Lung Cancer

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Thoracic & Head/Neck
Medical Oncology

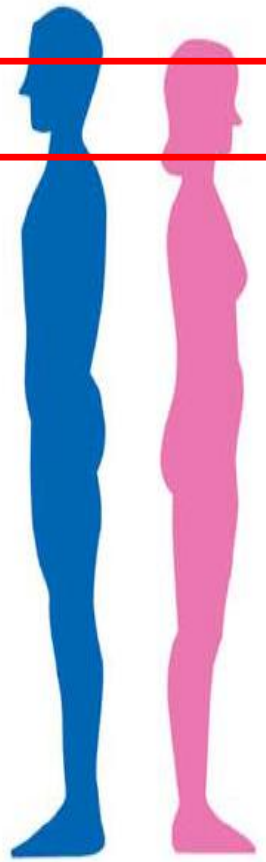
Banner
MD Anderson
Cancer Center
Making Cancer History®

Lung Cancer

1. Epidemiology and etiology of lung cancer
2. Lung cancer screening
3. Management of NSCLC
4. Diagnosis and management of SCLC and paraneoplastic syndrome

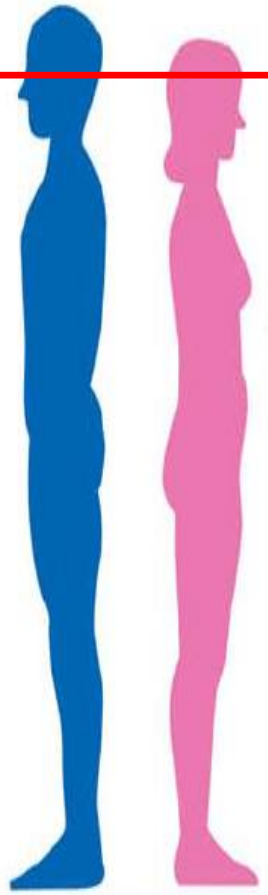
Estimated New Cancer Patients in 2017

Males				Females		
Prostate	161,360	19%		Breast	252,710	30%
Lung & bronchus	116,990	14%		Lung & bronchus	105,510	12%
Colon & rectum	71,420	9%		Colon & rectum	64,010	8%
Urinary bladder	60,490	7%		Uterine corpus	61,380	7%
Melanoma of the skin	52,170	6%		Thyroid	42,470	5%
Kidney & renal pelvis	40,610	5%		Melanoma of the skin	34,940	4%
Non-Hodgkin lymphoma	40,080	5%		Non-Hodgkin lymphoma	32,160	4%
Leukemia	36,290	4%		Leukemia	25,840	3%
Oral cavity & pharynx	35,720	4%		Pancreas	25,700	3%
Liver & intrahepatic bile duct	29,200	3%		Kidney & renal pelvis	23,380	3%
All Sites	**836,150**	**100%**		**All Sites**	**852,630**	**100%**



Estimated Cancer Death in 2017

Males			Females		
Lung & bronchus	84,590	27%	Lung & bronchus	71,280	25%
Colon & rectum	27,150	9%	Breast	40,610	14%
Prostate	26,730	8%	Colon & rectum	23,110	8%
Pancreas	22,300	7%	Pancreas	20,790	7%
Liver & intrahepatic bile duct	19,610	6%	Ovary	14,080	5%
Leukemia	14,300	4%	Uterine corpus	10,920	4%
Esophagus	12,720	4%	Leukemia	10,200	4%
Urinary bladder	12,240	4%	Liver & intrahepatic bile duct	9,310	3%
Non-Hodgkin lymphoma	11,450	4%	Non-Hodgkin lymphoma	8,690	3%
Brain & other nervous system	9,620	3%	Brain & other nervous system	7,080	3%
All Sites	**318,420**	**100%**	**All Sites**	**282,500**	**100%**



Causes: Lung Cancer

1. **Smoking**

a. 1/7 will die of lung cancer
b. 85-90% of lung cancer death
c. Pipes and cigars
d. 2nd-hand smoking: 30% of non-smoker death (~3000/year)

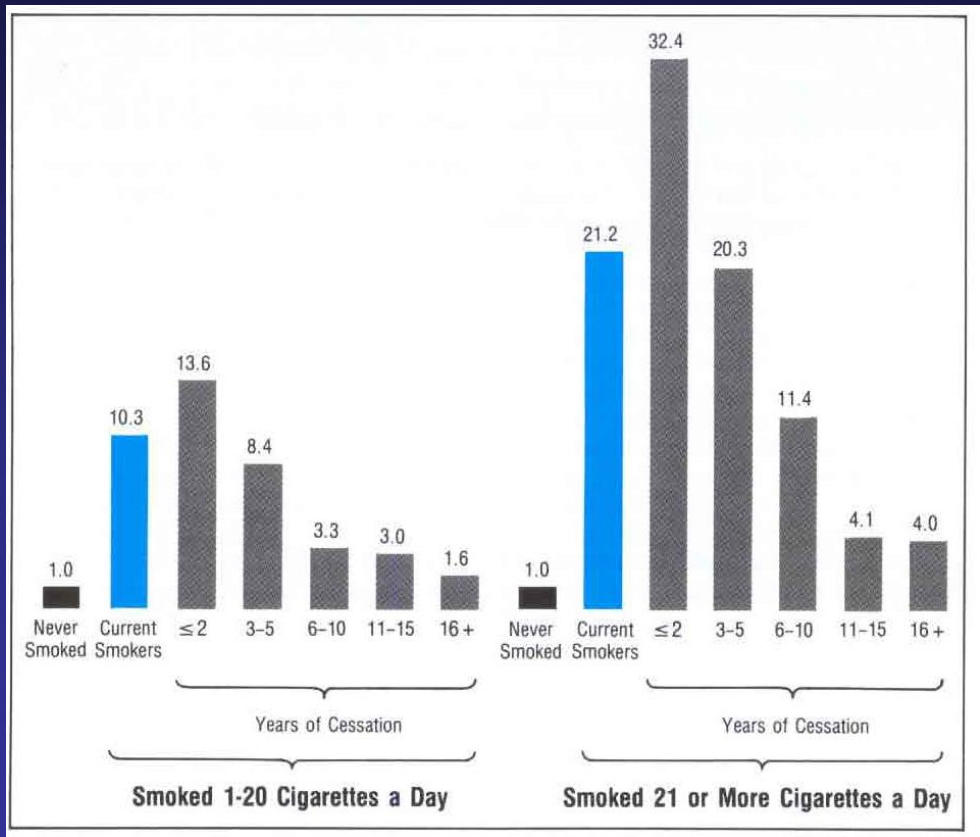


Fig. 5. Relative risks of lung cancer in ex-smokers, by number of years quit, women, Cancer Prevention Study II. Data from Garfinkel and Stellman.[8]

Causes: Lung Cancer

2. Occupational exposure

a. Asbestos

- 3-4% lung cancer
- Synergy: smoker 50-100 folds vs non-smoker 5 folds

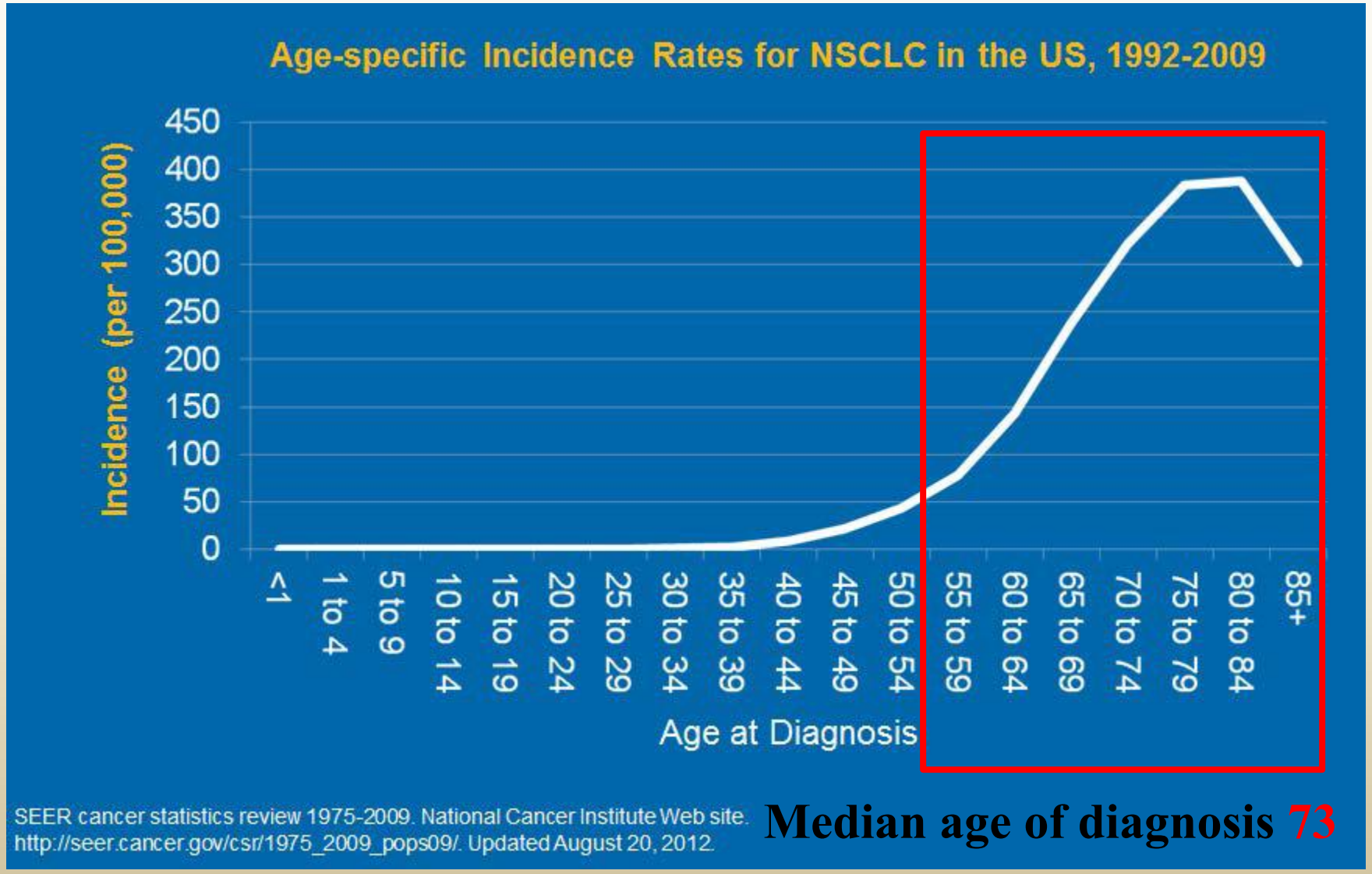
b. **Radon, polycyclic aromatic hydrocarbons, nickel, chromium85-90% of lung cancer death**

3. Air pollution, smoke from cooking and heating

4. Genetic predisposition

5. Age

Lung Cancer Incidence with Age



Screening

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 4, 2011 VOL. 365 NO. 5

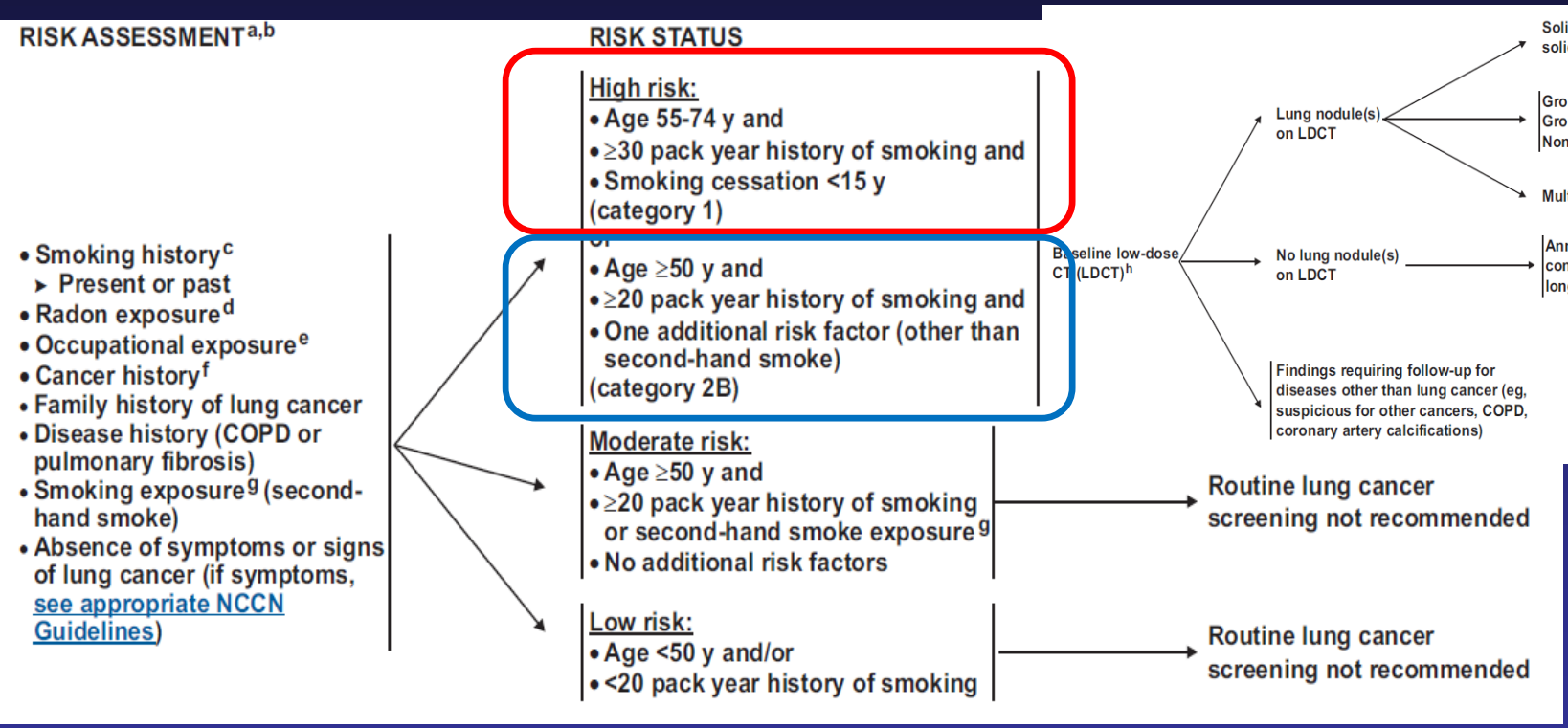
Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening

The National Lung Screening Trial Research Team*

53454 Pts: Annual low-dose CT vs AP CXR

20% reduction in lung cancer mortality at 6.5 years of follow-up

Screening



USPSTF: 55-79 y

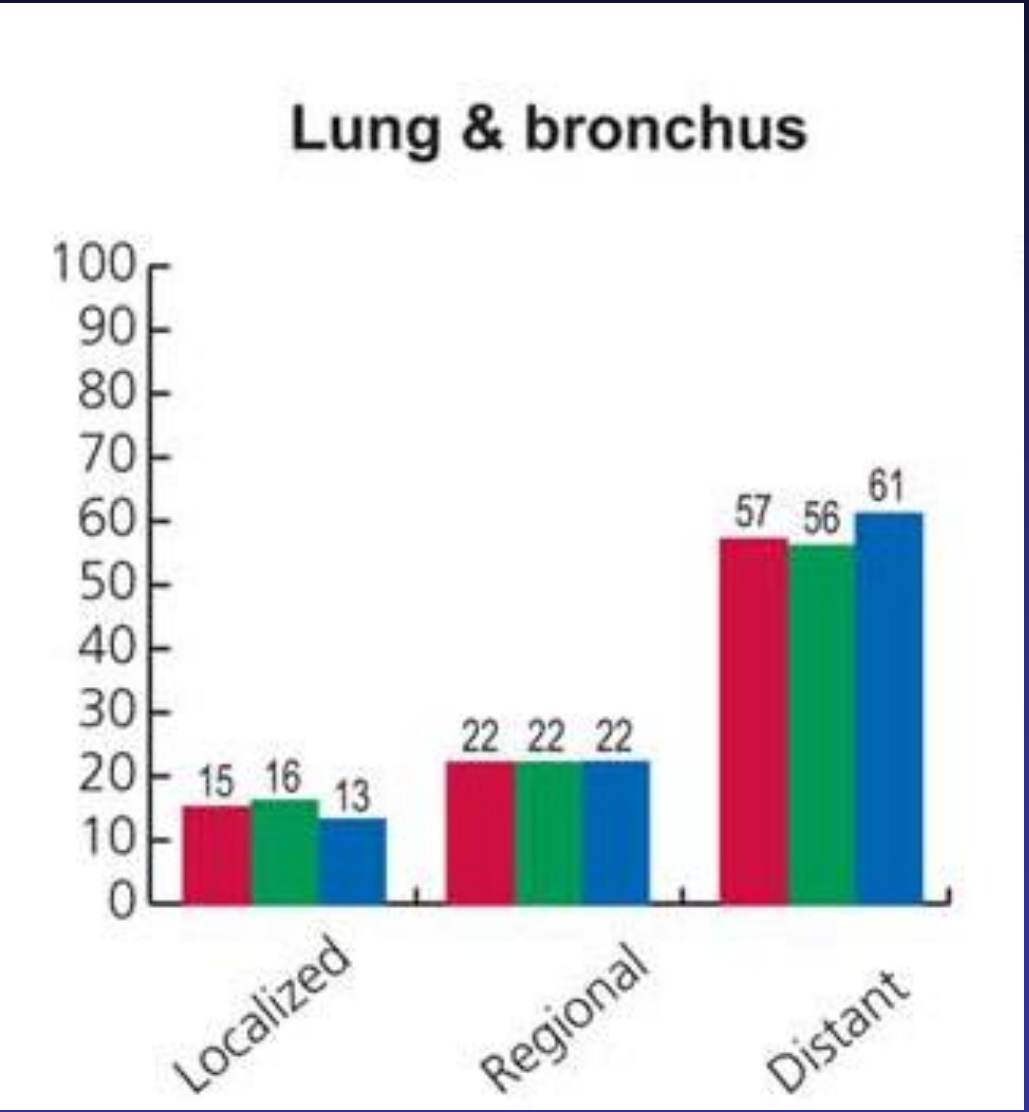
Presentation

1. Asymptomatic (sceening, incidental findings)

2. Symptoms

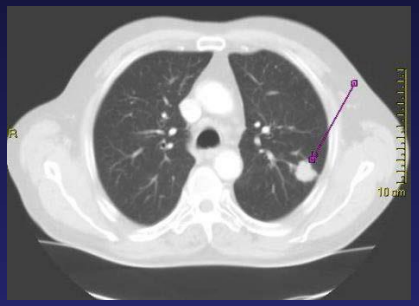
a. Cough, hemoptysis
b. Pneumonia
c. Pain
d. Weight loss
e. Paraneoplastic syndrome related to tumor growth (AdenoCa, SCLC)

