The Principles of Chemotherapy in Stage IV NSCLC

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2. Checklists before chemotherapy
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Introduction : Guideline adherence

Schulkes, K. J. G., et al. (2018). "Multidisciplinary decision-making regarding chemotherapy for lung cancer patients-An age-based comparison." Eur J Cancer Care (Engl) **27**(1).

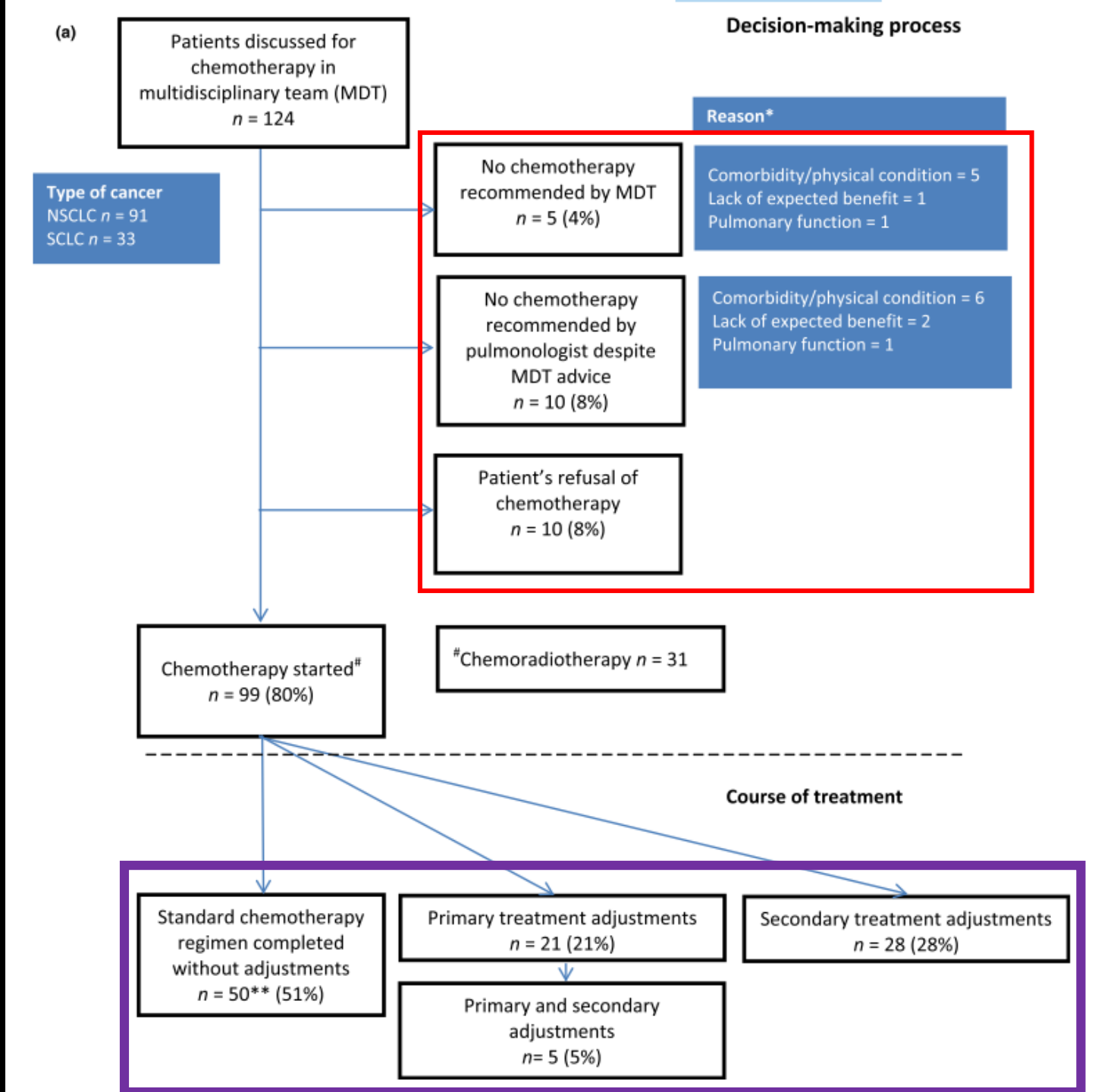
Newly diagnosed lung cancer

Multidisciplinary decision-making team (MDT)

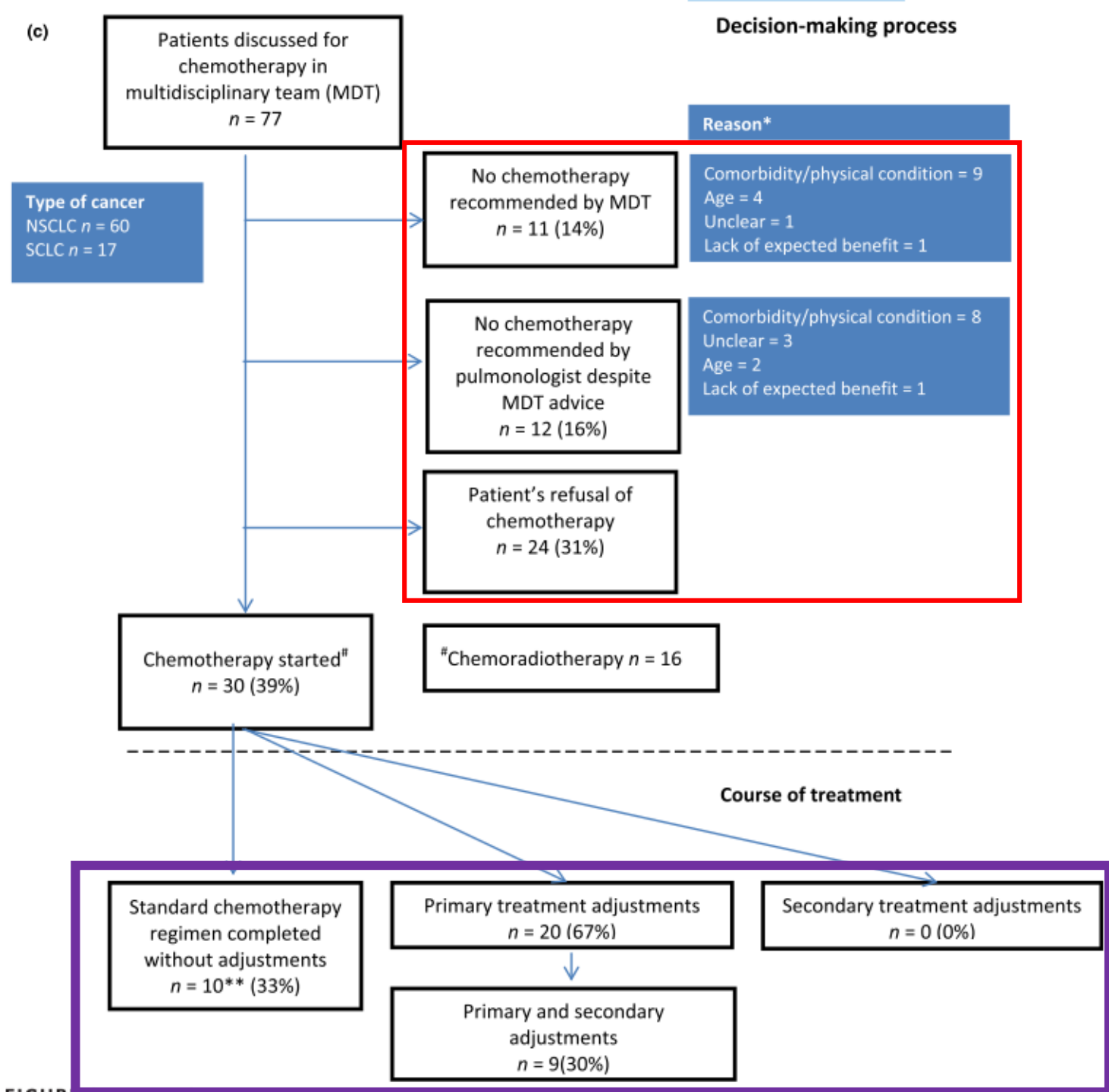
Thoracic oncologist (pulmonologist) and Patient

Final decision

Chemotherapy <65 years old



Chemotherapy >75 years old



Guideline adherence

- All : 29% (n = 85) of all patients
  - 40% (n = 50) for the youngest patients
  - 27% (n = 25) for the middle category
  - 13% (n = 10) of the elderly
- CCRT : 22 patients (32%) without treatment adaptations
- Unplanned Hospital admission
  - 49% in patients with a curative intent (n = 39)
  - 40% in patients with a palliative intent (n = 49)

Infections (n = 35)

Gastrointestinal toxicity (n = 13)

Haematologic toxicity (n = 12)

Introduction : Aim of Chemotherapy

In Advanced NSCLC

Palliative Chemotherapy

Life Extending Chemothearpy

Life Extending Chemotherapy

1st : Removal or controlling underlying disease
esp. pulmonary disease

2nd : Prevention of predictable deteriorating factors

3rd : Decision of 1st line regimen

4th : After PD-local therapy vs observation vs systemic chemoTx

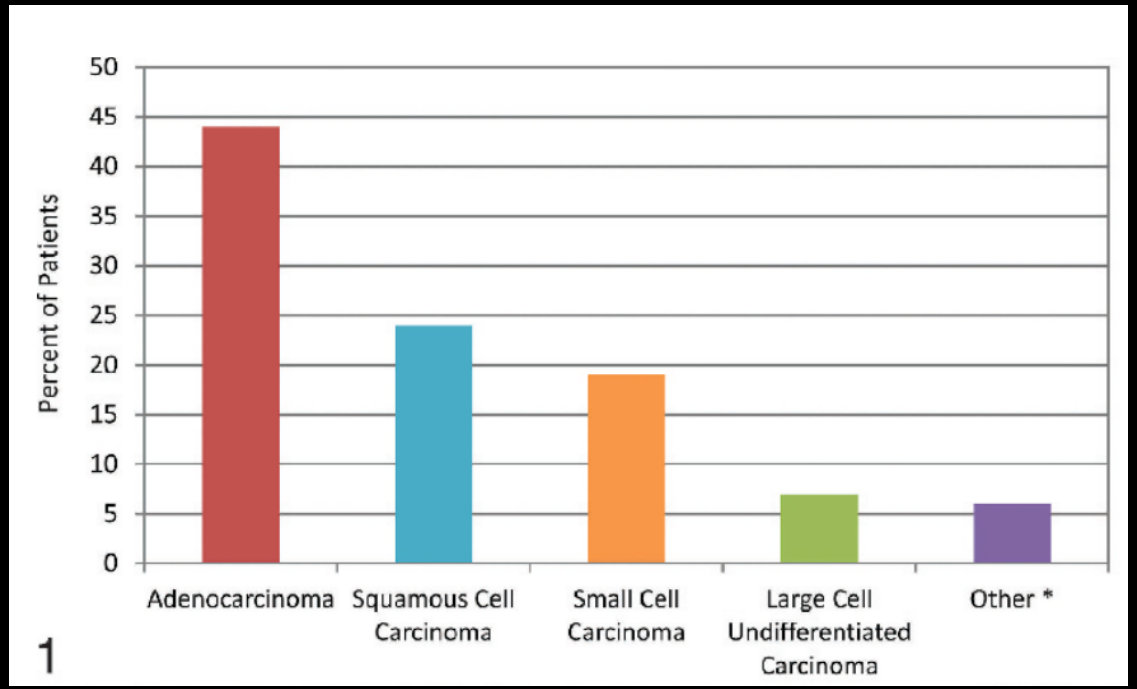
5th : when do we stop and wait?

Minimize adverse events

Cause of death : lung cancer

Nichols, L., et al. (2012). "Causes of death of patients with lung cancer." Arch Pathol Lab Med **136**(12): 1552-1557.

- EMR
- University of Pittsburgh Medical Center
- 100 cases of autopsies



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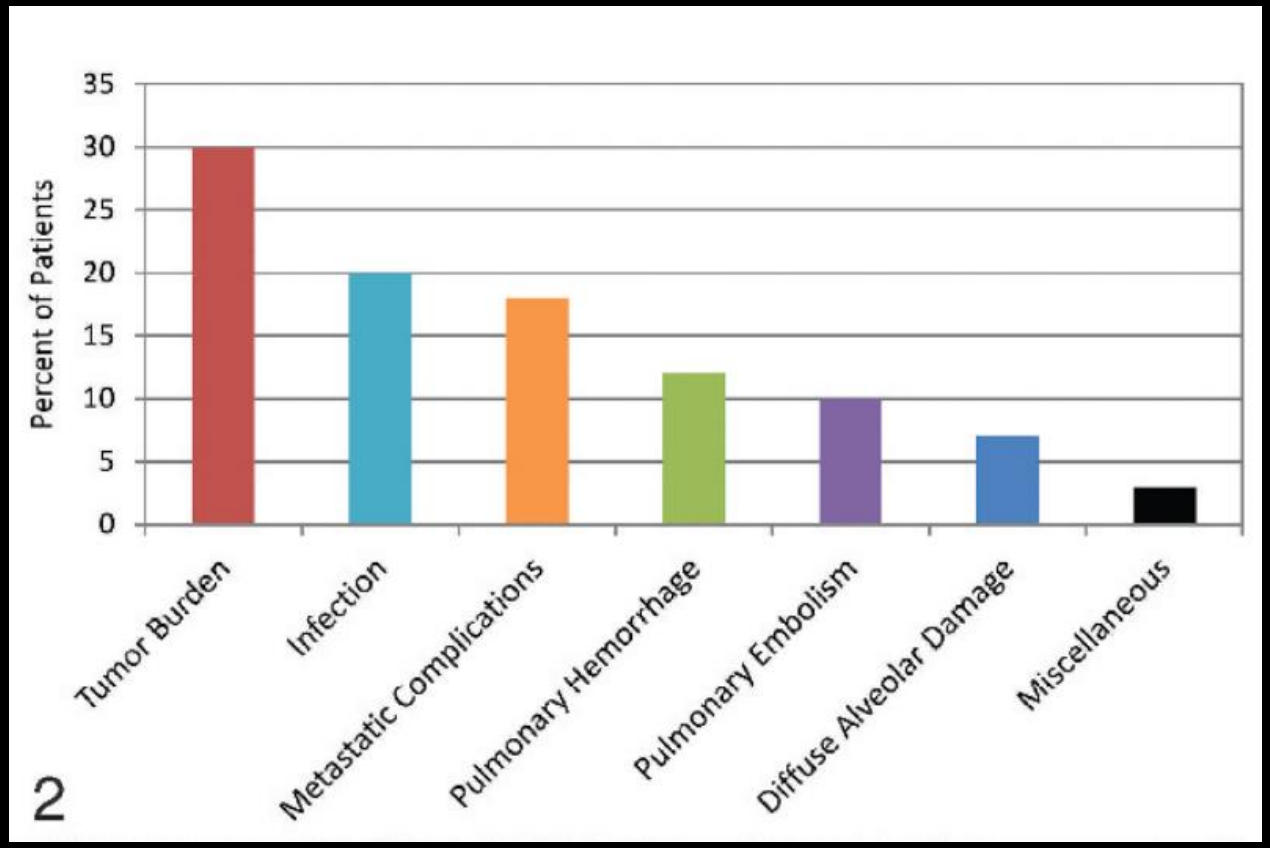


- Tumor related 45
- Infection 20
- 폐출혈
- 폐색전증
- DAD

Cause of death : lung cancer

Nichols, L., et al. (2012). "Causes of death of patients with lung cancer." Arch Pathol Lab Med **136**(12): 1552-1557.

- Emphysema , COPD, pulmonary fibrosis 48
- Infection 24
- Pneumonectomy or lobectomy 16
- Radiation 9
- Chemotherapy 7
- MI 6
- CI 3

Table 2. Contributing Causes of Death

Contributing Causes of Death	Cases, No.
Emphysema	30
Infection	24
Organ failure	23
Pneumonectomy or lobectomy	16
Pulmonary edema	15
Pulmonary thromboembolism	12
Pulmonary fibrosis, tumor burden	10 each
Radiation	9
Chronic obstructive pulmonary disease	8
Chemotherapy	7
Myocardial infarction	6
Diffuse alveolar damage	5
Pulmonary hemorrhage, marantic endocarditis	4 each
Hemorrhage, hypercoagulable state of malignancy, coagulopathy, anticoagulation, cardiopulmonary arrest	3 each
Anoxic encephalopathy, cerebral infarcts, second lung cancer, anemia, diverticulitis, pneumothoraces	2 each
Pleural effusions, hemothoraces, hepatic cirrhosis, brain metastasis, intestinal perforation, colonic dilatation, patent foramen ovale, intracardiac right-to-left shunt, Alzheimer disease, heavy narcotic use, extracorporeal membrane oxygenation, atrial fibrillation, left vocal cord paralysis, surgical manipulation of a leg, chronic steroid therapy, chest tube, hemiparesis, hyperkalemia, lumbar spinal cord compression, morbid obesity and diabetes mellitus	1 each

Underlying comorbidities

Lung

- COPD/Asthma
- ILD
- Destructive lung
- TB/NTM

Cardiovascular disease

- Ischemic heart disease
- Heart failure
- Arrhythmia
- Stroke

Kidney

- Renal insufficiency

Liver

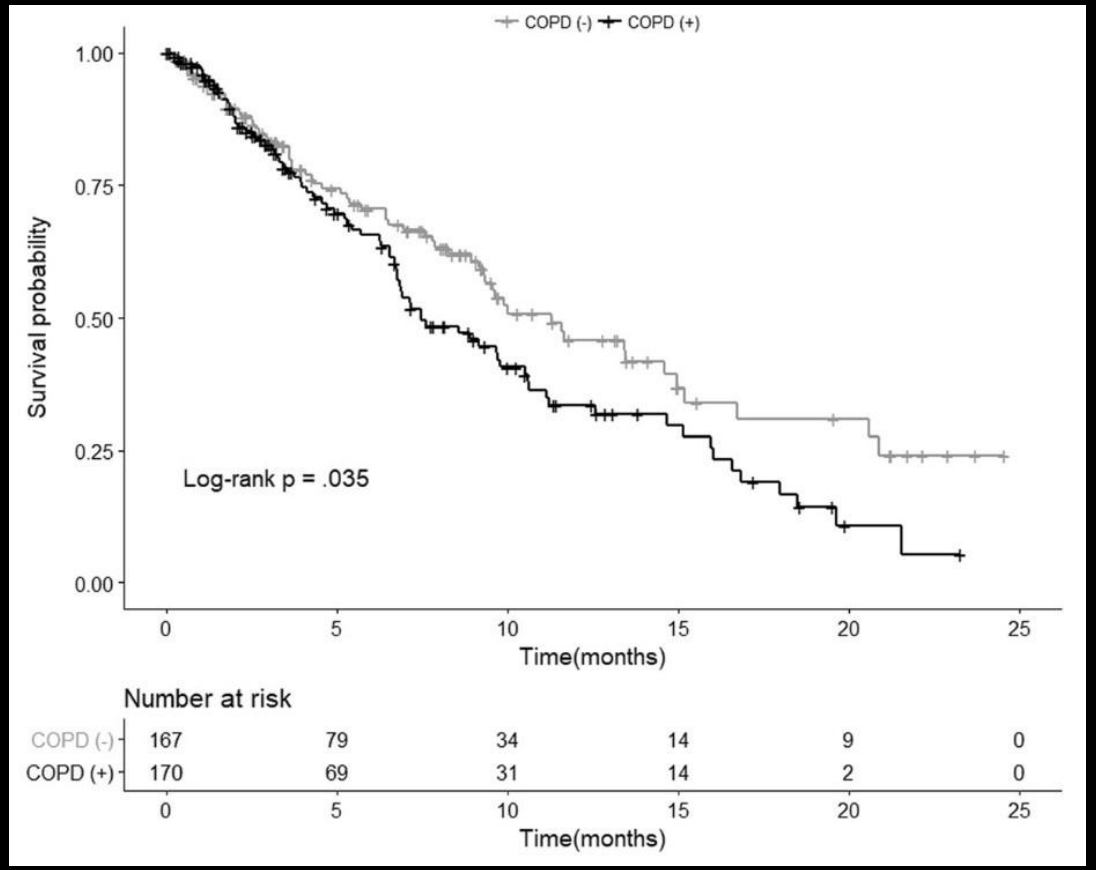
- Viral hepatitis

Connective tissue disease

- Rheumatoid arthritis
- Sjögren's syndrome

COPD : Mortality

Yi, Y. S., et al. (2018). "Effect of COPD on symptoms, quality of life and prognosis in patients with advanced non-small cell lung cancer." BMC Cancer 18(1): 1053.



