ΔΙΑΓΝΩΣΗ ΚΑΙ ΘΕΡΑΠΕΥΤΙΚΗ ΠΡΟΣΕΓΓΙΣΗ ΣΤΟΝ ΚΑΡΚΙΝΟ ΤΟΥ ΠΝΕΥΜΟΝΑ

INCIDENCE AND EPIDEMIOLOGY

Lung cancer is the leading cause of cancer mortality worldwide with 1.8 million newly diagnosed cases

Or

13% of all cancers diagnosed 2012

Esmo guidelines 2017

- The worldwide numbers are still rising despite an ongoing small decline in the western world

Esmo guidelines 2017

Lung Cancer Risk Factors

(2007 American Cancer Society Data)

- Gender
- Smoking history
- Older age
- Presence of airflow obstruction
- Genetic predisposition
- Occupational exposures

LUNG CANCER

(2007 American Cancer Society Data)

Relationship to Smoking

Etiology

Tobacco	Percent
active	85-87
passive	3-5

Lung Cancer and Smoking

(2007 American Cancer Society Data)

- ~90% of lung cancers attributed to smoking
- However, only 20% smokers will develop lung cancer in their lifetime.
  - ? Death from other causes ie. CAD, COPD
  - Genetic predisposition
- Risk decreases when stop smoking
- Yet, 50% of new cases are former smokers

SCREENING FOR LUNG CANCER

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Screening evaluated in relatively small trials failed to show benefit if periodically chest x-ray and/or sputum cytology and/or biomarkers were used

screening by these techniques is therefore not recommended

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The much larger National Lung Cancer Screening Trial (NLST) **comparing low–dose CT (LDCT)** to **chest x-ray** > 53000 current or former heavy smokers (>30p/y or < 15 years since smoking cessation) aged between 55-74 years showed

↓

20% reduction in lung cancer –related death and an overall –cause mortality reduction of 6.7%

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How screening for LC should become part of standard evidence based practice therefore needs to be analysed further

↓

screening for high risk groups ??
Referred to a dedicated programme

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DIAGNOSIS

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The most common diagnostic test for LC is fibreoptic bronchoscopy

1)endobronchial ultrasound (EBUS)

2) endoscopic ultrasound (EUS)

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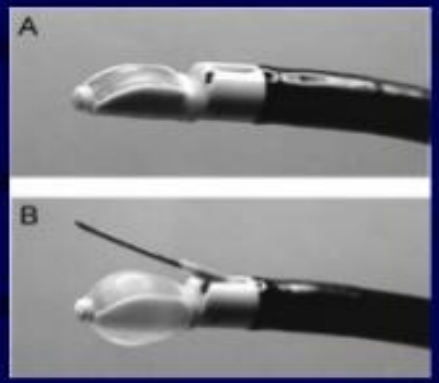
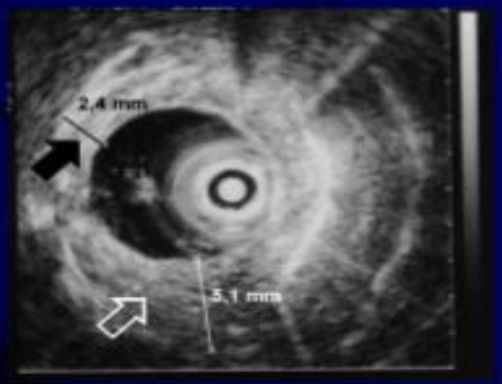
Newer Technologies

- Endobronchial Ultrasound (EBUS)



- Endoscopic Ultrasound (EUS)



in most cases this will be sufficient to diagnose LC although quite often the amount of obtained material is not sufficient to sub-classify the tumor in more detail

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Lung Cancer:

Transbronchial Needle Aspiration (TBNA)

- Allows biopsy of subcarinal & paratracheal lymph nodes during flexible bronchoscopy.
- Helpful for staging.
- Minimal risk to patient.

Lung Cancer:

CT - Guided Transthoracic Needle Biopsy

- Peripheral lesions away from diaphragm.
- 25% pneumothorax risk.
- May be beneficial for poor operative candidates.
- Remember:
  - **Negative needle biopsy result may be false negative.**

Staging of the Mediastinum

- Mediastinoscopy:
  - Mediastinal lymphadenopathy staging.
  - Central lesions.
  - Large peripheral lesions.
  - "Gold Standard."

Thoracoscopy

- This procedure can obtain samples of N2/N3 lymph nodes as well as fluid around the lungs and heart (VATS=video assisted thoracic surgery)

NCCN 2017

- Tumour biopsy is an essential procedure for patients with cancer, providing crucial information on diagnosis, prognosis, and prediction of response or resistance to treatment.

- For decades, biopsy has been, and continues to be, the standard of care.

- Moreover, analysis of biopsy tissue has been the only option to determine the tissue from where the cancer originated, as well as the patient's disease stage

- With the development of targeted therapies, it is now also essential to evaluate the presence or absence of specific molecular alterations in conjunction with known histologic features.

- Current biopsy procedures are invasive and, especially in NSCLC, often produce too few cells or tissue sections for extensive analysis; multiple biopsies are not feasible for many patients, such as the elderly and those with comorbidities.

- Although surgical biopsies typically provide the greatest amount of intact tumor tissue for analysis, the procedure is invasive, costly and time-consuming.

- Fine needle aspiration (FNA) and in general needle biopsy procedures are less invasive than standard surgical biopsy;
- however, they provide less tumor sample, query only a portion of the tumor, and can be difficult to analyze because of cellular necrosis or immune cell infiltration.

- Perhaps the greatest limitation to tissue-based biopsy techniques is that sampling of a single tumor may not capture all of the mutations present.

- Cancer evolves genetically over time, a property that allows tumors to metastasize and develop resistance to treatments that are initially effective.

- Because cancer cells can readily mutate, genetic heterogeneity can exist not only among different tumor sites within a single patient, but also within a single tumor.

- Thus a single tumor biopsy may provide limited information, underscoring the need for less invasive techniques, such as a liquid biopsy, that allows the potential for frequent testing of multiple tumor sites.

- Liquid biopsy is a minimally invasive test for assessing cancer genetic status based on the analysis of circulating free DNA (cfDNA) that is present in the plasma component of blood.

- liquid biopsies of cell circulating tumor DNA (ctDNA) represent a non-invasive means of obtaining genomic information and indentifying alterations that can help optimize treatment for pts with advanced cancer

Esmo /oncology news/madrid 2017

Table 1. Work-up for diagnosis and staging

	Mandatory	Optional
General	Medical history[a] Physical examination[a] Assessing comorbidity PS	
Imaging	X-ray thorax CT thorax[a] PET-CT thorax[a] MRI brain[b]	Bone scintigraphy Contrast enhanced-CT brain
Laboratory	Blood cell counts Renal function Liver enzymes Bone parameters	
Cardio-pulmonary function	FVC, FEV1, DLCO ECG If indicated: CPET	Ejection fraction, CAG
Tissue procurement	Bronchoscopy[b,c] EBUS/EUS mediastinal nodes[a] CT-guided biopsy	Mediastinoscopy

[a]Tests needed for clinical staging.
[b]See text.
[c]Depending on site and size of tumour with biopsy/aspiration/brush/washing.
CAG, coronary angiography; CPET, cardio pulmonary exercise testing; CT, computed tomography; DLCO, diffusing capacity of the lungs for carbon monoxide; EBUS, endoscopic bronchial ultrasound; ECG, electrocardiogram; EUS, endoscopic ultrasound; FEV1, forced expiratory volume in 1 second; FVC, forced expiratory vital capacity; MRI, magnetic resonance imaging; PET-CT, positron emission tomography computed tomography; PS, performance status.

The Principles of the TNM System

- 1. To aid the clinician in the planning of treatment
- 2. To give some indication of prognosis
- 3. To assist in evaluation of the results of treatment
- 4. To facilitate the exchange of information between treatment centres
- 5. To contribute to the continuing investigation of human cancer

- Η σταδιοποιηση στον καρκινο την στιγμη της διαγνωσης είναι ο πιο σημαντικος προγνωστικος παραγοντας επιβιωσης και οι θεραπευτικες επιλογες θα πρεπει να βασιζονται σε αυτη

- Οι περισσοτεροι ασθενεις κατά την στιγμη της διαγνωσης είναι προχωρημενου σταδιου, οπου η πενταετης επιβιωση είναι μολις 4%

- Η χειρουργικη εξαιρεση σχετιζεται με σημαντικα μεγαλυτερη επιβιωση αλλα μονο το 25% των ασθενων είναι υποψηφιοι για χειρουργικη αντιμετωπιση την στιγμη της διαγνωσης

- Από την πρωτη εφαρμογη του TNM συστηματος σταδιοποιησης του καρκινου του πνευμονα εχουν επιτευχθει σημαντικες αλλαγες

- Όπως και για τους υπολοιπους ογκους η σταδιοποιηση του καρκινου του πνευμονα αναδεικνυει την ανατομικη εκταση του ογκου , η οποια και είναι σημαντικη για την επιλογη της θεραπειας καθως και την εκτιμηση της προγνωσης

- Η επιβιωση υπολογιζεται από την ημερομηνια της διαγνωσης για την κλινικη σταδιοποιηση της νοσου και από την ημερομηνια του χειρουργειου για την παθολογοανατομικη σταδιοποιηση της νοσου και υπολογιζεται με την Kaplan-Meier method.

In pts with clinical stages I-III lessions a pretreatment pathological diagnosis is recommended prior to any curative treatment

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T – Primary Tumour		
Tx		Primary tumour cannot be assessed
T0		No evidence of primary tumour
T1		Tumour 3 cm or less in greatest diameter surrounded by lung or visceral pleura, without evidence of main bronchus
	T1a(mi)	Mininally invasive adenocarcinoma
	T1a	Tumour 1 cm or less in greatest diameter
	T1b	Tumour more than 1 cm but not more than 2 cm
	T1c	Tumour more than 2 cm but not more than 3 cm
T2		Tumour more than 3 cm but not more than 5 cm; or tumour with any of the following features: Involves main bronchus (without involving the carina), invades visceral pleura, associated with atelectasis or obstructive pneumonitis that extends to the hilar region
	T2a	Tumour more than 3 cm but not more than 4 cm
	T2b	Tumour more than 4 cm but not more than 5 cm
T3		Tumour more than 5 cm but not more than 7 cm or one tha directly invades any of the following: chest wall, phrenic nerve, parietal pericardium, or associated separate tumour nodule(s) in the same lobe as the primary
T4		Tumours more than 7 cm or one that invades any of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina; separate tumour nodule(s) in a different ipsilateral lobe to that of the primary

International Association for the Study of Lung Cancer, 2015

N – Regional Lymph Nodes		
Nx		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2		Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3		Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph node(s)

M – Distant Metastasis		
M0		No distant metastasis
M1		Distant metastasis
	M1a	Separate tumour nodule(s) in a contralateral lobe; tumour with pleaural or pericardial nodules or malignant pleural or pericardial effusion
	M1b	Single extrathoracic metastasis in a single organ
	M1c	Multiple extrathoracic metastases in one or several organs

International Association for the Study of Lung Cancer, 2015

STAGE	T	N	M
Occult	TX	N0	M0
0	Tis	N0	M0
IA1	T1a(mi)/T1a	N0	M0
IA2	T1b	N0	M0
IA3	T1c	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIB	T1a-T2b	N1	M0
	T3	N0	M0
IIIA	T1a-T2b	N2	M0
	T3	N1	M0
	T4	N0/N1	M0
IIIB	T1a-T2b	N3	M0
	T3/T4	N2	M0
IIIC	T3/T4	N3	M0
IVA	Any T	Any N	M1a/M1b
IVB	Any T	Any N	M1c

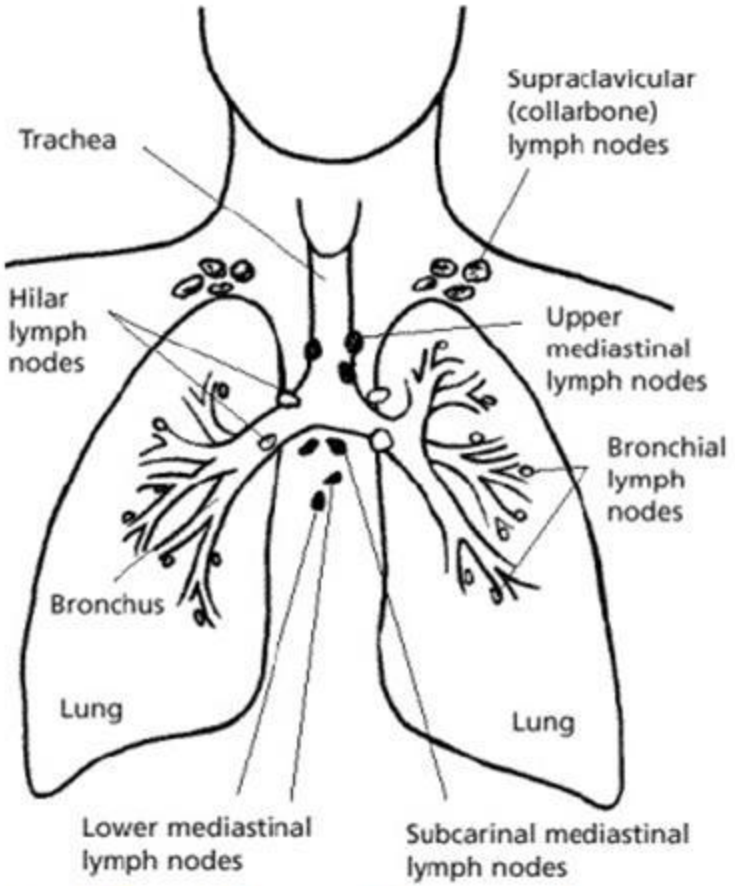
International Association for the Study of Lung Cancer, 2015

