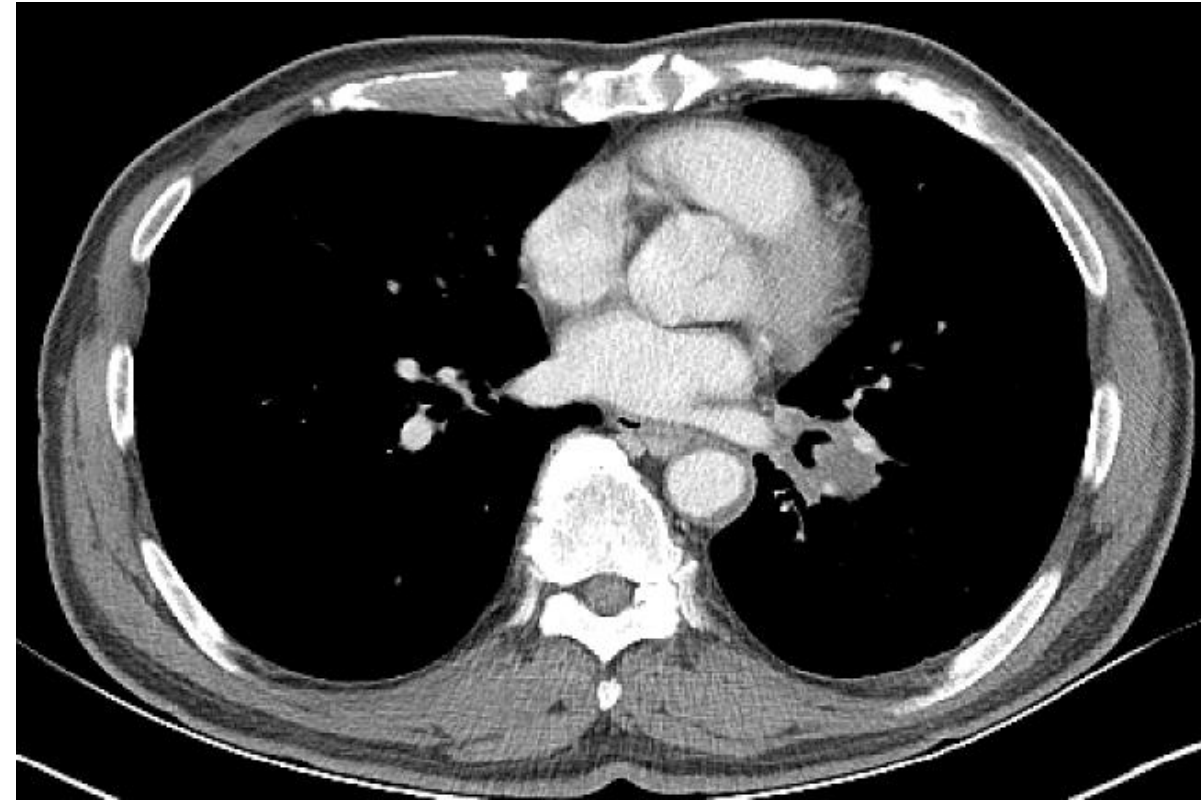
Squamous. T3N2M1a , pleura. 22C3 1%

- 1) 경과 관찰
- 2) Platinum based doublet treatment
- 3) IO (Pembrolizumab)
- 4) IO + IO (durvalumab + tremelimumab)
- 5) IO + Cytotoxic chemotherapy

Case 3

m/59, PS 1

Squamous. T3N2M1a , pleura. 22C3 1%



Pembrolizumab + taxol + carboplatin

Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score of 50% or Greater

Key Eligibility Criteria

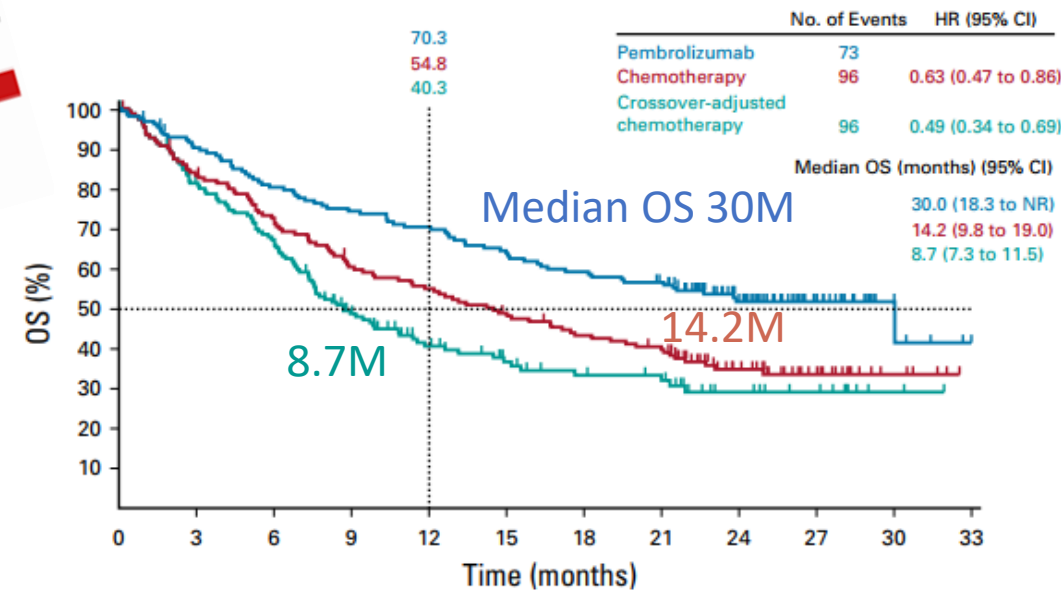
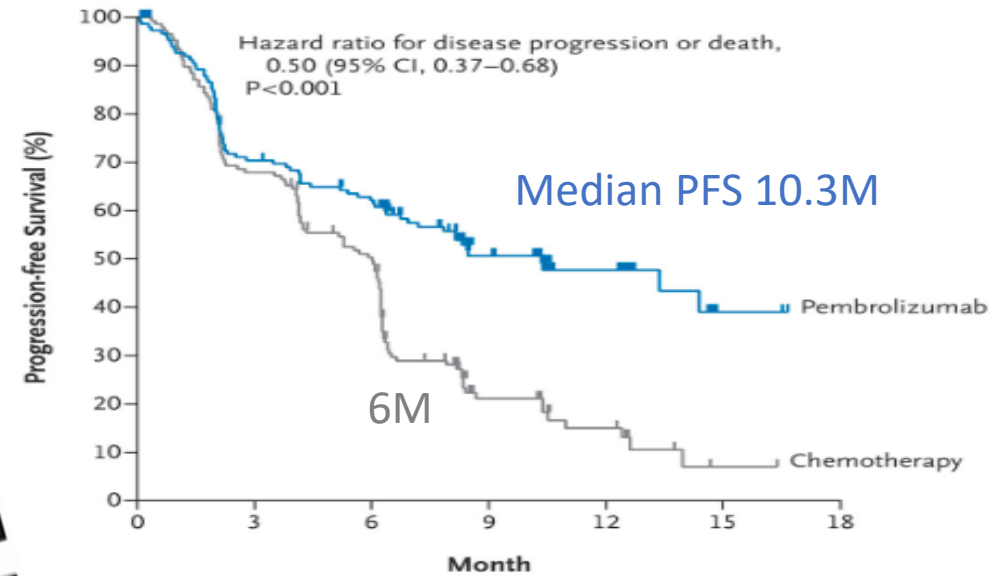
- Untreated stage IV NSCLC
- PD-L1 TPS $\geq 50\%$
- ECOG PS 0-1
- No activating *EGFR* mutation or *ALK* translocation
- No untreated brain metastases
- No active autoimmune disease requiring systemic therapy

R (1:1)
N = 305

Pembrolizumab
200 mg IV Q3W
(2 years)

FRONTLINE
CHANGING LIVES

Pembrolizumab (TPS $\geq 50\%$)

