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2023.9.18 제 297회 대한결핵 및 호흡기학회 심포지움

Current Guideline Review for Lung Cancer

연세의대 용인세브란스병원
호흡기알레르기내과 이은혜

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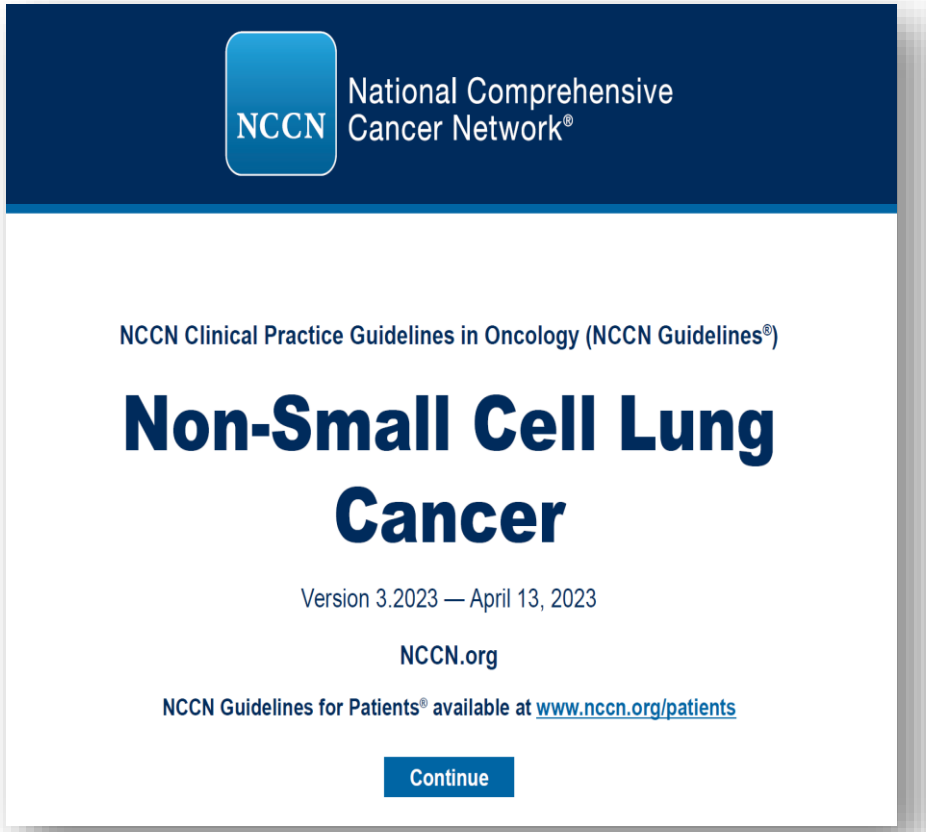
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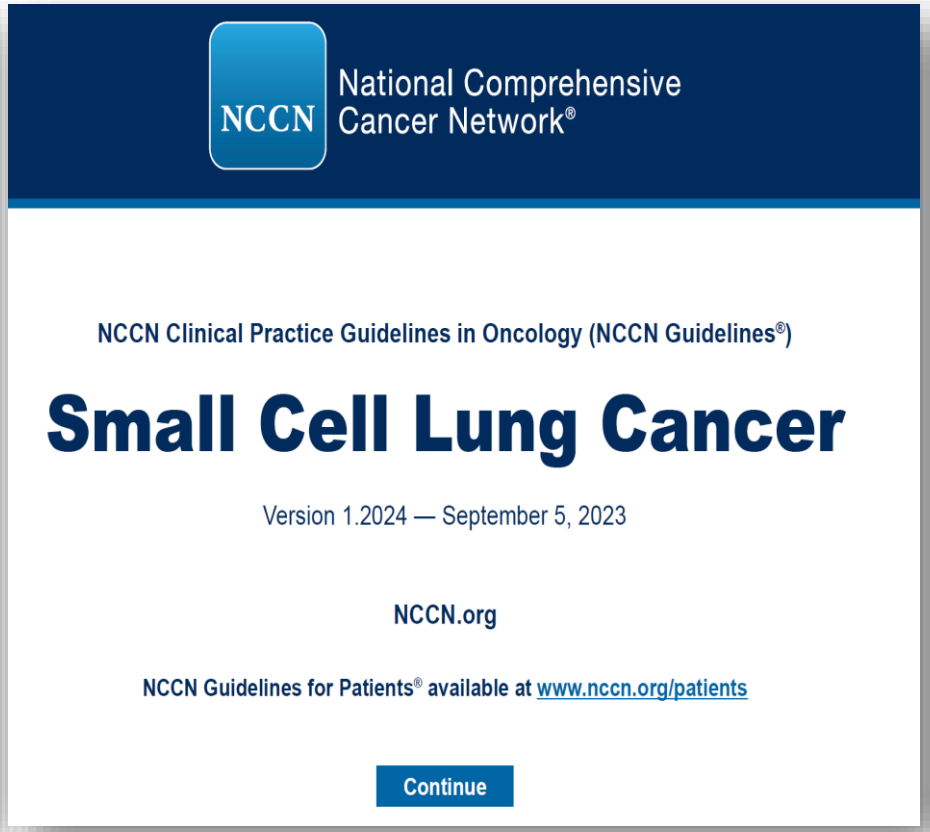
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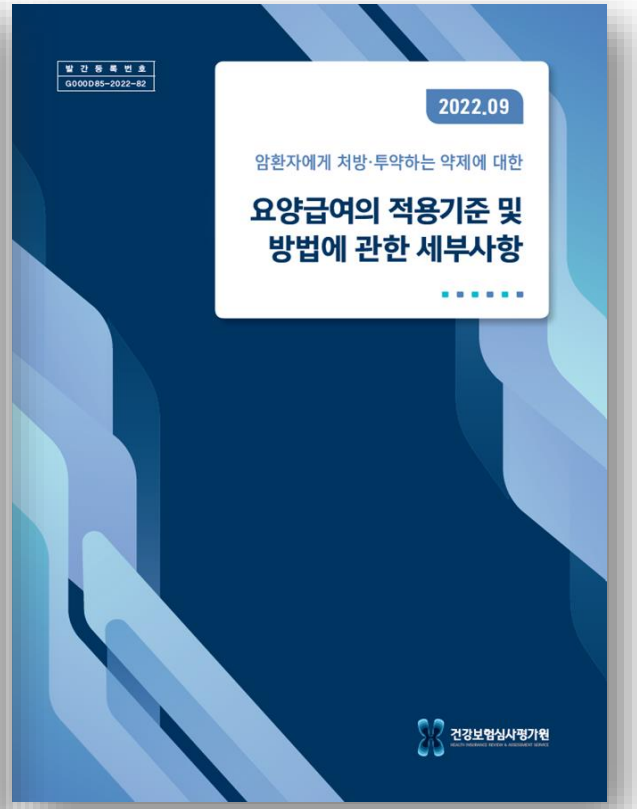
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건강보험심사평가원

Lung Cancer Introduction

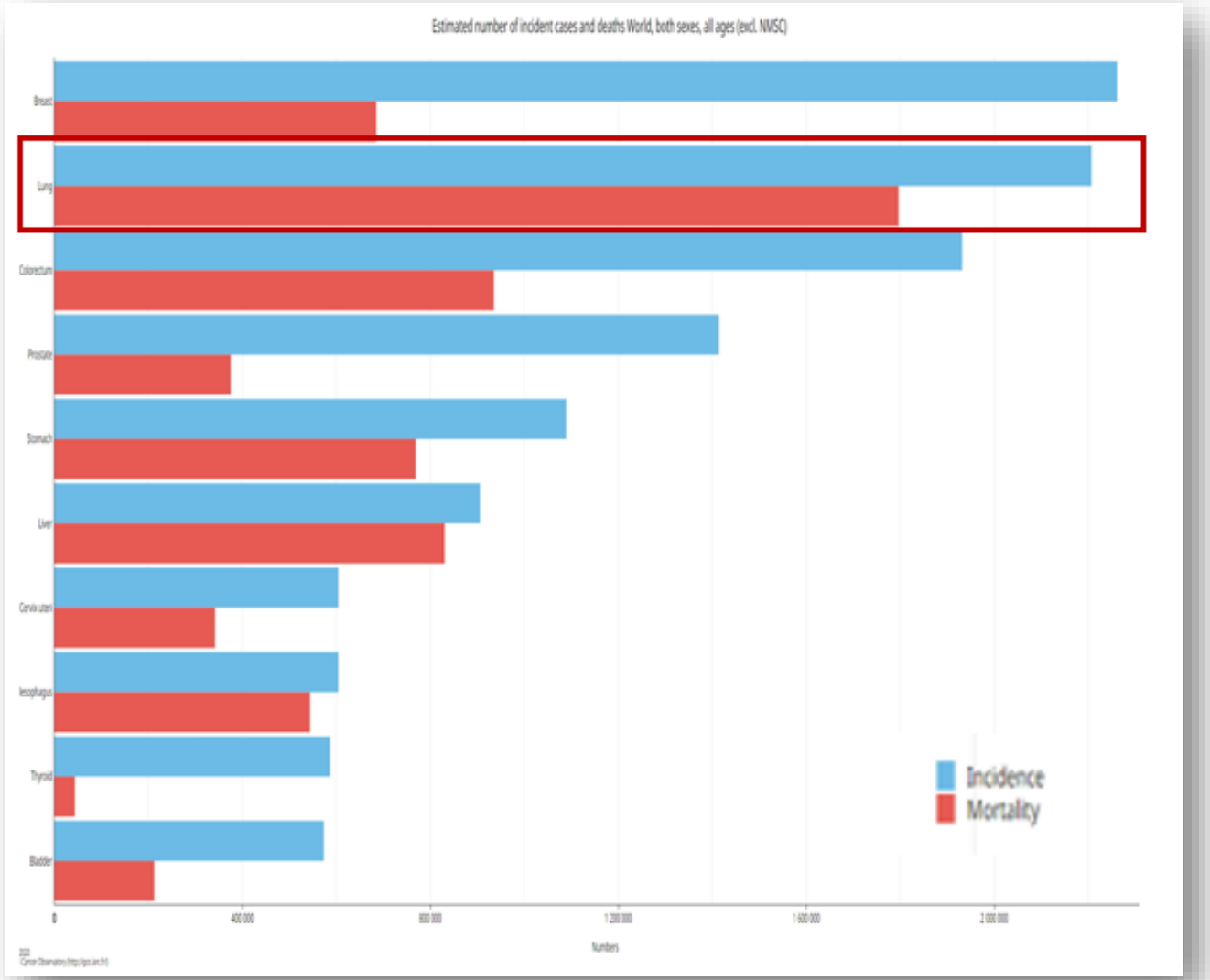
Lung Cancer disease burden

Epidemiology

- 2nd most frequent cause of cancer
  - 2.20 million in 2020
- Leading cause of cancer death worldwide
  - 1.80 million in 2020

Survival

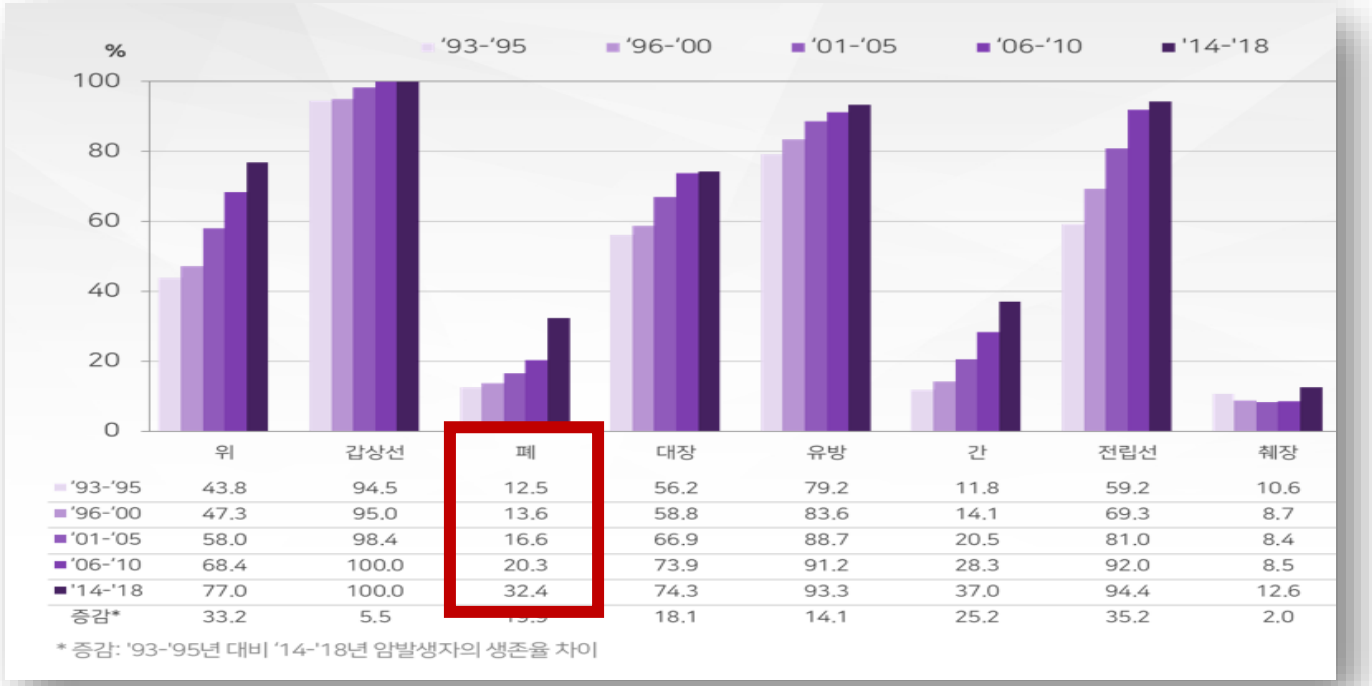
- 5-year survival of lung cancer: 10~20%
  (Breast 89%, colon 65%, prostate 70%)
- Only 16%~20% is diagnosed at early stage



Global Cancer Observatory 2020; A Systematic Analysis for the Global Burden of Disease Study 2019. JAMA Oncol 2022

Lung Cancer disease burden in Korea

암종	발생자수		차이	
	2020년 (A)	2019년 (B)	발생자수 (C=A-B)	백분율 (C/B*100)
갑상선	29,180	31,007	-1,827	-5.9
폐	28,949	30,241	-1,292	-4.3
대장	27,877	29,426	-1,549	-5.3
위	26,662	29,720	-3,058	-10.3
유방	24,923	25,024	-101	-0.4
전립선	16,815	16,965	-150	-0.9
간	15,152	15,749	-597	-3.8
췌장	8,414	8,154	260	3.2



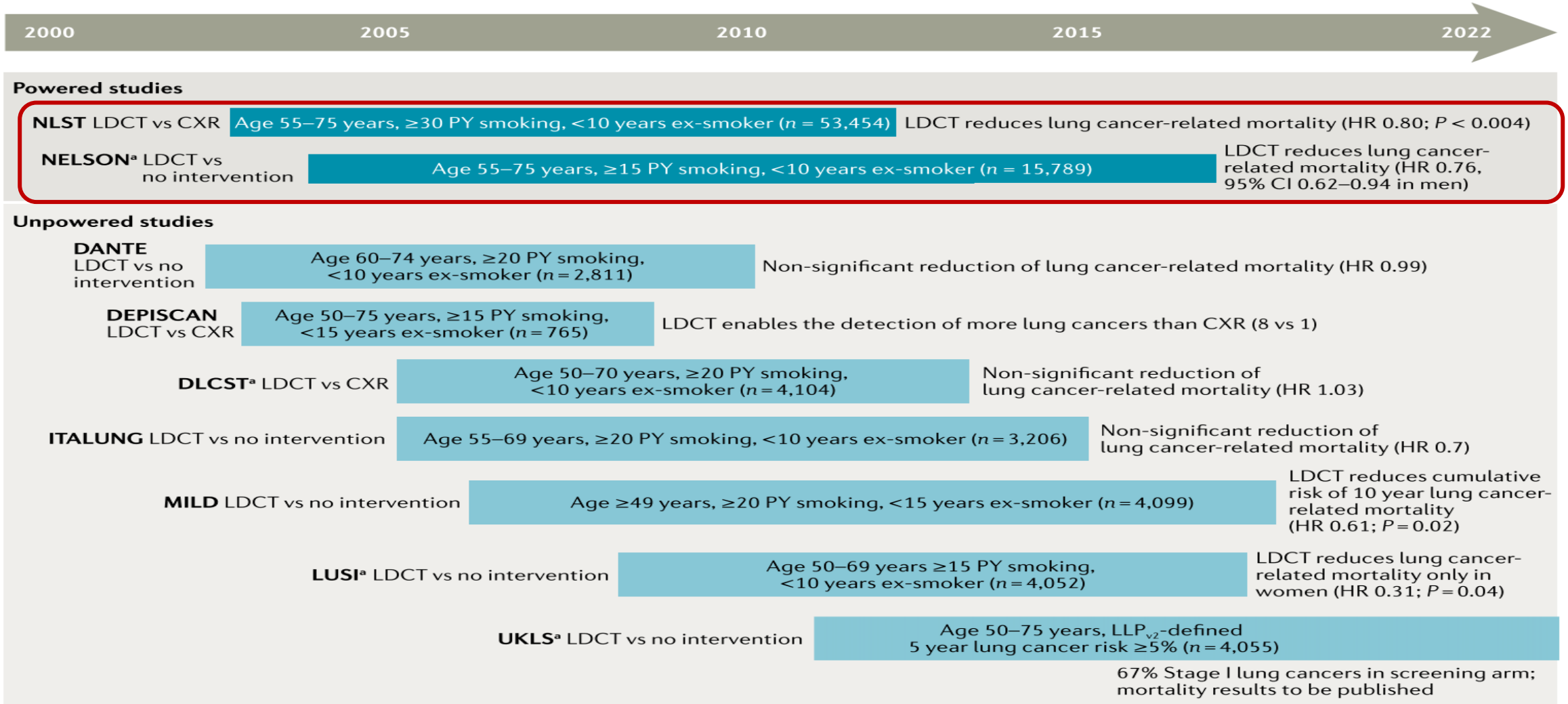
Incidence & Mortality

- 2nd most common in Korea (28,949 in 2020)
- Leading cause of cancer death (18,902 in 2020)

5-year Survival: 32~35%

2020 국가암등록통계 (국가암관리사업 중앙암등록본부)

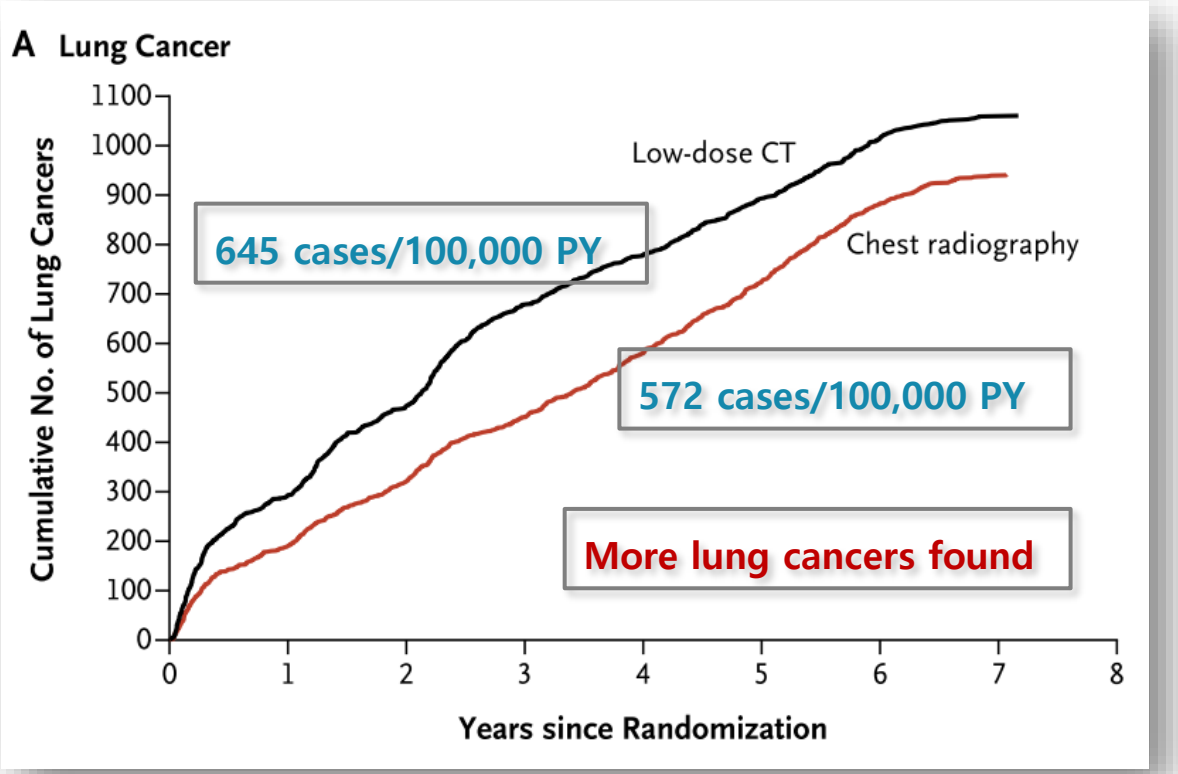
Major lung cancer screening clinical trials

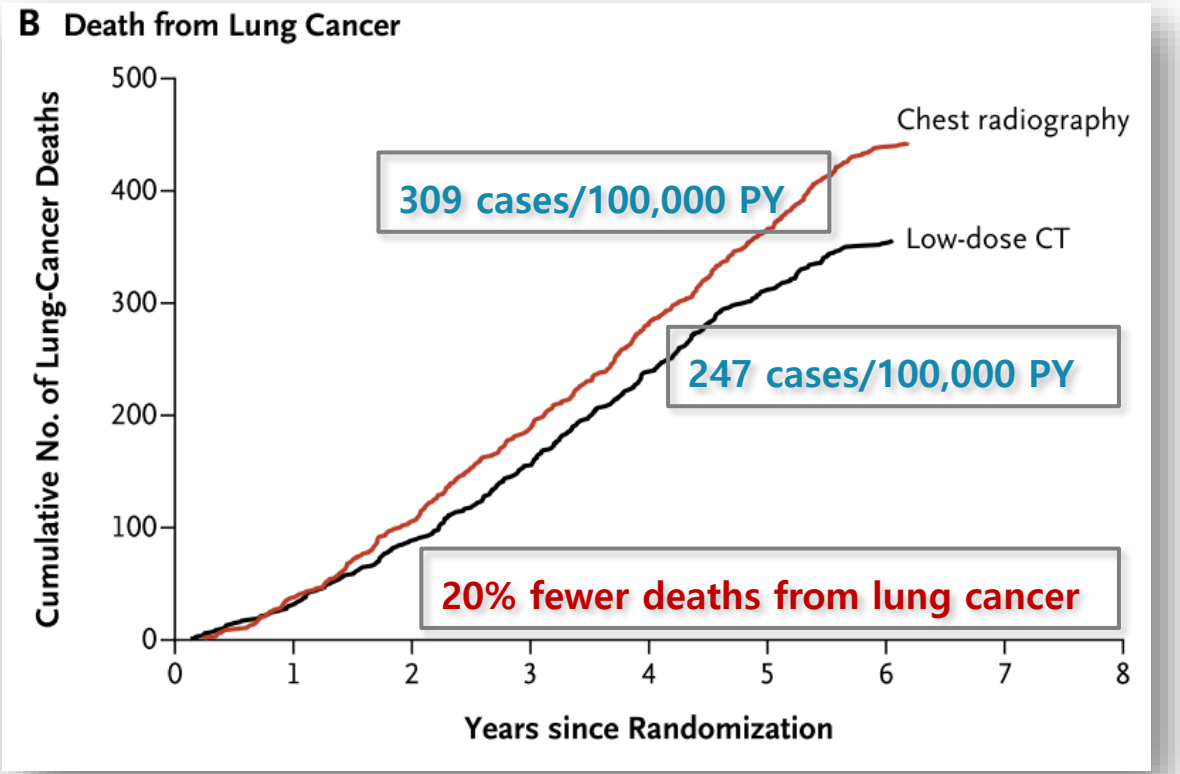


Oudkerk et al. Nat rev Clin Oncol 2021;18(3):135-51

National Lung Screening Trial (NLST)

The largest randomized controlled trial (90% stat power)





median duration of follow-up: 6.5 years

Aberle DR et al. NEJM 2011;365:395-409

National Lung Cancer Screening in South Korea

우리나라 폐암 검진사업 vs NLST

2017-2018 우리나라 폐암검진 시범사업

성과지표		우리나라 폐암검진 시범사업 (13,692명)	미국 NLST 보고 (최종, 1차검진기준, 26,309명)
양성률		15% (≥6 mm)	27% (≥4 mm)/ 14% (≥6 mm)
위양성률		15% (≥6 mm)	27% (≥4 mm)/ 13% (≥6 mm)
양성자 중 폐암 미진단율		97%	96%
폐암 발견율		0.6%	1.0%
폐암 조기* 발견율		68%	68% (최종)
폐암 병기 분포	I	42 (53.2%)	I : 407 (60.0%) (최종)
	II	12 (15.2%)	II : 51 (7.5%) (최종)
	III	16 (20.3%)	III : 126 (18.6%) (최종)
	IV	9 (11.4%)	IV : 95 (14.0%) (최종)

*I기와 II기

폐암 등록환자 1, 2 기 (21%) 대비 조기 발견이 68.4 % 로 높음

National Lung Cancer Screening in South Korea

국가 폐암 검진 추가 (2019년 8월)

암의 종류	검진 주기	검진 대상자; 연령 기준 등
위암	2년	40세 이상의 남·여
간암	6개월	40세 이상의 남·여 중 간암 발생 고위험군
대장암	1년	50세 이상의 남·여
유방암	2년	40세 이상의 여성
자궁경부암	2년	20세 이상의 여성
폐암	**2년**	**54-74세** 남·여 중 폐암 발생 고위험군

❖비고: "**폐암 발생 고위험군**"이란 **30갑년**(하루 평균 담배소비량(갑)×흡연기간(년)) 이상의 흡연력을 가진 **현재 흡연자**와 폐암 검진의 필요성이 높아 보건복지부 장관이 고시로 정하는 사람을 말한다.