8th Edition of the TNM Classification for Lung Cancer

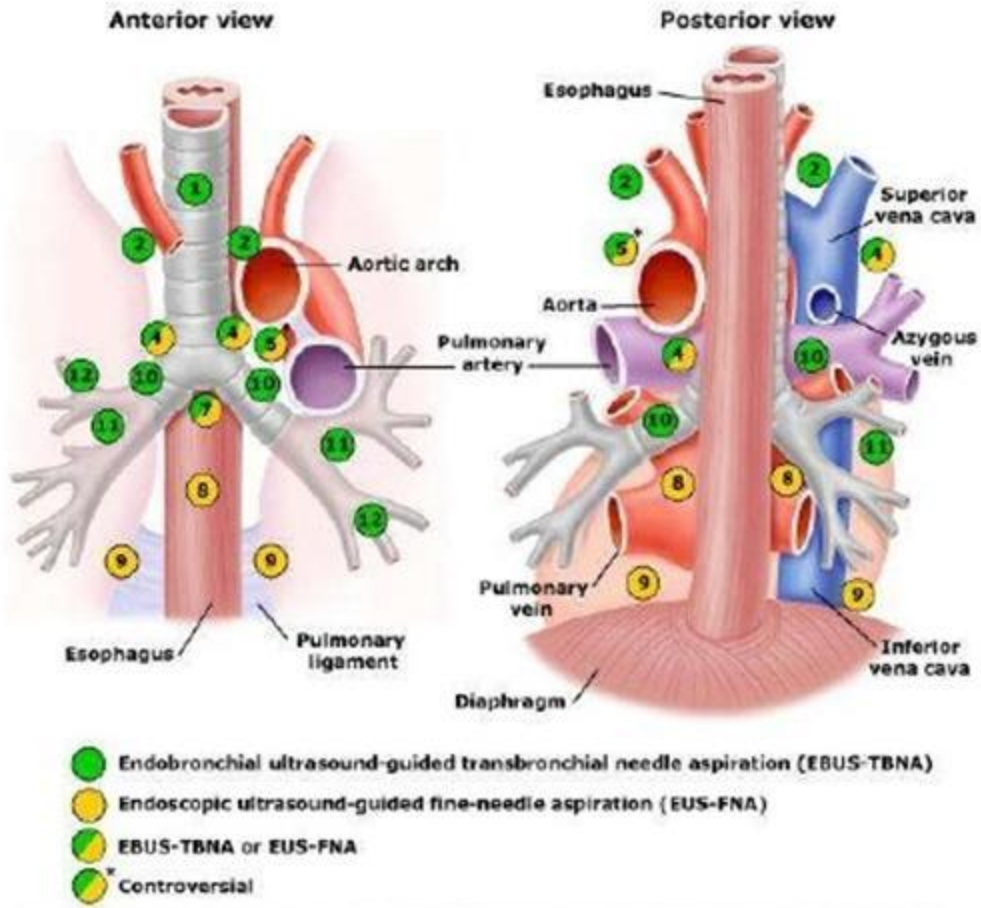
	N0	N1	N2	N3	M1 a	M1 b	M1c
T1a	IA1	IIB	IIIA	IIIB	IVA	IVA	IVB
T1b	IA2	IIB	IIIA	IIIB	IVA	IVA	IVB
T1c	IA3	IIB	IIIA	IIIB	IVA	IVA	IVB
T2a	IB	IIB	IIIA	IIIB	IVA	IVA	IVB
T2b	IIA	IIB	IIIA	IIIB	IVA	IVA	IVB
T3	IIB	IIIA	IIIB	IIIC	IVA	IVA	IVB
T4	IIIA	IIIA	IIIB	IIIC	IVA	IVA	IVB

International Association for the Study of Lung Cancer, 2015

Lung Lymph Nodes



WellSpring Oncology



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Serving Patients with Cancer - Advancing NCCN Member Institutions

NCCN National Comprehensive Cancer Network®

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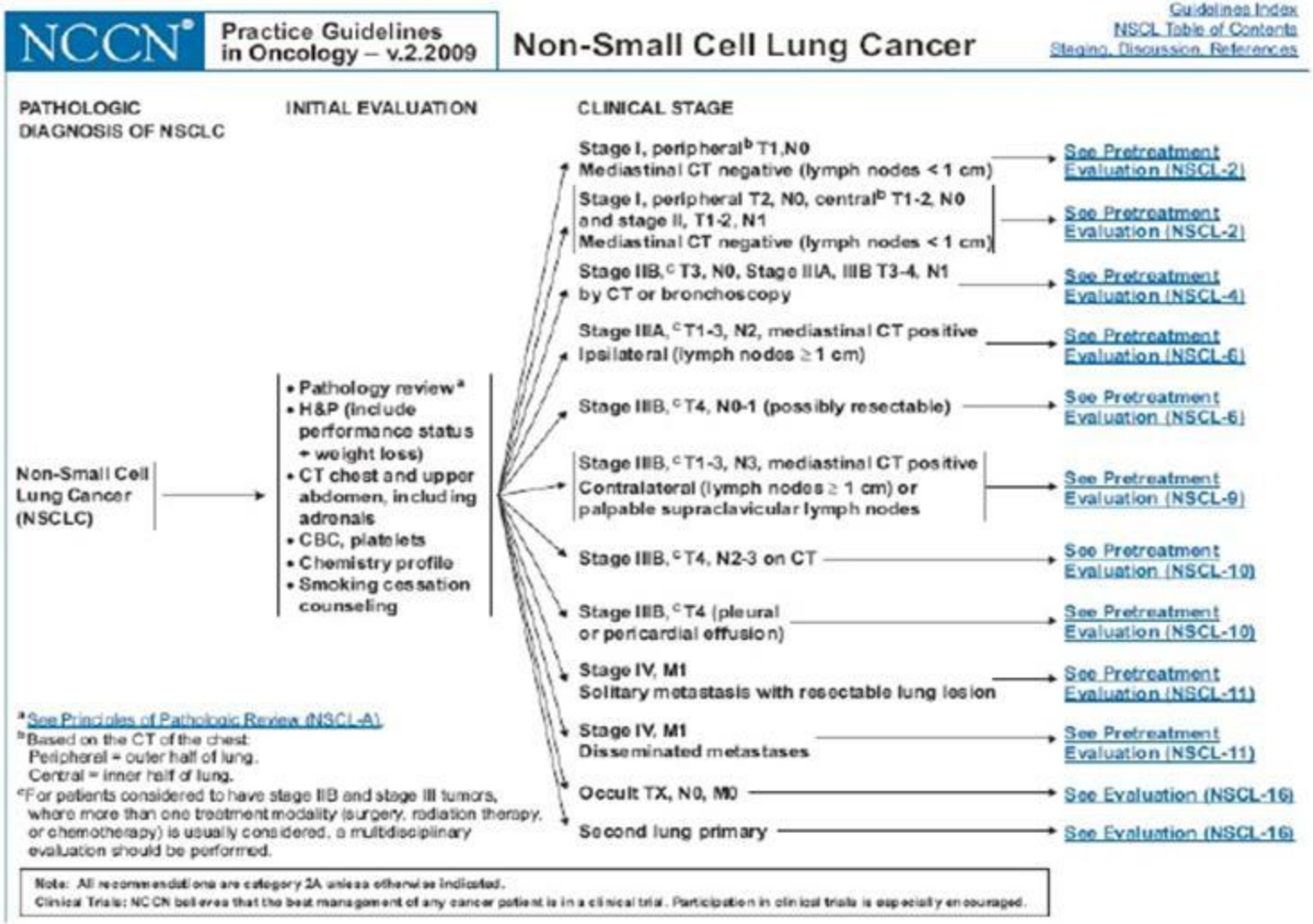
Click on any of the network locations to get more information about the cancer center and to find links to the NCCN Member Institution's web site.

WellSpring Oncology

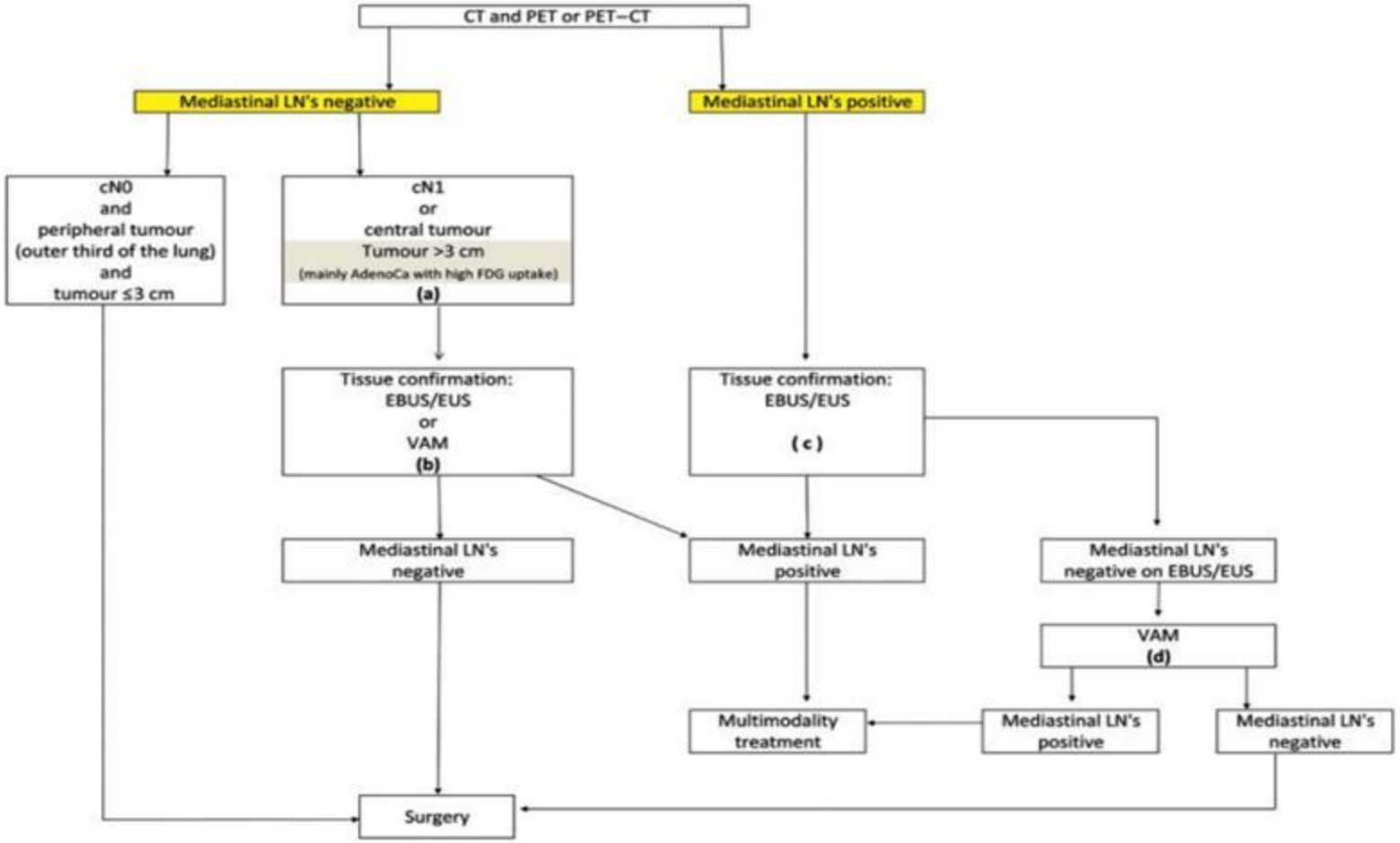


WellSpring Oncology

Treatment of Lung Cancer

- Stage I and II – surgery (if possible) and sometime postOp chemo or radiation
- Stage III – usually chemo plus radiation, sometime followed by surgery
- Stage IV – chemo or radiation, depending on the site of spread

WellSpring Oncology



(a) : In tumours > 3 cm (mainly in adenocarcinoma with high FDG uptake) invasive staging should be considered
(b) : Depending on local expertise to adhere to minimal requirements for staging
(c) : Endoscopic techniques are minimally invasive and are the first choice if local expertise with EBUS/EUS needle aspiration is available
(d) : Due to its higher NPV, in case of PET positive or CT enlarged mediastinal LN's, videoassisted mediastinoscopy (VAM) with nodal dissection or biopsy remain indicated when endoscopic staging is negative. Nodal dissection has an increased accuracy over biopsy

Figure 1. Suggested algorithm for locoregional lymph node staging in patients with non-metastatic NSCLC.
CT, computed tomography; EBUS, endoscopic bronchial ultrasound; EUS, endoscopic ultrasound; FDG, fluorodeoxyglucose; LN, lymph node; NPV, negative predictive value; NSCLC, non-small-cell lung cancer; PET, positron emission tomography; VAM, video-assisted mediastinoscopy.
Reprinted from [137] with permission.