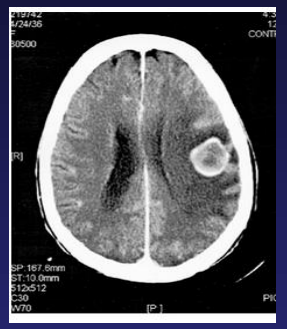
Stage at Diagnosis

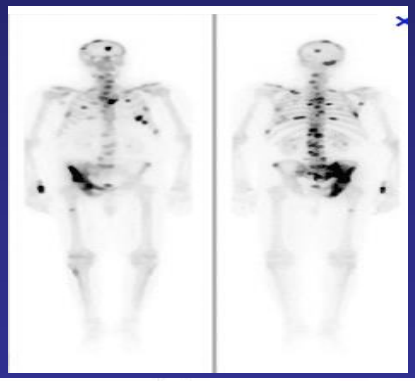


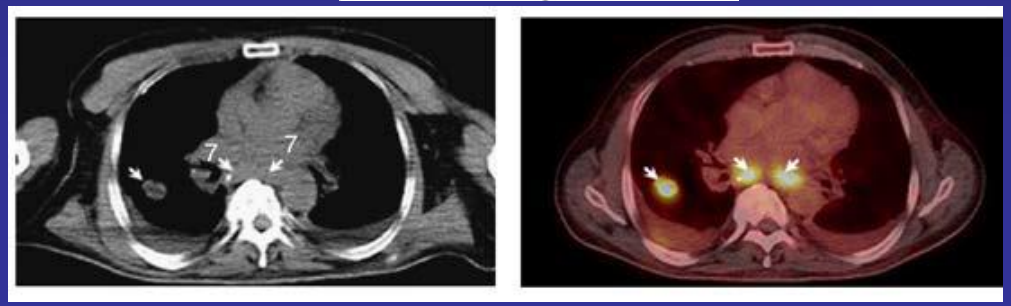
Workup and Staging

1. CT with contrast
2. MRI
3. Bone scan
4. PET-CT
5. Biopsy
6. Pulmonary function test
7. EBUS/Mediastinoscopy

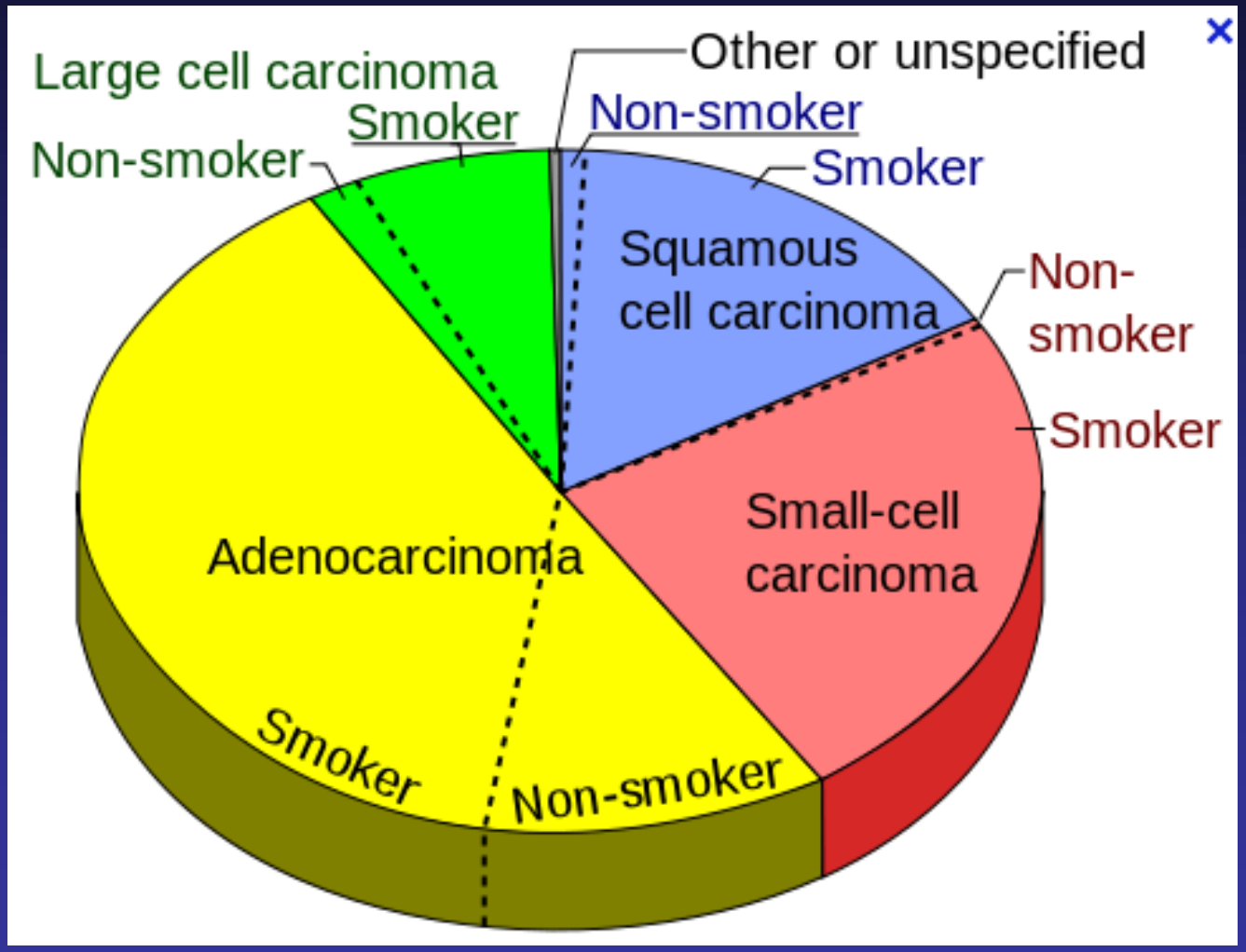


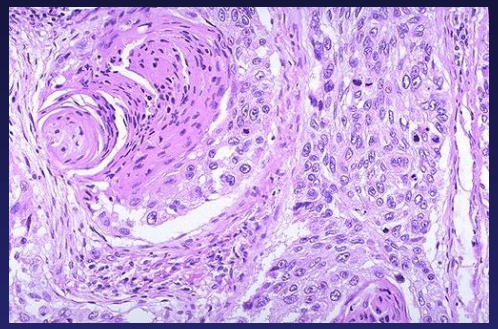


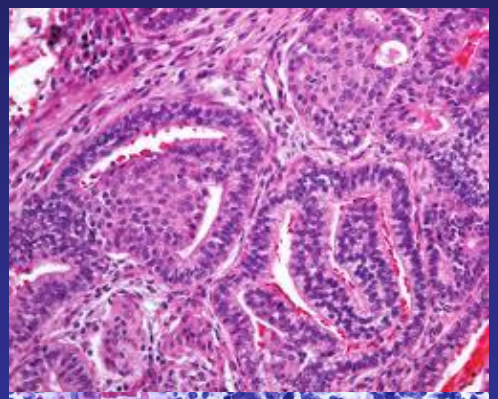


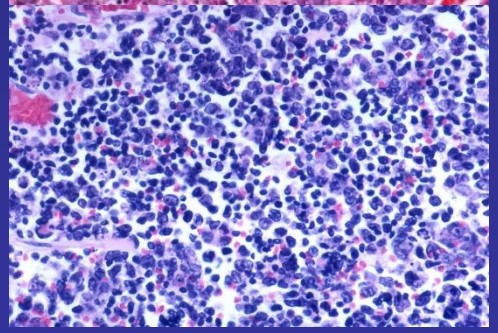


Lung Cancer:
Small Cell vs Non-Small Cell









NSCLC Staging

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2019
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

Table 1. **Definitions for T, N, M**

T		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
	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, carina; separate tumor nodule(s) in a ipsilateral lobe different from that of the primary

NSCLC Staging

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NCCN Guidelines Version 3.2019
Non-Small Cell Lung Cancer

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Table 1. **Definitions for T, N, M (continued)**

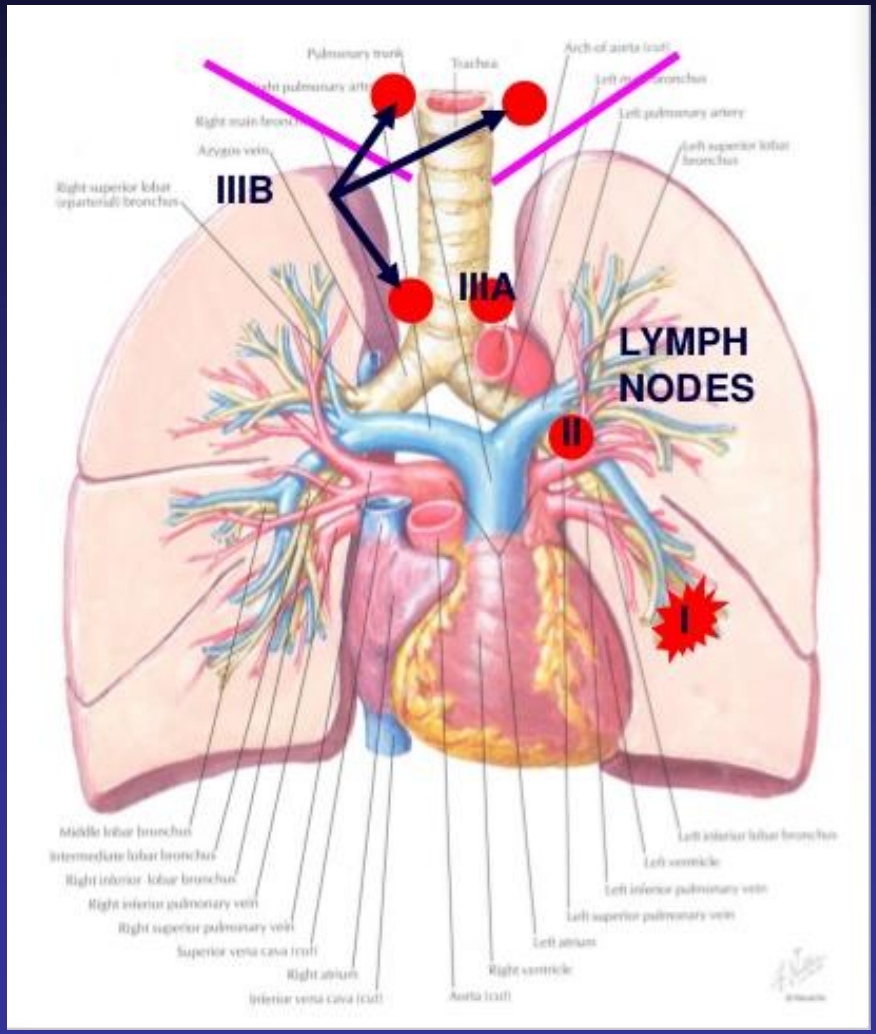
N		**Regional Lymph Nodes**
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2		Metastasis in ipsilateral mediastinal 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**
MX		Distant metastasis cannot be assessed
M0		No distant metastasis
M1		Distant metastasis
	M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodules or malignant pleural or pericardial effusion[a]
	M1b	Single extrathoracic metastasis in a single organ (including involvement of a single nonregional node)
	M1c	Multiple extrathoracic metastases in a single organ or in multiple organs

Table 2. **AJCC Prognostic Groups**

	T	N	M
Occult Carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA1	T1mi	N0	M0
	T1a	N0	M0
Stage IA2	T1b	N0	M0
Stage IA3	T1c	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
Stage IIB	T1a	N1	M0
	T1b	N1	M0
	T1c	N1	M0
	T2a	N1	M0
	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a	N2	M0
	T1b	N2	M0
	T1c	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0

	T	N	M
Stage IIIB	T1a	N3	M0
	T1b	N3	M0
	T1c	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N2	M0
	T4	N2	M0
Stage IIIC	T3	N3	M0
	T4	N3	M0
Stage IVA	Any T	Any N	M1a
	Any T	Any N	M1b
Stage IVB	Any T	Any N	M1c

NSCLC Staging and Therapy



Stage I: no LN involvement

Surgery vs SBRT

Stage II: local nodes

Surgery + Adjuvant chemo

Stage III: Mediastinal or supraclavicular LNs

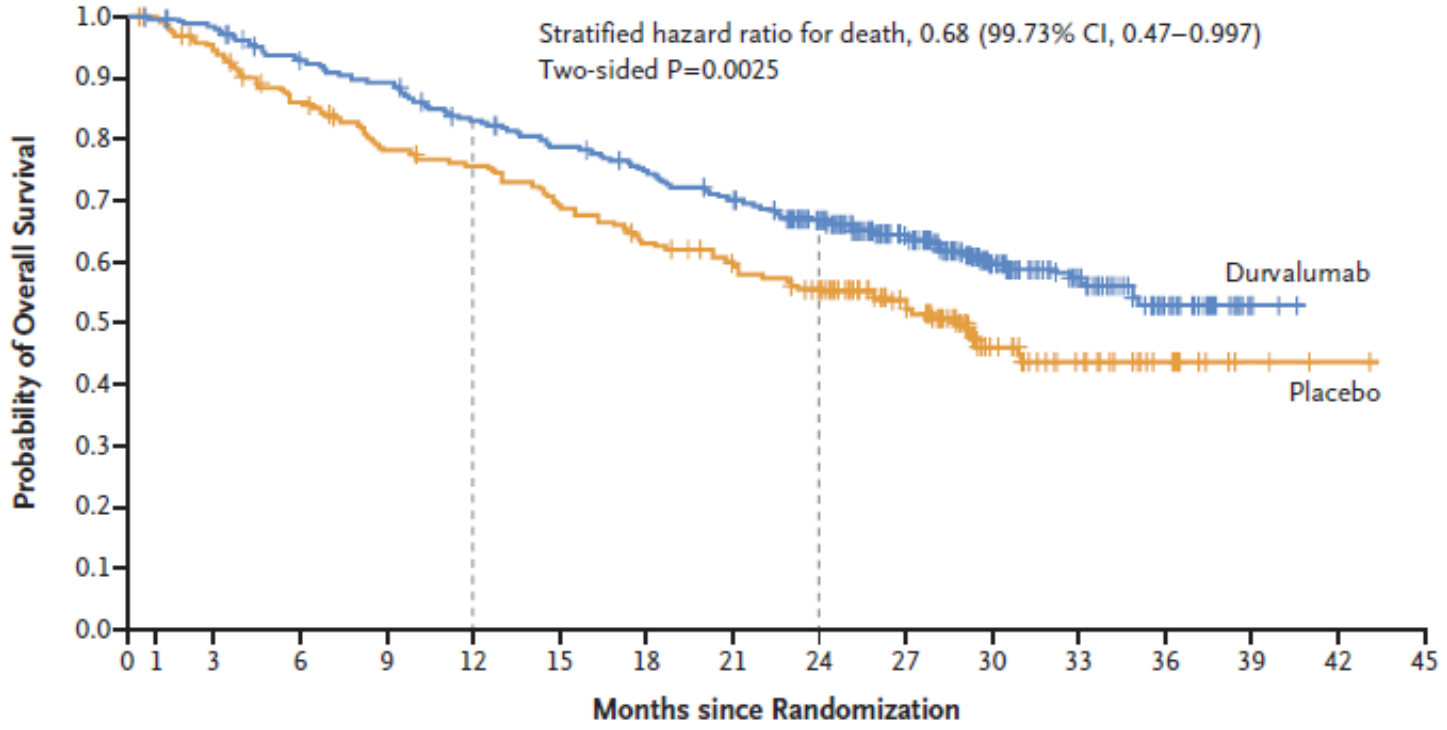
Concurrent chemoXRT + IO

Stage IV: contralateral lungs, pleural effusion, distant mets

Systemic therapy

NSCLC: Pacific study

	No. of Events/ Total No. of Patients	Median Overall Survival (95% CI)	12-Mo Overall Survival Rate (95% CI)	24-Mo Overall Survival Rate (95% CI)
		mo	%	%
Durvalumab	183/476	NR (34.7–NR)	83.1 (79.4–86.2)	66.3 (61.7–70.4)
Placebo	116/237	28.7 (22.9–NR)	75.3 (69.2–80.4)	55.6 (48.9–61.8)



No. at Risk															
Durvalumab	476	464	431	415	385	364	343	319	274	210	115	57	23	2	0	0
Placebo	237	220	198	178	170	155	141	130	117	78	42	21	9	3	1	0

Figure 2. Overall Survival in the Intention-to-Treat Population.