COPD : Underdiagnosis

Zhang, J., et al. (2013). "Prevalence of undiagnosed and undertreated chronic obstructive pulmonary disease in lung cancer population." Respirology **18**(2): 297-302.

Table 4 Comparisons of the appropriateness of management for chronic obstructive pulmonary disease (COPD) in patients with lung cancer between respiratory doctors and non-respiratory doctors

Clinical setting	Respiratory department	Non-respiratory departments	*P*-value
Recorded diagnosis of COPD (*n*/total (%))	32/92 (34.8)	18/613 (2.9)	<0.001
Subjects receiving GOLD-recommended treatment for stable COPD (*n*/total (%))	13/70 (18.6)	161/573 (28.1)	0.09
Subjects receiving GOLD-recommended treatment for acute exacerbation (*n*/total (%))	14/22 (63.6)	15/40 (37.5)	0.048

GOLD, Global Initiative for Chronic Obstructive Lung Disease.

DLCO : Independent prognostic marker

Liptay, M. J., et al. (2009). "Diffusion lung capacity for carbon monoxide (DLCO) is an independent prognostic factor for long-term survival after curative lung resection for cancer." J Surg Oncol **100**(8): 703-707.

A DLCO <40% best predicted decreased survival from causes other than cancer within stage I lung cancers

Dimopoulou, I., et al. (2002). "A prospective study of pulmonary function in patients treated with paclitaxel and carboplatin." Cancer 94(2): 452-458.

The combination of paclitaxel with carboplatin induced an isolated decrease in DLCO level in the absence of clinical or radiologic evidence of toxicity.

ILD : Risk factor

- Cho, J. Y., et al. (2018). "Characteristics, incidence, and risk factors of immune checkpoint inhibitor-related pneumonitis in patients with non-small cell lung cancer." Lung Cancer 125: 150-156.

Table 2. Risk factors of ICI-related pneumonitis

Variable	Univariate		Multivariate		
	OR	95% CI	OR	95% CI	P
Age ≥ 70 years	2.76	1.11-6.85	1.87	0.69-5.05	0.218
Interstitial lung disease	7.83	1.80-34.08	6.03	1.19-30.45	0.030
Extrathoracic metastasis	0.33	0.13-0.86	0.34	0.13-0.92	0.034

OR, odds ratio; CI, confidence interval

Stroke

Data of 20,707 subjects with cancer vs 675,594 without cancer for 7 follow-up years

Jang, H.-S., et al. (2019). "The Long-Term Effect of Cancer on Incident Stroke: A Nationwide Population-Based Cohort Study in Korea." **10**(52).

	Cancer group	Non-cancer group	*P* [a]	Cause-specific HR	*p*
ORIGINAL COHORT	**(*n* = 20,707)**	**(*n* = 679,594)**			
Any stroke*	3.43 (3.18, 3.68)	1.07 (1.05, 1.10)	<0.0001	1.35 (1.25, 1.46)	<0.0001
Ischemic stroke	3.10 (2.87, 3.35)	0.91 (0.89, 0.93)	<0.0001	1.39 (1.28, 1.51)	<0.0001
Hemorrhagic stroke	0.46 (0.38, 0.57)	0.21 (0.20, 0.22)	<0.0001	1.15 (0.93, 1.41)	0.2082
Death	21.96 (21.40, 22.53)	2.03 (2.00, 2.06)	<0.0001	4.84 (4.68, 5.02)	<0.0001
MATCHED COHORT	**(*n* = 20,707)**	**(*n* = 20,707)**			
Any stroke*	3.43 (3.18, 3.68)	3.04 (2.81, 3.28)	0.0220	1.29 (1.16, 1.43)	<0.0001
Ischemic stroke	3.10 (2.87, 3.35)	2.67 (2.45, 2.89)	0.0069	1.33 (1.19, 1.49)	<0.0001
Hemorrhagic stroke	0.46 (0.38, 0.57)	0.50 (0.41, 0.60)	0.6239	1.07 (0.81, 1.41)	0.6327
Death	21.96 (21.40, 22.53)	6.87 (6.53, 7.22)	<0.0001	3.60 (3.42, 3.80)	<0.0001

Stroke

Data of 20,707 subjects with cancer vs 675,594 without cancer for 7 follow-up years

TABLE 3 | Risk of stroke based on time since first cancer diagnosis.

Organ	Total		0–1 year		1–2 years		2–7 years	
	SubHR* (95% CI)	*P*	SubHR* (95% CI)	*P*	SubHR* (95% CI)	*P*	SubHR* (95% CI)	*P*
ISCHEMIC STROKE								
Lip, oral cavity, and pharynx	1.02 (0.69, 1.51)	0.9237	1.34 (0.30, 5.97)	0.7055	0.83 (0.35, 2.02)	0.6880	1.11 (0.70, 1.74)	0.6616
Digestive organs	1.13 (0.96, 1.33)	0.1510	3.33 (2.07, 5.37)	<0.0001	0.98 (0.60, 1.60)	0.9305	1.06 (0.87, 1.30)	0.5605
Respiratory/intrathoracic organs	1.29 (0.93, 1.78)	0.1304	5.03 (2.23, 11.35)	<0.0001	2.31 (0.92, 5.79)	0.0748	0.88 (0.57, 1.35)	0.5481
Thyroid/other endocrine glands	1.00 (0.45, 2.23)	>0.9999	1.00 (0.14, 7.11)	0.9993	1.01 (0.14, 7.17)	0.9931	1.00 (0.38, 2.68)	0.9940
Others	1.24 (1.02, 1.50)	0.0293	2.37 (1.44, 3.90)	0.0007	1.76 (1.04, 2.99)	0.0370	1.09 (0.87, 1.38)	0.4455
HEMORRHAGIC STROKE								
Lip, oral cavity, and pharynx	1.33 (0.30, 5.97)	0.7074	–	–	1.39 (0.31, 6.23)	0.6662		
Digestive organs	0.82 (0.55, 1.24)	0.3547	1.00 (0.32, 3.10)	>0.9999	1.58 (0.60, 4.16)	0.3510	0.79 (0.48, 1.31)	0.3638
Respiratory/intrathoracic organs	0.81 (0.39, 1.70)	0.5838	6.01 (0.72, 49.84)	0.0969	2.46 (0.22, 27.09)	0.4633	0.47 (0.17, 1.32)	0.1525
Thyroid/other endocrine glands	1.00 (0.20, 4.96)	0.9994	–	–	1.01 (0.14, 7.13)	0.9963		
Others	1.13 (0.69, 1.86)	0.6155	1.33 (0.30, 5.96)	0.7062	2.14 (0.54, 8.57)	0.2815	1.10 (0.63, 1.94)	0.7358

*SubHR, subdistribution hazard ratio. *Reference group is matched control.*

HBV hepatitis

예방적 항바이러스 치료의 적응증 및 재활성화 위험도 분류

가. HBsAg(+) 또는 HBV-DNA(+)로서 B형간염 재활성화 위험이 중등도·고위험군에 해당하는 항암화학요법(cytotoxic chemotherapy) 또는 면역억제요법을 받는 환자에게 투여 시 : 해당 요법 시행 동안 및 요법 종료 후 6개월까지

나. anti-HBc(+)로서 rituximab을 포함하는 요법을 투여하는 환자에게 투여 시 : 해당 요법 시행 동안 및 요법 종료 후 12개월까지

다. HBsAg(-), HBV-DNA(-), anti-HBc(+)로서 조혈모세포이식을 받는 만성 B형간염 환자에게 투여 시 : 총 18개월 투여까지

라. anti-HBc(+)인 공여자로부터 간을 공여 받는 수혜자로서 human anti-hepatitisB immunoglobulin 제제를 투여하지 않는 환자에게 투여 시 : 면역억제 요법 시행 동안 및 요법 종료 후 6개월까지

마. 허가사항을 초과하여 B형간염 예방요법으로서 아래와 같은 기준으로 투여 시 약값 전액을 환자가 부담토록 함.

1) 가, 나, 다 및 라 항의 각 투여기간 이후

2) HBsAg(+) 또는 HBX-DNA(+)로서 B형간염 재활성화 위험이 저위험군에 해당하는 항암화학요법(cytotoxic chemotherapy) 또는 면역억제요법을 받는 환자에게 투여하는 경우

사용 가능 약제: **LAM, CLV, L-dT, ADV, ETV, TDF** 중 하나를 사용할 수 있다.

HBV hepatitis

저위험군 항암제

traditional immunosuppressants	azathioprine, 6-mercaptopurine, methotrexate
표적치료제 등(EGFR/HER2/JAK/VEGF inhibitors 등)	cetuximab, erlotinib, trastuzumab, ruxolitinib, bevacizumab
TKI 억제제	sorafenib
Antimetabolites	fluorouracil
4주 이내 경구 스테로이드 사용 (용량 무관)	-
4주 이상 저용량 스테로이드	-

중등도 위험군 : 10~20mg/day ≧4weeks corticosteroid, prednisolone

Renal insufficiency

- Cisplatin
  - CrCl 46–60 mL/min, 50 % of full dose
  - CrCl 31–45 mL/min, 25 % of full dose
  - CrCl ≤ 30 mL/min, omit
- Carboplatin
  - CrCl < 30 mL/min, omit
- Etoposide
  - CrCl > 15–50 mL/min, 75% of full dose
  - CrCl < 15 mL/min, omit

Gemcitabine
- CrCl<30ml/min – consider dose reduction

- Pemetrexed
  - CrCl < 45 mL/min, omit
- Erlotinib
  - CrCl < 10 mL/min, omit
- Afatinib
  - CrCl 30-89 mL/min : No dosage adjustment necessary
  - CrCl 15-29 mL/min : 30 mg PO qDay
  - CrCl<15 mL/min : Not studied
- Osimertinib
  - CrCl 15-89 mL/min: No dose adjustment required
  - End-stage renal disease (ESRD): no recommend
- Gefitinib
  - not known
  - Patients with severe renal impairment should be treated with caution

- Vinorelbine
  - No adjustment is required
- Taxane
  - No adjustment is required
- Nivolumab
  - No adjustment is required
- Pembrolizumab
  - CrCl < 15 mL/min not known

Sci. Pharm. 2017

Checklists before chemotherapy

- Tumor characteristics : cell type, biomarker
- Tumor location, LN location, mets site
- Performance status
- Emergency Treatments : brain mets, spine mets, SVC syndrome
- Underlying comordities : COPD, CVD, autoimmune disease

Tumor characteristics

Cell type

- Squamous cell carcinoma
- Adenocarcinoma
- Adenosquamous cell carcinoma
- Large cell carcinoma
- Sarcomatoid carcinoma

EGFR mutation

ALK variants

ROS1

BRAF

RET

PD-L1 (22C3, SP263, SP142)

Special conditions

- With small cell differentiation
- Double or triple primary lung cancer with different cell types
- Primary lung cancer and other cancer(ex, glottic cancer, bladder cancer, esophageal cancer..)
- Primary EGFR T790M positive

Decision of regimen

Chemotherapy in Stage IV NSCLC : 1st line

NSCLC

Squamous cell ca

Non-squamous
- Adenocarcinoma
- Large cell carcinoma
- etc

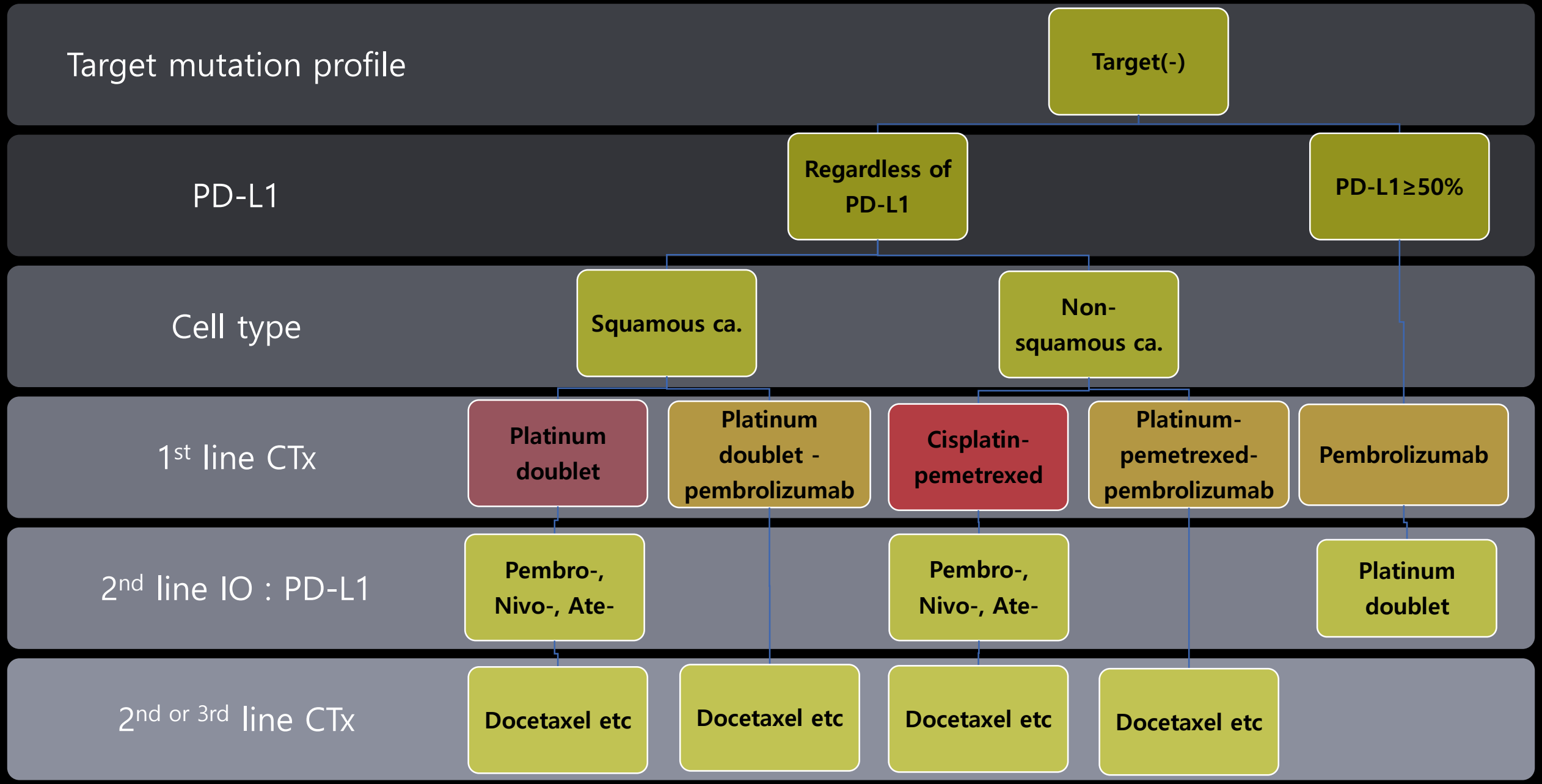
Immunologic predictor (PD-L1)
- 22C3
- Sp263
- sp142

Molecular target
- EGFR mutation
- ALK
- ROS1
- etc

None or less
- Platinum doublet
- Cisplatin-Pemetrexed(non-sq)
- Platinum doublet-pembro
- Beva+atezolizumab+carbo/taxol

High PD-L1 (22C3 or sp263 ≥ 50%)
- Pembrolizumab

Molecular target(+)
- EGFR-TKI (Osimertinib, Afatinib, Gefitinib, Erlotinib)
- Alectinib, Crizotinib, Ceritinib


Target mutation profile
PD-L1
Cell type
1st line CTx
2nd line IO : PD-L1
2nd or 3rd line CTx
Target(-)
Regardless of PD-L1
PD-L1≥50%
Squamous ca.
Non-squamous ca.
Platinum doublet
Platinum doublet - pembrolizumab
Cisplatin-pemetrexed
Platinum-pemetrexed-pembrolizumab
Pembrolizumab
Pembro-, Nivo-, Ate-
Pembro-, Nivo-, Ate-
Platinum doublet
Docetaxel etc
Docetaxel etc
Docetaxel etc
Docetaxel etc

Chemotherapy in Stage IV NSCLC: 2nd line

Platinum doublet (gemcitabine)

Cisplatin-Pemetrexed(non-sq)