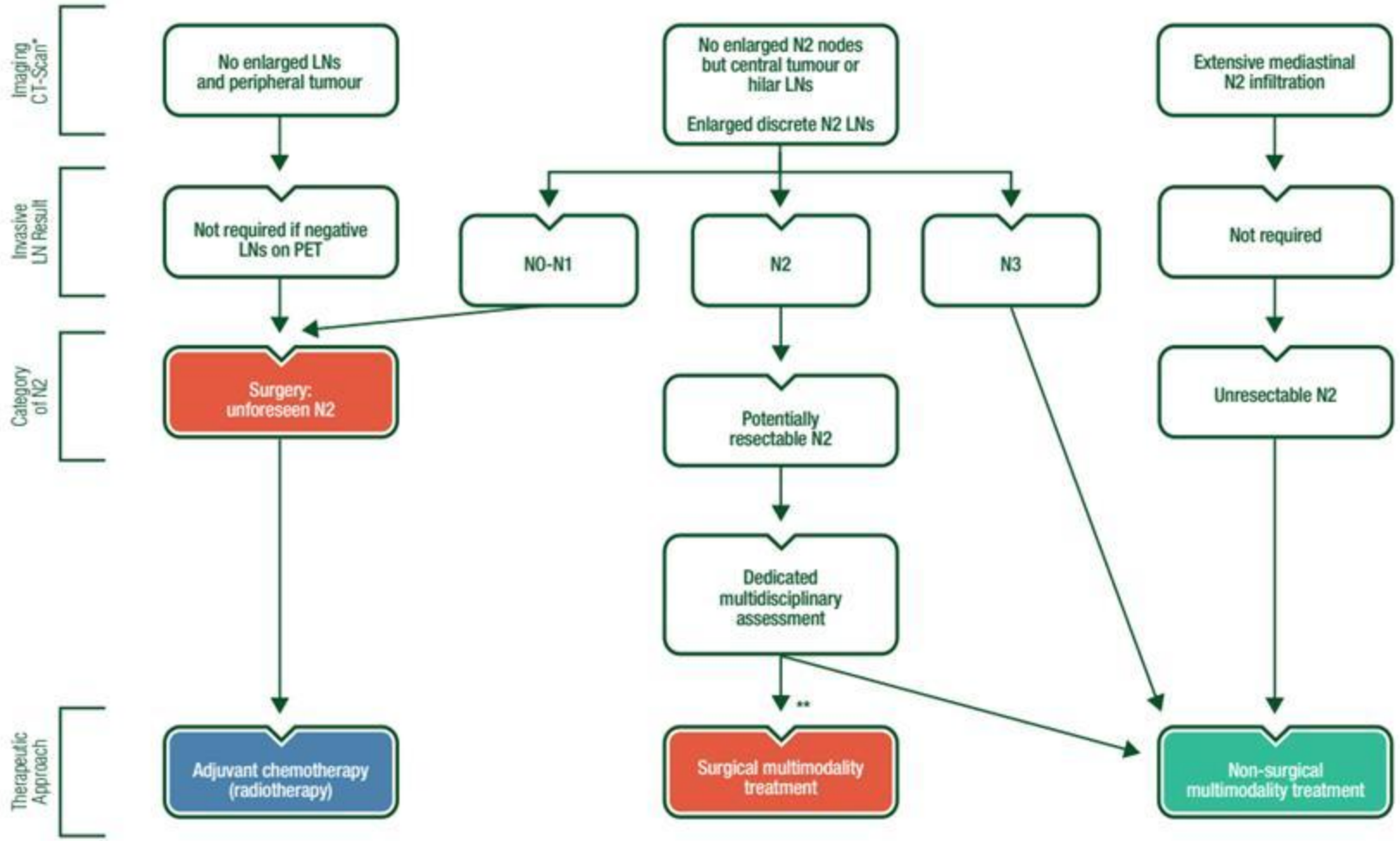


Figure 2. Treatment recommendations for patients with locoregional NSCLC, based on imaging, invasive lymph node staging tests and multidisciplinary assessment.
*Category description according to CT imaging as in ACCP staging document [42].
**See text for factors involved in the choice between non-surgical and surgical multimodality treatment.
ACCP, American College of Chest Physicians; CT, computed tomography; LN, lymph node; NSCLC, non-small-cell lung cancer; PET, positron-emission tomography.

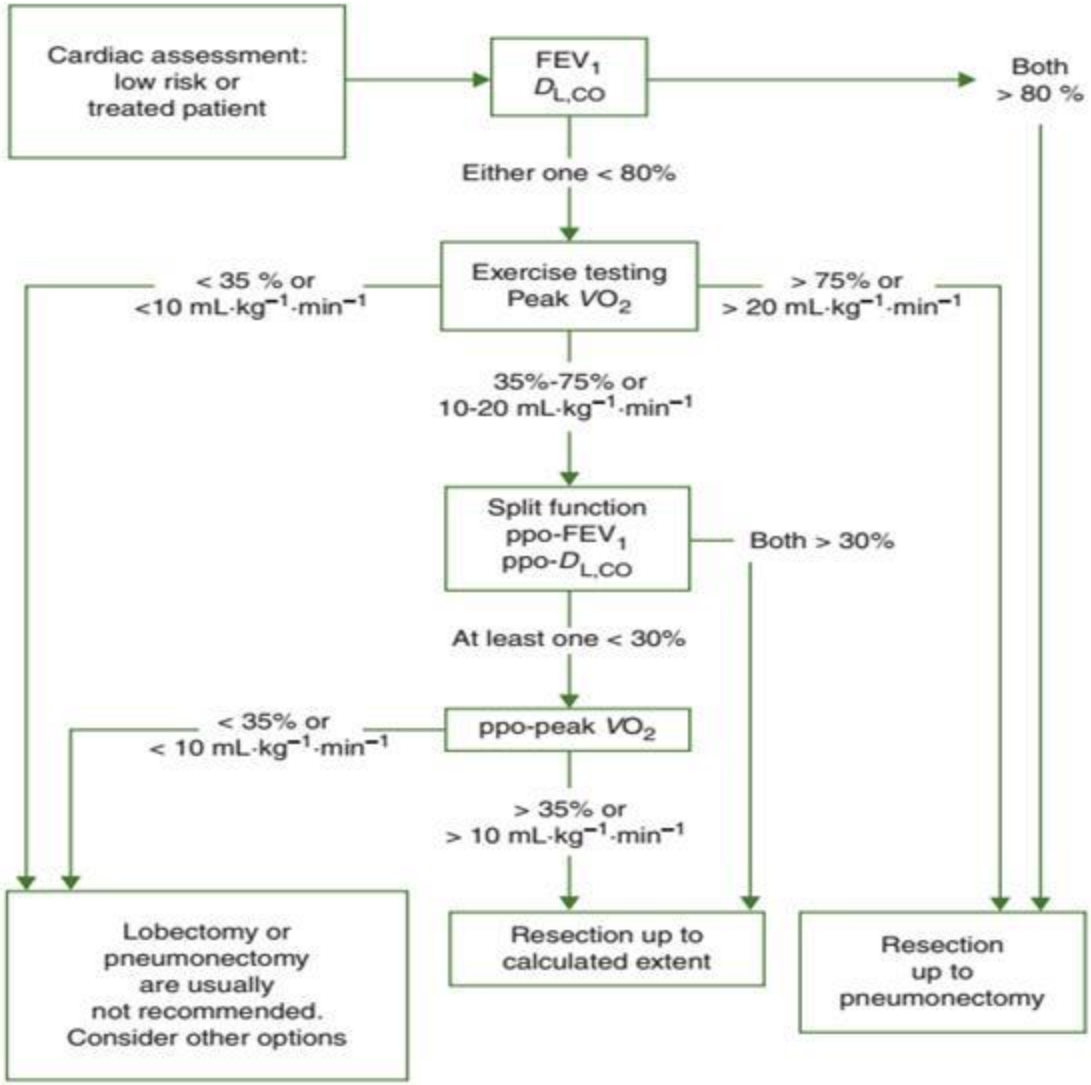


Figure 3. Preoperative respiratory evaluation.
DLCO, diffusing capacity of the lungs for carbon monoxide; FEV1, forced expiratory volume in 1 second; ppo, predicted postoperative; VO_2, oxygen consumption.
Reprinted from [50], with permission from the European Respiratory Society.

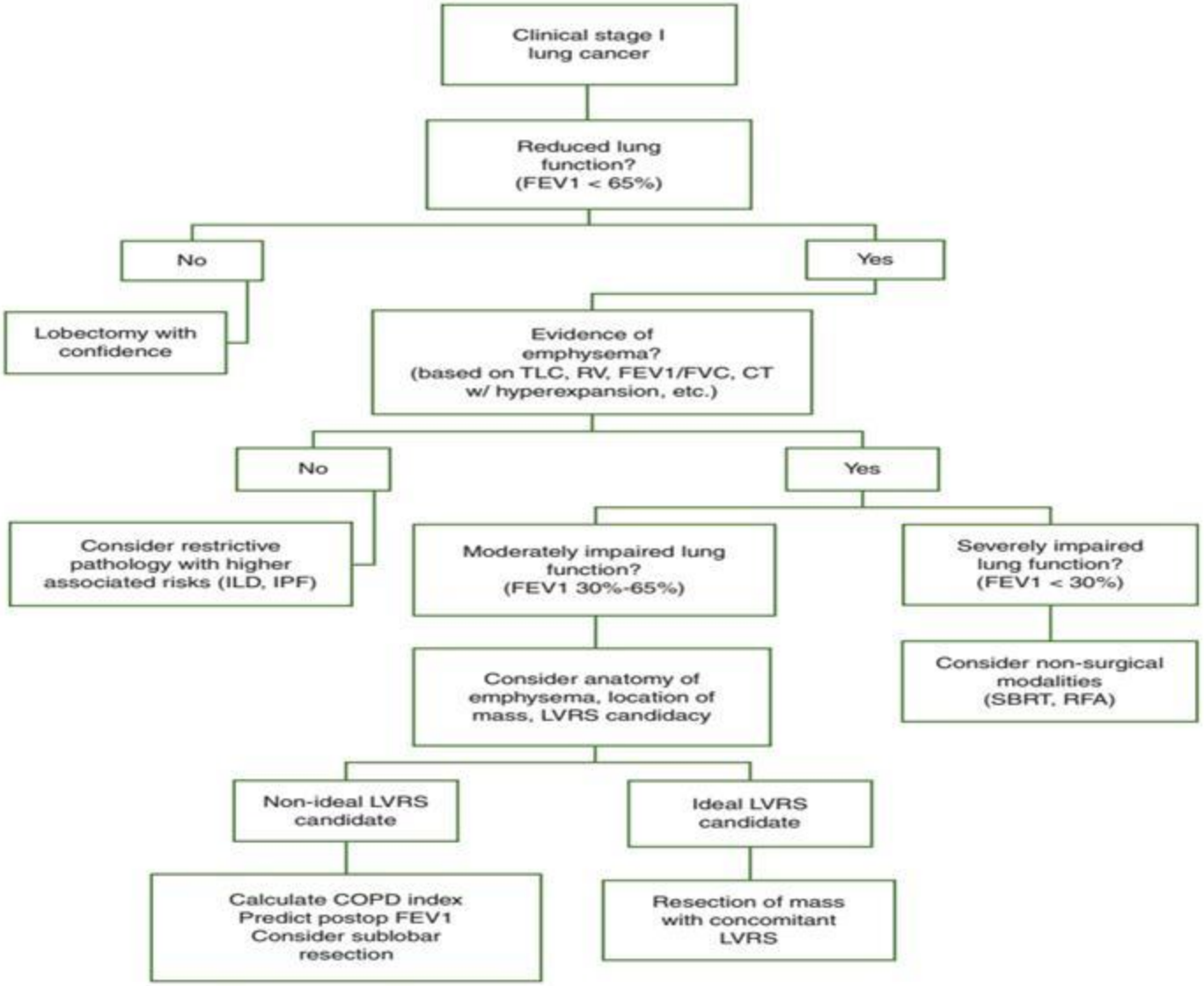


Figure 4. Algorithm for patients with clinical stage I lung cancer and limited pulmonary function due to emphysema.
CT, computed tomography; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume 1; FVC, forced vital capacity; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; LVRS, lung volume reduction surgery; RFA, radiofrequency ablation; RV, reserve volume; SBRT, stereotactic body radiotherapy; TLC, total lung capacity.
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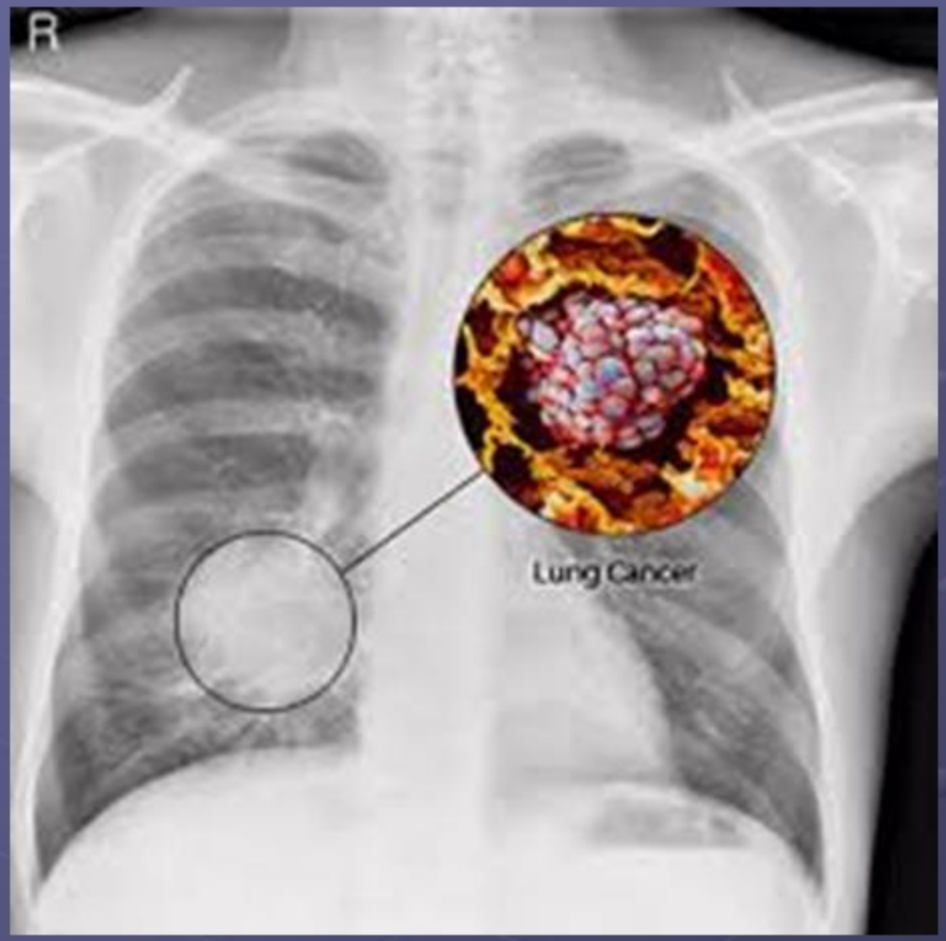