Stage IV NSCLC and Therapy

I. Cytotoxic chemotherapy

- Platinum, taxanes, gemcitabine, pemetrexate, vinorelbine

II. Biological therapy

- Bevecizumab, ramuciruamb
- Necitumumab

III. Targeted therapy

- EGFR
- ALK-fusion
- ROS 1
- HER2
- BRAF

IV. Immunotherapy

"Cytotoxic" Chemotherapy for Stage IV NSCLC

n=1725

Stage IV NSCLC

Record histology

R

Cisplatin 75 mg/m^2 Day 1 plus Pemetrexed 500 mg/m^2 Day 1

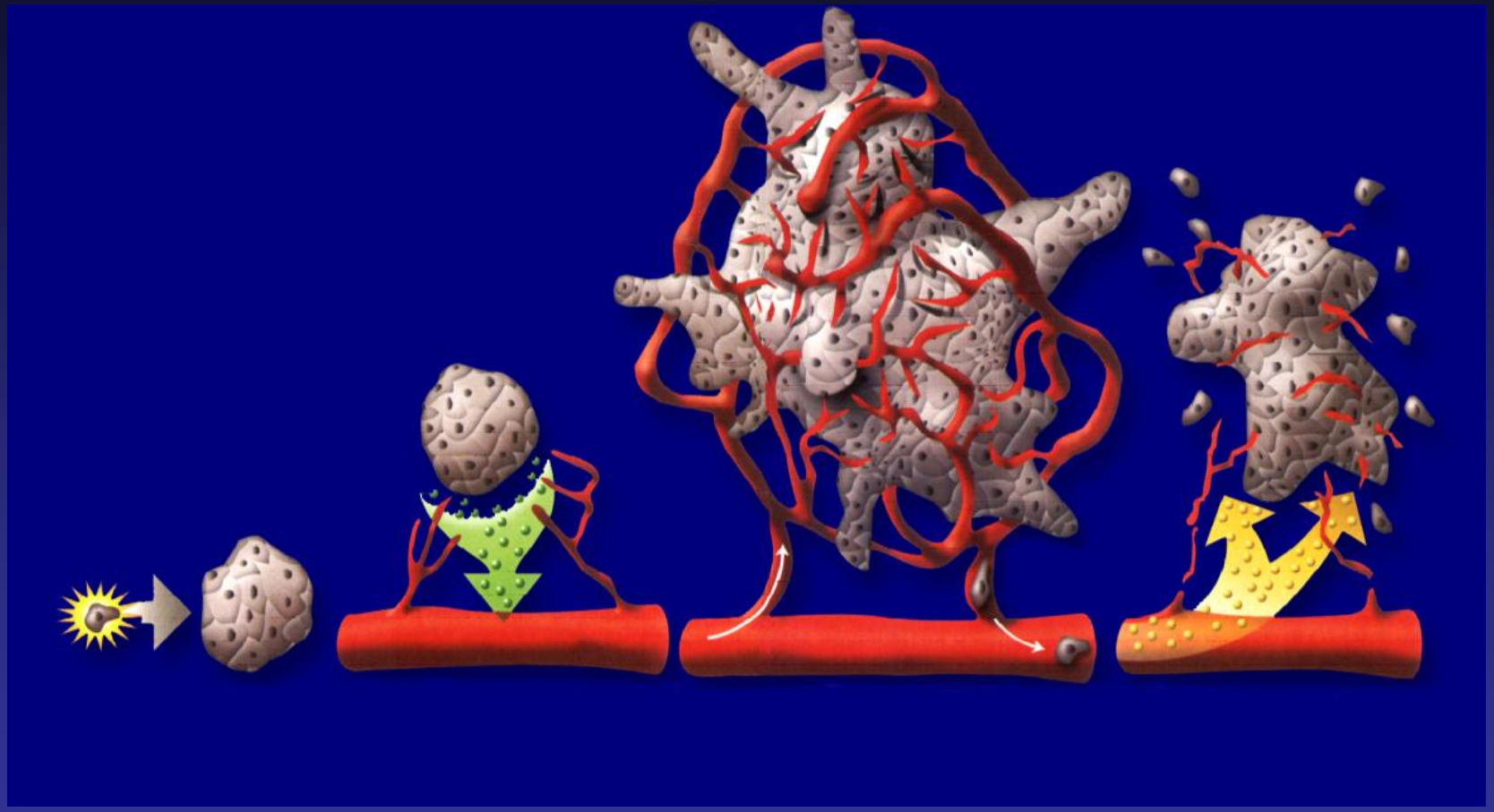
One cycle = 3 weeks, **stop at 6 cycles**

Cisplatin 75 mg/m^2 Day 1 plus Gemcitabine 1,250 mg/m^2 Days 1, 8

Results	Pem/Cis	Gem/Cis	HR
No. patients	862	863	
Median survival (mos)	10.3	10.3	0.94
Adenocarcinoma (847)	12.6	10.9	
Large cell (153)	10.4	6.7	
SqCC (473)	9.4	10.8	1.23

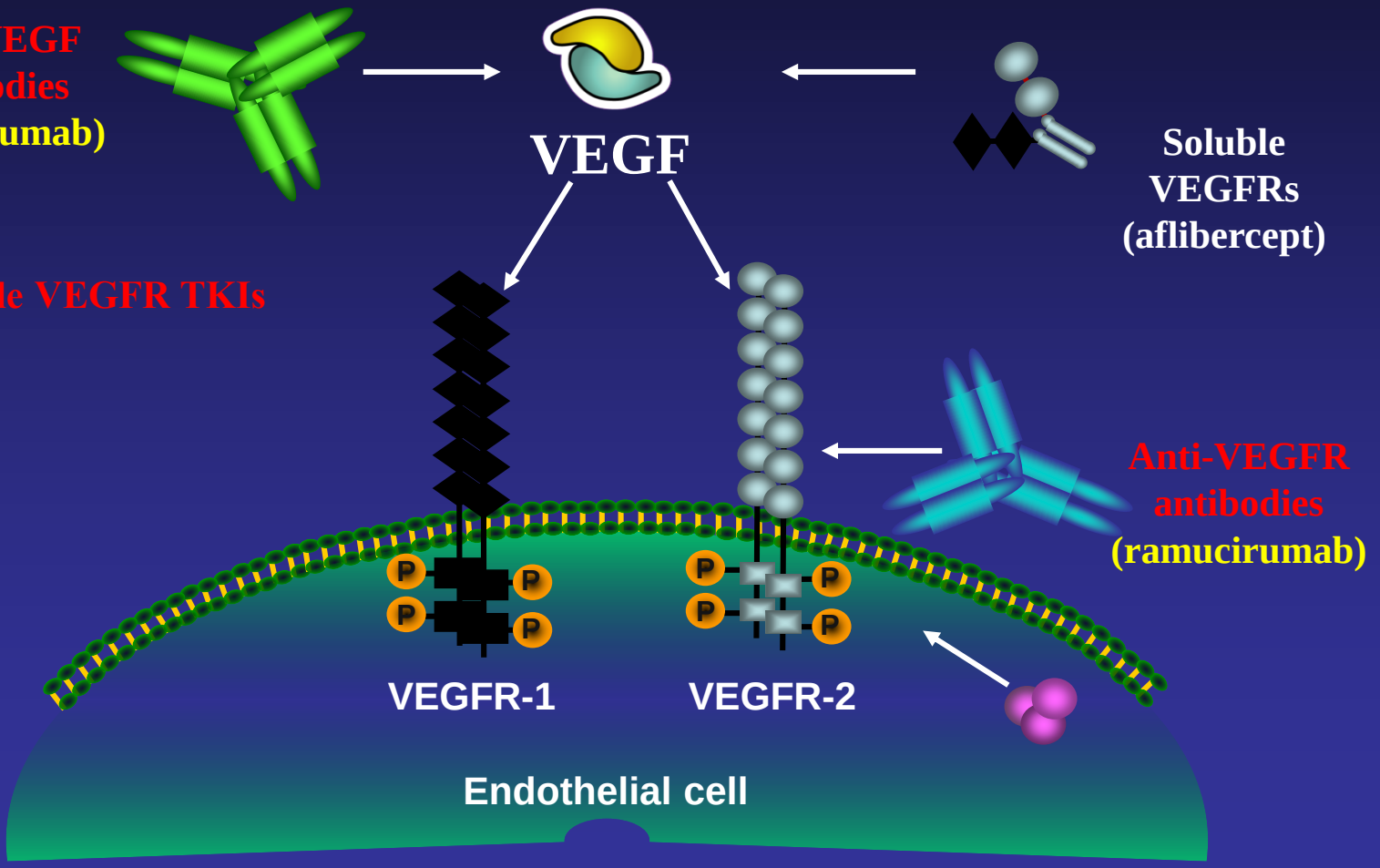
Scagliotti et al, 2008.

Anti-Angiogenesis



Judah Folkman NEJM: 285: 1182-1186, 1971

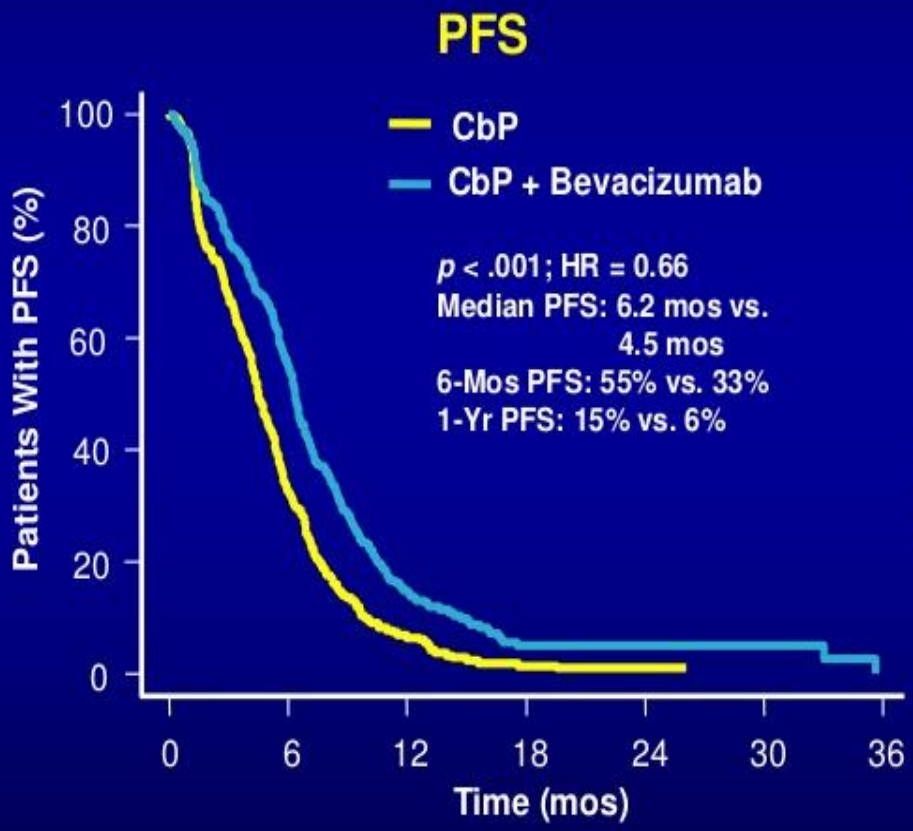
Agents Targeting the VEGF Pathway

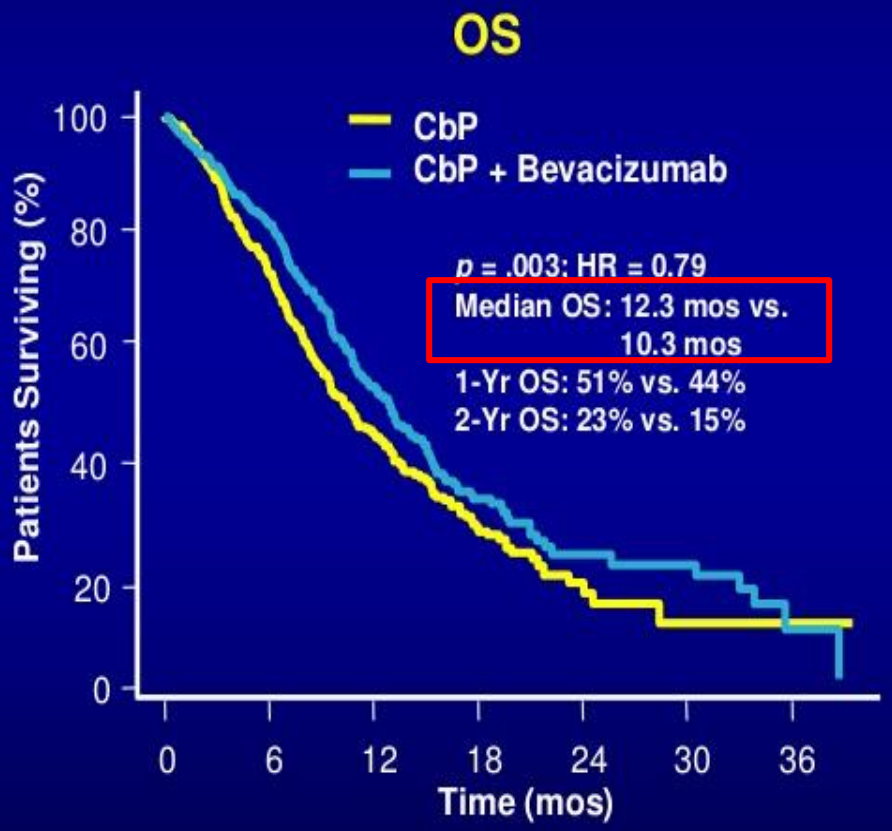


Podar K, et al. Blood. 2005:105:1383-1395. Gori B, et al. Ther Clin Risk Manag. 2011;7:429-440.

Target Angiogenesis: Bevacizumab

SQUAMOUS HISTOLOGY EXCLUDED
(for squamous histology, rate of hemoptysis 30% in phase 2 testing





RR: 15% for CbP Vs. 35% for CbP + Bevacizumab

Sandler et al, NEJM 2006.

Anti-Angiogenesis Side Effects

Hypertension

Arterial or venous thrombotic events

Gastrointestinal perforation (fistula)

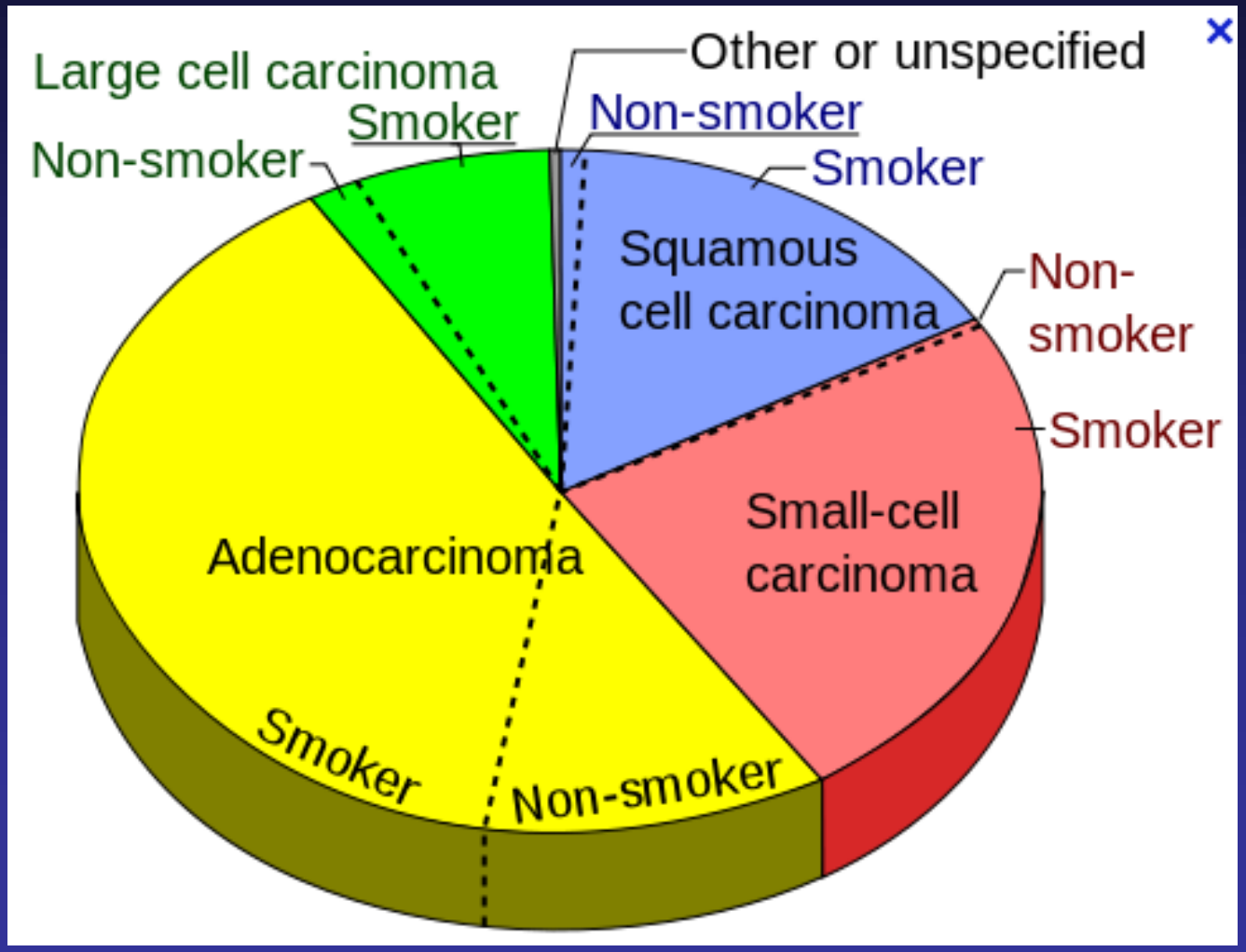
Bleeding

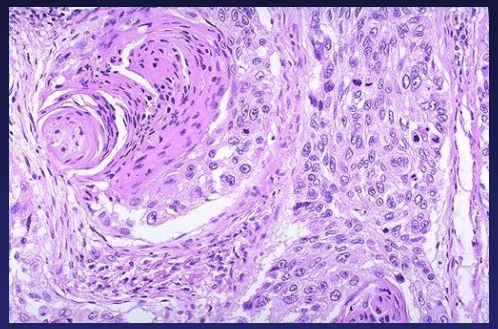
Delayed wound healing

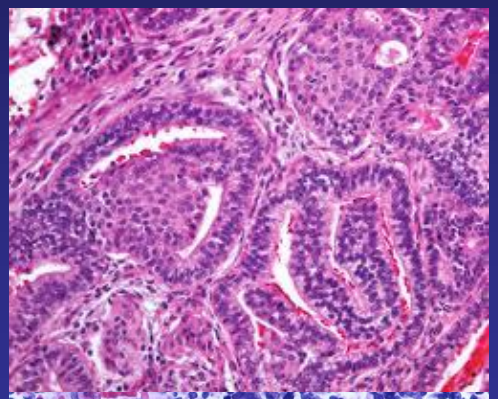
Proteinuria (nephrotic syndrome)

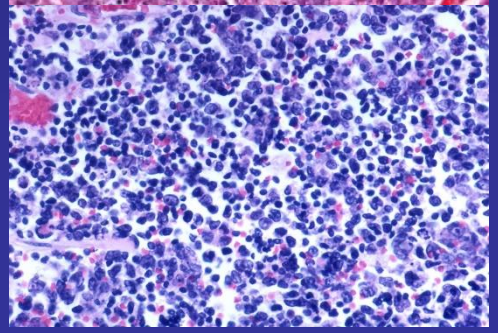
RPLE (reverse posterior leukoencephalopathy)