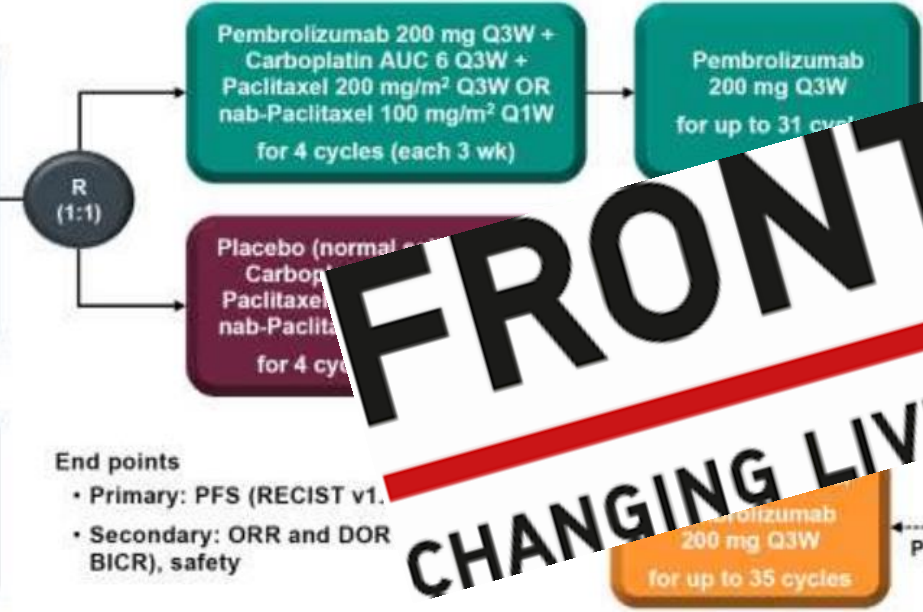


ORIGINAL ARTICLE

Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer

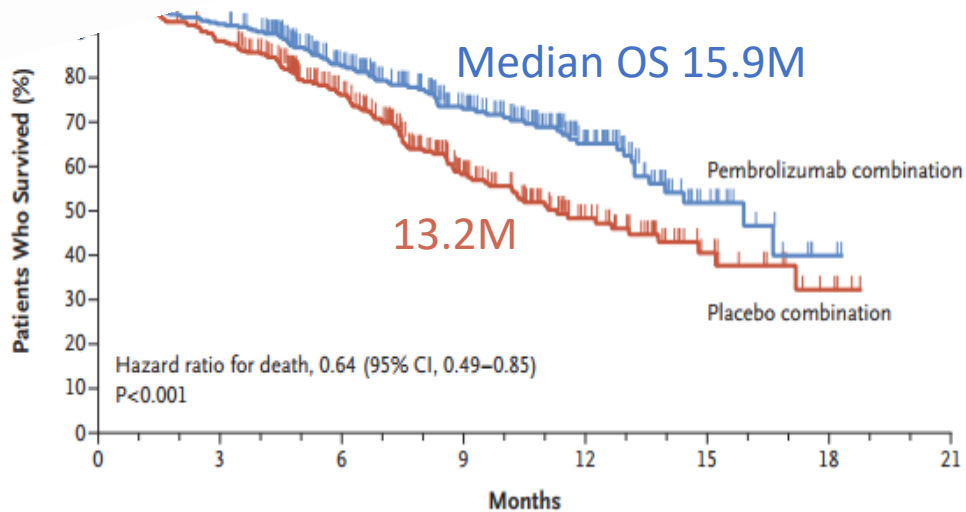
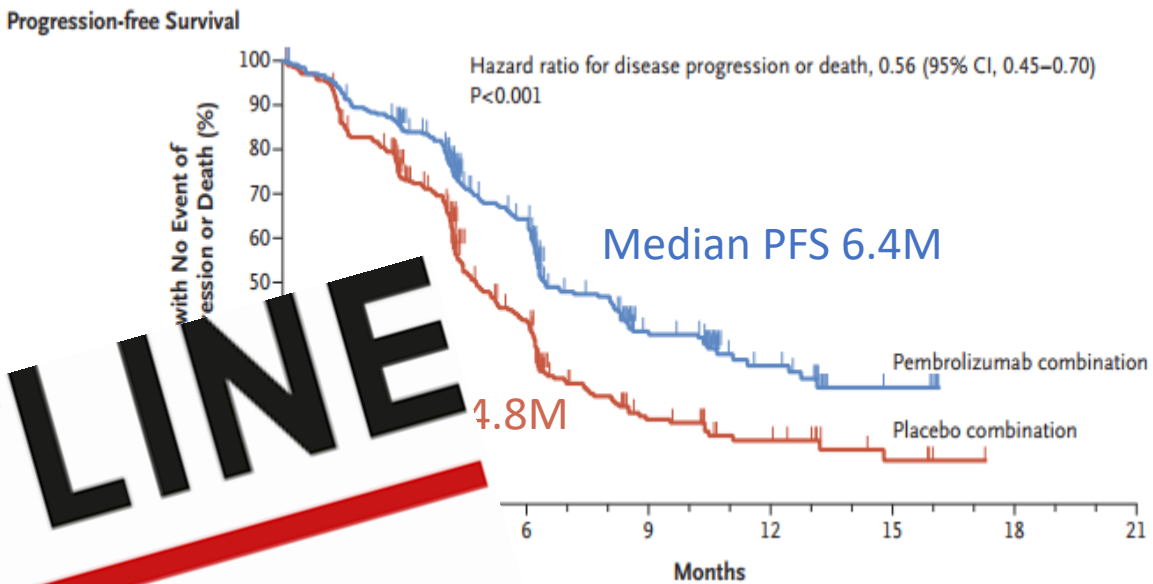
- Key Eligibility Criteria**
- Untreated stage IV NSCLC with squamous histology
 - ECOG PS 0 or 1
 - Provision of a sample for PD-L1 assessment
 - No symptomatic brain metastases
 - No pneumonitis requiring systemic steroids

- Stratification Factors**
- PD-L1 expression (TPS* <1% vs ≥1%)
 - Choice of taxane (paclitaxel vs nab-paclitaxel)
 - Geographic region (east Asia vs rest of world)



- End points**
- Primary: PFS (RECIST v1.1)
 - Secondary: ORR and DOR (BICR), safety

Pembro + taxol + carboplatin

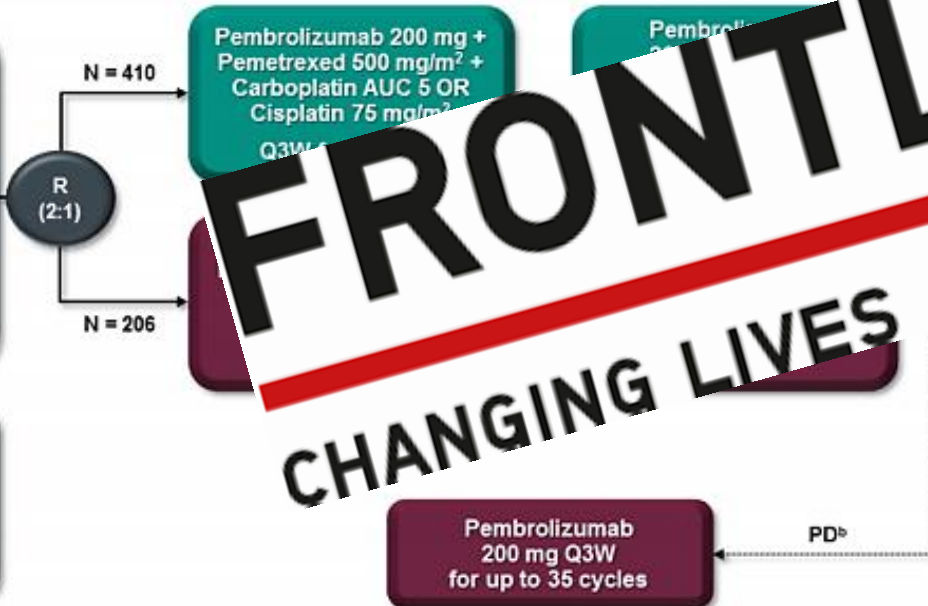


FRONTLINE
CHANGING LIVES

ORIGINAL ARTICLE

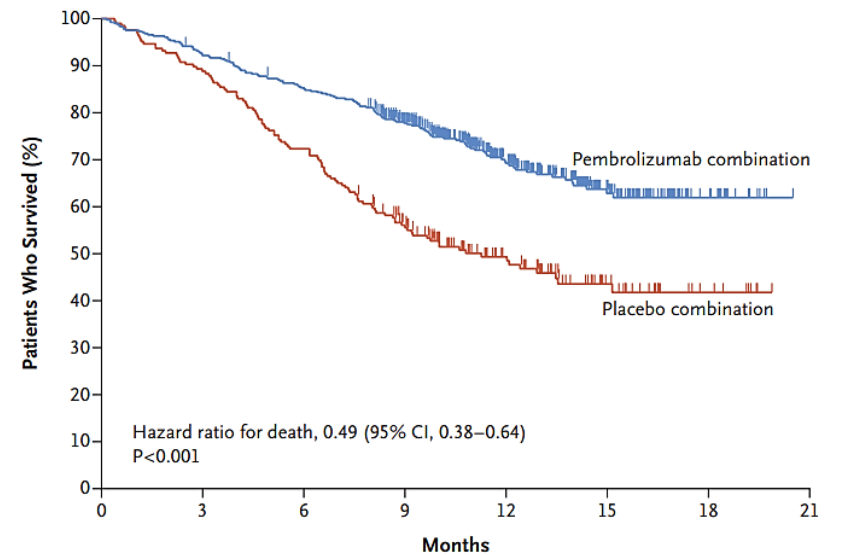
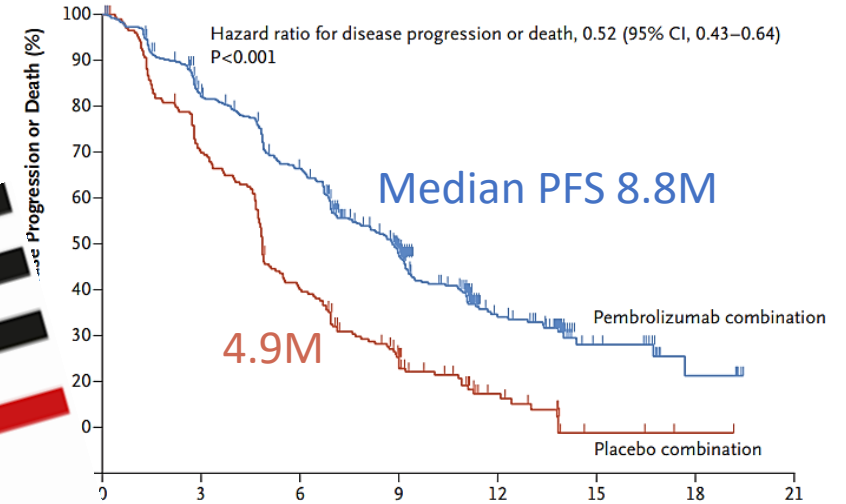
Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer

- Key Eligibility Criteria**
- Untreated stage IV nonsquamous NSCLC
 - No sensitizing EGFR or ALK alteration
 - ECOG PS 0 or 1
 - Provision of a sample for PD-L1 assessment
 - No symptomatic brain metastases
 - No pneumonitis requiring systemic steroids
- Stratification Factors**
- PD-L1 expression (TPS^a <1% vs ≥1%)
 - Platinum (cisplatin vs carboplatin)
 - Smoking history (never vs former/current)



Pembro + pemetrexed + platinum

A Progression-free Survival



No. at Risk

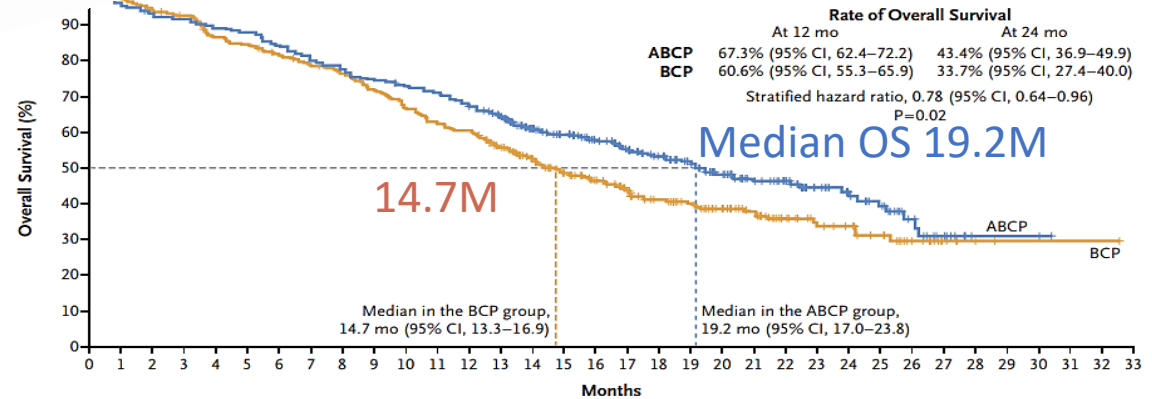
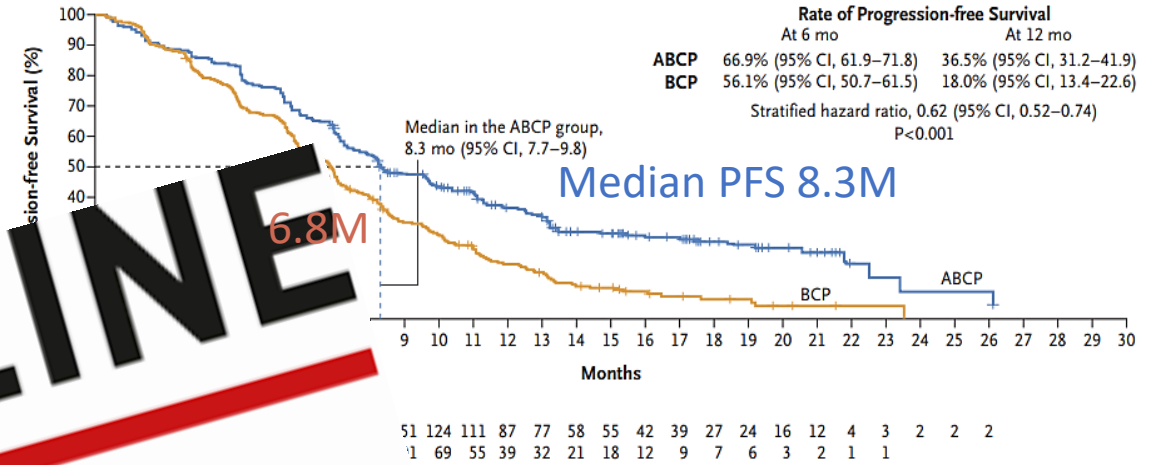
	0	3	6	9	12	15	18	21
Pembrolizumab combination	410	377	347	278	163	71	18	0
Placebo combination	206	183	149	104	59	25	8	0

ORIGINAL ARTICLE

Atezo + taxol + carbo + bevacizumab

Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC

A Kaplan–Meier Estimates of Progression-free Survival



No. at Risk

ABCP	359	339	328	323	314	310	296	284	273	264	256	250	235	218	188	167	147	133	119	103	84	66	57	41	34	28	16	9	2	2	2		
BCP	337	326	315	308	287	280	268	255	247	233	216	203	196	174	152	129	115	101	87	77	66	56	40	32	29	22	13	6	3	1	1	1	1

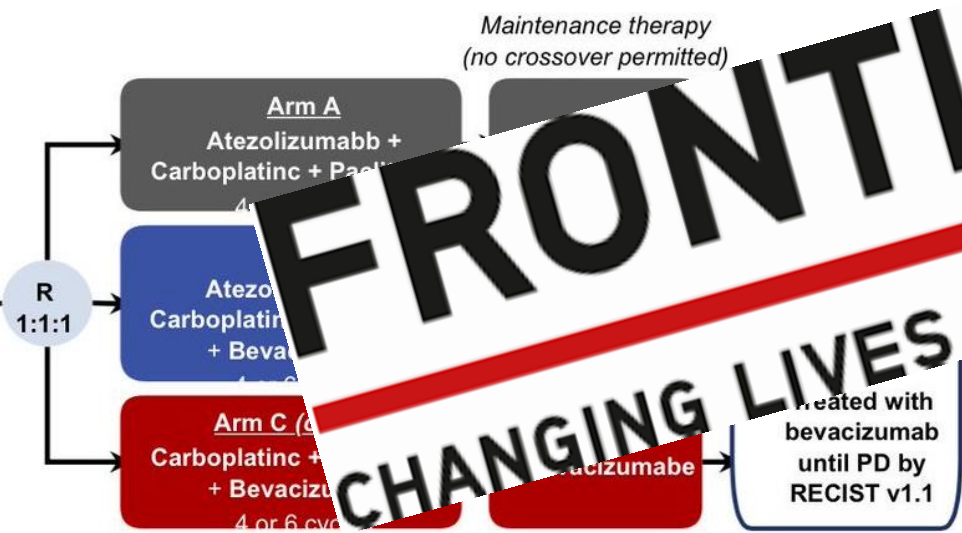
FRONTLINE

CHANGING LIVES

Stage IV or recurrent metastatic nonsquamous NSCLC
Chemotherapy-naive
Tumour tissue available for biomarker testing
Any PD-L1 IHC status