Προχωρημένος και μεταστατικός ΜΜΚΠ

Θεραπευτικός Αλγόριθμος 2017

Θεραπεία 1ης γραμμής με βάση τον ιστολογικό τύπο

	Pemetrexed/ Cisplatin (n = 862)	Gemcitabine/ Cisplatin (n = 863)	Hazard Ratio (95% CI)
ORR	31%	28%	NA
Median PFS	4.8 months	5.1 months	1.04 (0.94-1.15)
Nonsquamous	5.3 months	4.7 months	0.90 (0.79-1.02)
Squamous	4.4 months	5.5 months	1.36 (1.12-1.65)
Median OS	10.3 months	10.3 months	0.94 (0.84-1.05)
Nonsquamous	11.8 months	10.4 months	0.81 (0.70-0.94)*
Squamous	9.4 months	10.8 months	1.23 (1.00-1.51) †

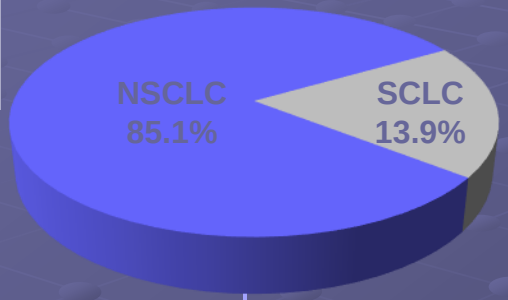
*p<0.005, †p<0.05

- Ο συνδυασμός gemcitabine/cisplatin επιτυγχάνει **σημαντικά καλύτερη επιβίωση σε ασθενείς με πλακώδες ΜΜΚΠ**
- Ο συνδυασμός pemetrexed/cisplatin επιτυγχάνει **σημαντικά καλύτερη επιβίωση σε ασθενείς με μη-πλακώδες ΜΜΚΠ**

Scagliotti et al, JCO, 2008, 26: 3543-51

NSCLC Disease Evolution

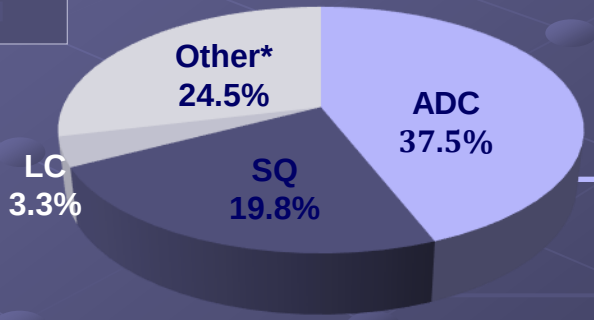
Past lung cancer landscape (pre-2008)[1-3]



NSCLC

Past NSCLC Landscape (2008-2011)[1-3]

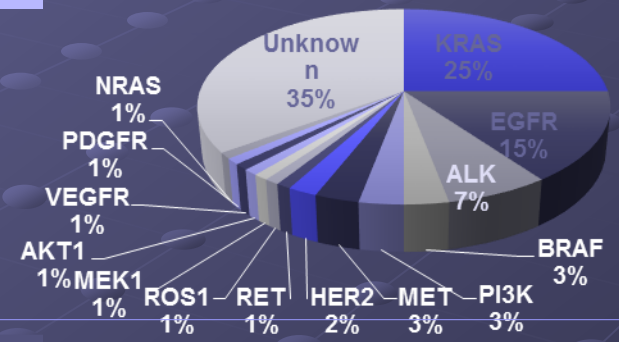
Histology becomes a factor for treatment



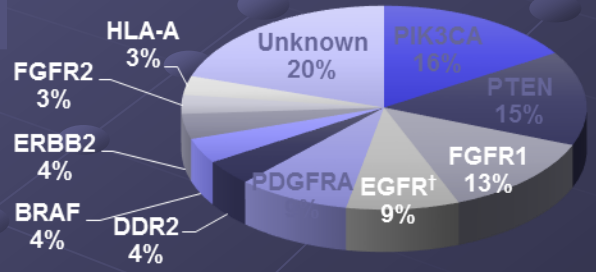
Current NSCLC Landscape[4-8]

Molecular pathology becomes a factor for targeted/ biomarker-driven therapies

ADC[4-6]



SQ[7,8]



* Mixed histology, not otherwise specified (NOS).

† Mostly EGFRvIII.

ADC, adenocarcinoma; LC, large cell; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer; SQ, squamous.

1. SEER Cancer Statistics Review, 1975-2007. Available at: http://seer.cancer.gov/csr/1975_2007. Accessed July 10, 2014.
2. NCCN Guidelines®. NSCLC. V3.2014.
3. Langer CJ et al. *J Clin Oncol*. 2010;28(36):5311-5320.
4. Pao W, Girard N. *Lancet Oncol*. 2011;12(2):175-180.
5. Hirsch FR. Oral presentation at IASLC 2012.
6. My Cancer Genome. Molecular Profiling of Lung Cancer. Available at: http://www.mycancergenome.org/content/disease/lung-cancer. Accessed May 17, 2013.
7. Kim HS, Pao W. *Lung Cancer*. 2013;80(3):249-255. http://dx.doi:org/10.1016/j.lungcan.2013.02.015.
8. TCGA Research Network. *Nature*. 2012;489(7417):519-525.

1η Γραμμή

Θεραπεία 1ης γραμμής με βάση τον ιστολογικό τύπο

Stage IIIB/IV NSCLC

PS 0 - 1

No prior chemo

B12/Folate in both arms

R

Pemetrexed 500 mg/m² Day 1
Cisplatin 75 mg/m² Day 1
Cycle = 21 days

- Primary objective: Overall Survival
- Non-inferiority design
- N = 1,725 patients, enrollment complete
- Final analysis at 1,190 deaths

Cisplatin 75 mg/m² Day 1
Gemcitabine 1,250 mg/m² Day 1, 8
Cycle = 21 days

Scagliotti et al, JCO, 2008, 26: 3543-51

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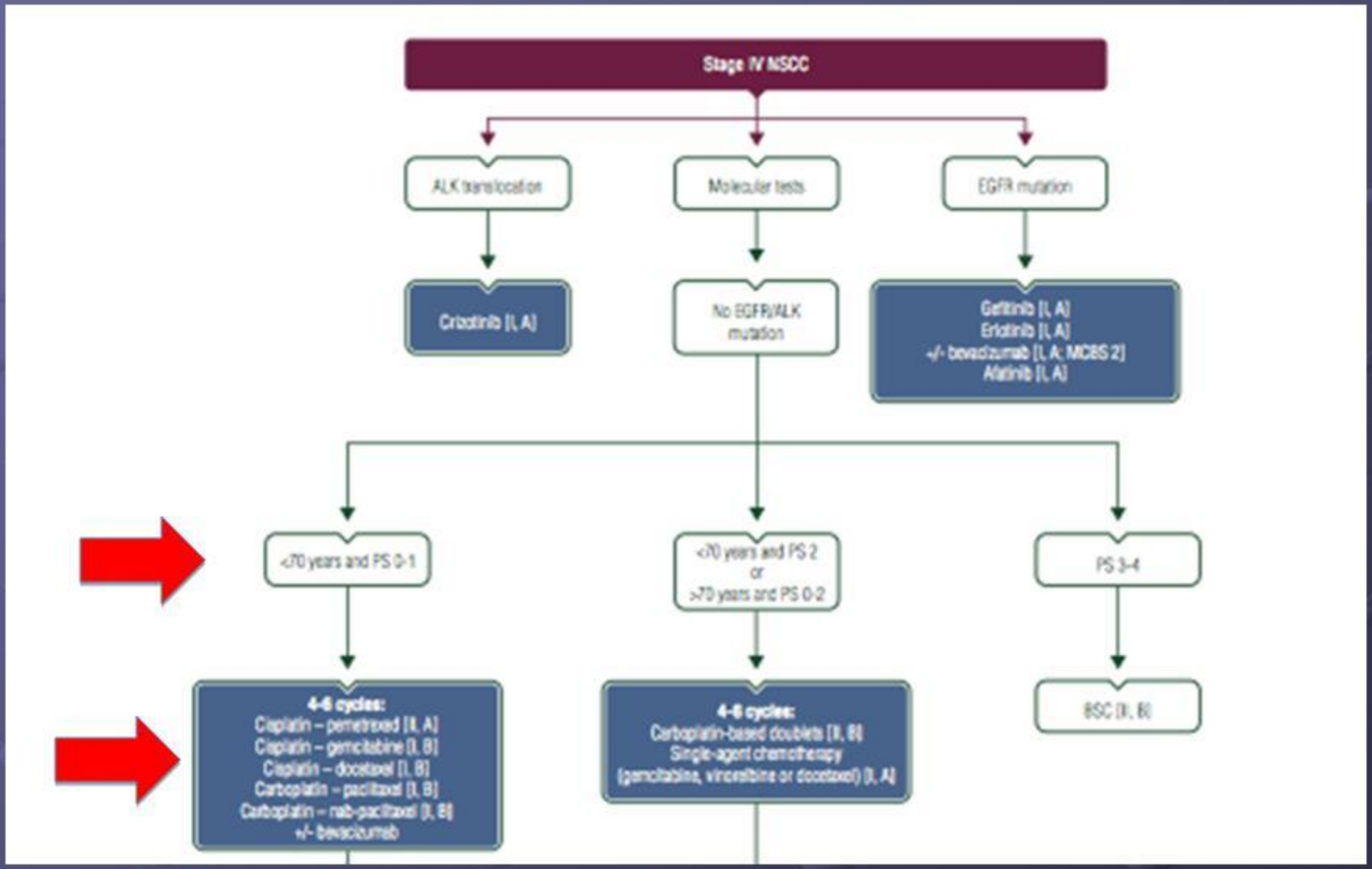
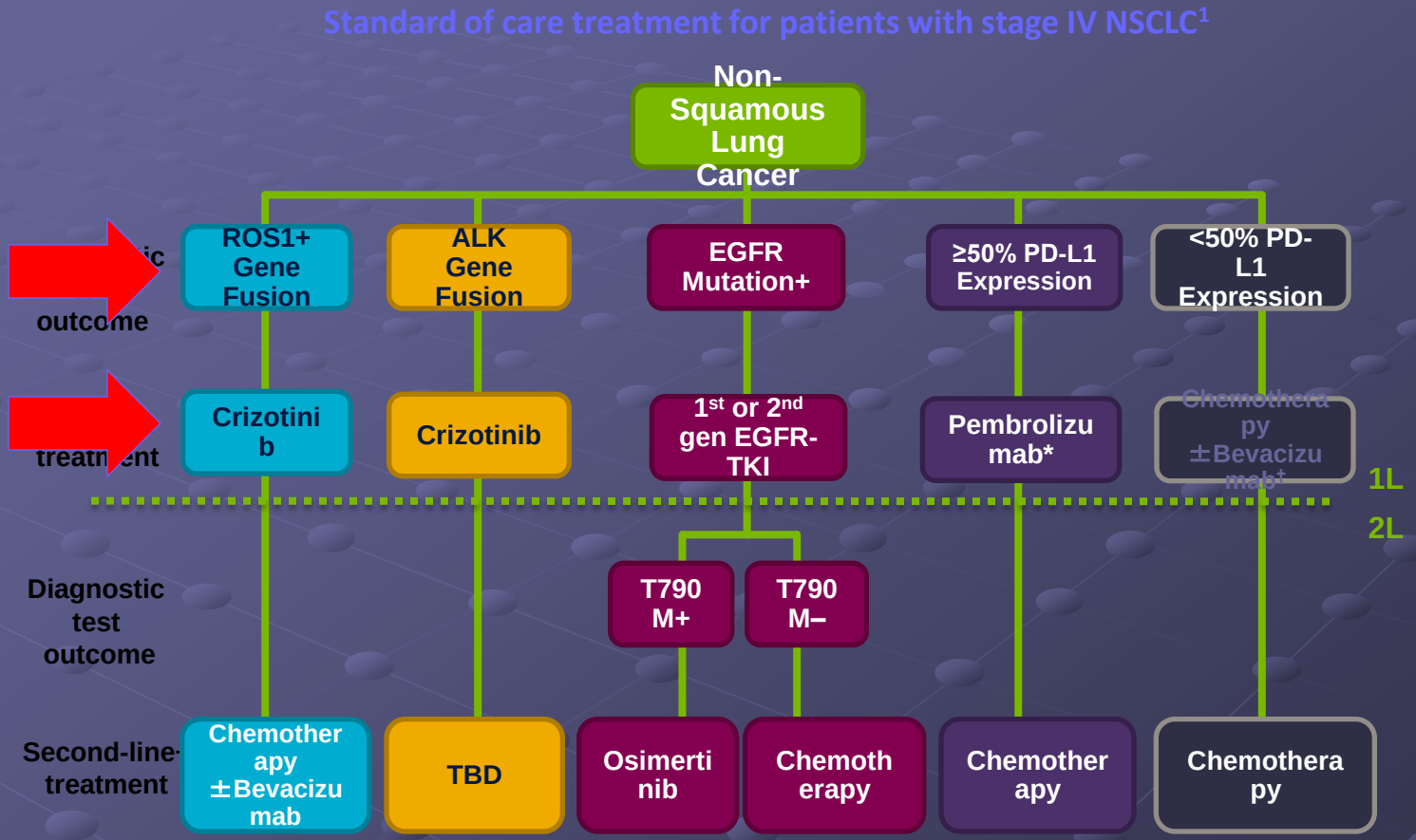
Scagliotti et al, JCO, 2008, 26: 3543-51