Platinum doublet-pembro

Beva+atezolizumab+carbo/taxol

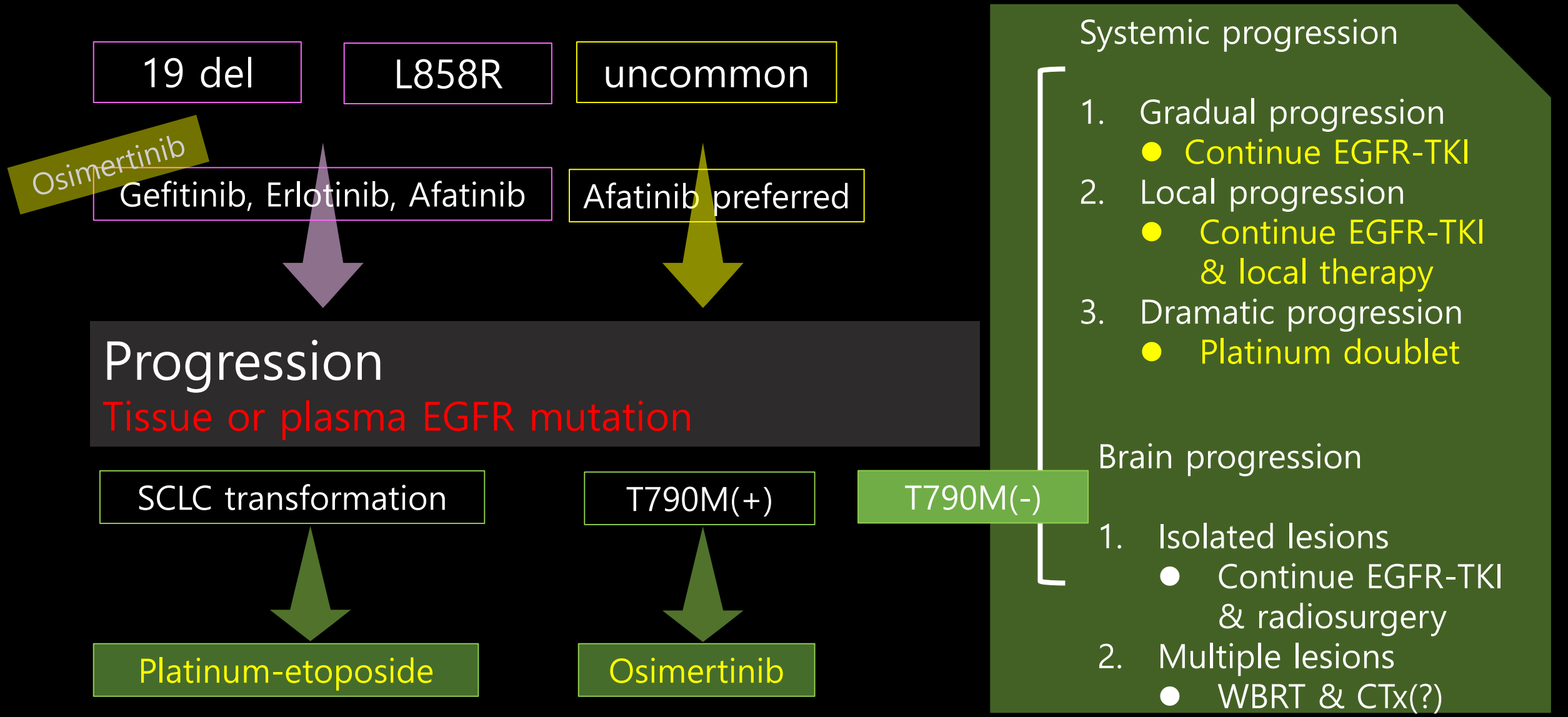
Immune checkpoint inhibitor

- Pembrolizumab(22c3 or SP263≥50%)
- Nivolumab(SP263≥10%)
- Atezolizumab (SP142≥5%)
- Pembrolizumab(22c3 or SP263≥1%)
- Nivolumab(no PD-L1)
- Atezolizumab(no PD-L1)

Cytotoxic Chemotherapy

- Taxane, Gemcitabine, Vinorelbine
- Pemetrexed

Nonsqumous NSCLC EGFRm +



1st line choice?

79/M

2017.5.31 흉통

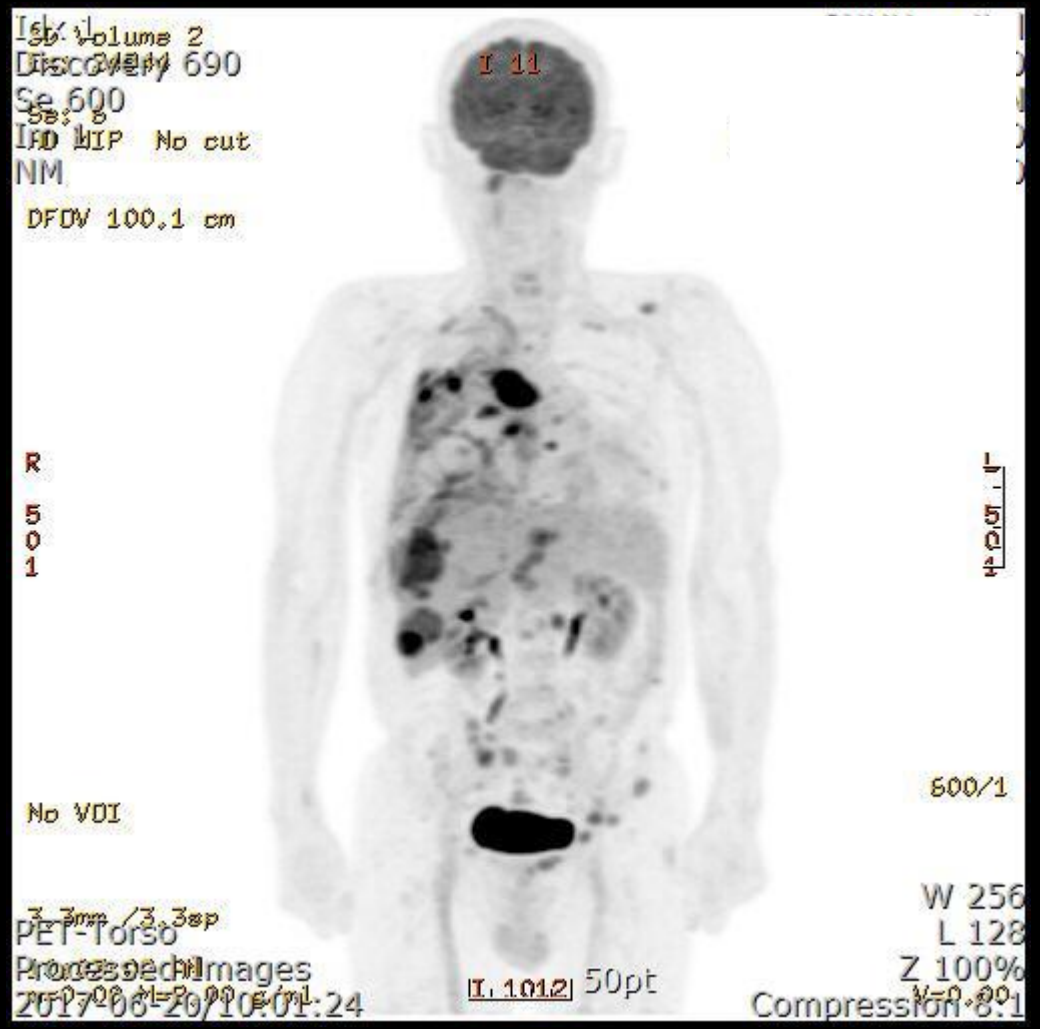
PCNB : RLL-large cell carcinoma

EGFR wild

ALK negative

High PD-L1

NSCLC T2aN2M1c IVB multiple bone mets

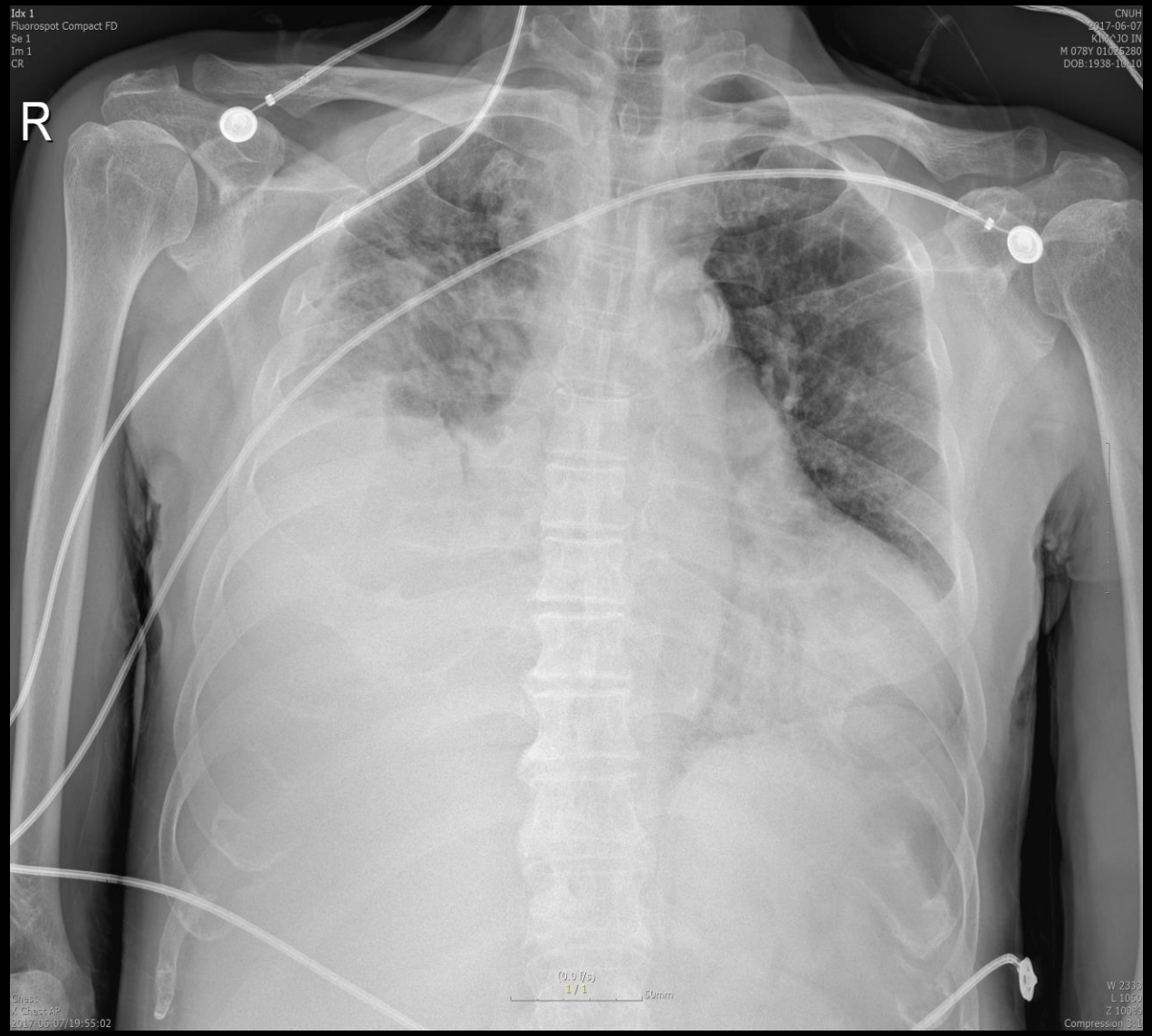


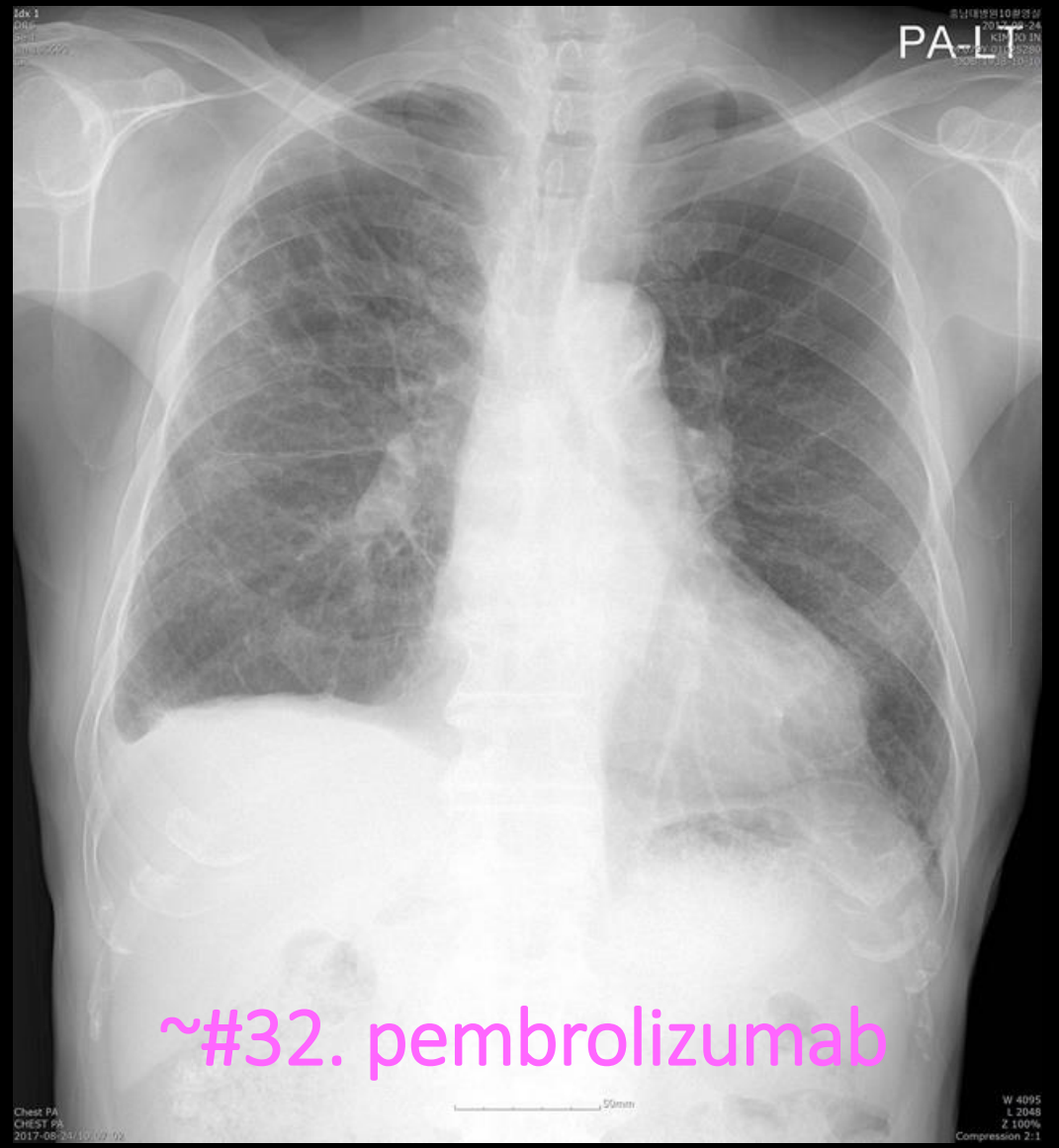
Consideration

- Highest response rate?
- Which one is more safe?
- After Tx, QOL of patients ?
- Duration of treatment (how long~~)

Guidelines

ECOG, PFTs, age, tumor location





After #1-3 pembrolizumab (200mg)

Keywords in advanced NSCLC_NCCN

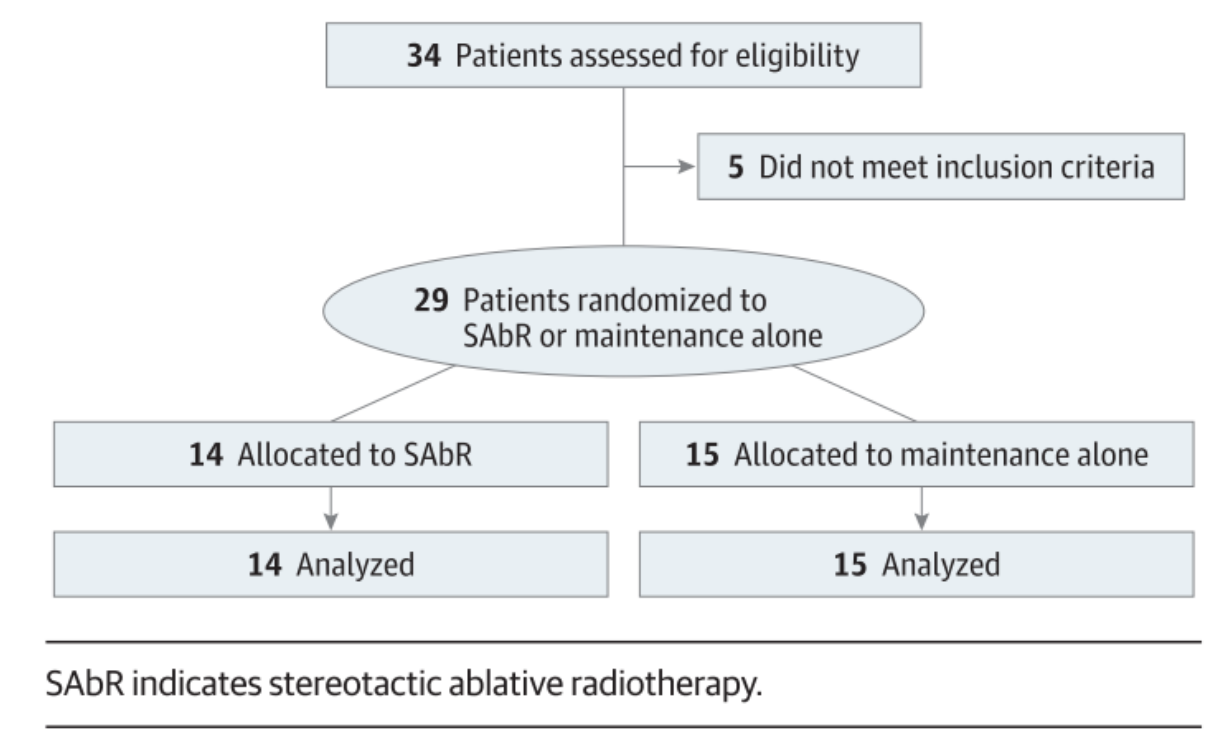
NSCL-C 5 of 10

- Advanced/Metastatic NSCLC (Stage IV)
  - Bullet 2 modified: "Definitive RT to oligometastases *(limited number is not universally defined but clinical trials have included up to 3–5 metastases),* particularly SABR, is an appropriate option in such cases if it can be delivered safely to the involved sites. *In 2* randomized phase II trials, significantly improved progression-free survival was found for local consolidative therapy (RT or surgery) to oligometastatic lesions versus maintenance systemic therapy or observation for patients not progressing on systemic therapy ~~for local consolidative therapy.~~"
  - Bullet 3 added: "In the setting of progression at a limited number of sites on a given line of systemic therapy (oligoprogression), local ablative therapy to the oligoprogressive sites may extend the duration of benefit of the current line of systemic therapy."
  - Bullet 4 added: "When treating oligometastatic/oligoprogressive lesions, if SABR is not feasible, other dose-intensive accelerated/ hypofractionated conformal radiation therapy regimens may be used."