Stratification factors:
Sex
PD-L1 IHC expression
Liver metastases

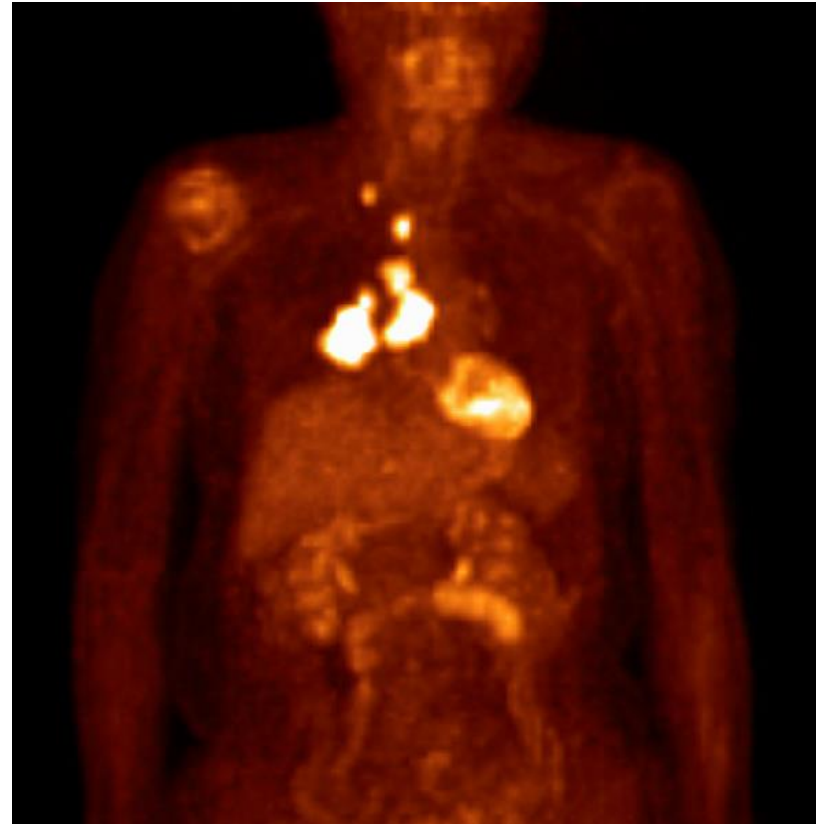
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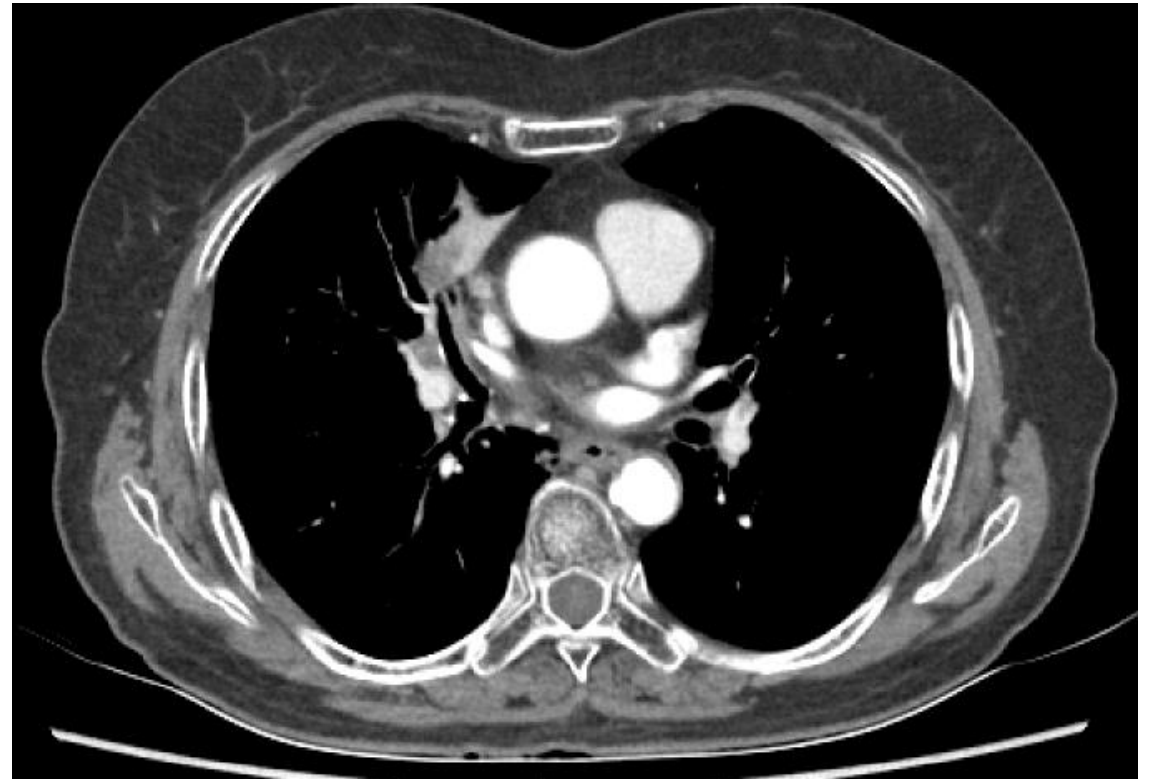
Case 4.

- F/74
- adenoca. RML/RUL T2bN3M0, EGFR/ALK (-/-)
- SP263/142 (100/10%)



Case 4.

CCRT(Taxol-Carbo) 18.7/13~9/19, 60Gy → PR



Case 4. 적절한 치료는?

F/74

adenoca. T2bN3M0, SP263/142 (100/10%)

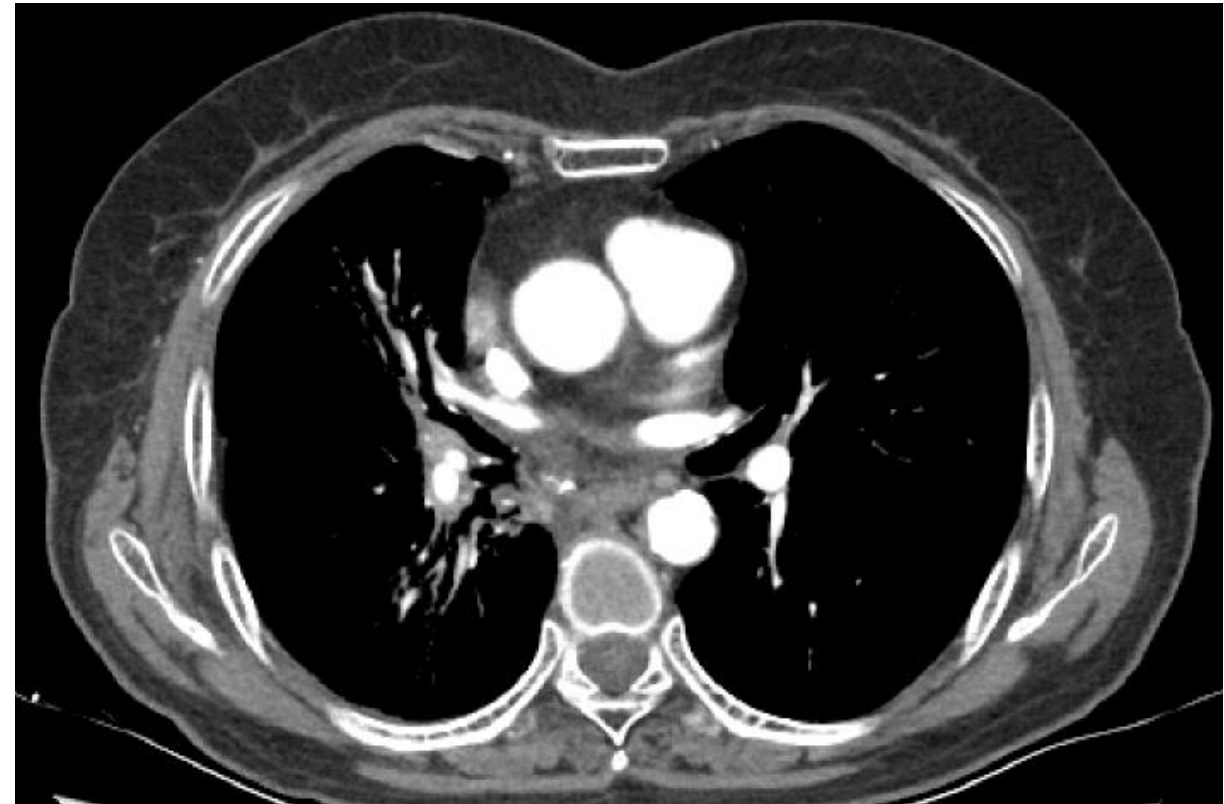
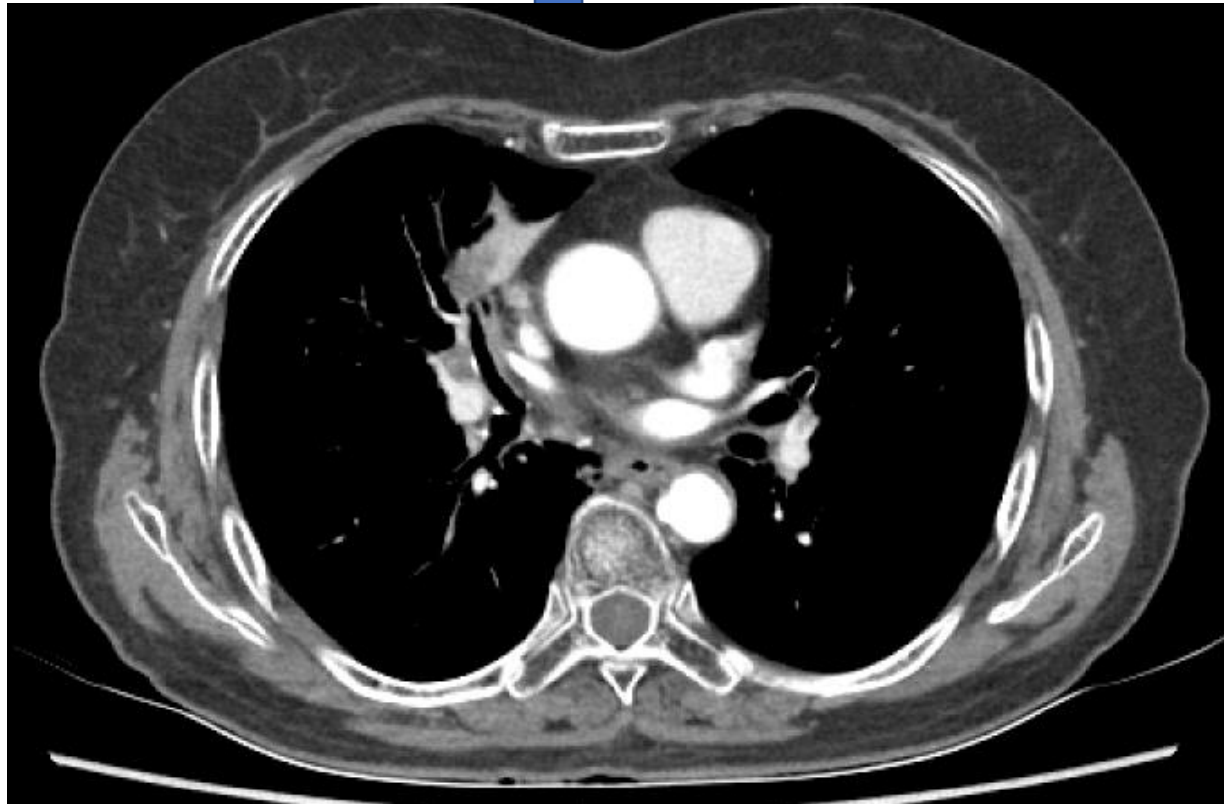
CCRT (taxol-carbo)

- 1) 경과 관찰
- 2) 동일 약제로 consolidation chemotherapy
- 3) IO (**Durvalumab** or pembrolizumab or atezolizumab)
- 4) IO + IO (durvalumab + tremelimumab)
- 5) Surgery

Case 4.