ESMO Guidelines 2016



ASCO treatment guideline for patients Stage IV NSCLC

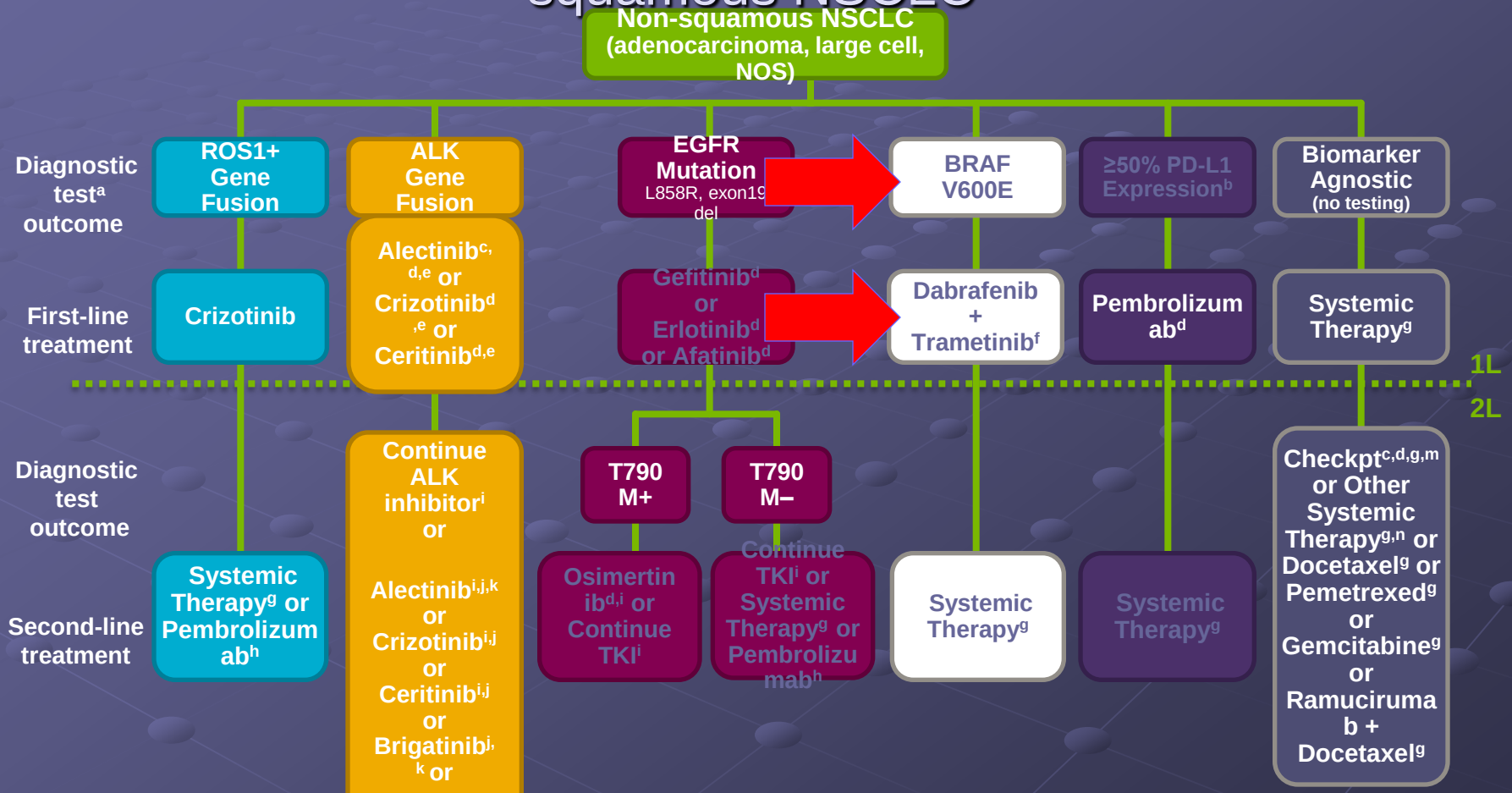


*Per ASCO guidelines, pembrolizumab + chemotherapy is not recommended for use in the first line setting in NSCLC. †only if patients are receiving carboplatin or paclitaxel.

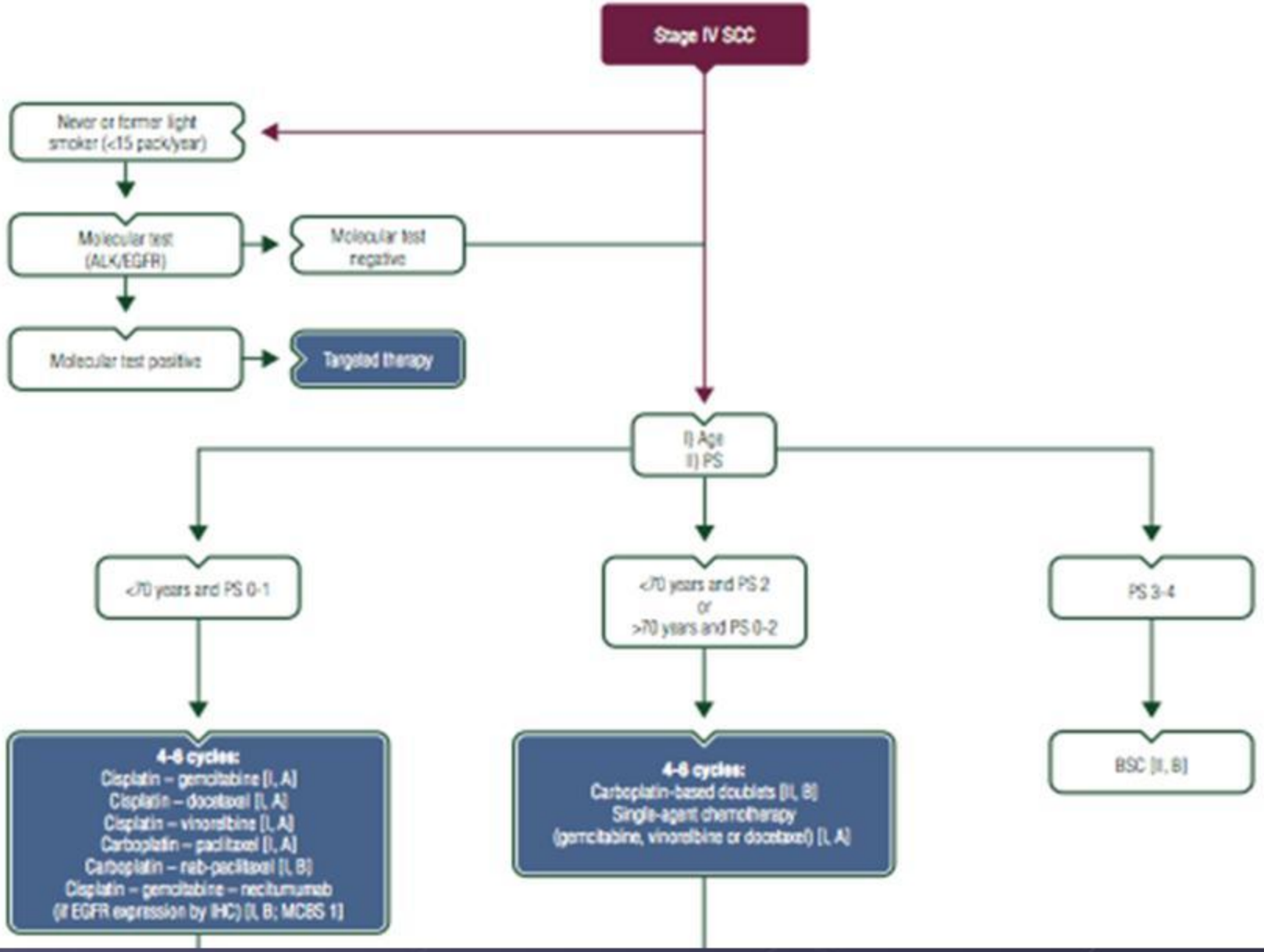
1L, first line; 2L, 2nd line; ALK, anaplastic lymphoma kinase; chemo, chemotherapy; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; ROS1, c-ros oncogene 1; TBD, to be determined; WT, wild-type.

1. Hanna N, et al. *J Clin Oncol*. 2017. doi: 10.1200/JCO.2017.74.6065. [Epub ahead of print].

National Comprehensive Cancer Network® (NCCN®) treatment guideline for patients with metastatic non-squamous NSCLC



ESMO GUIDELINES



2η Γραμμή

Can immunotherapy replace chemotherapy in second-line treatment of advanced NSCLC?

What is cancer immunotherapy?

- Cancer immunotherapy aims to exploit the immune system's ability to recognise and destroy cancer cells[1]

- The immune system provides long-term memory

  Treatment with an immunotherapy can lead to:

  - durable disease control *and*
  - long-term survival

1. Armstrong AC, et al. *BMJ* 2001;323:1289–1293
2. June CH. *J Clin Invest* 2007;117:1466–1476

Immunoediting: The role of the immune system in cancer development and progression

Elimination
Cancer immunosurveillance

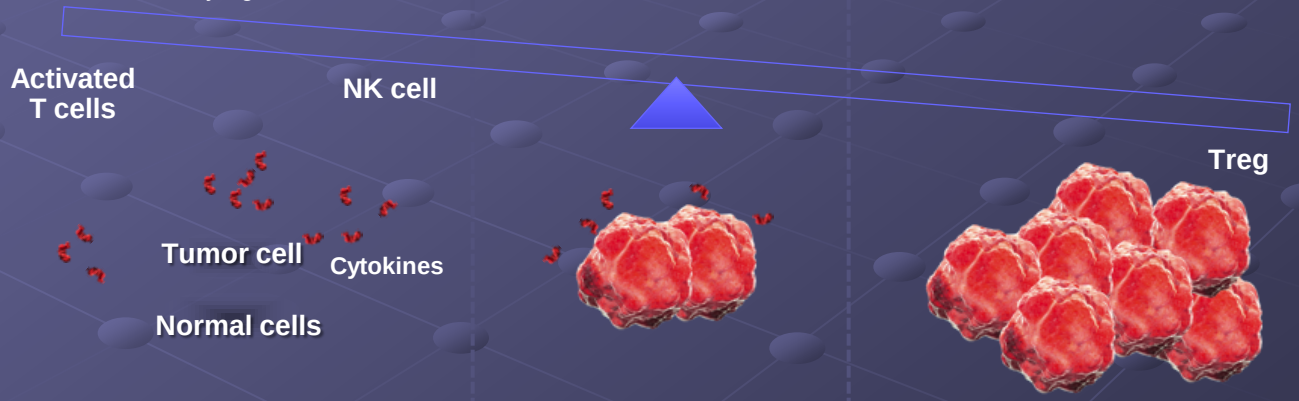
- Effective antigen processing/presentation
- Effective activation and function of effector cells
  - eg, T-cell activation without co-inhibitory signals

Equilibrium
Cancer dormancy

- Genetic instability
- Tumor heterogeneity
- Immune selection

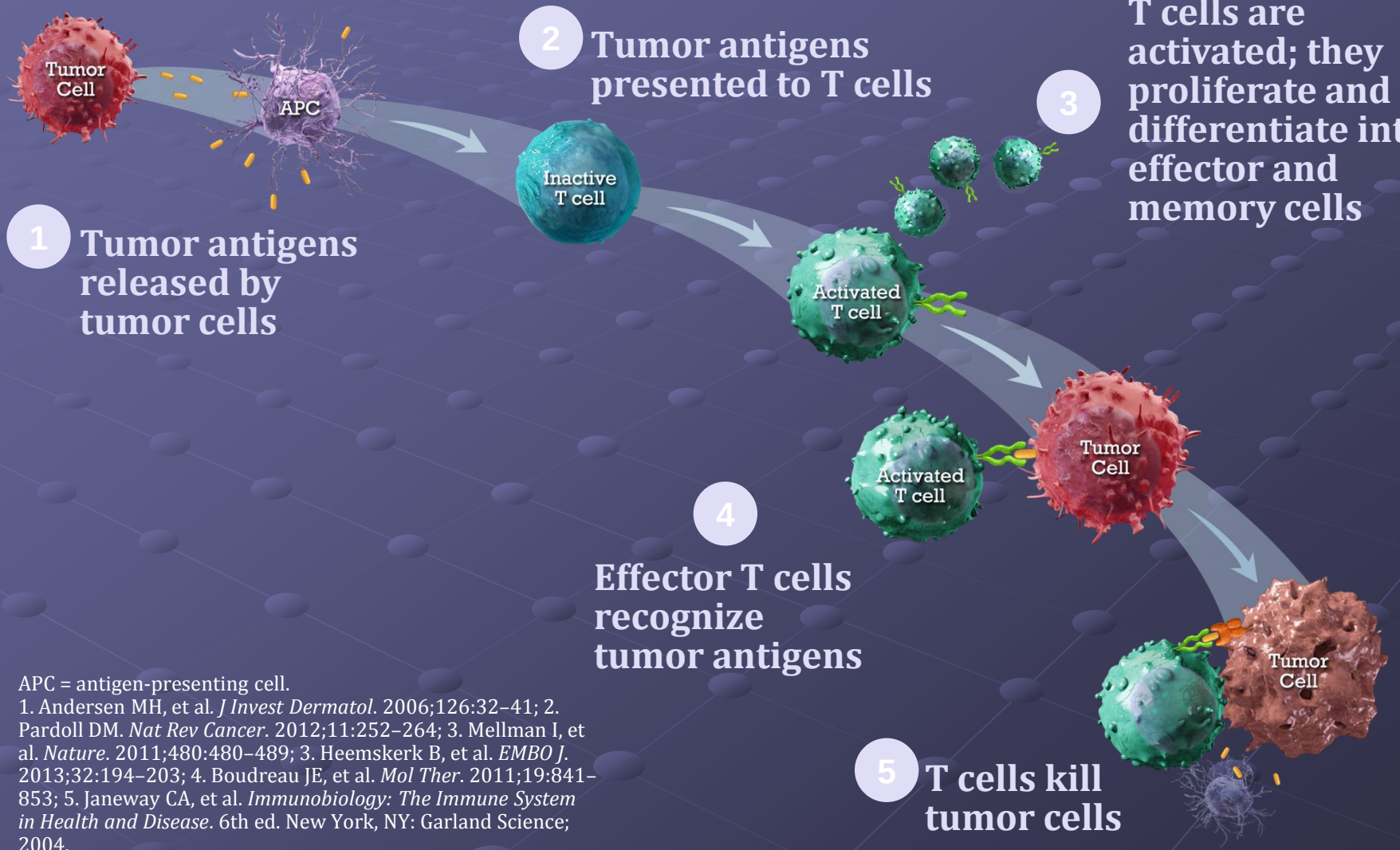
Escape
Cancer progression

- Tumors may avoid elimination by the immune system through outgrowth tumor cells that can suppress, disrupt, or “escape” the immune system



NK = natural killer; Treg = regulatory T cell.
Adapted from Vesely MD, et al. *Ann Rev Immunol*. 2011;29:235-271.

