폐암의 진단검사 및 진료를 위한 팁

경북의대 이신엽

History of lung cancer screening

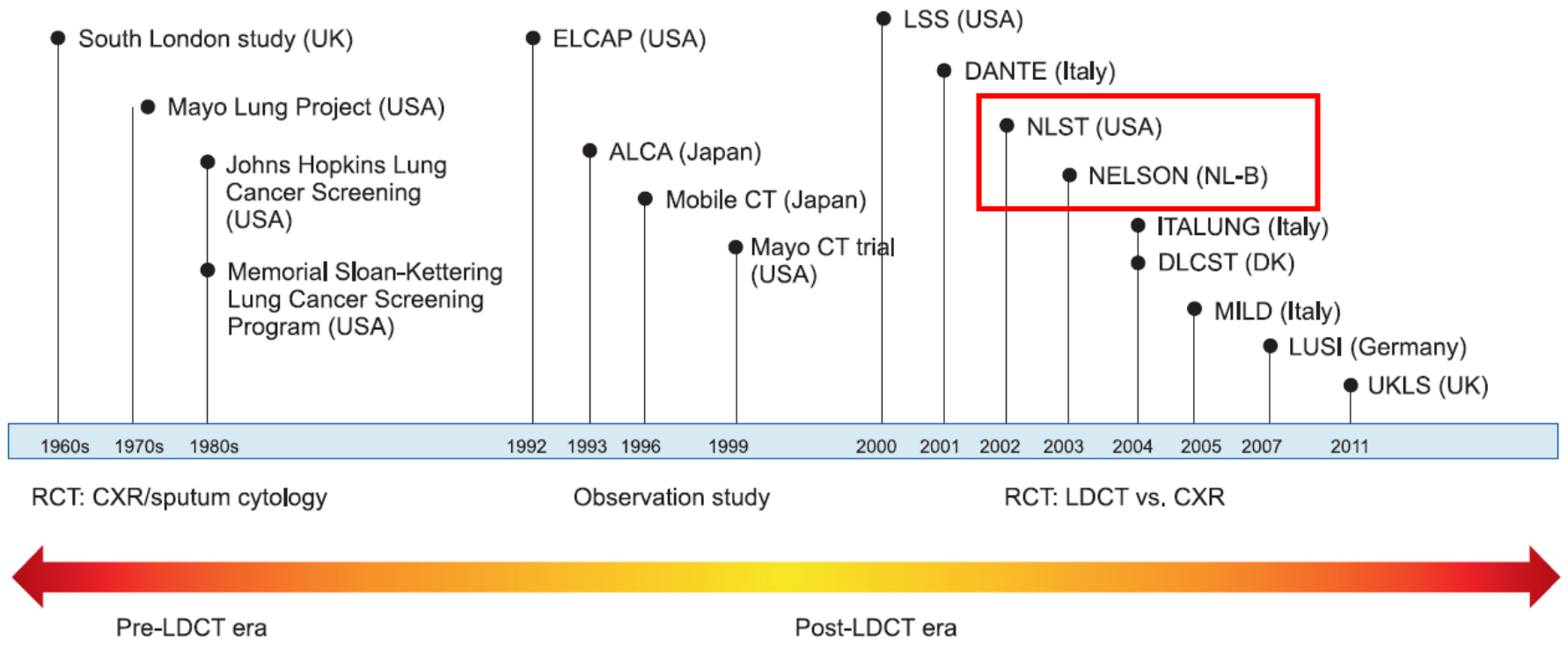


Figure 1. History of lung cancer screening. CT: computed tomography; CXR: chest X-ray; DANTE: Detection and Screening of Early Lung Cancer; LDCT: low-dose chest CT; LSS: Lung Screening Study; NLST: National Lung Screening Trial; RCT: randomized controlled trials; UKLS: UK Lung Screen.

Tuberc Respir Dis 2014;77:55-59

LDCT screening can reduce lung cancer mortality in high-risk population

NLST (National Lung Screening Trial) (n = 53,454)
US National Lung Screening Trial
LDCT vs CXR: longest diameter-based
Age 55–75 years,
≥30 PY smoking, <15 years ex-smoker
LDCT reduces lung cancer-related mortality (HR 0.80; $P < 0.004$)

N Engl J Med 2011;365:395-409.

NELSON (Nederlands–Leuvens Longkanker Screenings Onderzoek) (n = 15,789)
Dutch–Belgian lung-cancer screening trial
LDCT vs no intervention: volume-based
Age 55–75 years
>25 yr of >15 cigarettes/d or >30yr of >10 cigarettes/d, ≤10 years ex-smoker
LDCT reduces lung cancer-related mortality (HR 0.76, 95% CI 0.62–0.94 in men)
0.67, 95% CI 0.38–1.14 in women)

N Engl J Med 2020;382:503-13.

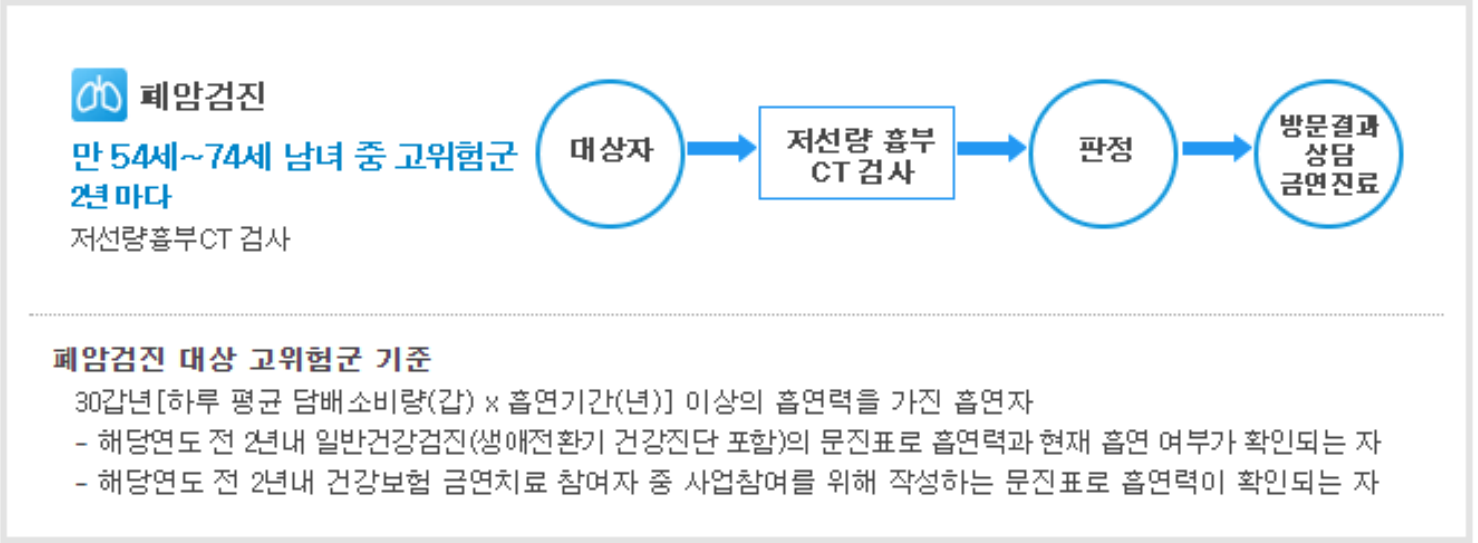
Percent of stage I cases detected in lung cancer screening RCTs

Risk factors of lung cancer

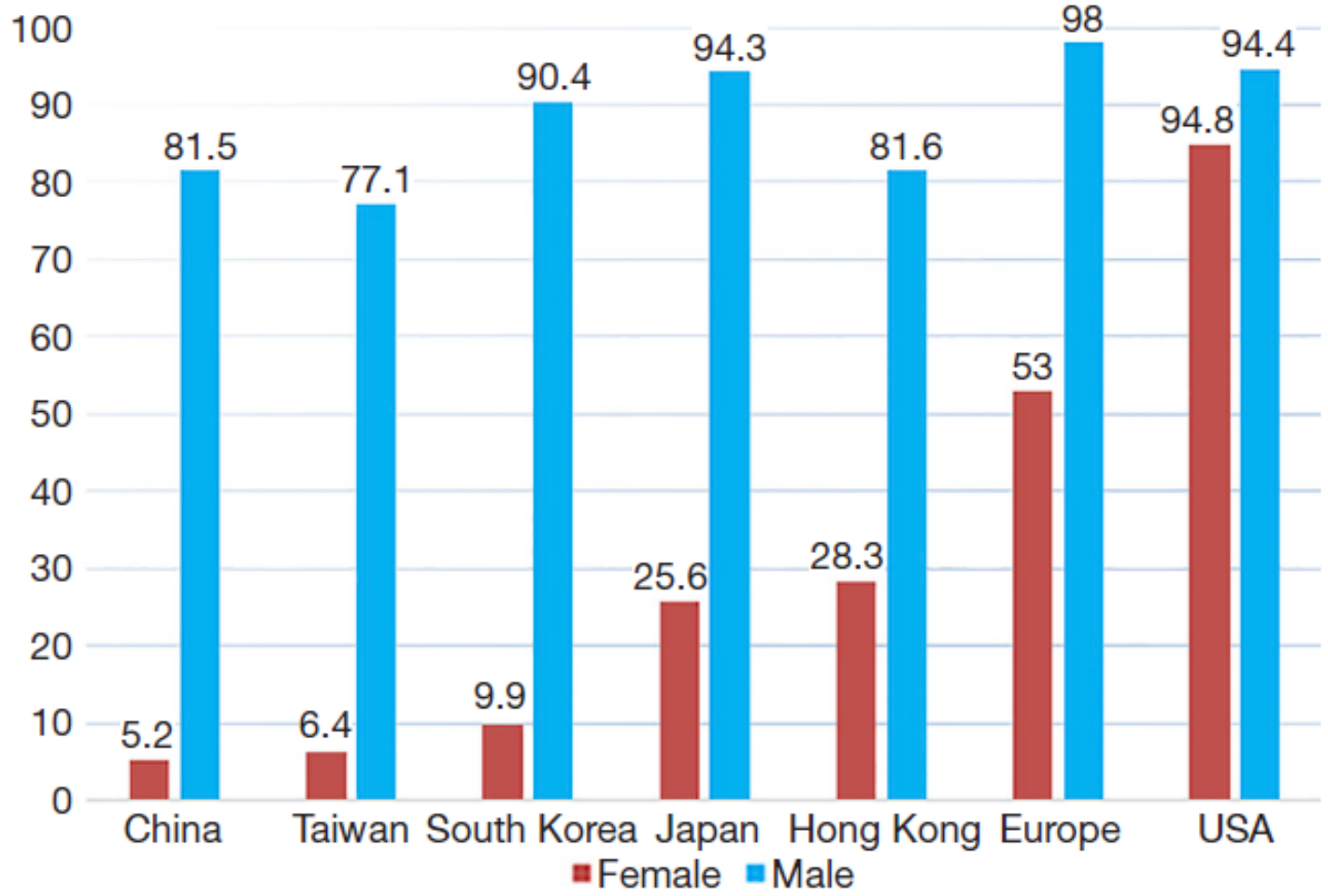
- Smoking (85 ~ 90%)
- Secondhand smoke
- radon, asbestos, uranium, arsenic...
- Air pollution (PM, indoor)
- Family history of lung cancer
- Chronic lung disease
- Genetic susceptibility

✓ Prediction models integrating several risk factors are under investigation.

Korean National Lung Cancer Screening



Smoking prevalence of lung cancer patients by gender



Transl Lung Cancer Res. 2018;7:450-463

Lung-RADS® Version 1.1

Assessment Categories Release date: 2019

Category Descriptor	Lung-RADS Score	Findings	Management	Risk of Malignancy	Est. Population Prevalence
Incomplete	**0**	Prior chest CT examination(s) being located for comparison Part or all of lungs cannot be evaluated	Additional lung cancer screening CT images and/or comparison to prior chest CT examinations is needed	n/a	1%
Negative No nodules and definitely benign nodules	**1**	No lung nodules Nodule(s) with specific calcifications: complete, central, popcorn, concentric rings and fat containing nodules	Continue annual screening with LDCT in 12 months	< 1%	90%
Benign Appearance or Behavior Nodules with a very low likelihood of becoming a clinically active cancer due to size or lack of growth	**2**	**Perifissural nodule(s)** *(See Footnote 11)* < 10 mm (524 mm^3) **Solid nodule(s):** < 6 mm (< 113 mm^3) new < 4 mm (< 34 mm^3) **Part solid nodule(s):** < 6 mm total diameter (< 113 mm^3) on baseline screening **Non solid nodule(s) (GGN):** <30 mm (<14137 mm^3) **OR** ≥ 30 mm (≥ 14137 mm^3) and unchanged or slowly growing **Category 3 or 4 nodules unchanged for ≥ 3 months**			

Probably Benign Probably benign finding(s) - short term follow up suggested; includes nodules with a low likelihood of becoming a clinically active cancer	**3**	**Solid nodule(s):** ≥ 6 to < 8 mm (≥ 113 to < 268 mm^3) at baseline **OR** new 4 mm to < 6 mm (34 to < 113 mm^3)	6 month LDCT	1-2%	5%
		Part solid nodule(s) ≥ 6 mm total diameter (≥ 113 mm^3) with solid component < 6 mm (< 113 mm^3) **OR** new < 6 mm total diameter (< 113 mm^3)			
		Non solid nodule(s) (GGN) ≥ 30 mm (≥ 14137 mm^3) on baseline CT or new			
Suspicious Findings for which additional diagnostic testing is recommended	**4A**	**Solid nodule(s):** ≥ 8 to < 15 mm (≥ 268 to < 1767 mm^3) at baseline **OR** growing < 8 mm (< 268 mm^3) **OR** new 6 to < 8 mm (113 to < 268 mm^3)	3 month LDCT; PET/CT may be used when there is a ≥ 8 mm (≥ 268 mm^3) solid component	5-15%	2%
		Part solid nodule(s): ≥ 6 mm (≥ 113 mm^3) with solid component ≥ 6 mm to < 8 mm (≥ 113 to < 268 mm^3) **OR** with a new or growing < 4 mm (< 34 mm^3) solid component			
		Endobronchial nodule			
Very Suspicious Findings for which additional diagnostic testing and/or tissue sampling is recommended	**4B**	**Solid nodule(s)** ≥ 15 mm (≥ 1767 mm^3) **OR** new or growing, and ≥ 8 mm (≥ 268 mm^3)	Chest CT with or without contrast, PET/CT and/or tissue sampling depending on the *probability of malignancy and comorbidities. PET/CT may be used when there is a ≥ 8 mm (≥ 268 mm^3) solid component. *For new large nodules that develop on an annual repeat screening CT, a 1 month LDCT may be recommended to address potentially infectious or inflammatory conditions*	> 15%	2%
		Part solid nodule(s) with: a solid component ≥ 8 mm (≥ 268 mm^3) **OR** a new or growing ≥ 4 mm (≥ 34 mm^3) solid component			
	4X	Category 3 or 4 nodules with additional features or imaging findings that increases the suspicion of malignancy			
Other Clinically Significant or Potentially Clinically Significant Findings (non lung cancer)	**S**	**Modifier - may add on to category 0-4 coding**	As appropriate to the specific finding	n/a	10%

고형 결절

크기	발견시기/변화	범주
<6 mm	첫 검진	2
	변화 없음	2
	크기 증가	4A
	새로 발생 (**<4** mm)	2
	새로 발생 (**4-6** mm)	3
6-8 mm	첫 검진	3
	변화 없음	2
	크기 증가	4A
	새로 발생	4A
8-15 mm	첫 검진	4A
	변화 없음	2
	크기 증가	4B
	새로 발생	4B
≥15 mm	첫 검진	4B
	변화 없음	2
	크기 증가	4B
	새로 발생	4B

부분 고형 결절

크기	발견시기/변화	범주
<6 mm	첫 검진	2
	변화 없음	2
	크기 증가 (**고형<4** mm)	4A
	크기 증가 (**고형 4-6** mm)	4B
	새로 발생	3
≥6 mm (**고형<6** mm)	첫 검진	3
	변화 없음	2
	크기 증가 (**고형<4** mm)	4A
	크기 증가 (**고형 4-6** mm)	4B
	새로 발견 (**고형<4** mm)	4A
	새로 발견 (**고형 4-6** mm)	4B
≥6 mm (**고형 6-8** mm)	첫 검진	4A
	변화 없음	2
	크기 증가	4B
	새로 발생	4B
≥8 mm (고형 **≥8** mm)	첫 검진	4B
	변화 없음	2
	크기 증가	4B
	새로 발견	4B

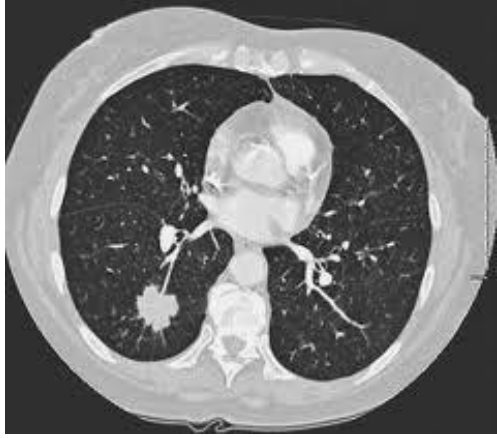
간유리 결절

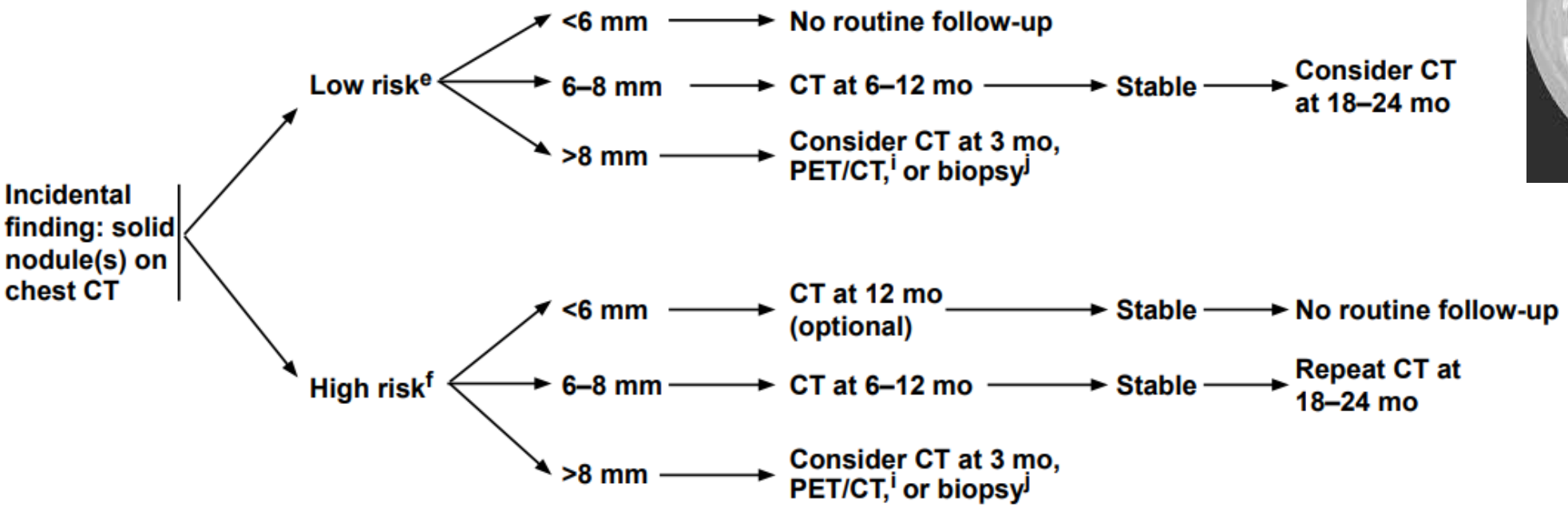
크기	발견시기/변화	범주
<30 mm	첫 검진	2
	변화 없음	2
	크기 증가	2
	새로 발견	2
≥30 mm	첫 검진	3
	변화 없음	2
	크기 증가	2
	새로 발생	3