Lung Cancer:
Small Cell vs Non-Small Cell



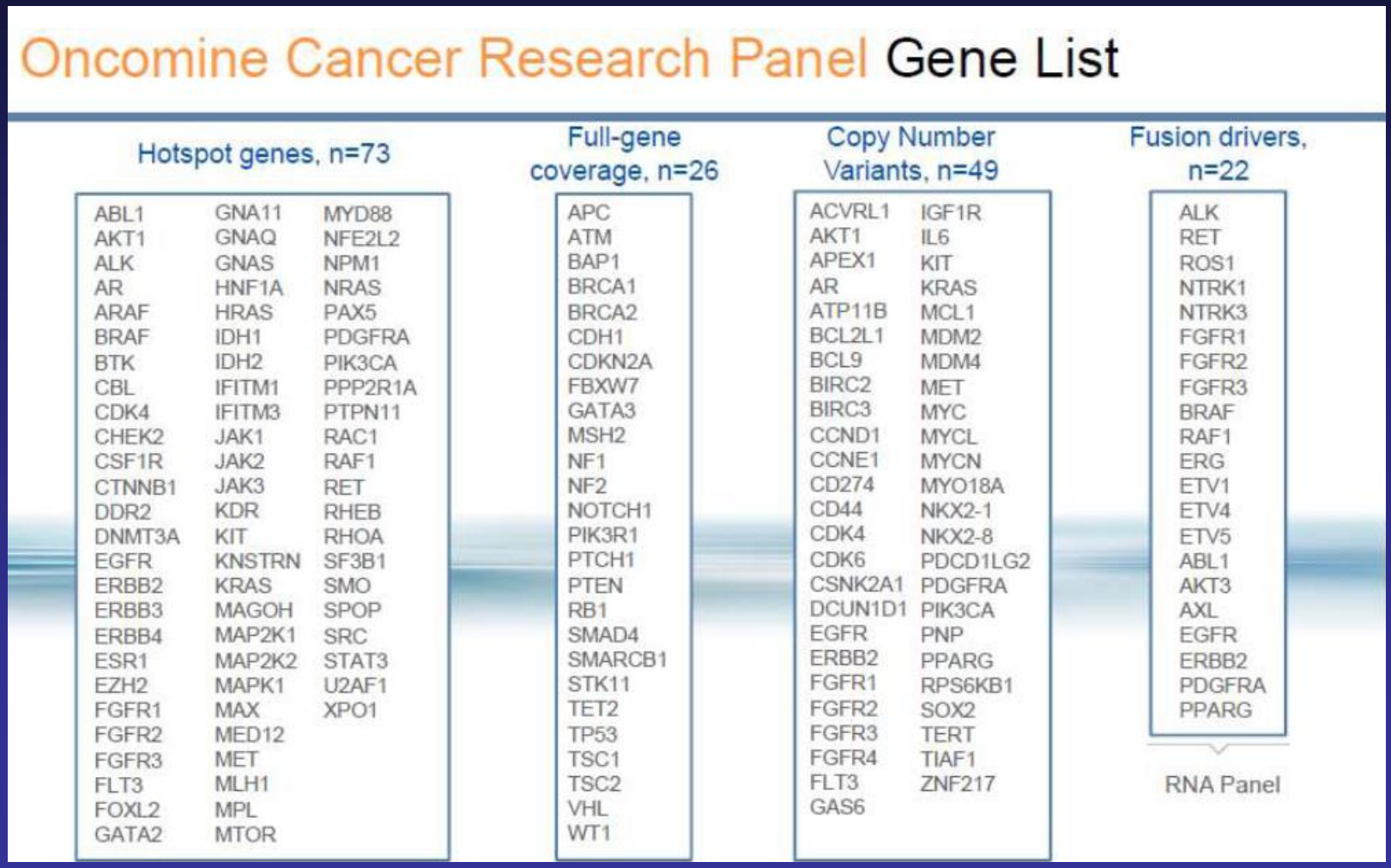






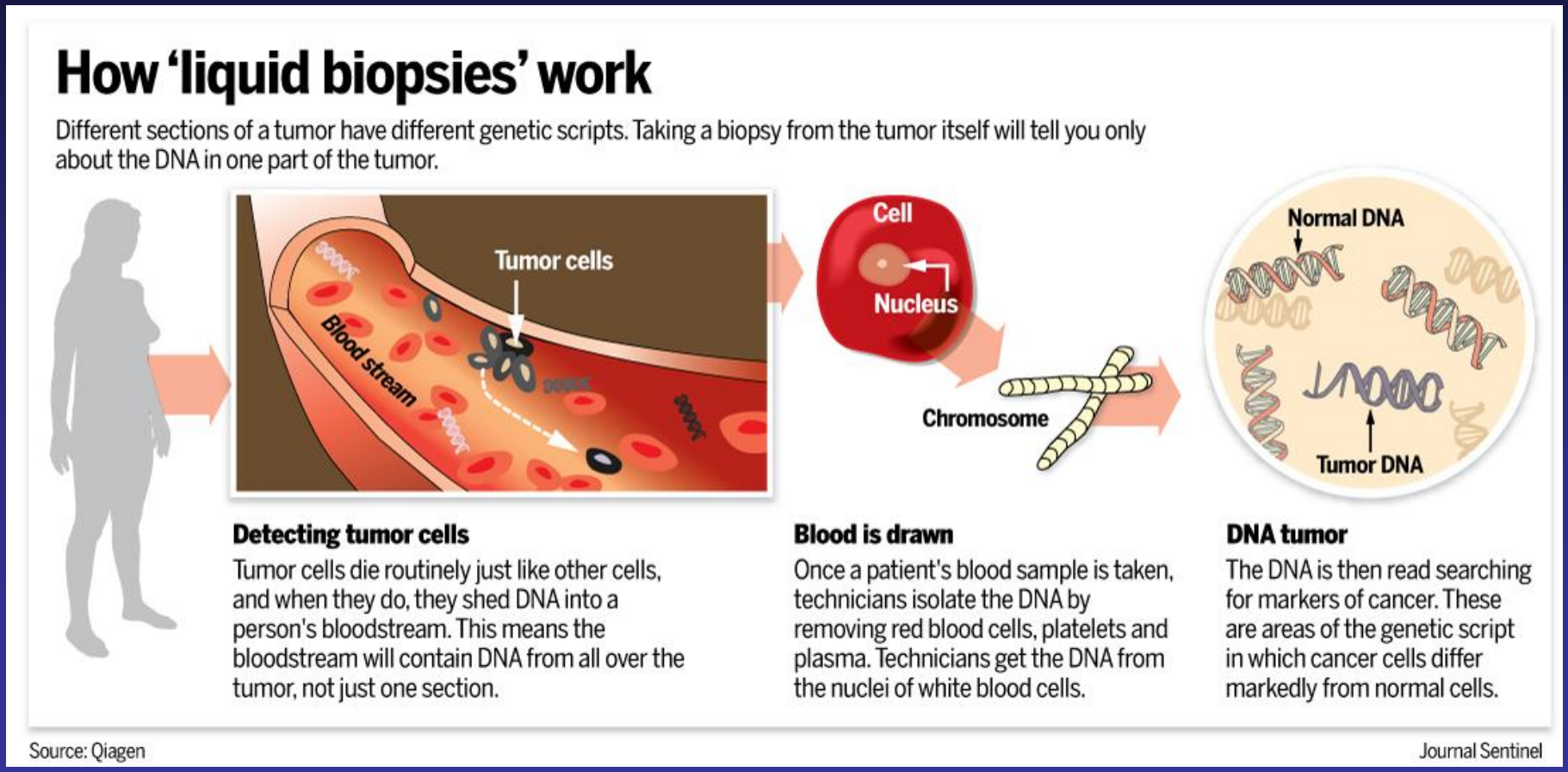
Lung Cancer: Non-Small Cell

NGS for Mutational Analysis using FFPE

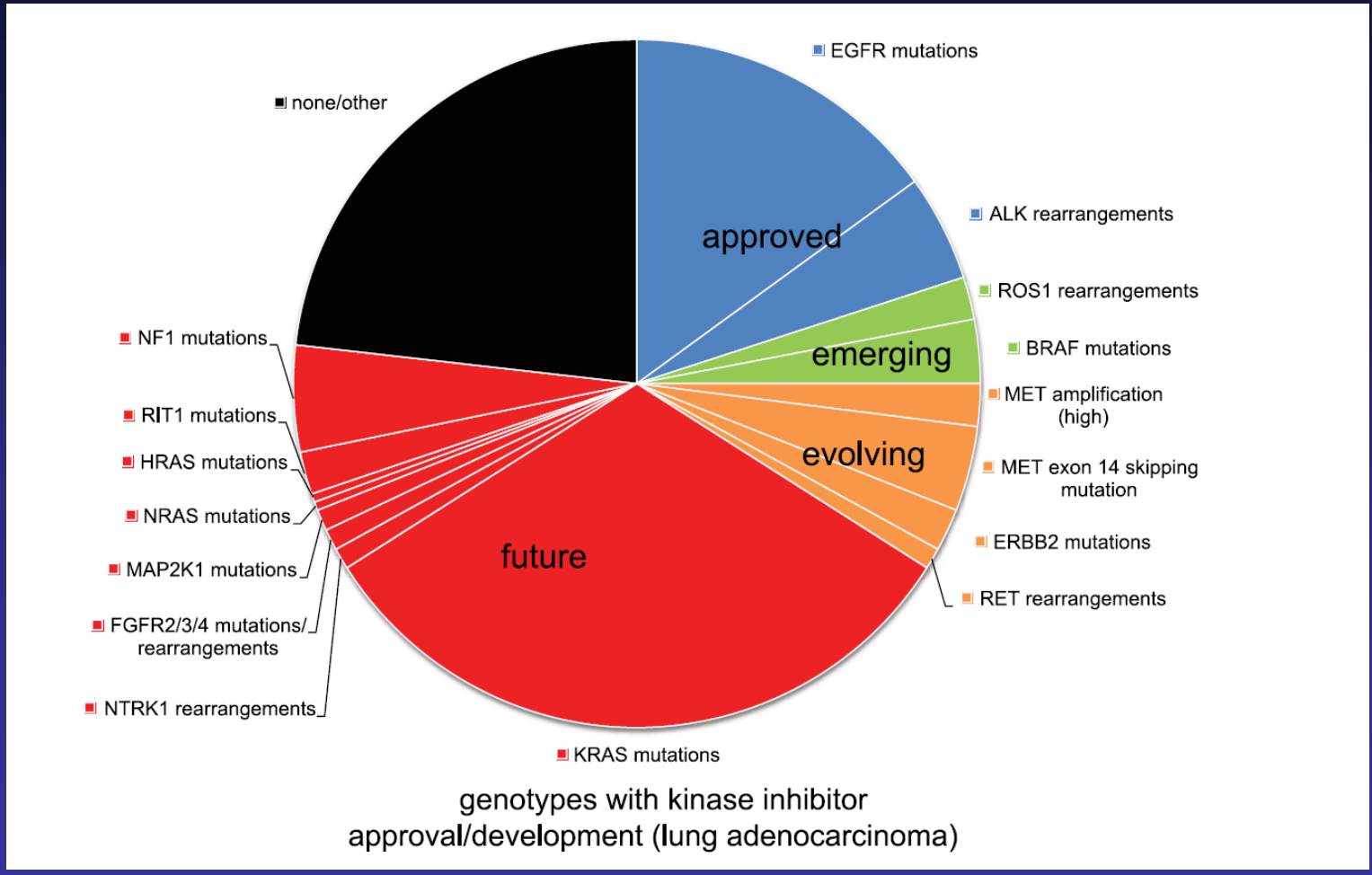


Liquid Biopsy

A broad term to describe blood-based testing for genetic mutations

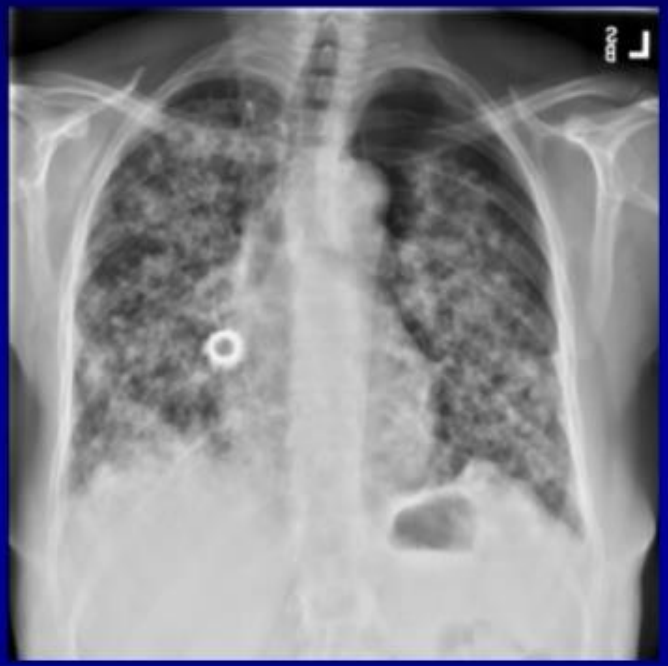


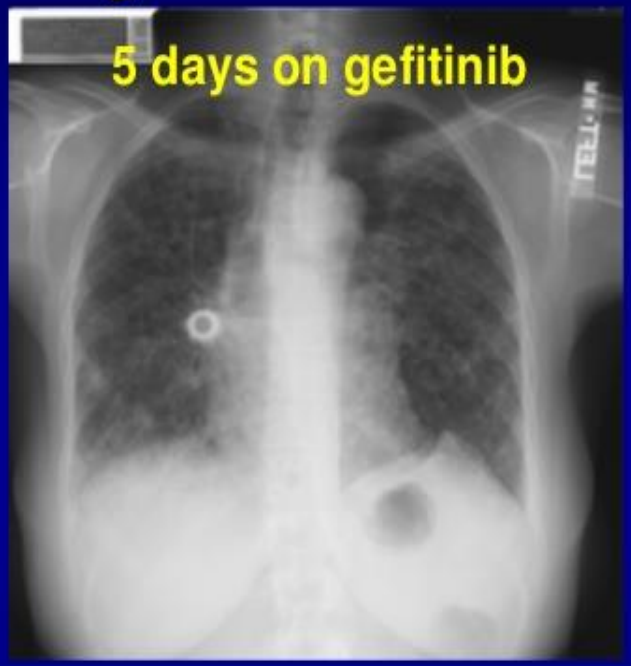
Molecular Subsets of Lung Cancer Defined by Driver Mutation