Definitive RT to oligometastases or oligoprogression

SABR in limited mets NSCLC

Iyengar, P., et al. (2018). "Consolidative Radiotherapy for Limited Metastatic Non-Small-Cell Lung Cancer: A Phase 2 Randomized Clinical Trial." JAMA Oncol **4**(1): e173501.

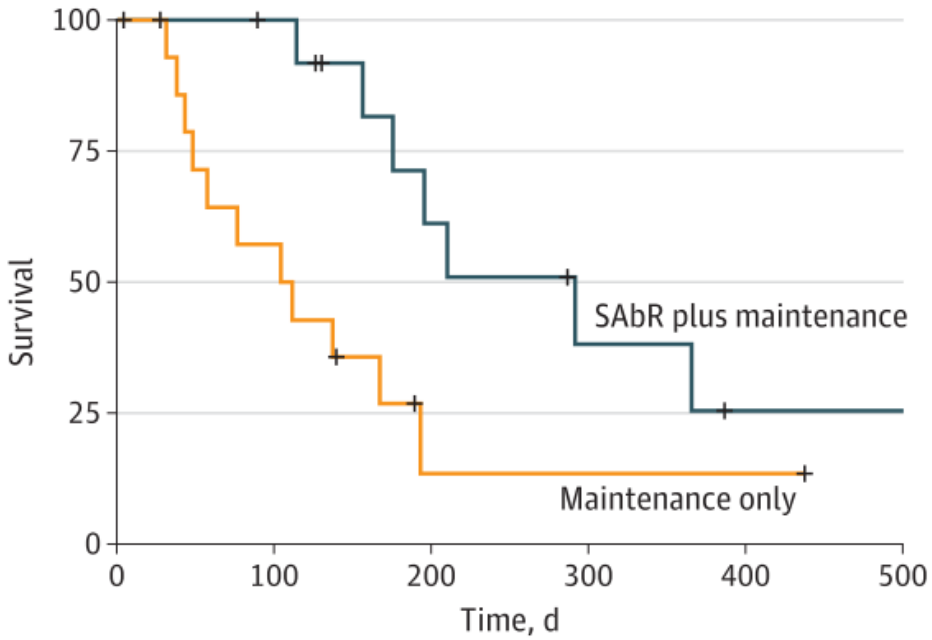


5 sites of extracranial

with no more than 3 sites in the liver

SABR is in the plan

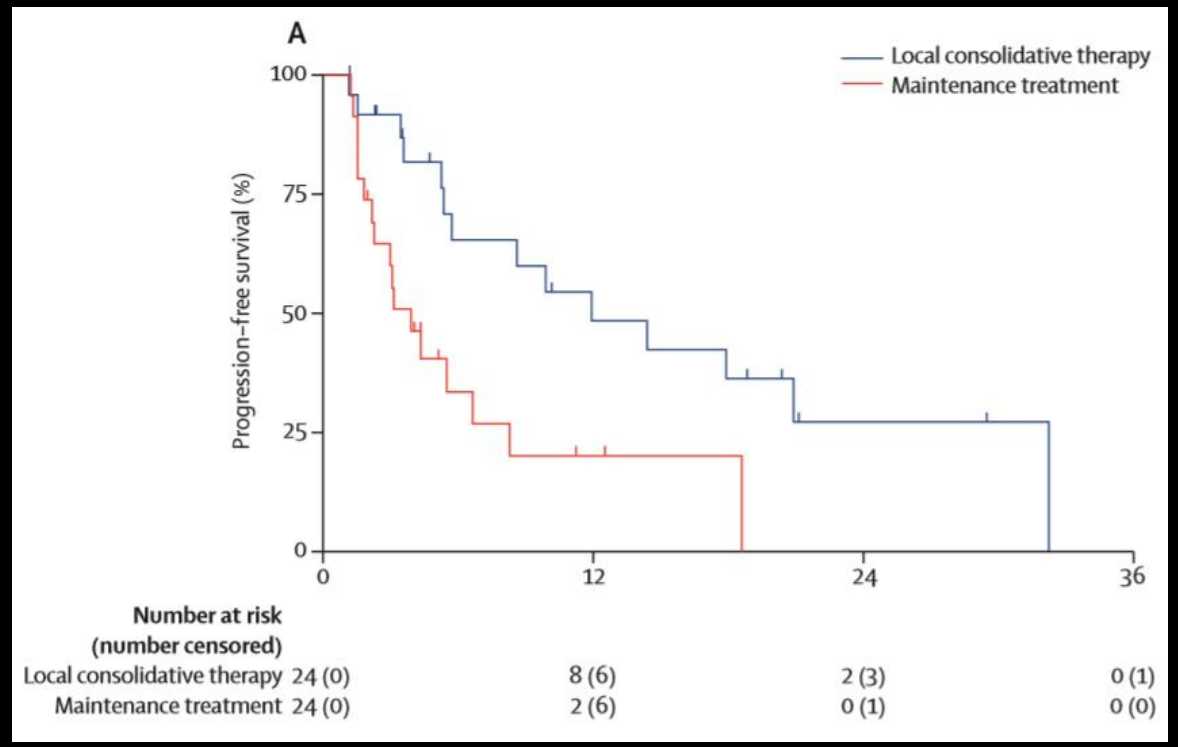
Figure 2. Analysis of Progression-Free Survival



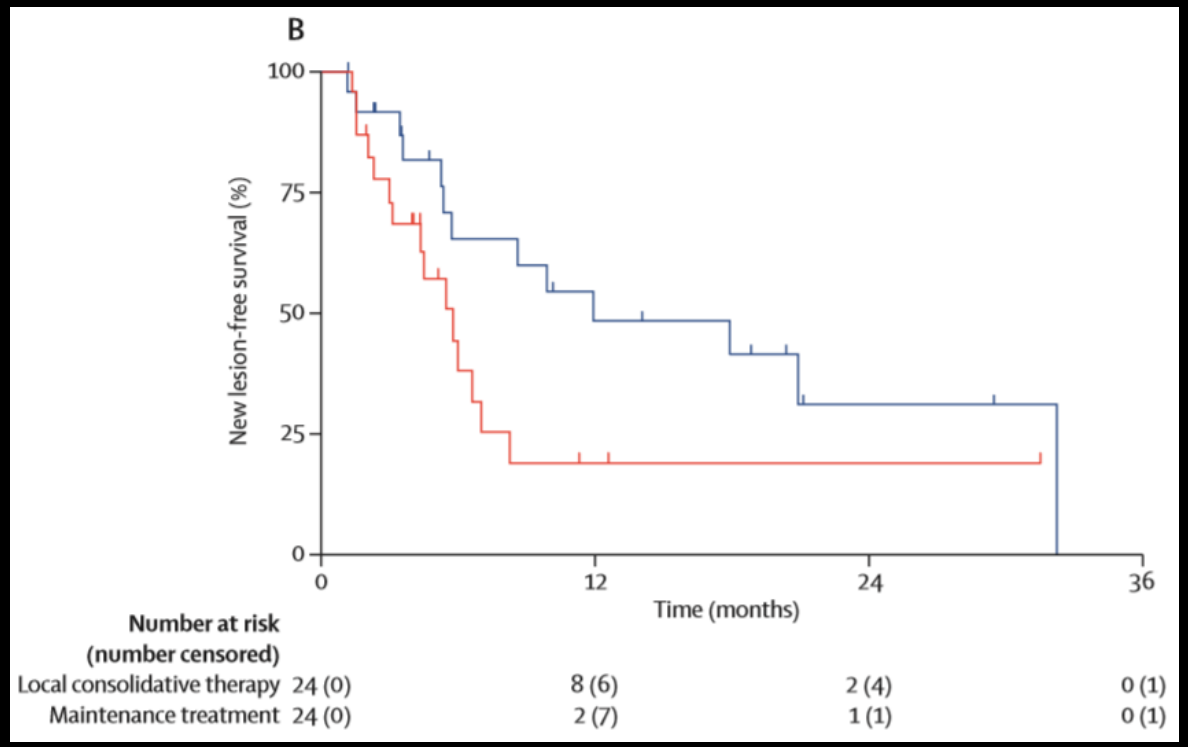
No. at risk					
SAbR plus maintenance	14	12	6	3	1
Maintenance only	15	8	1	1	1

Log-rank testing reveals a statistically significant benefit in progression-free survival for SAbR-plus-maintenance chemotherapy (hazard ratio, 0.304; 95% CI, 0.113-0.815; *P* = .01). SAbR indicates stereotactic ablative radiotherapy.

Gomez, D. R., et al. (2016). "Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study." Lancet Oncol 17(12): 1672-1682.



PFS (11.9 M vs 3.9 M, HR=0.35. p=0.0054)



New lesions free survival

Chemotherapeutics

- Platinum (cisplatin/carboplatin)
- Gemcitabine, taxane, vinorelbine,
- Pemetrexed
- Immune checkpoint inhibitors (pembrolizumab, atezolizumab, nivolumab, durvalumab)
- EGFR TKI (1^{st}/2^{nd}/ 3^{rd} generation)
- ALK inhibitors (alectinib, crizotinib, ceritinib)
- Anti-VEGF : bevacizumab, ramucirumab

Chemotherapeutics : Platinum

Cisplatin

- 60~75 mg/m^2

Carboplatin

- AUC 4-6
- Maximum dose
  - ✓AUC 4 : 600mg
  - ✓AUC 5 : 750mg
  - ✓AUC 6 : 900mg

Cisplatin-vinorelbine
Cisplatin pemetrexed in Korea
Cisplatin etoposide

http://ctep.cancer.gov/content/docs/Carboplatin_Information_Letter.pdf

Chemotherapeutics : Pemetrexed

- Cisplatin + pemetrexed – pemetrexed maintenance
- Single pemetrexed
- Pre and post dexamethasone-the reason why?
- Folic acid ? 400 mcg but,

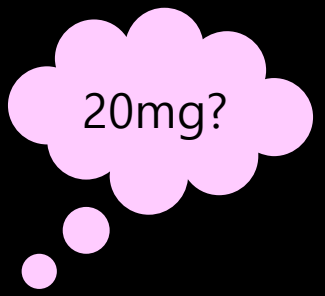
  low-dose oral folic acid preparation or multivitamin with folic acid on a daily basis
- Vitamin B12 : 1000 mcg IM

Chemotherapeutics : Pemetrexed

Immediatly	Early	Late
Hypersensitivity (1%)	Rash (14%)	Neuropathy (9%)
Nausea/vomiting (31%)	Abdominal pain	Thromboembolism
Constipation (6%)	Mucositis (esophagitis..) (15%)	Pneumonitis
Anorexia (22%)	Alopecia (6%)	
Fatigue (34%)	Edema	
	Fatigue (30%)	
	Hepatitis (10%)	
	Myelosuppression ± infection, bleeding	

Chemotherapeutics : Taxane

- Paclitaxel, Docetaxel, Nab-paclitaxel
- 3 weeks or weekly
- Response rate : 20~35% with single
  30~50% with platinum + taxane
- Premedication : Avil, cimetidine, dexamethasone



Taxane : toxicities

Paclitaxel>>

Hypersensitivity Reaction
(4~10%)

Docetaxel>>

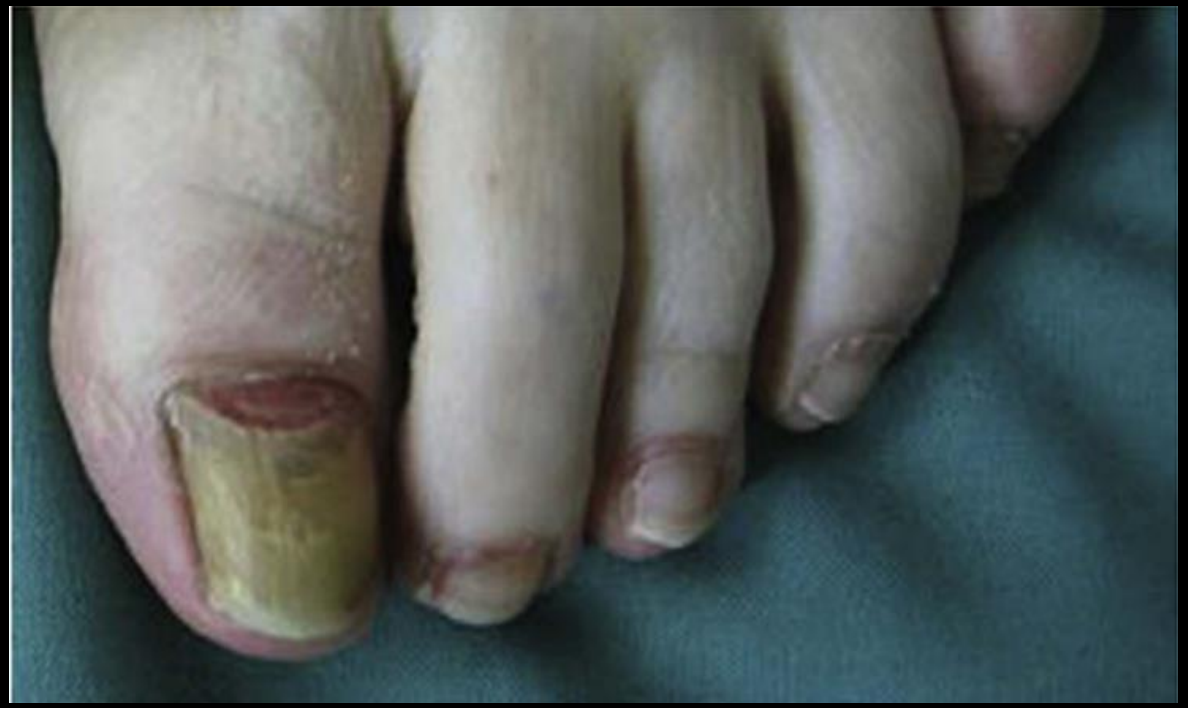
Bone marrow depression

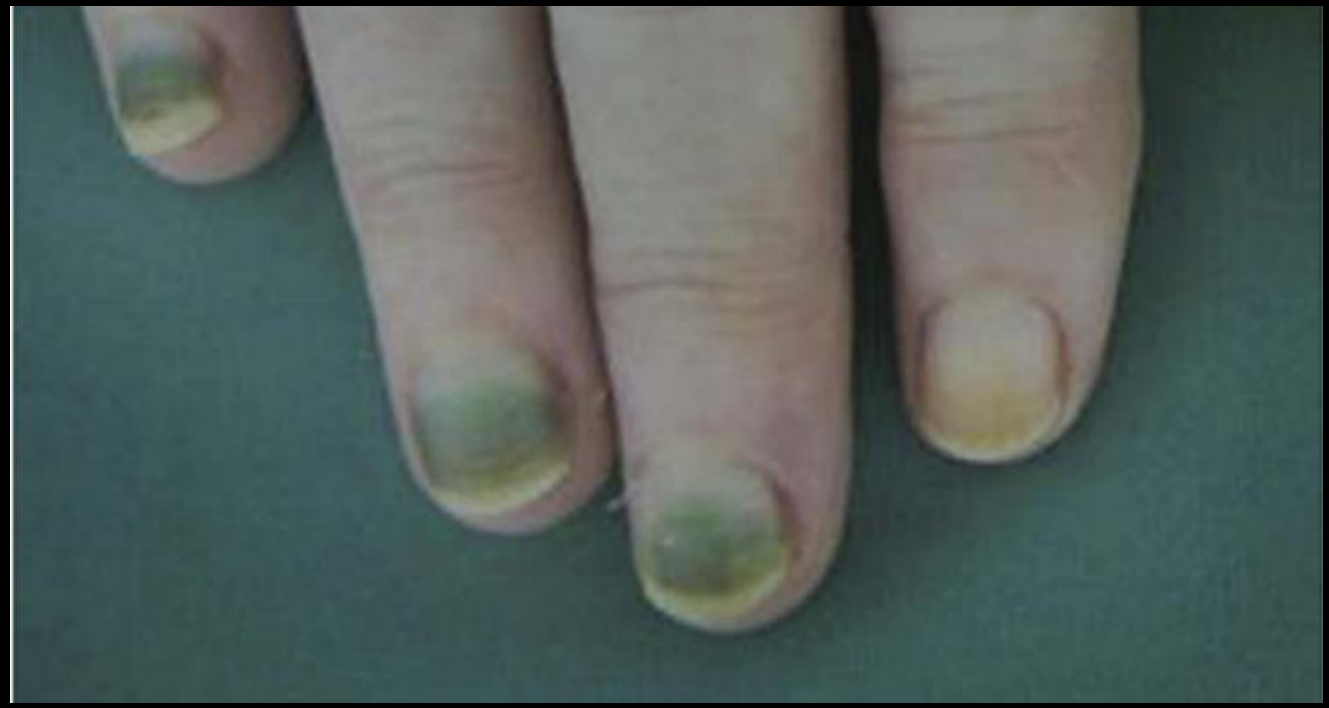
Esp, neutropenia

Alopecia

Peripheral sensory neuropathy

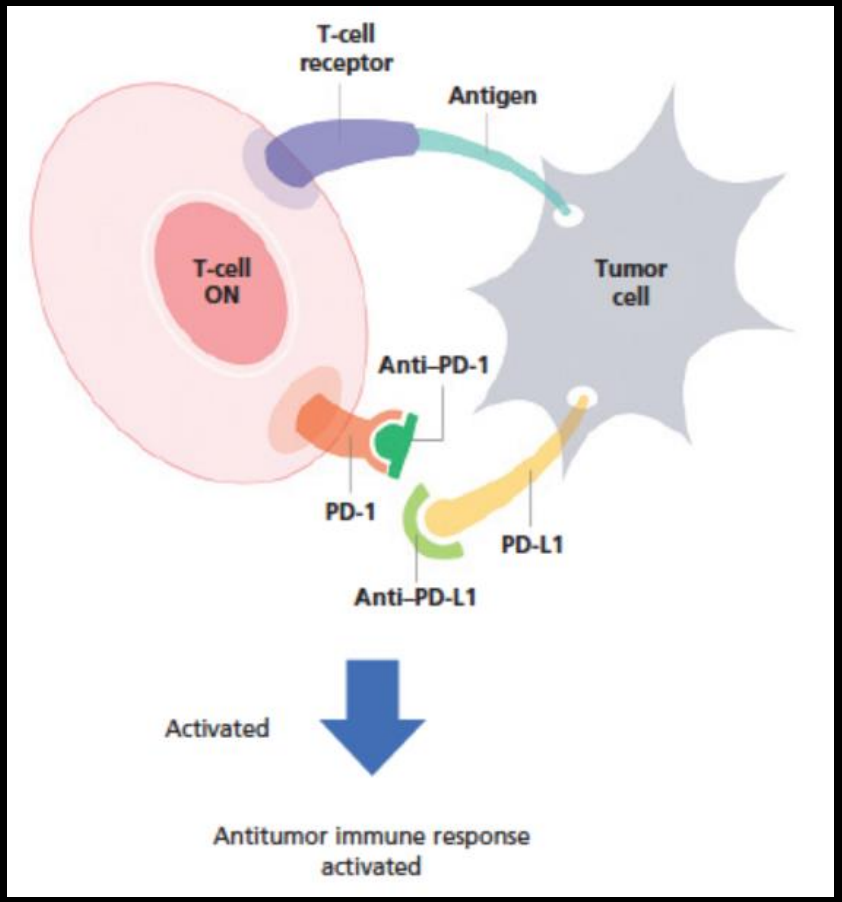
Nail toxicities
Fatigue
Fluid retention





Chemotherapeutics
Immune checkpoint inhibitors

- 1st line
  - Pembrolizumab PD-L1>50%
  - Pembrolizumab + platinum doublet
  - Atezolizumab + bevacizumab + platinum doublet
- 2n line
  - Atezolizumab
  - Nivolumab
  - Pembrolizumab