기타 분류 기준	범주
기관지 내 결절	4A
범주 **3,4+추가** 영상 소견 폐경화, 무기폐, 림프절확대, 기타 (침상변연 등 자유기술)	4X
결절 외 의미 있는 소견	S

범주	범주 설명	악성 가능성	
0	불완전	평가 불능	이전 흉부 CT 필요 또는 추가 흉부 CT 시행 필요
1	이상 없음	< 1%	**12개월 후** LDCT
2	양성 결절	< 1%	**12개월 후** LDCT [**2b**: 범주 3,4에 해당하나 양성 가능성이 높은 영상소견]
3	경계선 결절	1-2%	**6개월 후** LDCT
4A	폐암 의심	5-15%	**3개월 후** LDCT, 고형 부분 ≥8mm인 경우 PET/CT 시행 가능
4B, X	폐암 매우 의심	> 15%	**즉시** 흉부 CT, 고형 부분 ≥8mm인 경우 PET/CT 시행 가능, 조직검사 Annual CT에서 발견된 새로운, 큰 결절은 1개월 후 F/U CT 고려(염증배제)

Solid nodules f/u

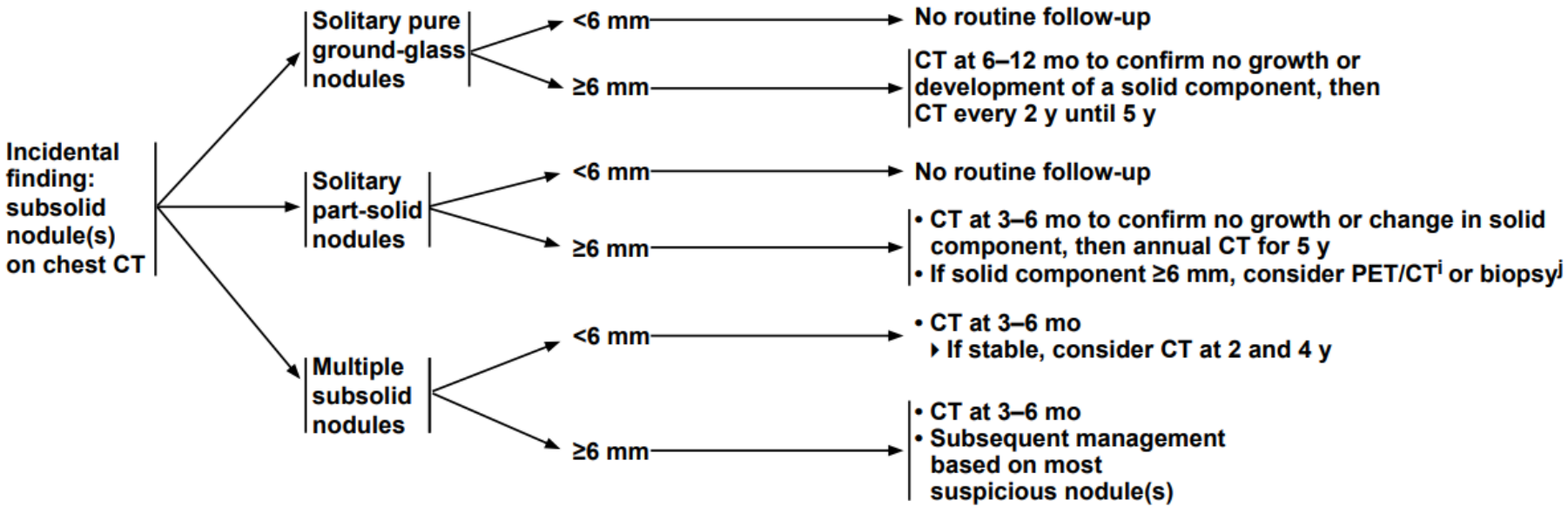


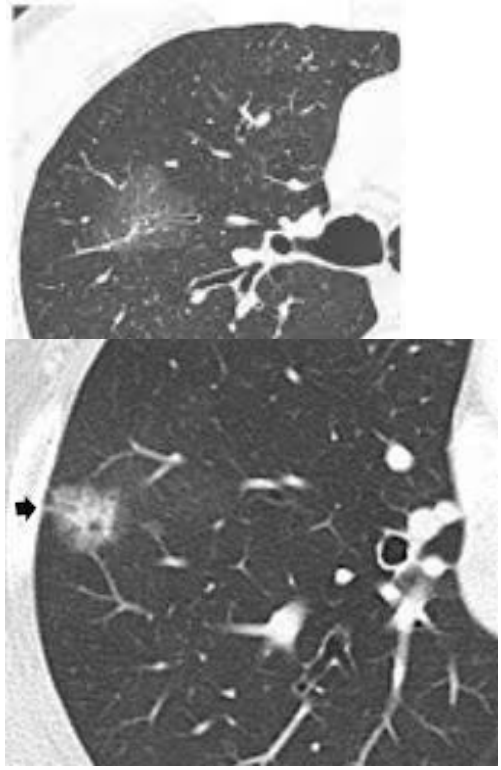


- The most important radiologic factor is change or stability compared with a previous image.
- Low risk = minimal or absent history of smoking or other known risk factors
- High risk = history of smoking or other known risk factors
  Known risk factor include history of lung cancer in a first-degree relative, exposure to asbestos, radon, or uranium.

NCCN guidelines, Non-small cell lung cancer, 2022v1

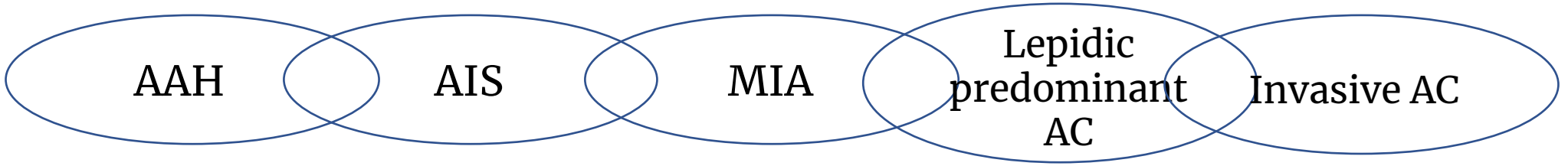
Subsolid nodules f/u





- GGN: Focal nodular increased attenuation with preserved bronchial/vascular margins
- Classification of subsolid nodules (SSNs)
  - Pure GGN
  - Mixed GGN (mGGN): GGN with solid component = Part-solid nodule
- Transient GGN (less than 3 months)
  - Focal infection/inflammation, pulmonary infiltrates with eosinophilia, organizing pneumonia
- Persistent GGN over 3 months
  - High probability of premalignant or malignant lesion (AAH/AIS)
  - Focal interstitial fibrosis

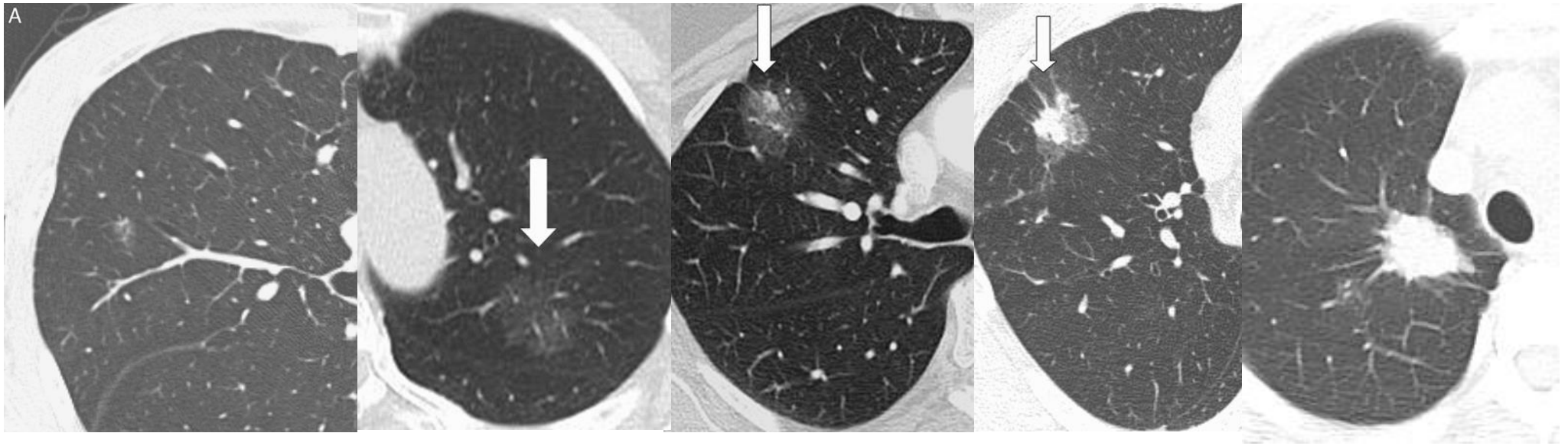
Correlation of CT-pathology in SSNs



More likely invasive, faster growing

Ground glass component

Solid component



Surgical resection of GGNs

- Pure GGN over 15 mm
- Part solid GGN with a solid portion of 6 mm or more
- A significant increased in size (over 2 mm)
- Appearance of a solid portion

※ Limitation of biopsy of GGN

- Small size
- Procedure-related complication
- False-negative result
- High correlation between CT finding and pathological finding

Principles of diagnostic evaluation

- Patients with a strong clinical suspicion of stage I or II lung cancer (based on risk factors and radiologic appearance) do not require a biopsy before surgery.
  - A biopsy adds time, costs, and procedural risk and may not be needed for treatment decisions.
  - A preoperative biopsy may be appropriate if a non-lung cancer diagnosis is strongly suspected that can be diagnosed by core biopsy or fine-needle aspiration (FNA).
  - A preoperative biopsy may be appropriate if an intraoperative diagnosis appears difficult or very risky.[1]
  - If a preoperative tissue diagnosis has not been obtained, then an intraoperative diagnosis (ie, wedge resection, needle biopsy) is necessary before lobectomy, bilobectomy, or pneumonectomy.[1]
- Bronchoscopy should preferably be performed during the planned surgical resection, rather than as a separate procedure.
  - Bronchoscopy is required before surgical resection (NSCL-2).
  - A separate bronchoscopy may not be needed for treatment decisions before the time of surgery and adds time, costs, and procedural risk.
  - A preoperative bronchoscopy may be appropriate if a central tumor requires pre-resection evaluation for biopsy, surgical planning (eg, potential sleeve resection), or preoperative airway preparation (eg, coring out an obstructive lesion).
- Invasive mediastinal staging is recommended before surgical resection for most patients with clinical stage I or II lung cancer (NSCL-2).
  - Patients should preferably undergo invasive mediastinal staging (mediastinoscopy) as the initial step before the planned resection (during the same anesthetic procedure), rather than as a separate procedure. For patients undergoing endobronchial ultrasound (EBUS)/ endoscopic ultrasound (EUS) staging, this may require a separate procedure to allow evaluation if onsite rapid cytology interpretation is not available.
  - A separate staging procedure adds time, costs, coordination of care, inconvenience, and an additional anesthetic risk.
  - Preoperative invasive mediastinal staging may be appropriate for a strong clinical suspicion of N2 or N3 nodal disease or when intraoperative cytology or frozen section analysis is not available.

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- In patients with suspected non-small cell lung cancer (NSCLC), many techniques are available for tissue diagnosis.
  - Diagnostic tools that should be routinely available include:
    - Sputum cytology
    - Bronchoscopy with biopsy and transbronchial needle aspiration (TBNA)
    - Image-guided transthoracic needle core biopsy (preferred) or FNA
    - Thoracentesis
    - Mediastinoscopy
    - Video-assisted thoracic surgery (VATS) and open surgical biopsy
  - Diagnostic tools that provide important additional strategies for biopsy include:
    - EBUS–guided biopsy
    - EUS–guided biopsy
    - Navigational bronchoscopy
    - Robotic bronchoscopy
- The preferred diagnostic strategy for an individual patient depends on the size and location of the tumor, the presence of mediastinal or distant disease, patient characteristics (such as pulmonary pathology and/or other significant comorbidities), and local experience and expertise.
  - Factors to be considered in choosing the optimal diagnostic step include:
    - Anticipated diagnostic yield (sensitivity)
    - Diagnostic accuracy including specificity and particularly the reliability of a negative diagnostic study (ie, true negative)
    - Adequate volume of tissue specimen for diagnosis and molecular testing
    - Invasiveness and risk of procedure
    - Efficiency of evaluation
      - Access and timeliness of procedure
      - Concomitant staging is beneficial, because it avoids additional biopsies or procedures. It is preferable to biopsy the pathology that would confer the highest stage (ie, to biopsy a suspected metastasis or mediastinal lymph node rather than the pulmonary lesion). Therefore, PET/CT imaging is frequently best performed before a diagnostic biopsy site is chosen in cases of high clinical suspicion for aggressive, advanced-stage tumors.
    - Technologies and expertise available
    - Tumor viability at proposed biopsy site from PET/CT imaging
  - Decisions about the optimal diagnostic steps for suspected stage I to III lung cancer should be made by thoracic radiologists, interventional radiologists, and thoracic surgeons who devote a significant portion of their practice to thoracic oncology. Multidisciplinary evaluation should also include a pulmonologist or thoracic surgeon with expertise in advanced bronchoscopic techniques for diagnosis.

- The least invasive biopsy with the highest yield is preferred as the first diagnostic study.
  - ◊ Patients with central masses and suspected endobronchial involvement should undergo bronchoscopy.
  - ◊ Patients with peripheral (outer one-third) nodules may benefit from navigational bronchoscopy, radial EBUS, or transthoracic needle aspiration (TTNA).
  - ◊ Patients with suspected nodal disease should be biopsied by EBUS, EUS, navigational bronchoscopy, or mediastinoscopy.
    - – EBUS provides access to nodal stations 2R/2L, 4R/4L, 7, 10R/10L, and other hilar nodal stations if necessary.
    - – An EBUS-TBNA negative for malignancy in a clinically (PET and/or CT) positive mediastinum should undergo subsequent mediastinoscopy prior to surgical resection.
    - – EUS–guided biopsy provides additional access to stations 5, 7, 8, and 9 lymph nodes if these are clinically suspicious.
    - – TTNA and anterior mediastinotomy (ie, Chamberlain procedure) provide additional access to anterior mediastinal (stations 5 and 6) lymph nodes if these are clinically suspicious. If TTNA is not possible due to proximity to aorta, VATS biopsy is also an option.
  - ◊ EUS also provides reliable access to the left adrenal gland.
  - ◊ Rapid on-site evaluation (ROSE), when available, helps to increase diagnostic and molecular yield.
  - ◊ Lung cancer patients with an associated pleural effusion should undergo thoracentesis and cytology. A negative cytology result on initial thoracentesis does not exclude pleural involvement. An additional thoracentesis and/or thoracoscopic evaluation of the pleura should be considered before starting curative intent therapy.
  - ◊ Patients suspected of having a solitary site of metastatic disease should have tissue confirmation of that site if feasible.
  - ◊ Patients suspected of having metastatic disease should have confirmation from one of the metastatic sites if feasible.
  - ◊ Patients who may have multiple sites of metastatic disease—based on a strong clinical suspicion—should have biopsy of the primary lung lesion or mediastinal lymph nodes if it is technically difficult or very risky to biopsy a metastatic site.