CCRT(Taxol-Carbo) 18.7/13~9/19, 60Gy → Durvalumab EAP (18. 10/24 ~)

8 M

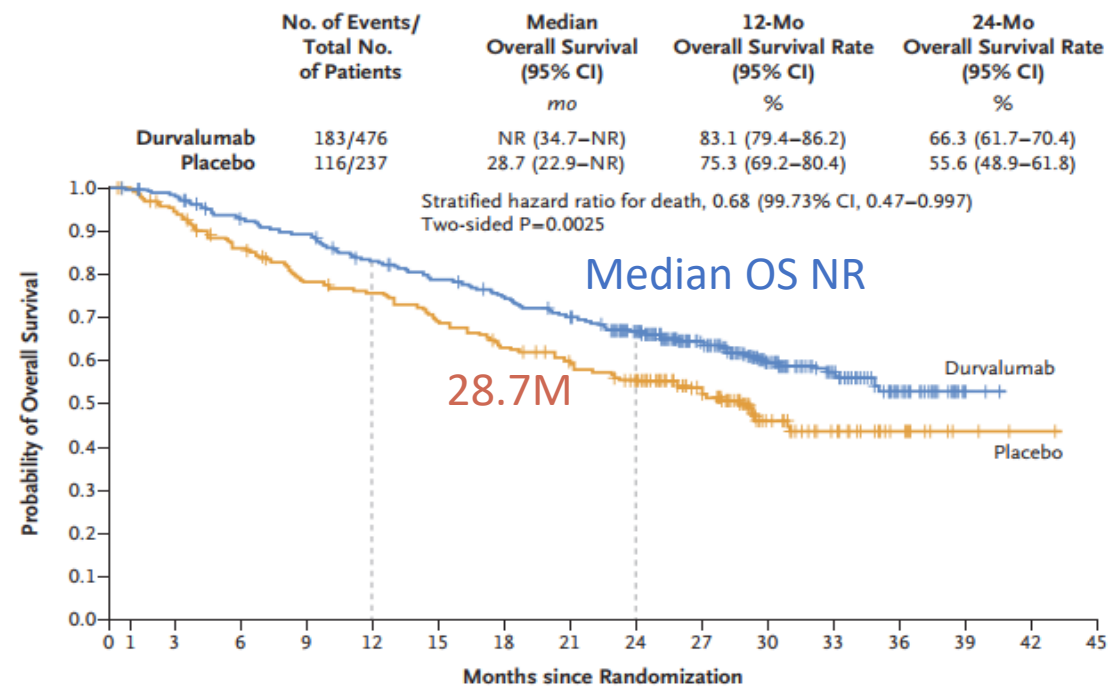
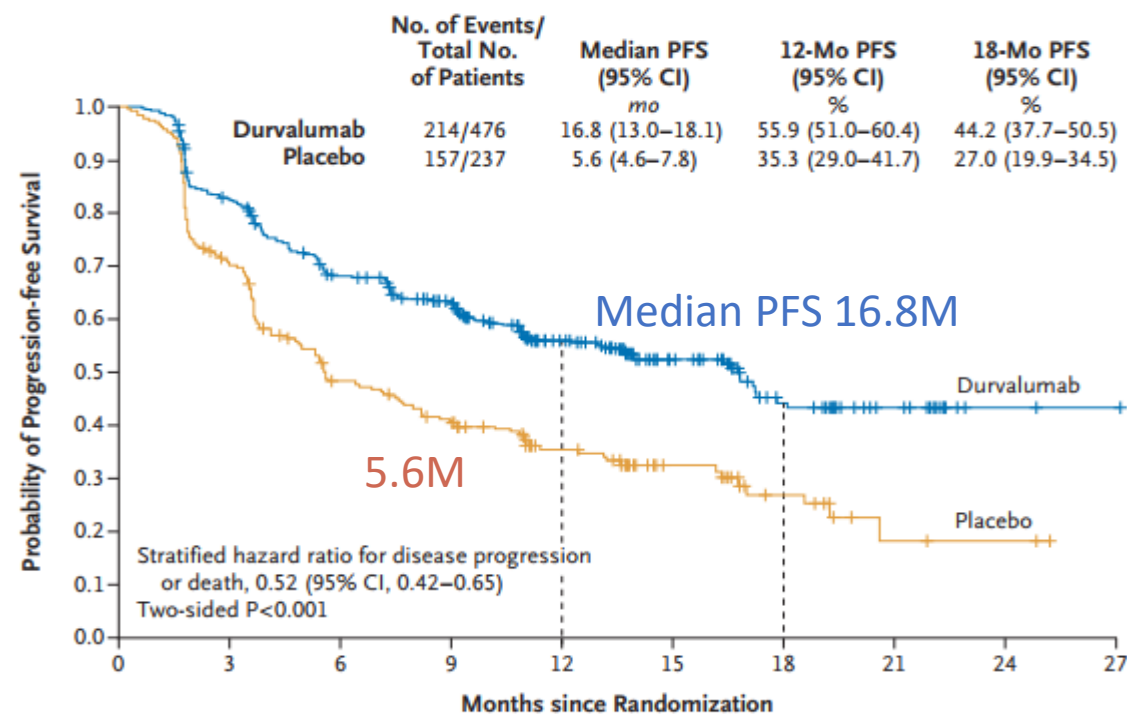
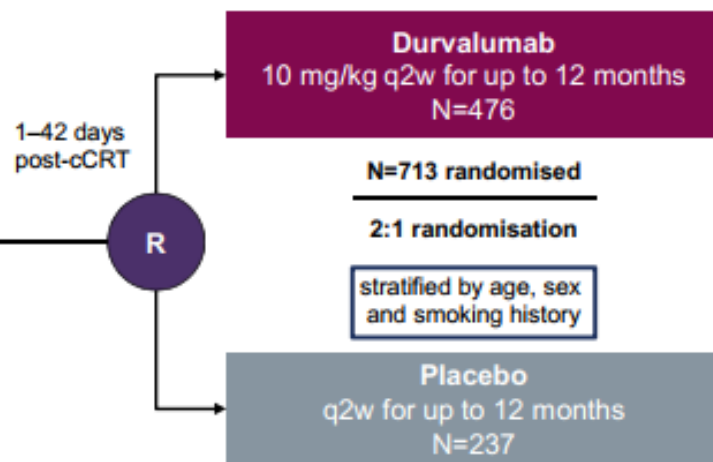