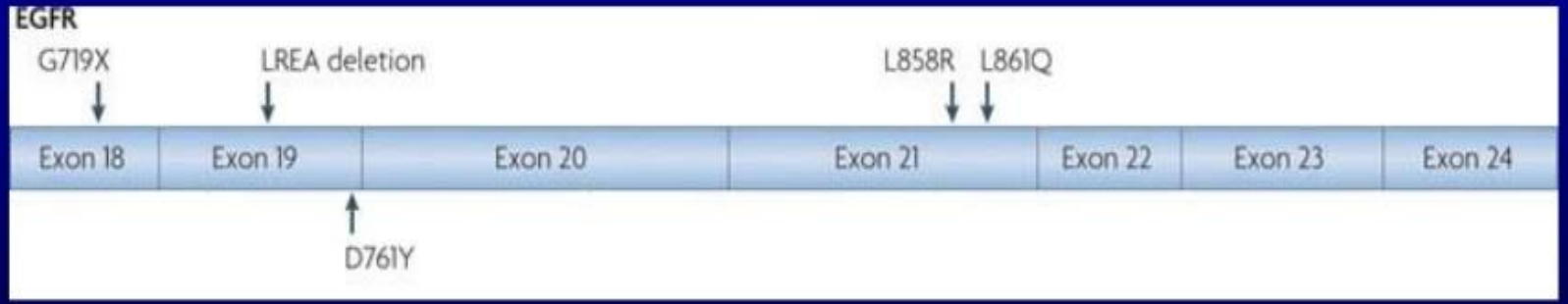


Ther Adv Respir Dis
2016, Vol. 10(2) 113–129

The Biggest Discovery: *EGFR* Activating Mutations

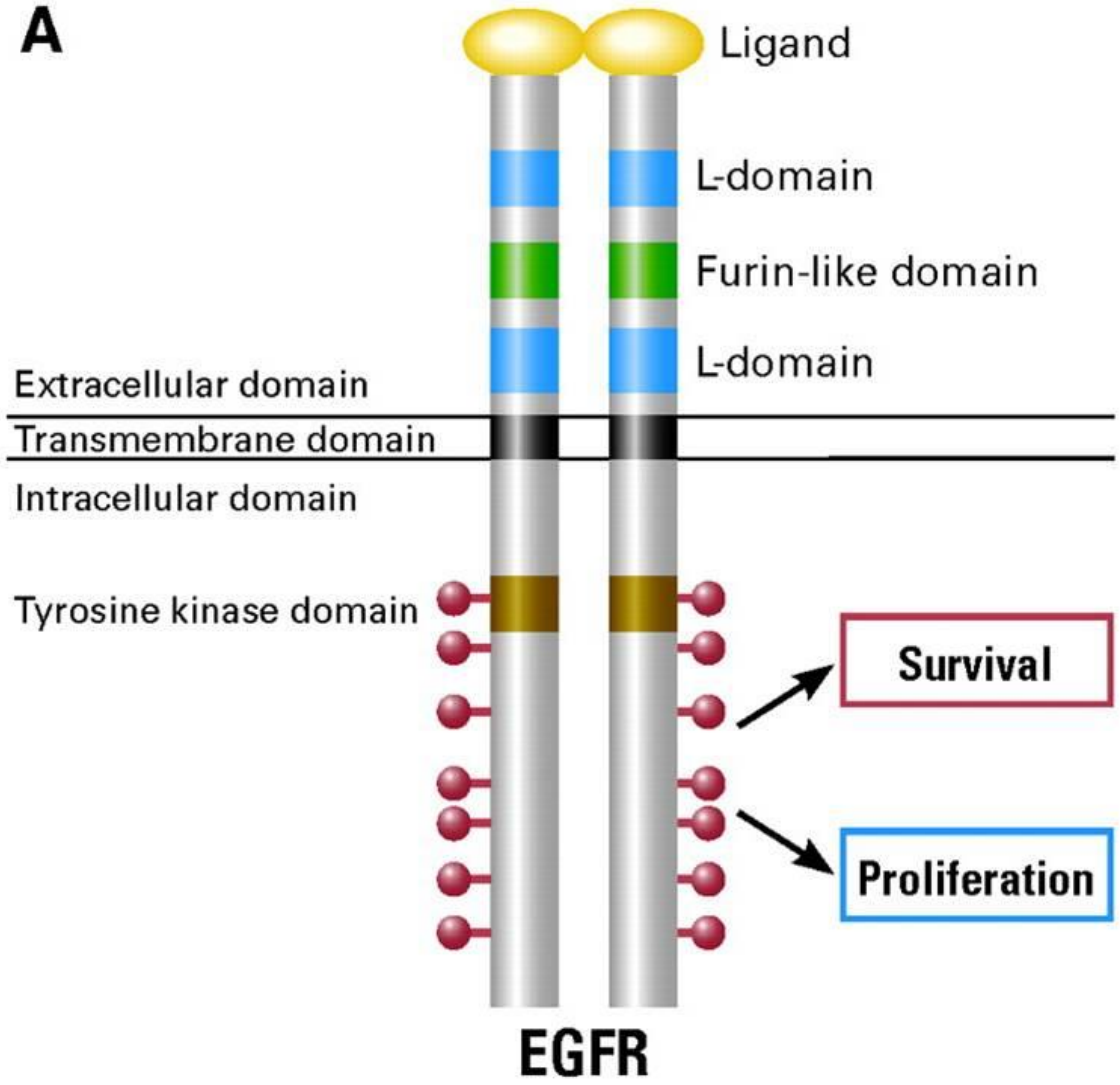


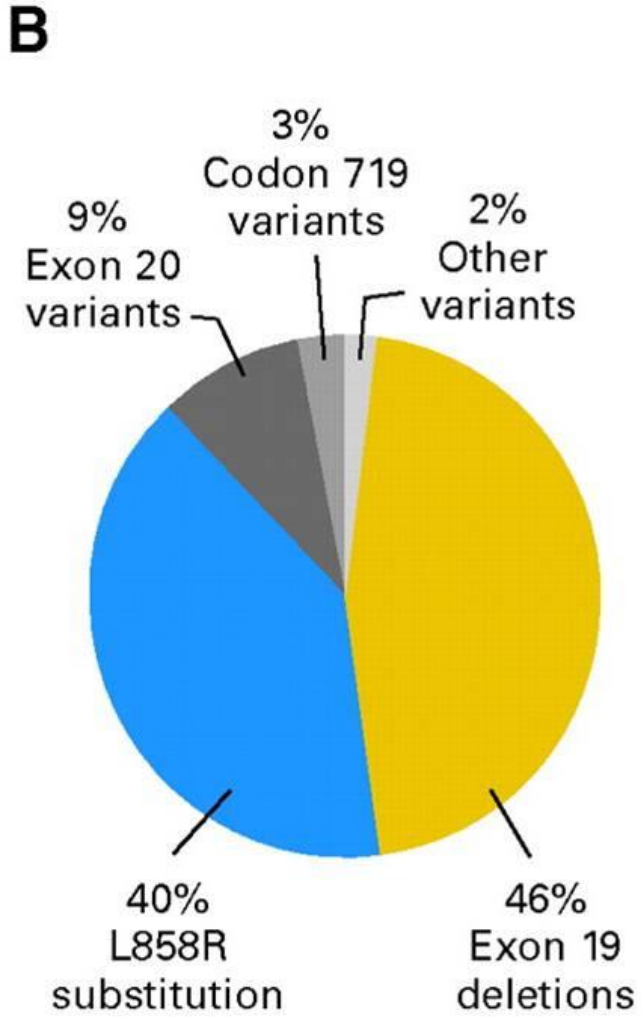




Pao, Nature Reviews Cancer **10**, 760-774

Anti-EGFR Therapy





Anti-EGFR Therapy

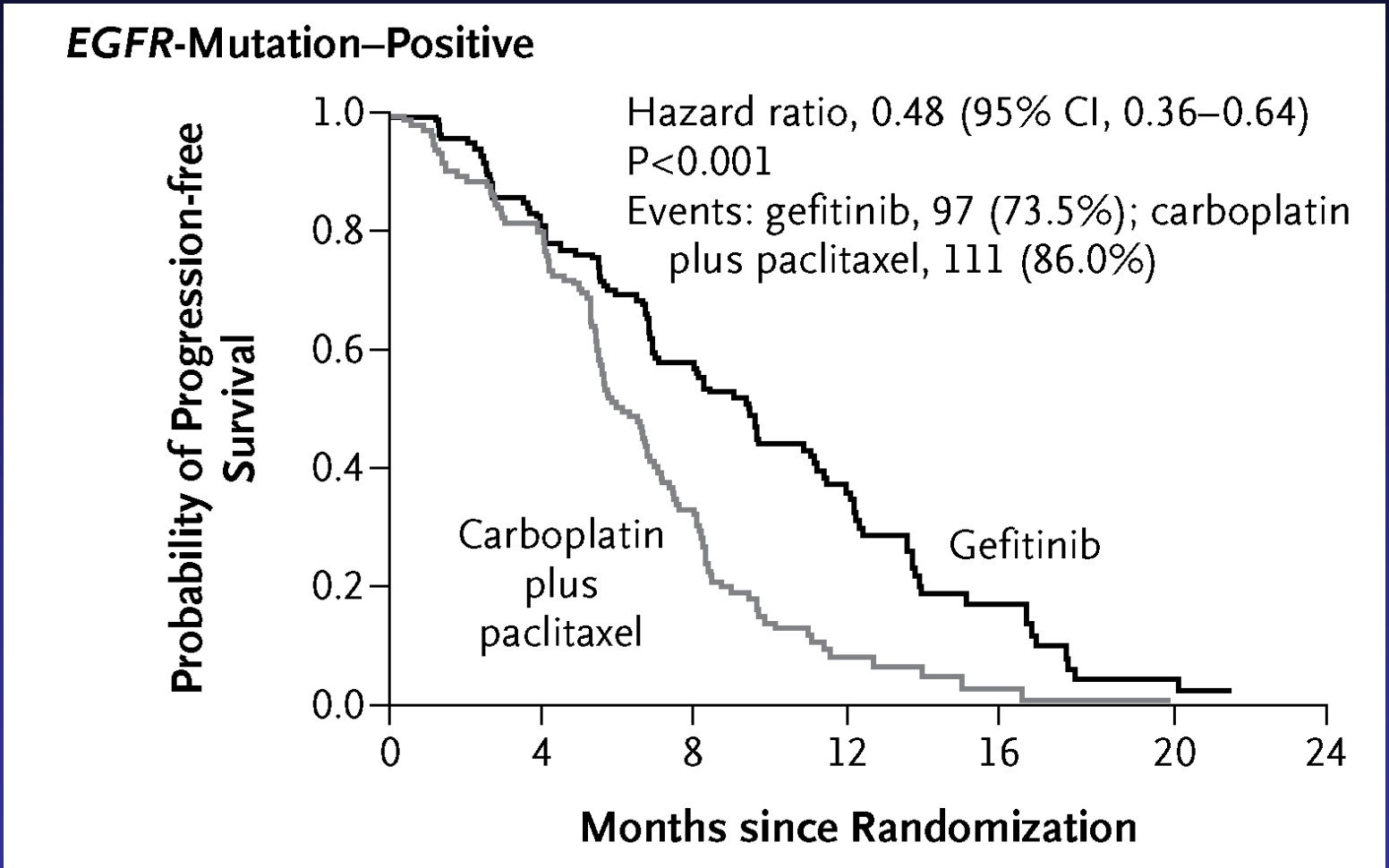
1st-Generation TKI:

Gifitinib (Iressa)
Erlotinib (Tarceva)

2nd-Generation TKI

Afatinib (Gilotrif)
Dacomitinib

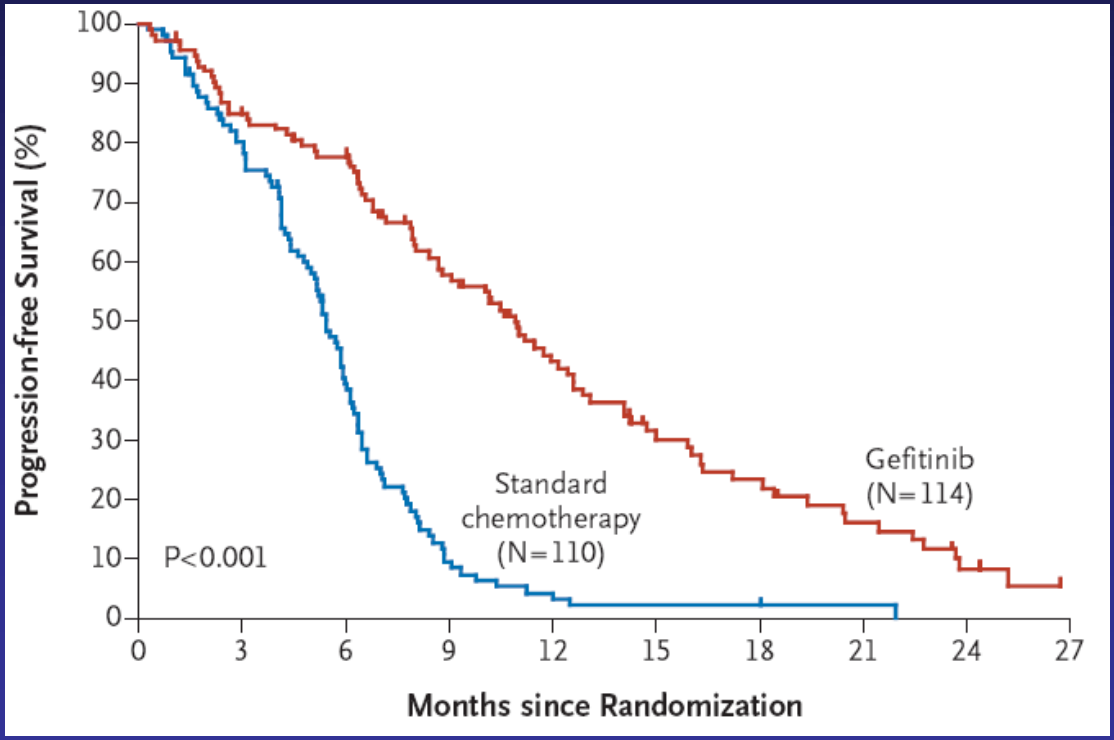
In patients with EGFR mutant NSCLC, EGFR TKI are better than platinum-doublet chemotherapy



Mok TS, et al. *N Engl J Med*. 2009;361(10):947-957.

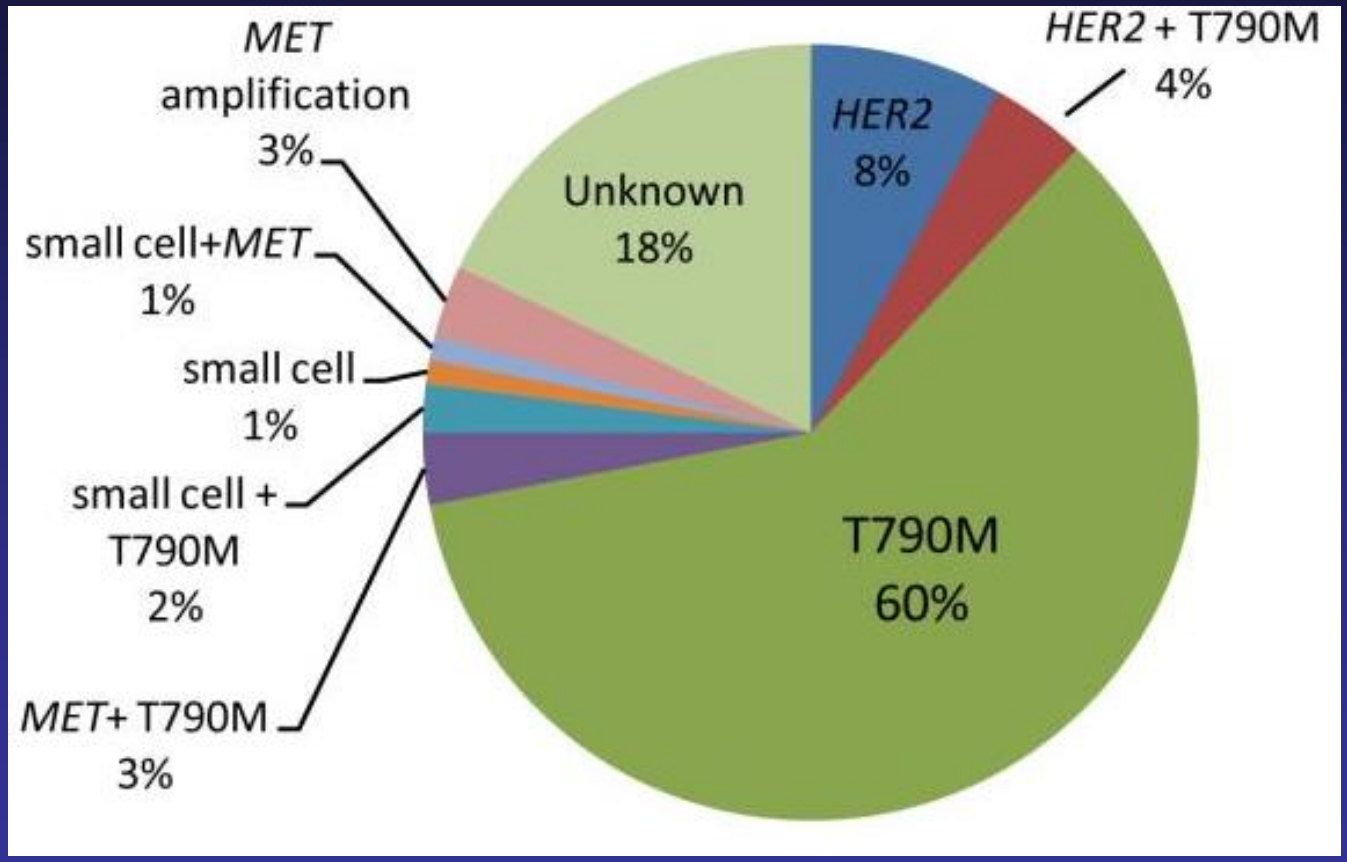
All patients will develop acquired resistance to EGFR TKI

Median 10.8 vs 5.4 months, HR 0.30, P



Maemondo, NEJM 2010

Mechanisms of Acquired Resistance to 1st/2nd Generation EGFR TKIs



Yu et al, CCR 2013

Anti-EGFR Therapy

1st-Line therapy:

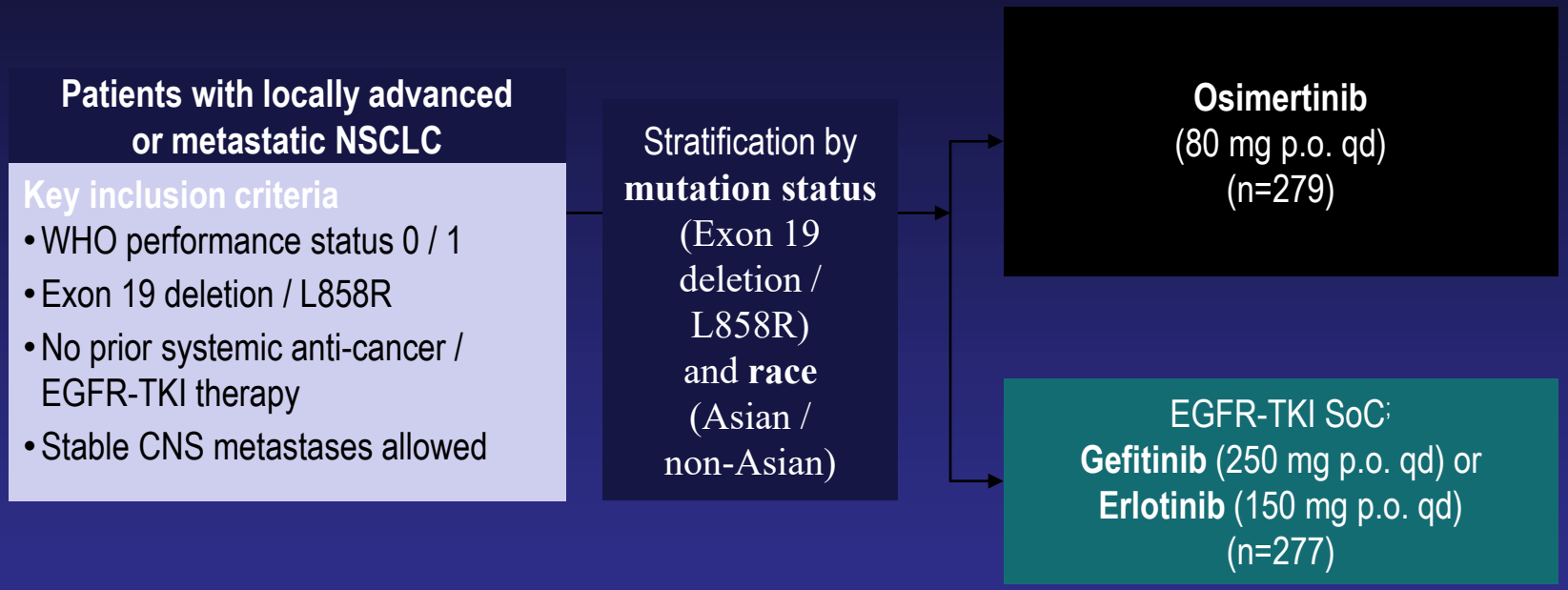
Gifitinib (Iressa)
Erlotinib (Tarceva)

Afatinib (Gilotrif)
Dacomitinib

2nd-Line therapy: to target T790M mutation

Osimertinib (Tagrisso)

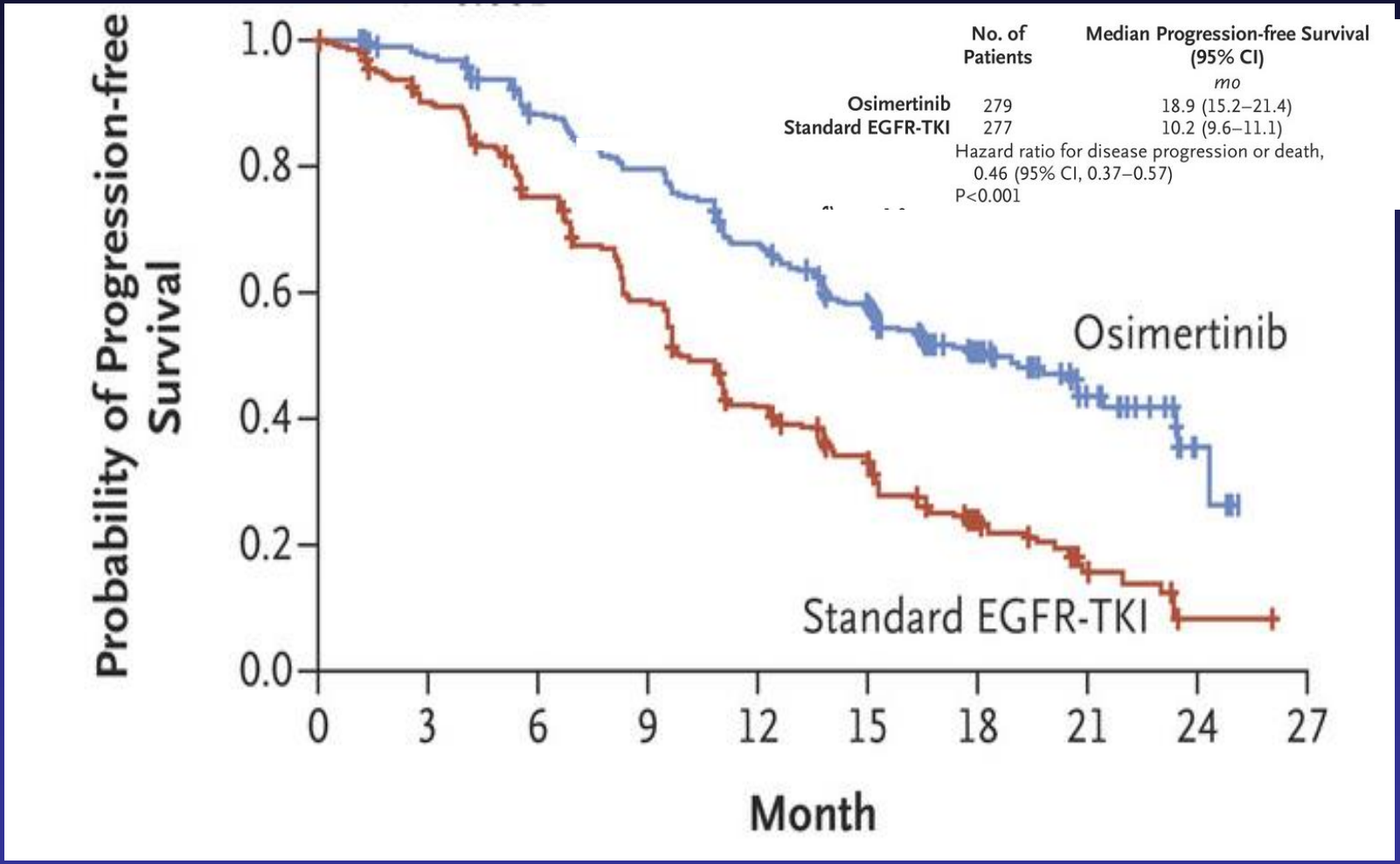
Osimertinib vs Gefitinib/Erlotinib Randomized Trial (FLAURA)