Staging evaluation

- 흉부내 병기
  : 흉부 전산화단층촬영(CT scan)
  PET/CT scan (종격동 평가)
  기관지내시경

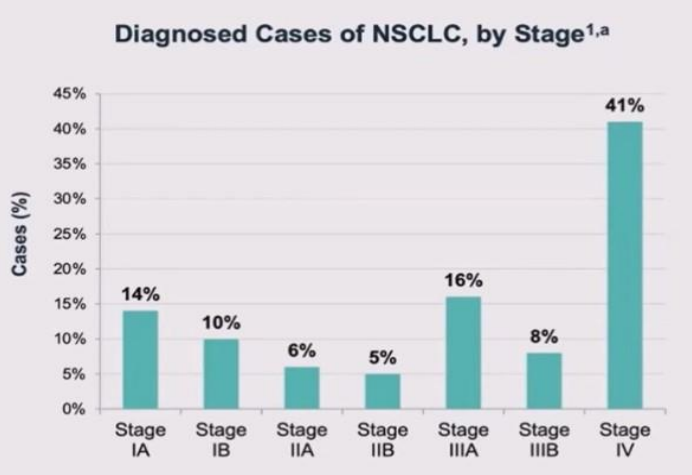
- 원격전이 평가 (흔한 전이 부위: 뇌, 간, 부신, 뼈)
  : Brain MRI(CT scan) + whole body PET/CT scan
  필요시 bone scan, abdominal CT scan 등

- 침습적 종격동 병기 판정(근치적 절제술을 고려하는 경우)
  : mediastinoscopy(1, 2, 3, 4, anterior 7),
  anterior mediasinotomy(5, 6),
  VATS(5, 6, 8, 9 ipsilateral),
  EBUS-TBNA(1, 2, 4, anterior 7),
  EUS-FNA(1L, 2L, 4L, 5, posterior 7, 8, 9)

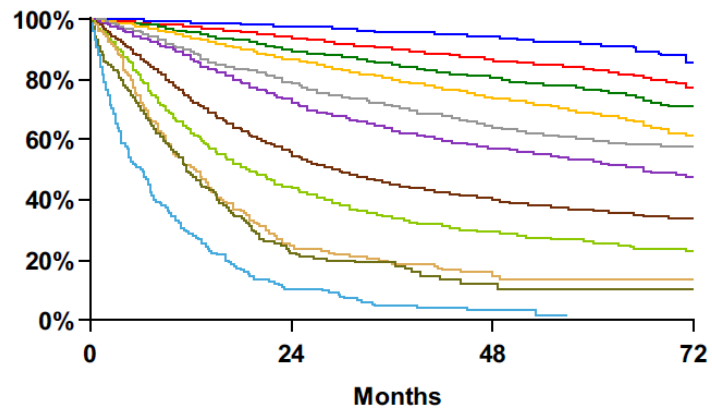
Clinical stages and survival – NSCLC

TNM Classification 8th edition

	N0	N1	N2	N3	M1a	M1b	M1c
T1a	IA1	IIB	IIIA	IIIB	IVA	IVA	IVB
T1b	IA2	IIB	IIIA	IIIB	IVA	IVA	IVB
T1c	IA3	IIB	IIIA	IIIB	IVA	IVA	IVB
T2a	IB	IIB	IIIA	IIIB	IVA	IVA	IVB
T2b	IIA	IIB	IIIA	IIIB	IVA	IVA	IVB
T3	IIB	IIIA	IIIB	IIIC	IVA	IVA	IVB
T4	IIIA	IIIA	IIIB	IIIC	IVA	IVA	IVB



Proposed	Events / N	MST	24 Month	60 Month
IA1	68 / 781	NR	97%	92%
IA2	505 / 3105	NR	94%	83%
IA3	546 / 2417	NR	90%	77%
IB	560 / 1928	NR	87%	68%
IIA	215 / 585	NR	79%	60%
IIB	605 / 1453	66.0	72%	53%
IIIA	2052 / 3200	29.3	55%	36%
IIIB	1551 / 2140	19.0	44%	26%
IIIC	831 / 986	12.6	24%	13%
IVA	336 / 484	11.5	23%	10%
IVB	328 / 398	6.0	10%	0%

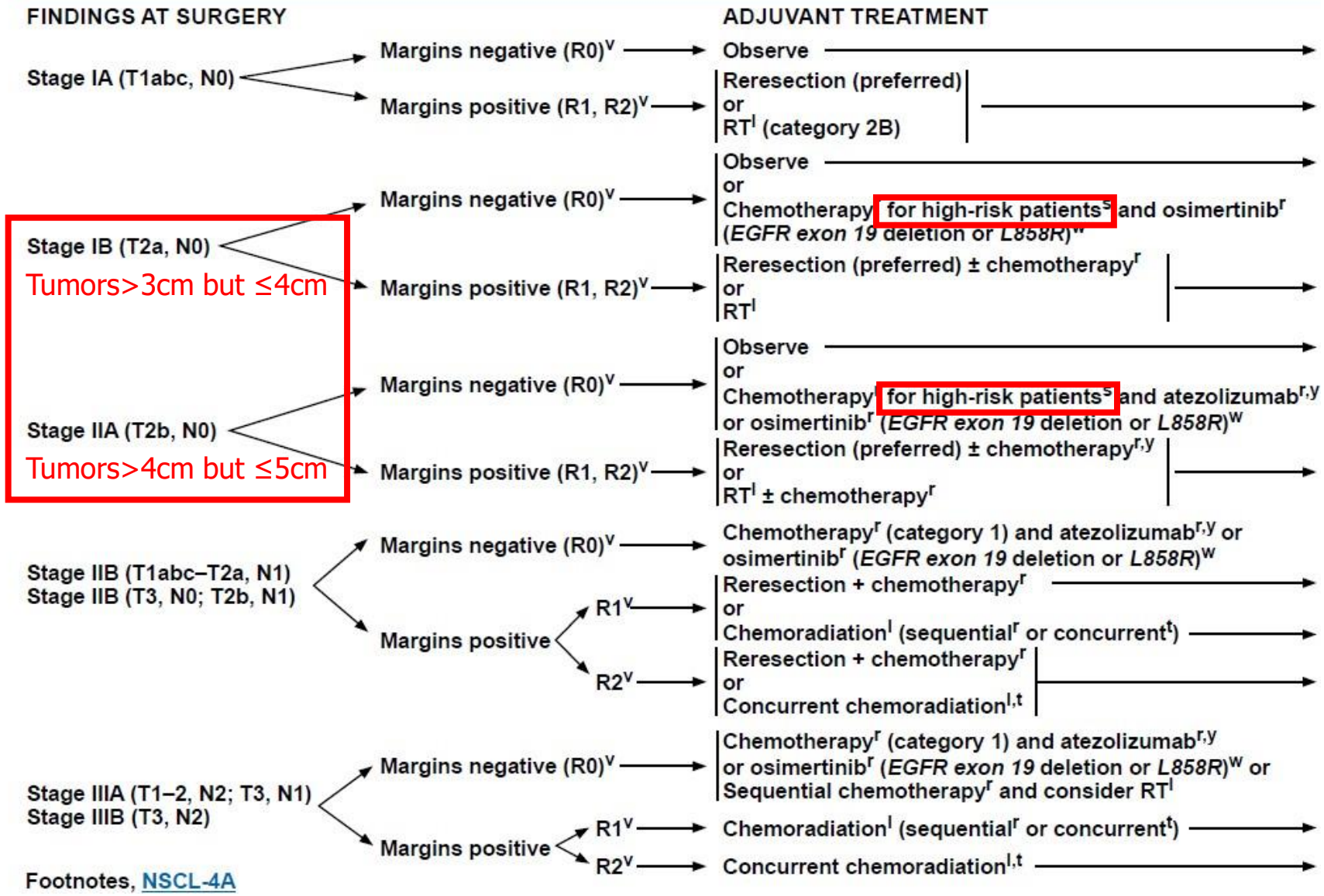


Goldstraw P, et al., JTO, *2016.*

Treatment summary by stage

	NSCLC				SCLC	
병기	I	II	III	IV	limited	extensive
Front-line therapy	OP	OP ± (Neo) adjuvant CTx	Multimodality or If unresectable : CCRT + durvalumab consolidation	Target ICI±CTx CTx	CCRT + PCI	CTx + ICI
치료목적	Cure	Cure	Cure	Palliation	Cure	Palliation

Adjuvant treatment



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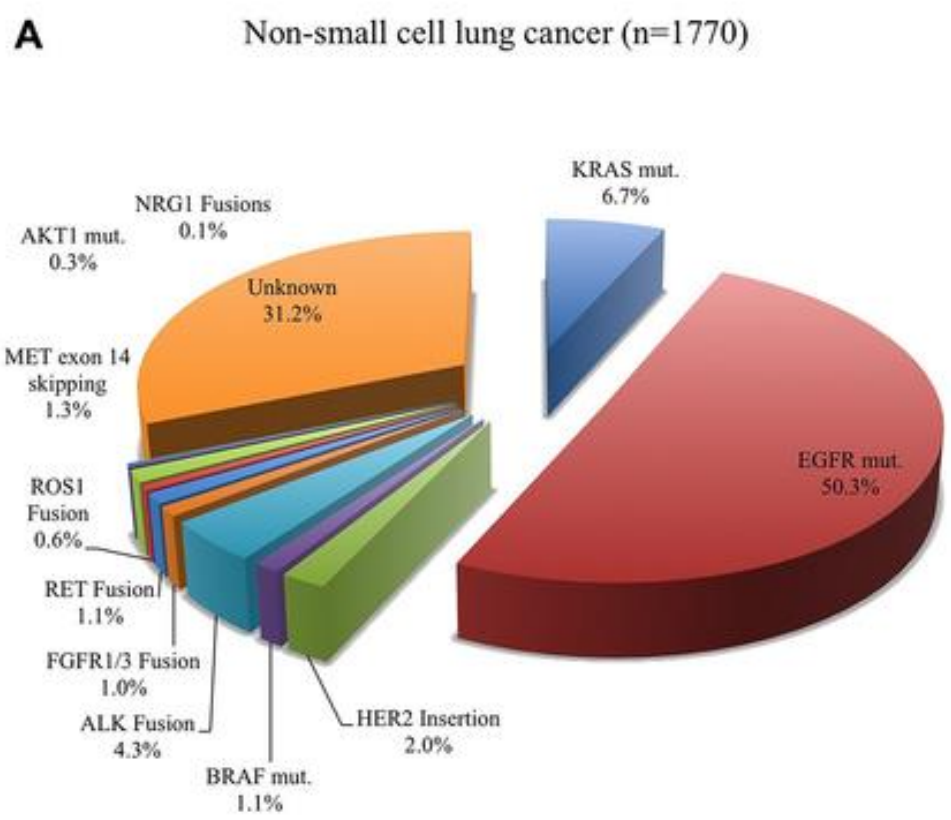
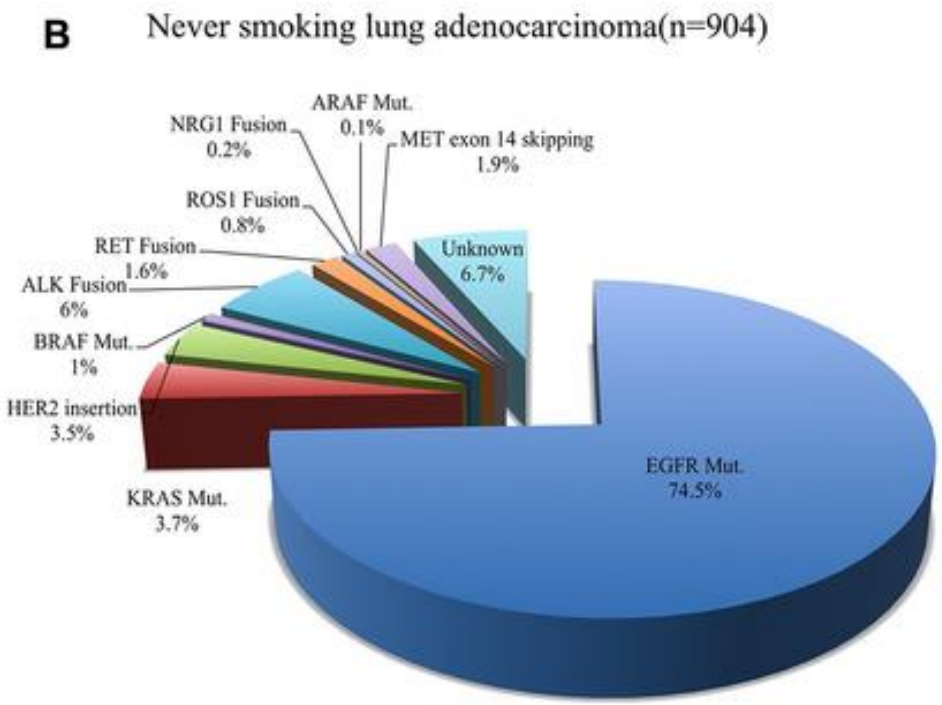
T2a, T2bN0 High-risk patients

NCCN Guidelines

- Tumors>4cm (T2bN0 = stage IIA)
- Visceral pleural involvement
- Vascular invasion
- Poorly differentiated tumors (including lung neuroendocrine tumors, excluding well-differentiated neuroendocrine tumors)
- Wedge resection
- Unknown LN status (Nx)

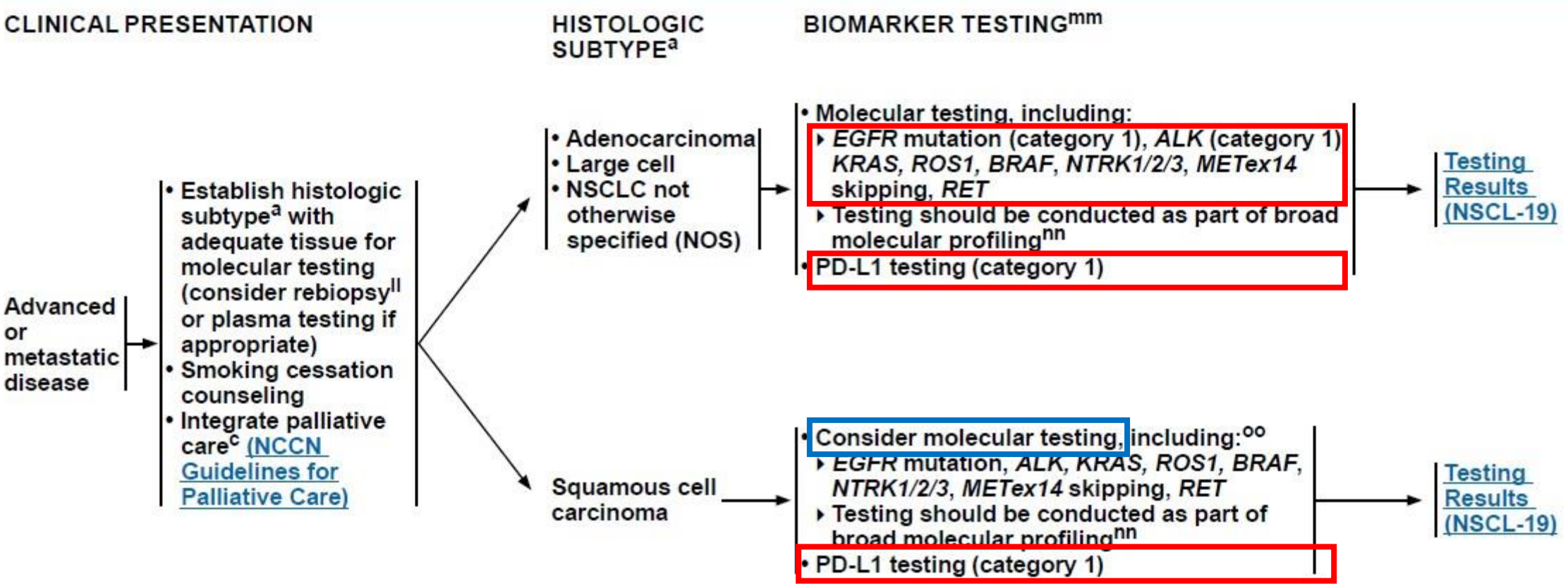
Driver mutations in NSCLC





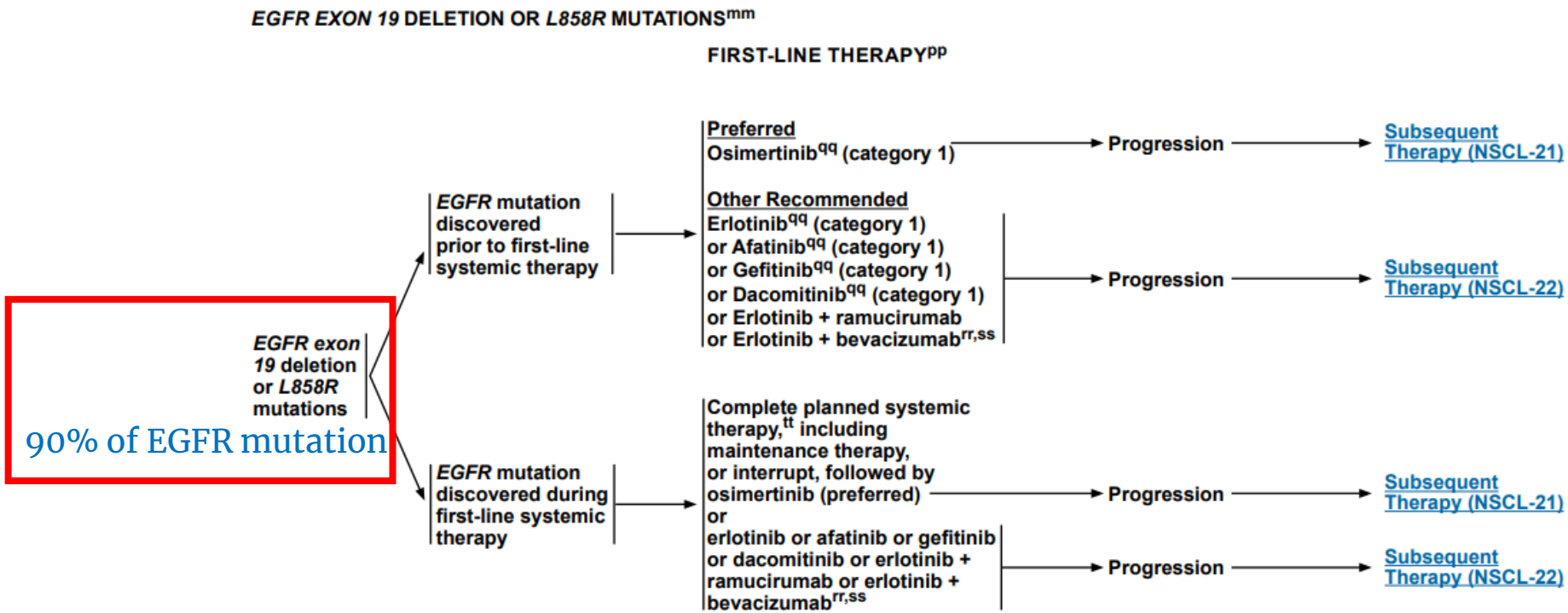
Zheng D, et al., Oncotarget, *2016.*

Biomarker testing



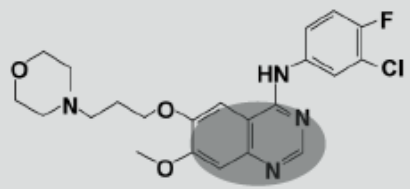
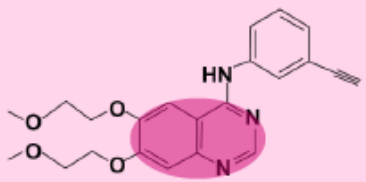
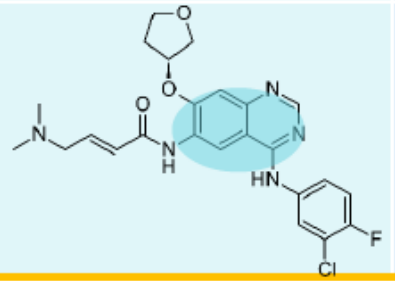
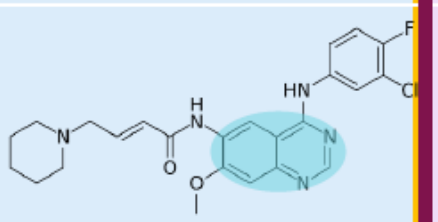
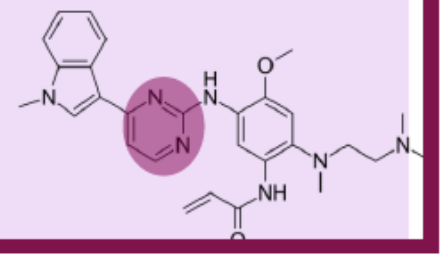
NCCN guidelines, Non-small cell lung cancer, 2022v1