ORIGINAL ARTICLE

Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC

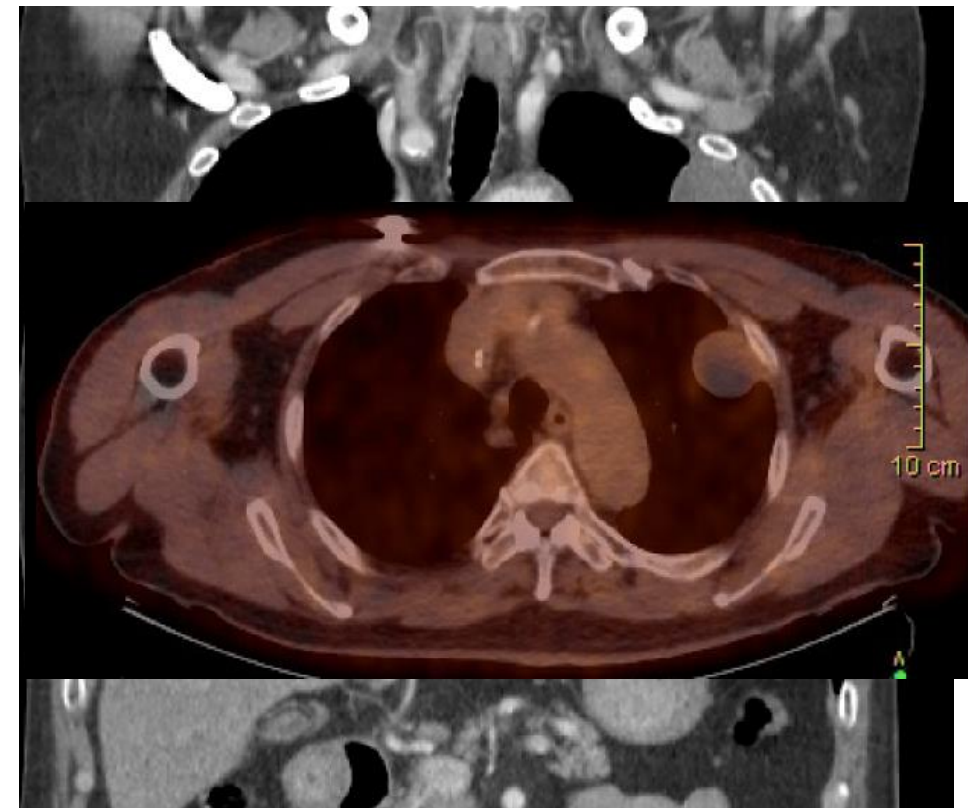
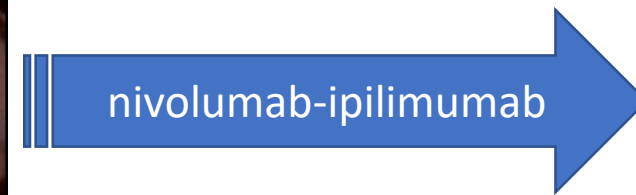
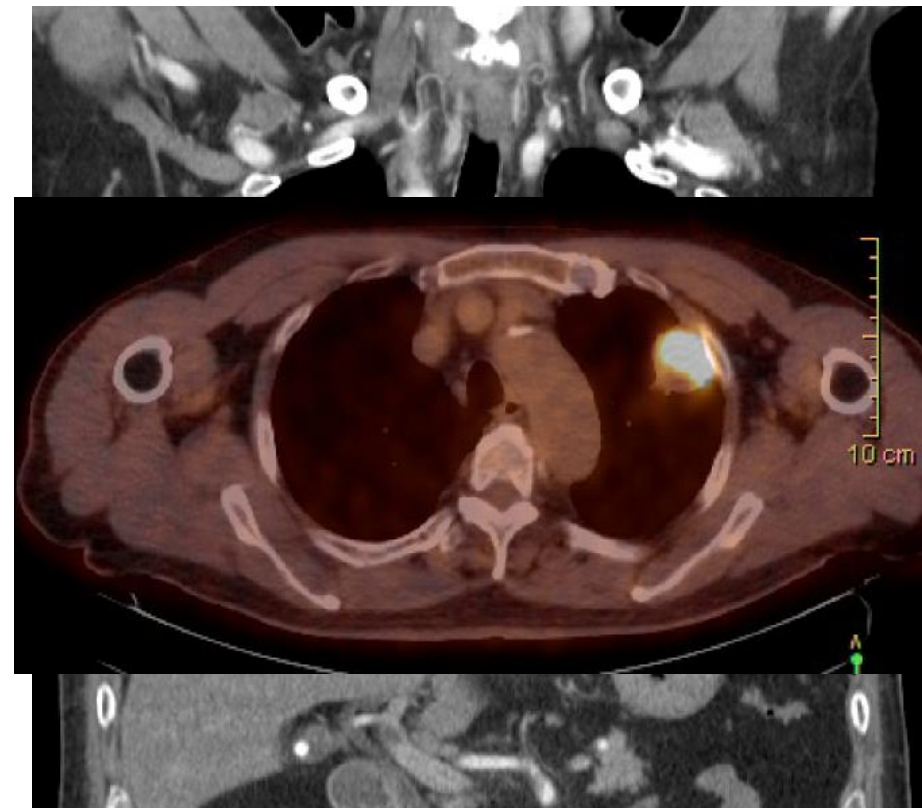
- ◆ Unresectable, Stage III NSCLC without progression after definitive platinum-based cCRT (≥2 cycles)
- ◆ 18 years or older
- ◆ WHO PS score 0 or 1
- ◆ If available, archived pre-cCRT tumour tissue for PD-L1 testing*

All-comers population (i.e. irrespective of PD-L1 status)

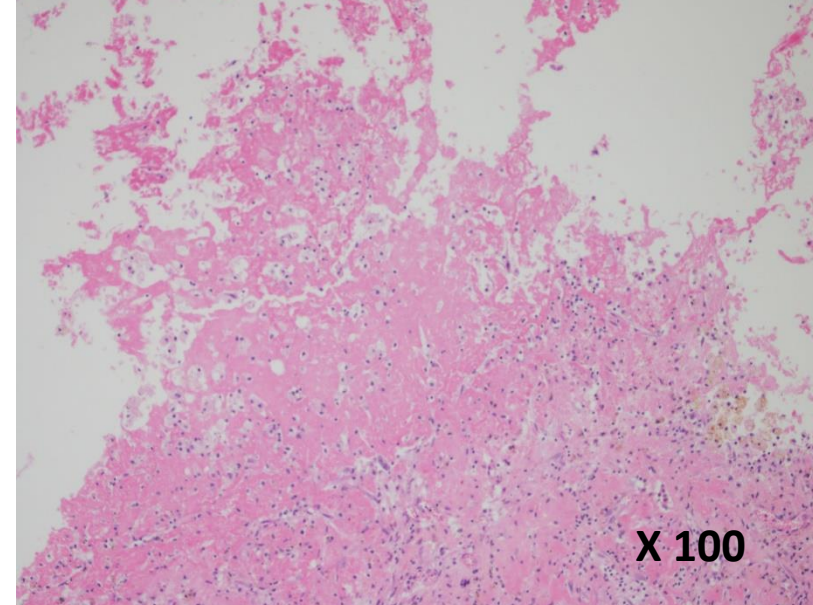
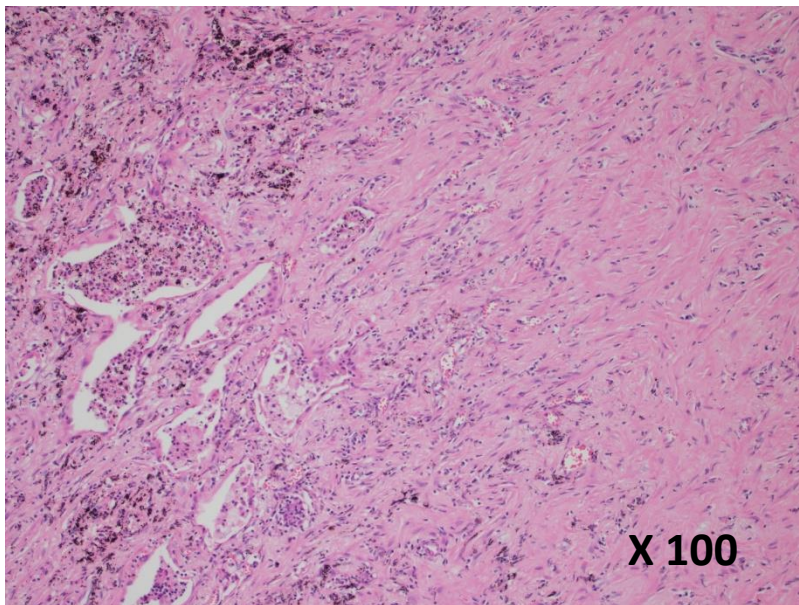
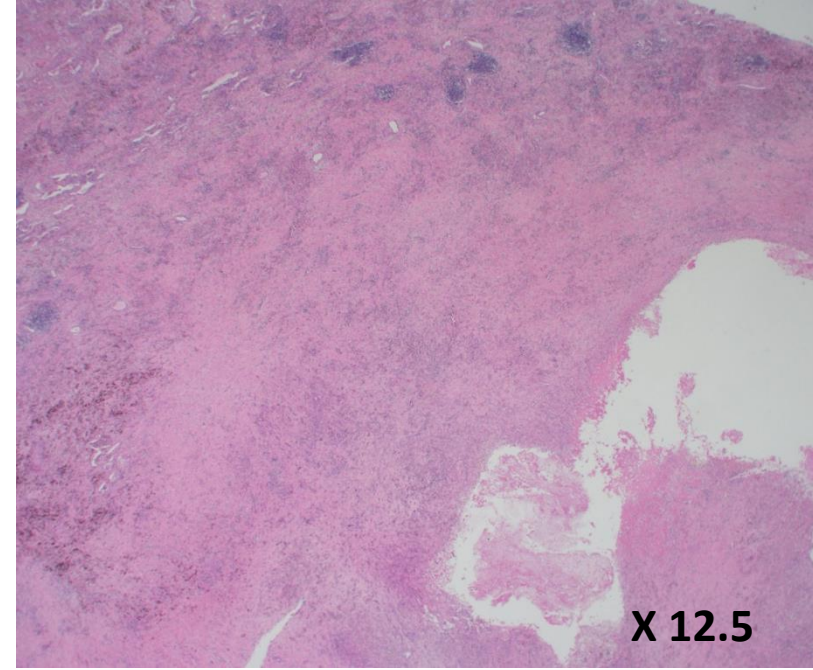