National Lung Cancer Screening in South Korea

Lung-RADS (Lung Imaging Reporting And Data System category

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
	서서히 커짐	2
	새로 발생	3

기타 분류 기준	범주
흉막주변결절<장경10mm	2
기관지 내 결절	4A
범주 3,4+**추가** 영상 소견 폐경화, 무기폐, 림프절확대, 기타 (침상변연 등 자유기술)	4X
결절 외 의미 있는 소견	S

검진음성 ↑ ↓ 검진양성

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	경계성 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)

National Lung Cancer Screening in South Korea

Participants: 55 and 74 years of age, Smoking≥30 PY, quit within 15years

	수검자	이상소견없음 (Cat 1)	양성결절 (Cat 2)	경계성결절 (Cat 3)	폐암의심 (Cat 4)	기타
2019	79,537	51,287	20,980	3,628	3,642	17,566
2020	90,104	56,096	25,969	4,340	3,699	35,472
2021	116,377	67,239	39,006	5,433	4,699	59,534
Total	286,018	174,622	85,955	13,401	12,040	112,572
(%)		(61.1)	(30.1)	(4.7)	(4.2)	(39.4)

2023년 표적치료연구회 리더심포지움 박영식교수님 강의록 발췌, 국가통계포털 KOSIS

Lung Nodule follow up (Solid)

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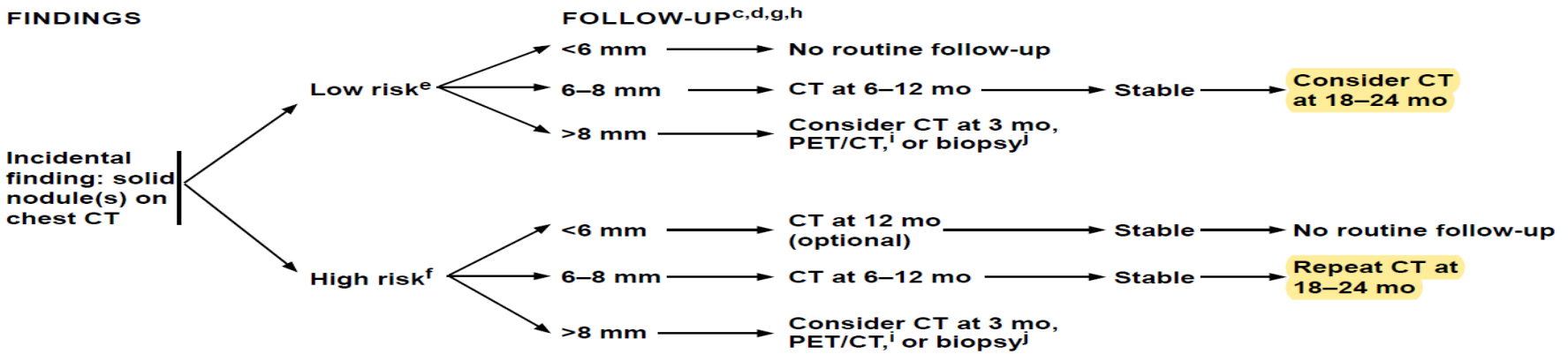

[c] Principles of Diagnostic Evaluation (DIAG-A 1 of 3).
[d] The most important radiologic factor is change or stability compared with a previous imaging study.
[e] Low risk = minimal or absent history of smoking or other known risk factors.
[f] High risk = history of smoking or other known risk factors. Known risk factors include history of lung cancer in a first-degree relative; exposure to asbestos, radon, or uranium.
[g] Non-solid (ground-glass) nodules may require longer follow-up to exclude indolent adenocarcinoma.
[h] Adapted from Fleischner Society Guidelines: MacMahon H, Naidich DP, Goo JM, et al. Guidelines for management of incidental pulmonary nodules detected on CT images: From the Fleischner Society 2017. Radiology 2017;284:228-243. ©Radiological Society of North America. Fleischner Society Guidelines do not direct whether or not contrast is necessary or if an LDCT is appropriate. LDCT is preferred unless there is a reason for contrast enhancement for better diagnostic resolution.
[i] PET/CT performed skull base to knees or whole body. A positive PET result is defined as a standardized uptake value (SUV) in the lung nodule greater than the baseline mediastinal blood pool. A positive PET scan finding can be caused by infection or inflammation, including absence of lung cancer with localized infection, presence of lung cancer with associated (eg, postobstructive) infection, and presence of lung cancer with related inflammation (eg, nodal, parenchymal, pleural). A false-negative PET scan can be caused by a small nodule, low cellular density (nonsolid nodule or ground-glass opacity [GGO]), or low tumor avidity for FDG (eg, adenocarcinoma in situ [previously known as bronchoalveolar carcinoma], carcinoid tumor).
[j] If empiric therapy is contemplated without tissue confirmation, multidisciplinary evaluation that at least includes interventional radiology, thoracic surgery, and interventional pulmonology is required to determine the safest and most efficient approach for biopsy, or to provide consensus that a biopsy is too risky or difficult and that the patient can proceed with therapy without tissue confirmation. (IJsseldijk MA, et al. J Thorac Oncol 2019;14:583-595.)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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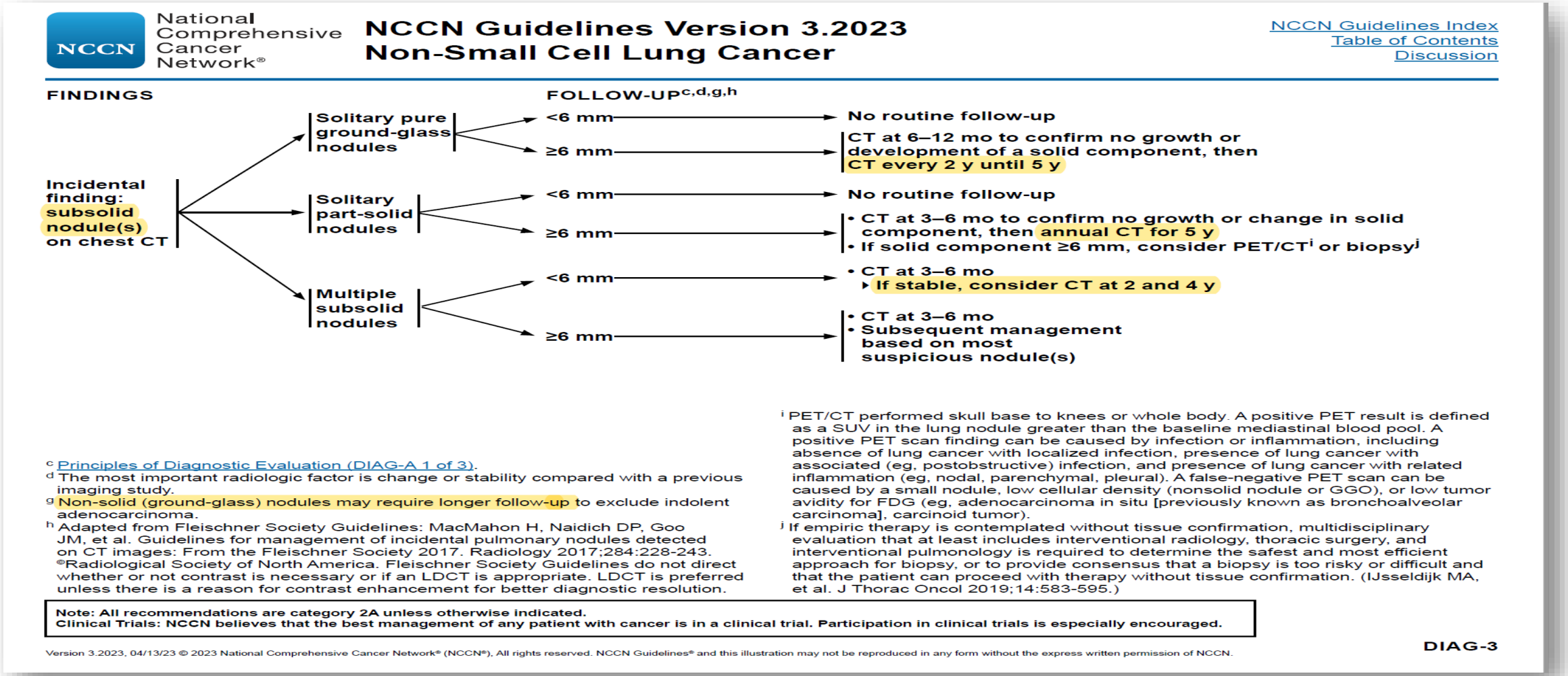
Lung Nodule follow up (Sub-Solid)



Resectable NSCLC (Stage I & II)

Stage IA NSCLC

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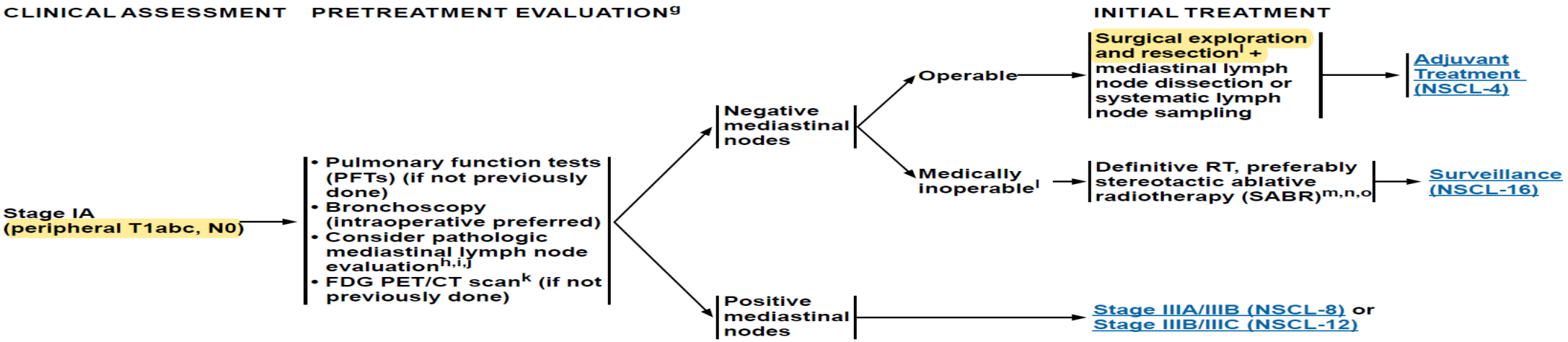

[g] Testing is not listed in order of priority and is dependent on clinical circumstances, institutional processes, and judicious use of resources.
[h] Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy. An EBUS-TBNA negative for malignancy in a clinically (PET and/or CT) positive mediastinum should undergo subsequent mediastinoscopy prior to surgical resection.
[i] There is low likelihood of positive mediastinal lymph nodes when these nodes are CT and PET negative in peripheral tumors (outer third of lung) <3 cm. Thus, pretreatment pathologic mediastinal evaluation is optional in these settings. Invasive mediastinal staging is recommended for central tumors.
[j] In patients who are medically inoperable, while mediastinal biopsy is generally preferred, the risks in selected patients may outweigh the benefits.
[k] PET/CT performed skull base to knees or whole body. Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.
[l] Principles of Surgical Therapy (NSCL-B).
[m] Principles of Radiation Therapy (NSCL-C).
[n] Image-guided thermal ablation (IGTA) therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients not receiving SABR or definitive RT. Principles of Image-Guided Thermal Ablation Therapy (NSCL-D).
[o] If empiric therapy is contemplated without tissue confirmation, multidisciplinary evaluation that at least includes interventional radiology, thoracic surgery, and interventional pulmonology is required to determine the safest and most efficient approach for biopsy, or to provide consensus that a biopsy is too risky or difficult and that the patient can proceed with therapy without tissue confirmation. (IJsseldijk MA, et al. J Thorac Oncol 2019;14:583-595.)

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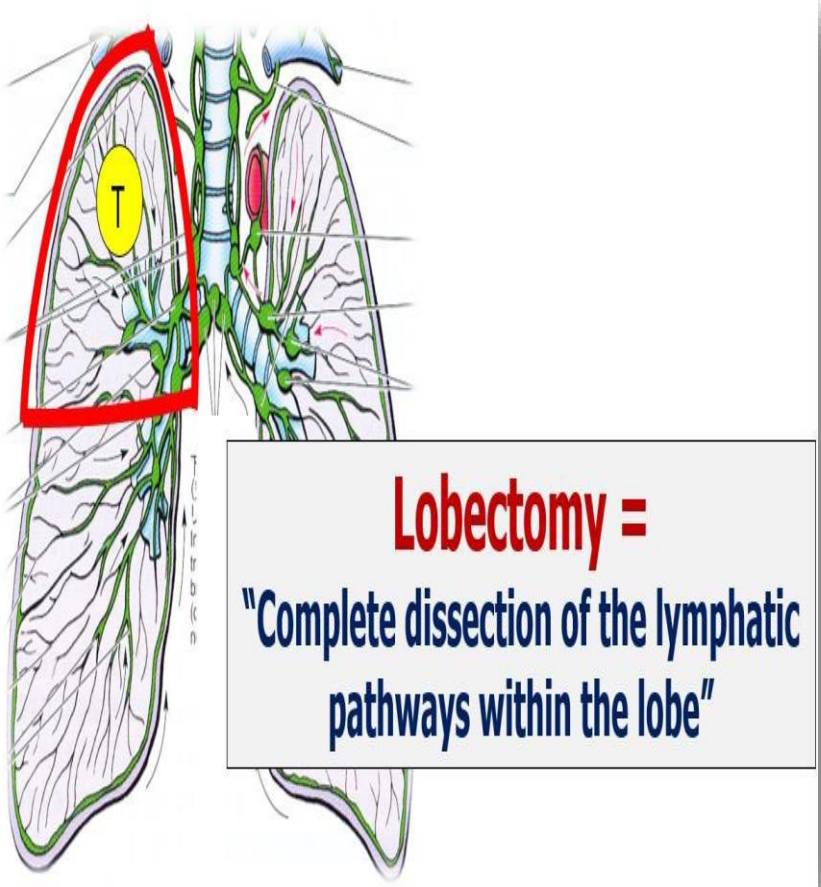
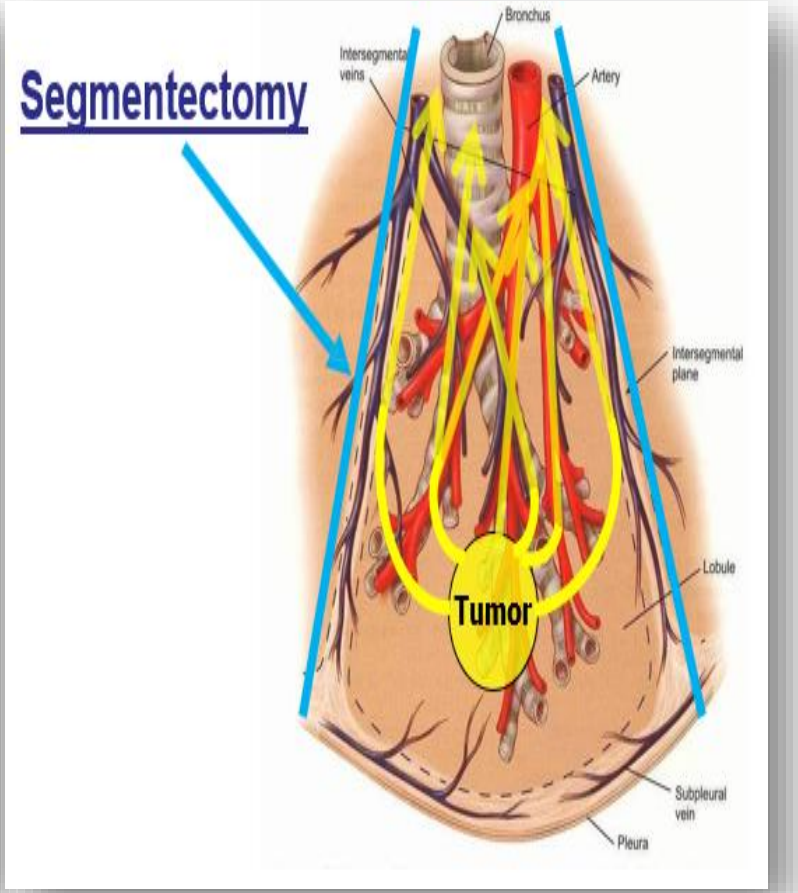
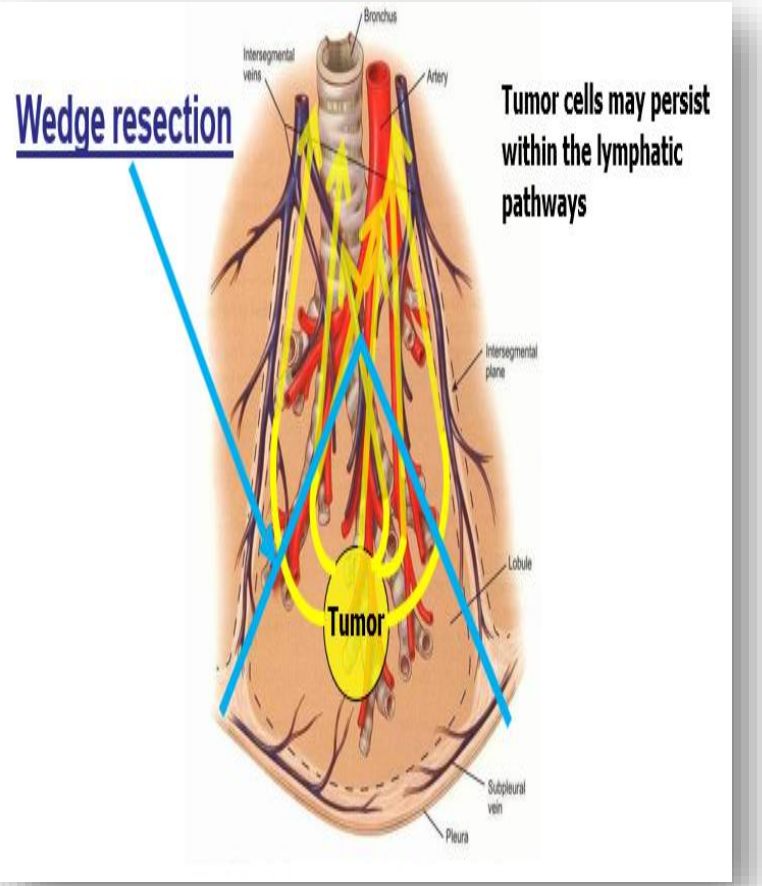
Stage IA NSCLC Surgery







Stage IA NSCLC Surgery

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PRINCIPLES OF SURGICAL THERAPY

Evaluation

- Determination of resectability, surgical staging, and *pulmonary resection should be performed by thoracic surgeons who perform lung cancer surgery as a prominent part of their practice*.
- CT and PET/CT used for staging should be within 60 days before proceeding with surgical evaluation.
- For medically operable disease, resection is the preferred local treatment modality (other modalities include SABR, thermal ablation such as radiofrequency ablation, and cryotherapy). Thoracic surgical oncology consultation should be part of the evaluation of any patient being considered for curative local therapy. In cases where SABR is considered for high-risk or borderline operable patients, a multidisciplinary evaluation including a radiation oncologist is recommended.
- The overall plan of treatment as well as needed imaging studies should be determined before any non-emergency treatment is initiated.
- Thoracic surgeons should actively participate in multidisciplinary discussions and meetings regarding patients with lung cancer (eg, multidisciplinary clinic and/or tumor board).
- Patients who actively smoke should be provided counseling and smoking cessation support (NCCN Guidelines for Smoking Cessation). While patients who actively smoke have a mildly increased incidence of postoperative pulmonary complications, these should not be considered a prohibitive risk for surgery. Surgeons should not deny surgery to patients solely due to smoking status, as surgery provides the predominant therapy for patients with early-stage lung cancer.

Resection

- Anatomic pulmonary resection is preferred for the majority of patients with NSCLC.
- Sublobar resection - Segmentectomy and wedge resection should achieve parenchymal resection margins ≥2 cm or ≥ the size of the nodule.
- Sublobar resection should also sample appropriate N1 and N2 lymph node stations unless not technically feasible without substantially increasing the surgical risk.
- Segmentectomy (preferred) or wedge resection is appropriate in selected patients for the following reasons:
  - Poor pulmonary reserve or other major comorbidity that contraindicates lobectomy
  - Peripheral nodule[a] ≤2 cm with at least one of the following:
    - Pure AIS histology
    - Nodule has ≥50% ground-glass appearance on CT
    - Radiologic surveillance confirms a long doubling time (≥400 days)
- VATS or minimally invasive surgery (including robotic-assisted approaches) should be strongly considered for patients with no anatomic or surgical contraindications, as long as there is no compromise of standard oncologic and dissection principles of thoracic surgery.
- In high-volume centers with significant VATS experience, VATS lobectomy in selected patients results in improved early outcomes (ie, decreased pain, reduced hospital length of stay, more rapid return to function, fewer complications) without compromise of cancer outcomes.
- Lung-sparing anatomic resection (sleeve lobectomy) is preferred over pneumonectomy, if anatomically appropriate and margin-negative resection is achieved.
- T3 (invasion) and T4 local extension tumors require en-bloc resection of the involved structure with negative margins. If a surgeon or center is uncertain about potential complete resection, consider obtaining an additional surgical opinion from a high-volume specialized center.

Margins and Nodal Assessment (see NSCL-B 2 of 4)

The Role of Surgery in Patients with Stage IIIA (N2) NSCLC (see NSCL-B 2 of 4 through NSCL-B 4 of 4)

[a] Peripheral is defined as the outer one third of the lung parenchyma.