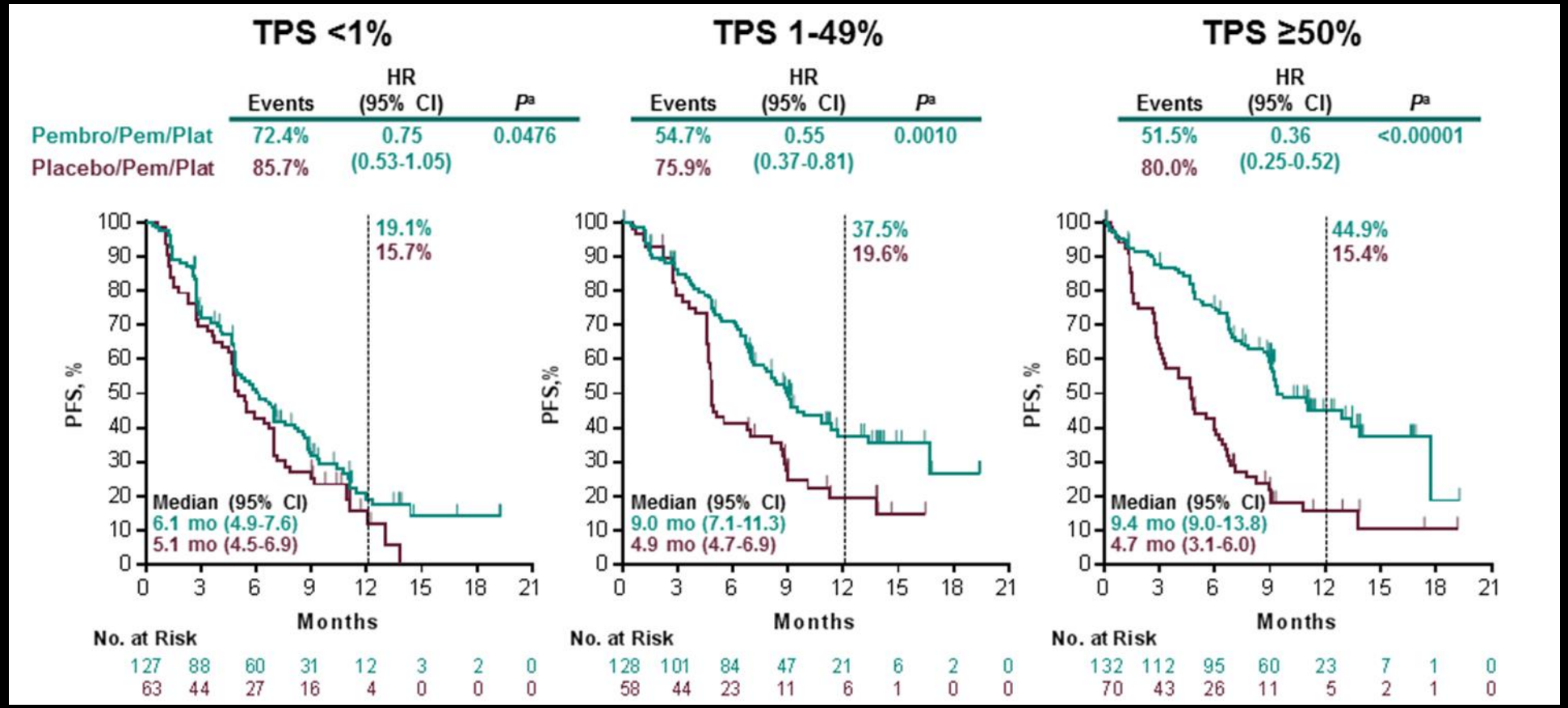


Cancer immunotherapy: PD-1 and beyond. www.smartpatients.com/targets/PD-1

Keynote 189

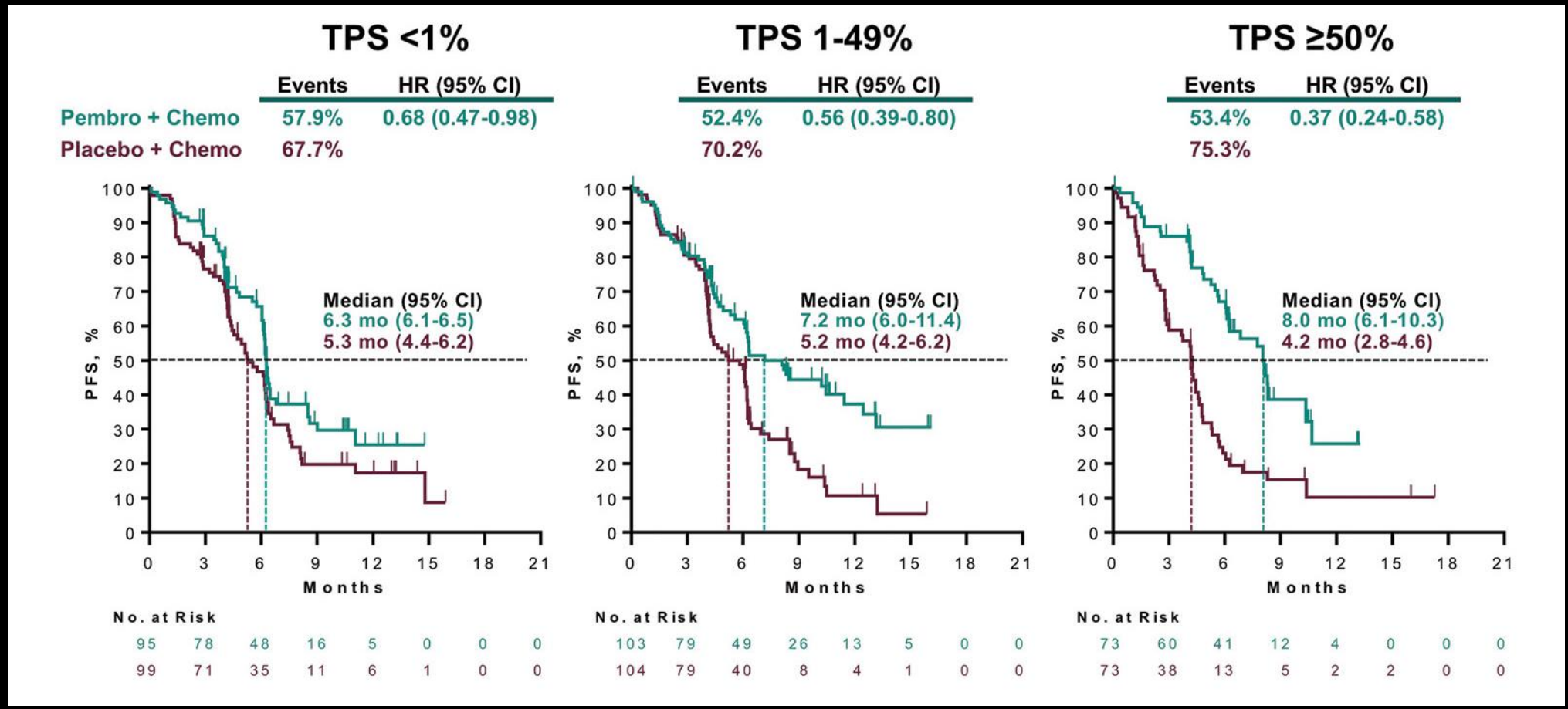
The Best IO regimen of 1st line

Platinum-pemetrexed-placebo vs Platinum-pemetrexed-pembrolizumab in non-squamous ca

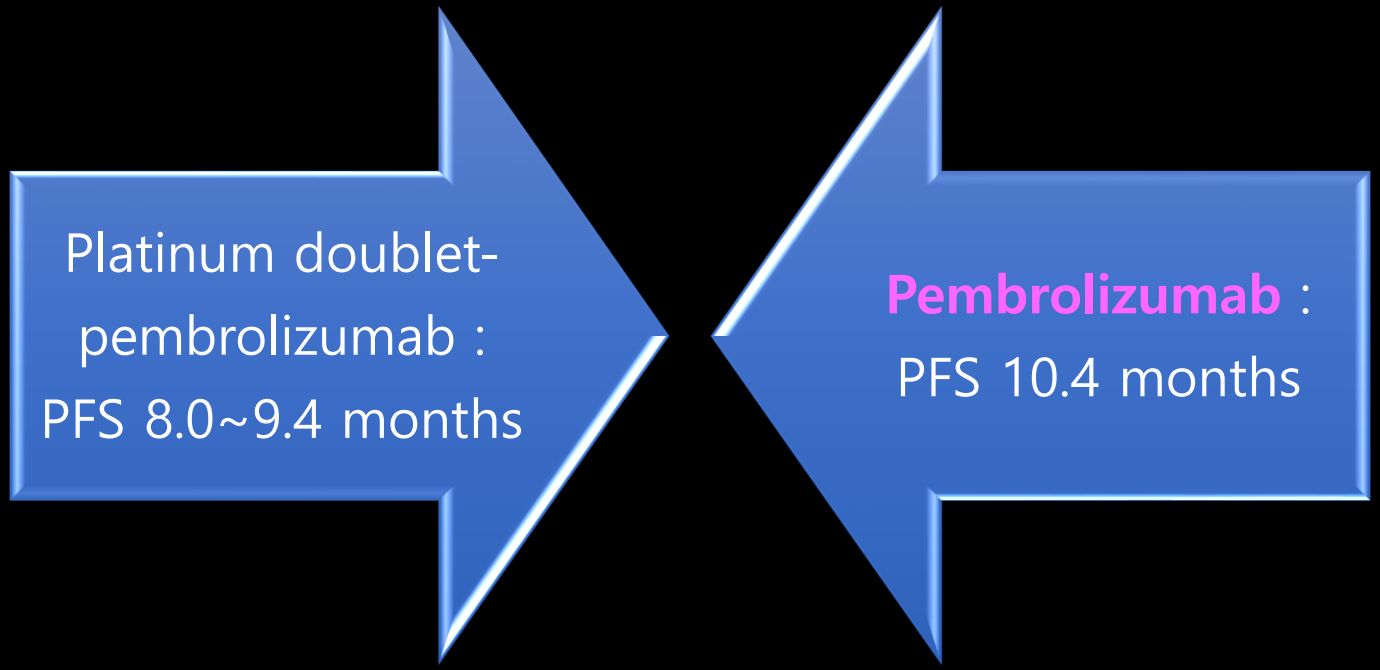


The Best IO regimen of 1st line

Keynote 407 : carbo-taxol-pembroilzumab vs carbo-taxol-placebo in squamous cell ca

