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Small cell and non-small cell lung cancer

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Banner Health®

Agenda

1. Small cell lung cancer (SCLC)
2. Non-small cell lung cancer (NSCLC)

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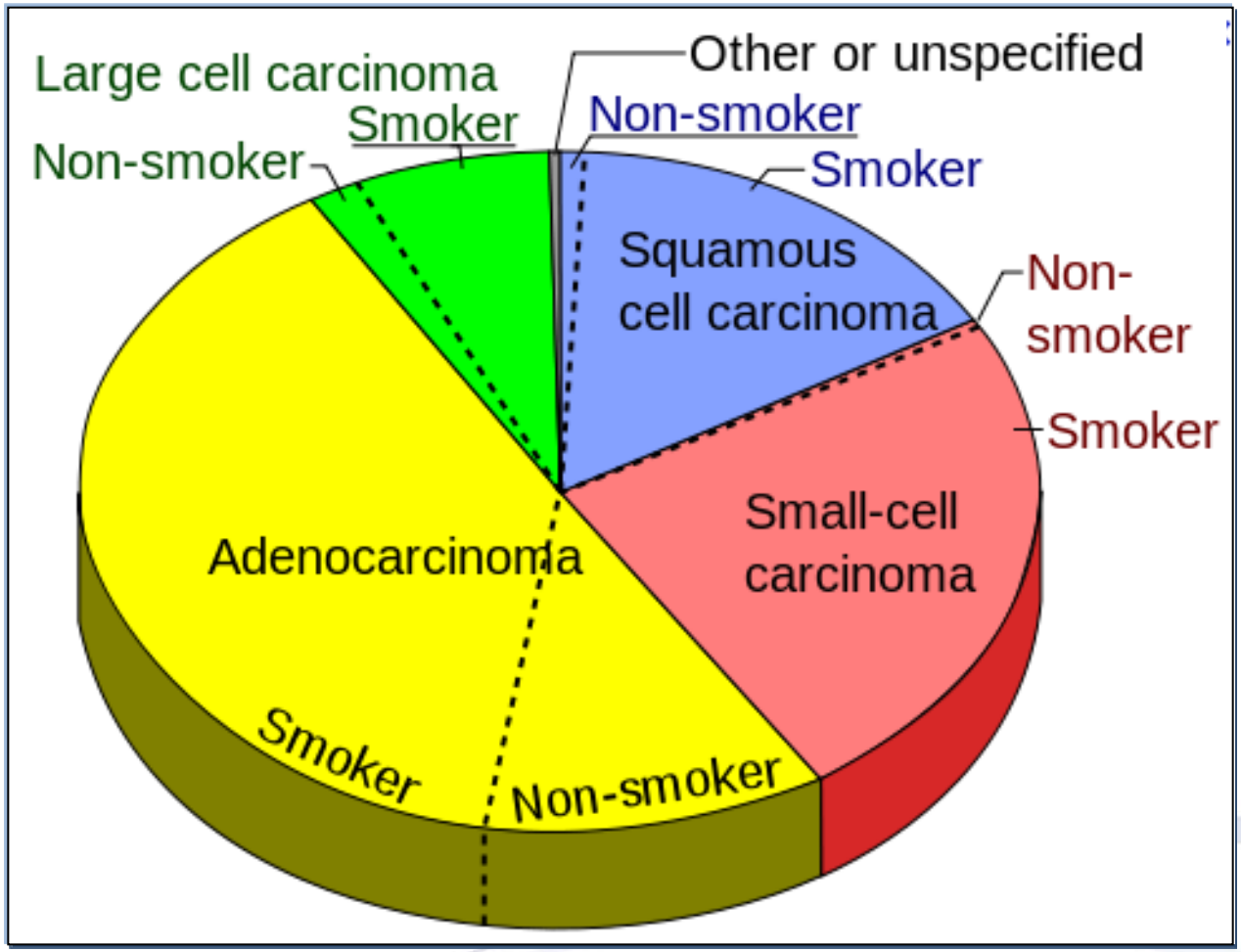
What is cancer?

- Cancer was already known to ancient Egyptians and succeeding civilizations
  - But only affected a small number of people

- Once infectious diseases were controlled due to public health improvements and improved medical care, cancer became more common with increased life expectancy
  - *Today* 1 in 3 people will develop cancer
    - Approximately 1 in 4 males will die of it
    - Approximately 1 in 5 females will die of it

- Cancer is a disorder of cells and it usually appears as a tumor made up of a mass of cells, but this is the end point
  - A whole series of changes have occurred to lead to this disorder
  - Occurs typically at an older age

Types of lung cancer: Non-small cell and small cell lung carcinoma



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Lung cancer by the numbers (per year)

- USA
  - 220,000 new patients with lung cancer
  - 165,300 patients with non-small cell lung carcinoma
  - 115,000 patients with adenocarcinoma
  - 25,000 patients with small cell lung carcinoma
  - 28,500 patients with lung cancer, who never smoked

- World
  - 1.5 million patients with lung cancer

NCI SEER Cancer Statistics, WHO Fact Sheet

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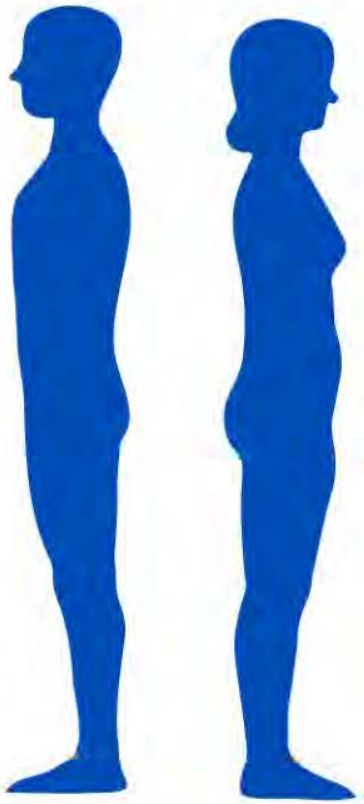
New cancer patients in USA (per year)