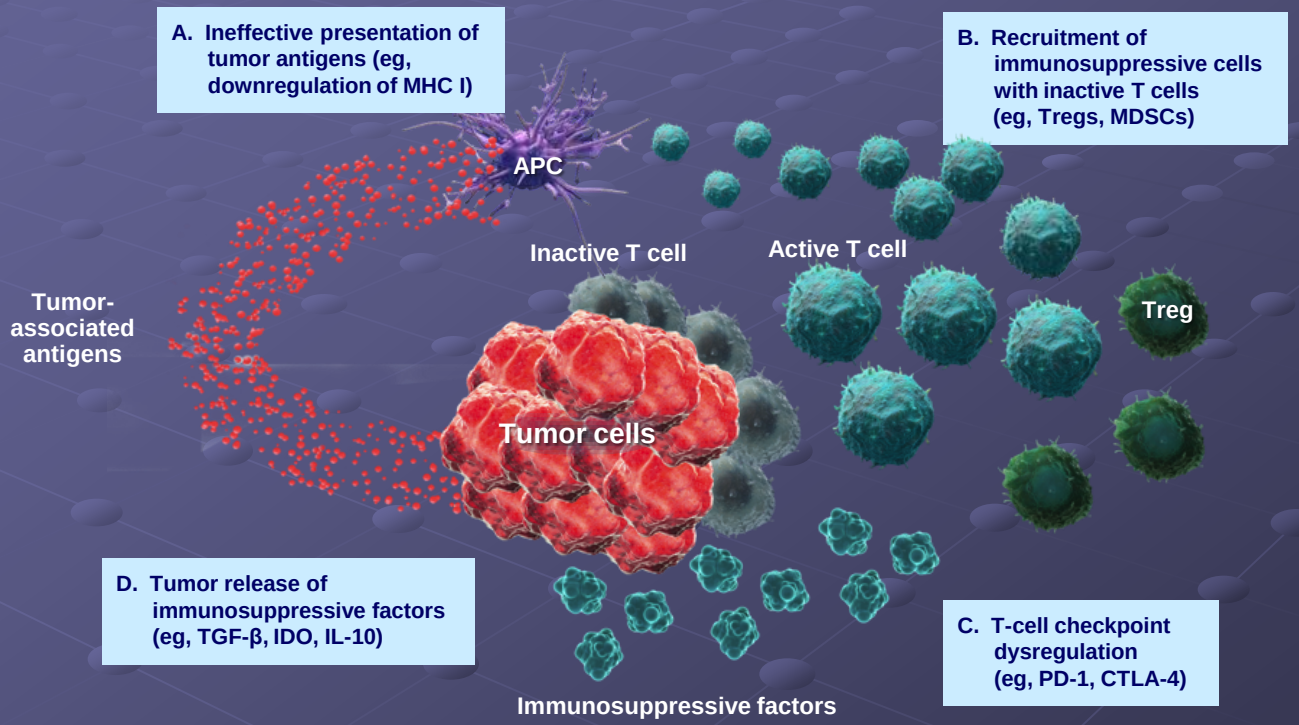
The T-Cell Antitumor Response[1–6]



APC = antigen-presenting cell.

1. Andersen MH, et al. *J Invest Dermatol*. 2006;126:32–41; 2. Pardoll DM. *Nat Rev Cancer*. 2012;11:252–264; 3. Mellman I, et al. *Nature*. 2011;480:480–489; 3. Heemskerk B, et al. *EMBO J*. 2013;32:194–203; 4. Boudreau JE, et al. *Mol Ther*. 2011;19:841–853; 5. Janeway CA, et al. *Immunobiology: The Immune System in Health and Disease*. 6th ed. New York, NY: Garland Science; 2004.

Tumors use complex, overlapping mechanisms to evade and suppress the immune system



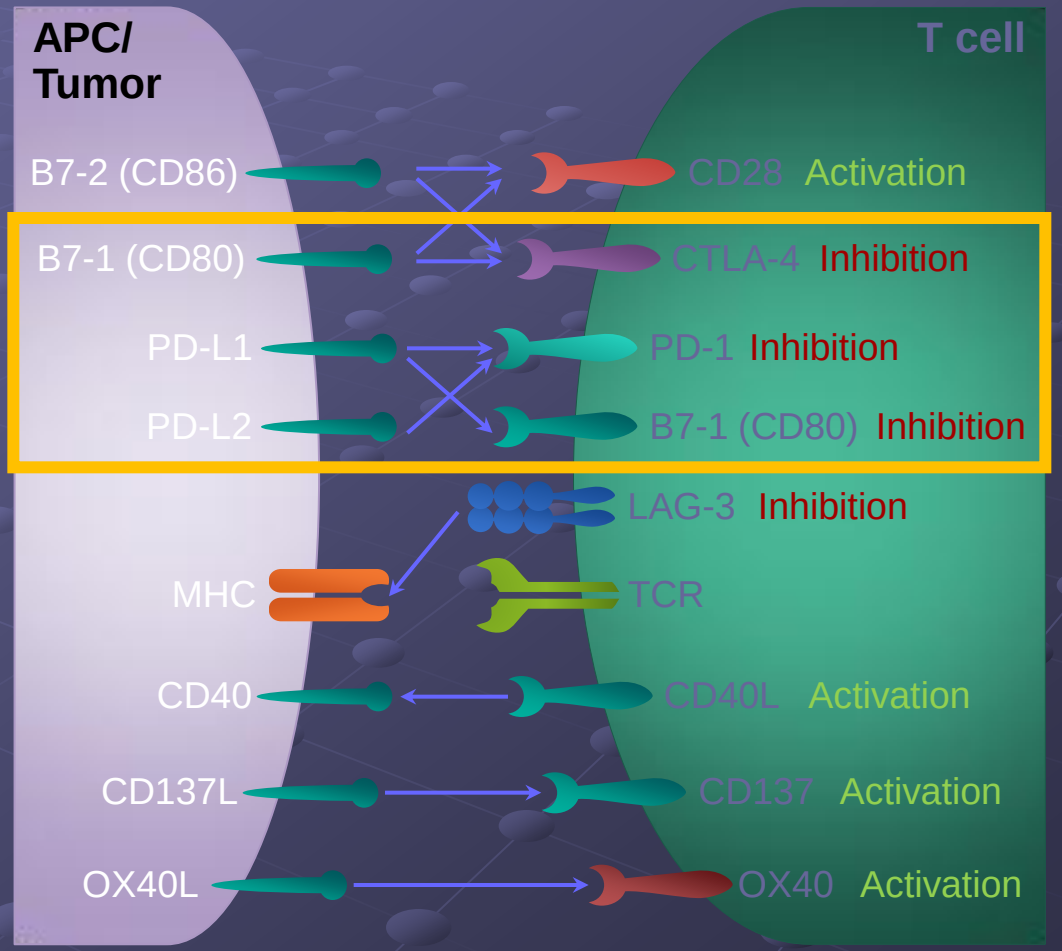
CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; IDO = indoleamine 2,3-dioxygenase; IL = interleukin; MDSC = myeloid-derived suppressor cell; MHC = major histocompatibility complex; PD-1 = programmed death-1; TGF-β = transforming growth factor beta; Treg = regulatory T cell.

Vesely MD et al. *Ann Rev Immunol*. 2011;29:235–271.

Regulation of T-Cell Activation: Balancing Activating and Inhibitory Signals

- Immune checkpoints limit, or "check," an ongoing immune response
- Prevents damage to the body's healthy tissues
  - Negative co-stimulation, also called "co-inhibition," helps shut down immune responses
  - PD-1, CTLA-4, and LAG-3 are examples of co-inhibitory "checkpoint
  - Amplitude and quality of a T-cell response is regulated by a balance of activating and inhibitory signals

" molecules



CTLA-4 = cytotoxic T-lymphocyte antigen-4; LAG-3 = lymphocyte activation gene-3; PD-1 = programmed death-1; PD-L1 = programmed death-ligand 1.

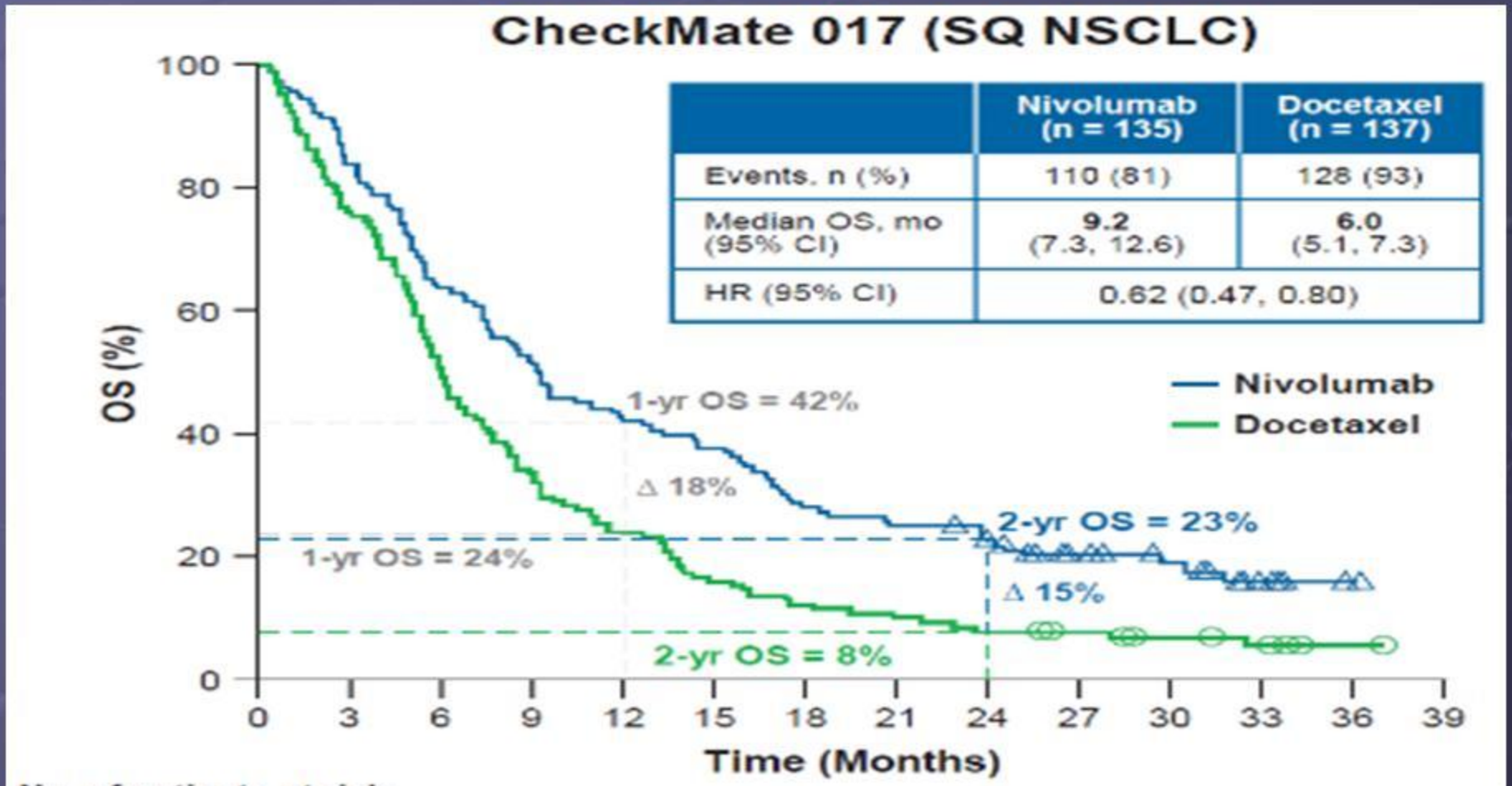
Pardoll DM. *Nat Rev Cancer*. 2012;12:252–264.

- **Programmed death-ligand 1** (PD-L1)

- The binding of PD-L1 to PD-1 transmits an inhibitory signal that reduces the proliferation of these T cells and can also induce apoptosis,