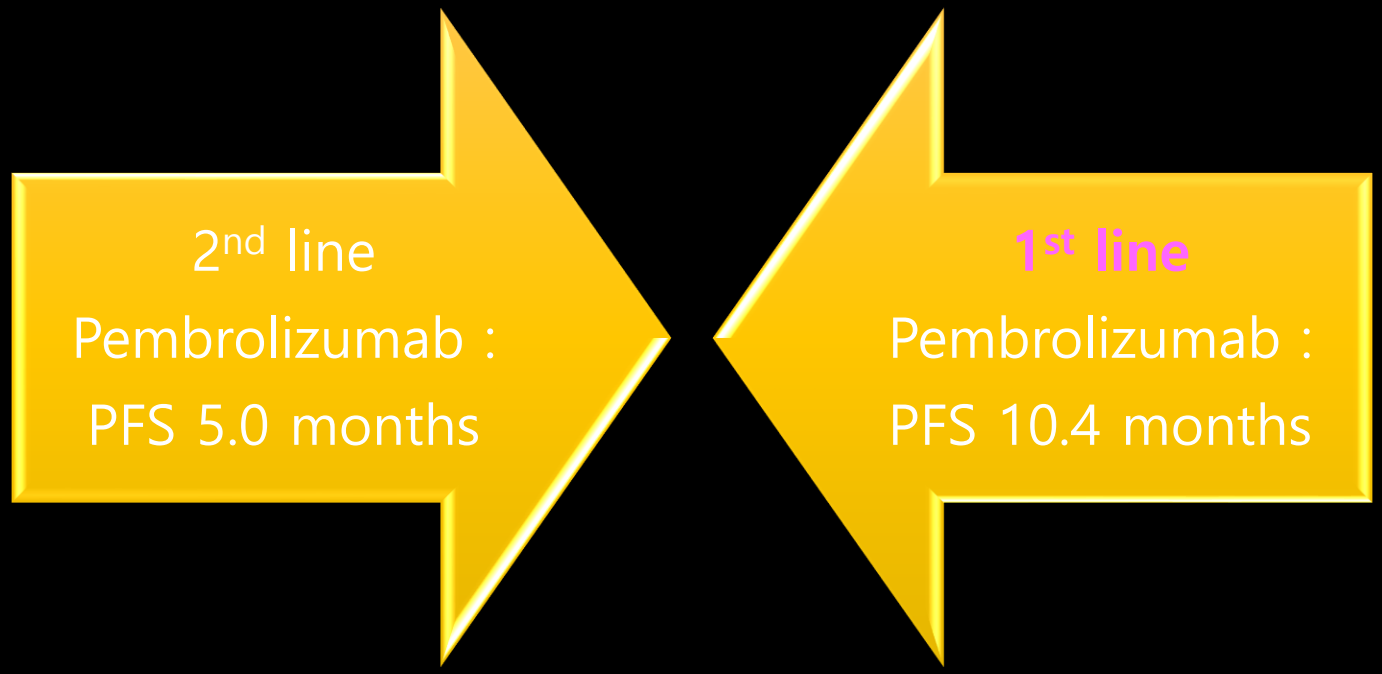


1st line If, PD-L1>50%

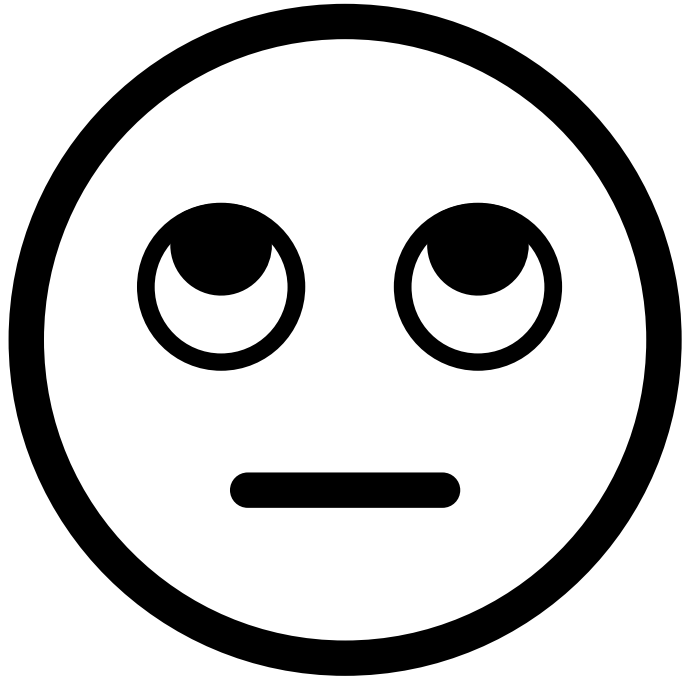


Single
Pembrolizumab

1st line vs 2nd line pembrolizumab

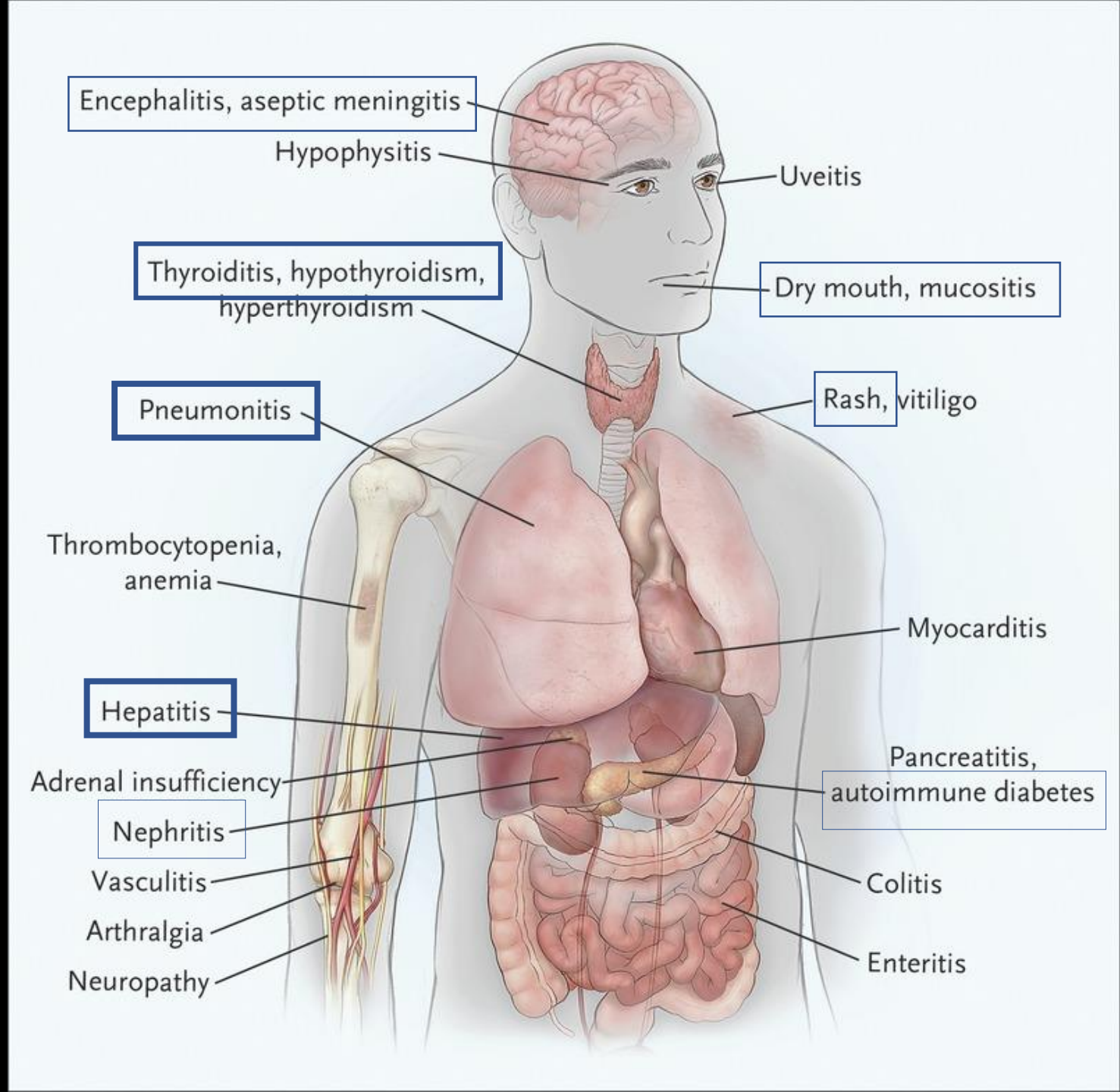


1st line >>



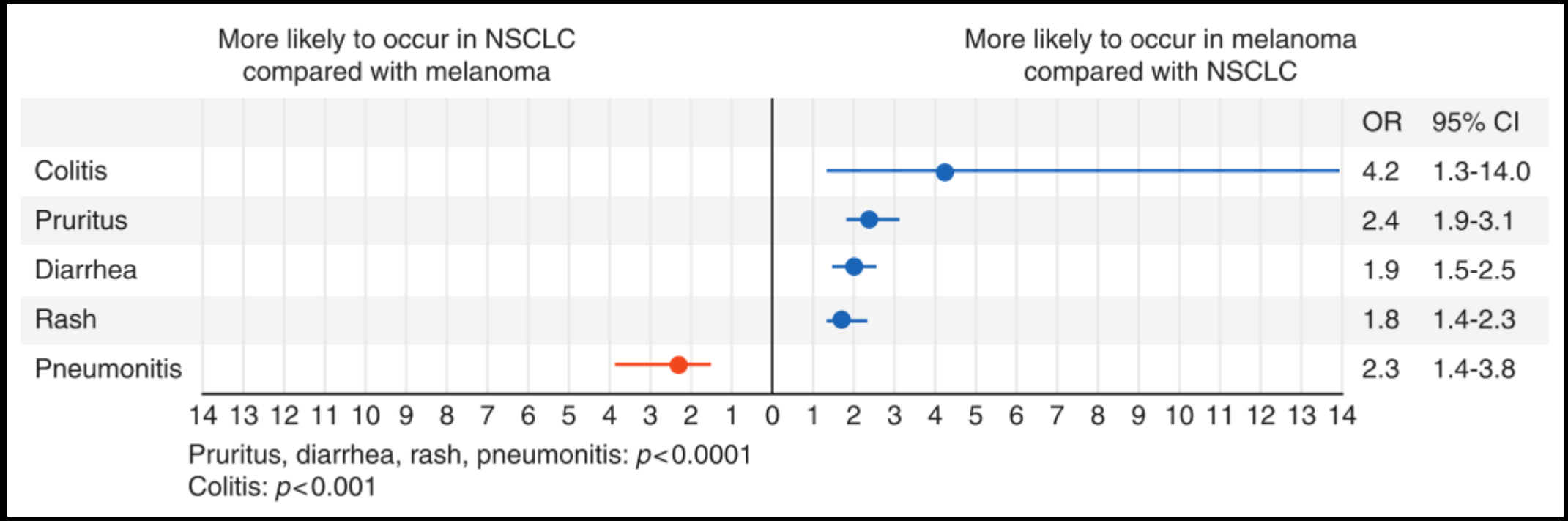
Which IO is the best ?

Immune related adverse events



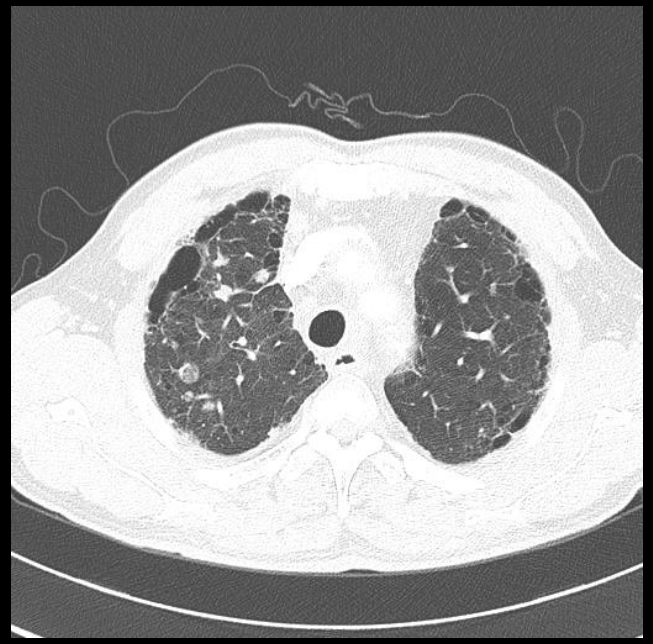
Adverse events : pneumonitis

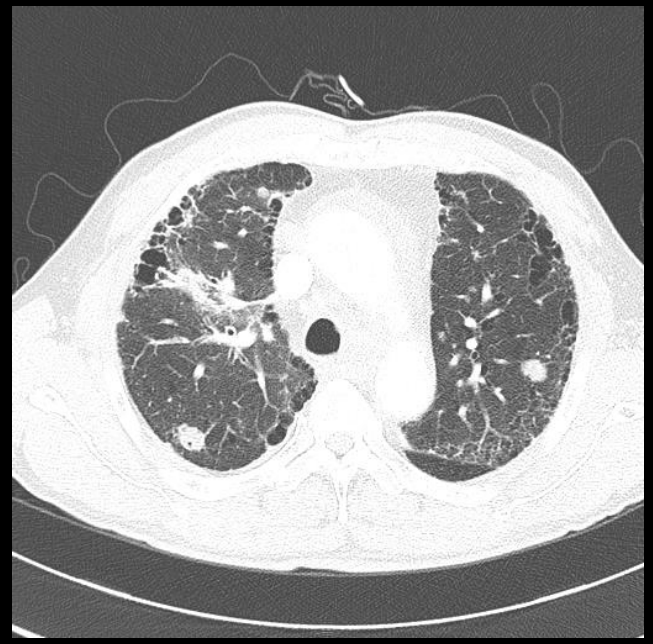
- Khoja, L., et al. (2017). "Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: a systematic review." Ann Oncol 28(10): 2377-2385.

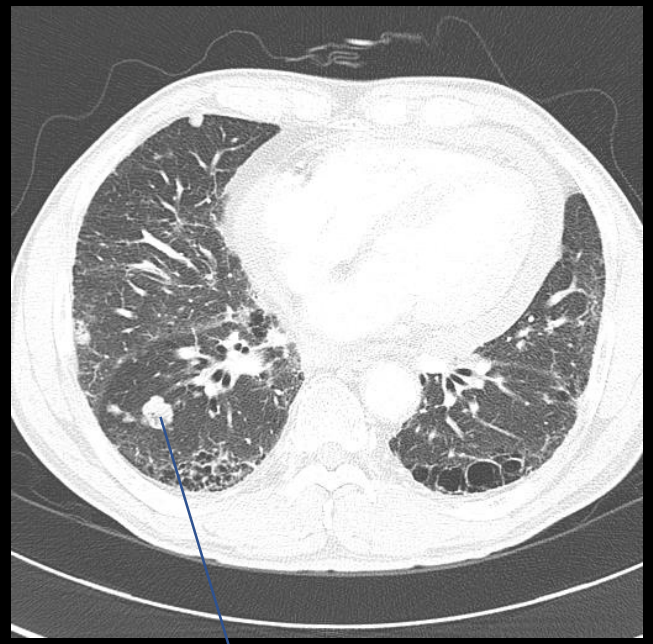


Case

- 2018.3) Chest CT : multiple variable sized nodules, scattered in both 5 lobes

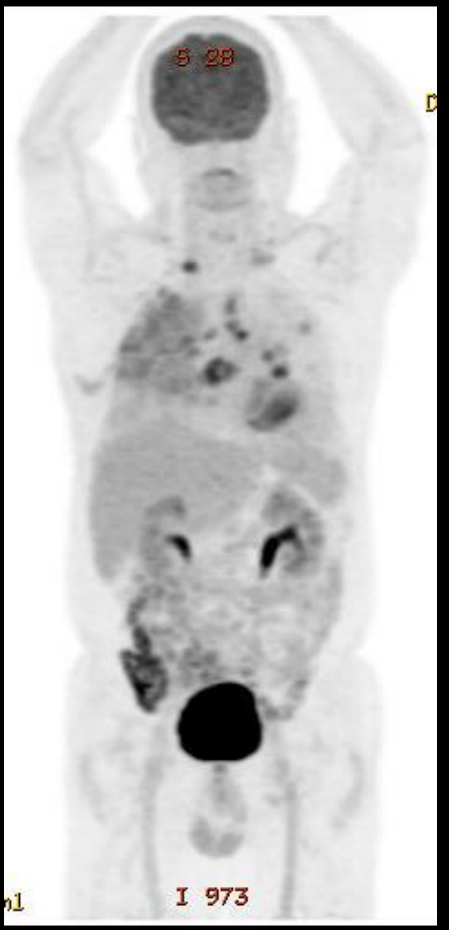






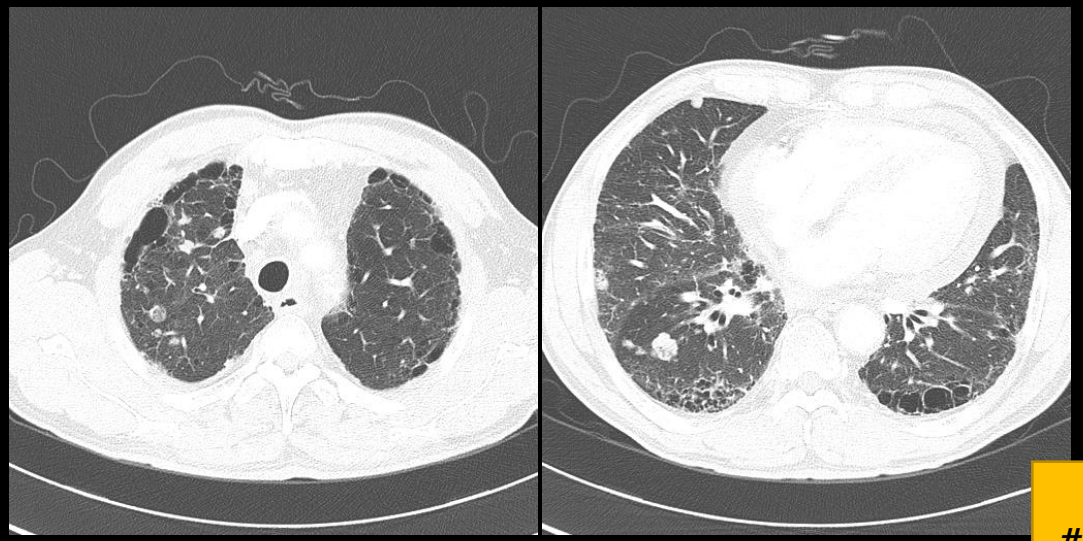
2018.03.06

PCNB : Squamous cell carcinoma
High PD-L1 expression (TPS 70%)

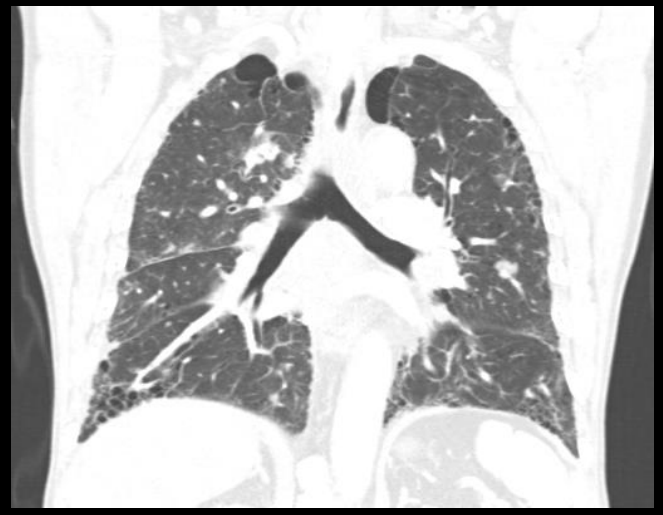


2018.03.15

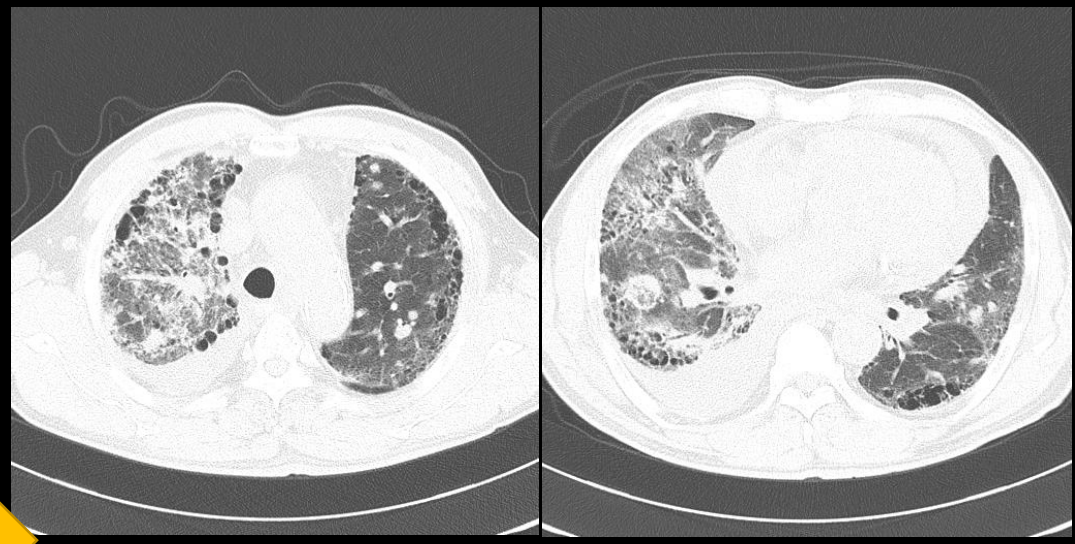
Clinical course



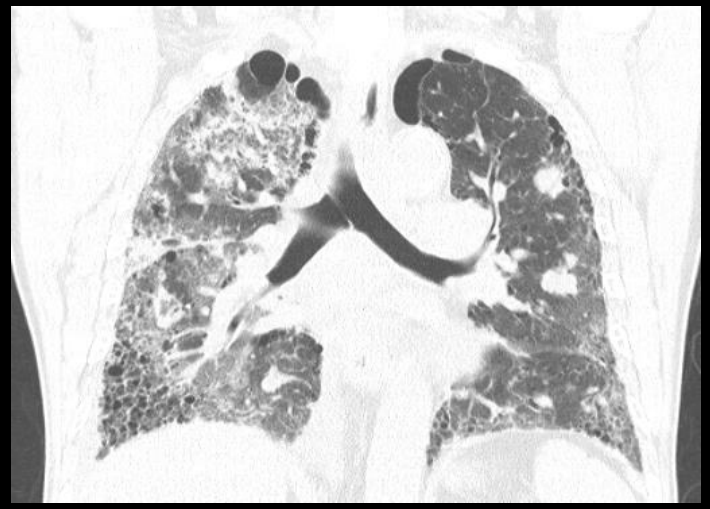
2018.03.06



2018.3.22
#1. pembrolizumab
(1st line)



2018.04.01



Adverse events : pneumonitis

- Asymptomatic appearance of infiltrates on lung imaging is more common.
- Symptomatic pneumonitis is seen in =1%. (~5%)
- More common with anti-PD-1/anti-PD-L1 than anti-CTLA-4 therapy

- Grade 1: Asymptomatic, only radiological changes
- Grade 2: Mild/Moderate new symptoms limiting instrumental activities of daily living
- Grade 3/4: Severe symptoms limiting self-care activities of daily living. Hypoxia or Respiratory failure requiring urgent interventions like endotracheal intubation or tracheostomy

Treatment : Pneumonitis

Grade 1 : stop IO

Grade 2 : stop IO & Oral prednisone 1mg/kg/day or equivalent

Grade 3 or 4 : I.V. Methyl prednisone 2–4mg/kg/day

Consider alternative immunosuppressive agent

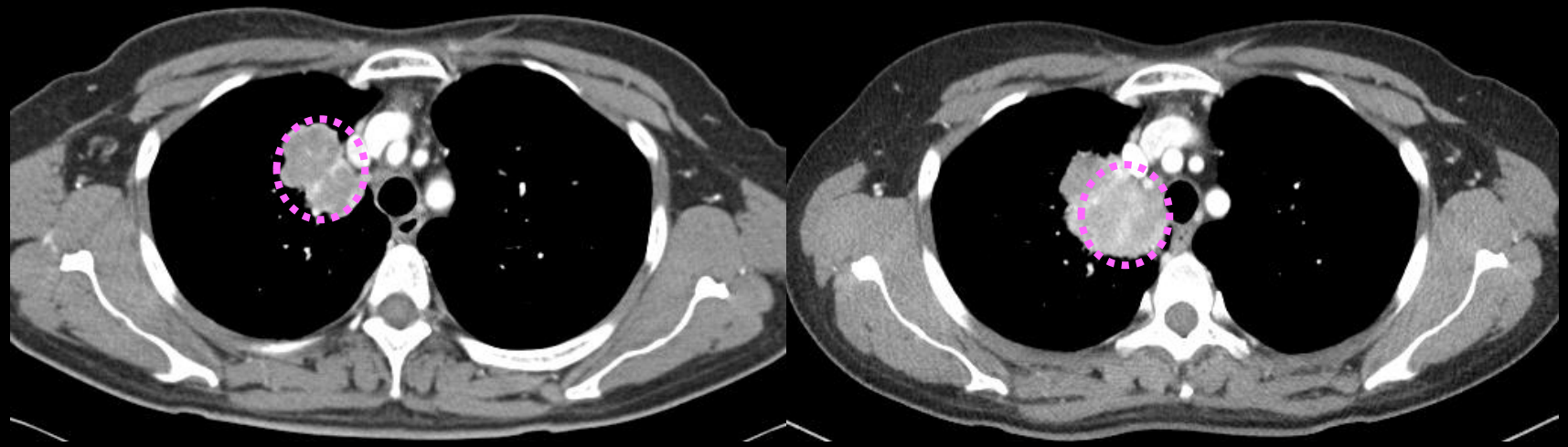
(Cyclophosphamide or Infliximab)

if symptoms don’t improve after 48 h.