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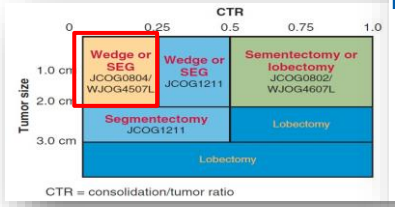


THORACIC: LUNG CANCER: CLINICAL TRIAL

A single-arm study of sublobar resection for ground-glass opacity dominant peripheral lung cancer

Check for updates

Kenji Suzuki, MD,[a] Shun-ichi Watanabe, MD,[b] Masashi Wakabayashi, MD,[c] Hisashi Saji, MD, PhD,[d] Keiju Aokage, MD,[e] Yasumitsu Moriya, MD,[f] Ichiro Yoshino, MD,[g] Masahiro Tsuboi, MD,[e] Shinichiro Nakamura, ME,[h] Kenichi Nakamura, MD,[c] Tetsuya Mitsudomi, MD,[i] and Hisao Asamura, MD,[j] on behalf of the West Japan Oncology Group and Japan Clinical Oncology Group

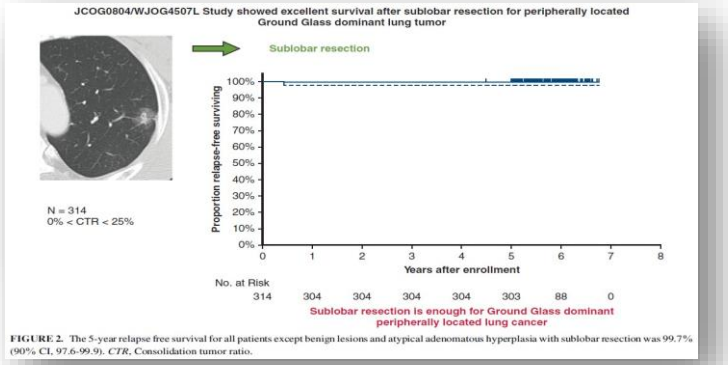
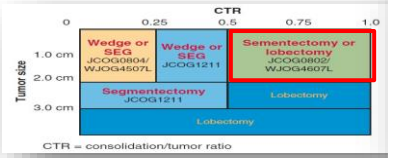


FIGURE 2. The 5-year relapse free survival for all patients except benign lesions and atypical adenomatous hyperplasia with sublobar resection was 99.7% (90% CI, 97.6-99.9). *CTR*, Consolidation tumor ratio.

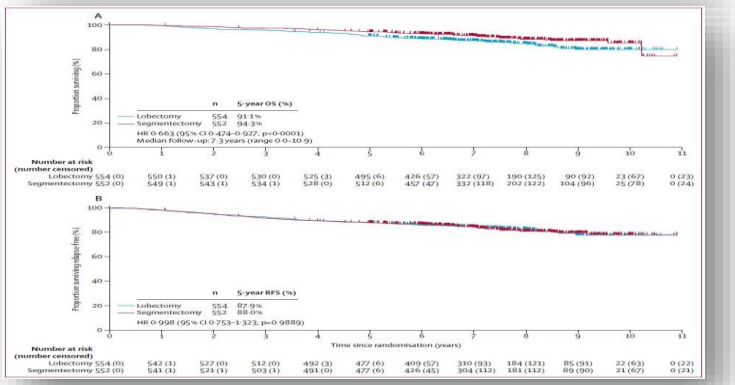
- JCOG 0804/WJOG4507L (J Thorac Cardiovasc Surg 2022;163:289-301)

5-year RFS 99.7%
5-year OS 99.4%



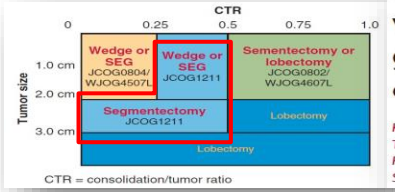
Segmentectomy versus lobectomy in small-sized peripheral non-small-cell lung cancer (JCOG0802/WJOG4607L): a multicentre, open-label, phase 3, randomised, controlled, non-inferiority trial

*Hisashi Saji, Morihito Okada, Masahiro Tsuboi, Ryu Nakajima, Kenji Suzuki, Keiju Aokage, Tadashi Aoki, Jiro Okami, Ichiro Yoshino, Hiroyuki Ito, Norihito Okumura, Masafumi Yamaguchi, Norihiko Ikeda, Masashi Wakabayashi, Kenichi Nakamura, Haruhiko Fukuda, Shinichiro Nakamura, Tetsuya Mitsudomi, Shun-ichi Watanabe, Hisao Asamura, on behalf of the West Japan Oncology Group and Japan Clinical Oncology Group**



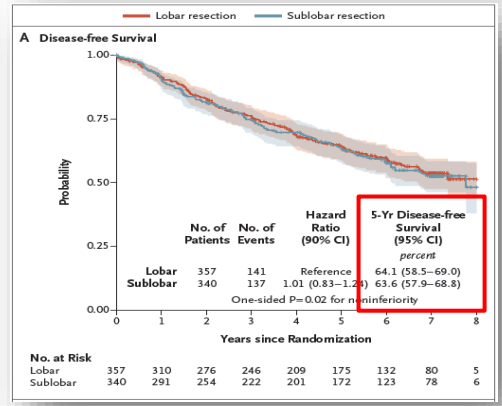
- JCOG 0802/WJOG4607L (Lancet 2022;399:1607-1617)

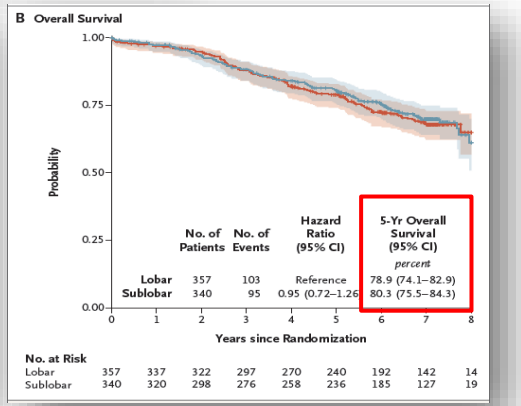
5-year OS
Segmentectomy 94.3%
Lobectomy 91.1%



Segmentectomy for ground-glass-dominant lung cancer with a tumour diameter of 3 cm or less including ground-glass opacity (JCOG1211): a multicentre, single-arm, confirmatory, phase 3 trial

Keiju Aokage, Kenji Suzuki, Hisashi Saji, Masashi Wakabayashi, Tomoko Kataoka, Yuta Sekino, Haruhiko Fukuda, Makoto Endo, Aritoshi Hattori, Takahiro Mimae, Tomohiro Miyoshi, Mitsuhiro Isaka, Hiroshige Yoshioka, Ryu Nakajima, Kazuo Nakagawa, Jiro Okami, Hiroyuki Ito, Hiroaki Kuroda, Masahiro Tsuboi, Norihito Okumura, Makoto Takahama, Yasuhisa Ohde, Tadashi Aoki, Yasuhiro Tsutani, Morihito Okada, Shun-ichi Watanabe, on behalf of the Japan Clinical Oncology Group





- JCOG1211 (Lancet Respir Med 2023;11:540-549)

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Lobar or Sublobar Resection for Peripheral Stage IA Non–Small-Cell Lung Cancer

Nasser Altorki, M.D., Xiaofei Wang, Ph.D., David Kozono, M.D., Ph.D., Colleen Watt, B.S., Rodney Landrenau, M.D., Dennis Wigle, M.D., Ph.D., Jeffrey Port, M.D., David R. Jones, M.D., Kazuhiro Yasufuku, M.D., Ph.D., Robert Keenan, M.D., Thomas Bauer, M.D., and Everett Vokes, M.D.

Tumor size ≤ 2cm, peripheral (outer third)

- CALGB140503 (N Engl J Med 2023;388:489-498)

2023년 Lung Cancer School 문영규 교수님 강의록 발췌

Resectable NSCLC, Medical inoperable, SBRTx

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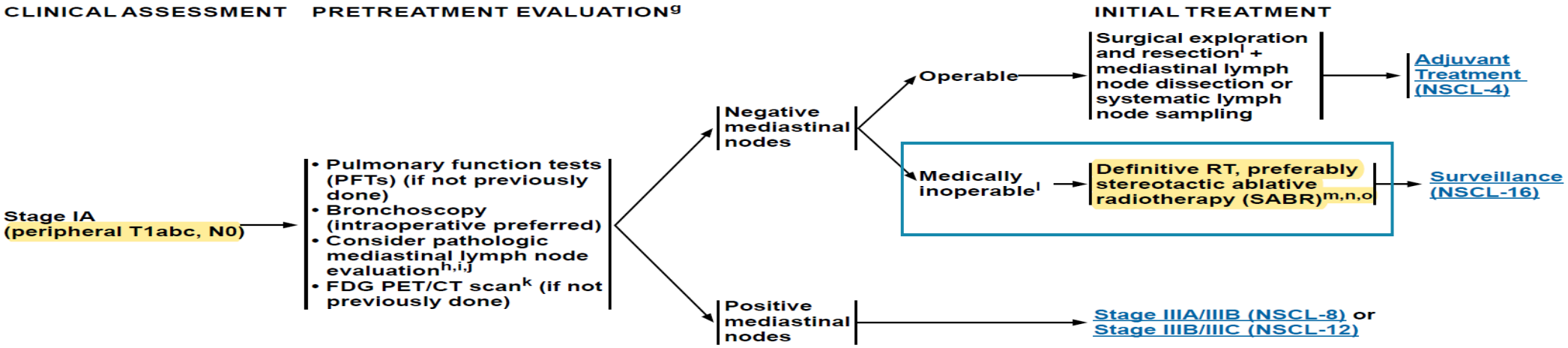

[g] Testing is not listed in order of priority and is dependent on clinical circumstances, institutional processes, and judicious use of resources.
[h] Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy. An EBUS-TBNA negative for malignancy in a clinically (PET and/or CT) positive mediastinum should undergo subsequent mediastinoscopy prior to surgical resection.
[i] There is low likelihood of positive mediastinal lymph nodes when these nodes are CT and PET negative in peripheral tumors (outer third of lung) <3 cm. Thus, pretreatment pathologic mediastinal evaluation is optional in these settings. Invasive mediastinal staging is recommended for central tumors.
[j] In patients who are medically inoperable, while mediastinal biopsy is generally preferred, the risks in selected patients may outweigh the benefits.
[k] PET/CT performed skull base to knees or whole body. Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.
[l] Principles of Surgical Therapy (NSCL-B).
[m] Principles of Radiation Therapy (NSCL-C).
[n] Image-guided thermal ablation (IGTA) therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select patients not receiving SABR or definitive RT. Principles of Image-Guided Thermal Ablation Therapy (NSCL-D).
[o] If empiric therapy is contemplated without tissue confirmation, multidisciplinary evaluation that at least includes interventional radiology, thoracic surgery, and interventional pulmonology is required to determine the safest and most efficient approach for biopsy, or to provide consensus that a biopsy is too risky or difficult and that the patient can proceed with therapy without tissue confirmation. (IJsseldijk MA, et al. J Thorac Oncol 2019;14:583-595.)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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Resectable NSCLC, Medical inoperable, SBRTx

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PRINCIPLES OF RADIATION THERAPY

IV. General Treatment Information

Early-Stage NSCLC (Stage I, selected node-negative Stage IIA)

- SABR (also known as SBRT)[19] has achieved good primary tumor control rates and overall survival, higher than conventionally fractionated radiotherapy. Although SABR is not proven equivalent to lobectomy, some prospective series have demonstrated similar overall and cancer-specific survival.[20-30]
- SABR is also an appropriate option for patients with high surgical risk (able to tolerate sublobar resection but not lobectomy [eg, age ≥75 years, poor lung function]).
- More modestly hypofractionated or dose-intensified conventionally fractionated 3D-CRT regimens are less preferred alternatives and may be considered if referral for SABR is not feasible.[31-33]
- In patients treated with surgery, postoperative radiotherapy (PORT) is not recommended unless there are positive margins (see *Locally Advanced NSCLC* in this section for patients upstaged to N2).
- Close follow-up and therapy for isolated local and/or locoregional recurrence after SABR have been shown to improve overall survival in a large retrospective study.[34]

SABR for Node-Negative Early-Stage NSCLC

- The high-dose intensity and conformity of SABR require minimizing the PTV.
- Dosing regimen
  - For SABR, intensive regimens of BED ≥100 Gy are associated with significantly better local control and survival than less intensive regimens.[35,36] In the United States, only regimens of ≤5 fractions meet the arbitrary billing code definition of SBRT, but slightly more protracted regimens are appropriate as well.[35,37] For centrally located tumors (defined variably as within 2 cm of the proximal bronchial tree and/or abutting mediastinal pleura) and even ultra-central tumors (defined as abutting the proximal bronchial tree), 4 to 10 fraction risk-adapted SABR regimens appear to be effective and safe,[38-41] while 54 to 60 Gy in 3 fractions is unsafe and should be avoided.[42] However, particular attention should be paid to tumors abutting the bronchial tree and esophagus to avoid severe toxicity. RTOG 0813 evaluated the toxicity of 5-fraction regimens and found no high-grade toxicities at 50 Gy in 5 fractions.[43]
- SABR is most commonly used for tumors up to 5 cm in size, though selected larger isolated tumors can be treated safely if normal tissue constraints are respected.[43,44]
- Prescription doses incompletely describe the actual delivered doses, which also strongly depend on how the dose is prescribed (to the isocenter vs. an isodose volume covering a proportion of the PTV), the degree of dose heterogeneity, whether tissue density heterogeneity corrections are used, and the type of dose calculation algorithm.[10,45,46] All of these must be considered when interpreting or emulating regimens from prior studies.

Table 2. Commonly Used Doses for SABR

Total Dose	# Fractions	Example Indications
25–34 Gy	1	Peripheral, small
45–60 Gy	3	Peripheral tumors
48–50 Gy	4	Central or peripheral tumors <4–5 cm
50–55 Gy	5	Central or peripheral tumors
60–70 Gy	8–10	Central tumors

Resectable Stage IB-II, IIIA NSCLC

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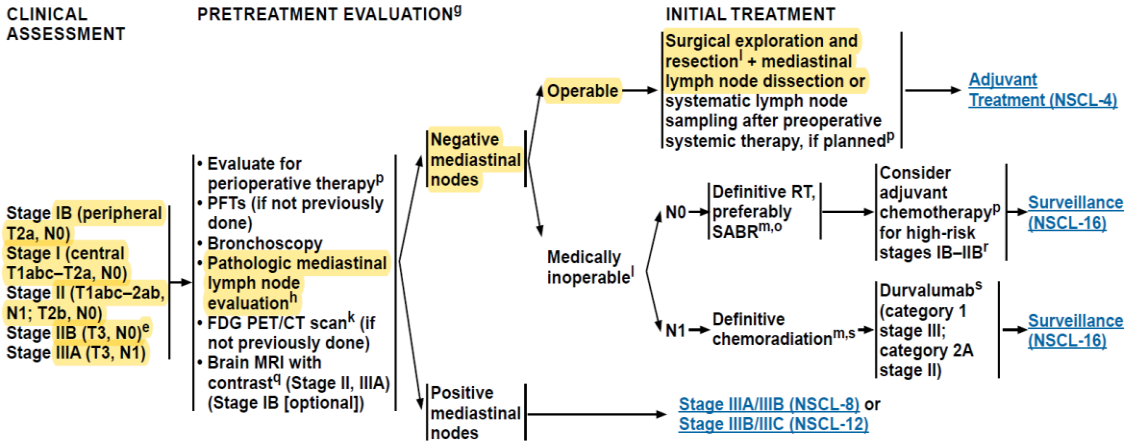

[e] T3, N0 related to size or satellite nodules.
[g] Testing is not listed in order of priority and is dependent on clinical circumstances, institutional processes, and judicious use of resources.
[h] Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy. An EBUS-TBNA negative for malignancy in a clinically (PET and/or CT) positive mediastinum should undergo subsequent mediastinoscopy prior to surgical resection.
[k] PET/CT performed skull base to knees or whole body. Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.
[l] Principles of Surgical Therapy (NSCL-B).
[m] Principles of Radiation Therapy (NSCL-C).
[o] If empiric therapy is contemplated without tissue confirmation, multidisciplinary evaluation that at least includes interventional radiology, thoracic surgery, and interventional pulmonology is required to determine the safest and most efficient approach for biopsy, or to provide consensus that a biopsy is too risky or difficult and that the patient can proceed with therapy without tissue confirmation. (IJsseldijk MA, et al. J Thorac Oncol 2019;14:583-595.)
[p] Perioperative Systemic Therapy (NSCL-E).
[q] If MRI is not possible, CT of head with contrast.
[r] Examples of high-risk factors may include poorly differentiated tumors (including lung neuroendocrine tumors [excluding well-differentiated neuroendocrine tumors]), vascular invasion, wedge resection, visceral pleural involvement, and unknown lymph node status (Nx). These factors independently may not be an indication and may be considered when determining treatment with adjuvant chemotherapy.
[s] Concurrent Chemoradiation Regimens (NSCL-F).

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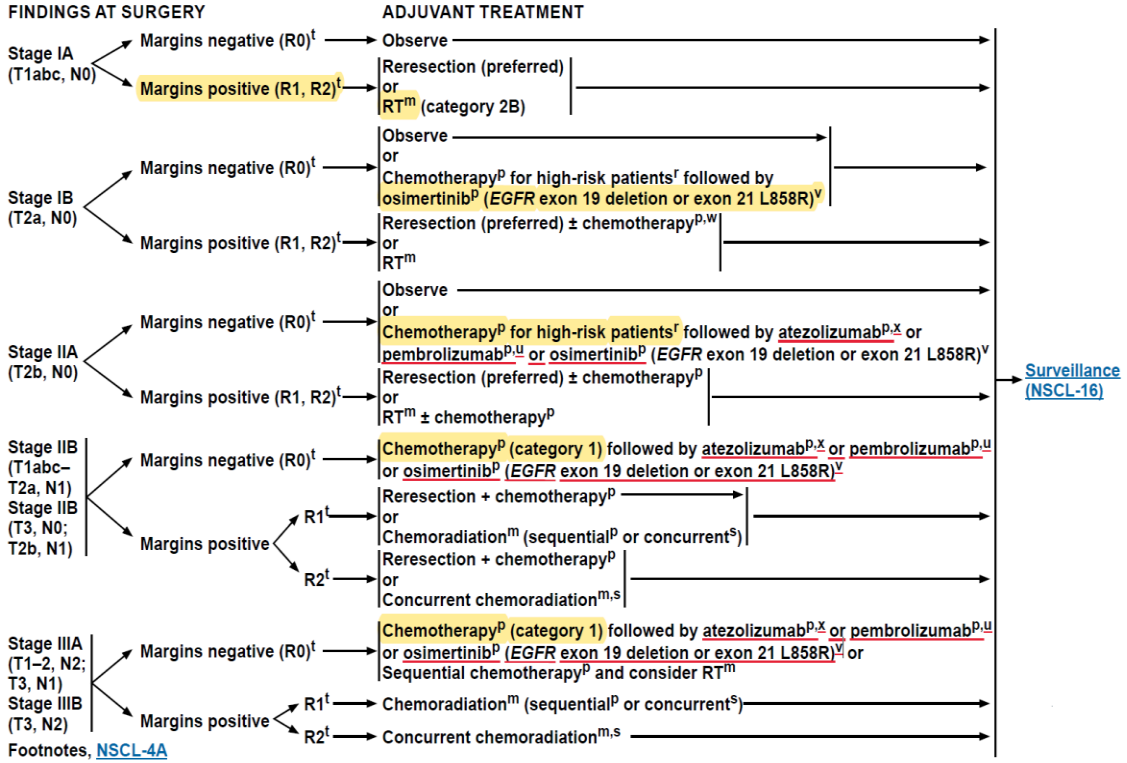

Footnotes, NSCL-4A

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Resectable Stage IB-II-IIIA NSCLC, adjuvant Therapy

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FINDINGS AT SURGERY		ADJUVANT TREATMENT
Stage IA (T1abc, N0)	Margins negative (R0)[t]	Observe
	Margins positive (R1, R2)[t]	Resection (preferred) or RT[m] (category 2B)
Stage IB (T2a, N0)	Margins negative (R0)[t]	Observe or Chemotherapy[p] for high-risk patients[r] followed by osimertinib[p] (*EGFR* exon 19 deletion or exon 21 L858R)[v]
	Margins positive (R1, R2)[t]	Resection (preferred) ± chemotherapy[p,w] or RT[m]
Stage IIA (T2b, N0)	Margins negative (R0)[t]	Observe or Chemotherapy[p] for high-risk patients[r] followed by atezolizumab[p,x] or pembrolizumab[p,u] or osimertinib[p] (*EGFR* exon 19 deletion or exon 21 L858R)[v]
	Margins positive (R1, R2)[t]	Resection (preferred) ± chemotherapy[p] or RT[m] ± chemotherapy[p]
Stage IIB (T1abc–T2a, N1) Stage IIB (T3, N0; T2b, N1)	Margins negative (R0)[t]	Chemotherapy[p] (category 1) followed by atezolizumab[p,x] or pembrolizumab[p,u] or osimertinib[p] (*EGFR* exon 19 deletion or exon 21 L858R)[v]
	Margins positive, R1[t]	Resection + chemotherapy[p] or Chemoradiation[m] (sequential[p] or concurrent[s])
	Margins positive, R2[t]	Resection + chemotherapy[p] or Concurrent chemoradiation[m,s]
Stage IIIA (T1–2, N2; T3, N1) Stage IIIB (T3, N2)	Margins negative (R0)[t]	Chemotherapy[p] (category 1) followed by atezolizumab[p,x] or pembrolizumab[p,u] or osimertinib[p] (*EGFR* exon 19 deletion or exon 21 L858R)[v] or Sequential chemotherapy[p] and consider RT[m]
	Margins positive, R1[t]	Chemoradiation[m] (sequential[p] or concurrent[s])
	Margins positive, R2[t]	Concurrent chemoradiation[m,s]

→ Surveillance (NSCL-16)

Footnotes, NSCL-4A

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NSCL-4

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PERIOPERATIVE SYSTEMIC THERAPY

Adjuvant Systemic Therapy
- Test for PD-L1 status, *EGFR* mutations, and *ALK* rearrangements (stages IB–IIIA, IIIB [T3,N2]).
  Principles of Molecular and Biomarker Analysis (NSCL-H).

Preferred (nonsquamous)
- Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1 every 21 days for 4 cycles[2]

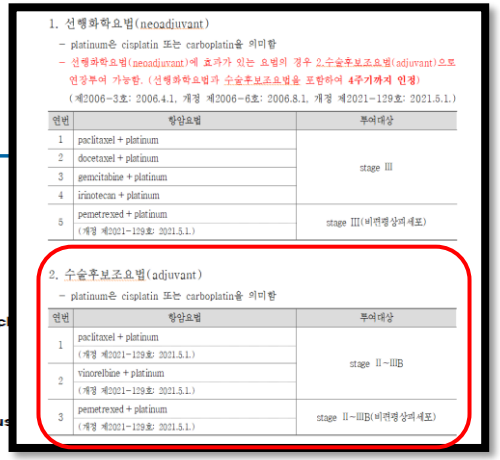
Preferred (squamous)
- Cisplatin 75 mg/m² day 1, gemcitabine 1250 mg/m² days 1 and 8, every 21 days for 4 cycles[3]
- Cisplatin 75 mg/m² day 1, docetaxel 75 mg/m² day 1 every 21 days for 4 cycles[4]

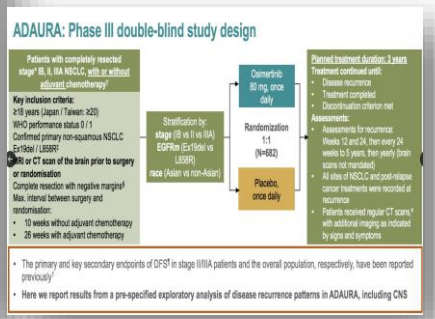
Other Recommended
- Cisplatin 50 mg/m² days 1 and 8; vinorelbine 25 mg/m² days 1, 8, 15, and 22, every 28 days for 4 cycles
- Cisplatin 100 mg/m² day 1, vinorelbine 30 mg/m² days 1, 8, 15, and 22, every 28 days for 4 cycles[6,7]
- Cisplatin 75–80 mg/m² day 1, vinorelbine 25–30 mg/m² days 1 and 8, every 21 days for 4 cycles
- Cisplatin 100 mg/m² day 1, etoposide 100 mg/m² days 1–3, every 28 days for 4 cycles[6]

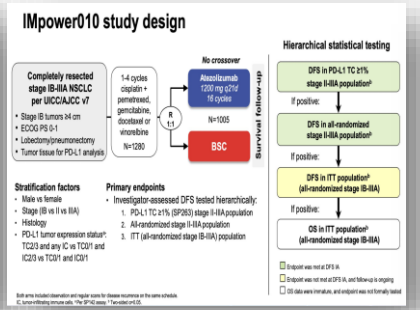
Useful in Certain Circumstances
- Chemotherapy Regimens for Patients Not Candidates for Cisplatin-Based Therapy
  - Carboplatin AUC 6 day 1, paclitaxel 200 mg/m² day 1, every 21 days for 4 cycles[8]
  - Carboplatin AUC 5 day 1, gemcitabine 1000 mg/m² days 1 and 8, every 21 days for 4 cycles[9]
  - Carboplatin AUC 5 day 1, pemetrexed 500 mg/m² day 1 every 21 days for 4 cycles[10] (nonsquamous

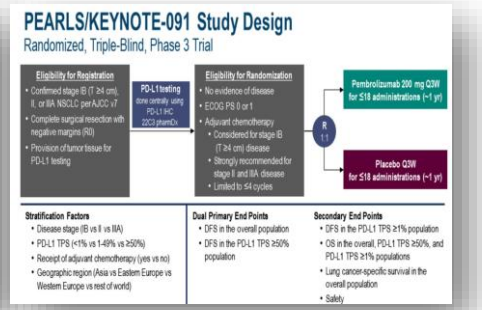
All chemotherapy regimens listed above can be used for sequential chemotherapy/RT.