- **Primary endpoint:** PFS
- **Secondary endpoints:** response rate, duration of response, disease control rate, depth of response, overall survival, patient reported outcomes, safety

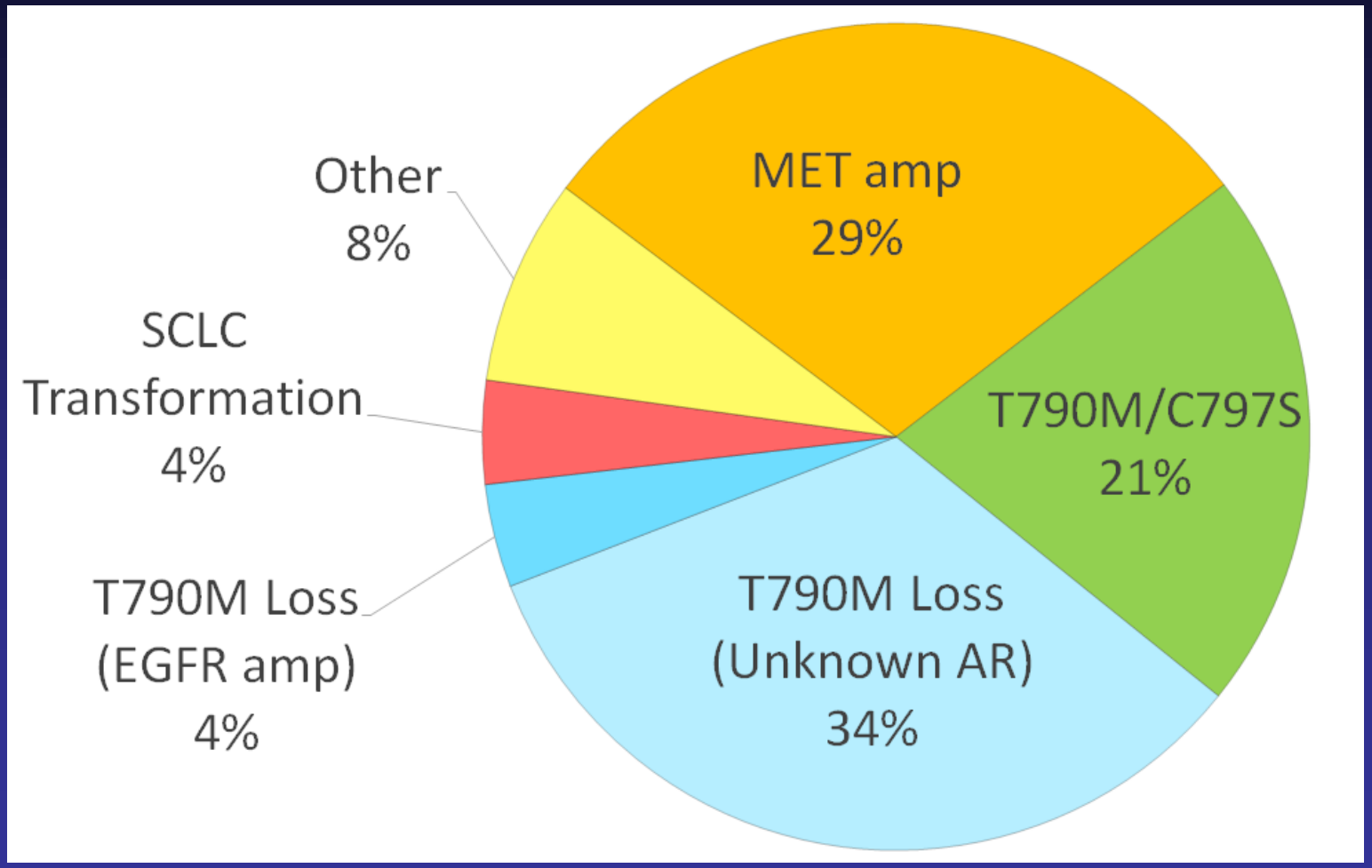
Soria et al, NEJM 2018

Osimertinib vs Gefitinib/Erlotinib Progression-Free Survival



Soria, NEJM 2018

Acquired Resistance to Osimertinib



Piotrowska, et al ASCO 2017

Targeted Therapy

EGFR
ALK rearrangement (Crizotinib, Brigatinib, Ceritinib, Alectinib, Lorlatinib)
ROS 1 rearrangement (Crizotinib, Ceritinib, Cabozantinib, Entrectinib)
HER2 (TDM1, Afatinib)
RET rearrangement (Cabozantinib, Vendetanib, Alectinib)
BRAF (Vemurafenib + combinmetinib or Debrafenib + trametinib)
C-MET (Crizotinib, Cabozantinib)
NTRK (Larotrectinib, Entrectinib)

Cancer Immmunotherapy

1. **Monoclonal antibody therapy (Passive, i.e. Bevacizumab)**

2. **Vaccination (NSCLC: MAGE A3, MUC-1, EGFR)**

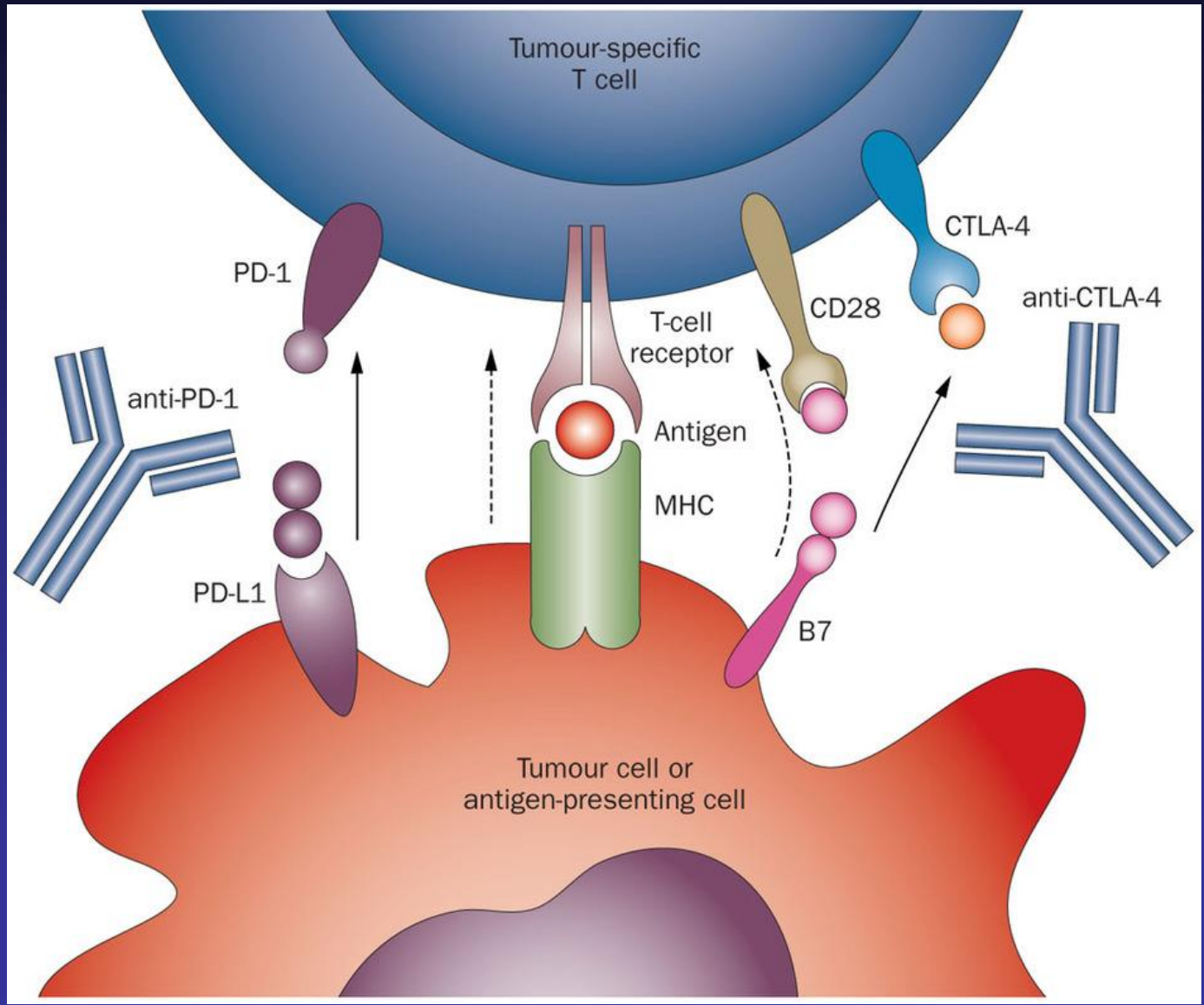
3. **Enhancement of antigen presentation (stimulation of Toll-like receptors 7, 8 or 9, dendritic cells or anti-CD40 agonistic antibody)**

4. **Cell based immunotherapy (Allogeneic SCT, CAR T-cell)**

5. **Cytokines (for example, IL-2 or interferon-α)**

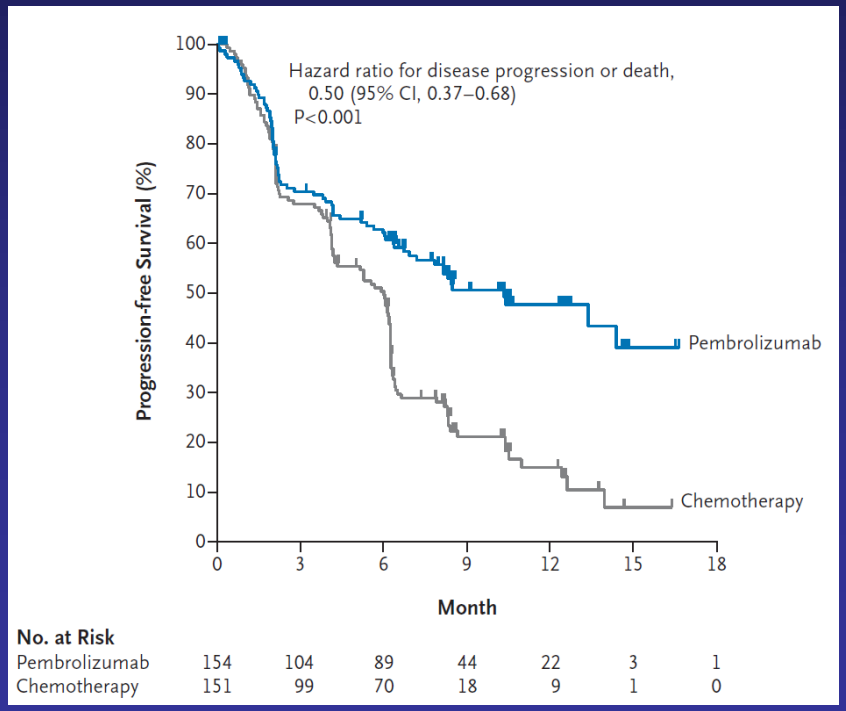
6. ***Checkpoint inhibitors (Anti-CTLA4, -PD-1, -PD-L1)***

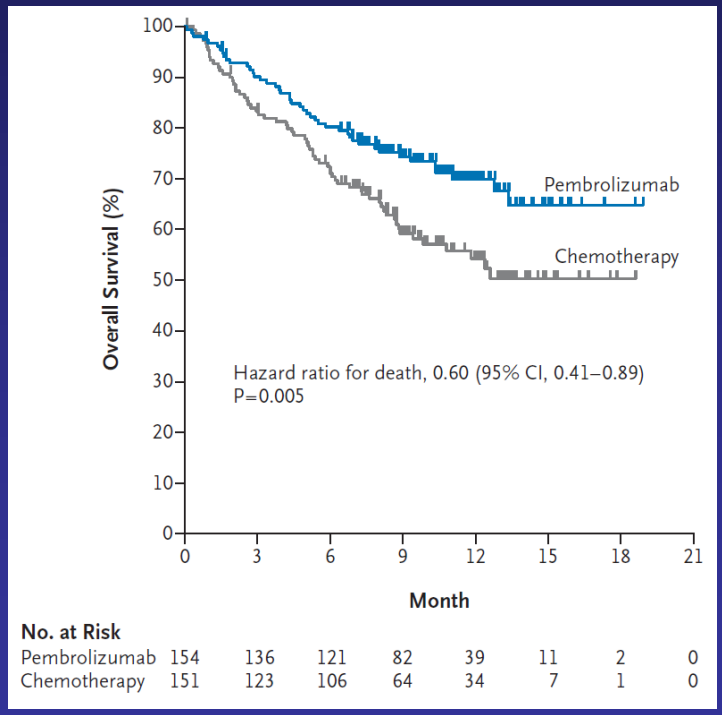
Cancer Immunotherapy



PD1 Blockade for NSCLC
1st-Line

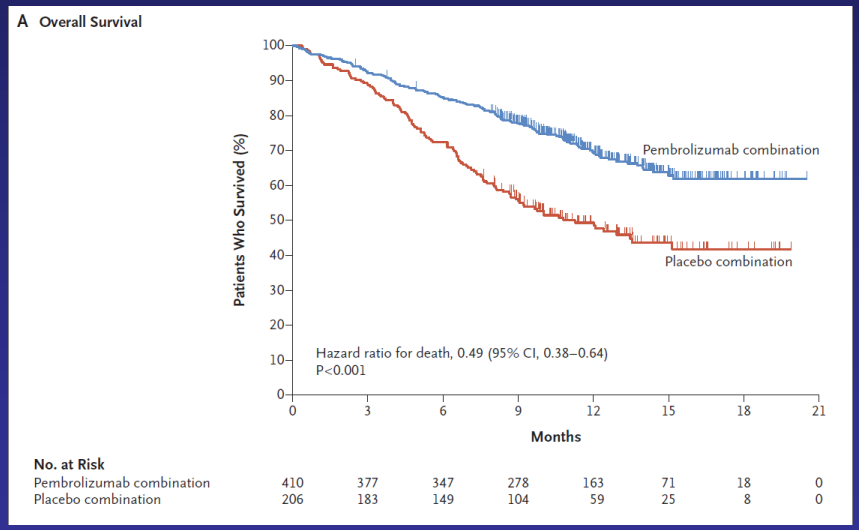
Keynote 24: Pembrolizumab for PDL1 > 50% in TCs