EGFR mutation positive

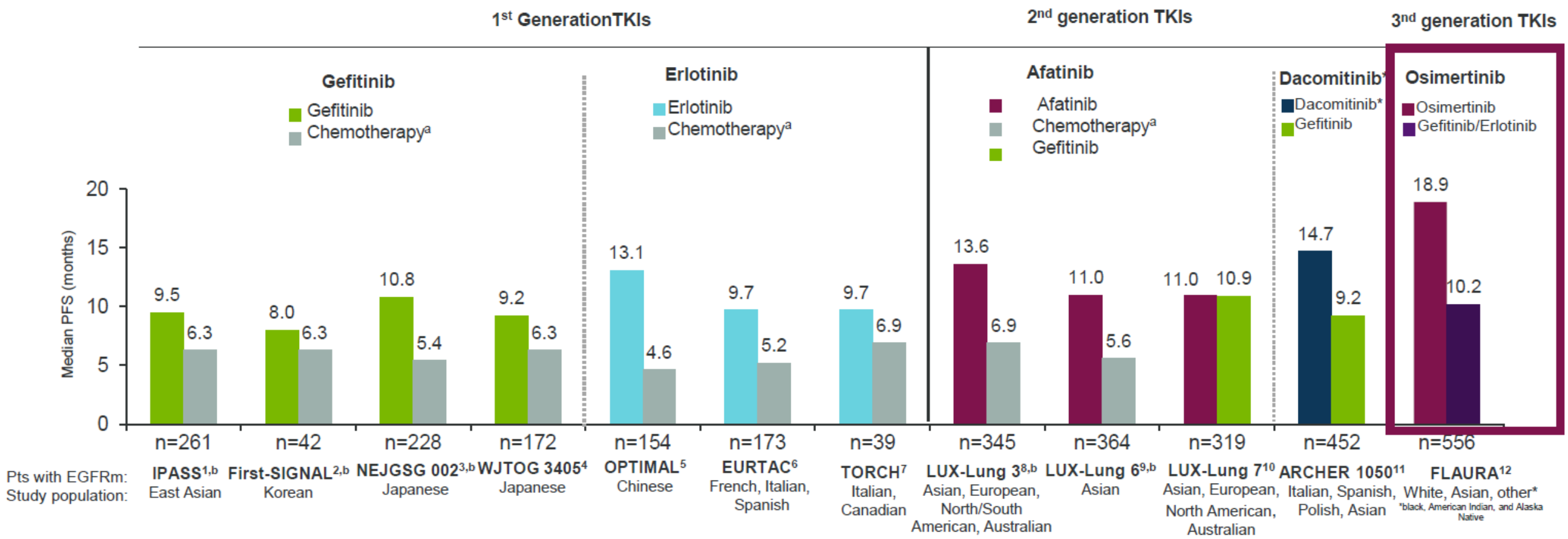


EGFR mutation	Diagnostics	drug
E19del, L858R	PANAMutyper R EGFR Cobas EGFR mutation test v2 GenesWell ddEGFR Mutation Test Pyrosequencing NGS Oncomine Dx target test	Osimertinib (Tagrisso정), gefitinib (Iressa정), erlotinib (Tarceva정), afatinib (Giotrif 정), dacomitinib (Vizimpro정), erlotinib+ramucirumab (Cyramza 주), elotinib+bevacizumab (Avastin주)
S768I, L861Q, G719X		afatinib, osimertinib, (erlotinib, gefitinib, dacomitinib)
E20ins		amivantamab, mobocertinib (2L)

Different generation of EGFR TKIs

	First generation		Second generation		Third generation
Drug	**Gefitinib[1,2,3]**	**Erlotinib[4,5,6]**	**Afatinib7-11**	**Dacomitinib[12-13]**	**Osimertinib[14-16]**
Company	AstraZeneca	Roche	Boehringer Ingelheim	Pfizer	AstraZeneca
Status	Approved	Approved	Approved	Approved	Approved
EGFR inhibition	Reversible	Reversible	Covalent, irreversible	Covalent, irreversible	Covalent, irreversible
Primary Target	wt-EGFR, EGFR: ex19del, L858R	wt-EGFR, EGFR: ex19del, L858R	wt-EGFR, EGFR: ex19del, L858R, wt-HER2, HER2 amp, HER4[a]	wt-EGFR, EGFR: ex19del, L858R, wt-HER2, mutant-HER2, HER2 amp, HER4[a]	EGFR: L858R, ex19del, T790M
Chemical structure (backbone highlighted)					
	Iressa정	**Tarceva정**	**Giotrif정**	**Vizimpro정**	**Tagrisso정**

PFS among generation EGFR-TKIs



Erlotinib + ramucirumab (VEGFR2 mAb): RELAY trial
mPFS 19.4 mo (vs 12.4 erlotinib) OS not met

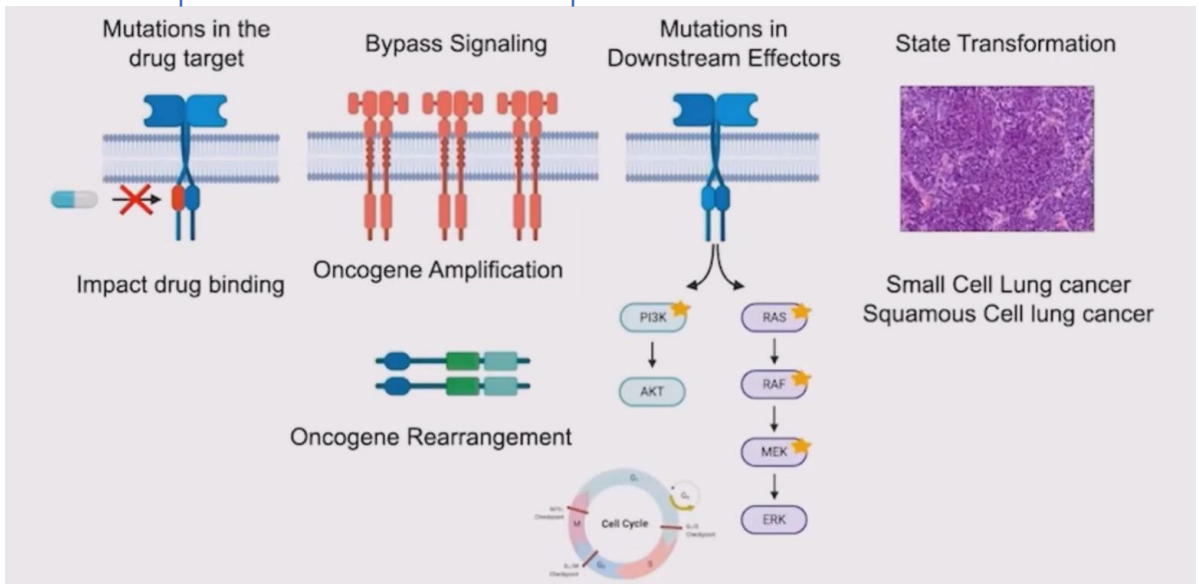
Erlotinib + bevacizumab (VEGF mAb) – NEJ026 trial
mPFS 16.9 mo (vs 13.3 erlotinib) OS not met

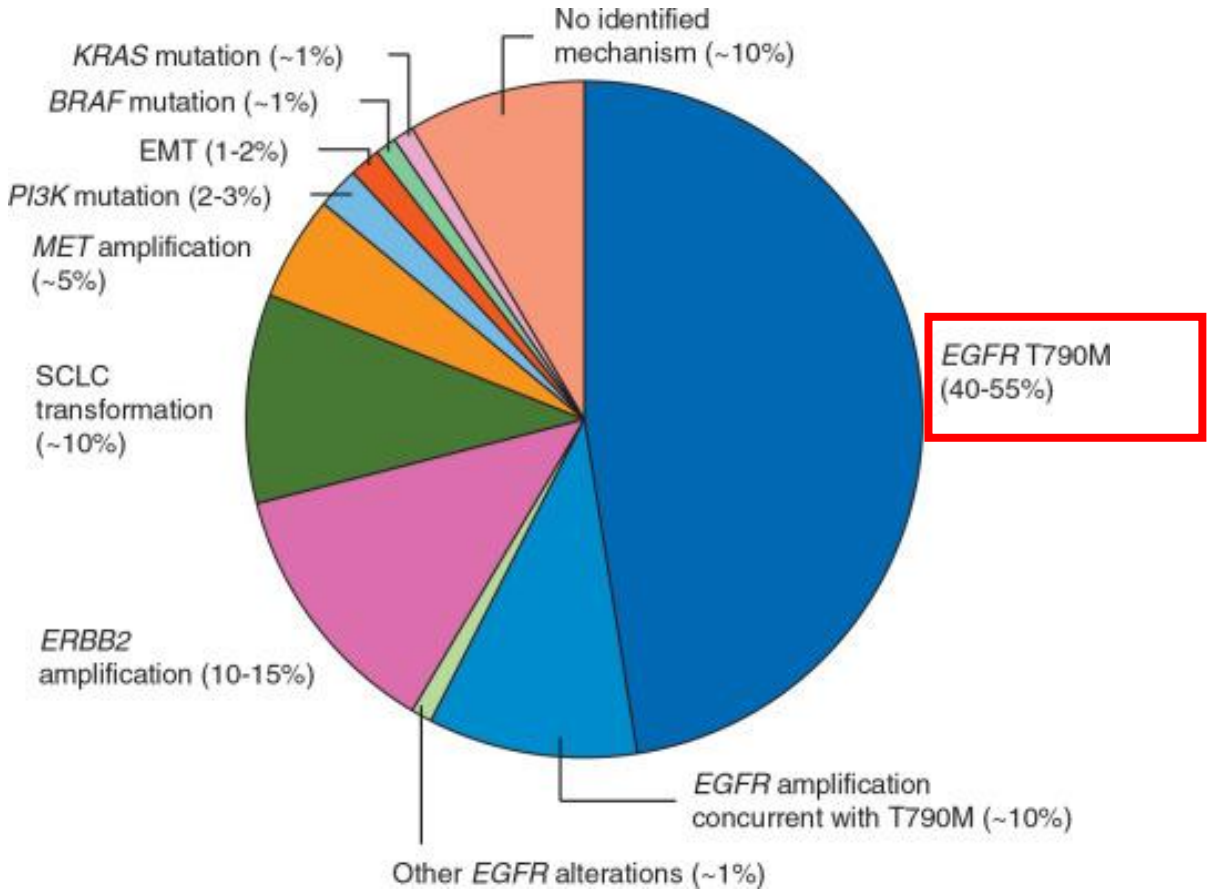
Dacomitinib (Vizimpro): ARCHER 1050
Dose reduction in 66%
mOS 34.1 mo vs 26.8 mo (vs gefitinib)
Excluded brain metastasis
, but brain PD 1/227 vs 11/225

Mechanisms of acquired resistance to first- and second-generation EGFR TKIs

Next generation TKIs

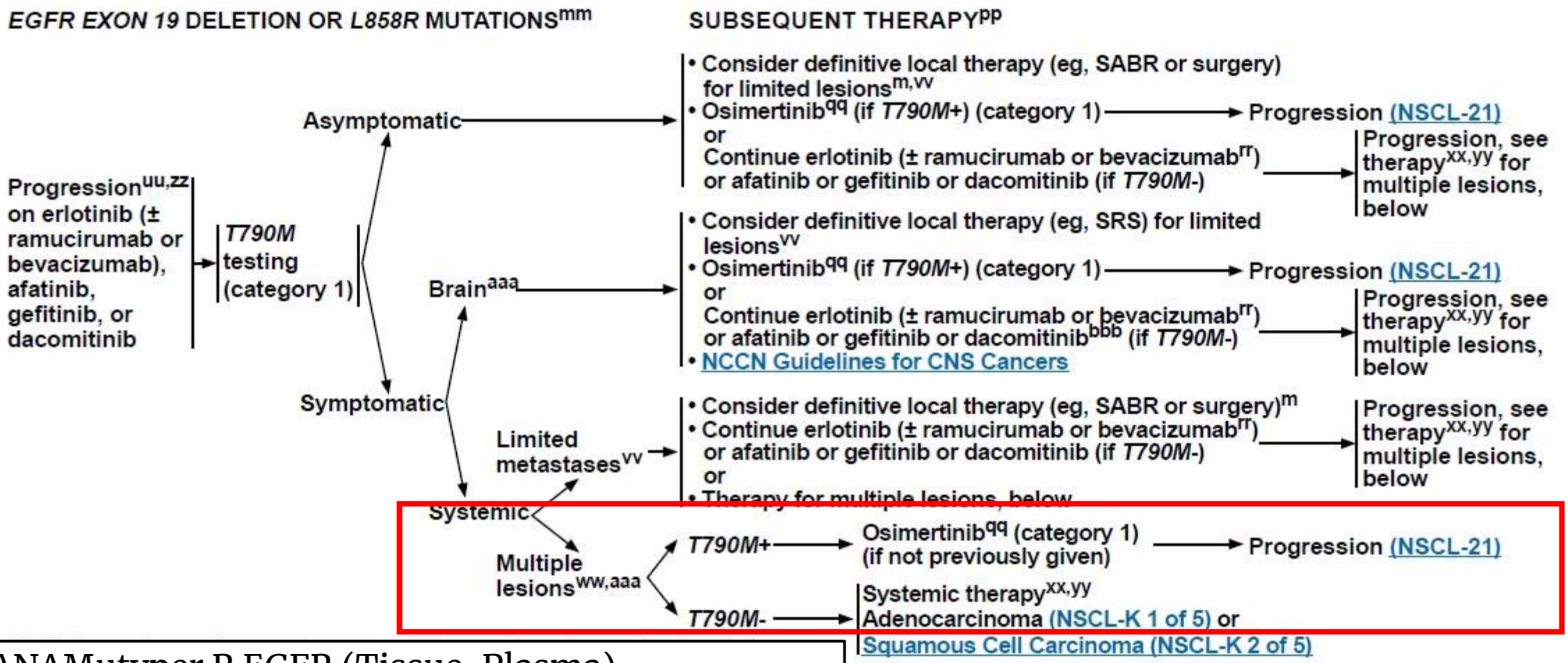
Combination approach





Ann Oncol. 2018;29(suppl_1):i10-i19

Progression after 1st/2nd generation TKIs



PANAMutyper R EGFR (Tissue, Plasma)
Cobas EGFR mutation test v2 (Tissue, Plasma)
GenesWell ddEGFR Mutation Test (Tissue)

Osimertinib, Lazertinib (국내)

T790M detection

	Tissue biopsy	Liquid biopsy
Gold standard	Yes	
Invasiveness	High	Low
Reflecting tumor heterogeneity	Low	High
Turnaround time	Longer	Shorter
Convenience for serial measurement	No	Yes
Detection of transdiff. to SCLC or SQ	Yes	No
Sensitivity	Higher	Lower
Limitation	Patient performance Insufficient samples	Low sensitivity for low tumor burden
		Non-shedding tumors: 15-20% -lack of tumor vascularization -low proliferation rate -CNS-only disease

Plasma T790M positivity
: similar efficacy of Osimertinib
as tissue T790M positivity

<u>Usual practice</u>
EGFR mutation by ctDNA first

If T790M(+): Osimertinib
If T790M(-) : tissue rebiopsy

1st line osimertinib

Resistance after 1st/2nd Gen TKIs d/t T790M: 50 ~ 60 %

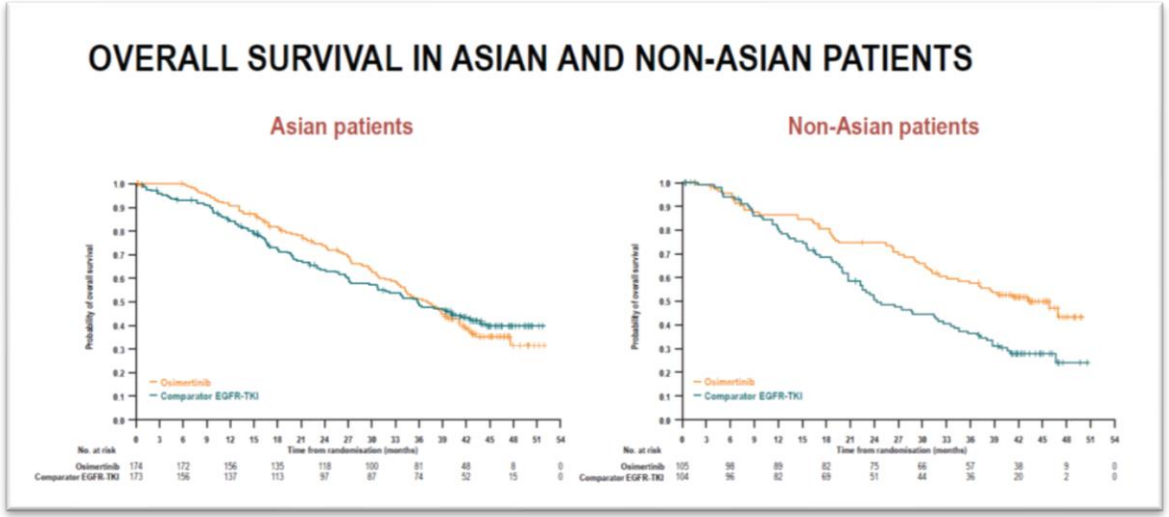
Rebiopsy success: 60 ~ 80 %

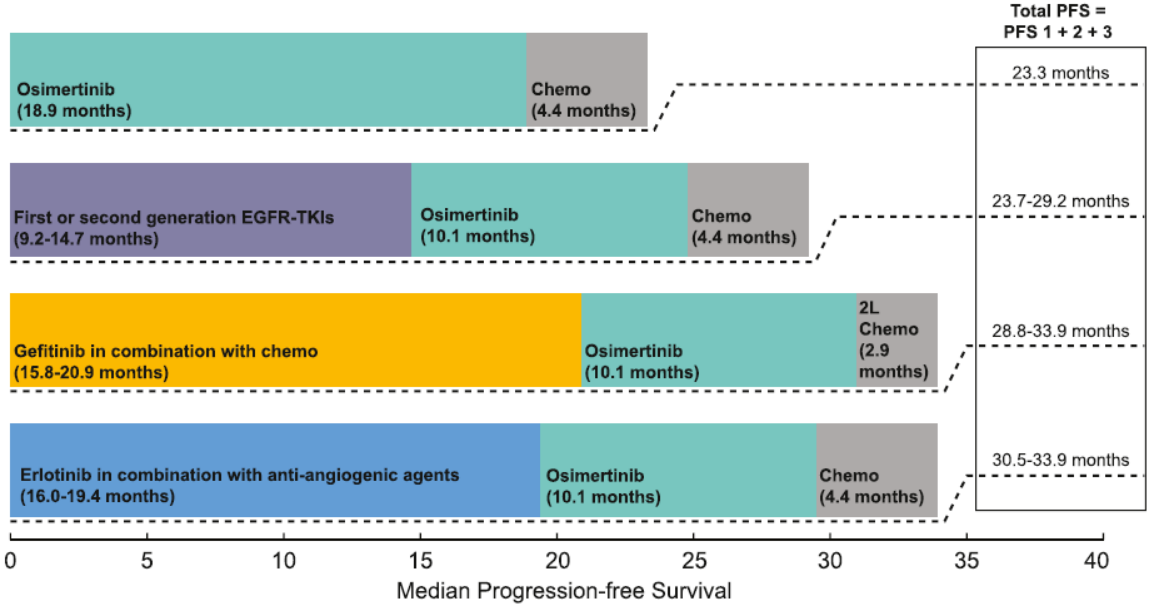
Eligible for osimertinib: 30 ~ 40% of 1L EGFR-TKI resistance

FLAURA trial (N Engl J Med 2020;382:41-50.)