Men 822,300	
Prostate	29%
Lung & bronchus	14%
Colon & rectum	9%
Urinary bladder	6%
Melanoma of skin	5%
Kidney & renal pelvis	5%
Non-Hodgkin lymphoma	4%
Oral cavity	3%
Leukemia	3%
Pancreas	3%
All Other Sites	19%

Source: American Cancer Society, 2011



Women 774,370	
30%	Breast
14%	Lung & bronchus
9%	Colon & rectum
6%	Uterine corpus
5%	Thyroid
4%	Non-Hodgkin lymphoma
4%	Melanoma of skin
3%	Kidney & renal pelvis
3%	Ovary
3%	Pancreas
16%	All Other Sites

Source: American Cancer Society, 2011.

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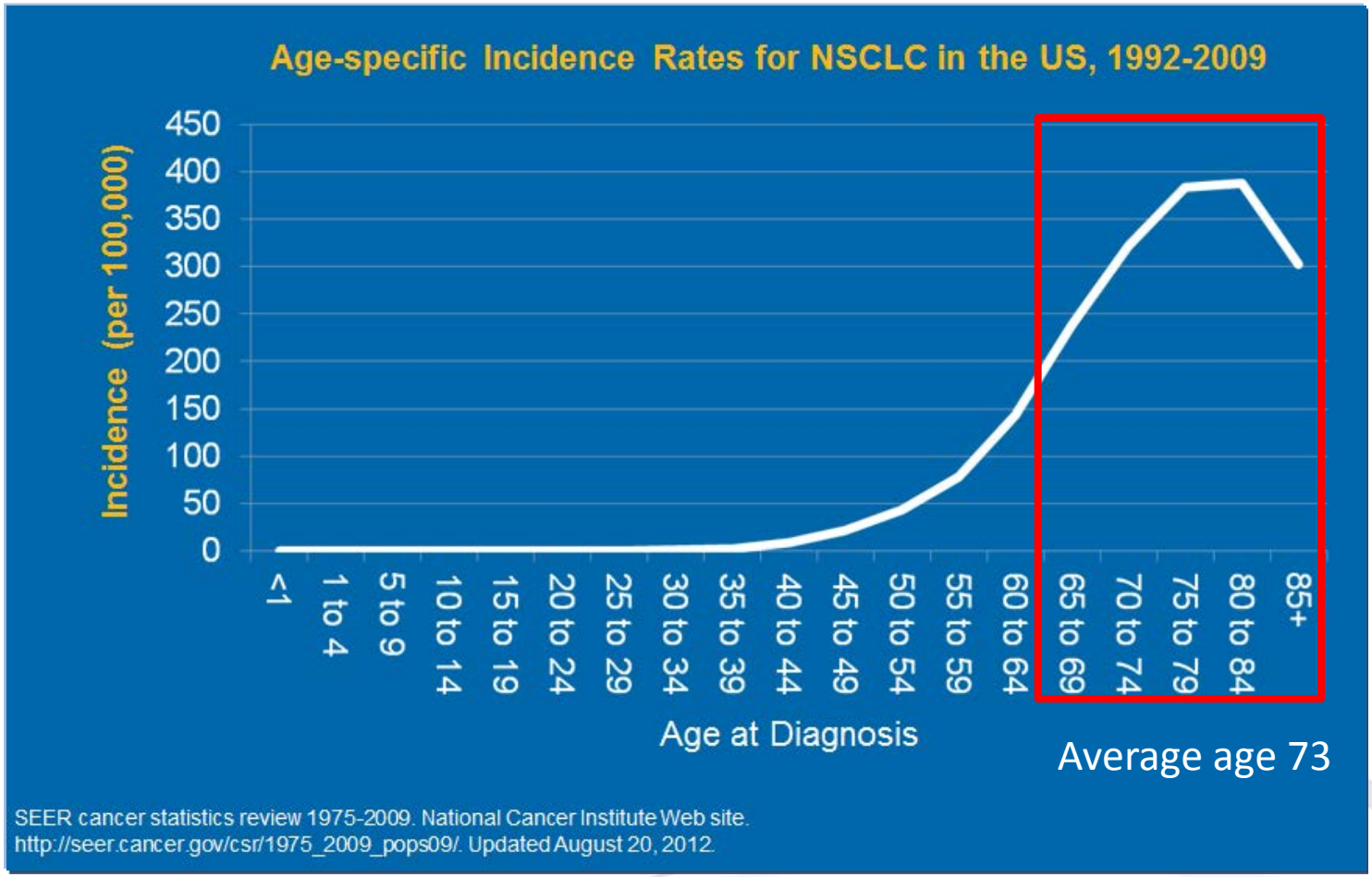
Lung cancer is a disease of increased age