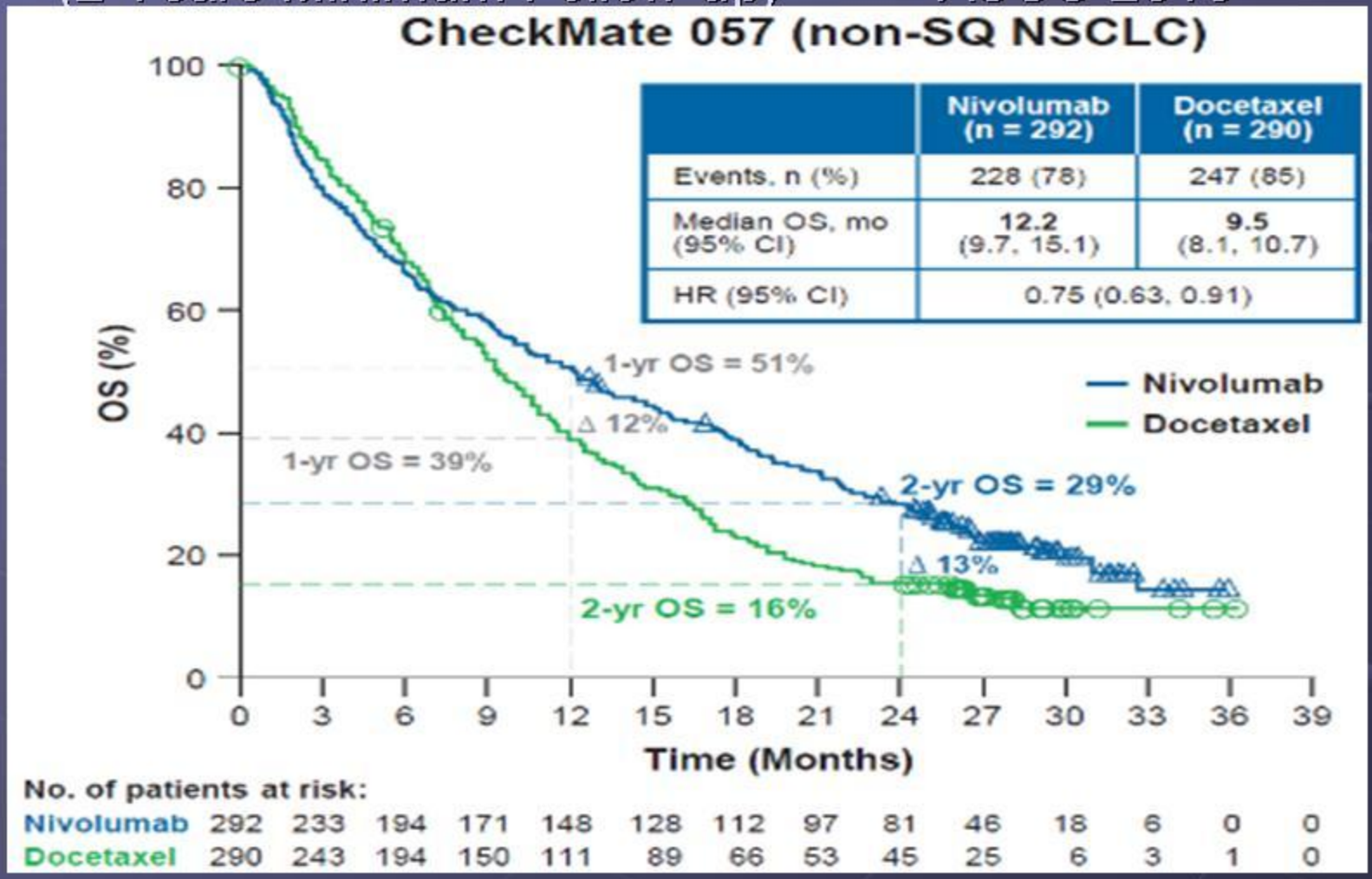
NIVOLUMAB 2ND LINE-SQUAMOUS NSCLC

(2 Years Minimum Follow-up) - ASCO 2016



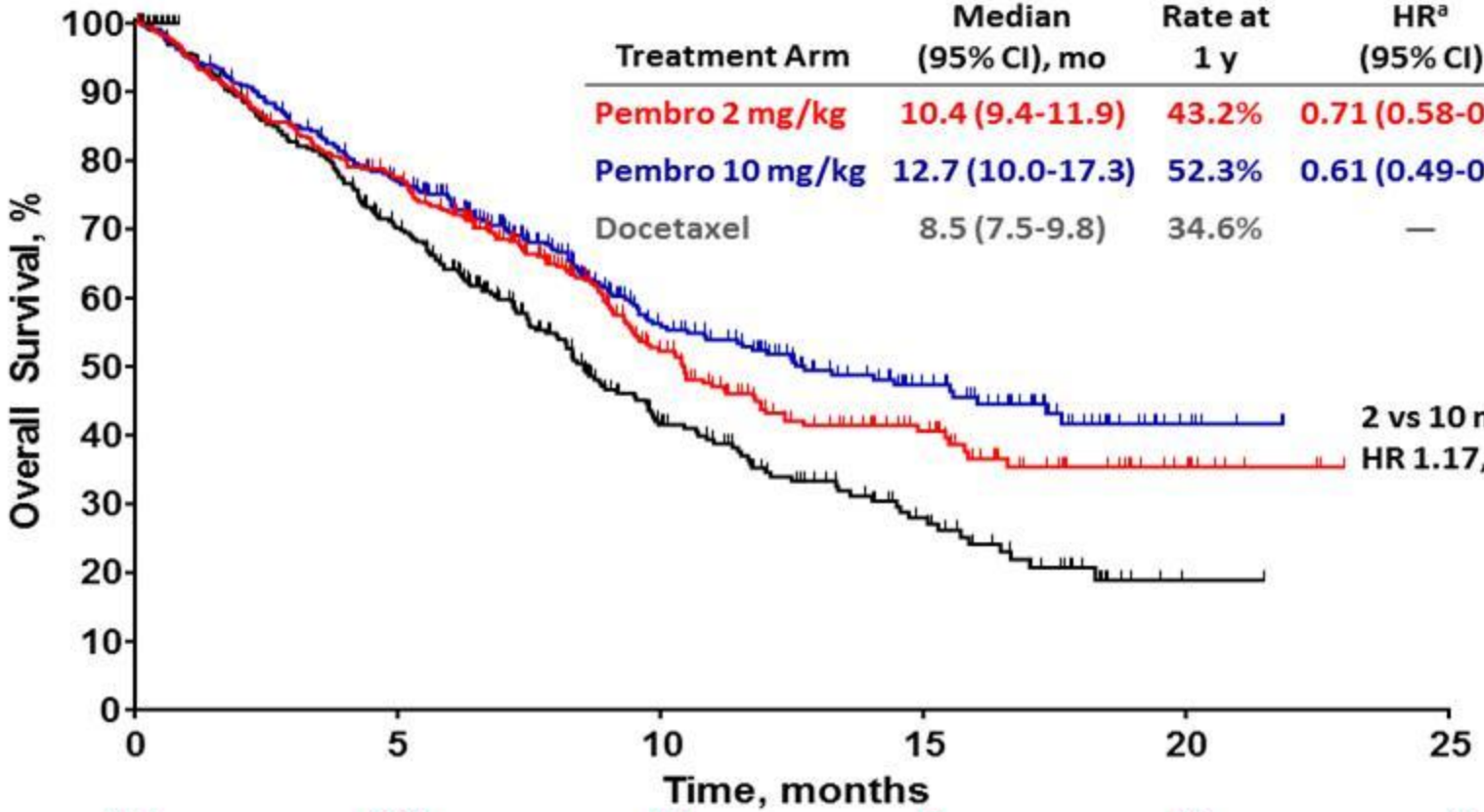
NIVOLUMAB 2ND LINE- NON SQUAMOUS NSCLC

(2 Years Minimum Follow-up) - ASCO 2016



RS Herbst. Presented December 20, 2015

OS, PD-L1 TPS ≥1% (Total Population)



Treatment Arm	Median (95% CI), mo	Rate at 1 y	HR[a] (95% CI)	*P*
Pembro 2 mg/kg	10.4 (9.4-11.9)	43.2%	0.71 (0.58-0.88)	0.0008
Pembro 10 mg/kg	12.7 (10.0-17.3)	52.3%	0.61 (0.49-0.75)	<0.0001
Docetaxel	8.5 (7.5-9.8)	34.6%	—	—

2 vs 10 mg/kg:
HR 1.17, 95% CI 0.94-1.45

Analysis cut-off date: September 30, 2015.

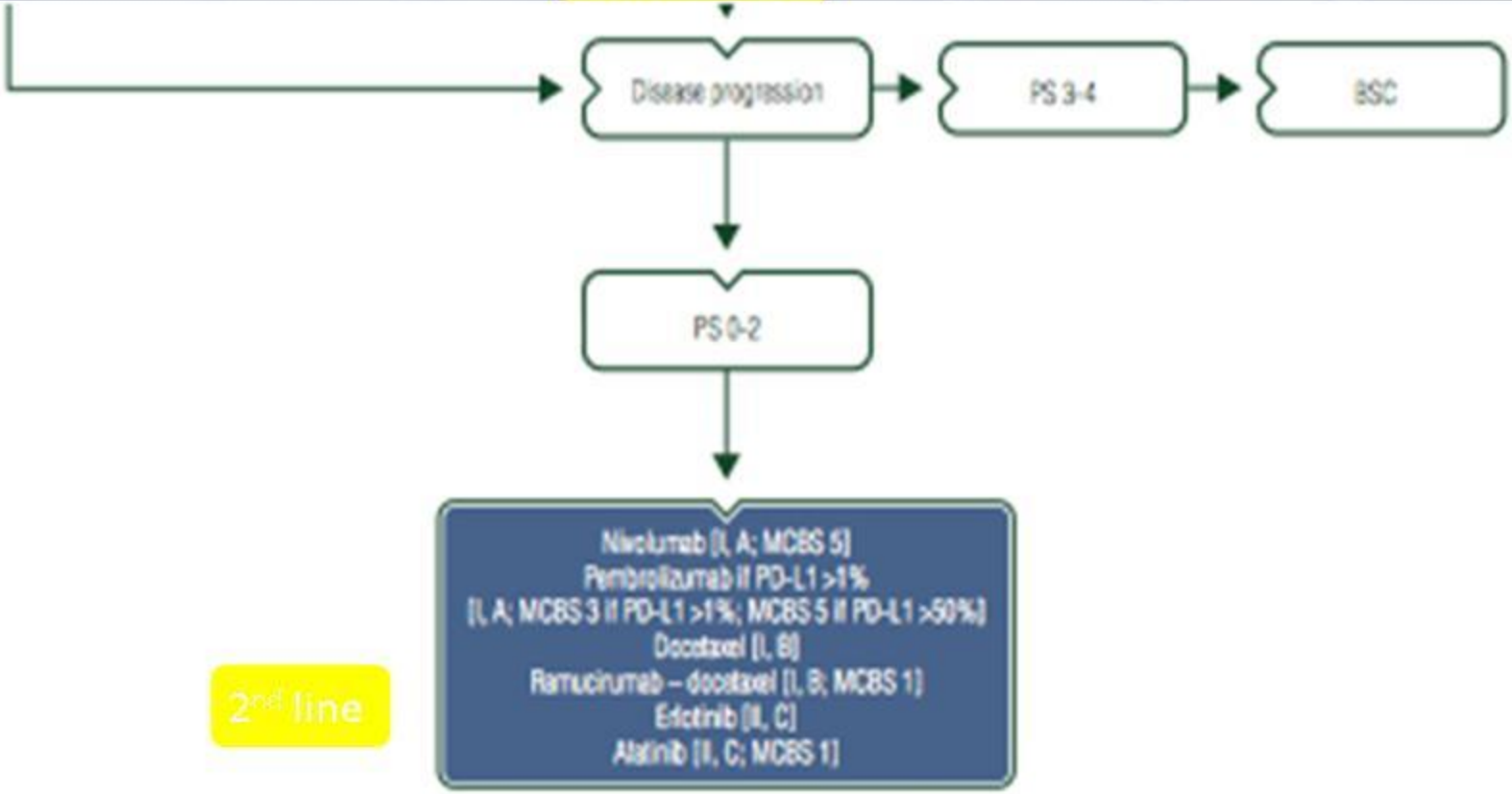
*Comparison of pembrolizumab vs docetaxel.

clinical practice guidelines

Annals of Oncology 27 (Supplement 5): v1–v27, 2016
doi:10.1093/annonc/mdw326

Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

SQUAMOUS



2nd line

clinical practice guidelines

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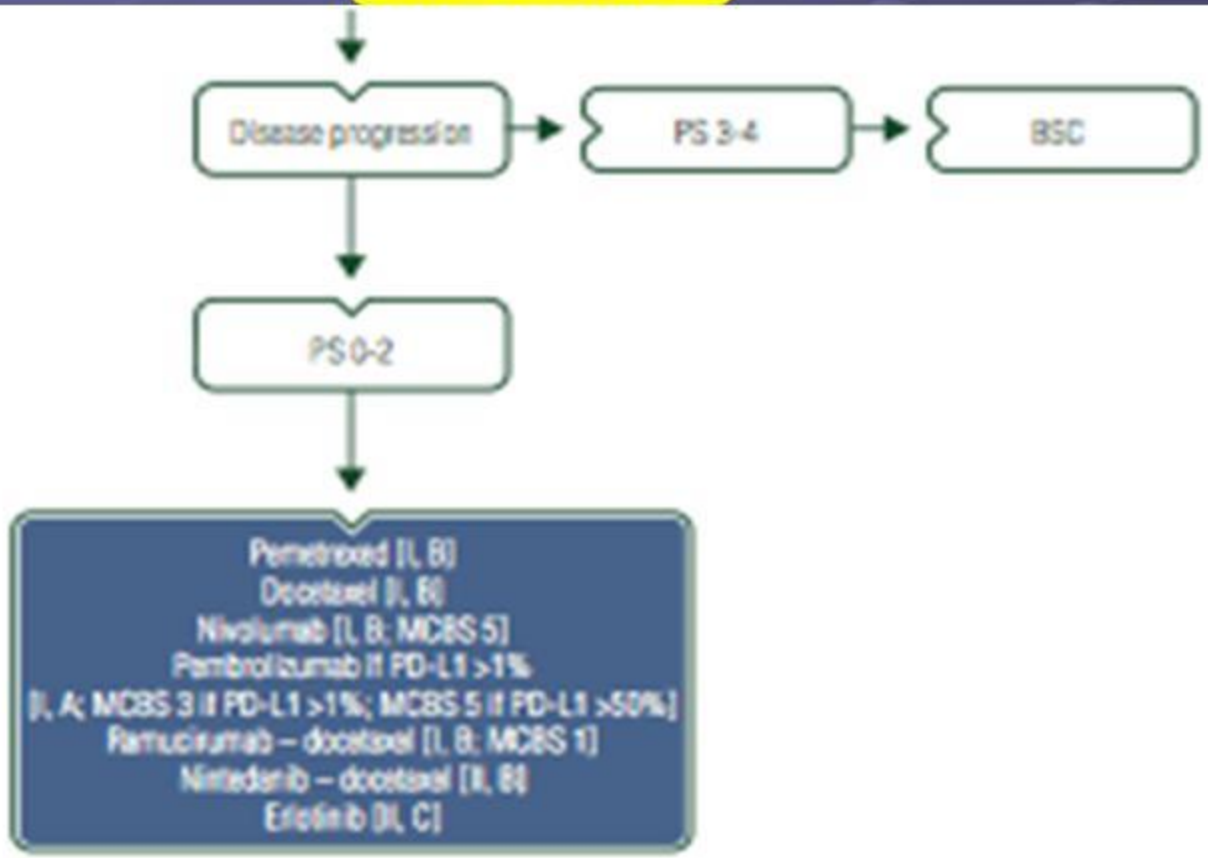
Non-SQUAMOUS