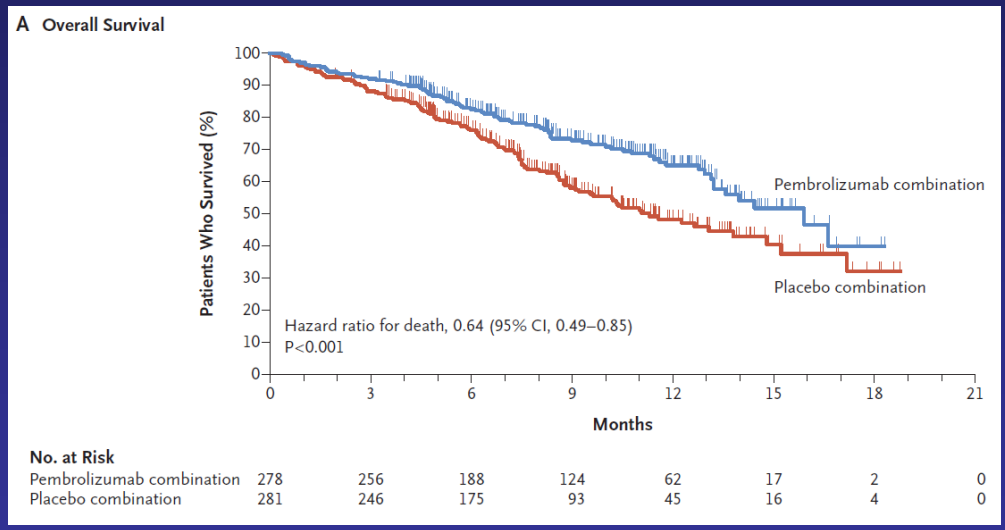


PD1 Blockade for NSCLC 1st-Line

Keynote 189

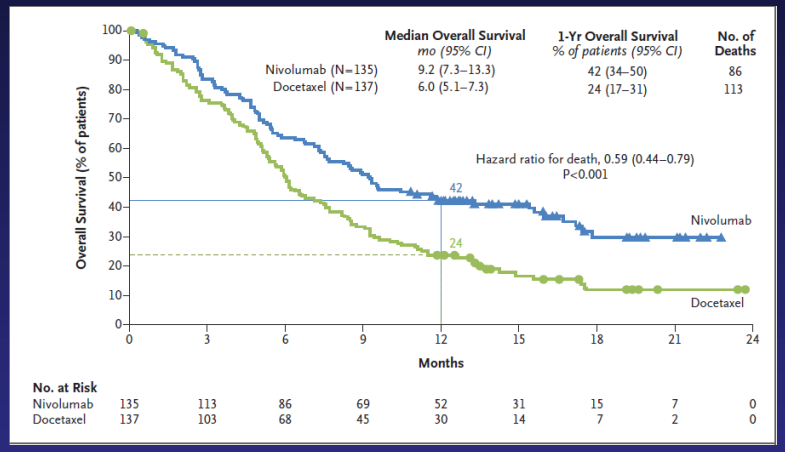


Keynote 407

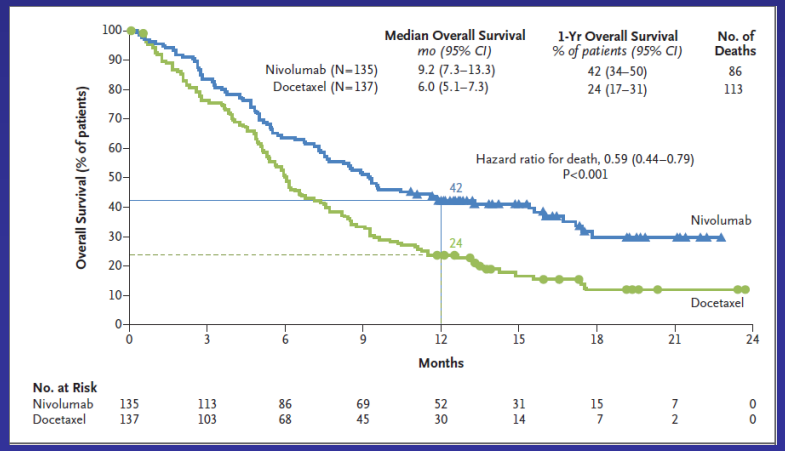


PD1/PDL1 Blockade for NSCLC 2ND -Line

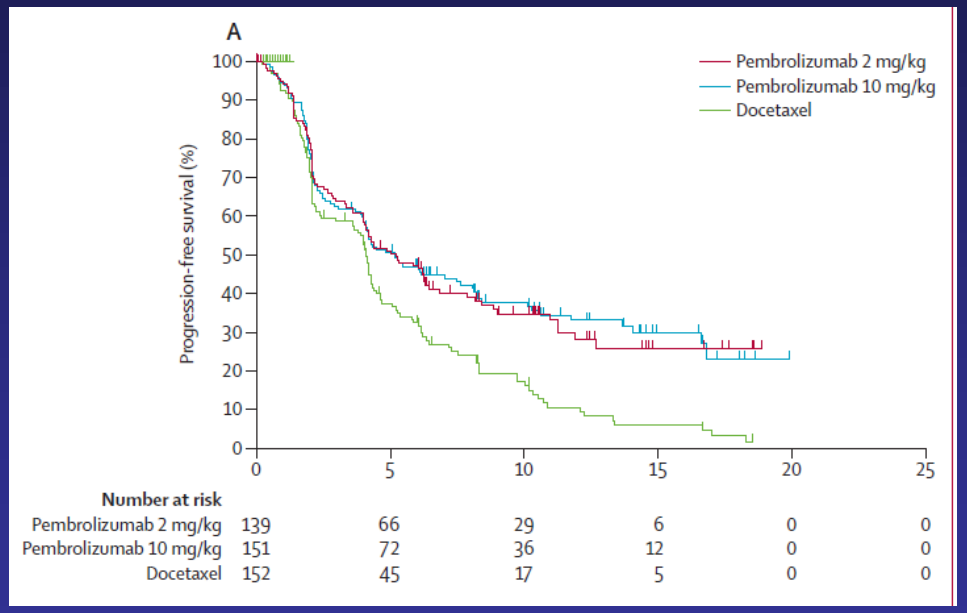
Checkmate 17 for SCC : Nivolumab



Checkmate 57 for non- SCC : Nivolumab

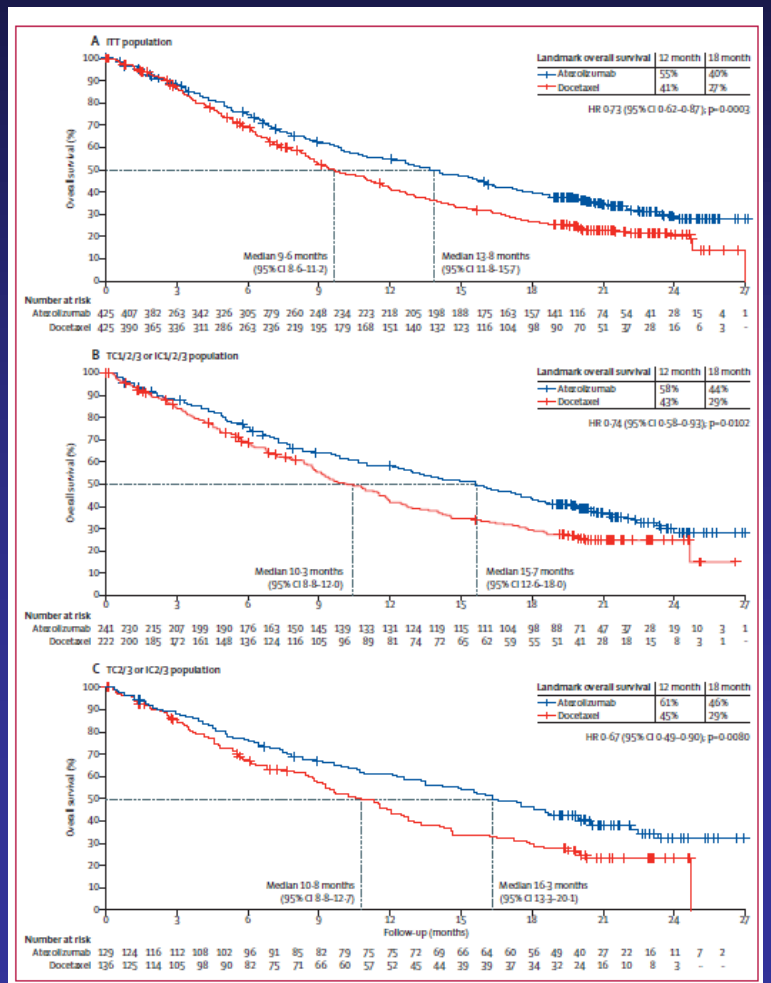


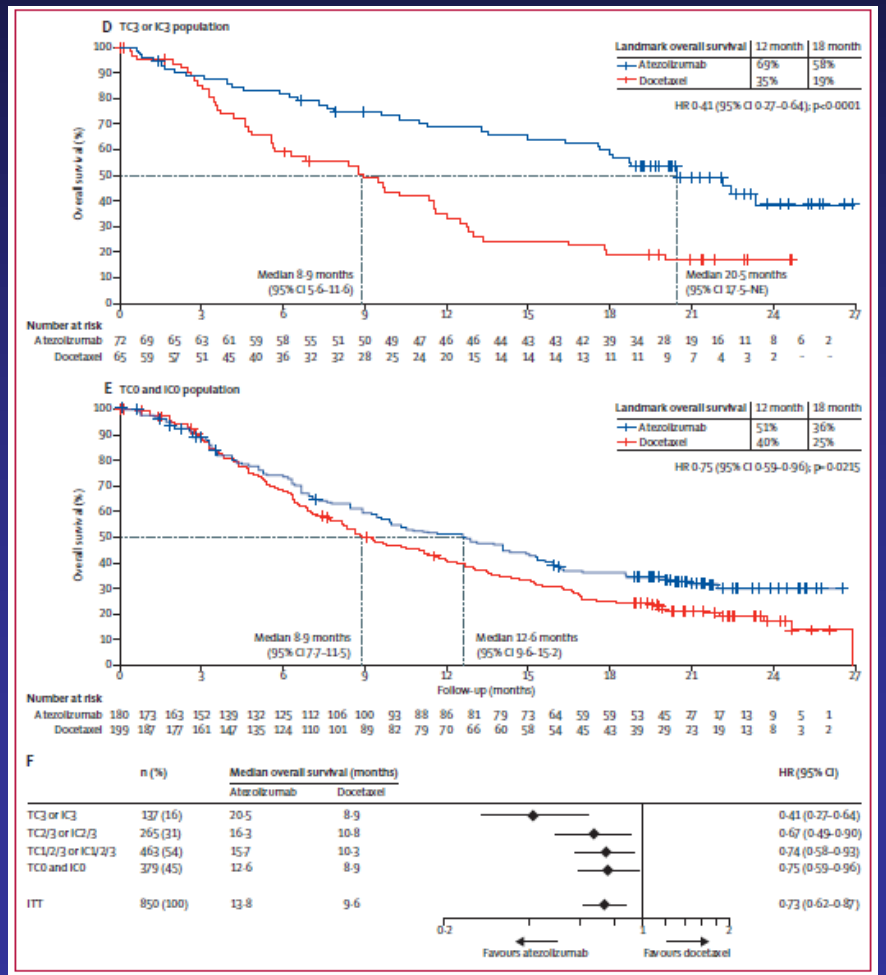
Keynote 10: Pembrolizumab



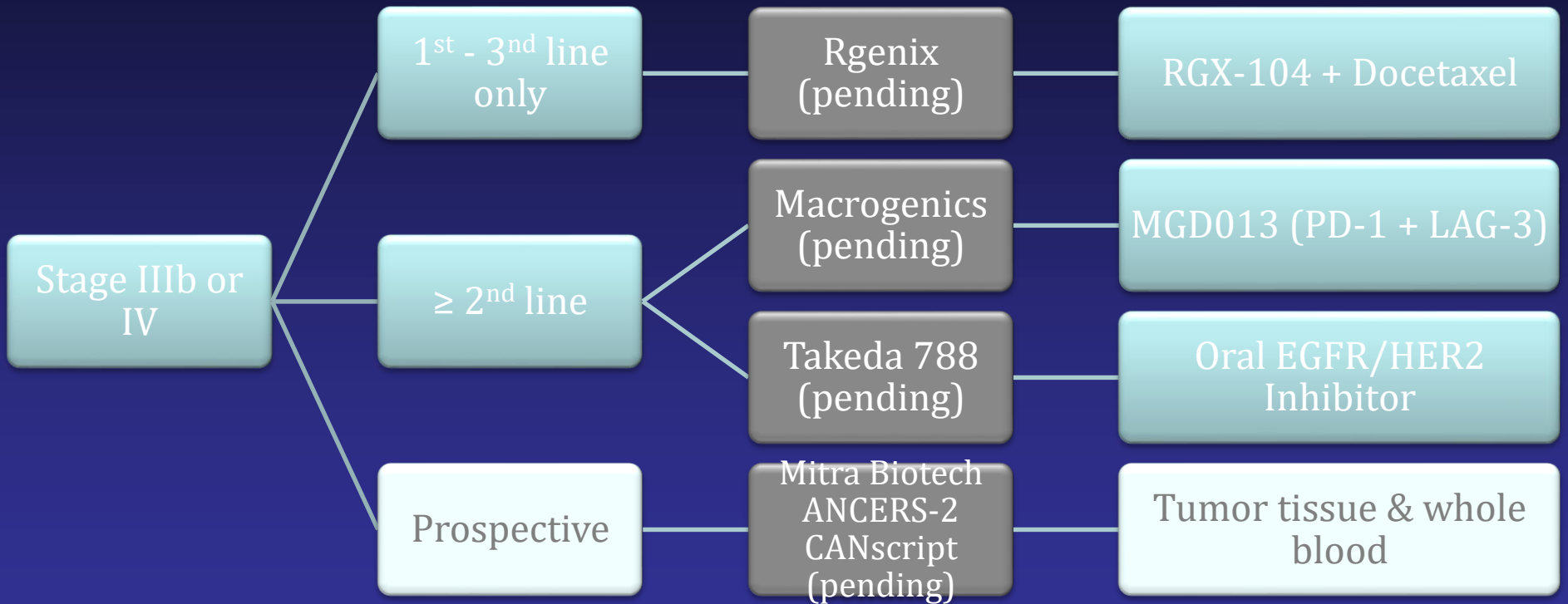
PDL1 Blockade for NSCLC
2ND -Line

OAK Trial: Atezolizumab PDL1 assessed in both TCs and ITCs



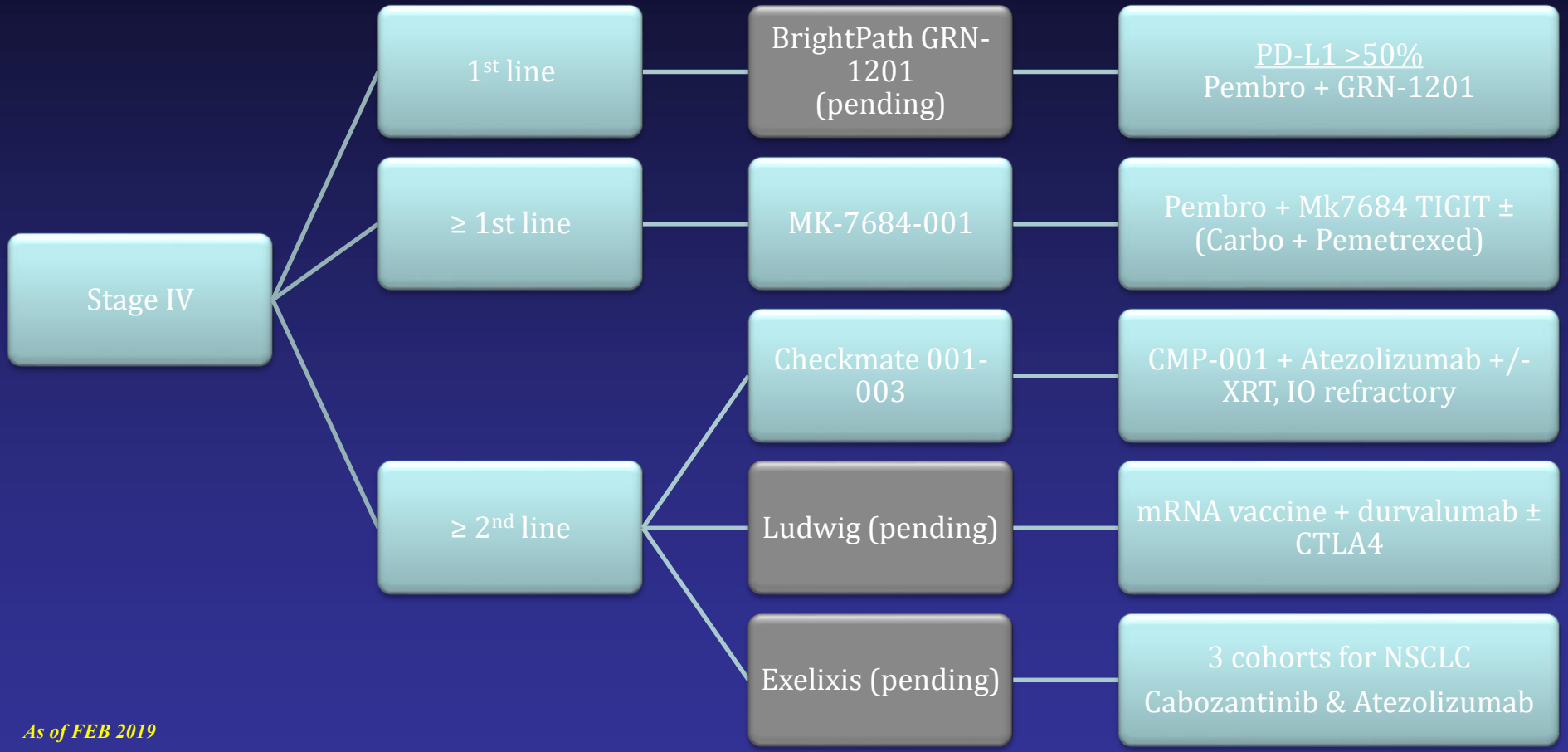


BMDACC LUNG / HEAD & NECK RESEARCH : NSCLC



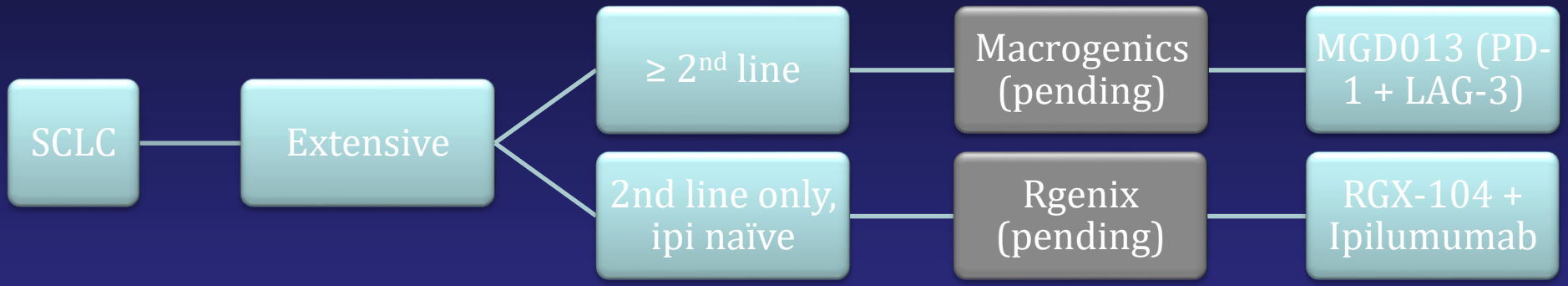
As of FEB 2019

BMDACC LUNG / HEAD & NECK RESEARCH : NSCLC



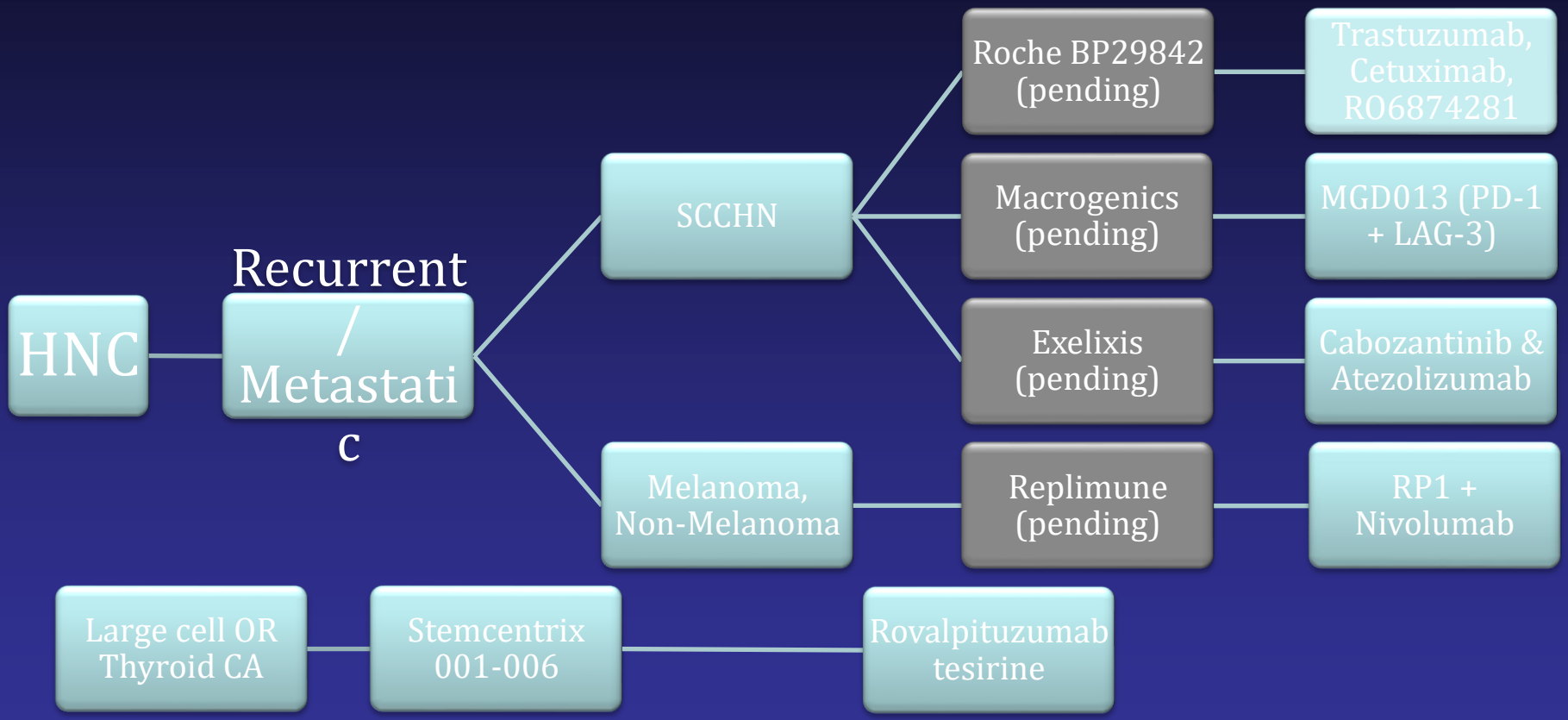
As of FEB 2019

BMDACC LUNG / HEAD & NECK RESEARCH : SCLC



As of FEB 2019

BMDACC LUNG / HEAD & NECK RESEARCH : HNC



As of FEB 2019

PD-1 Blockade: Immune-Mediated Toxicities

Occasionally(5% to 20%)