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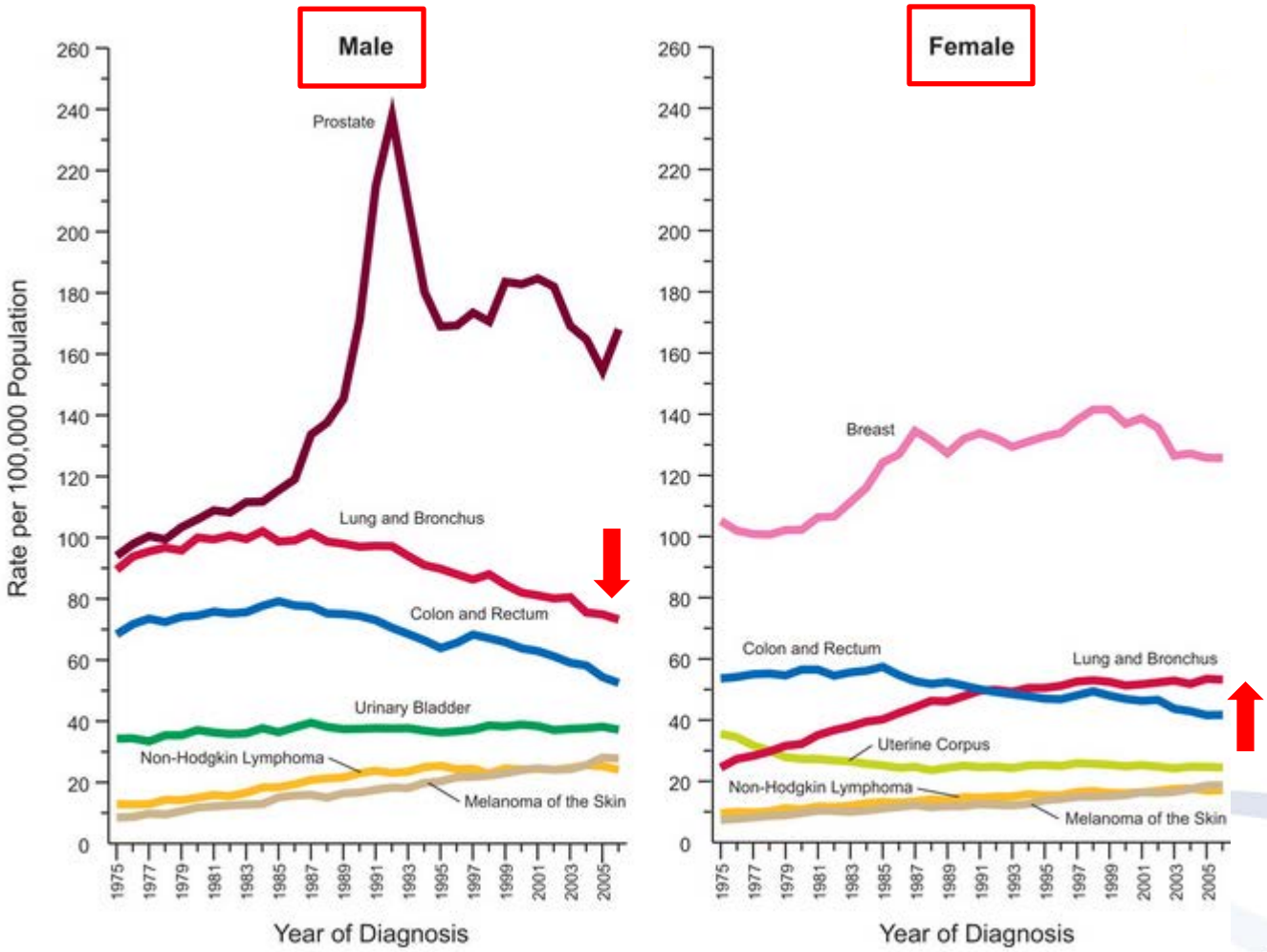
Trends of new cancer patients from 1975 to 2006



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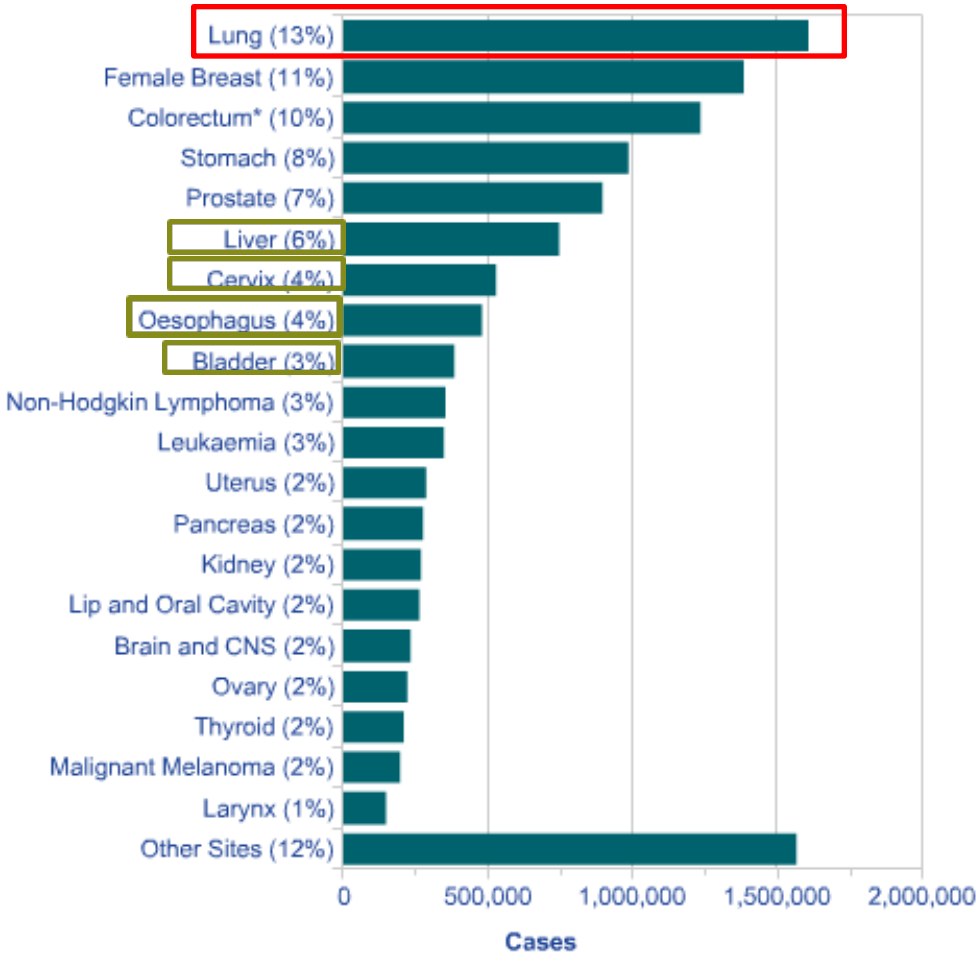
Cancer worldwide