Case 5. Neoadjuvant tx. with IO

- m/73
- adenoca. LUL, T3N0M0, SP263 >95%

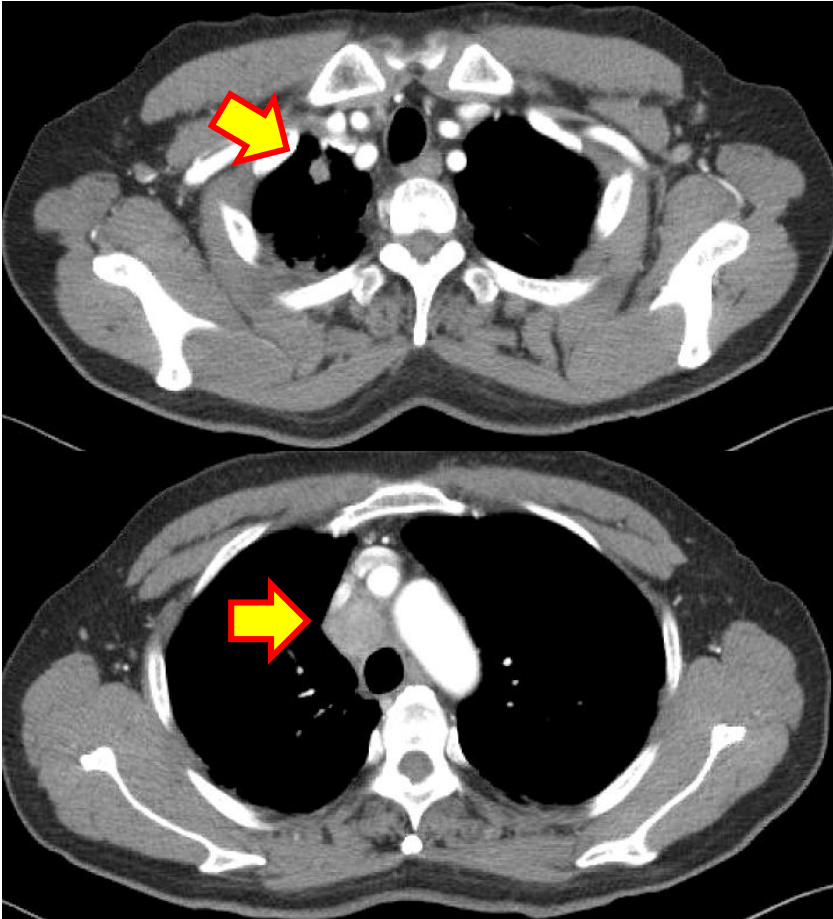


Case 5. (LULobectomy, pCR) Pathology

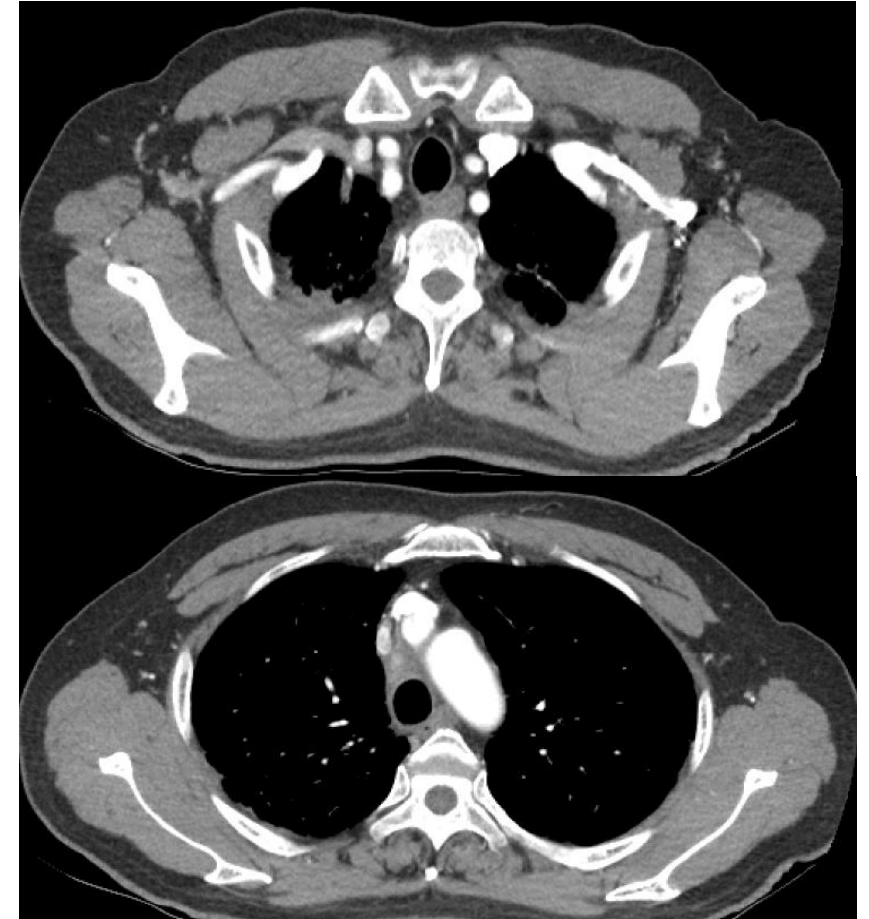


Case 6.

- m/73
- adenoca. LUL, T1bN2M0, SP263 70%

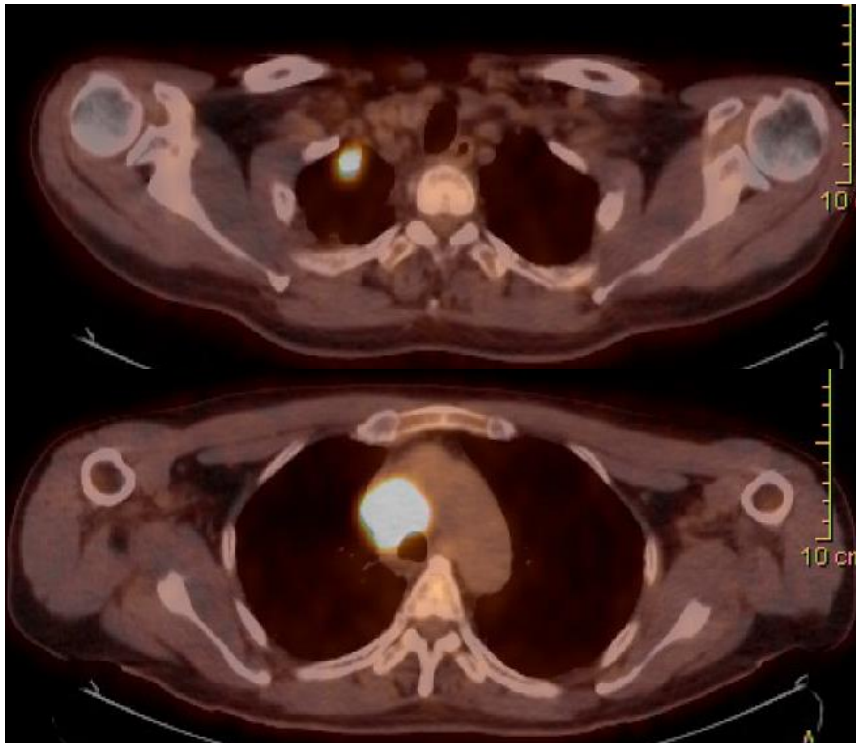


nivolumab-pem-carbo

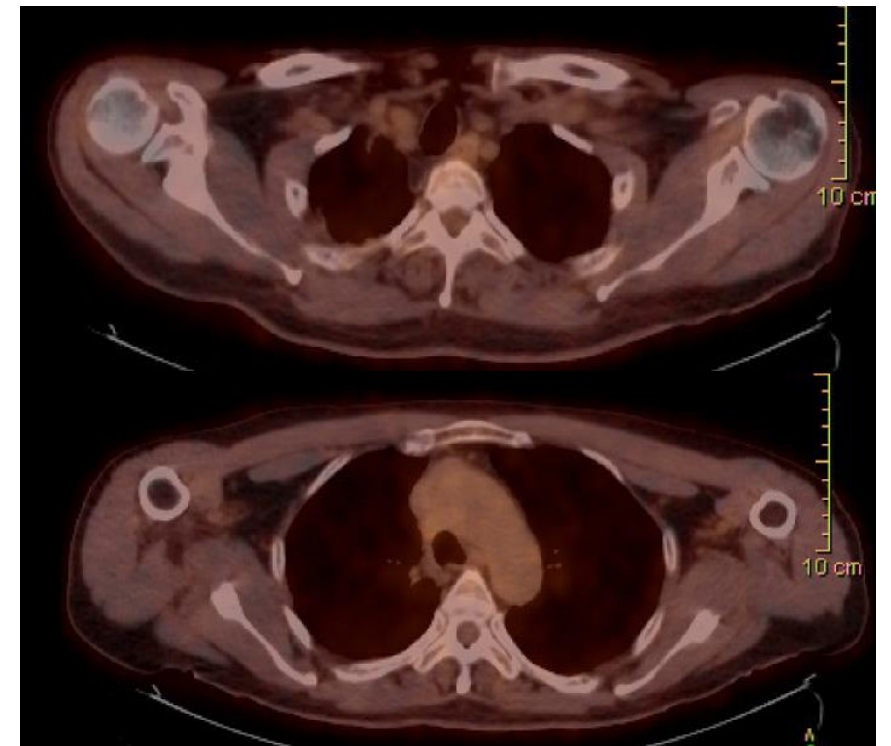


Case 6. (RULobectomy, pCR)