- Fatigue, headache, arthralgia, fevers, chills, lethargy
- **Diarrhea/colitis**
  - Initiate steroids early, taper slowly
- Hepatitis, liver/pancreatic enzyme abnormalities
- Rash: maculopapular, pruritus, vitiligo
  - Topical treatments
- Infusion reactions
- Endocrinopathies: thyroid, adrenal, hypophysitis

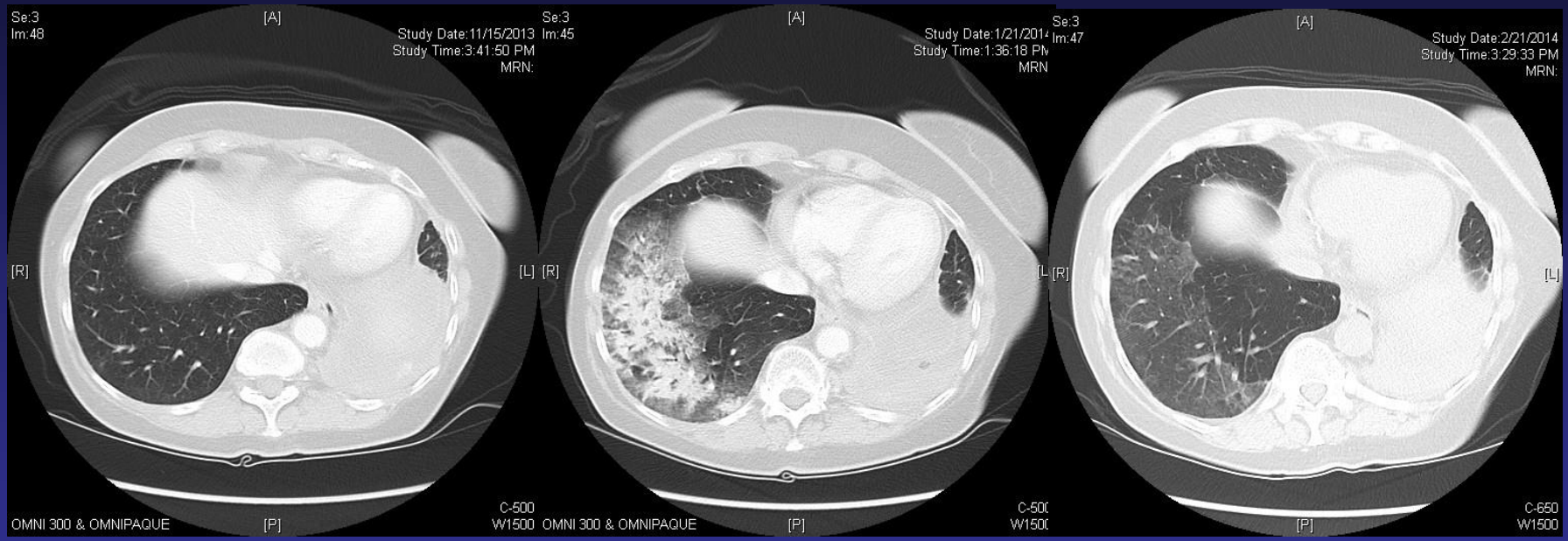
Rare (< 5%)

- **Pneumonitis**
  Grade 3/4 toxicities uncommon
  Low grade reversible with steroids and discontinuation
- Anemia

Extremely Rare (< 1%)

- Episcleritis/uveitis
- Nephritis
- Neuropathies, Guillain-Barré, myasthenia gravis
- Thrombocytopenia
- Pancreatitis
- Nephritis
- Lymphadenopathy (sarcoid)
- Toxic epidermal necrolysis, Stevens-Johnson syndrome

Immune-Related Pneumonitis

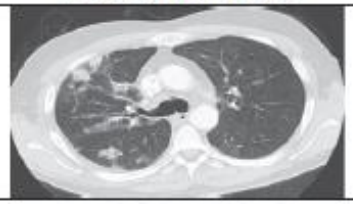
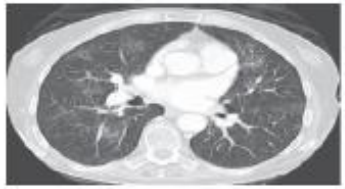
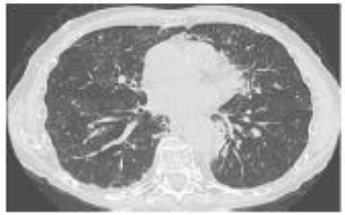
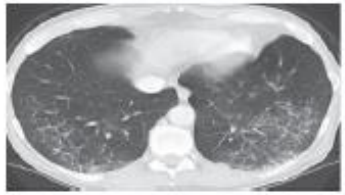
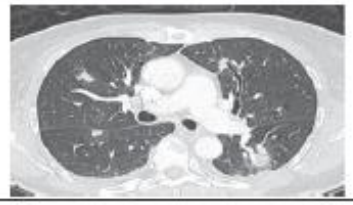


11/15/2013:
Prepneumonitis

1/21/14:
Pneumonitis

2/21/14:
Improved with steroids; taper completed 3/7/14

Immune-Related Pneumonitis

Radiologic Subtypes	Representative Image	Description
Cryptogenic organizing pneumonia-like (n = 5, 19%)		Discrete patchy or confluent consolidation with or without air bronchograms Predominantly peripheral or subpleural distribution
Ground glass opacities (n = 10, 37%)		Discrete focal areas of increased attenuation Preserved bronchovascular markings
Interstitial (n = 6, 22%)		Increased interstitial markings, interlobular septal thickening Peribronchovascular infiltration, subpleural reticulation Honeycomb pattern in severe patient cases
Hypersensitivity (n = 2, 7%)		Centrilobular nodules Bronchiolitis-like appearance Tree-in-bud micronodularity
Pneumonitis not otherwise specified (n = 4, 15%)		Mixture of nodular and other subtypes Not clearly fitting into other subtype classifications

SCLC- Epidemiology

~ 10 % of all lung cancer cases in U.S.

25,000 estimated cases per year

Incidence decreasing globally

Male:female ratio ~ 1:1

SCLC

SCLC represents one end of a spectrum of pulmonary neuroendocrine tumor characterized by

- Grade (inverse correlation to differentiation)

  low: typical carcinoid
  moderate: atypical carcinoid
  high: LCNEC, SCLC

- Biologic behavior

- Response to cytotoxins

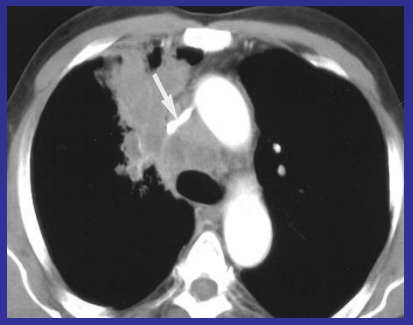
SCLC

Clinical Presentation

Short duration of symptoms (≤ 3 mos)

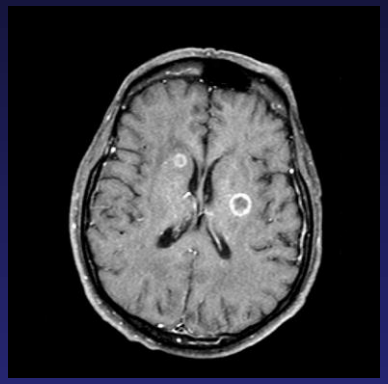
Endobronchial tumor (cough, wheeze, dyspnea, obstructive pneumonia, hemoptysis)

Regional extension (dysphagia, hoarseness, SVC syndrome, pain)

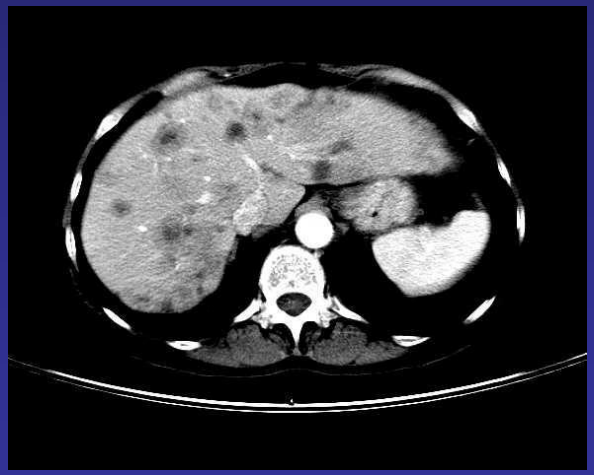


SCLC

Clinical Presentation



Metastatic disease (abdominal pain, vomiting, headache, focal neurologic deficits, seizure, bone pain)



Systemic symptoms (asthenia, anorexia, weight loss)

SCLC
Paraneoplastic Syndromes

Endocrine:

Syndrome	Hormone
Hyponatremia	ADH
Cushing's	ACTH
Acromegaly	GHRP

Course of endocrine syndromes parallels course of cancer

SCLC

Paraneoplastic Syndromes

Neurologic:

Syndrome	Antibody
Lambert-Eaton	Anti-VGCC
[Cerebellar Degeneration/	[Anti-Hu, -CV2
Encephalitis/Neuropathy]	ANNA-3, PCA-2]
Opsoclonus/myoclonus	Anti-Ri
Retinal Blindness	Anti-recoverin
Stiff –person syndrome	Anti-amphiphysin

Successful treatment of cancer commonly has no impact on neurologic syndrome **(Beukelaar J Oncol 2006)**

SCLC – Natural History

VA Lung Group Study

Median survival (placebo): Distant Metastases 6 wks
: Limited to chest 12 wks

NCI Autopsy series 30 days post-resection

Mediastinal disease: 90%
Distant metastatic disease: 63%

(Matthews et al Cancer Chemother Rep 1973)

SCLC- Staging

- Prior to use of combination chemotherapy TNM staging not prognostic
- In modern era TNM staging used to identify stage I patients who may benefit from resection (T1-2, NO)
- Revision of 2-stage VALG system in common usage

SCLC- Treatment

Limited Disease (LD) (35-40% of pts) (TNM stages I-III)

- Tumor confined to one hemithorax and regional lymph nodes
- Tumor must be encompassed by a tolerable radiation port

Treatment: Platinum-based chemo concurrently with XRT, followed by consolidation chemotherapy

SCLC- Treatment

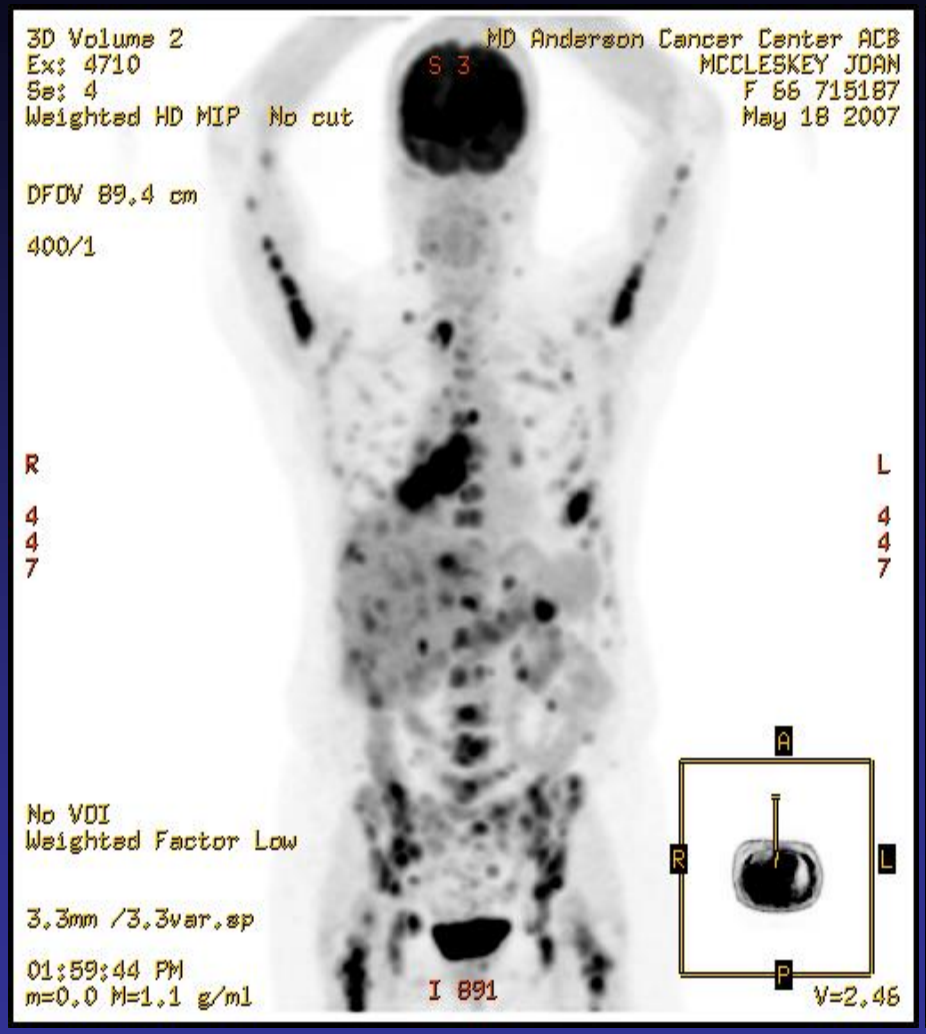
Extensive Disease (ED)

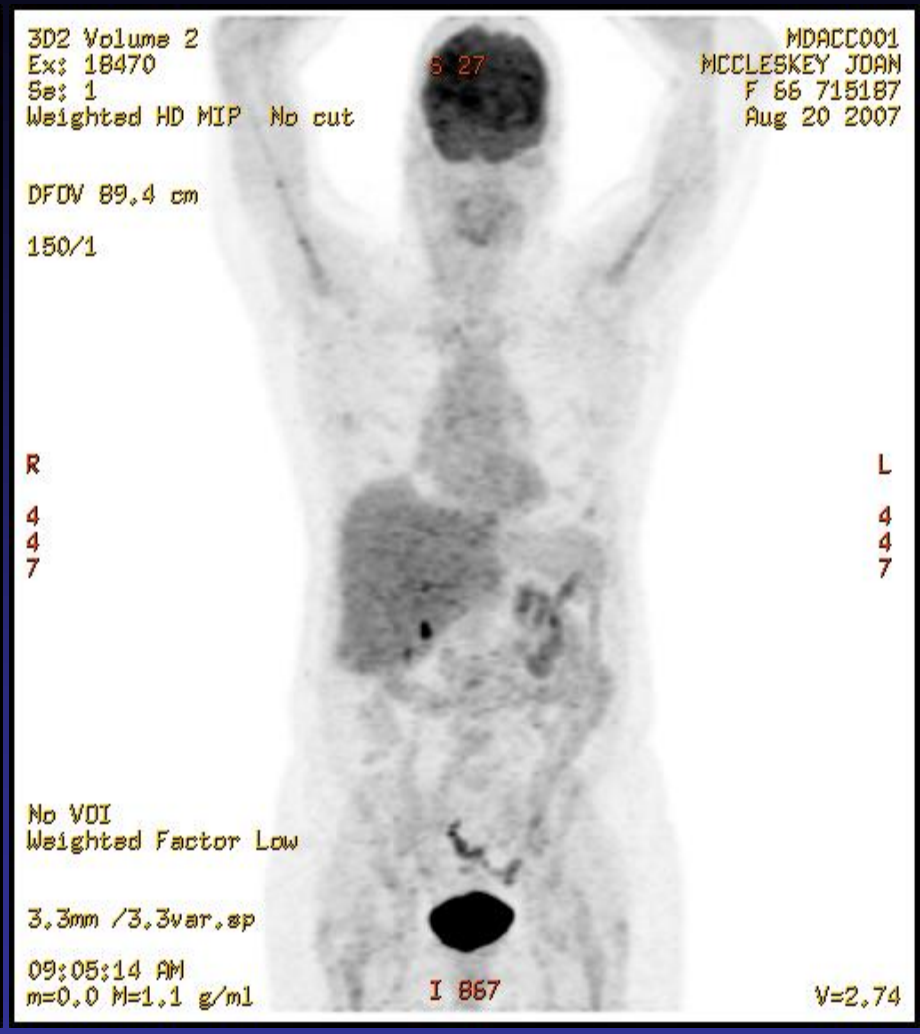
(≅ 60% of pts) (TNM stages wet IIIB and IV):

- Tumor outside the confines of LD
- Includes malignant pericardial and pleural effusion

Treatment: Platinum-based chemotherapy

SCLC s/p Etoposide/Carbo x 3





SCLC - *Treatment*

Prophylactic Cranial Irradiation

- Brain metastases in ≅ 40% of patients during course of disease.
- Probability of brain disease increases with increasing duration of survival.
- PCI significantly reduces rate of CNS relapse in randomized trials.

SCLC – *Treatment*

Prophylactic Cranial Irradiation

- **Meta analysis:**

  5% 3-year survival benefit for patients in "CR" (85% LD) (Auperin NEJM 1999)

- **EORTC Phase III in ED responders :**

  Symptomatic brain mets: 17% vs 41%
  (HR 0.27)

  Median PFS/OS 15/29 wks vs 12/23 wks
  (HR 0.68) (Slotman NEJM 2007)

SCLC

Treatment Outcomes- Clinical Trials

	LD	ED
Overall response (%)	80-100	60-100
Complete response (%)	50-90	15-40
Median Survival (mos)	18-30	8-12
2-yr survival (%)	40-50	5-15
5-yr survival (%)	15-25	1-2