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Causes of lung cancer

1. SMOKING, SMOKING, and SECOND HAND SMOKING

2. Radiation (Radon, …)
3. Chemicals (Air pollution, smoke from cooking and heating, asbestos…)
4. Genetic predisposition
5. ? Age (Genetic instability)

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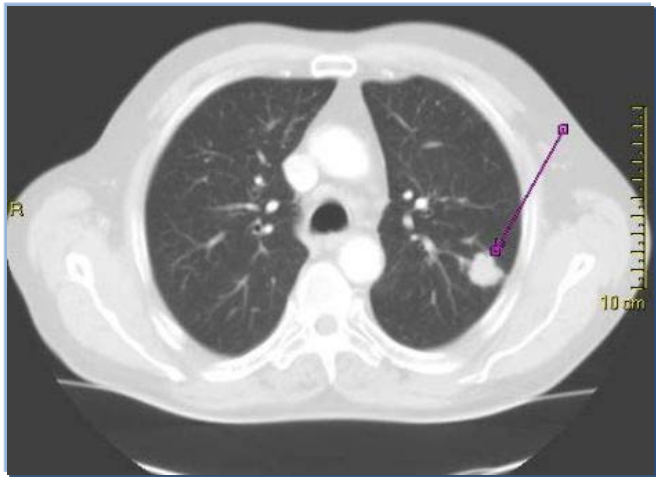
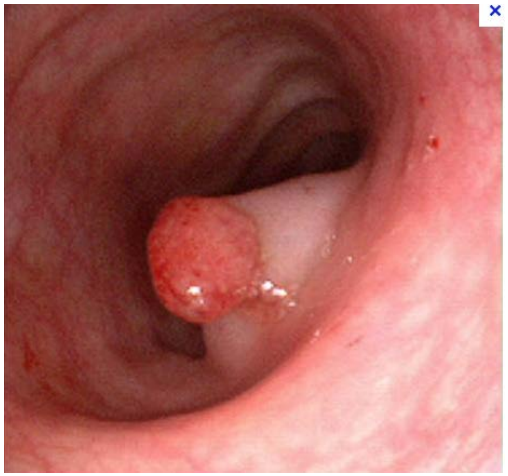
Clinical presentation

1. **Asymptomatic:**
   Tumor lesion found by screening study (e.g. CT chest, mammography, colonoscopy, …)





2. **Symptoms:**
   - Weight loss
   - Fatigue
   - Pain
   - Tumor growth causing local or general symptom (Bleeding, obstruction, para-neoplastic syndrome, lab abnormalities…)
   - Other unspecific symptoms

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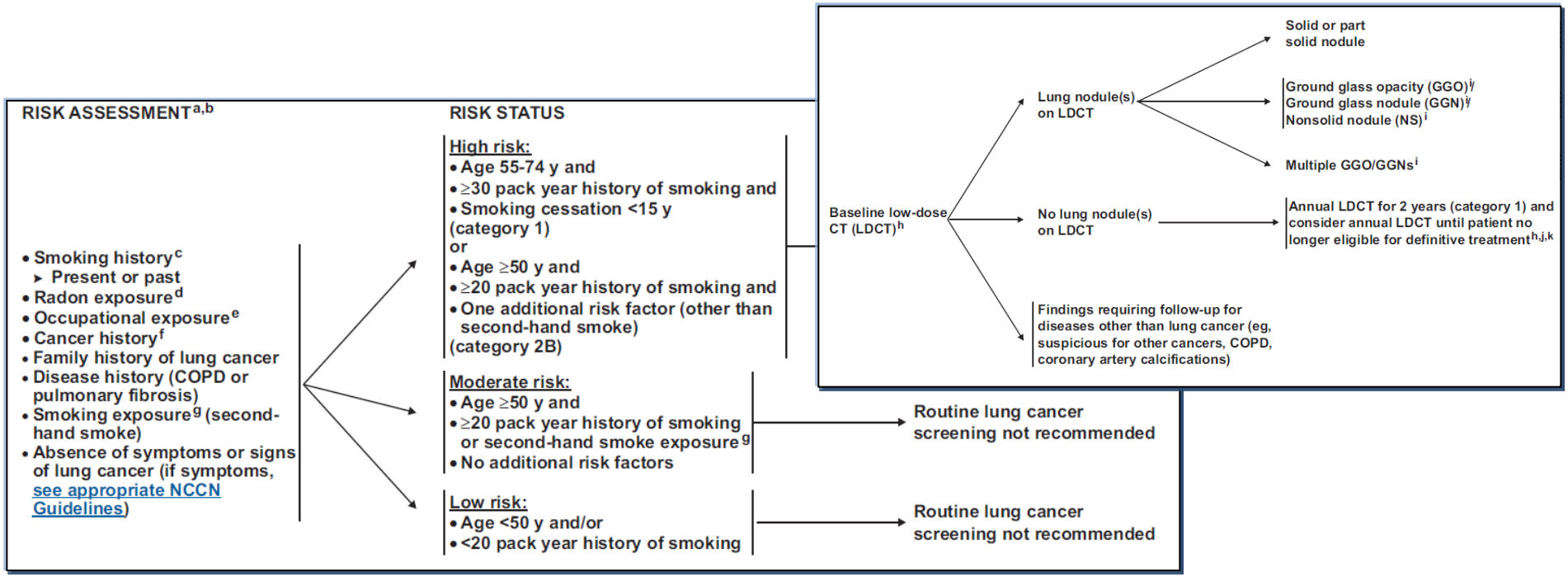
Lung cancer screening