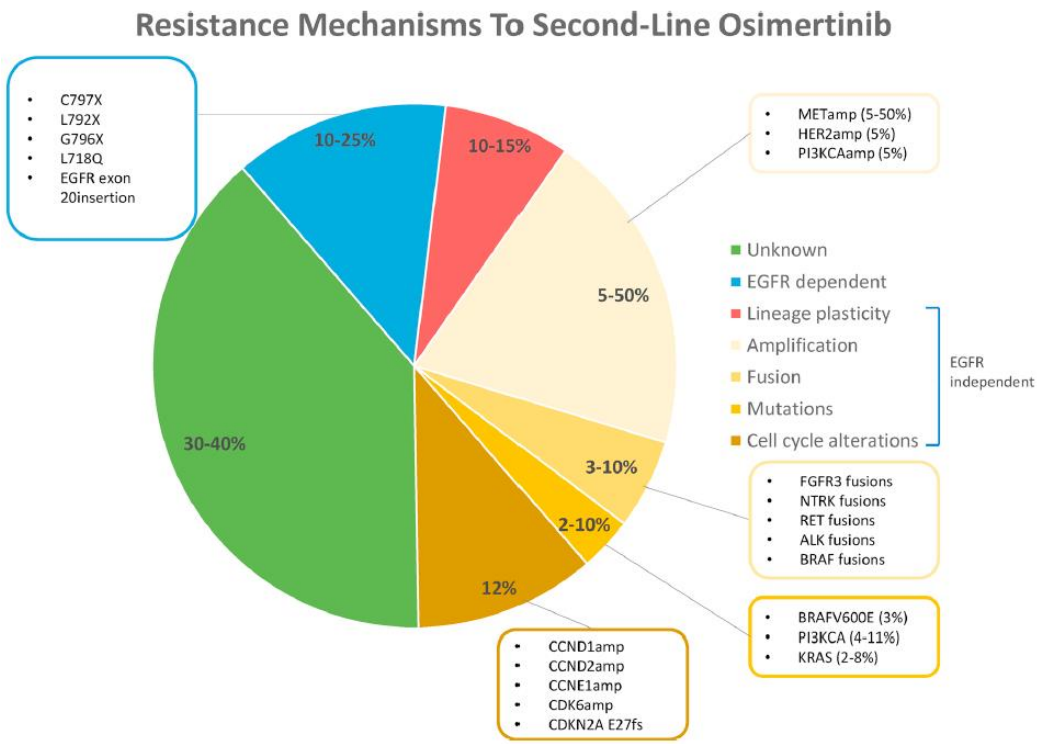
PFS vs gefitinib HR 0.46 (0.37-0.57)

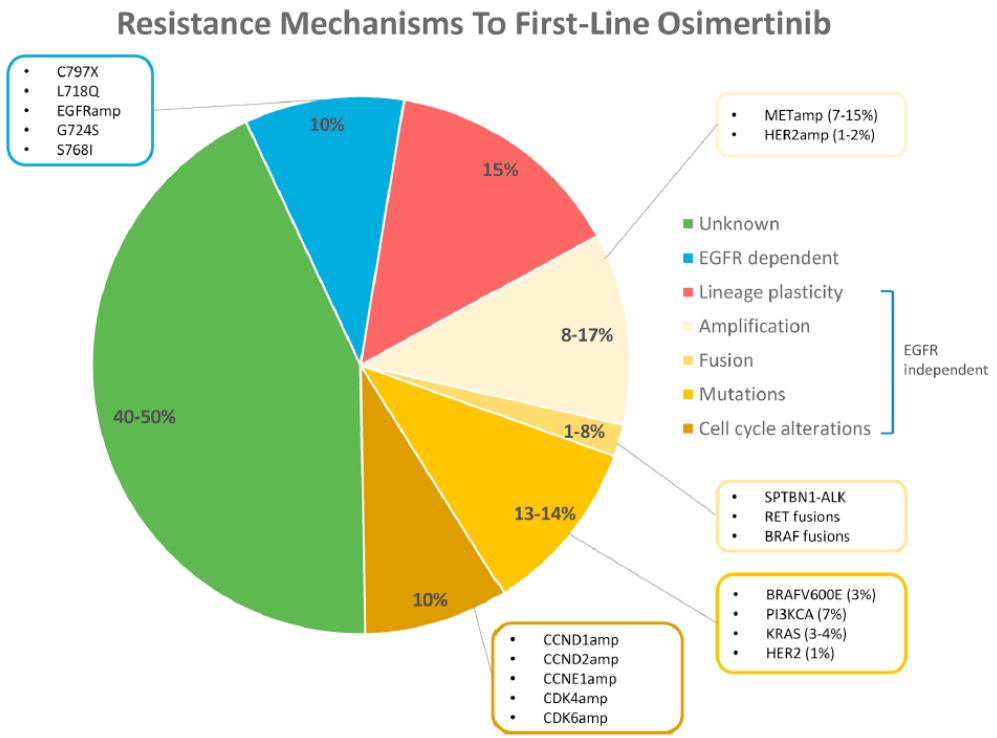
OS vs gefitinib HR 0.80 (0.64-1.00)





Mechanisms of osimertinib resistance





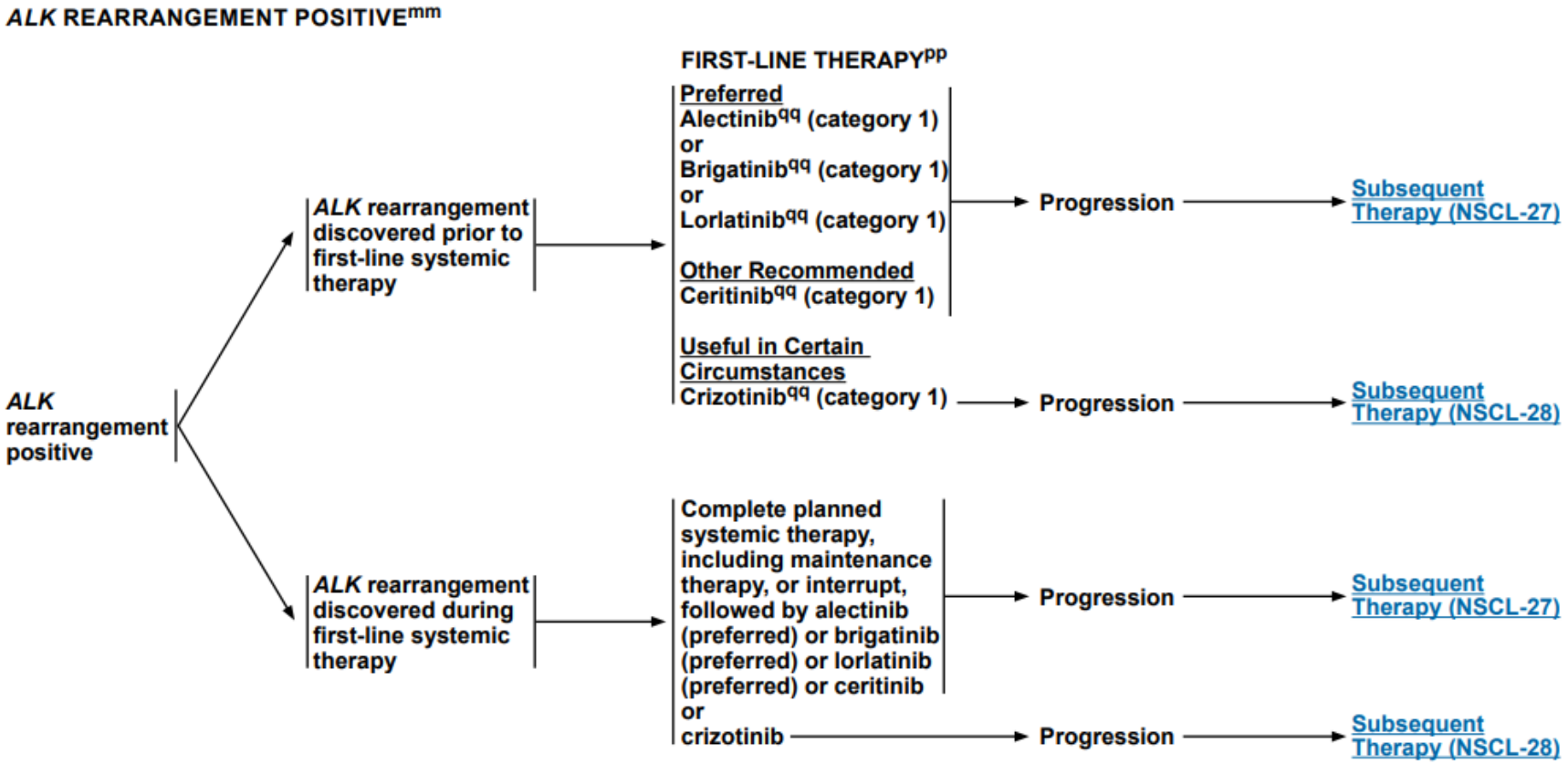
m/c: MET amplification, EGFR C797S

Ex) Amivantamab (EGFR-MET bispecific antibody)+ lazertinib

Lung Cancer. 2020;147:123-129.

ALK rearrangement positive

Alectinib (Alecensa정), brigatinib (Alunbrig정), lorlatinib (Lorviqua정), crizotinib (Xalkori정), Ceritinib (Zykadia정)



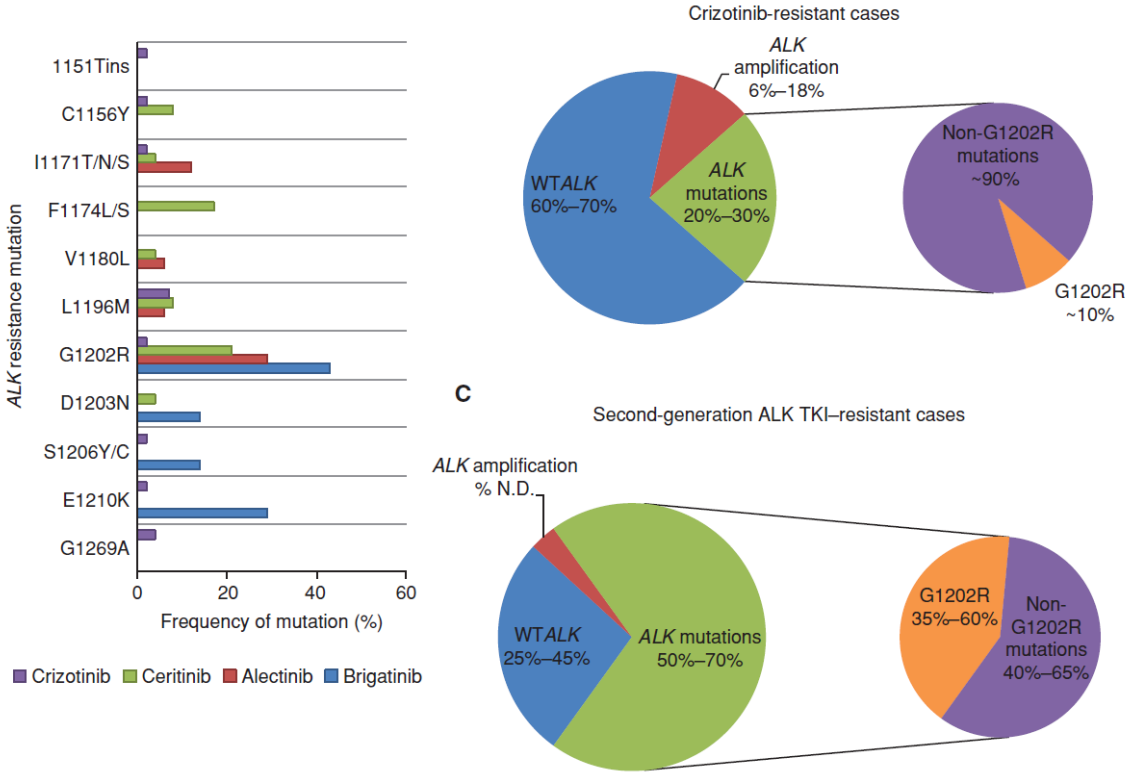
VENTANA anti-ALK(D5F3) CDx
Vysis ALK Break Apart FISH
: NGS에서 확인되었더라도 위의 2가지 중 하나로 confirm 필요

	Crizotinib (n=171)		Ceritinib (n=189)		Alectinib (n=152)		Brigatinib (n=136)	
AEs	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Vision Disorder	71%	1%	-	-	2%	0%	-	-
Diarrhea	61%	2%	85%	5%	12%	0%	49%	1%
Nausea	56%	1%	69%	3%	14%	1%	26%	1%
Edema	49%	1%	-	-	17%	0%	4%	1%
Vomiting	46%	2%	66%	5%	7%	0%	18%	1%
Constipation	43%	2%	19%	0%	-	-	15%	0%
Elevated AST/ALT	36%	14%	60%	31%	15%	5%	-	-
Decreased Appetite	30%	2%	34%	1%	-	-	7%	1%
Fatigue	29%	3%	29%	4%	-	-	-	-
Dysgeusia	26%	0%	-	-	3%	0%	4%	0%
Headache	22%	1%	16%	0%	-	-	-	-
Abdominal Pain	-	-	25%	2%	-	-	4%	1%
Myalgia	-	-	-	-	16%	0%	6%	0%
Musculoskeletal Pain	-	-	-	-	7%	0%	4%	0%
Neuropathy	20%	1%	-	-	-	-	-	-
Pyrexia	19%	0%	18%	0%	-	-	-	-
Dizziness	18%	0%	-	-	8%	0%	-	-
Asthenia	13%	0%	17.5%	3%	-	-	-	-
Photosensitivity	-	-	-	-	5%	1%	-	-
ILD	2.9%	1%	2.1%	1.2%	0.4%	0.4%	3%	-

1. Solomon B et al, NEJM 2014 2. Soria JC et al. Lancet. 2017;389(10072):917-929 3. Solange P et al. N Engl J Med 2017;377:829 4. Camidge P et al. N Engl J Med 2018;379:2027

with food with food

Ontarget ALK-TKI resistance



Cellular ALK phosphorylation mean IC_{50} (nmol/L)

Mutation status	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
Parental Ba/F3	763.9	885.7	890.1	2774.0	11293.8
EML4–ALK V1	38.6	4.9	11.4	10.7	2.3
EML4–ALK C1156Y	61.9	5.3	11.6	4.5	4.6
EML4–ALK I1171N	130.1	8.2	397.7	26.1	49.0
EML4–ALK I1171S	94.1	3.8	177.0	17.8	30.4
EML4–ALK I1171T	51.4	1.7	33.6[a]	6.1	11.5
EML4–ALK F1174C	115.0	38.0[a]	27.0	18.0	8.0
EML4–ALK L1196M	339.0	9.3	117.6	26.5	34.0
EML4–ALK L1198F	0.4	196.2	42.3	13.9	14.8
EML4–ALK G1202R	381.6	124.4	706.6	129.5	49.9
EML4–ALK G1202del	58.4	50.1	58.8	95.8	5.2
EML4–ALK D1203N	116.3	35.3	27.9	34.6	11.1
EML4–ALK E1210K	42.8	5.8	31.6	24.0	1.7
EML4–ALK G1269A	117.0	0.4	25.0	ND	10.0
EML4–ALK D1203N+F1174C	338.8	237.8	75.1	123.4	69.8
EML4–ALK D1203N+E1210K	153.0	97.8	82.8	136.0	26.6