Systemic Therapy Following Previous Adjuvant Systemic Therapy
- Osimertinib 80 mg daily[11]
  - Osimertinib for patients with completely resected stage IB–IIIA or stage IIIB (T3, N2) NSCLC and positive for *EGFR* (exon 19 deletion, exon 21 L858R) mutations who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy.
- Atezolizumab 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks for up to 1 year[12]
  - Atezolizumab for patients with completely resected stage IIB–IIIA, stage IIIB (T3, N2), or high-risk stage IIA NSCLC with PD-L1 ≥1% and negative for *EGFR* exon 19 deletion or exon 21 L858R mutations or *ALK* rearrangements who received previous adjuvant chemotherapy and with no contraindications to immune checkpoint inhibitors.*
- Pembrolizumab 200 mg every 3 weeks or 400 mg every 6 weeks for up to 1 year[13]
  - Pembrolizumab for patients with completely resected stage IIB–IIIA, stage IIIB (T3, N2), or high-risk stage IIA NSCLC and negative for *EGFR* exon 19 deletion or exon 21 L858R mutations or *ALK* rearrangements who received previous adjuvant chemotherapy and with no contraindications to immune checkpoint inhibitors.*









11 Wu Y-L, Tsuboi M, He J, et al. Osimertinib in resected EGFR-mutated non-small-cell lung cancer (ADAURA). N Engl J Med 2020;383:1711-1723.
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13 O'Brien M, Paz-Ares L, Marreaud S, et al. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB-IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. Lancet Oncol 2022;23:1274-1286.

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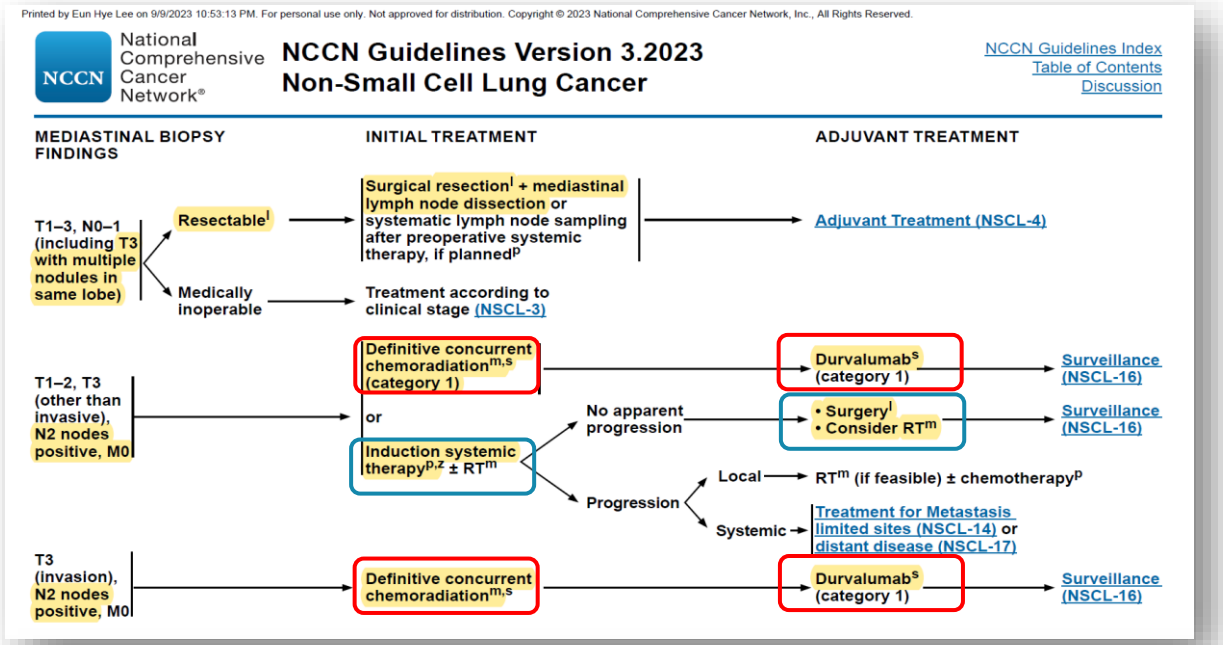
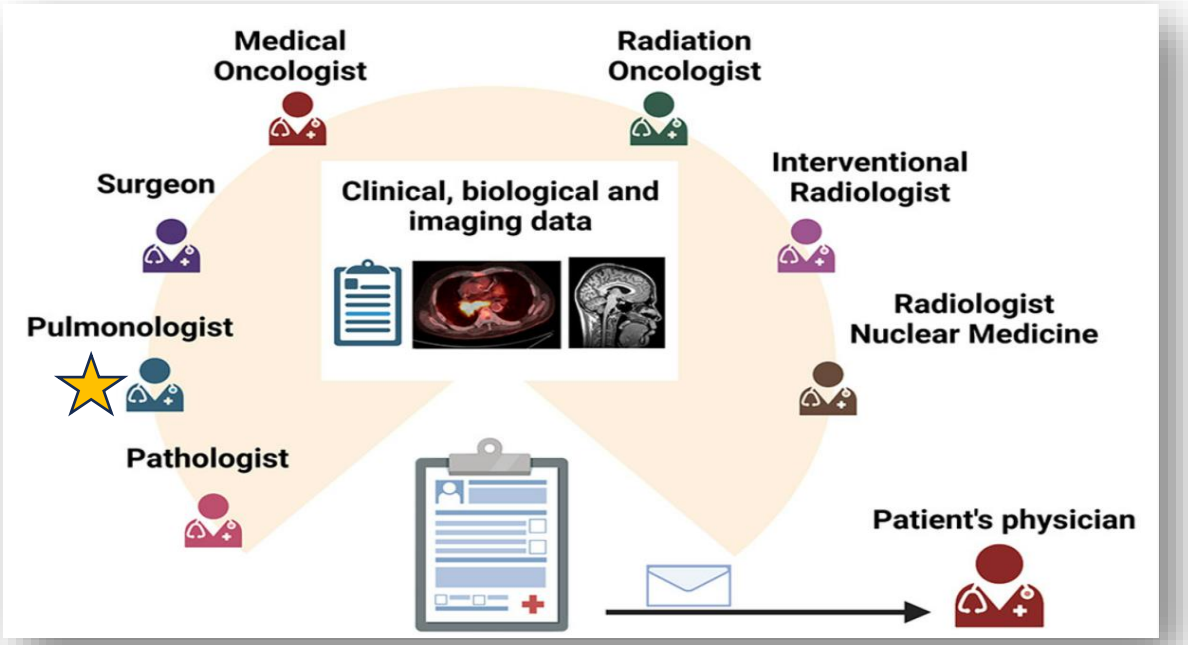
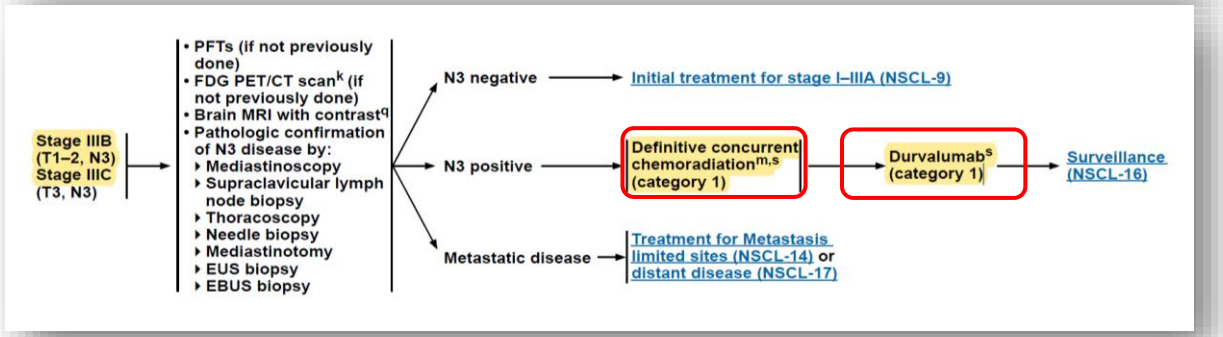
Stage III NSCLC

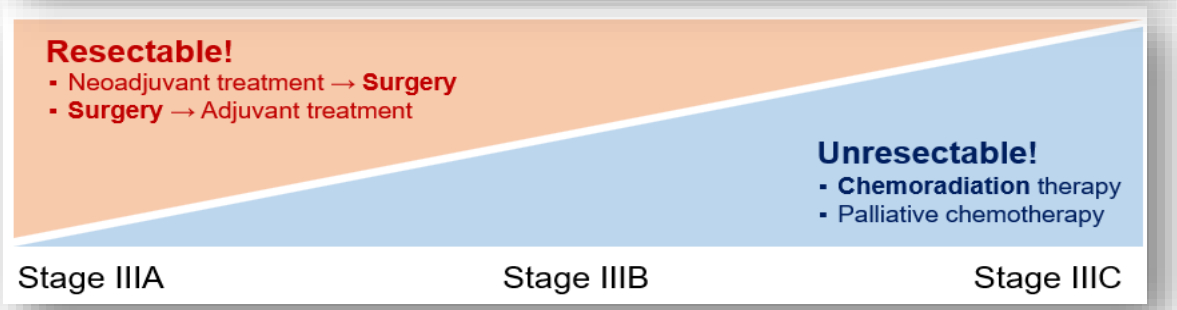
(Multidisciplinary Approach)

Stage III NSCLC, Multidisciplinary Approach









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Stage III NSCLC, Multidisciplinary Approach, Surgery, Perioperative Chemotherapy

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PERIOPERATIVE SYSTEMIC THERAPY

Neoadjuvant Systemic Therapy

- All patients should be evaluated for preoperative therapy, with strong consideration for nivolumab + chemotherapy for those patients with tumors ≥4 cm or node positive and no contraindications to immune checkpoint inhibitors.* Otherwise refer to the Neoadjuvant Systemic Therapy for Patients Not Candidates for Immune Checkpoint Inhibitors.
- Test for PD-L1 status, *EGFR* mutations, and *ALK* rearrangements (stages IB–IIIA, IIIB [T3,N2]).
  Principles of Molecular and Biomarker Analysis (NSCL-H)
- After surgical evaluation, patients likely to receive adjuvant chemotherapy may be treated with induction systemic therapy as an alternative.

Neoadjuvant Systemic Therapy in Patients Candidates for Immune Checkpoint Inhibitors

- Nivolumab 360 mg and platinum-doublet chemotherapy every 3 weeks for 3 cycles[1]
  - Platinum-doublet chemotherapy options include:
    - Carboplatin AUC 5 or AUC 6 day 1, paclitaxel 175 mg/m² or 200 mg/m² day 1 (any histology)
    - Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1 (nonsquamous histology)
    - Cisplatin 75 mg/m² day 1, gemcitabine 1000 mg/m² or 1250 mg/m² days 1 and 8 (squamous histology)
    - Cisplatin 75 mg/m² day 1, paclitaxel 175 mg/m² or 200 mg/m² day 1 (any histology)
  - Chemotherapy Regimens for Patients Not Candidates for Cisplatin-Based Therapy
    - Carboplatin AUC 5 or AUC 6 day 1, pemetrexed 500 mg/m² day 1 (nonsquamous histology)
    - Carboplatin AUC 5 or AUC 6 day 1, gemcitabine 1000 mg/m² or 1250 mg/m² days 1 and 8 (squamous histology)

Neoadjuvant Systemic Therapy for Patients Not Candidates for Immune Checkpoint Inhibitors

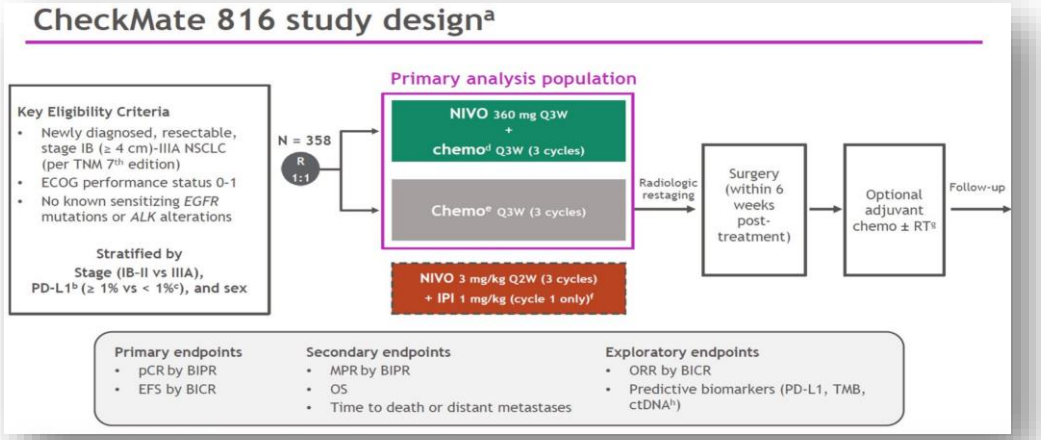
Preferred (nonsquamous)
- Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1 every 21 days for 4 cycles[2]

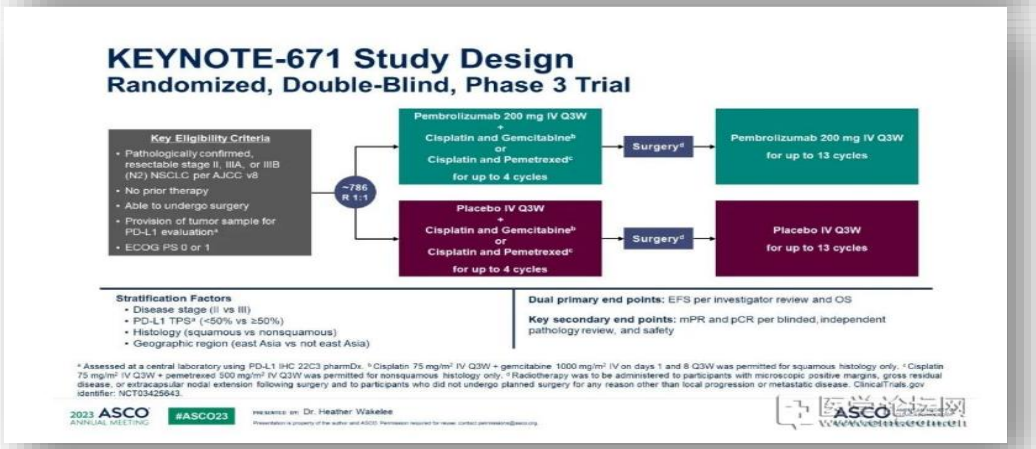
Preferred (squamous)
- Cisplatin 75 mg/m² day 1, gemcitabine 1250 mg/m² days 1 and 8, every 21 days for 4 cycles[3]
- Cisplatin 75 mg/m² day 1, docetaxel 75 mg/m² day 1 every 21 days for 4 cycles[4]

Other Recommended
- Cisplatin 50 mg/m² days 1 and 8; vinorelbine 25 mg/m² days 1, 8, 15, and 22, every 28 days for 4 cycles[5]
- Cisplatin 100 mg/m² day 1, vinorelbine 30 mg/m² days 1, 8, 15, and 22, every 28 days for 4 cycles[6,7]
- Cisplatin 75–80 mg/m² day 1, vinorelbine 25–30 mg/m² days 1 and 8, every 21 days for 4 cycles
- Cisplatin 100 mg/m² day 1, etoposide 100 mg/m² days 1–3, every 28 days for 4 cycles[6]

Useful in Certain Circumstances
- Chemotherapy Regimens for Patients Not Candidates for Cisplatin-Based Therapy
  - Carboplatin AUC 6 day 1, paclitaxel 200 mg/m² day 1, every 21 days for 4 cycles[8]
  - Carboplatin AUC 5 day 1, gemcitabine 1000 mg/m² days 1 and 8, every 21 days for 4 cycles[9] (squamous histology)
  - Carboplatin AUC 5 day 1, pemetrexed 500 mg/m² day 1 every 21 days for 4 cycles[10] (nonsquamous histology)

All chemotherapy regimens listed above can be used for sequential chemotherapy/RT.





1 Forde PM, Spicer J, Lu S, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer (Chekmate 816). N Engl J Med 2022;386:1973-1985
* Wakelee H, Liberman M et al. Perioperative Pembrolizumab for Early-Stage Non-Small-Cell Lung Cancer (Keynote 671). N Engl J Med 2023;389(6):491-503.

➔국내비급여, 2023.9 기준

Stage III NSCLC, Multidisciplinary Approach, CCRT

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CONCURRENT CHEMORADIATION REGIMENS

Concurrent Chemoradiation Regimens[€]

Preferred (nonsquamous)
- Carboplatin AUC 5 on day 1, pemetrexed 500 mg/m² on day 1 every 21 days for 4 cycles; concurrent thoracic RT[1,*,†,‡]
- Cisplatin 75 mg/m² on day 1, pemetrexed 500 mg/m² on day 1 every 21 days for 3 cycles; concurrent thoracic RT[2,3,*,†,‡] ± additional 4 cycles of pemetrexed 500 mg/m²[†,§]
- Paclitaxel 45–50 mg/m² weekly; carboplatin AUC 2, concurrent thoracic RT[4,*,†,‡] ± additional 2 cycles every 21 days of paclitaxel 200 mg/m² and carboplatin AUC 6[†,§]
- Cisplatin 50 mg/m² on days 1, 8, 29, and 36; etoposide 50 mg/m² days 1–5 and 29–33; concurrent thoracic RT[5,6,*,†,‡]

Preferred (squamous)
- Paclitaxel 45–50 mg/m² weekly; carboplatin AUC 2, concurrent thoracic RT[6,*,†,‡] ± additional 2 cycles every 21 days of paclitaxel 200 mg/m² and carboplatin AUC 6[†,§]
- Cisplatin 50 mg/m² on days 1, 8, 29, and 36; etoposide 50 mg/m² days 1–5 and 29–33; concurrent thoracic RT[5,6,*,†,‡]

Consolidation Immunotherapy for Patients with Unresectable Stage II/III NSCLC, PS 0–1, and No Disease Progression After Definitive Concurrent Chemoradiation

Durvalumab 10 mg/kg IV every 2 weeks or 1500 mg every 4 weeks for up to 12 months (patients with a body weight of ≥30 kg)[7,8]
(category 1 for stage III; category 2A for stage II)

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PRINCIPLES OF RADIATION THERAPY

Please note: Tables 2–5 provide doses and constraints used commonly or in past clinical trials as useful references rather than specific recommendations.

Table 4. Commonly Used Doses for Conventionally Fractionated and Palliative RT

Treatment Type	Total Dose	Fraction Size	Treatment Duration
Definitive RT with or without chemotherapy	60–70 Gy	2 Gy	6–7 weeks
Preoperative RT	45–54 Gy	1.8–2 Gy	5 weeks
Postoperative RT • Negative margins • Extracapsular nodal extension or microscopic positive margins • Gross residual tumor	 50–54 Gy 54–60 Gy 60–70 Gy	 1.8–2 Gy 1.8–2 Gy 2 Gy	 5–6 weeks 6 weeks 6–7 weeks

Table 5. Normal Tissue Dose-Volume Constraints for Conventionally Fractionated RT with Concurrent Chemotherapy[†,‡]

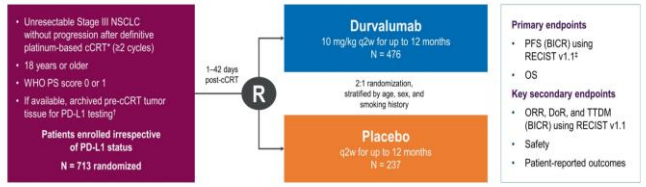
OAR	Constraints in 30–35 fractions
Spinal cord	Max ≤50 Gy
Lung	V20 ≤35%–40%;[§] MLD ≤20 Gy
Heart	V50 ≤25%; Mean ≤20 Gy
Esophagus	Mean ≤34 Gy; Max ≤105% of prescription dose; V60 ≤17%; contralateral sparing is desirable
Brachial plexus	Median dose ≤69 Gy

Vxx = % of the whole OAR receiving ≥xx Gy.

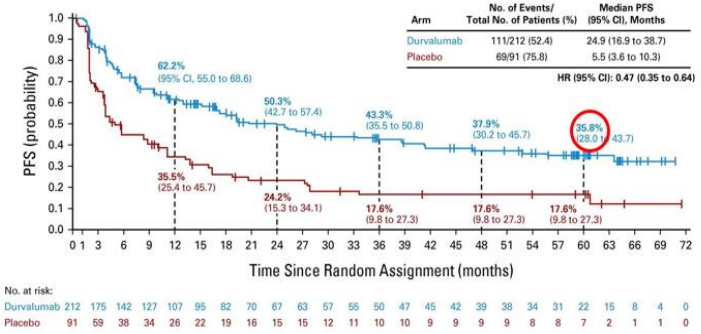
†These constraints represent doses that generally should not be exceeded, based on a

PACIFIC: Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter, International Trial

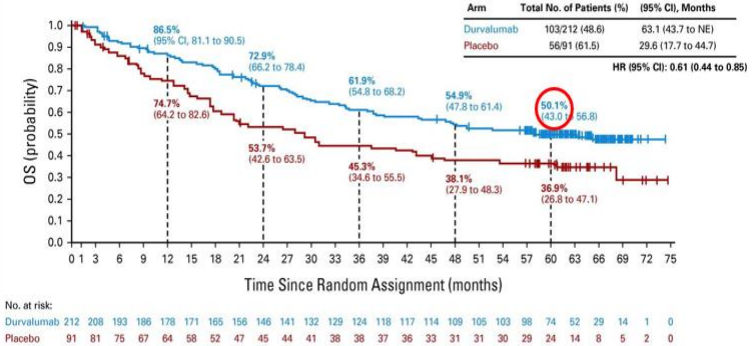
급여



- Updated analyses of OS and PFS, assessed ~5 years after the last patient was randomized (data cutoff: 11 January 2021; exploratory, post-hoc analysis)
  - Treatment effects were estimated using stratified log-rank tests in the ITT population
  - Medians and yearly landmark rates were estimated using the Kaplan–Meier method



▪ Progression-free survival of patients with PD-L1 TC ≥ 1%



▪ Overall survival of patients with PD-L1 TC ≥ 1%

[8] Faivre-Finn C, Vicente D, Kurata T, et al. Four-year survival with durvalumab after chemoradiotherapy in stage III NSCLC-an update from the PACIFIC trial. J Thorac Oncol 2021;16:860-867.