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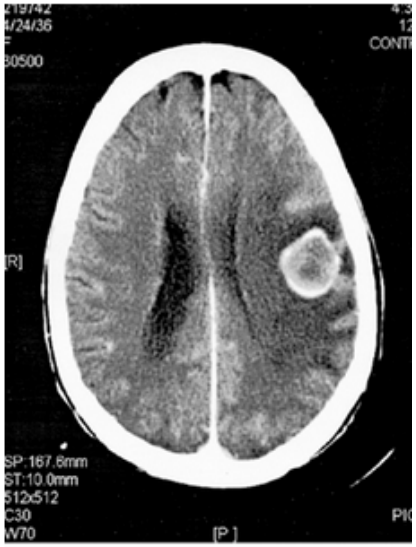
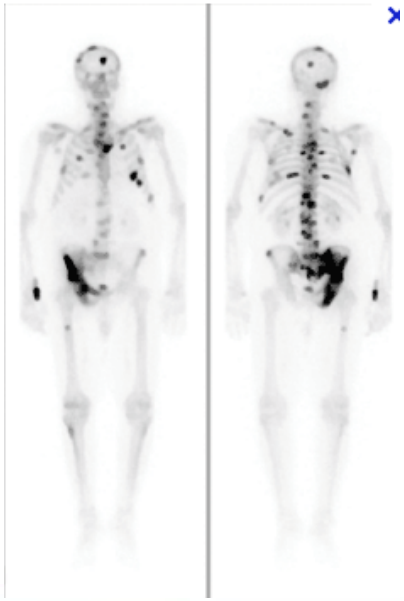
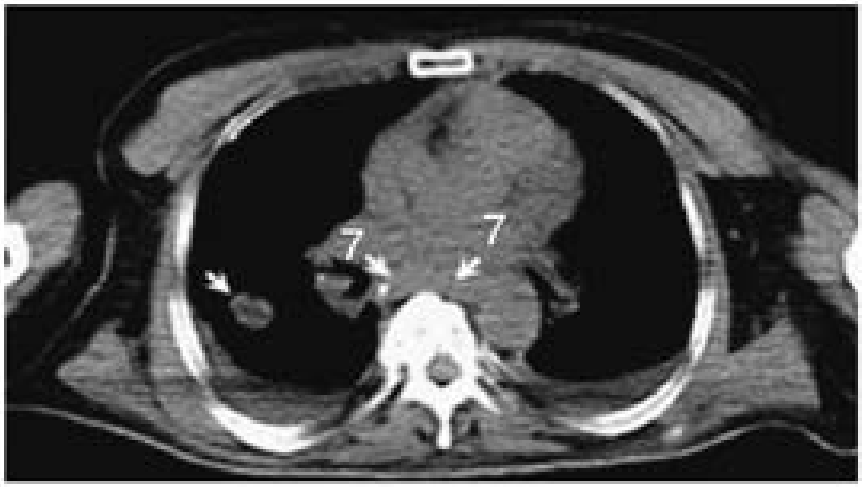
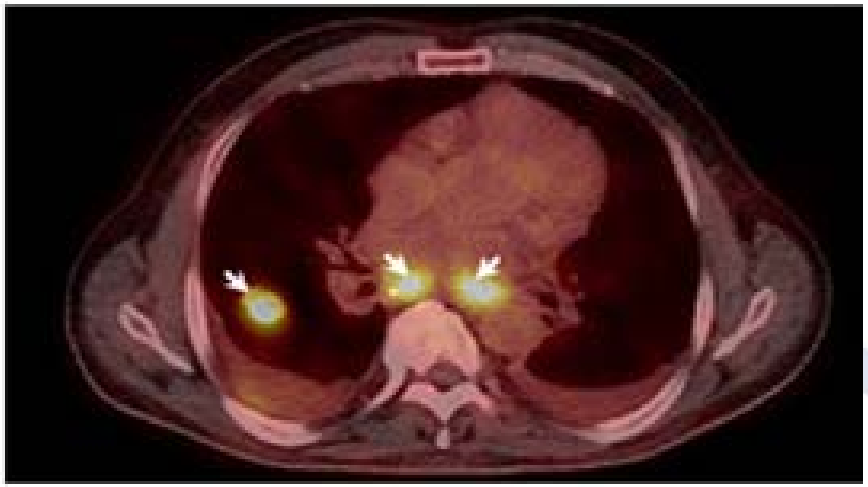
Imaging studies & staging