$IC_{50} \leq 50$ nmol/L

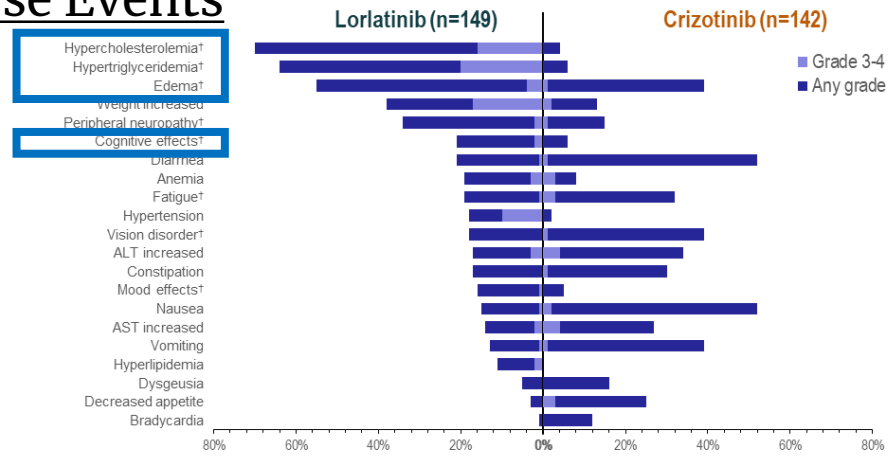
$IC_{50} > 50 < 200$ nmol/L

$IC_{50} \geq 200$ nmol/L

1st line	Median PFS	HR (95% CI) vs crizotinib
Alectinib	25.7 months	0.50 (0.36-0.70)
Brigatinib	24.0 months	0.49 (0.35-0.68)
Lorlatinib	NR	0.28 (0.19-0.41)

Intracranial efficacy:
lorlatinib>alectinib or brigatinib>crizotinib

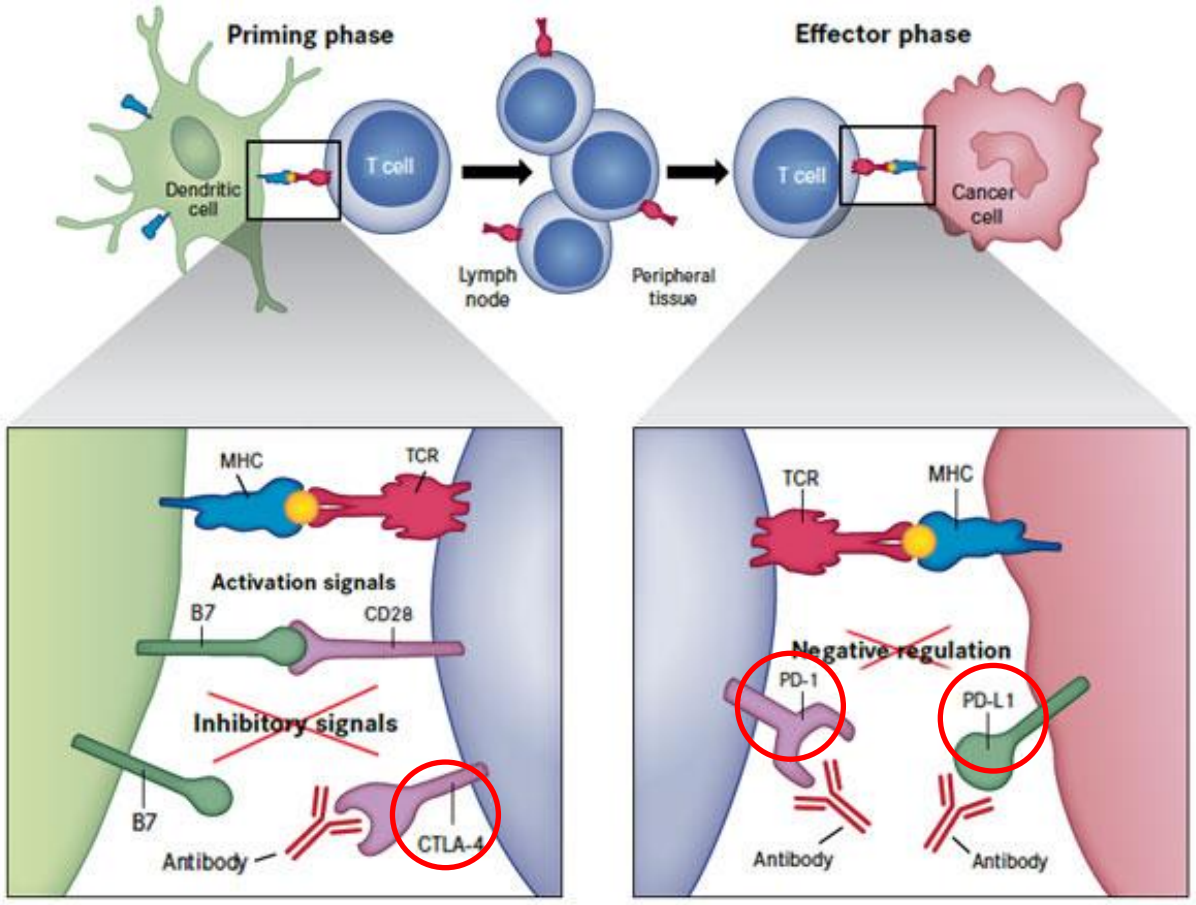
Adverse Events

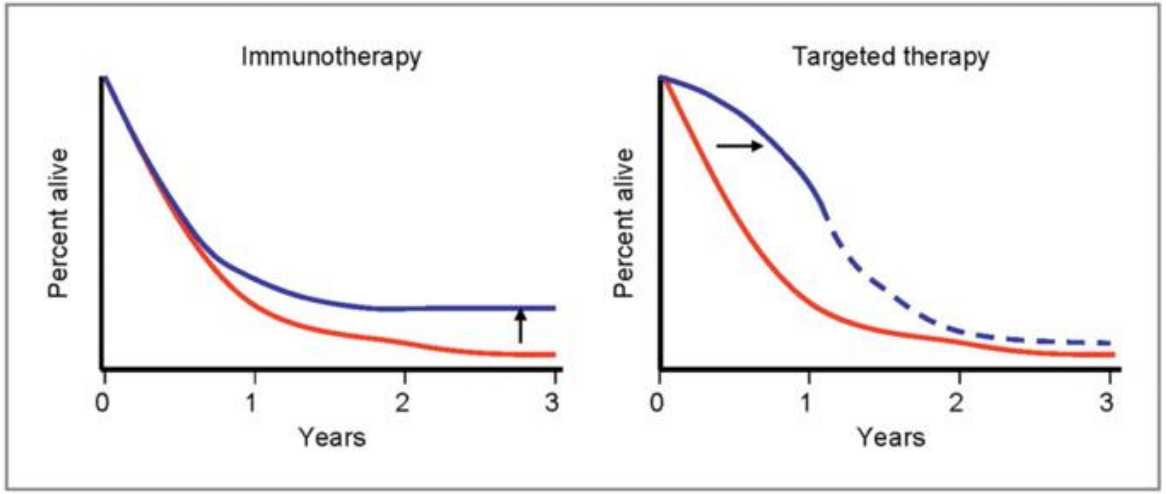


Other driver mutations and targeted agents

mutation	Diagnostics	Drug
ROS1 rearrangement	AmoyDx ROS1 Gene Fusions Detection Kit ROS1 SP384 Assay (screening) Oncomine Dx target test	Enterectinib (Rozlytrek캡슐, 허), crizotinib (급), ceritinib (허초), lorlatinib (2L)
BRAF V600E	NGS Oncomine Dx target test PNAClamp BRAF Mutation Detection Kit (screening)	Dabrafenib+trametinib (Rafinlar캡슐 +Meqsel정, 급), vmurafenib, dabrafenib
NTRK 1/2/3 fusion	NGS	Larotrectinib (Vitrakvi캡슐, 허), entrectinib (허)
METex14 skipping	NGS Oncomine Dx target test	Capmatinib (Tabrecta정, 허가전), tepotinib, crizotinib
RET rearrangement	NGS	Selpercatinib 허가전, pralsetinib 허가전, cabozantinib
KRAS G12C	NGS	Sotorasib (2L)허가전

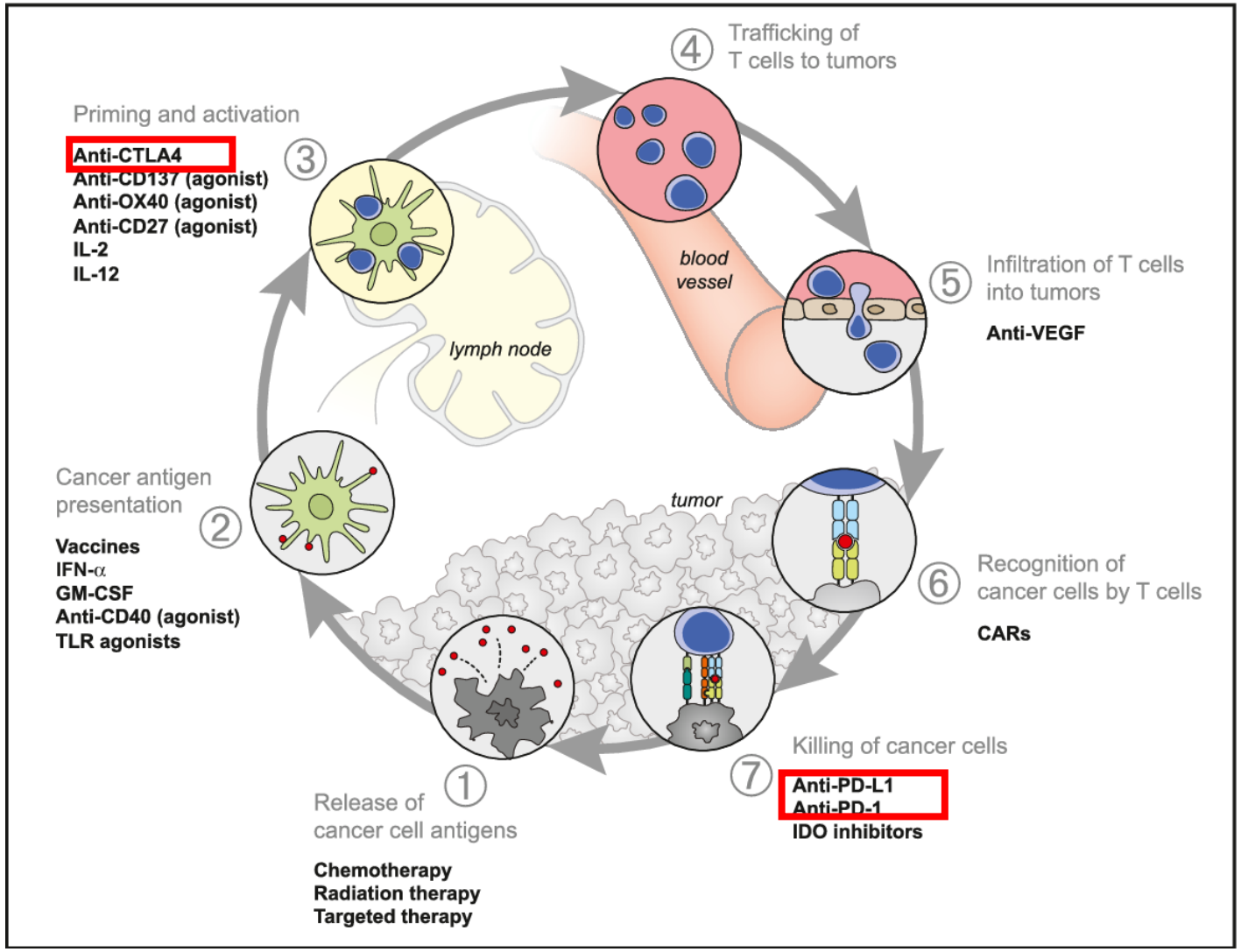
Immune checkpoint inhibitor





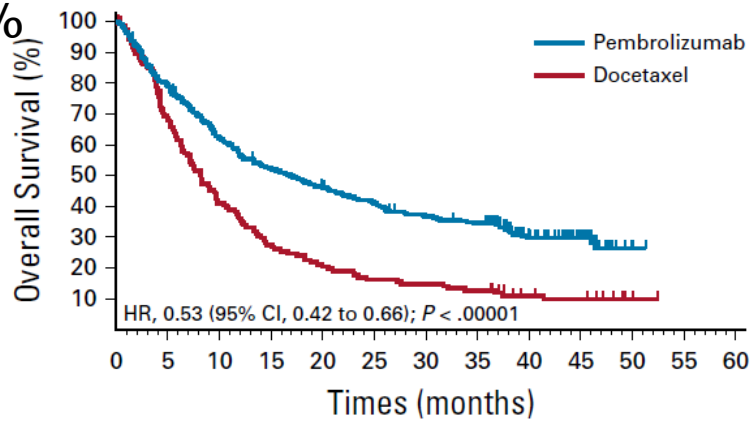
N Engl J Med 2012;366:2517-9

Cancer immunity cycle



2L mono NSCLC PD-L1 > 50% ORR 30%

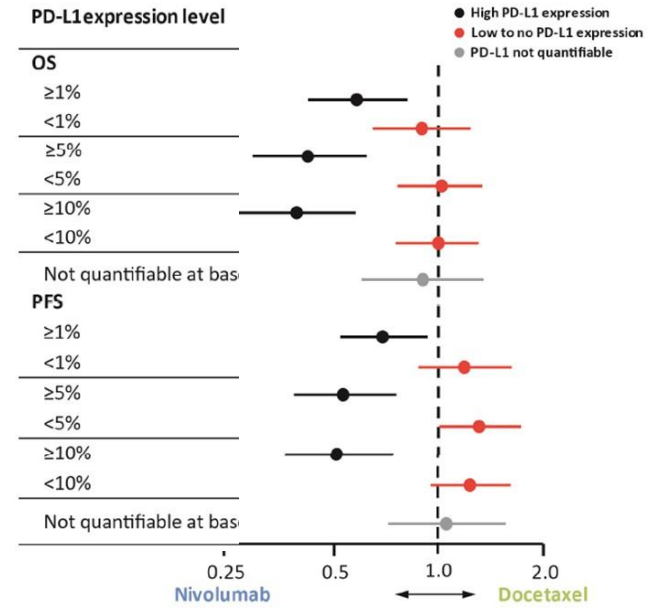
	Overall survival events, n/N (%)	Median overall survival, months (95% CI)	36-month overall survival rate, % (95% CI)
Pembrolizumab	199/290 (68.6)	16.9 (12.3 to 21.4)	34.5 (29.0 to 40.1)
Docetaxel	127/152 (83.6)	8.2 (6.4 to 9.8)	12.7 (7.9 to 18.8)



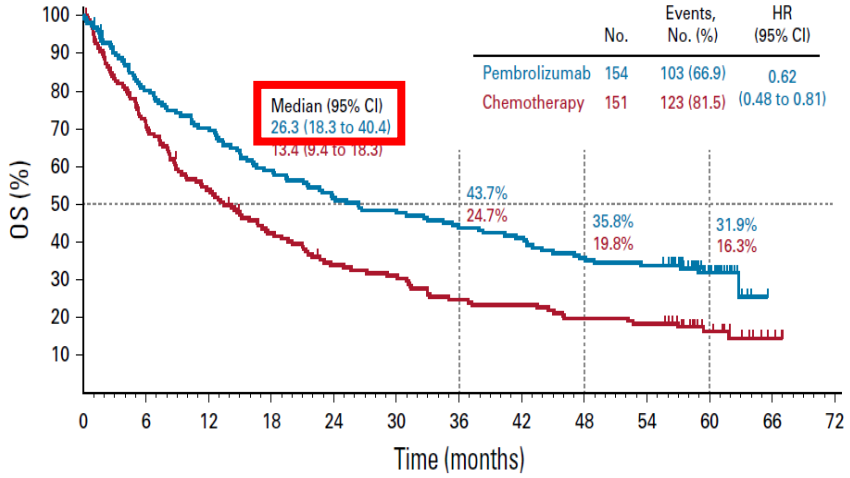
No. at risk:

Pembrolizumab	290	229	178	149	131	115	101	94	50	26	1	0	0
Docetaxel	152	97	58	39	29	23	21	18	10	8	1	0	0

2L mono Non-SQ



1L mono NSCLC PD-L1 > 50% ORR 46%

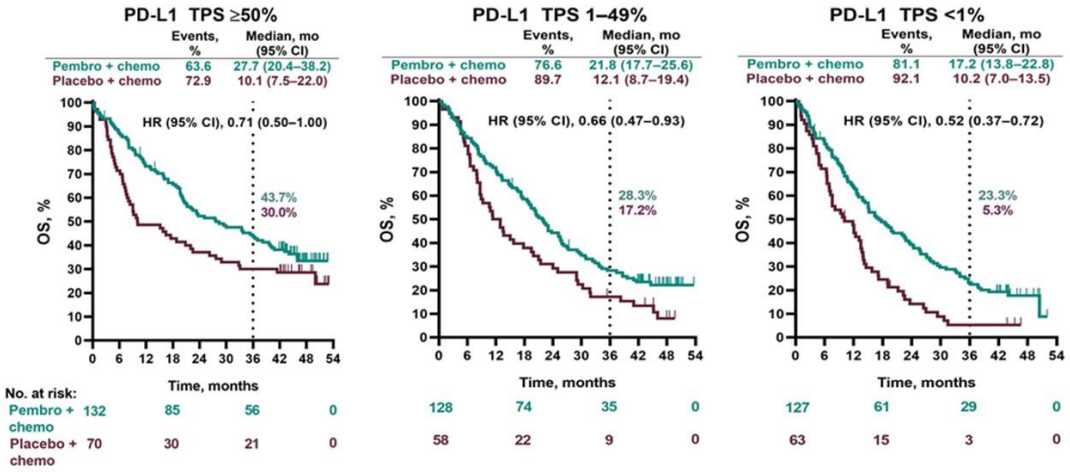


No. at risk:

Pembrolizumab	154	121	106	89	78	73	66	62	54	51	20	0	0
Chemotherapy	151	108	80	61	48	44	35	33	28	26	13	3	0