Stage IV NSCLC

Stage IV NSCLC

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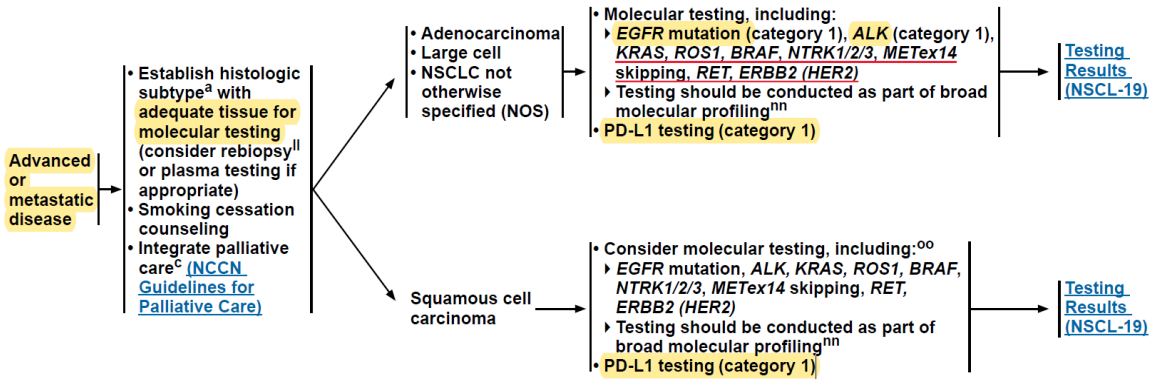

[a] Principles of Pathologic Review (NSCL-A).
[c] Temel JS, et al. N Engl J Med 2010;363:733-742.
[ll] If there is insufficient tissue to allow testing for all of *EGFR*, *KRAS*, *ALK*, *ROS1*, *BRAF*, *NTRK1/2/3*, *MET*, *RET*, and *ERBB2 (HER2)* repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes.
[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).

[nn] The NCCN NSCLC Guidelines Panel strongly advises broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is defined as molecular testing that identifies all biomarkers identified in NSCL-19 in either a single assay or a combination of a limited number of assays, and optimally also identifies emerging biomarkers (NSCL-I). Tiered approaches based on low prevalence of co-occurring biomarkers are acceptable. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC. Emerging Biomarkers to Identify Patients for Therapies (NSCL-I).
[oo] Lam VK, et al. Clin Lung Cancer 2019;20:30-36.e3; Sands JM, et al. Lung Cancer 2020;140:35-41.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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TESTING RESULTS[ll,mm]

EGFR exon 19 deletion or exon 21 L858R mutation positive	NSCL-20
EGFR S768I, L861Q, and/or G719X mutation positive	NSCL-23
EGFR exon 20 insertion mutation positive	NSCL-24
KRAS G12C mutation positive	NSCL-25
ALK rearrangement positive	NSCL-26
ROS1 rearrangement positive	NSCL-29
BRAF V600E mutation positive	NSCL-31
NTRK1/2/3 gene fusion positive	NSCL-32
METex14 skipping mutation positive	NSCL-33
RET rearrangement positive	NSCL-34
ERBB2 (HER2) mutation positive	NSCL-35
PD-L1 ≥1% and negative for actionable molecular biomarkers above	NSCL-36
PD-L1 <1% and negative for actionable molecular biomarkers above	NSCL-37

[ll] If there is insufficient tissue to allow testing for all of *EGFR*, *KRAS*, *ALK*, *ROS1*, *BRAF*, *NTRK1/2/3*, *MET*, *RET*, and *ERBB2 (HER2)* repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes.
[mm] Principles of Molecular and Biomarker Analysis (NSCL-H).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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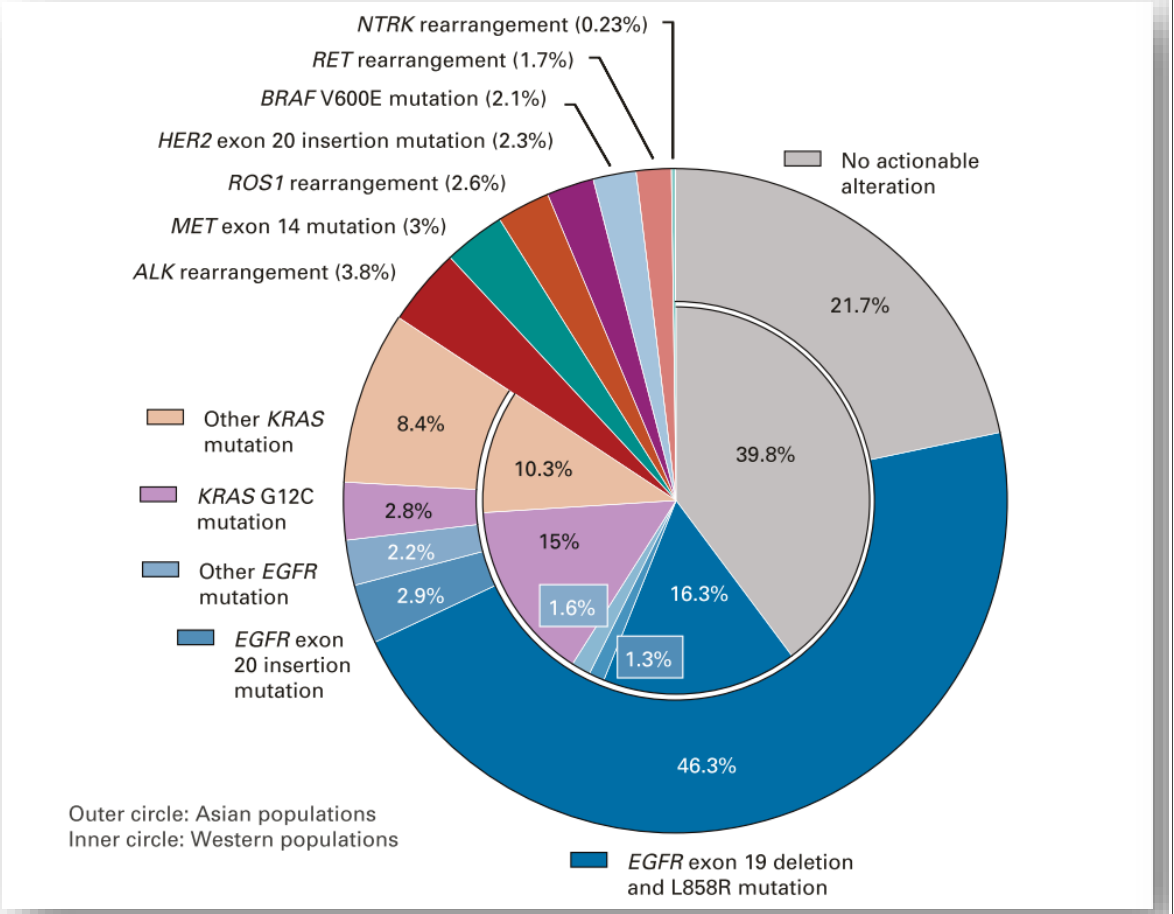
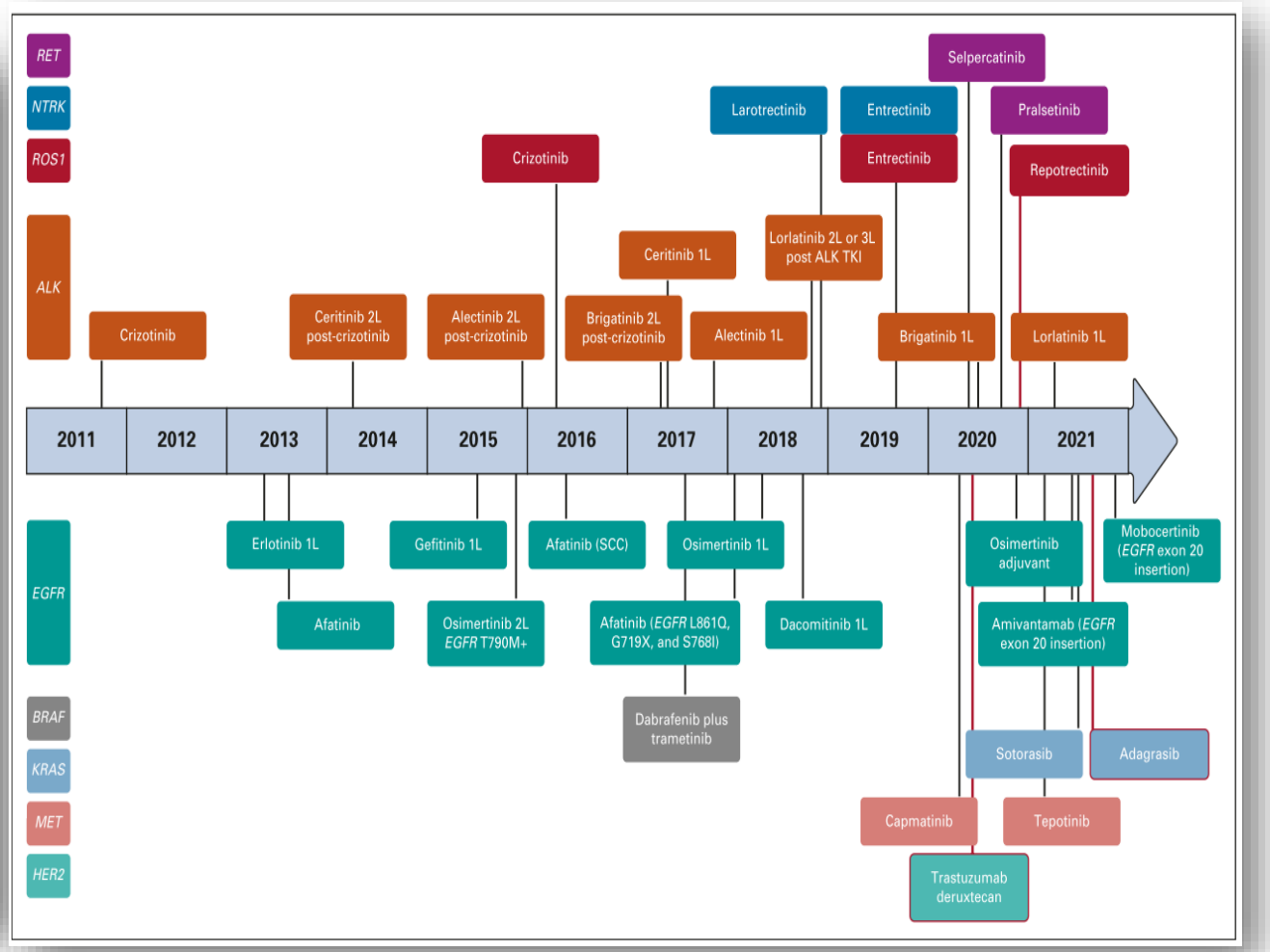
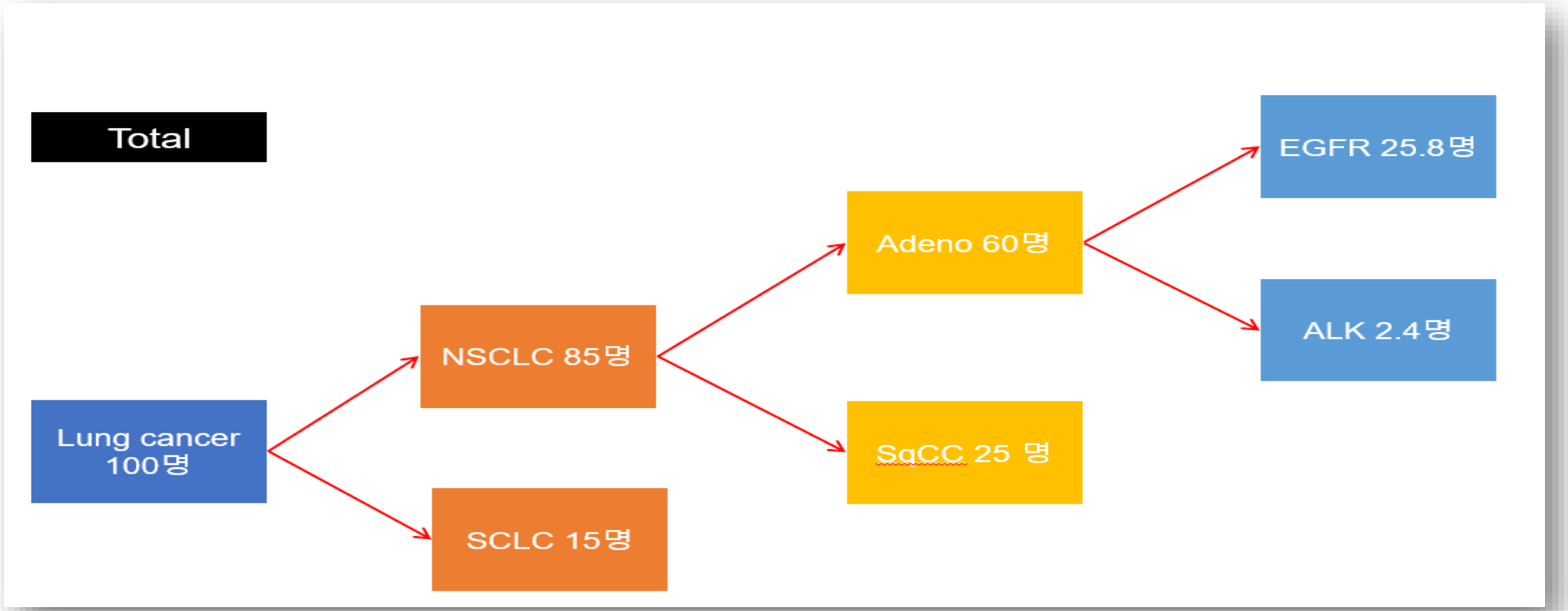
Lung cancer Targeted Treatment





Tan AC et al. J Clin Oncology 2022;40:611-625.

NSCLC subtype



In patients with adenocarcinoma, the frequency of EGFR mutations was 43% (range, 20%–56%), while that of the EMK4-ALK gene was less than 5%

Stage IV NSCLC, EGFR positive

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EGFR EXON 19 DELETION OR EXON 21 L858R MUTATIONS[mm]

FIRST-LINE THERAPY[pp]

- *EGFR* exon 19 deletion or exon 21 L858R mutations
  - *EGFR* mutation discovered prior to first-line systemic therapy
    - Preferred: Osimertinib[qq] (category 1) → Progression → Subsequent Therapy (NSCL-21)
    - Other Recommended: Erlotinib[qq] (category 1) or Afatinib[qq] (category 1) or Gefitinib[qq] (category 1) or Dacomitinib[qq] (category 1) or Erlotinib + ramucirumab or Erlotinib + bevacizumab[rr,ss] → Progression → Subsequent Therapy (NSCL-22)
  - *EGFR* mutation discovered during first-line systemic therapy
    - Complete planned systemic therapy,[tt] including maintenance therapy, or interrupt, followed by osimertinib (preferred) → Progression → Subsequent Therapy (NSCL-21)
    - or erlotinib or afatinib or gefitinib or dacomitinib or erlotinib + ramucirumab or erlotinib + bevacizumab[rr,ss] → Progression → Subsequent Therapy (NSCL-22)

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***EGFR* S768I, L861Q, and/or G719X MUTATIONS[mm]**

FIRST-LINE THERAPY[pp]

- *EGFR* S768I, L861Q, and/or G719X mutations
  - *EGFR* mutation discovered prior to first-line systemic therapy
    - Preferred: Afatinib[qq] → Progression → Subsequent Therapy (NSCL-22)
    - or Osimertinib[qq] → Progression → Subsequent Therapy (NSCL-21)
    - Other Recommended: Erlotinib[qq] or Gefitinib[qq] or Dacomitinib[qq] → Progression → Subsequent Therapy (NSCL-22)
  - *EGFR* mutation discovered during first-line systemic therapy
    - Complete planned systemic therapy,[tt] including maintenance therapy, or interrupt, followed by afatinib (preferred) → Progression → Subsequent Therapy (NSCL-22)
    - or osimertinib (preferred) → Progression → Subsequent Therapy (NSCL-21)
    - or erlotinib or gefitinib or dacomitinib → Progression → Subsequent Therapy (NSCL-22)

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***EGFR* EXON 20 INSERTION MUTATION[mm]**

FIRST-LINE THERAPY[ccc] | SUBSEQUENT THERAPY[pp]

- *EGFR* exon 20 insertion mutation
  - Systemic therapy: Adenocarcinoma (NSCL-K 1 of 5) or Squamous Cell Carcinoma (NSCL-K 2 of 5)
  - Tumor response evaluation
    - Progression → Amivantamab-vmjw or Mobocertinib → Progression
    - If not received previously,[ddd] • Amivantamab-vmjw or • Mobocertinib or Systemic Therapy, Subsequent[fff] (NSCL-K 4 of 5) → Progression → Systemic Therapy, Subsequent[fff] (NSCL-K 4 of 5)
    - Progression
    - Response or stable disease → 4–6 cycles (total)[eee] → Tumor response evaluation
      - Progression → Amivantamab-vmjw or Mobocertinib
      - Response or stable disease → Maintenance therapy (NSCL-K 3 of 5) → Progression

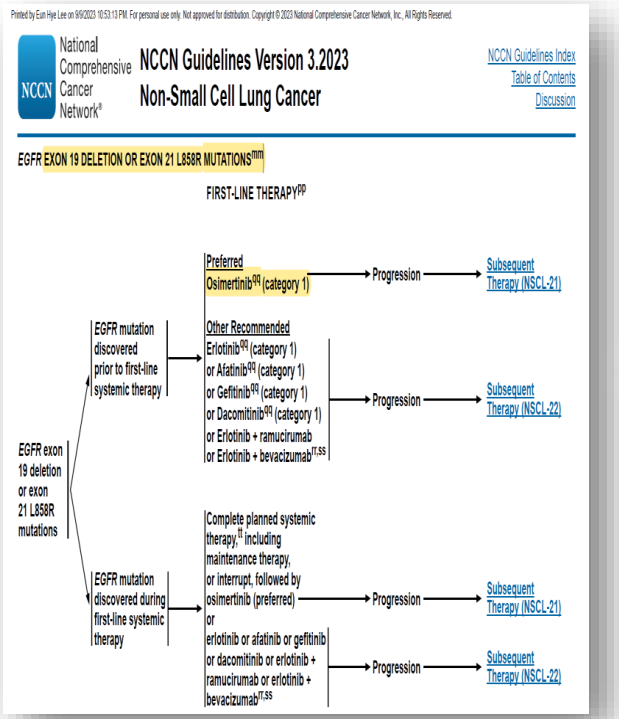
국내 1,2세대 TKI 급여

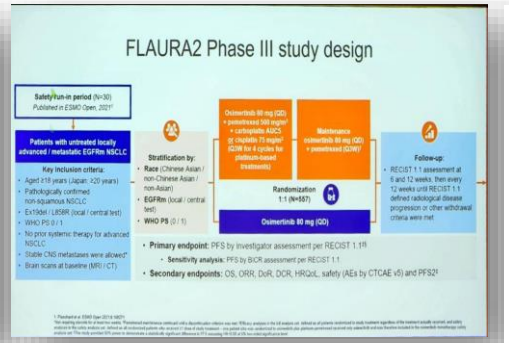
급여

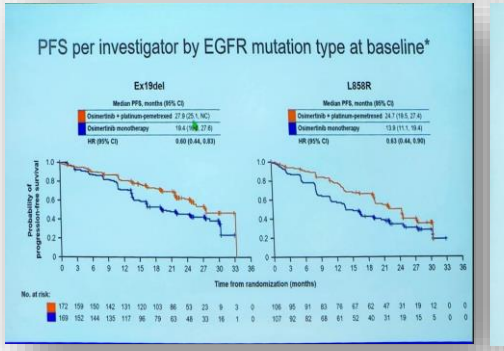
비급여

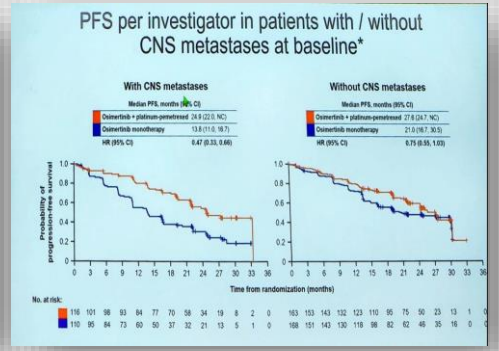
3세대 TKI, 1st line 비급여, Lasertinib EAP

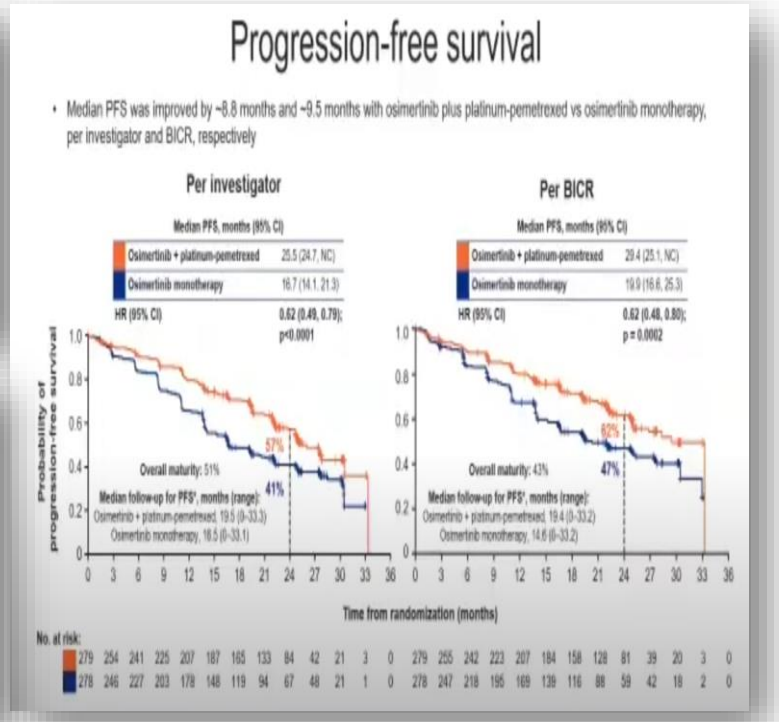
Stage IV NSCLC, EGFR positive, TKI + chemotherapy







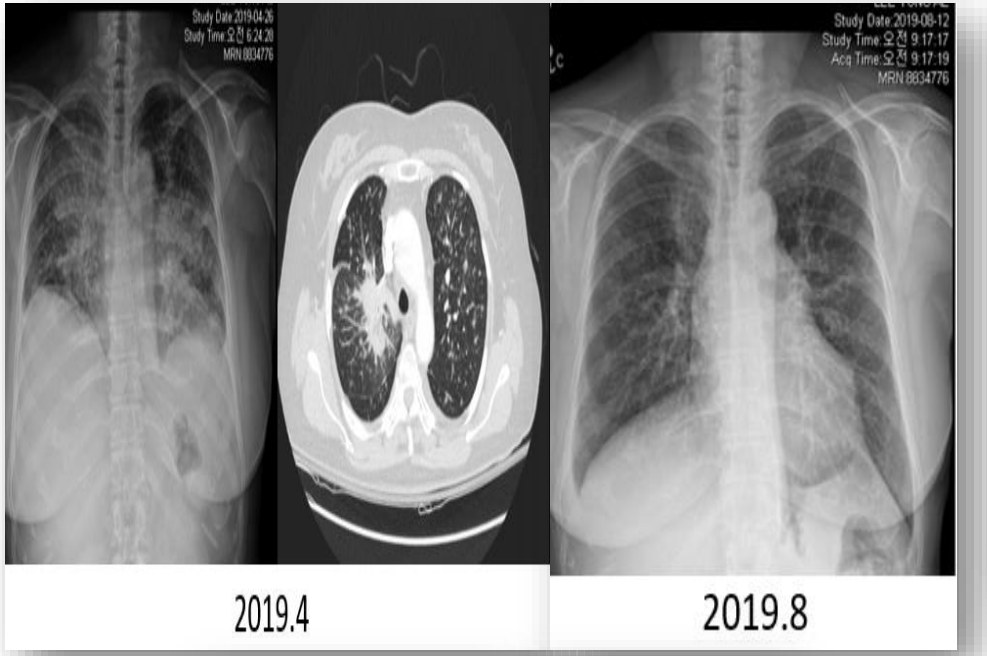




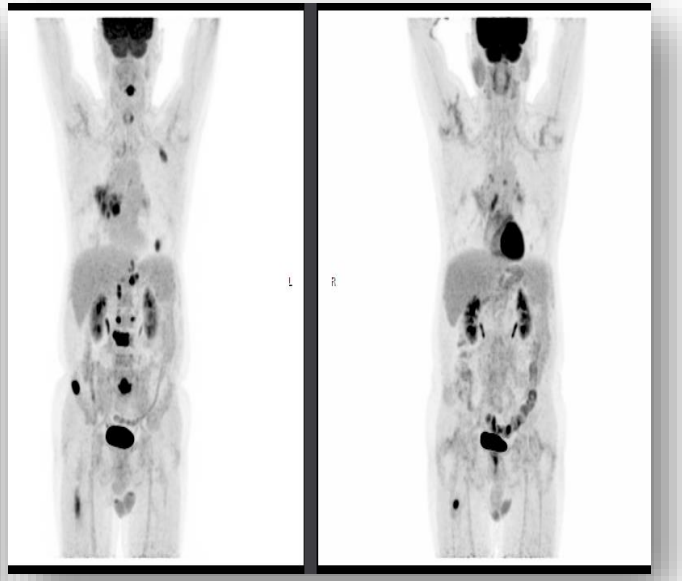
- **Osimertinib + platinum-pemetrexed demonstrated a statistically significant improvement in PFS over Osimertinib monotherapy in patients with EGFRm advanced NSCLC (HR: 0.62)**
  - ✓ **Investigator assessed mPFS : 25.5 vs 16.7 months (8.8 months improvement)**
  - ✓ **BICR-assessed mPFS : 29.4 vs 19.9 months (9.5 months improvement)**