1. X Ray
2. Ultrasound
3. CT
4. MRI
5. PET/CT
6. Nuclear medicine studies









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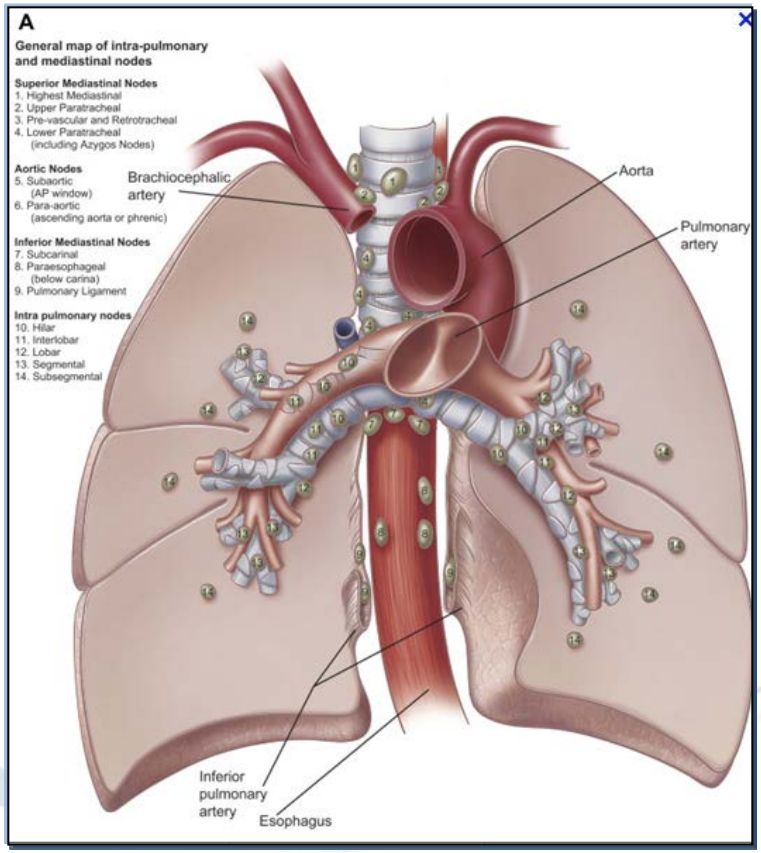
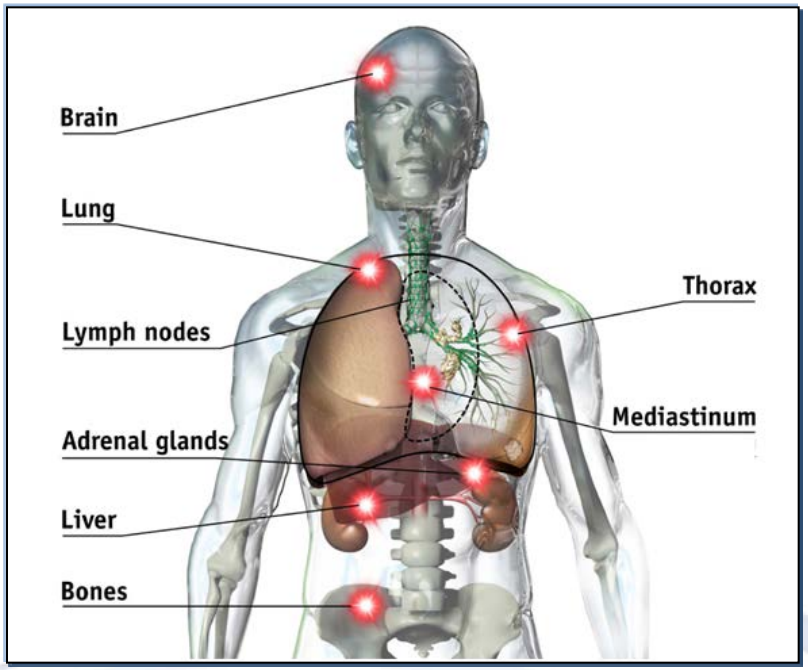
Lung cancer stages

Stage 1: The cancer is located *only* in the lungs
Stage 2: The cancer is in the lung and *nearby lymph nodes*
Stage 3: Cancer is found in the lung and in the *lymph nodes* in the *middle of the chest* (locally advanced disease)
Stage 4: Cancer has spread to both lungs, to fluid around the lungs, or organs outside the chest.





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Staging lung cancer

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2012 Staging Non-Small Cell Lung Cancer

NCCN Guidelines Index
NSCLC Table of Contents
Discussion

Table 6. 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
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)[a]
T1a	Tumor ≤ 2 cm in greatest dimension
T1b	Tumor > 2 cm but ≤ 3 cm in greatest dimension
T2	Tumor > 3 cm but ≤ 7 cm or tumor with any of the following features:[b] Involves main bronchus, ≥ 2 cm distal to the carina Invades visceral pleura Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumor > 3 cm but ≤ 5 cm in greatest dimension
T2b	Tumor > 5 cm but ≤ 7 cm in greatest dimension
T3	Tumor > 7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus < 2 cm distal to the carina[a] but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe
T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; separate tumor nodule(s) in a different ipsilateral lobe

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 nodules or malignant pleural (or pericardial) effusion[c]
M1b	Distant metastasis

[a] The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1.

[b] T2 tumors with these features are classified T2a if ≤ 5 cm or if size cannot be determined, and T2b if > 5 cm but ≤ 7 cm

[c] Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as T1, T2, T3, or T4.