1L ICI+CTx combo, Non-SQ

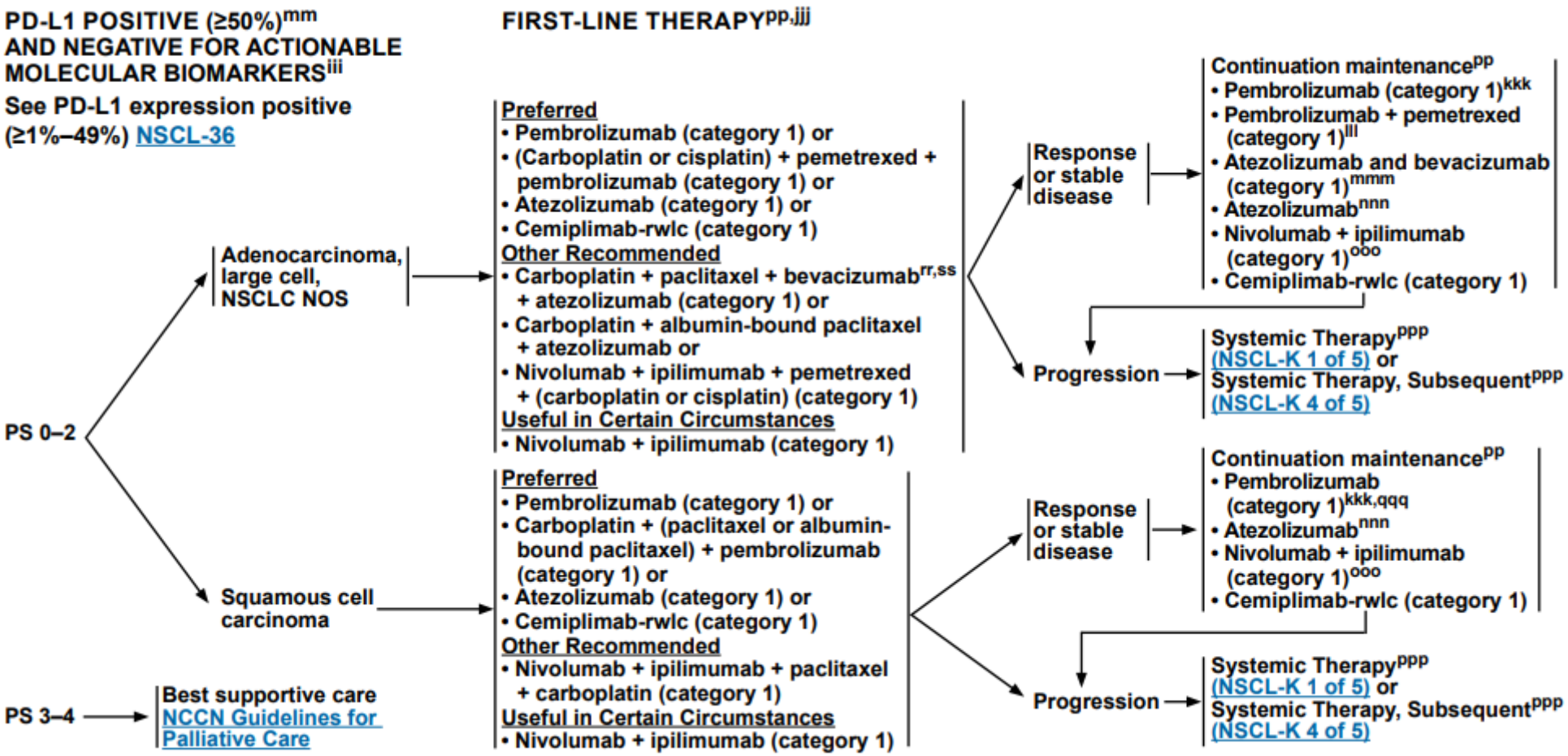
ORR 62% 50% 33%



No. at risk:

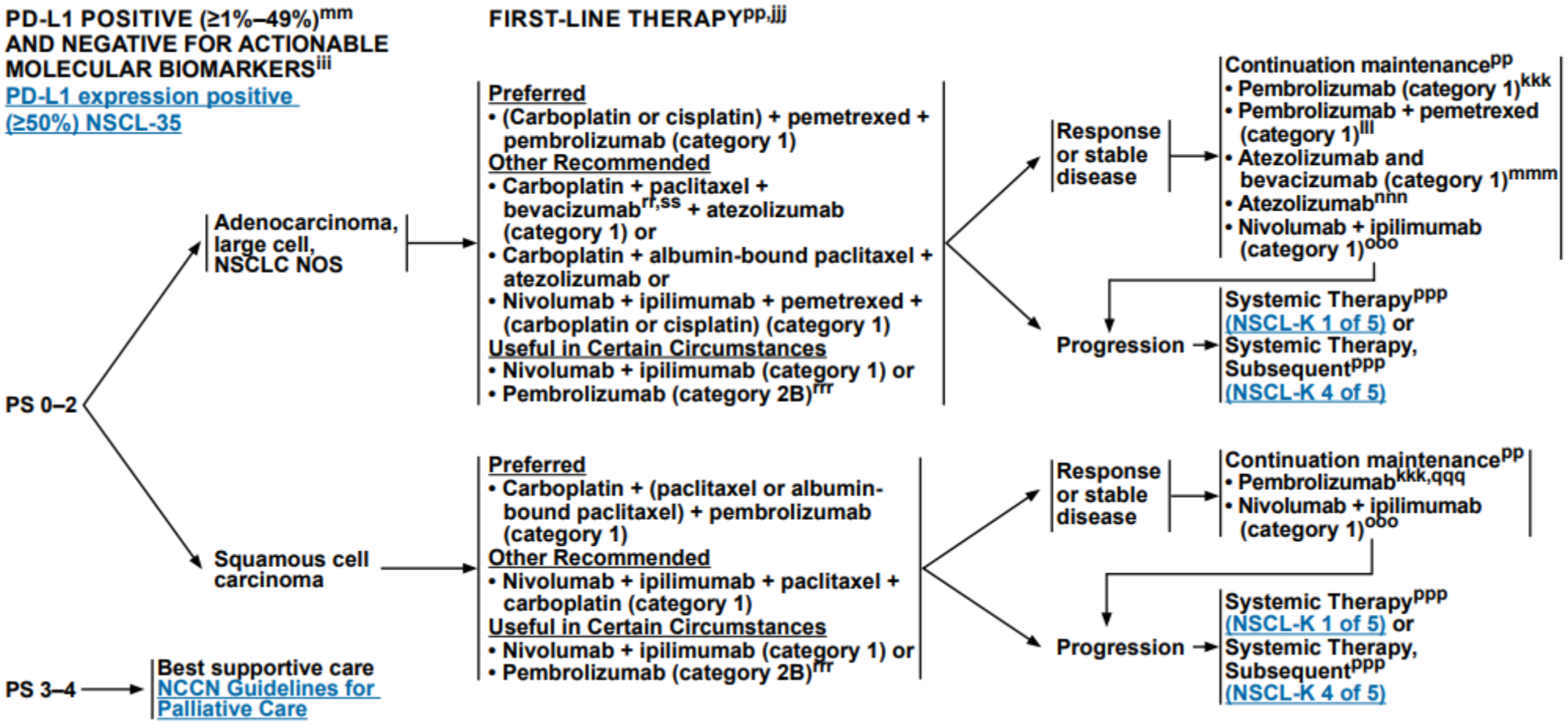
Pembro + chemo	132	85	56	0	
Placebo + chemo	70	30	21	0	
	128	74	35	0	
	58	22	9	0	
	127	61	29	0	
	63	15	3	0	

PD-L1 ≥ 50%



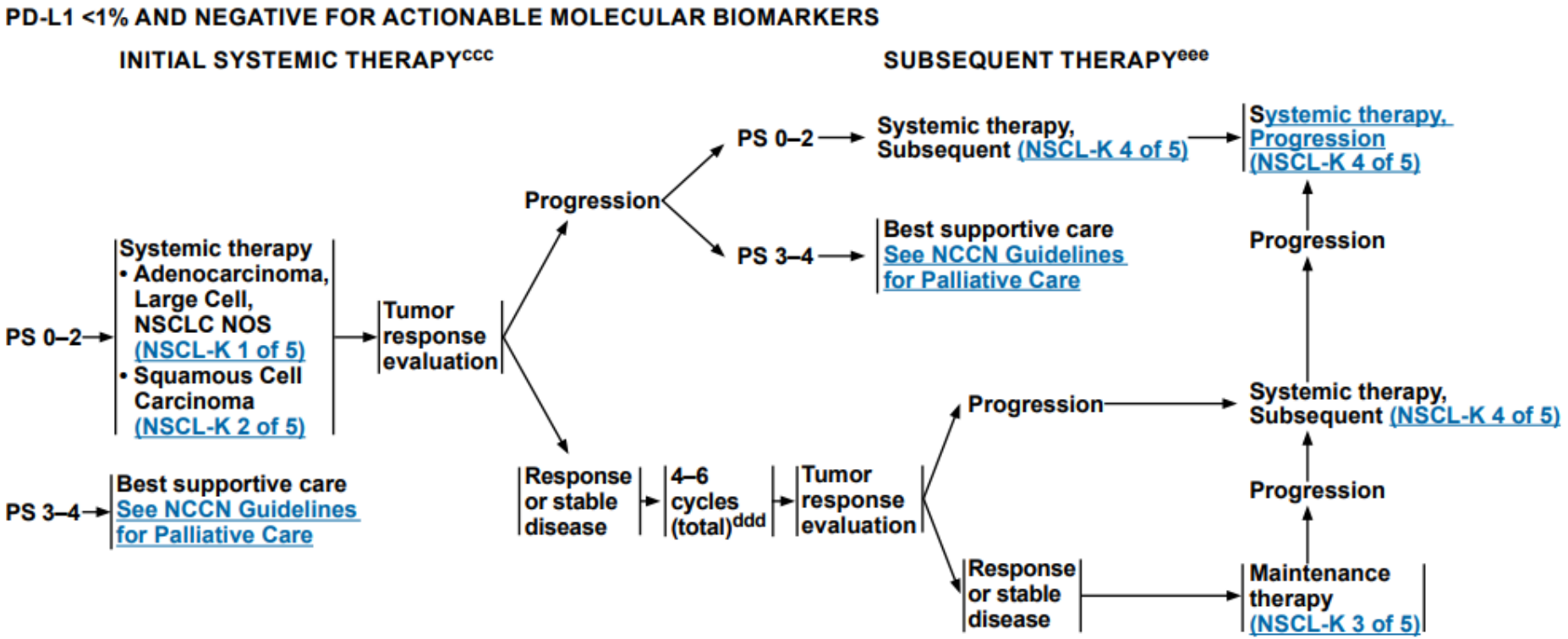
NCCN guidelines, Non-small cell lung cancer, 2022v1

PD-L1 1~49%



NCCN guidelines, Non-small cell lung cancer, 2022v1

PD-L1 < 1%



ADENOCARCINOMA, LARGE CELL, NSCLC NOS (PS 0–1)

No contraindications to PD-1 or PD-L1 inhibitors[d]

Preferred

- Pembrolizumab/carboplatin/pemetrexed (category 1)[1,2,e]
- Pembrolizumab/cisplatin/pemetrexed (category 1)[2,e]

Other Recommended

- Atezolizumab/carboplatin/paclitaxel/bevacizumab[e] (category 1)[3,f,g,h,i]
- Atezolizumab/carboplatin/albumin-bound paclitaxel[4,e]
- Nivolumab/ipilimumab[5,d]
- Nivolumab/ipilimumab/pemetrexed/(carboplatin or cisplatin) (category 1) [6,e]

SQUAMOUS CELL CARCINOMA (PS 0–1)

No contraindications to PD-1 or PD-L1 inhibitors[d]

Preferred

- Pembrolizumab/carboplatin/paclitaxel (category 1)[34,e]
- Pembrolizumab/carboplatin/albumin-bound paclitaxel (category 1)[34,e]

Other recommended

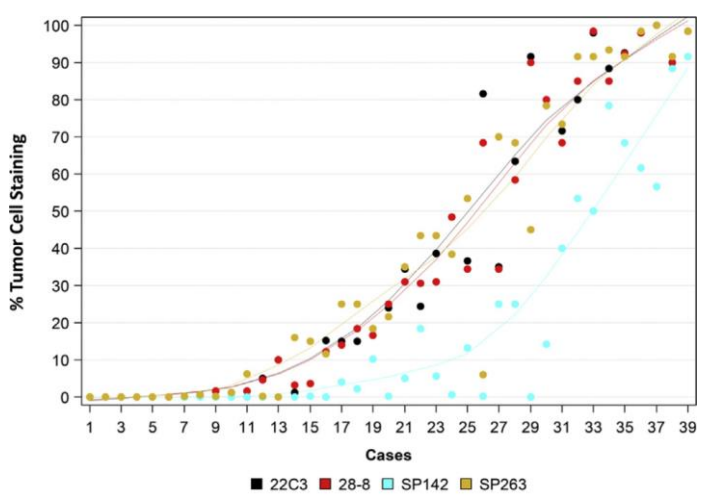
- Nivolumab/ipilimumab[5,e]
- Nivolumab/ipilimumab/paclitaxel/carboplatin (category 1)[6,e]

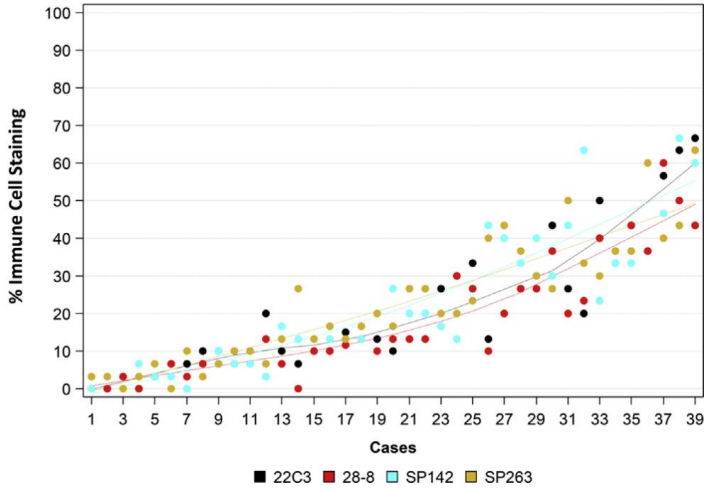
NCCN guidelines, Non-small cell lung cancer, 2022v1

Multiple antibodies & no standardized interpretation

Drug	Drug Target	PD-L1 IHC assay	PD-L1 Ab epitope	Auto stainer	Detection system
Nivolumab	PD1	**28-8**	Extracellular	Dako Link 48	Envision Flex
Pembrolizumab	PD1	**22C3**	Extracellular		
Atezolizumab	PD-L1	**SP142**	Cytoplasmic	Ventana Benchmark	Optiview + Amplification
Durvalumab	PD-L1	**SP263**	Cytoplasmic		Optiview
Avelumab	PD-L1	**73-10**	Cytoplasmic	Dako Link 48	Envision Flex

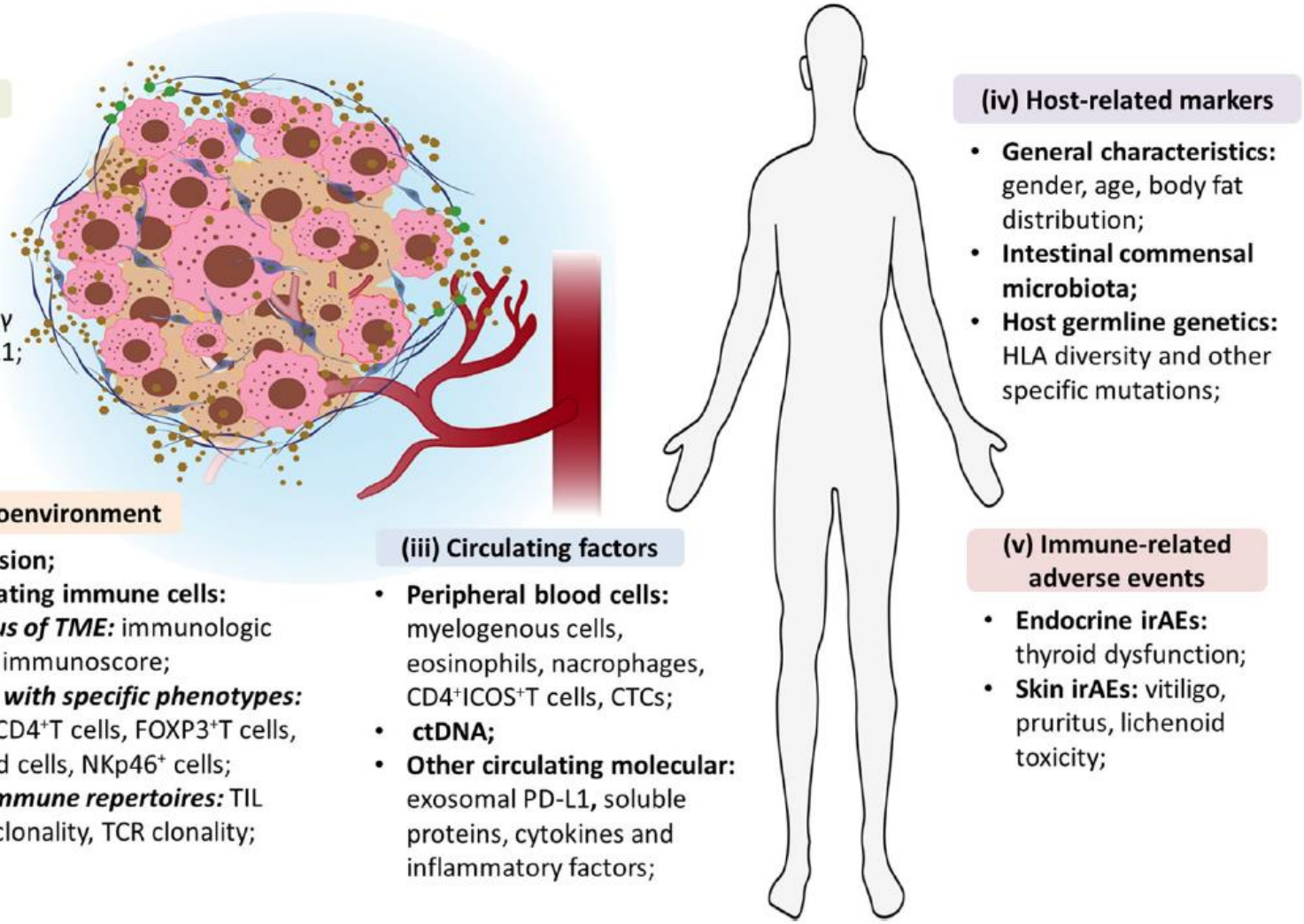
PD-L1 expression on tumor & immune cells Blueprint phase1