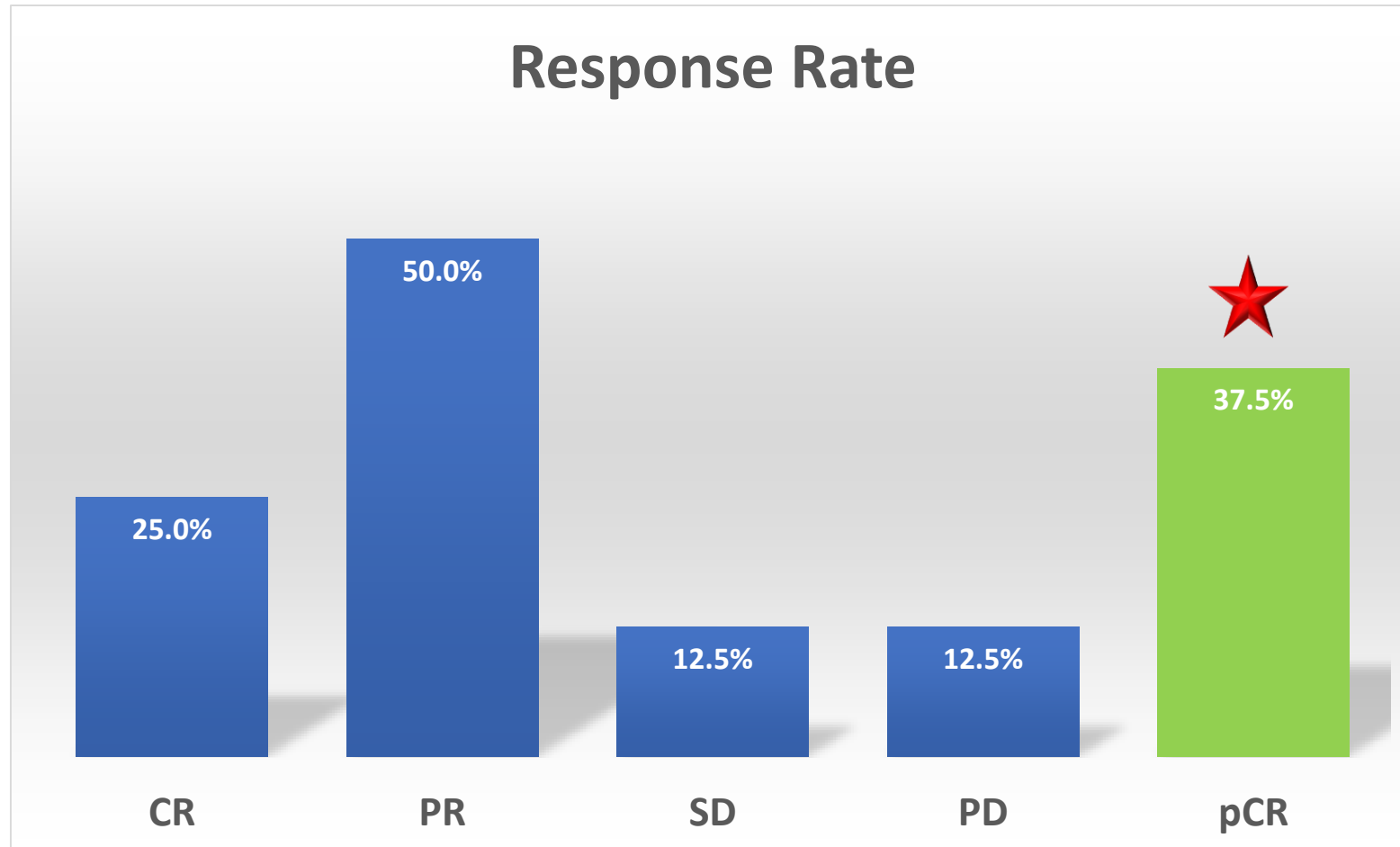
- m/73
- adenoca. LUL, T1bN2M0, SP263 70%



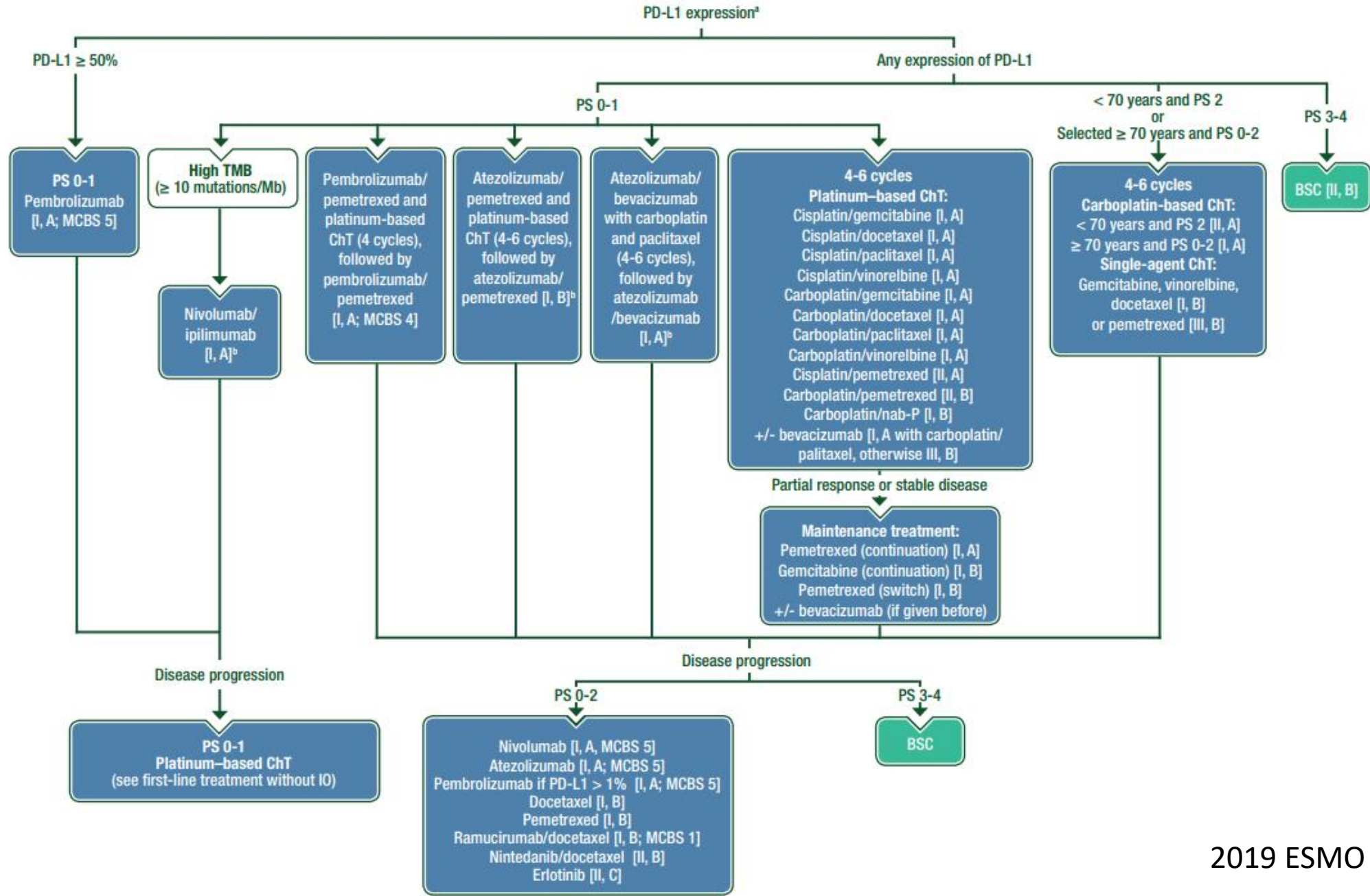
nivolumab-pem-carbo



Results 10-10 or 10-chemo



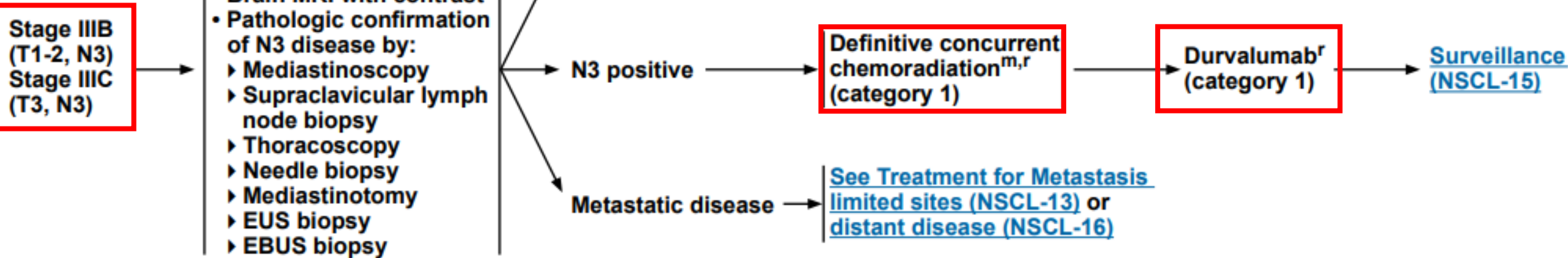
Stage IV NSCC: Molecular tests negative (ALK/BRAF/EGFR/ROS1)



CLINICAL ASSESSMENT

PRETREATMENT EVALUATION

INITIAL TREATMENT





감사합니다.

Sung Yong Lee, M.D.,



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