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Prognostic factors

1. Cancer type
2. Grade
3. Molecular characteristics (EGFR, Her2, …)
4. Stage
5. Size and location
6. Therapy response
7. Genetic background (Ethnicity, …)
8. Performance status
9. Age
10. Comorbidities
11. Social support

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SMALL CELL LUNG CANCER (SCLC)

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Small cell lung cancer (SCLC) key messages

- Incidence: 25000 patients / year, ! Declining rate
- Cause: Smoking (Asbestos, radon)
- Neuroendocrine tumor
- Molecular characteristics: Poorly understood
  - Tumour-suppressor gene FHIT
  - Mitotic spindle assembly checkpoint protein MAD1
  - Others: RB1, p53, KRAS, EGFR
- Clinical: Paraneoplastic syndroms, local symptoms
- Stage: Limited stage – extensive stage (60% to 70%)
- Therapy:
  1. Surgery
  2. Radiation, palliative whole brain radiation
  3. Chemotherapy (Cisplatin/carboplatin, etoposide, irinotecan/topotecan, …)
  4. Concurrent chemoradiation with BID XRT
  5. Targeted agents: None approved
- Very sensitive to chemotherapy and radiation, but not curable
- Poor prognosis: 5 y survival stage III/IV 8%
- New (?) targets: PI3K, bcl-2, src, HIF1a, …

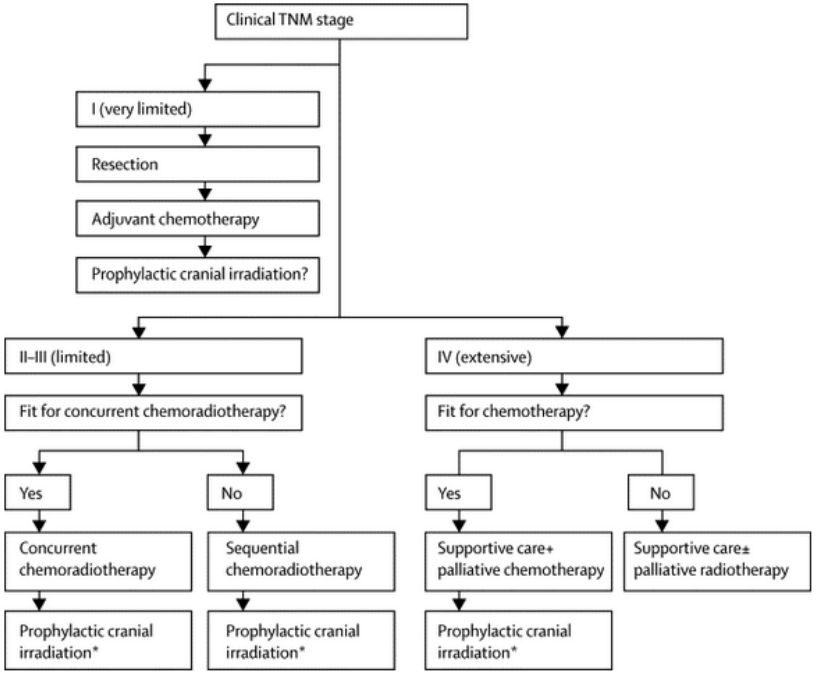

Figure 3. Simplified algorithm for the management of SCLCSCLC=small-cell lung cancer. *If not progressive after induction treatment

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NON-SMALL CELL LUNG CANCER (NSCLC)

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Lung cancer therapy

- **Local therapies**:
  - Surgery (Stage I, II, IIIa)
  - Radiation (Stage I, II, III, IV)

- **Systemic therapy**:
  - Chemotherapy (Stage Ib - IV)
  - Targeted therapies: Erlotinib=Tarceva, Crizotinib=Xalkori (Stage IV)
  - Anti-angiogenesis (Avastin) (Stage IV)
  - Cancer Immunotherapy Nivolumab approved 3/4/15.
  - Trials: Cancer Immunotherapy, new inhibitors… (Stage IV)
  - Hormone therapy, transplantation, … (Not in lung cancer)

- **Supportive care**:
  - Pain medicine
  - Nausea meds
  - Growth factors (G-CSF…), prophylactic antibiotics
  - Appetite stimulants, GI protectants, seizure meds, antidepressants, sleep aids, anticoagulants…

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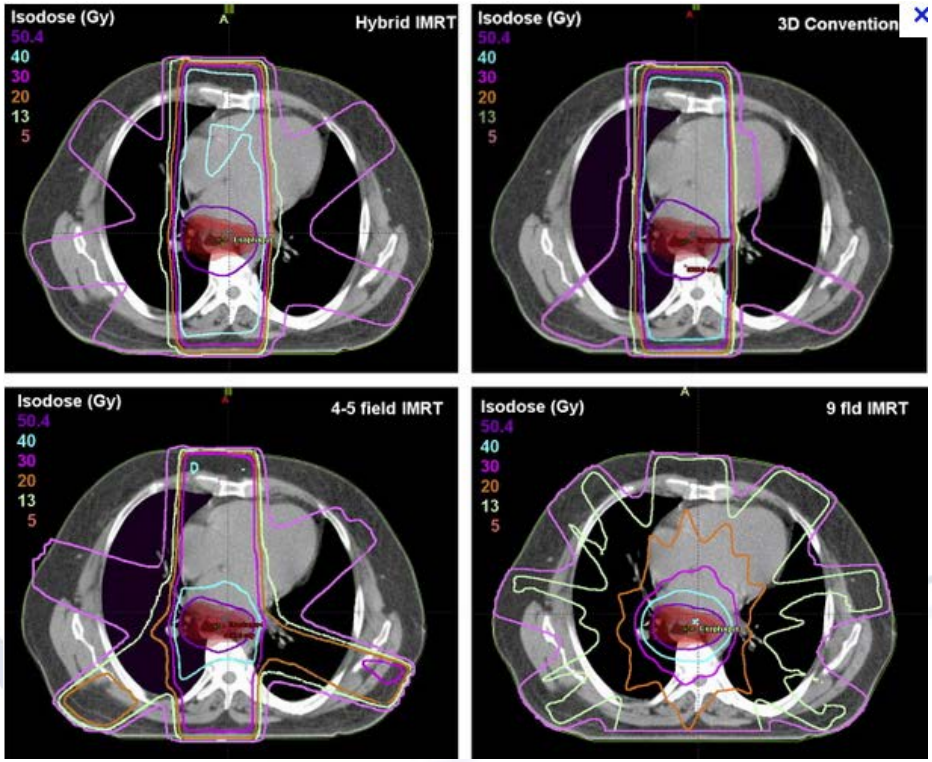
Radiation therapy