Stabe IV NSCLC, Targeted therapy

- F/63, never smoker, EGFR 19del adenoca
- 1L afatinib 2019.4~
- 2L Osimertinib 2021.4 ~

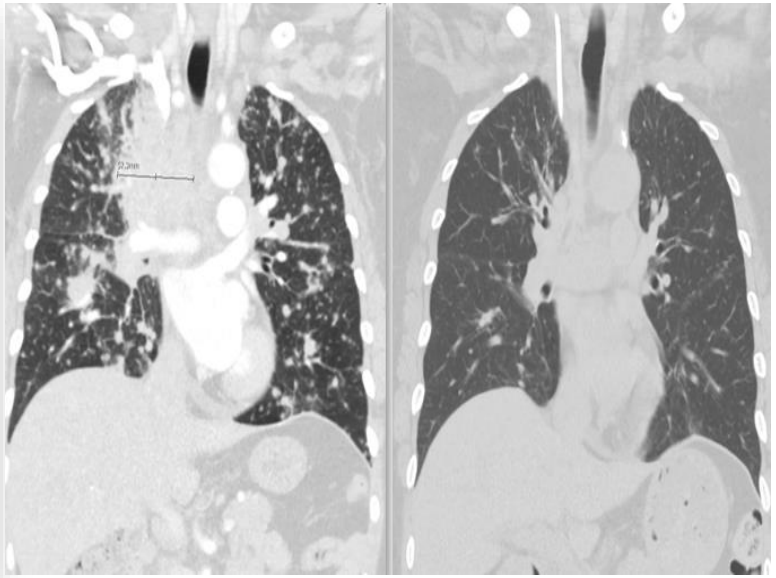


- M/64 ALK positive Adenoca
- 1L alectinib 2020.5~,
- 2L lorlatinib 2022.8~



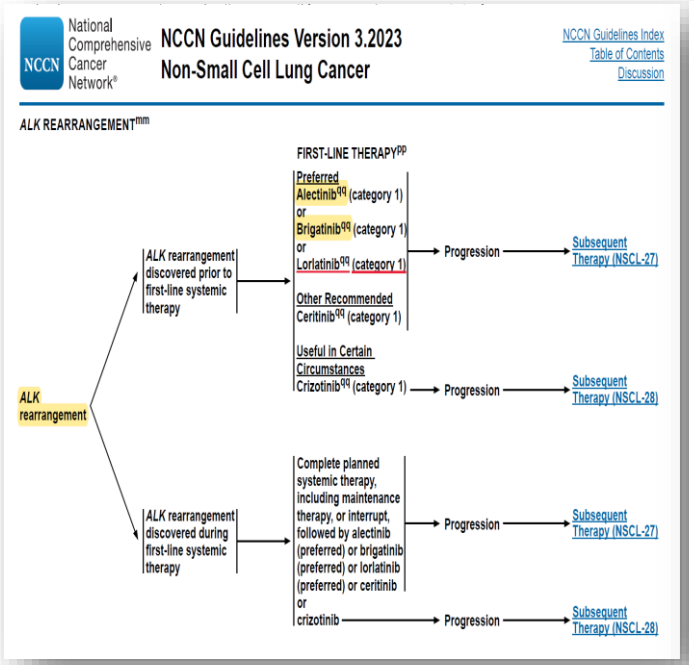
- 2020.5 ➔ 2023.5

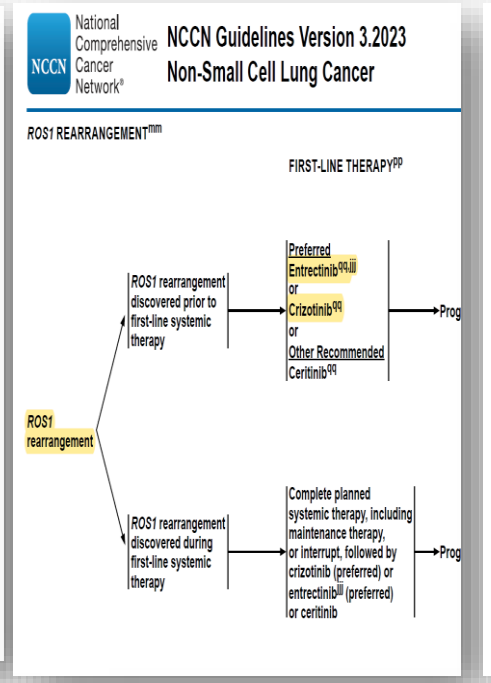
- F/60 EGFR20 insertion Adenoca
- 1L pem/cis 2020.6~/ pemetrexed~
- 2L Mobocertinib 2022.4~

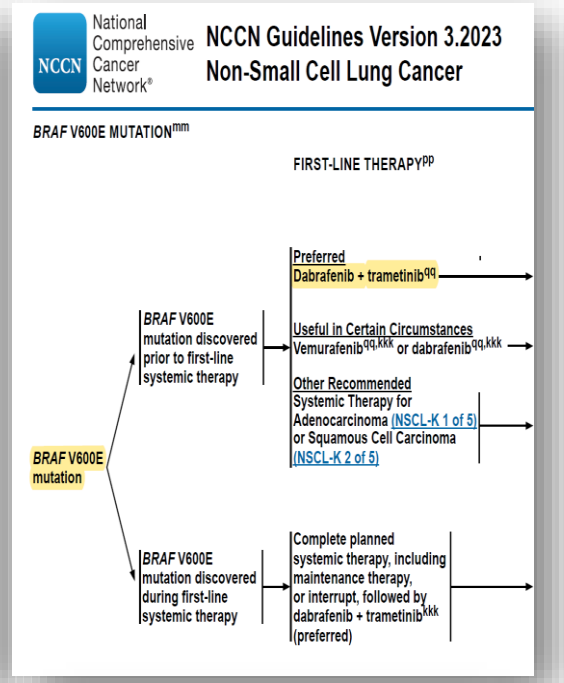


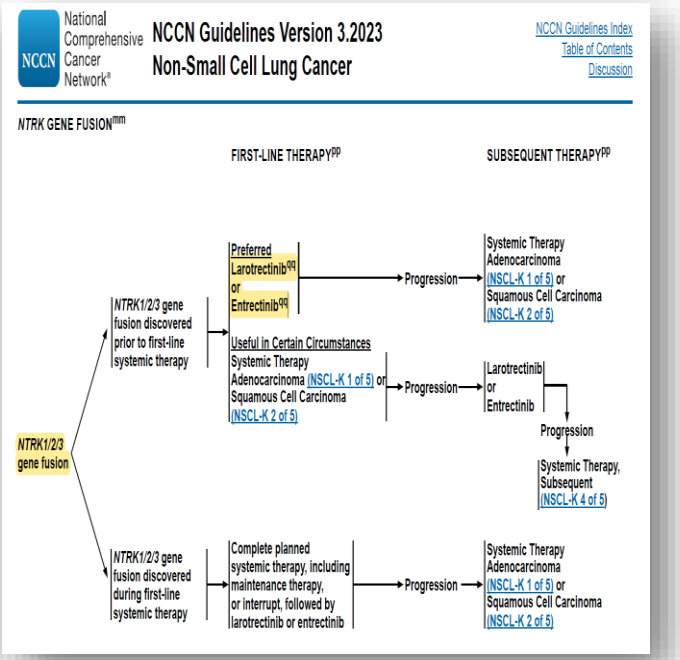
- 2020.6 ➔ 2023.4

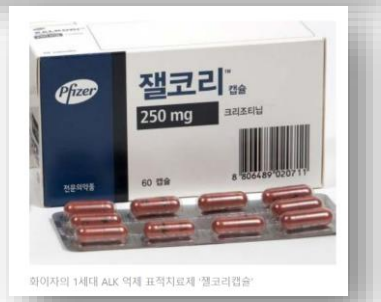
Stage IV NSCLC, other driver mutation positive (국내급여, 2023.9 기준)



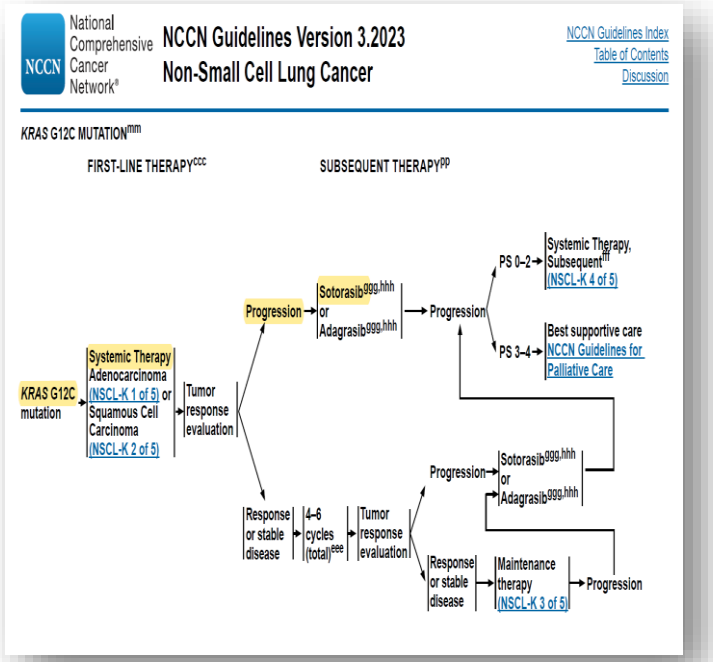


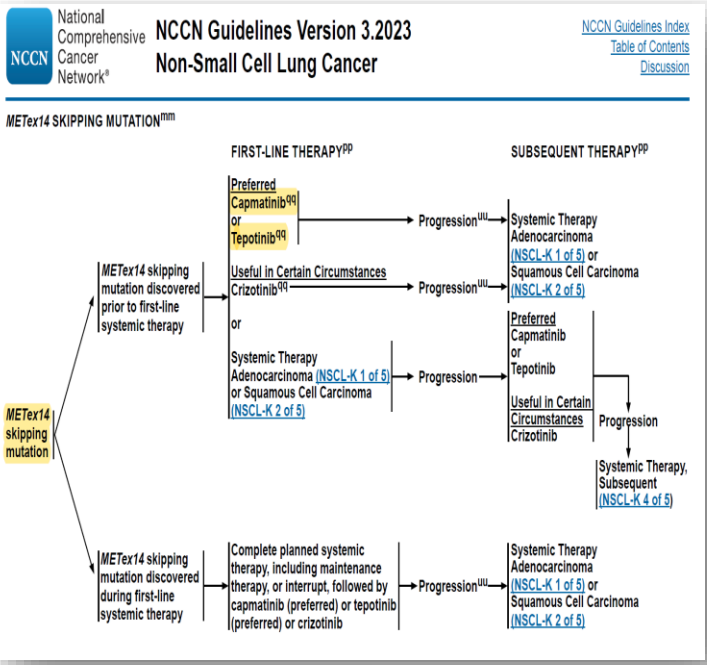


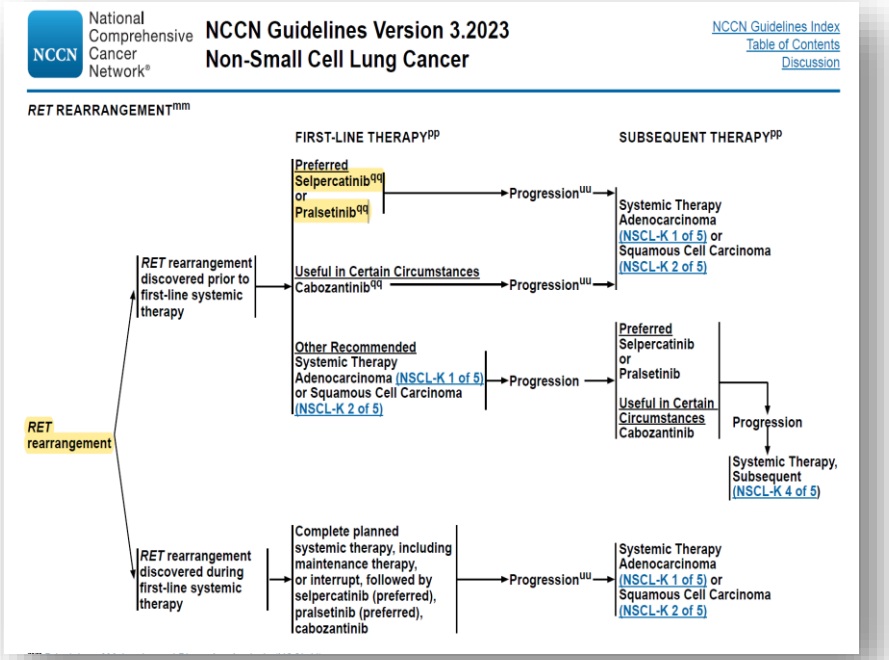




Stage IV NSCLC, other driver mutation positive (국내,비급여, 2023.9 기준)







Stage IV NSCLC, driver mutation negative

4. 고식적요법(palliative)

- platinum은 cisplatin 또는 carboplatin을 의미함

가. 투여단계: 1차(first-line)

- stage ⅢA 이상으로 각 연번의 투여대상에 해당하는 경우 요양급여를 인정함

연번	항암요법	투여대상
1	bevacizumab(100/100) + paclitaxel + carboplatin ※ 'bevacizumab'은 약값 전액을 본인이 부담토록 함 (제2008-7호: 2008.9.1, 개정 제2010-12호: 2010.12.15, 개정 제2014-15호: 2014.3.5.)	수술이 불가능한 진행성, 전이성 또는 재발성 비편평상피세포 (EGFR 활성돌연변이가 있는 경우는 제외)
2	bevacizumab(100/100) + gemcitabine + cisplatin ※ 'bevacizumab'은 약값 전액을 본인이 부담토록 함 (제2014-15호: 2014.3.5.)	
3	dacomitinib (제2020-321호: 2020.12.1.)	EGFR 활성돌연변이가 있는 국소 진행성 또는 전이성
4	pembrolizumab[주1] (제2022-38호: 2022.3.1.)	PD-L1 발현 양성(발현 비율 ≧ 50%[주3])이면서, EGFR 또는 ALK 변이가 없는 진행성 (stage Ⅳ) ※ 선행화학요법/수술후보조요법, 근치적항암화학방사선요법 치료 종료 후 6개월 이후 재발한 경우 포함 ※ 관해공고요법으로 durvalumab 치료 실패 시 급여 불가함

연번	항암요법	투여대상
5	pembrolizumab[주1] + pemetrexed + platinum (제2022-38호: 2022.3.1.)	EGFR 또는 ALK 변이가 없는 전이성 비편평상피세포 ※ 선행화학요법/수술후보조요법, 근치적항암화학방사선요법 치료 종료 후 6개월 이후 재발한 경우 포함 ※ 관해공고요법으로 durvalumab 치료 실패 시 급여 불가함 ※ platinum은 초기 4주기 병용 투여 이후 투여하지 아니함 ※ pemetrexed는 최대 2년까지 급여 인정함
6	pembrolizumab[주1] + paclitaxel + carboplatin (제2022-38호: 2022.3.1.)	전이성 편평상피세포 ※ 선행화학요법/수술후보조요법, 근치적항암화학방사선요법 치료 종료 후 6개월 이후 재발한 경우 포함 ※ 관해공고요법으로 durvalumab 치료 실패 시 급여 불가함 ※ paclitaxel과 carboplatin은 초기 4주기 병용 투여 이후 투여하지 아니함
7	atezolizumab[주1] (제2022-113호: 2022.5.1.)	PD-L1 발현 양성(발현비율 TC3 또는 IC3[주2])이면서, EGFR 또는 ALK 변이가 없는 전이성 ※ 선행화학요법/수술후보조요법, 근치적항암화학방사선요법 치료 종료 후 6개월 이후 재발한 경우 포함 ※ 관해공고요법으로 durvalumab 치료 실패 시 급여 불가함

Stage IV NSCLC, driver mutation negative (Adenocarcinoma)

KEYNOTE-189 Study design

Adenocarcinoma

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

R (2:1)[a]
N = 616

Pembrolizumab 200 mg + Pemetrexed 500 mg/m² + Carboplatin AUC 5 OR Cisplatin 75 mg/m² Q3W for 4 cycles

→ **Pembrolizumab 200 mg Q3W for up to 31 cycles + Pemetrexed 500 mg/m² Q3W**

Placebo (normal saline) + Pemetrexed 500 mg/m² + Carboplatin AUC 5 OR Cisplatin 75 mg/m² Q3W for 4 cycles

→ **Placebo (normal saline) for up to 31 cycles + Pemetrexed 500 mg/m² Q3W**

Second-Course Pembrolizumab[b]

Pembrolizumab 200 mg Q3W 17 cycles (1 year)

Pembrolizumab 200 mg Q3W 35 cycles (2 year)

Crossover Pembrolizumab[c]

- **Dual primary endpoints:** OS and PFS (RECIST v1.1, independent central review)
- **Secondary endpoints:** ORR, DOR and safety
- **Exploratory endpoint:** PFS2

- **In the placebo + chemo arm:**
  117 patients (Effective Crossover Rate = 57%) received subsequent anti-PD-(L)1 therapy, including on-study crossover

PFS2 defined as time from randomization to investigator-assessed disease progression that led to cessation of second-line therapy, start of third-line therapy, or death. a. Randomization was stratified by: PD-L1 expression (TPS ≥ 1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin), and smoking status (never vs. former/current). b. Patients who had SD or better after completing 35 cycles of pembrolizumab or had stopped trial treatment after achieving CR and received ≥ 8 cycles of treatment, but then experienced PD, could receive second-course pembrolizumab for 17 cycles (~1 year) if they had received no new anticancer therapy since the last dose of pembrolizumab. c. Patients could cross over to pembrolizumab monotherapy after PD per RECIST v1.1 by blinded independent central review.

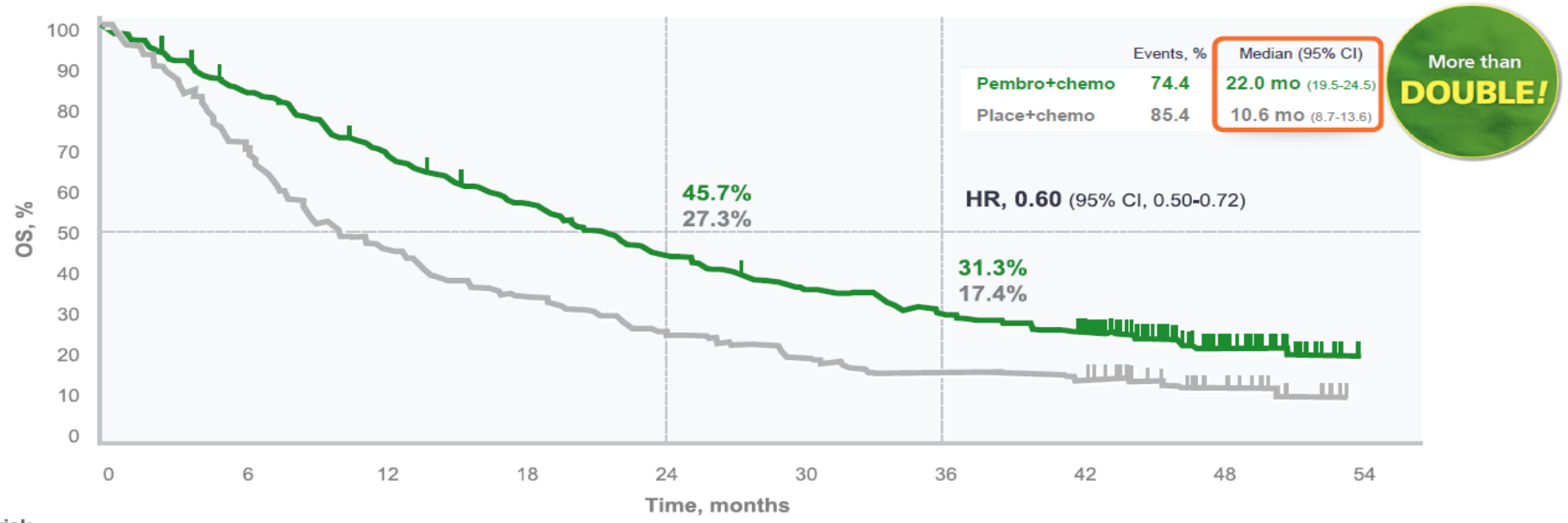
1. Gray, et al. KN189. Presented at WCLC 2020.

KEYTRUDA (pembrolizumab) Injection 100mg

Stage IV NSCLC, driver mutation negative (Adenocarcinoma)

Overall Survival, ITT Population

Adenocarcinoma



Data cutoff: August 28, 2020.

1. Gray, et al. KN189. Presented at WCLC 2020.

KEYTRUDA (pembrolizumab) Injection 100mg

Stage IV NSCLC, driver mutation negative (Squamous Carcinoma)

KEYNOTE-407 Study design

Squamous carcinoma

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[a] <1% vs. ≥1%)
- Choice of taxane (paclitaxel vs. nab-paclitaxel)
- Geographic region (east Asia vs. rest of world)

R (1:1)

Pembrolizumab 200 mg Q3W + Carboplatin AUC 6 Q3W + Paclitaxel 200 mg/m² Q3W OR nab-Paclitaxel 100 mg/m² Q1W for 4 cycles (each 3 wk)

→ **Pembrolizumab 200 mg Q3W for up to 31 cycles**

Placebo (normal saline) **Q3W + Carboplatin AUC 6 Q3W + Paclitaxel 200 mg/m² Q3W OR nab-Paclitaxel 100 mg/m² Q1W for 4 cycles** (each 3 wk)

→ **Placebo** (normal saline) **Q3W for up to 31 cycles**

PD[b]

→ **Optional Crossover[b] Pembrolizumab 200 mg Q3W for up to 35cycles**

~50% of Effective Crossover Rate!

End Points

Primary:	PFS (RECIST v1.1, BICR) and OS
Secondary:	ORR and DOR (RECIST v1.1, BICR), safety

BICR=blinded independent central radiologic review

a. Percentage of tumor cells with membranous PD-L1 staining assessed using the PD-L1 HC 22C3 pharmDx assay. b. Patients could crossover during combination therapy or monotherapy. To be eligible for crossover, PD must have been verified by BICR and all safety criteria had to be met.