2nd line

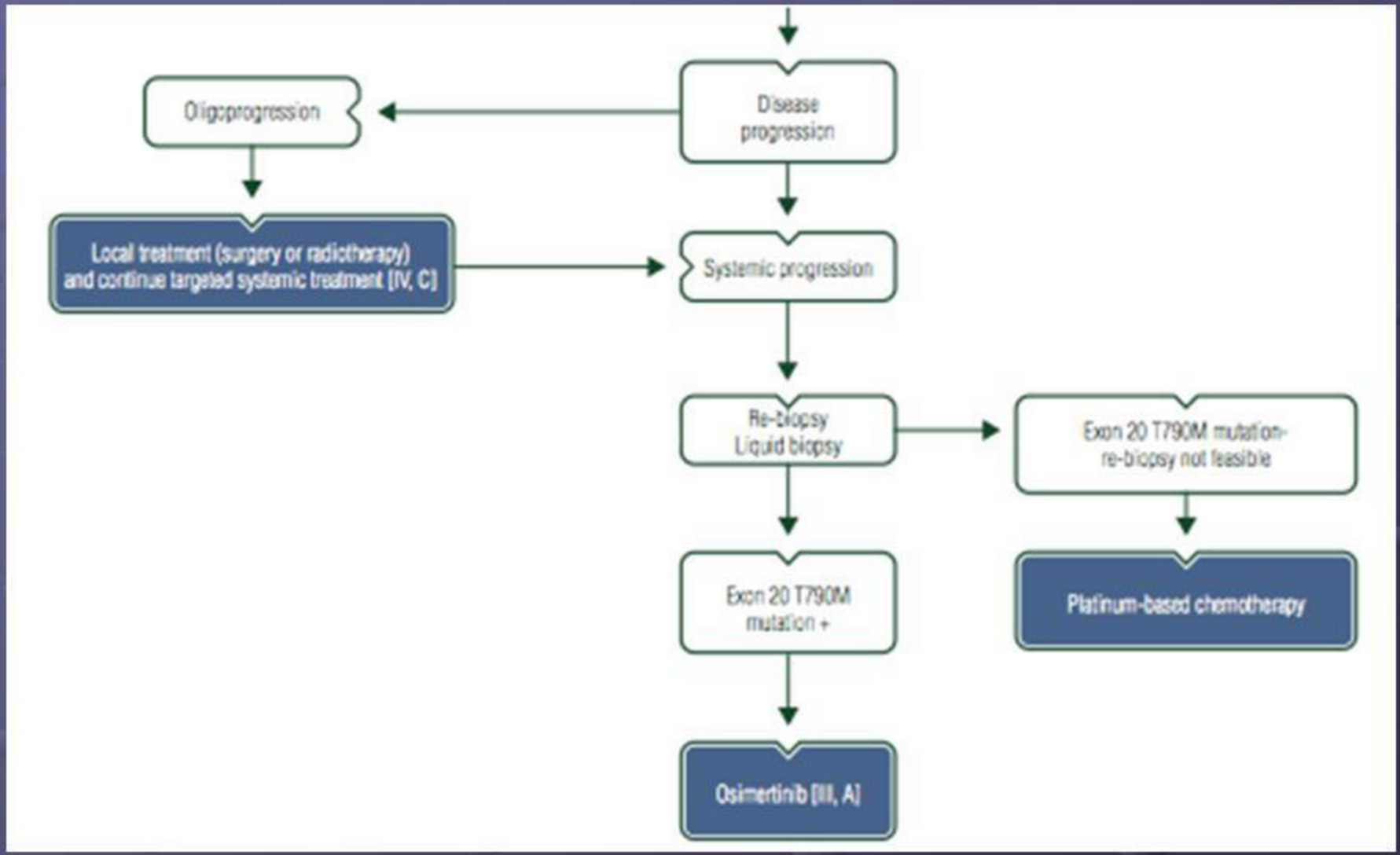
2η Γραμμή

EGFR mutant

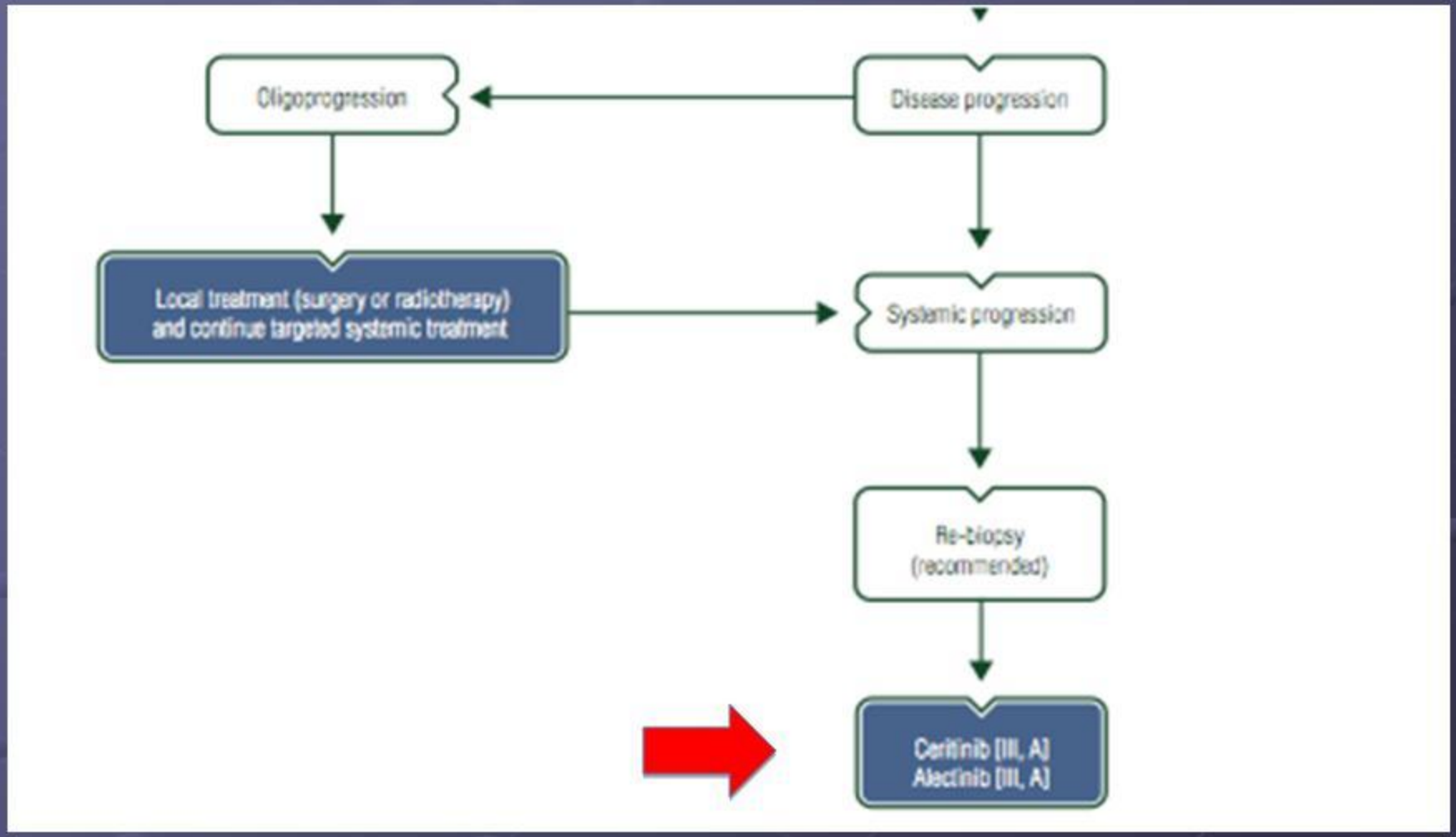
OR

ALK rearranged

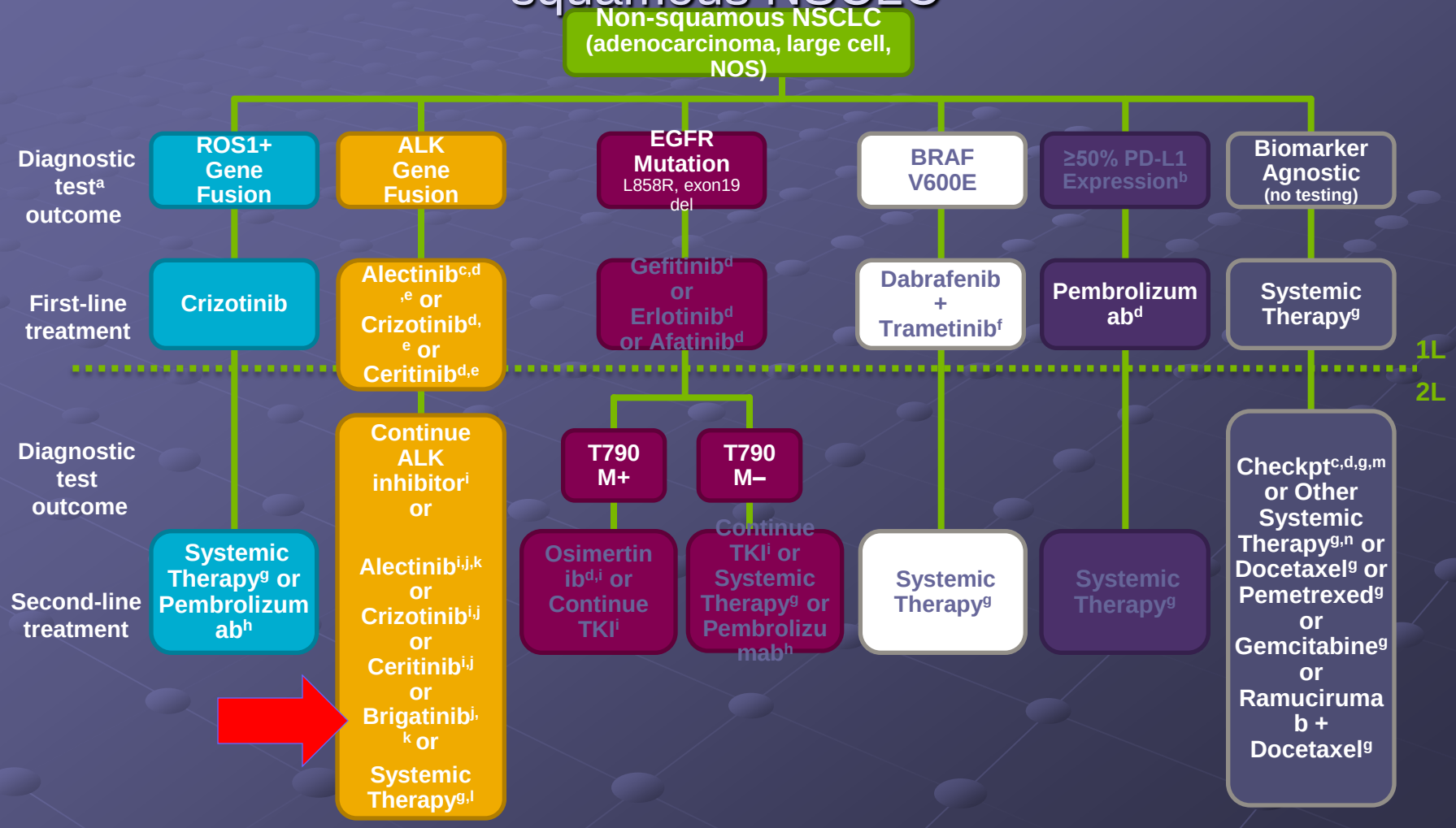
ESMO Guidelines EGFR mut



ESMO Guidelines ALK rearranged



National Comprehensive Cancer Network® (NCCN®) treatment guideline for patients with metastatic non-squamous NSCLC



GUIDELINES/ΑΝΑΚΟΙΝΩΣΕΙΣ

- **ESMO**=European Society for Medical Oncology

- **NCCN**=National Comprehensive Cancer Network/evidence –based cancer guidelines

  a not-for-profit alliance of leading cancer centers devoted to patient care, research, and education, ...

  ASCO=American Society of Clinical Oncology

GUIDELINES/ΑΝΑΚΟΙΝΩΣΕΙΣ

- **IASCL=** International Association for the study of lung cancer

- **WHO / CHEST/ BTS/ ERS**

- Multidisciplinary approach
- Multimodality treatment

over the past decade, it has become evident that subsets of NSCLC can be further defined at the molecular level by recurrent 'driver' mutations that occur in multiple oncogenes, including AKT1, ALK, BRAF, EGFR, HER2, KRAS, MEK1, MET, NRAS, PIK3CA, RET, and ROS1

- Driver' mutations lead to constitutive activation of mutant signaling proteins that induce and sustain tumorigenesis.

- ROS1 is a receptor tyrosine kinase (RTK) of the insulin receptor family.
- More recently, ROS1 fusions were identified as a potential "driver" mutation in non-small cell lung cancer (1%)
- ROS1 fusions contain an intact tyrosine kinase domain.

- Signaling downstream of ROS1 fusions results in activation of cellular pathways known to be involved in cell growth and cell proliferation

- ROS1 fusions are associated with sensitivity in vitro to tyrosine kinase inhibitors that inhibit ROS1

The anaplastic lymphoma kinase (ALK) is a receptor tyrosine kinase that is aberrant in a variety of malignancies.

All ALK fusions contain the entire ALK tyrosine kinase domain.

Epidermal growth factor receptor (EGFR) belongs to a family of receptor tyrosine kinases (RTKs) that include EGFR/ERBB1, HER2/ERBB2/NEU, HER3/ERBB3, and HER4/ERBB4.

- Binding of a growth factor (e.g., EGF, HGF) to a receptor tyrosine kinase activates the receptor tyrosine kinase and typically causes the dimerization of the two receptor monomers. The receptors are activated by phosphorylation within their kinase domains. Once the receptor is turned on, numerous downstream pathways are activated including MAP kinase signaling, JAK/STAT signaling, and PI3K/AKT1/MTOR signaling. Specific nodes in the pathway that are therapeutically actionable are noted.

My cancer genome

ECOG Performance Status

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

- Multidisciplinary approach
- Multimodality treatment