Pseudoprogression

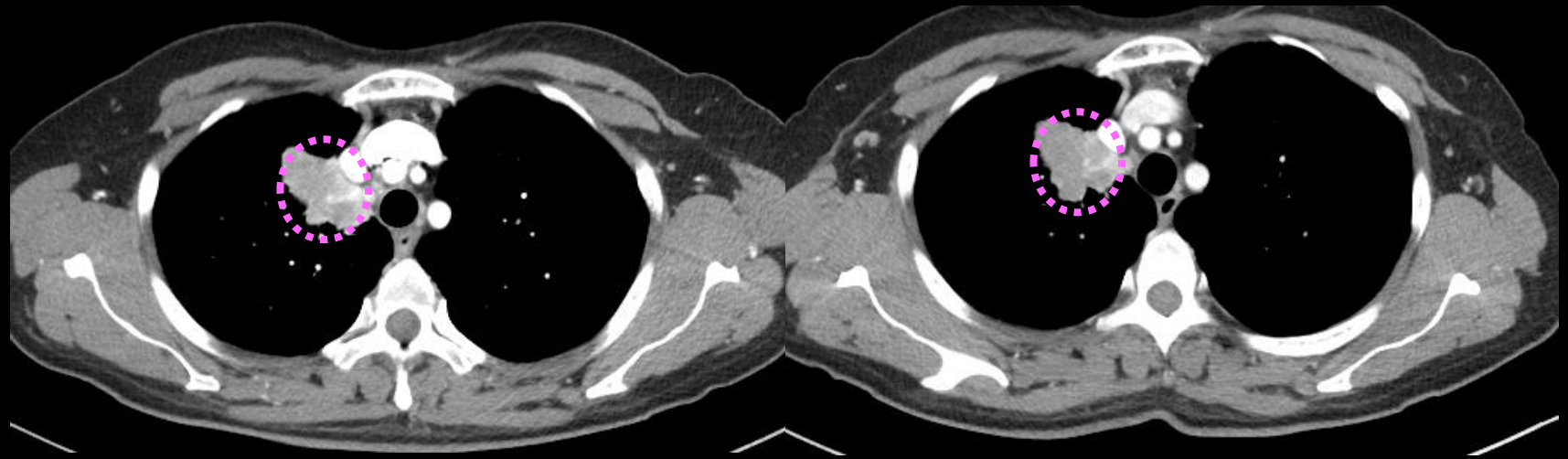
Reports	Agent	No. of evaluated patients	No. of unconventional responses	Rate (%)	Primary evaluation criteria
Nishino M et al. (2017)	Nivolumab or Pembrolizumab	160	1	0.6	irRECIST
Gettinger et al. (2016)	Nivolumab	52	3	5.8	RECIST 1.1
Gettinger et al. (2015)	Nivolumab	129	6	4.7	RECIST 1.0
Borghaei et al. (2015)	Nivolumab	287	16	5.6	RECIST 1.1
Kim et al. (2017)	PD-1/PD-L1 inhibitors	41	2	4.9	irRC and RECIST 1.1

Case



Pre-treatment

After 3 cycles



After 6 cycles

After 9 cycles

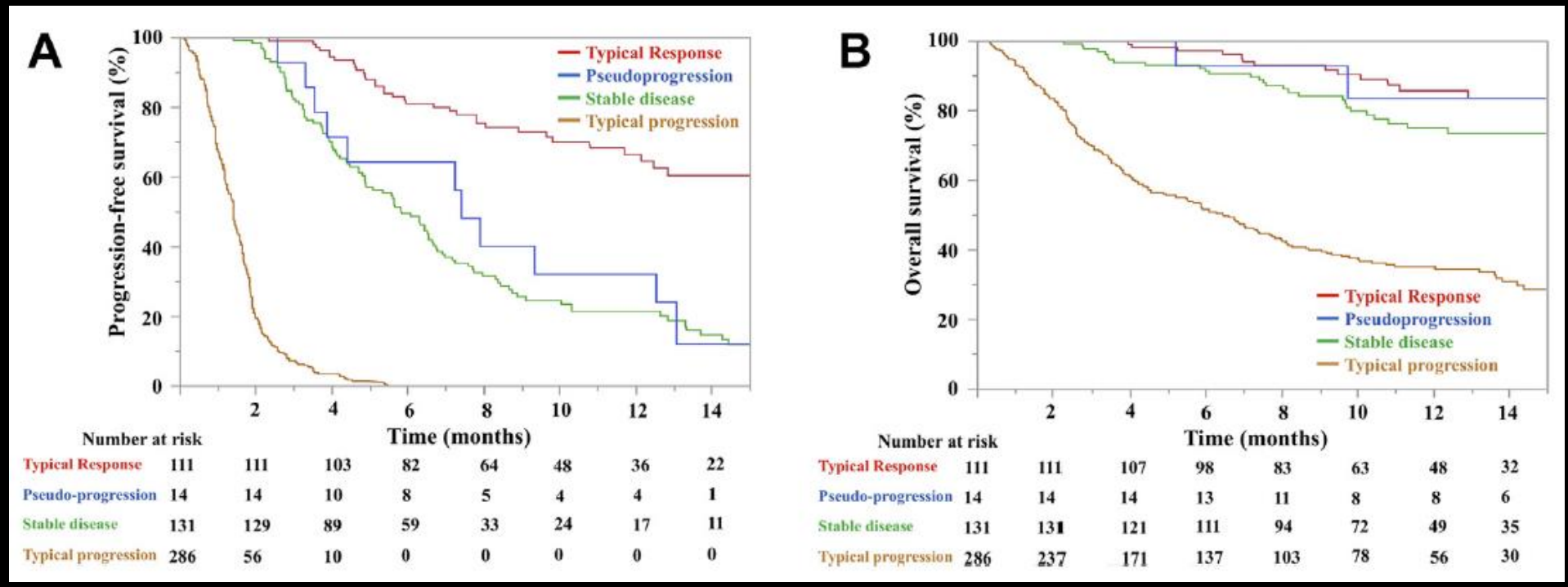
- 55/F, adenocarcinoma, stage IV
- high PD-L1 expression (TPS≥50%)
- 2nd line, pembrolizumab

- Ongoing 14 cycles

Outcome of Pseudoprogression

Duration of response : shorter than typical response

Survival benefit : markedly better than typical progression



FUJIMOTO, Daichi, et al. *Journal of Thoracic Oncology*, 2018.

NCCN guidelines 2019 v 3.

1. Immune checkpoint inhibitors are associated with a delay in benefit when compared with targeted therapy or cytotoxic chemotherapy

2. Contraindication to immunotherapy
   - Active or previously documented autoimmune disease
   - Current use of immunosuppressive agents
   - Presence of an oncogene

NSCLC

NSCLC EGFR m(+)

EGFR T790M(+)

2003 gefitinib in unselected NSCLC pt.

2004 erlotinib in unselected NSCLC pt

2004
EGFRM+ with gefitinib response

2005
Acquired T790M in tissue

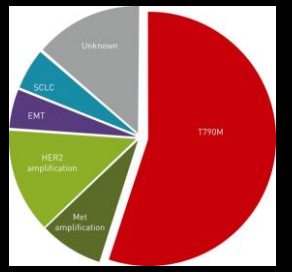
200?~ Acquired resistance mechanism

Predictor? EGFR mutation, EGFR gene amplification, EGFR protein expression

2009 gefitinib in EGFR m+ NSCLC

2013 erlotinib/afatinib in EGFR m+ NSCLC

2009
EGFR m+ in plasma



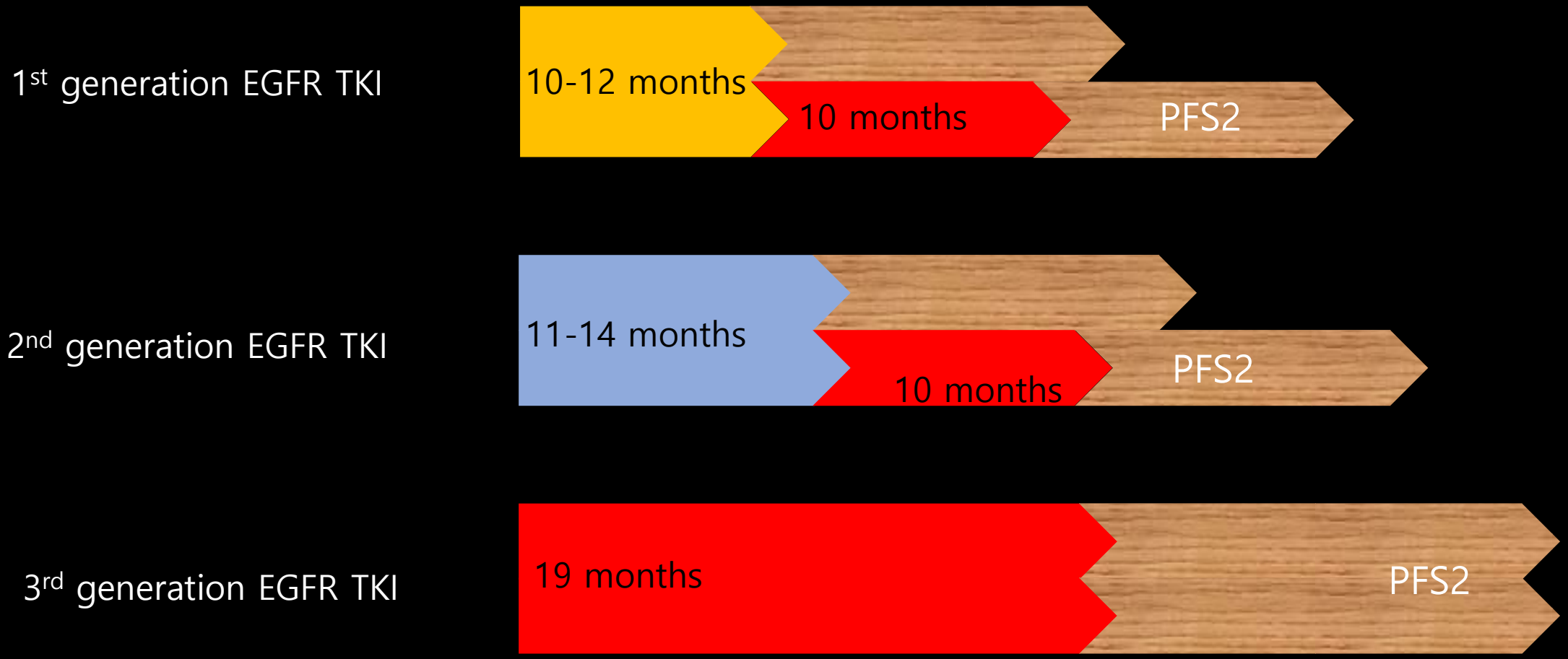
Plasma EGFR T790M mutation or Tissue EGFR T790M mutation

2015 osimertinib in T790M+ after 1st or 2nd EGFR TKI

2018 1st line Osimertinib in EGFR m+ NSCLC

2015
EGFR C797S

Which one is the best 1st line regimen?



Disease flare after EGFR TKI discontinuation

Chen, H. J., et al. (2013). "Disease flare after EGFR tyrosine kinase inhibitor cessation predicts poor survival in patients with non-small cell lung cancer." Pathol Oncol Res 19(4): 833-838.

10~20%

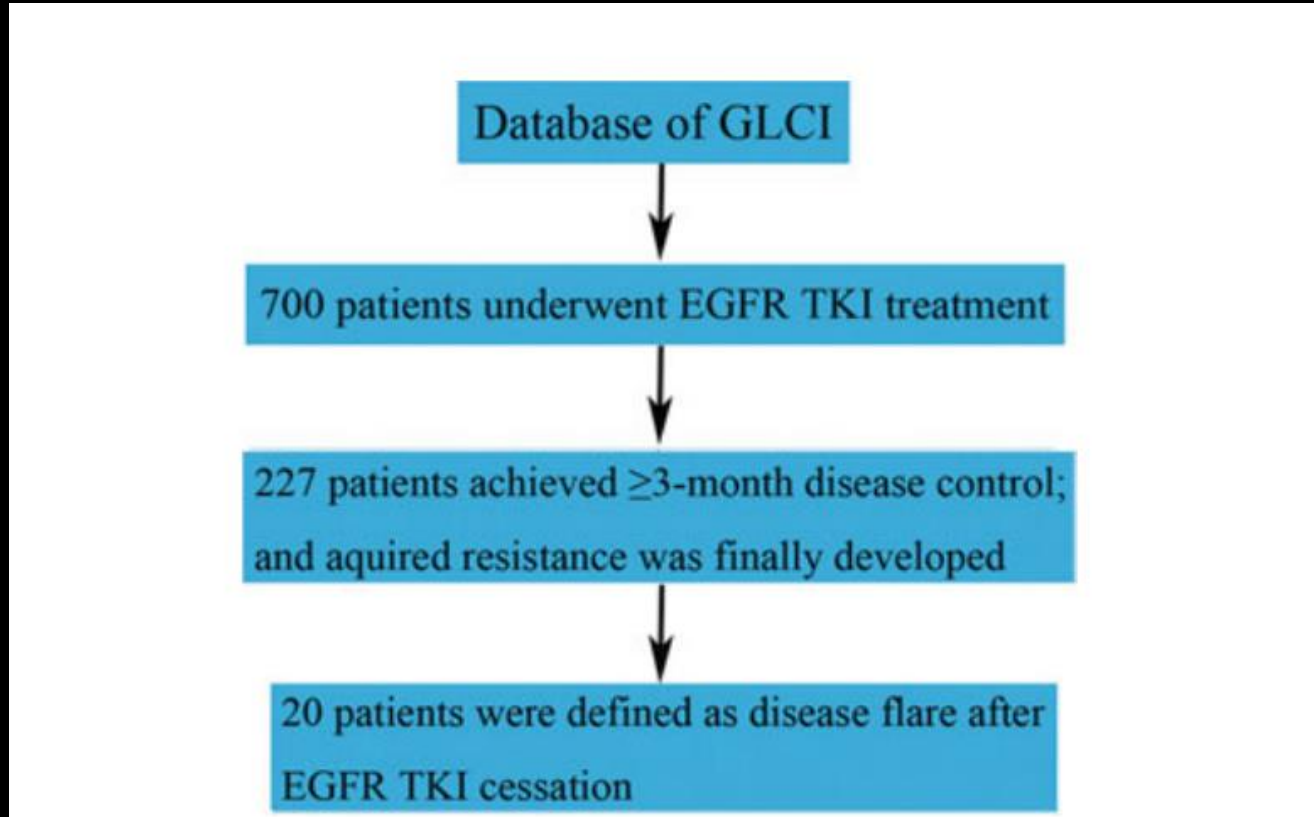


Fig. 1 Flow chart of screening patients with disease flare. GLCI, Guangdong Lung Cancer Institute

No.	Symptomatic deterioration	Progressive sites	Events	Interval[a] (day)
1	Dyspnea	Pleural effusion	Hospitalization	13
2	Dyspnea	Pleural effusion, lungs, and supraclavicular LN	Death	7
3	Emotional unresponsiveness	lungs and brain	Death	18
4	Dyspnea	Pleural effusion	Hospitalization	3
5	Dyspnea	Pericardial effusion and liver	Hospitalization	7
6	Cough	Liver	Hospitalization	7
7	Dyspnea	Pericardial effusion	Hospitalization	5
8	Dyspnea	Pleural effusion	Hospitalization	12
9	Deteriorated PS	Liver, lung, and chest wall	Hospitalization	13
10	Deteriorated PS	Multiple brain	Death	8
11	Headache	Multiple brain	Death	18
12	Dyspnea	Pleural effusion	Hospitalization	4
13	Dyspnea	Pleural effusion	Hospitalization	18
14	Dyspnea	Lung and mediastinal LN	Death	4
15	Hemoptysis	Lungs	Death	4
16	Headache	Multiple brain	Hospitalization	12
17	Coma	Multiple brain	Death	5
18	Bone pain	Multiple bones	Hospitalization	7
19	Bone pain	Multiple bones	Hospitalization	5
20	Seizure	Multiple brain	Hospitalization	8

[a] Time from TKI cessation to the onset of disease flare. *LN* lymph nodes; *PS* performance status

Additional Issues : How many cycles?