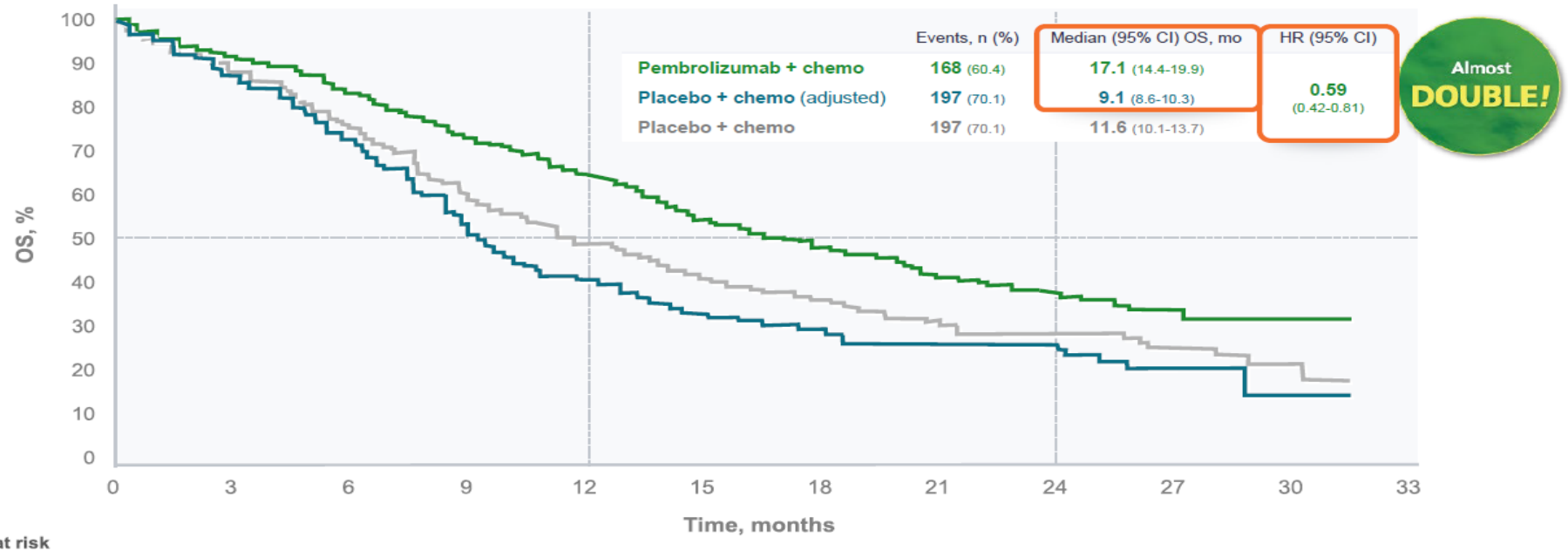
A Rhobinson, et al. KN407. Presented at ELCC 2020.

KEYTRUDA (pembrolizumab) Injection 100mg

Stage IV NSCLC, driver mutation negative (Squamous Carcinoma)

Cross-over adjusted Overall Survival, ITT population

Squamous carcinoma



No.at risk												
Pembrolizumab + chemo	278	256	232	203	180	150	119	80	46	14	4	0
Placebo + chemo (adjusted)	281	244	202	142	98	66	53	35	17	7	2	0
Placebo + chemo	281	245	210	163	137	113	91	61	36	16	3	0

1. Paz-Ares L, et al. A Randomized, Placebo-Controlled Trial of Pembrolizumab Plus Chemotherapy in Patients With Metastatic Squamous NSCLC: Protocol-Specified Final Analysis of KEYNOTE-407. *JTO*. 2020;15(10):1657-69

KEYTRUDA (pembrolizumab) Injection 100mg

Small Cell Lung cancer

Small Cell Lung Cancer

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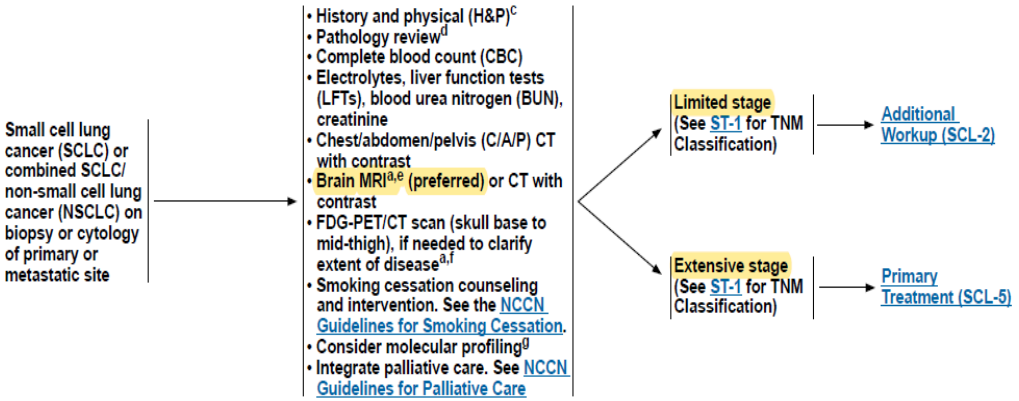

[a] If extensive stage is established, further staging evaluation is optional. However, brain imaging MRI (preferred), or CT with contrast is recommended in all patients.
[b] Workup of SCLC should be expedited, with studies done in parallel whenever possible.
[c] Signs and Symptoms of Small Cell Lung Cancer (SCL-A).
[d] Principles of Pathologic Review (SCL-B).
[e] Brain MRI is more sensitive than CT for identifying brain metastases and is preferred over CT.
[f] If FDG-PET/CT is not available, bone scan may be used to identify metastases. Pathologic confirmation is recommended for lesions detected by FDG-PET/CT that alter stage.
[g] Comprehensive molecular profiling can be considered in rare cases—particularly for patients with extensive-stage/relapsed SCLC who do not smoke tobacco, lightly smoke, have remote smoking history, or have diagnostic or therapeutic dilemma, or at time of relapse—if not previously done, because this may change management.

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***Table 1* - Definition of small cell lung cancer consists of two stages:**
(1) Limited-stage: Stage I-III (T any, N any, M0) that can be safely treated with definitive radiation doses. Excludes T3-4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan.
(2) Extensive-stage: Stage IV (T any, N any, M 1a/b/c), or T3-4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan.

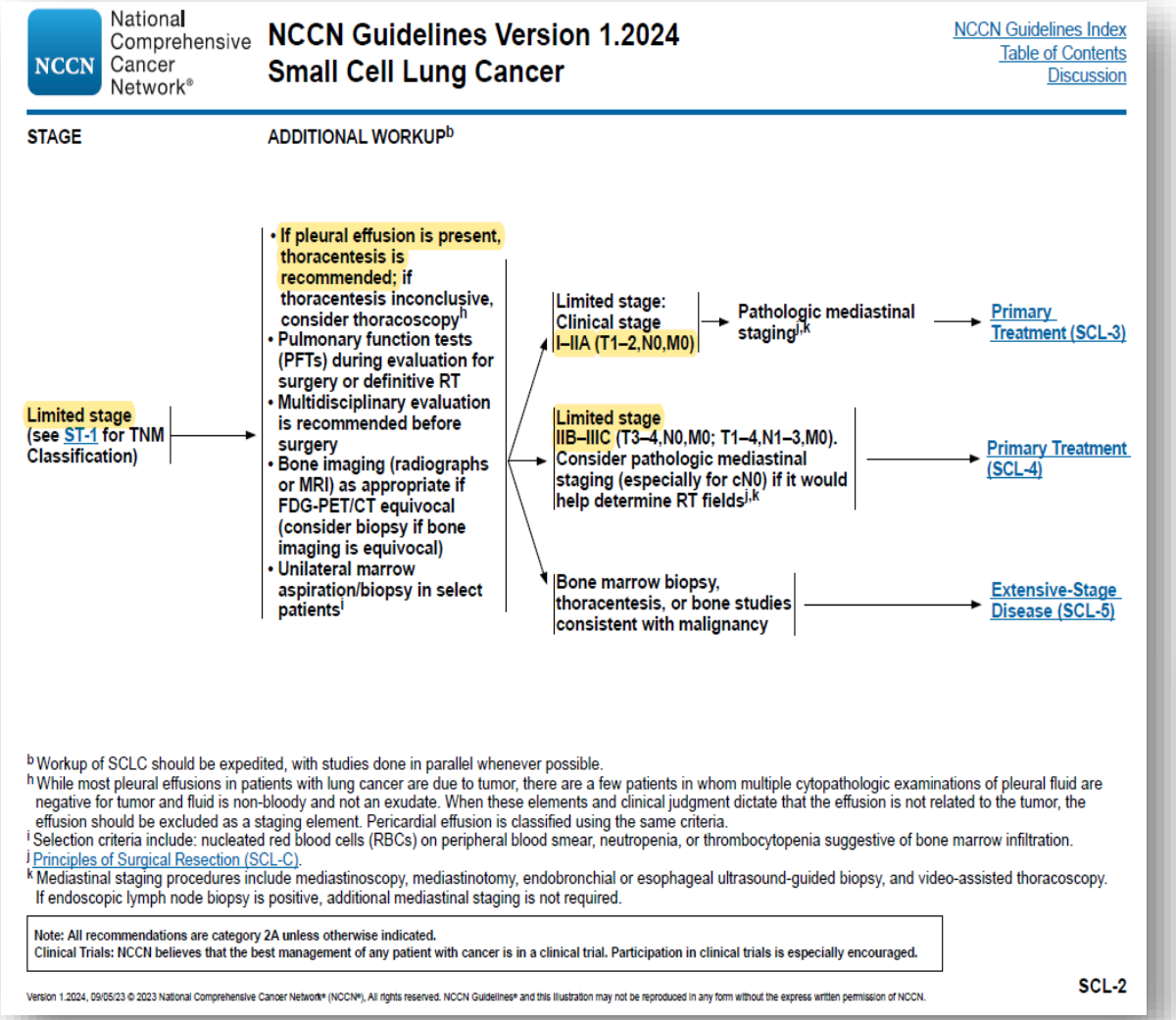
***Table 2* - American Joint Committee on Cancer (AJCC) Eighth ed., 2017 Definitions of TNM**

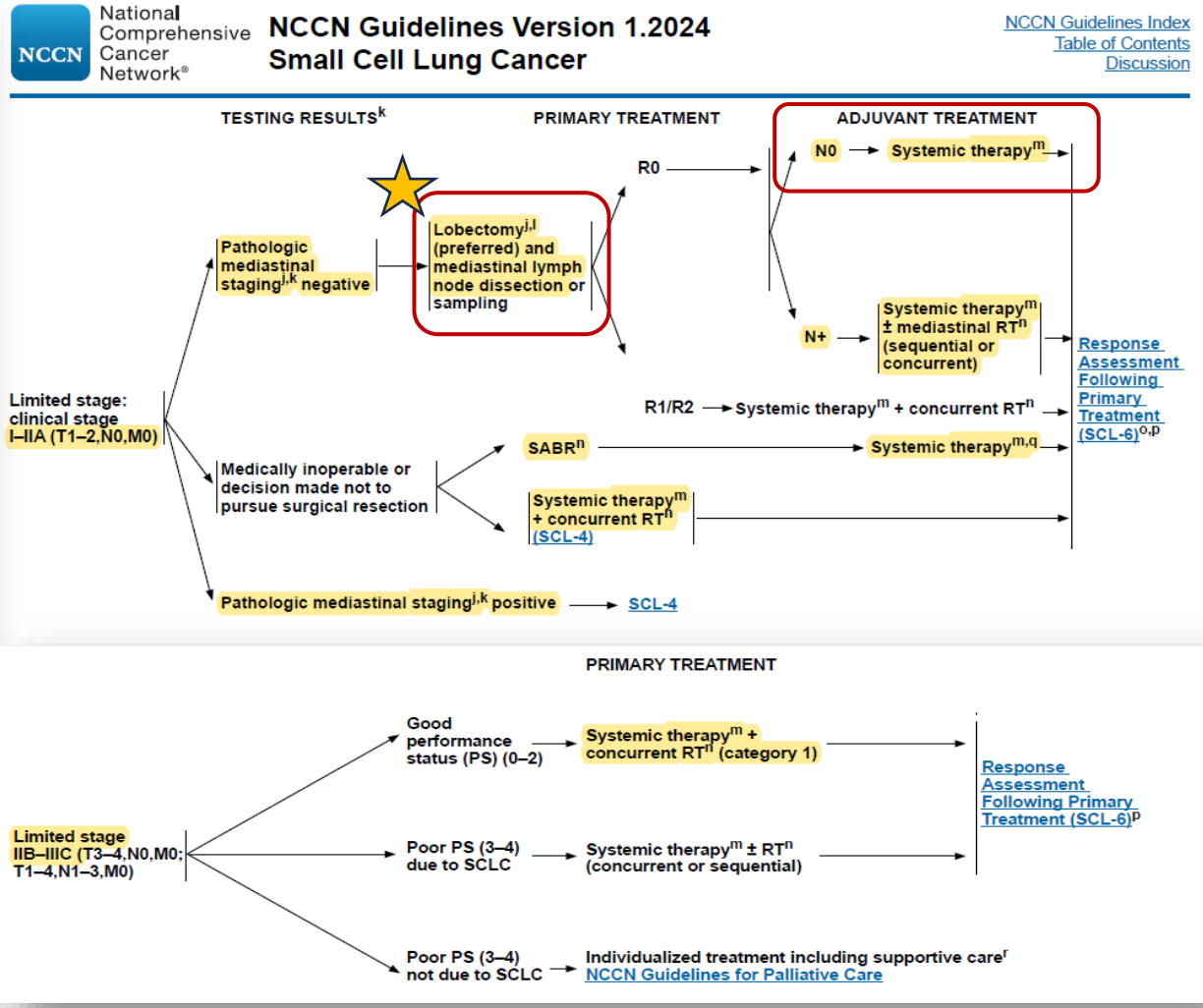
		Primary Tumor
TX		Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0		No evidence of primary tumor
Tis		Carcinoma *in situ* Squamous cell carcinoma *in situ* (SCIS) Adenocarcinoma *in situ* (AIS): adenocarcinoma with pure lepidic pattern, ≤3 cm in greatest dimension
T1		Tumor ≤3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)
	T1mi	Minimally invasive adenocarcinoma: adenocarcinoma (≤3 cm in greatest dimension) with a predominantly lepidic pattern and ≤5 mm invasion in greatest dimension
	T1a	Tumor ≤1 cm in greatest dimension. A superficial, spreading tumor of any size whose invasive component is limited to the bronchial wall and may extend proximal to the main bronchus also is classified as T1a, but these tumors are uncommon.
	T1b	Tumor >1 cm but ≤2 cm in greatest dimension
	T1c	Tumor >2 cm but ≤3 cm in greatest dimension
T2		Tumor >3 cm but ≤5 cm or having any of the following features: (1) Involves the main bronchus, regardless of distance to the carina, but without involvement of the carina; (2) Invades visceral pleura (PL1 or PL2); (3) Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung. T2 tumors with these features are classified as T2a if ≤4 cm or if the size cannot be determined and T2b if >4 cm but ≤5 cm.
	T2a	Tumor >3 cm but ≤4 cm in greatest dimension
	T2b	Tumor >4 cm but ≤5 cm in greatest dimension
T3		Tumor >5 cm but ≤7 cm in greatest dimension or directly invading any of the following: parietal pleura (PL3), chest wall (including superior sulcus tumors), phrenic nerve, parietal pericardium; or separate tumor nodule(s) in the same lobe as the primary
T4		Tumor >7 cm or tumor of any size invading one or more of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina; separate tumor nodule(s) in an ipsilateral lobe different from that of the primary

Continued

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

Small Cell Lung Cancer (Limited)





Small Cell Lung Cancer (Limited, T1-2,N0), Surgery

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PRINCIPLES OF SURGICAL RESECTION

- Stage I–IIA SCLC is diagnosed in less than 5% of patients with SCLC.
- Patients most likely to benefit from surgery are those with SCLC that is clinical stage I–IIA (T1–2,N0,M0) after standard staging evaluation (including CT of the chest and upper abdomen, brain imaging, and FDG-PET/CT imaging).[1,2]
  - Prior to resection, all patients should undergo mediastinoscopy or other surgical mediastinal staging to rule out occult nodal disease. This may also include an endoscopic staging procedure.
  - For patients undergoing definitive surgical resection, the preferred operation is lobectomy with mediastinal lymph node dissection or systematic lymph node sampling (eg, ≥3 N2 and ≥1 N1 stations).[3,4,5,6,7]
- In patients who do not smoke, small lesions that are presumed to be small cell carcinoma on biopsy should be resected because they are likely carcinoids that have been misdiagnosed (NCCN Guidelines for Neuroendocrine and Adrenal Tumors).
- Surgery may be considered for selected patients with T3 (based on size), N0 SCLC, if invasive mediastinal lymph node staging is negative.
- Intraoperative diagnosis of likely SCLC in a patient with no prior biopsy
  - Mediastinal lymph node dissection or systematic lymph node sampling with frozen section is recommended to assess extent of disease and overall burden of disease.
  - If primary site and lymph nodes appear resectable, perform anatomic resection, preferably lobectomy. Should not do pneumonectomy if needed to encompass nodal metastatic disease.
- Patients who undergo complete resection should be treated with postoperative systemic therapy.[8] Patients without nodal metastases should be treated with systemic therapy alone. Patients with N2 or N3 nodal metastases should be treated with postoperative concurrent or sequential systemic therapy and mediastinal RT. Patients with N1 nodal metastases may be considered for postoperative mediastinal radiation.
- The benefit of PCI is unclear in patients who have undergone definitive therapy for pathologic stage I (T1-2a,N0,M0); see SCL-F.

[1] Lad T, Piantadosi S, Thomas P, et al. A prospective randomized trial to determine the benefit of surgical resection of residual disease following response of small cell lung cancer to combination chemotherapy. Chest 1994;106:320S-323S.
[2] Yang CJ, Chan DY, Shah SA, et al. Long-term survival after surgery compared with concurrent chemoradiation for node-negative small cell lung cancer. Ann Surg 2018;268:1105-1112.
[3] Katz MHG, Francescatti AB, Hunt KK; Cancer Surgery Standards Program of the American College of Surgeons. Technical Standards for Cancer Surgery: Commission on Cancer Standards 5.3-5.8. Ann Surg Oncol 2022;29:6549-6558.
[4] Darling GE, Allen MS, Decker PA, et al. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery Oncology Group Z0030 Trial. J Thorac Cardiovasc Surg 2011;141:662-670.
[5] Darling GE, Allen MS, Decker PA, et al. Number of lymph nodes harvested from a mediastinal lymphadenectomy: results of the randomized, prospective American College of Surgeons Oncology Group Z0030 trial. Chest 2011;139:1124-1129.
[6] Osarogiagbon RU, Decker PA, Ballman K, et al. Survival Implications of Variation in the Thoroughness of Pathologic Lymph Node Examination in American College of Surgeons Oncology Group Z0030 (Alliance). Ann Thorac Surg 2016;102:363-369.
[7] Su S, Scott WJ, Allen MS, et al. Patterns of survival and recurrence after surgical treatment of early stage non-small cell lung carcinoma in the ACOSOG Z0030 (ALLIANCE) trial. J Thorac Cardiovasc Surg 2014;147:747-752: Discussion 752-753.
[8] Yang CE, Chan DY, Speicher PJ, et al. Role of adjuvant therapy in a population-based cohort of patients with early-stage small-cell lung cancer. J Clin Oncol 2016;34:1057-1064.

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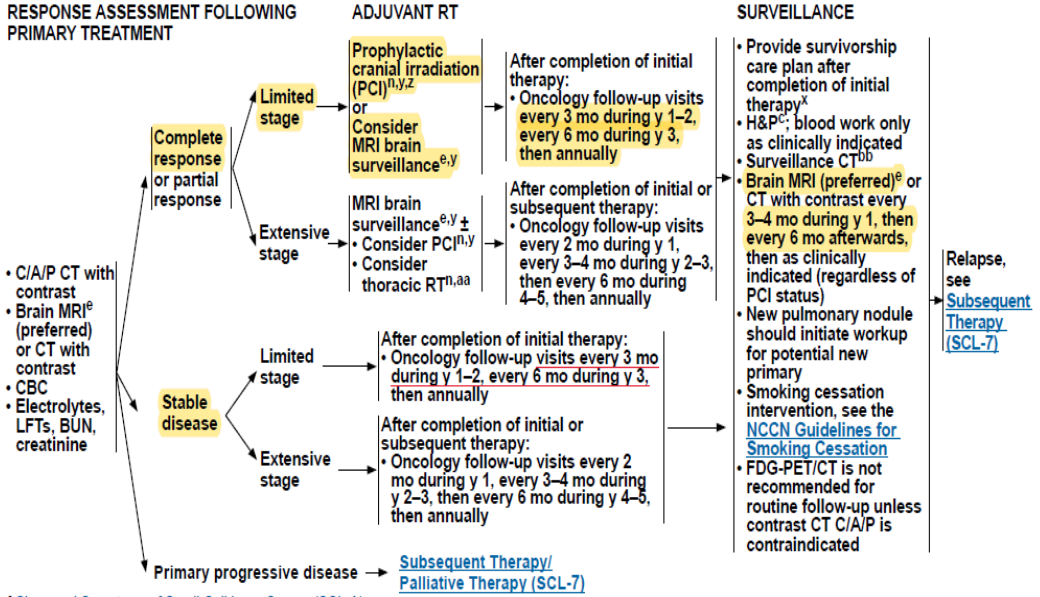

[c] Signs and Symptoms of Small Cell Lung Cancer (SCL-A).
[e] Brain MRI is more sensitive than CT for identifying brain metastases and is preferred over CT.
[n] Principles of Radiation Therapy (SCL-F).
[x] NCCN Guidelines for Survivorship.
[y] PCI is not recommended in patients with poor PS or impaired neurocognitive function. Increased cognitive decline after PCI has been observed in older adults (≥60 years) in prospective trials; the risks and benefits of PCI versus close brain surveillance, MRI (preferrred) or CT with contrast, should be carefully discussed with these patients.
[z] The benefit of PCI is unclear in patients who have undergone definitive therapy for pathologic stage I (T1-2a,N0,M0) SCLC. See Principles of Radiation Therapy (SCL-F).
[aa] Sequential RT to thorax in selected patients, especially with residual thoracic disease and low-bulk extrathoracic metastatic disease that has responded to systemic therapy.
[bb] Most NCCN Member Institutions use CT chest ± abdomen/pelvis every 2–6 months (more frequently in years 1–2 and less frequently thereafter).