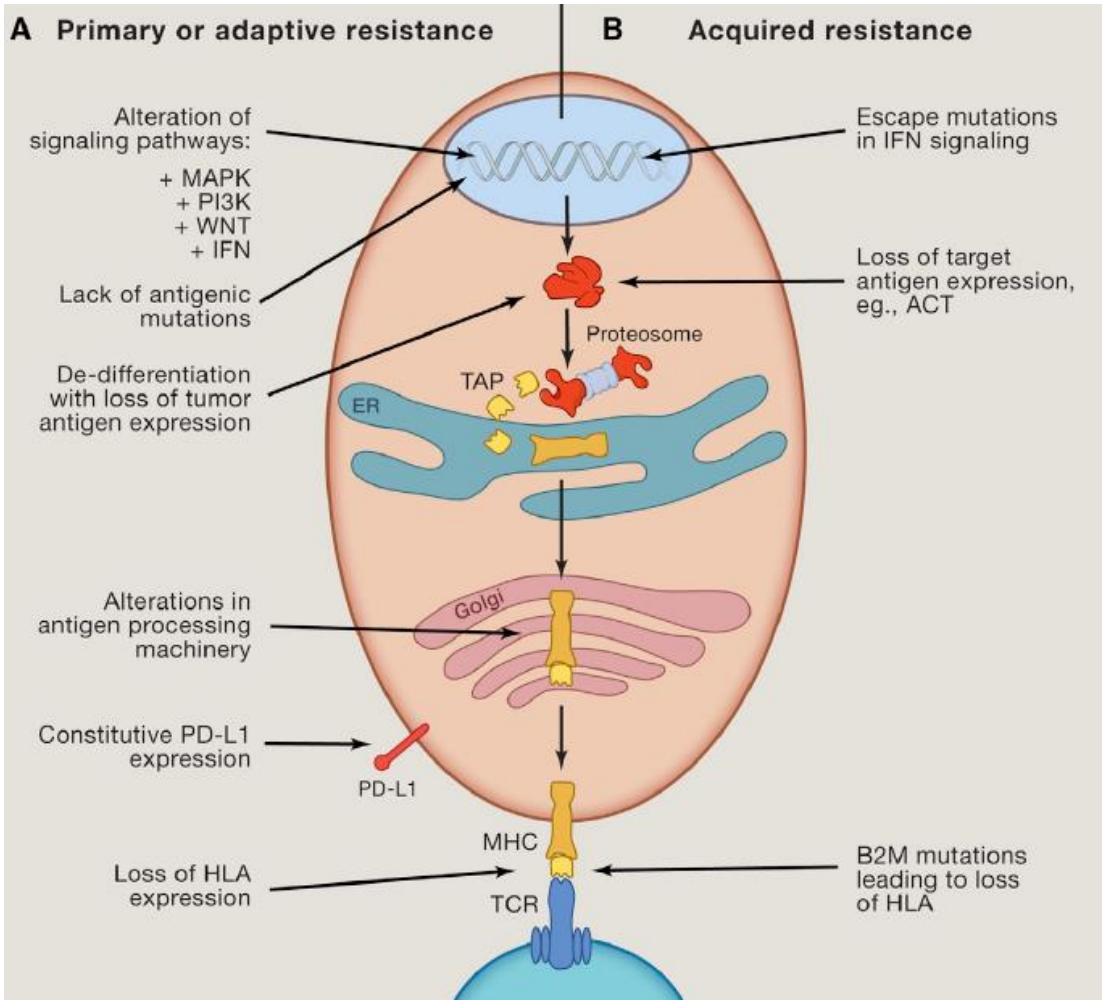


J Thorac Oncol 2017;12:208-22

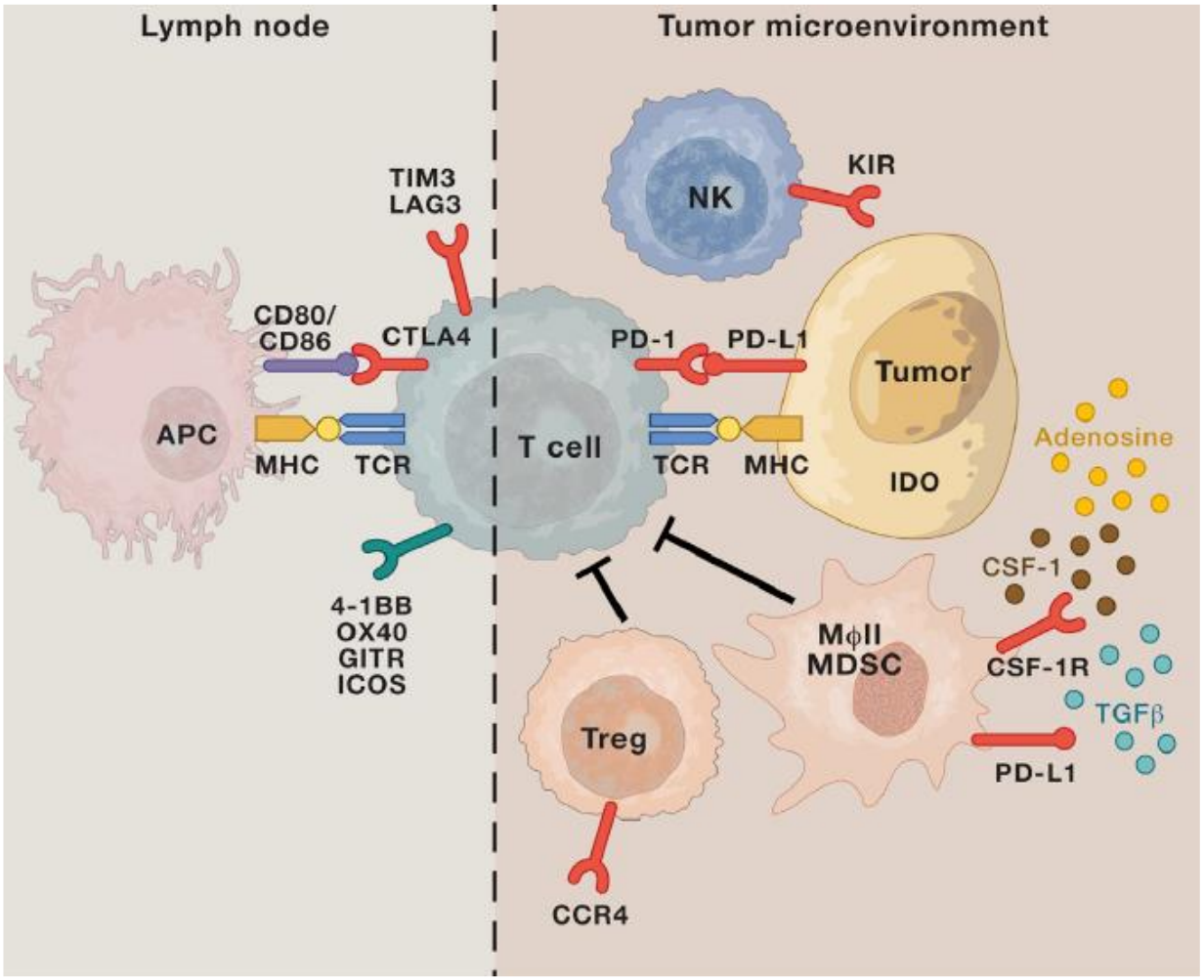
Predictive biomarkers for ICI efficacy



Resistance to Immunotherapy



Intrinsic Mechanisms

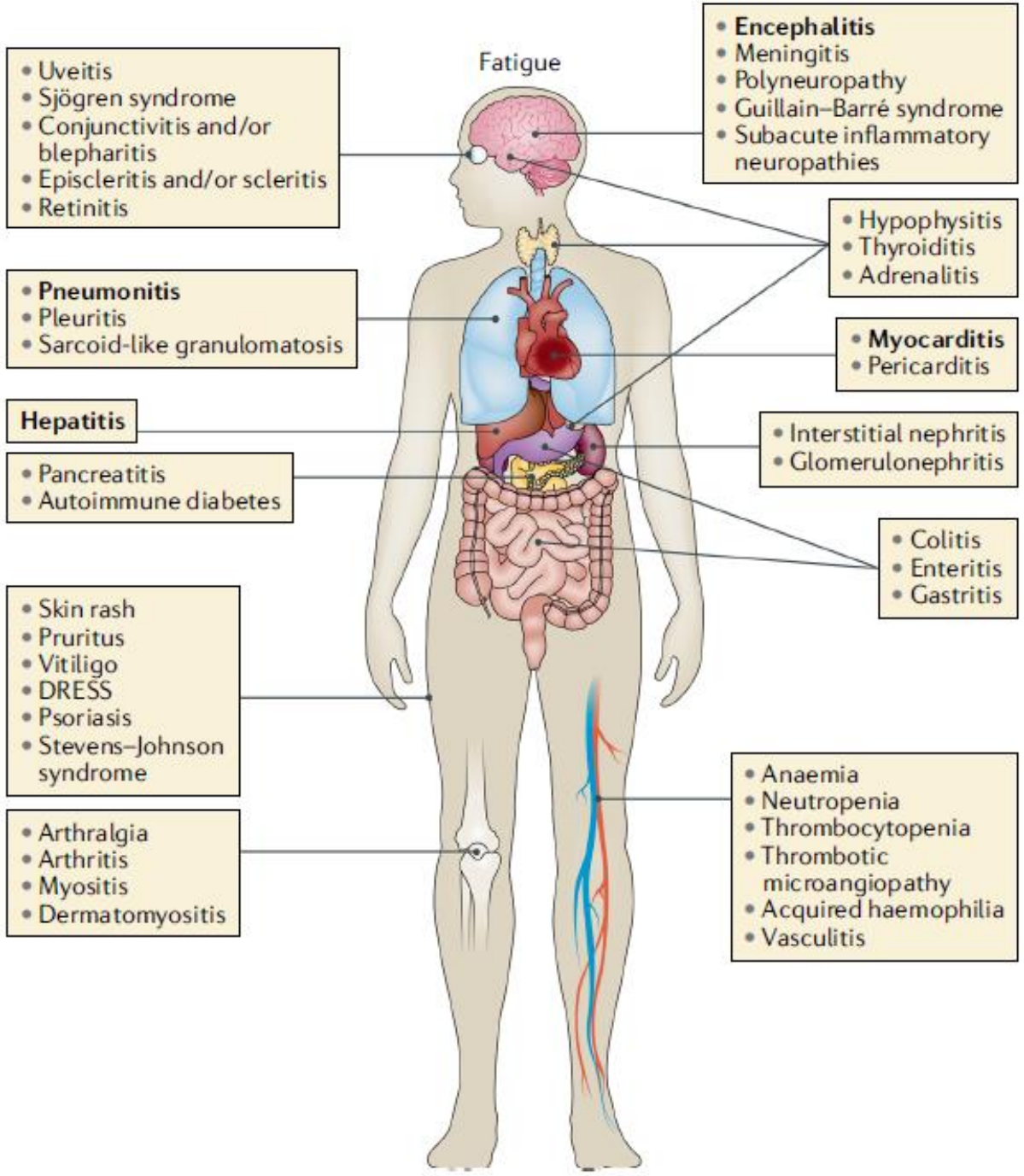


Extrinsic Mechanisms

Cell. 2017;168:707-723.

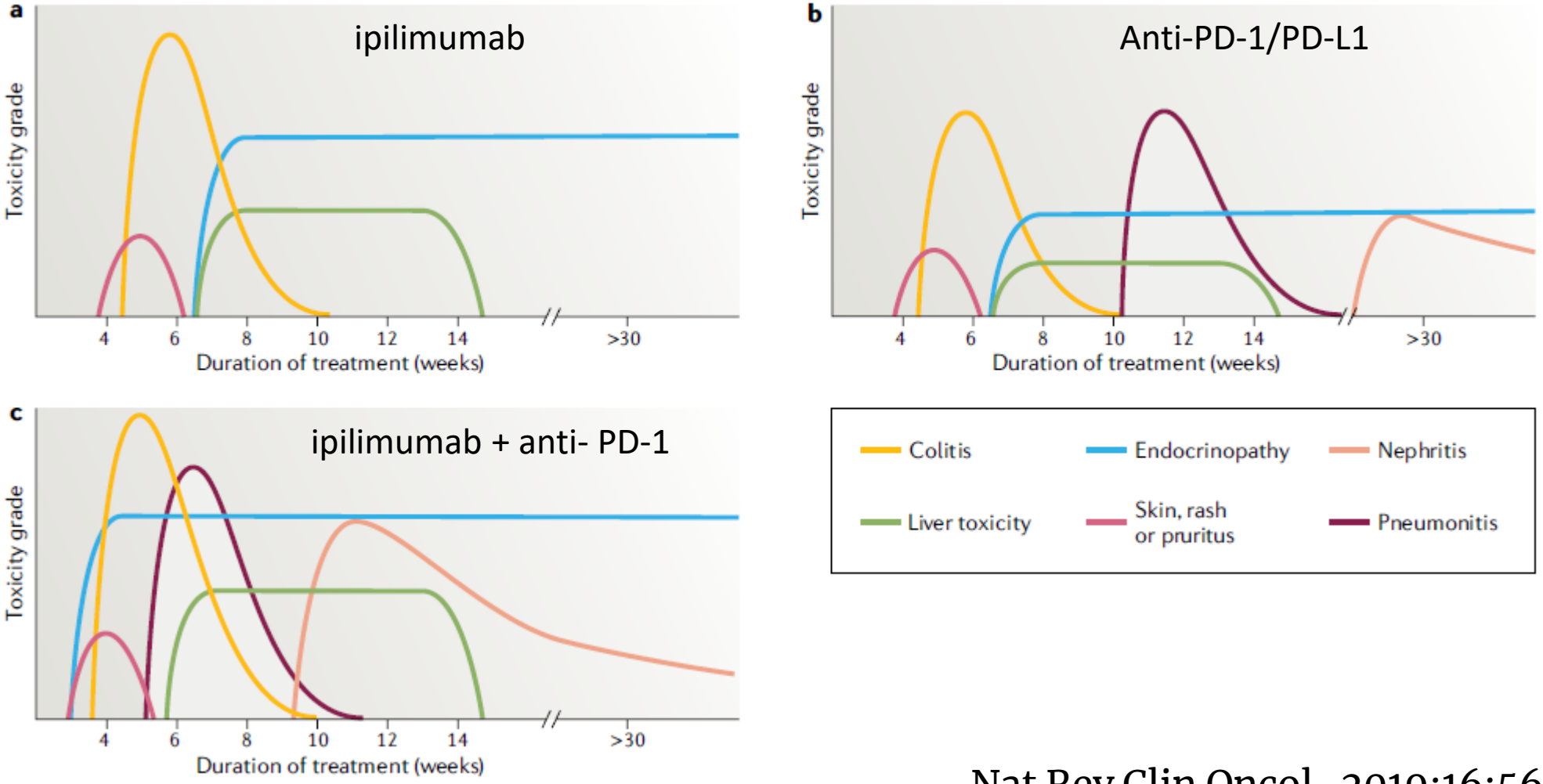
The spectrum of irAEs by affected organ or organs

- Checkpoint inhibition is associated with a unique spectrum of side effects termed **"immune-related adverse events (irAEs)"**
- Usually develop w/i first few weeks to months after initiation
- Can present at any time – even after cessation of I-O Tx



Nat Rev Clin Oncol . 2019;16:563-580.

Kinetics of main irAEs



Nat Rev Clin Oncol . 2019;16:563–580.

The overall management approach for irAEs

Gr	Steroid	Other immunosuppressant	Subsequent immunotherapy
1	Not recommended	Not recommended	Continue
2	Topical or systemic steroid 0.5~1mg/kg/d	Not recommended	Temporarily suspend in case of skin or endocrine disorders
3	Systemic steroid 1~2mg/kg/d for 3d, then reduce 1mg/kg/d	If unresolved after 3~5d steroid therapy, consult to organ specialist	Suspend and decision based on risk/benefit ratio
4	Systemic steroid 1~2mg/kg/d for 3d, then reduce 1mg/kg/d	If unresolved after 3~5d steroid therapy, consult to organ specialist	Permanently discontinue

Eur J Cancer. 2016;54:139-48

*Immunosuppressants: tumor necrosis factor (TNF)-alpha antagonists (ex,infliximab), azathioprine, mycophenolate mofetil (MMF), etc.

✓ Beneficial responses can persist despite the use of immunosuppression to treat immune-related adverse events.

General rules of immuno-oncology therapy according to toxicity grade

Organ	Grade 1	Grade 2	Grade 3	Grade 4
Skin	Continue	Continue	Delay or D/C	Delay or D/C
Kidney	Continue	Delay	Delay	D/C
Endocrine	Continue	Delay	D/C	D/C
GI tract	Continue	Delay	D/C	D/C
Liver	Continue	Delay	D/C	D/C
Nervous	Continue	Delay	D/C	D/C
Lung	May delay	Delay	D/C	D/C

<u>Permanent discontinuation</u>

- Criteria for permanent discontinuation of drug (CTC grade/ severity)
- Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent)
- Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing

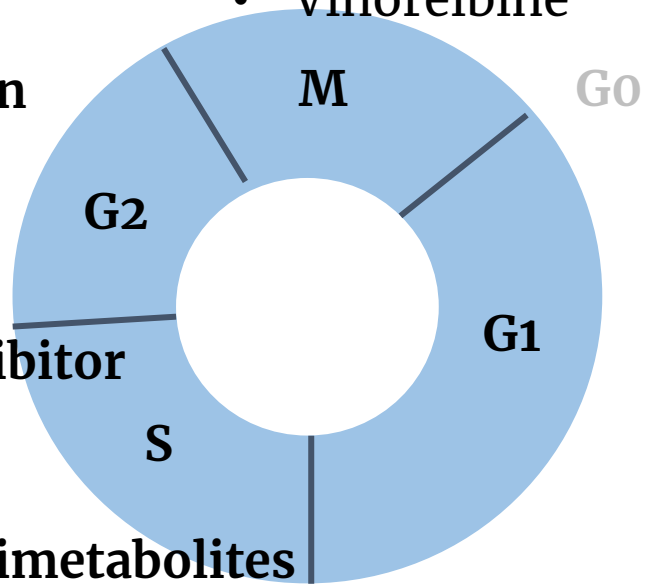
Chemotherapeutic drugs

Cell cycle specific
Effective for
high growth fraction
malignancies

Taxane
- Paclitaxel
- Docetaxel

Vinca alkaloids
- Vinorelbine

Epipodophyllotoxin
- Etoposide



Topoisomerase I inhibitor
- Irinotecan
- Topotecan

Antimetabolites
- Gemcitabine
- Methotrexate
- Pemetrexed

Cell cycle non-specific
For both high and low
growth fraction malignancies

- Cisplatin
- Alkylating agents (cytoxan)

General supportive care

NCCN National Comprehensive Cancer Network®

- Cancer pain
- Antiemesis
- Cancer-associated VTE
- Cancer-related fatigue
- Distress management
- Hematopoietic growth factors
- Management of Immunotherapy-related toxicities
- Palliative care
- Prevention and treatment of cancer-related infections
- Smoking cessation
- Survivorship