- Number of cycles of first line platinum doublet

  Recommendation : 4 ~ 6 cycles (PFS, adverse events)
  if, scheduled maintenance Tx : 4 cycles
  if, platinum combined taxane : 4 cycles

- Number of cycles over 2nd line

Additional Issues : Dose

- Dose intensity (dose/time) : dose reduction and Tx interval
  - Afatinib
  - Cytotoxic chemotherapy

- Dose- AUC, fixed, mg/kg, mg/m^2

Fixed dose

- 1st line pembrolizumab : 200mg
- Nivolumab : 3 mg/kg, fixed doses of 240 mg every 2 week
- Atezoluzumab : 1200mg
- Target agents

Additional Issues : Response

- Per 2 or 3 cycles
- Chest CT with or without enhancement
- Not recommended : Regular f/u with PET-CT or Brain MRI

Take home messages

1. Chemotherapy can not solve everything.
   - ➢Chemotherapy with local Tx

2. Individualized strategies
   - ➢underlying disease
   - ➢Extent of tumor
   - ➢tumor growing pattern
   - ➢watch and wait

Take home messages

3. Unpredictable problem→predictable
   - Neutropenic fever
   - Pneumonia
   - Pneumonitis
   - Hemoptysis

4. NCCN guideline vs 심평원 심사기준

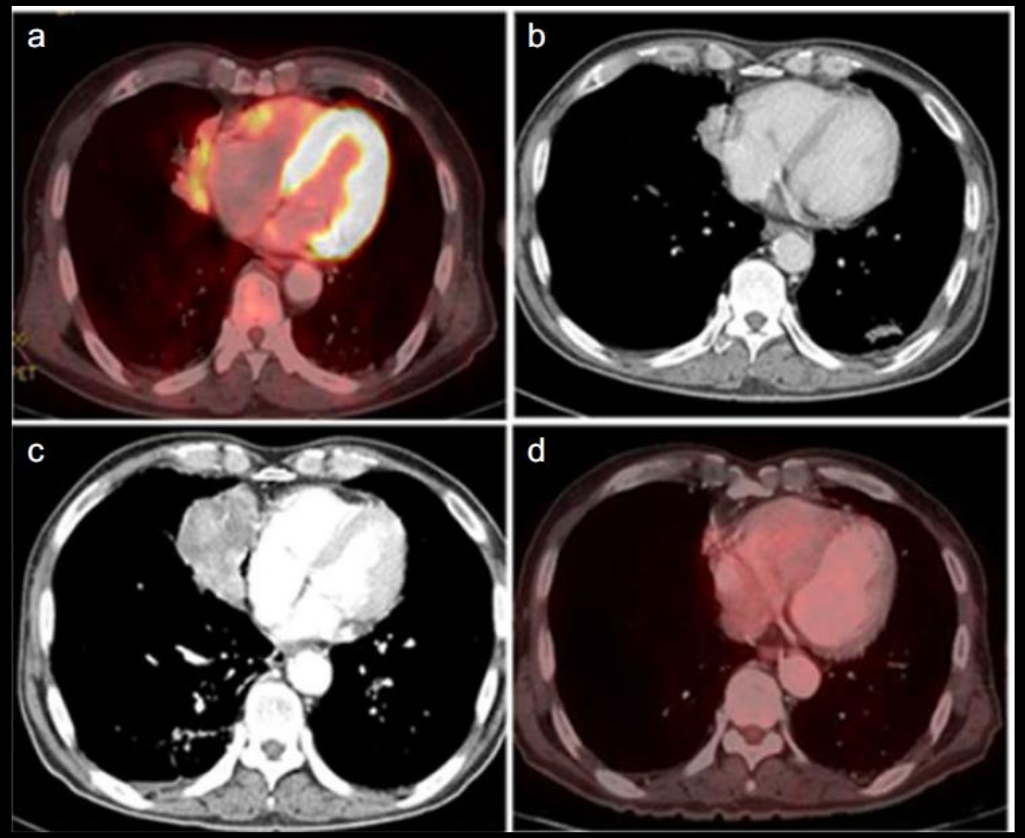
5. 사전 연명 치료

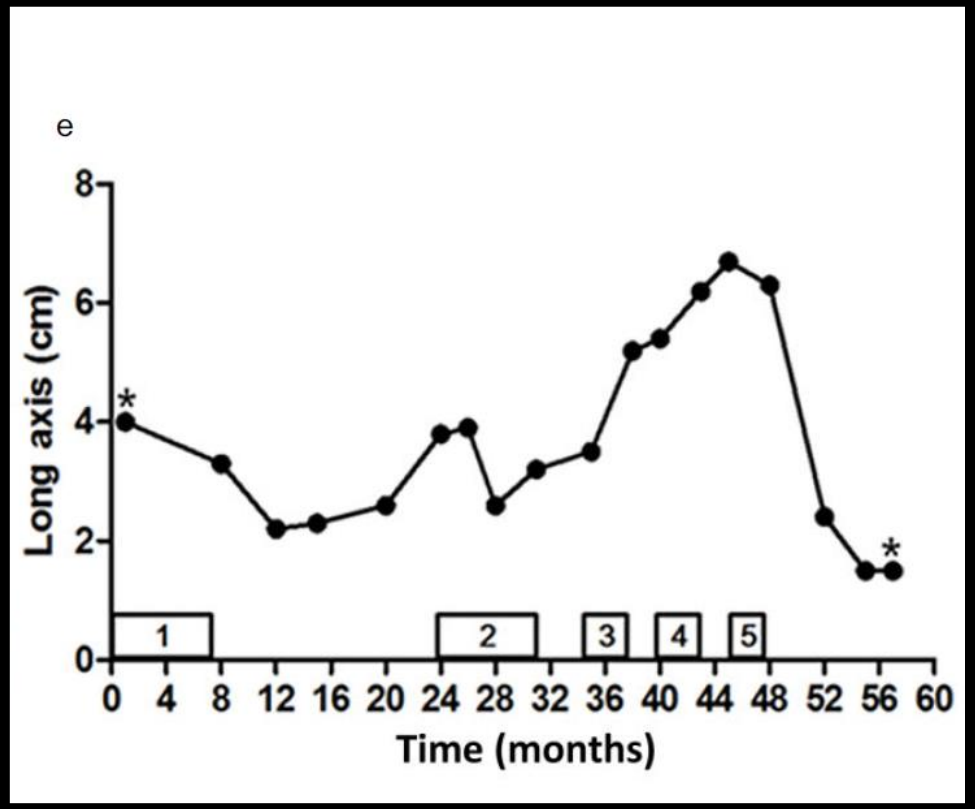
CASE REPORT

Spontaneous regression of non-small cell lung cancer that progressed after multiple chemotherapies: A case report

Chaeuk Chung[1], Dong Il Park[1], Sun Young Kim[1,3], Ju Ock Kim[1], Sung Soo Jung[1], Hee Sun Park[1], Jae Young Moon[1], Sung Min Kim[2], Min Ji Cho[1], Sang Ok Jung[1], Choong Sik Lee[4] & Jeong Eun Lee[1,3]

1 Division of Pulmonology, Department of Internal Medicine, College of Medicine, Chungnam National University, Deajeon, Korea
2 Department of Nuclear Medicine, College of Medicine, Chungnam National University, Deajeon, Korea
3 Cancer Institute of Chungnam National University, Deajeon, Korea
4 Department of Pathology, College of Medicine, Chungnam National University, Deajeon, Korea



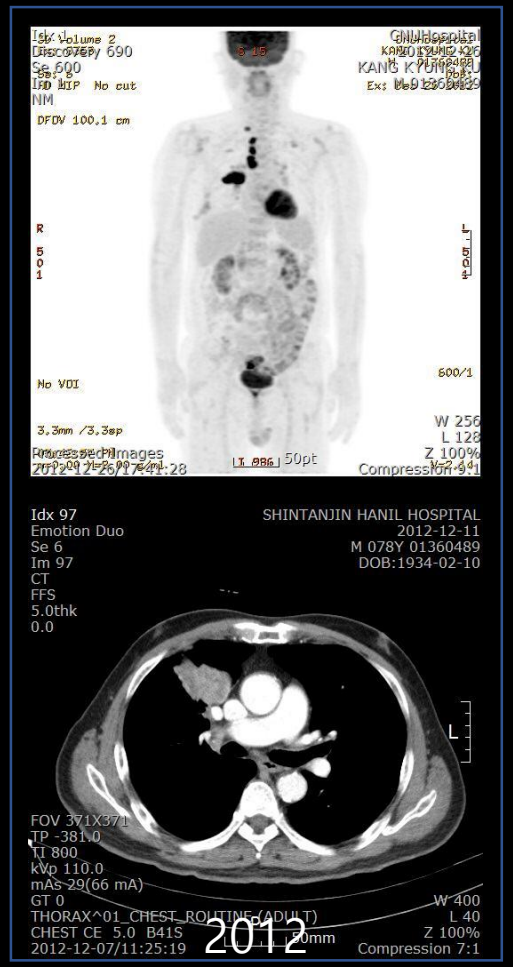


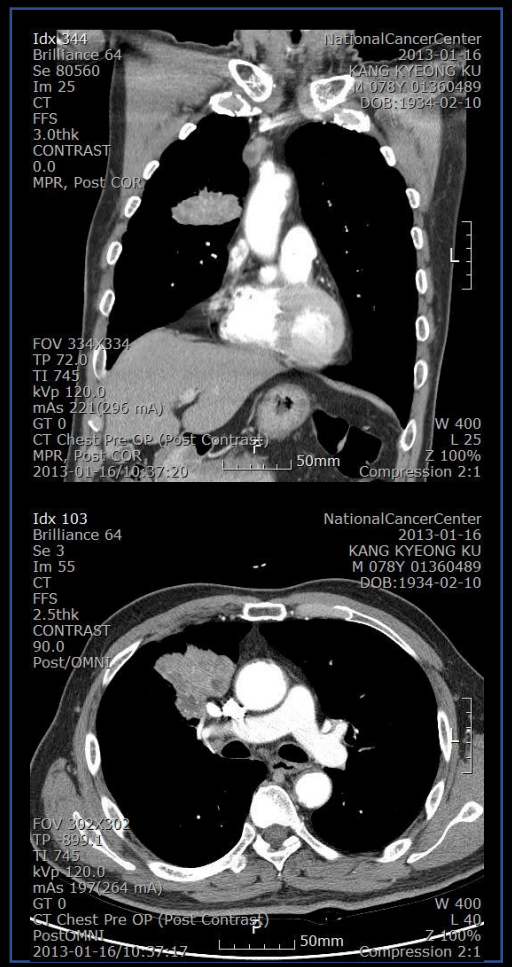
Case Report

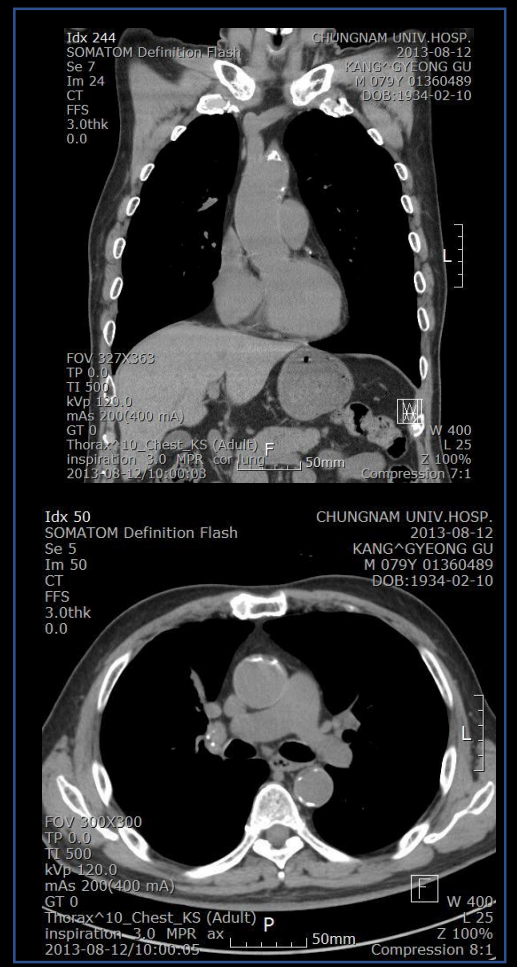
Spontaneous regression in advanced squamous cell lung carcinoma

Yeon Hee Park, Bo Mi Park, Se Yeon Park, Jae Woo Choi, Sun Young Kim, Ju Ock Kim, Sung Soo Jung, Hee Sun Park, Jae Young Moon, Jeong Eun Lee

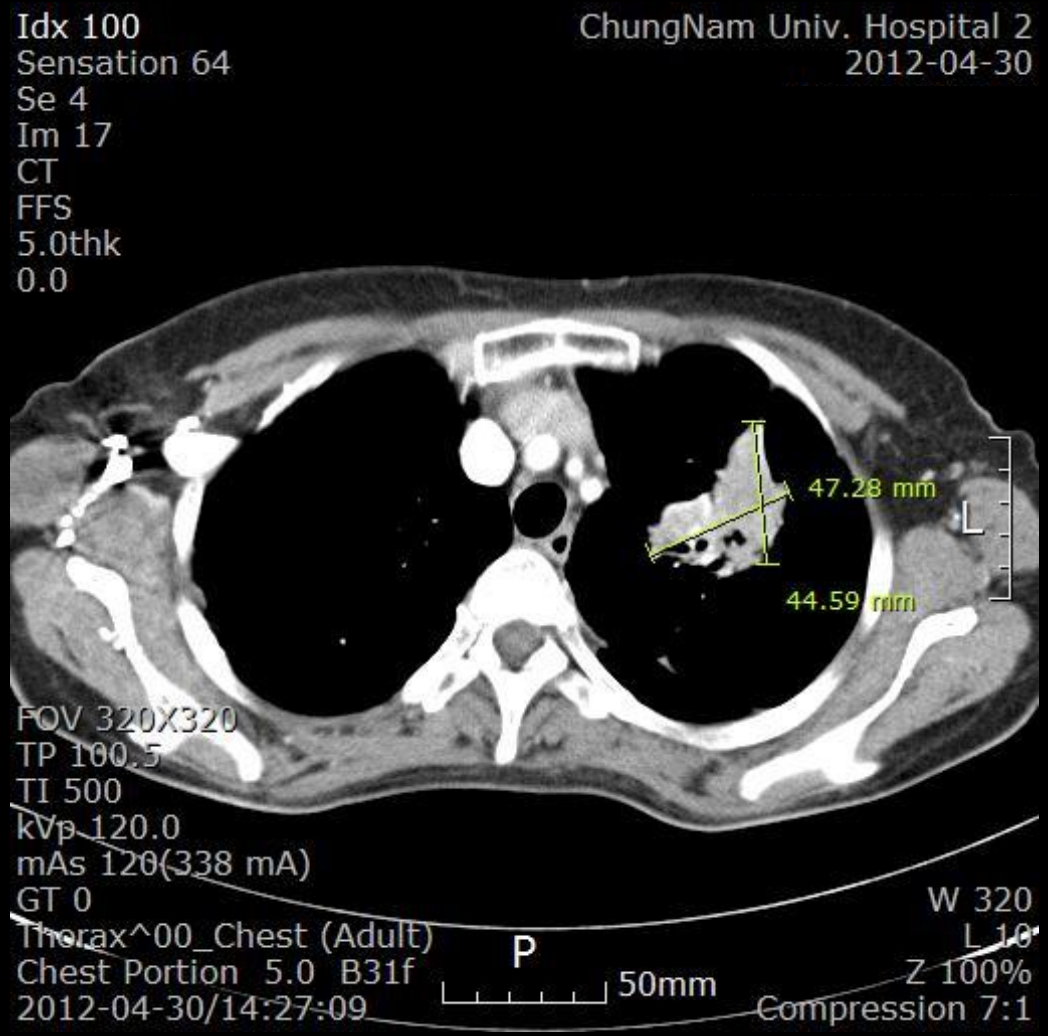
81/M 비소세포폐암 4기

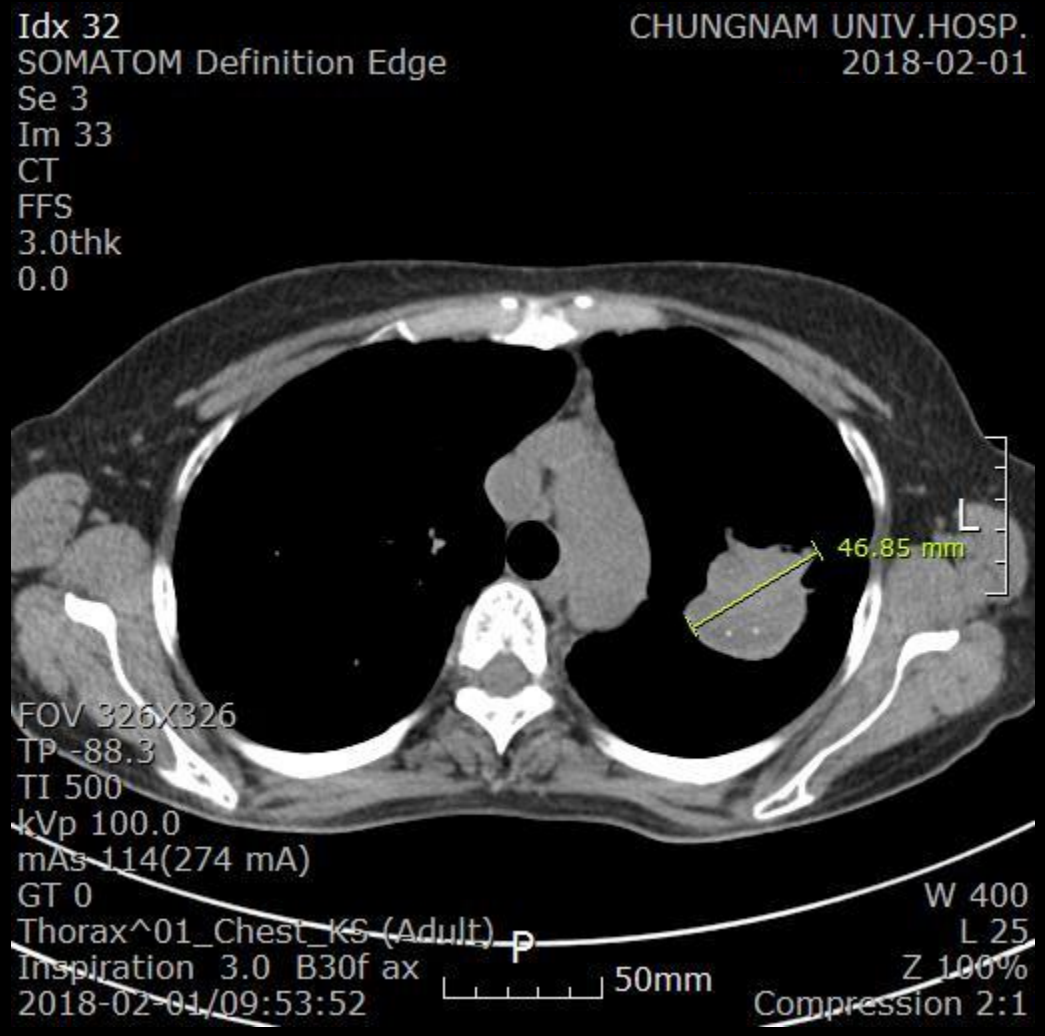






- 67/F
- 2012.5.14) NSCLC [adeno, T4N0M1a, IV] EGFR wild, ALK(-)
- 2012.5.24~) #1~ #6. Cis+alimta (Best response : PR)





경청해주셔서 감사합니다.