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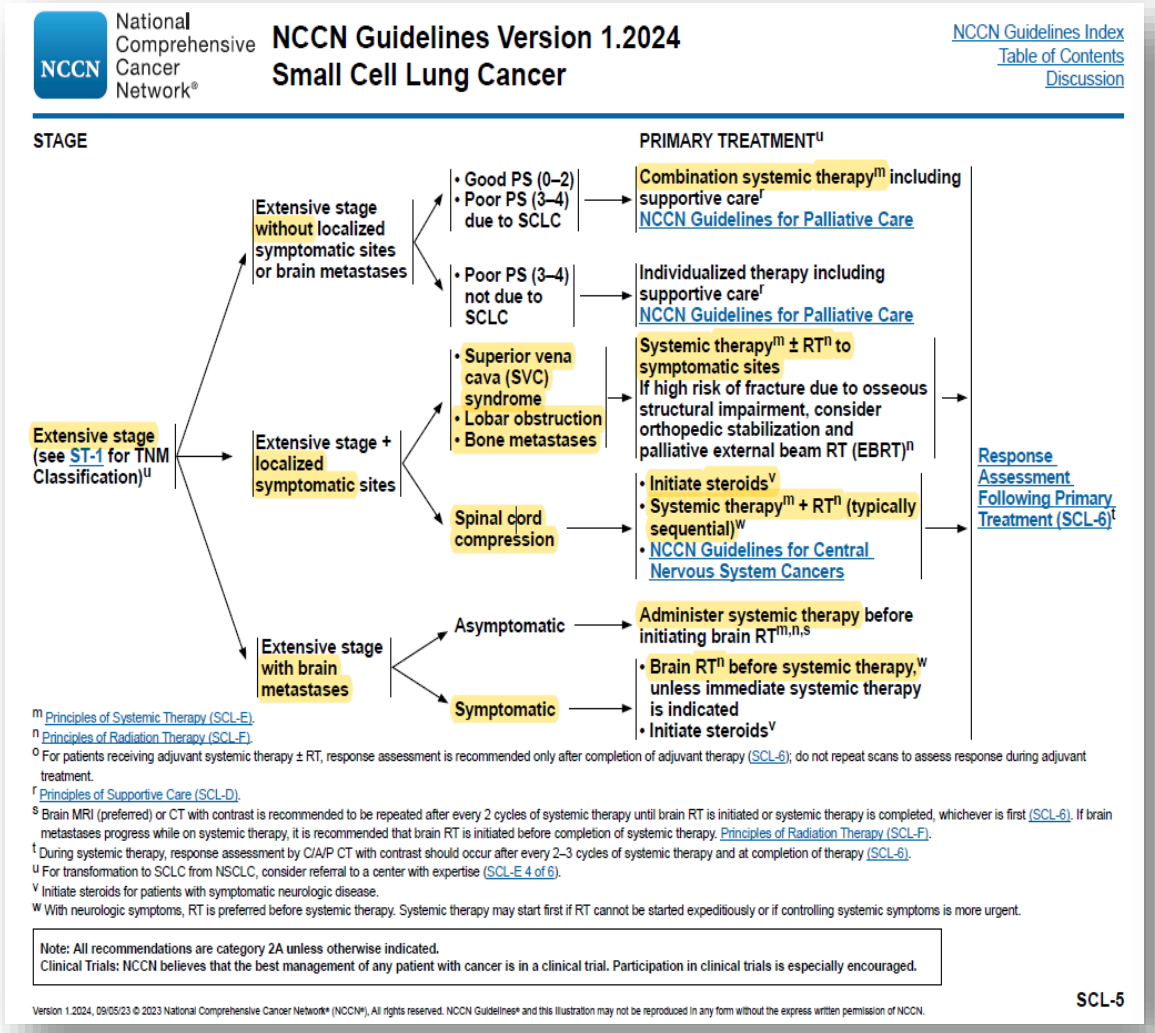
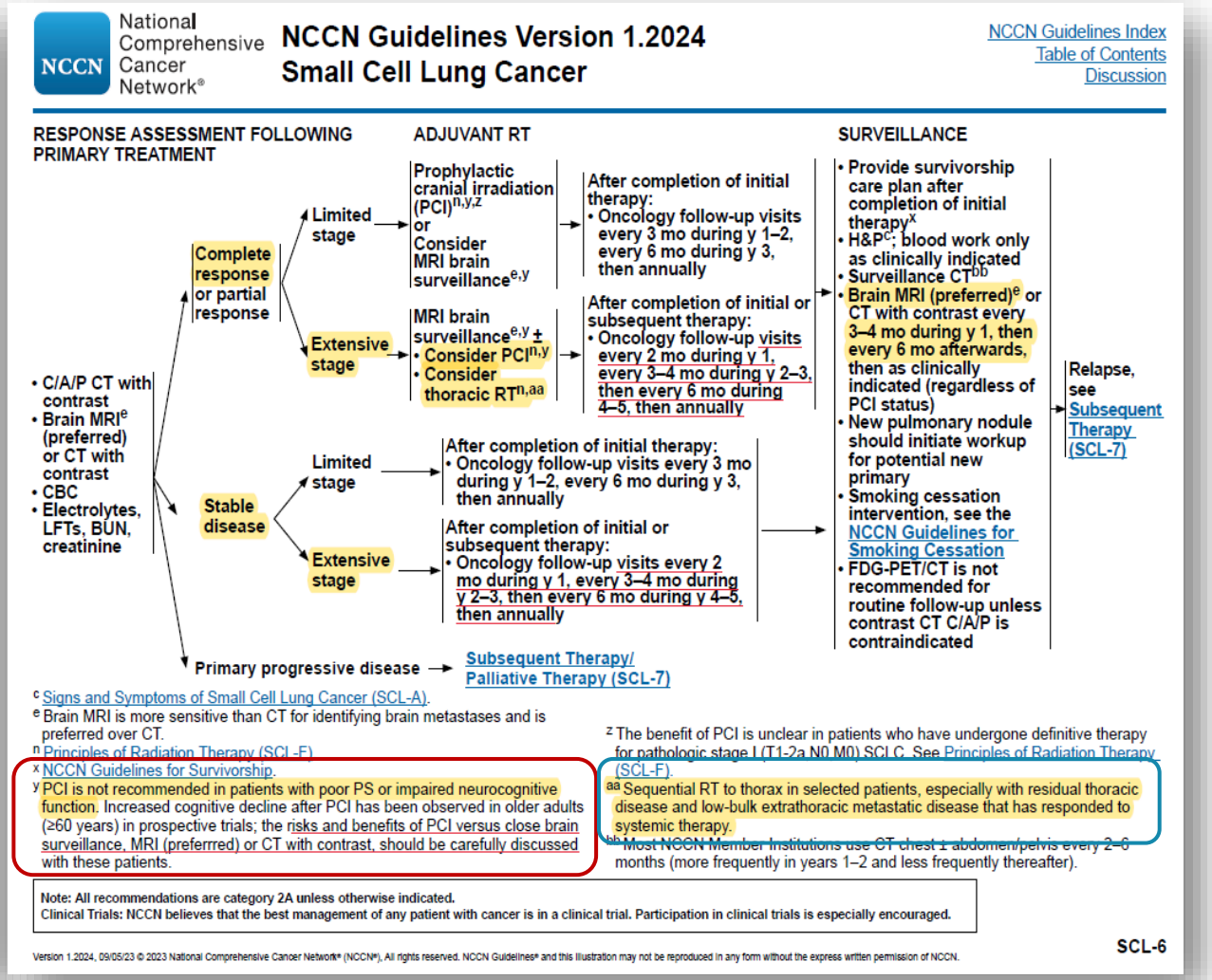
Small Cell Lung Cancer (Extensive)





Small Cell Lung Cancer, Chemotherapy

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PRINCIPLES OF SYSTEMIC THERAPY

PRIMARY OR ADJUVANT THERAPY FOR LIMITED-STAGE SCLC:

Four cycles of systemic therapy are recommended.
Planned cycle length should be every 21–28 days during concurrent RT.
During systemic therapy + RT, cisplatin/etoposide is recommended (category 1).
The use of myeloid growth factors is not recommended during concurrent systemic therapy plus RT (category 1 for not using GM-CSF).[1]

Preferred Regimens
- Cisplatin 75 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3[2]
- Cisplatin 60 mg/m² day 1 and etoposide 120 mg/m² days 1, 2, 3[3]

Other Recommended Regimens
- Cisplatin 25 mg/m² days 1, 2, 3 and etoposide 100 mg/m² days 1, 2, 3[2]
- Carboplatin area under the curve (AUC) 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3[a,4]

PRIMARY THERAPY FOR EXTENSIVE-STAGE SCLC[e]:

Four cycles of therapy are recommended, but some patients may receive up to 6 cycles based on response and tolerability after 4 cycles.

Preferred Regimens
- Carboplatin AUC 5 day 1 and etoposide 100 mg/m² days 1, 2, 3 and atezolizumab 1200 mg day 1 every 21 days x 4 cycles followed by maintenance atezolizumab 1200 mg day 1, every 21 days (category 1 for all)[b,d,5]
- Carboplatin AUC 5 day 1 and etoposide 100 mg/m² days 1, 2, 3 and atezolizumab 1200 mg day 1 every 21 days x 4 cycles followed by maintenance atezolizumab 1680 mg day 1, every 28 days[b,d]
- Carboplatin AUC 5–6 day 1 and etoposide 80–100 mg/m² days 1, 2, 3 and durvalumab 1500 mg day 1 every 21 days x 4 cycles followed by maintenance durvalumab 1500 mg day 1 every 28 days (category 1 for all)[b,c,d,6]
- Cisplatin 75–80 mg/m² day 1 and etoposide 80–100 mg/m² days 1, 2, 3 and durvalumab 1500 mg day 1 every 21 days x 4 cycles followed by maintenance durvalumab 1500 mg day 1 every 28 days (category 1 for all)[b,c,d,6]

Other Recommended Regimens
- Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3[7]
- Cisplatin 75 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3[8]
- Cisplatin 80 mg/m² day 1 and etoposide 80 mg/m² days 1, 2, 3[9]
- Cisplatin 25 mg/m² days 1, 2, 3 and etoposide 100 mg/m² days 1, 2, 3[10]

Useful in Certain Circumstances
- Carboplatin AUC 5 day 1 and irinotecan 50 mg/m² days 1, 8, 15[11]
- Cisplatin 60 mg/m² day 1 and irinotecan 60 mg/m² days 1, 8, 15[12]
- Cisplatin 30 mg/m² days 1, 8 and irinotecan 65 mg/m² days 1, 8[13]

Footnotes (SCL-E 2 of 6)
Subsequent Systemic Therapy (SCL-E 3 of 6)
Response Assessment (SCL-E 4 of 6)
References (SCL-E 5 of 6)

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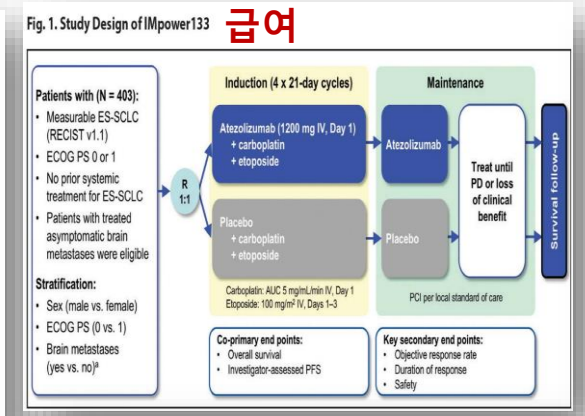

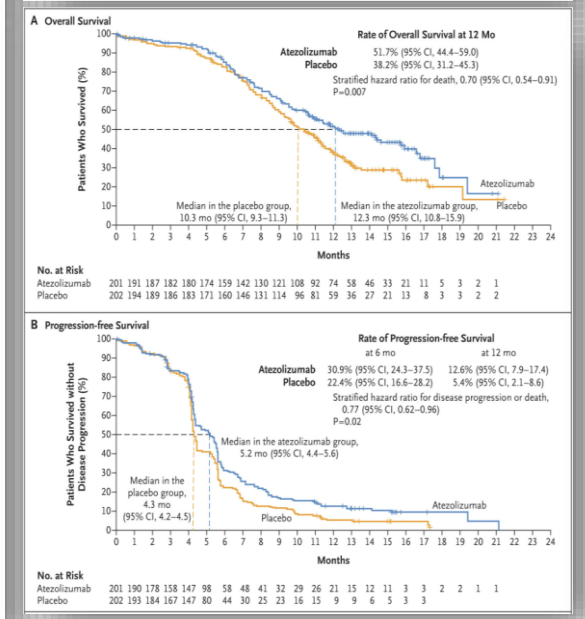

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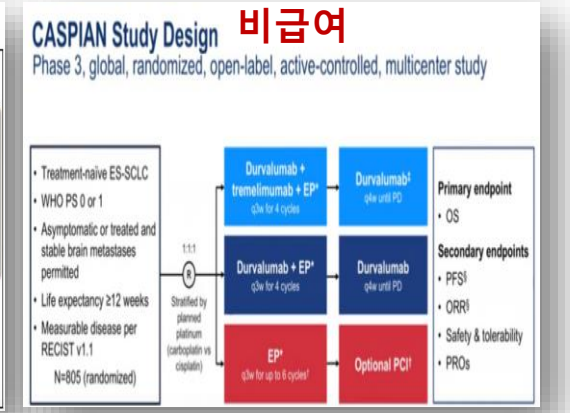

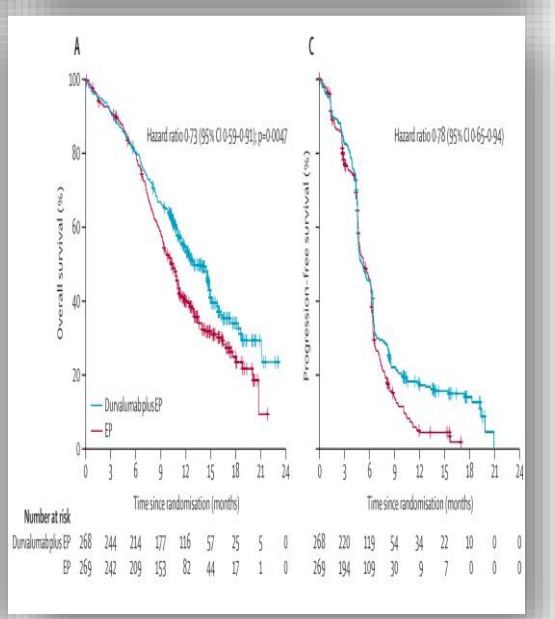

Small Cell Lung Cancer, Subsequent Chemotherapy

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Discussion

SCLC SUBSEQUENT SYSTEMIC THERAPY (PS 0–2)[f],
Consider dose reduction or growth factor support for patients with PS 2.

CHEMOTHERAPY-FREE INTERVAL (CTFI) >6 MONTHS

Preferred Regimens
- Clinical trial enrollment
- Re-treatment with platinum-based doublet[g,34,35,37-39]

Other Recommended Regimens
- Lurbinectedin[17,36]
- Topotecan oral (PO) or intravenous (IV)[14-16,28]
- Irinotecan[h,21,28]

CTFI ≤6 MONTHS

Preferred Regimens
- Clinical trial enrollment
- Lurbinectedin[17,36] 비급여
- Topotecan oral (PO) or intravenous (IV)[14-16,28,37]
- Irinotecan[h,21,28]
- Re-treatment with platinum-based doublet may be considered for CTFI 3–6 months[g,37,38,39]

Other Recommended Regimens
- Nivolumab or pembrolizumab (if not previously treated with an ICI)[b, 29,30,31,32,33]
- Paclitaxel[18,19]
- Temozolomide[22,23]
- Cyclophosphamide/doxorubicin/vincristine (CAV)[14]
- Docetaxel[20]
- Gemcitabine[26,27,40]
- Oral etoposide[24,25]

[b] Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or concurrent use of immunosuppressive agents. For safety reasons, do not use ICIs in patients who have recently received TKIs.
[f] Subsequent systemic therapy refers to second-line and beyond therapy..
[g] Rechallenging with the original regimen or similar platinum-based regimen, as shown on SCL-E 1, is recommended if there has been a CTFI of more than 6 months and may be considered if there has been a CTFI of at least 3 to 6 months.
[h] For patients with CNS disease, consider using irinotecan

References (SCL-E 5 of 6)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial

비급여

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Summary

Background Few options exist for treatment of patients with small-cell lung cancer (SCLC) after failure of first-line therapy. Lurbinectedin is a selective inhibitor of oncogenic transcription. In this phase 2 study, we evaluated the activity and safety of lurbinectedin in patients with SCLC after failure of platinum-based chemotherapy.

Methods In this single-arm, open-label, phase 2 basket trial, we recruited patients from 26 hospitals in six European countries and the USA. Adults (aged ≥18 years) with a pathologically proven diagnosis of SCLC, Eastern Cooperative Oncology Group performance status of 2 or lower, measurable disease as per Response Criteria in Solid Tumors (RECIST) version 1.1, absence of brain metastasis, adequate organ function, and pre-treated with only one previous chemotherapy-containing line of treatment (minimum 3 weeks before study initiation) were eligible. Treatment consisted of 3·2 mg/m² lurbinectedin administered as a 1-h intravenous infusion every 3 weeks until disease progression or unacceptable toxicity. The primary outcome was the proportion of patients with an overall response (complete or partial response) as assessed by the investigators according to RECIST 1.1. All treated patients were analysed for activity and safety. This study is ongoing and is registered with ClinicalTrials.gov, NCT02454972.

Findings Between Oct 16, 2015, and Jan 15, 2019, 105 patients were enrolled and treated with lurbinectedin. Median follow-up was 17·1 months (IQR 6·5–25·3). Overall response by investigator assessment was seen in 37 patients (35·2%; 95% CI 26·2–45·2). The most common grade 3–4 adverse events (irrespective of causality) were haematological abnormalities—namely, anaemia (in nine [9%] patients), leucopenia (30 [29%]), neutropenia (48 [46%]), and thrombocytopenia (seven [7%]). Serious treatment-related adverse events occurred in 11 (10%) patients, of which neutropenia and febrile neutropenia were the most common (five [5%] patients for each). No treatment-related deaths were reported.

Interpretation Lurbinectedin was active as second-line therapy for SCLC in terms of overall response and had an acceptable and manageable safety profile. Lurbinectedin could represent a potential new treatment for patients with SCLC, who have few options especially in the event of a relapse, and is being investigated in combination with doxorubicin as second-line therapy in a randomised phase 3 trial.

[17] Trigo J, Subbiah V, Besse B, et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial. Lancet Oncol

Small Cell Lung Cancer, Subsequent Chemotherapy, Lurbinectedin

	All patients (n=105)	Chemotherapy-free interval <90 days (n=45)	Chemotherapy-free interval ≥90 days (n=60)
RECIST responses			
Complete response	0	0	0
Partial response	37 (35%)	10 (22%)	27 (45%)
Stable disease*	35 (33%)	13 (29%)	22 (37%)
Progressive disease	28 (27%)	18 (40%)	10 (17%)
Not evaluable†	5 (5%)	4 (9%)	1 (2%)
Overall response, % (95% CI)	35·2% (26·2–45·2)	22·2% (11·2–37·1)	45·0% (32·1–58·4)
Disease control, % (95% CI)‡	68·6% (58·8–77·3)	51·1% (35·8–66·3)	81·7% (69·6–90·5)
Duration of response			
Disease progression, relapse, or death events in responding patients, n/N (%)	29/37 (78%)	9/10 (90%)	20/27 (74%)
Median duration of response, months	5·3 (4·1–6·4)	4·7 (2·6–5·6)	6·2 (3·5–7·3)
Patients still responding at 6 months	43·0% (25·6–60·5)	11·7% (0·0–33·1)	55·3% (34·5–76·0)
Progression-free survival			
Progression-free survival events, n (%)	90 (86%)	41 (91%)	49 (82%)
Median progression-free survival, months (95% CI)	3·5 (2·6–4·3)	2·6 (1·3–3·9)	4·6 (2·8–6·5)
4-month progression-free survival (95%CI)	46·6% (36·7–56·5)	29·1% (15·3–42·8)	59·9% (47·1–72·7)
6-month progression-free survival (95% CI)	32·9% (23·3–42·5)	18·8% (6·8–30·9)	43·5% (30·1–56·9)
Overall survival			
Deaths	66 (63%)	37 (82%)	29 (48%)
Median overall survival, months (95% CI)	9·3 (6·3–11·8)	5·0 (4·1–6·3)	11·9 (9·7–16·2)
6-month overall survival (95%CI)	67·1% (57·6–76·7)	45·8% (30·4–61·3)	83·6% (73·7–93·5)
12-month overall survival (95% CI)	34·2% (23·2–45·1)	15·9% (3·6–28·2)	48·3% (32·5–64·1)

RECIST=Response Evaluation Criteria in Solid Tumors. *Includes five patients with partial response not confirmed. †Five patients were not evaluable because they had no radiological assessment during treatment due to early death from malignant disease (n=2), symptomatic deterioration because of disease progression (n=2), and patient refusal (n=1). ‡Partial response or stable disease.

Table 2: **Overall efficacy of lurbinectedin treatment by investigator assessment and subgroup analyses by chemotherapy-free interval**

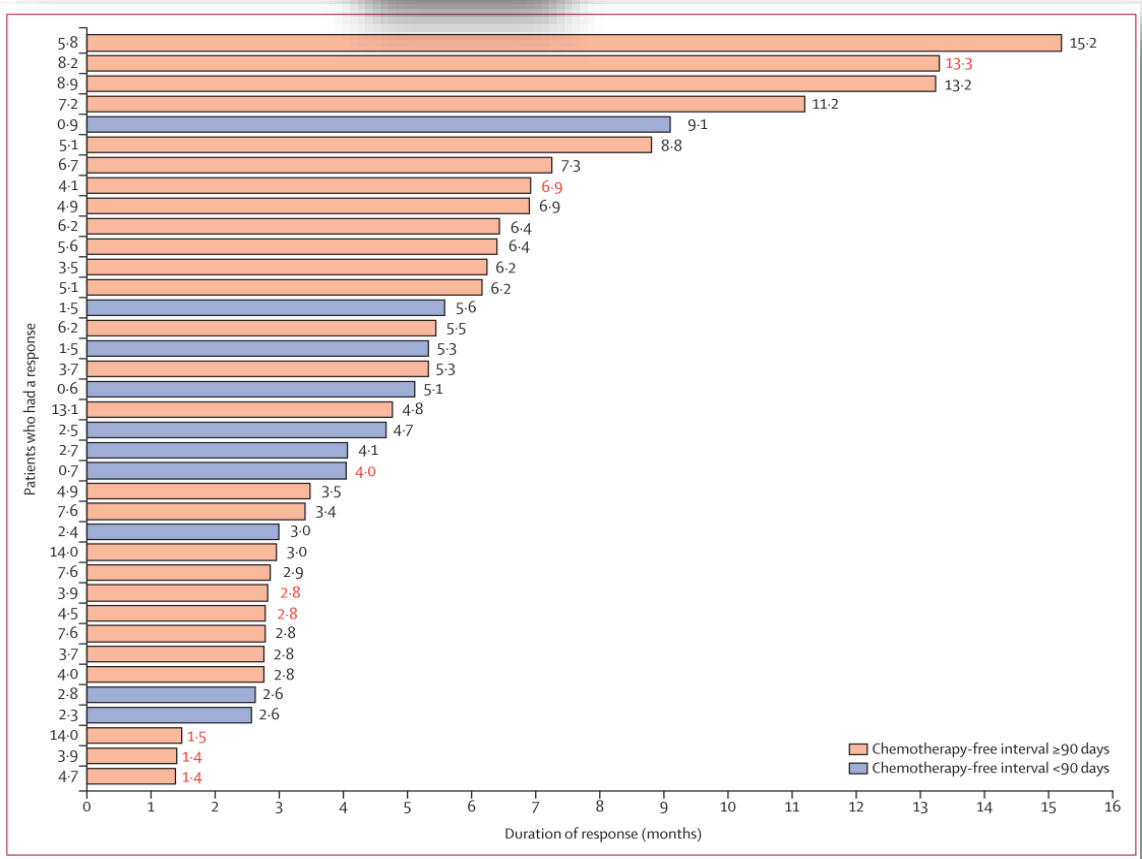

Figure 1: **Duration of response by investigator assessment**
Each bar represents a patient with SCLC who responded to treatment (n=37). Data shown on the left of each bar are the chemotherapy-free interval (months); data shown on the right of each bar are the duration of response (0 is the time of starting response). Data in red font refer to eight patients censored at the cutoff date: seven with no documented progression (under follow-up) and one who discontinued treatment due to an investigator's decision and then received further therapy. SCLC=small-cell lung cancer.

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Lung cancer treatment complication management

Infection, septic shock

- Neutropenic fever
- Septic shock
- Life threatening pneumonia

Radiation pneumonitis

- High dose steroid
- PCP pneumonia
- Septrin prophylaxis

TKI & IO-related complication

- Diarrhea, rash, paronychia..
- Hypo, hyperthyroidism, adrenal insufficiency
- GI toxicity, LFT elevation, neurologic complication

Summary

- Low dose chest CT Lung cancer screening: more lung cancer detection, Brings forward early-stage disease, lung cancer mortality reduction
- In stage I NSCLC, Sublobar resection is non-inferior compared to the traditional lobectomy in selected patients.
- SABR (or SBRT) can serve as an effective treatment alternative in medically inoperable early lung cancer
- Stage III NSCLC : can be considered for perioperative chemo and surgical treatment, and also considerations for CCRT, making multidisciplinary approach extremely important.
- The survival rate and prognosis of stage IV NSCLC vary significantly depending on the presence of driver mutations, cancer subtypes, and the response to immunotherapy (importance of NGS for Identifying driver mutations is emphasized)
- The combination of immune-checkpoint inhibitors (ICI) with platinum-based chemotherapy has become the treatment of choice for ED-SCLC; however, the prognosis remains unfavorable for ED-SCLC, need to fine more effective treatment strategies that can offer better prognostic outcomes
- Effective management of the side effects associated with cancer treatment is crucial for improving patient prognosis

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