1. Conventional photon radiotherapy
2. Photon radiotherapy using high precision techniques
   - Fractionated stereotactic radiotherapy (FSRT)
   - Stereotactic Radiosurgery (SRS)
   - Intensity Modulated Radiotherapy (IMRT)
3. Particle Therapy: Protons, Carbon Ions



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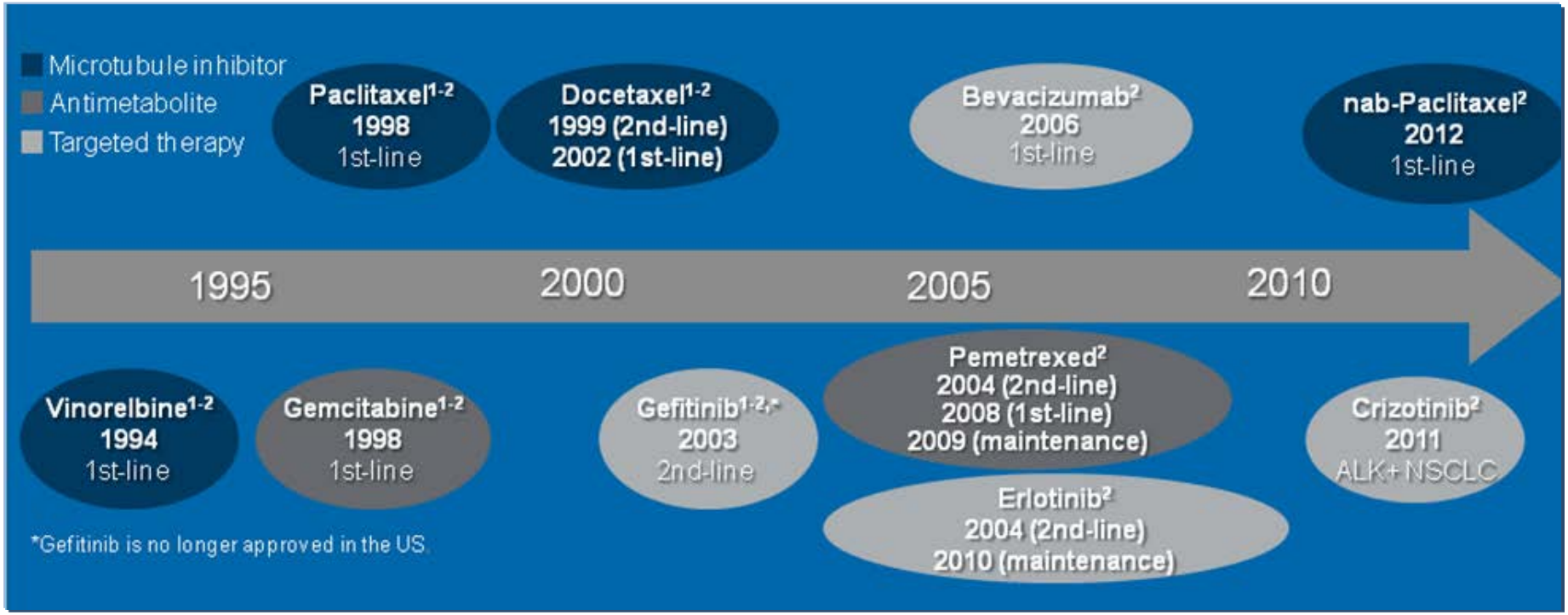
New FDA approved drugs for lung cancer therapy



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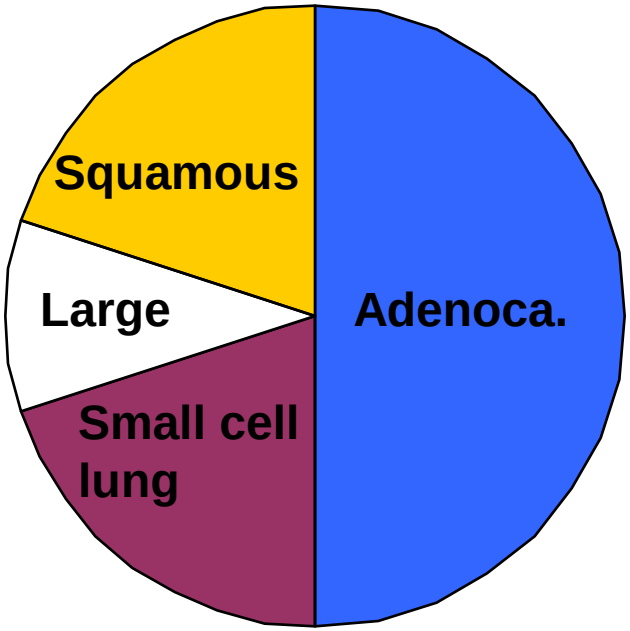
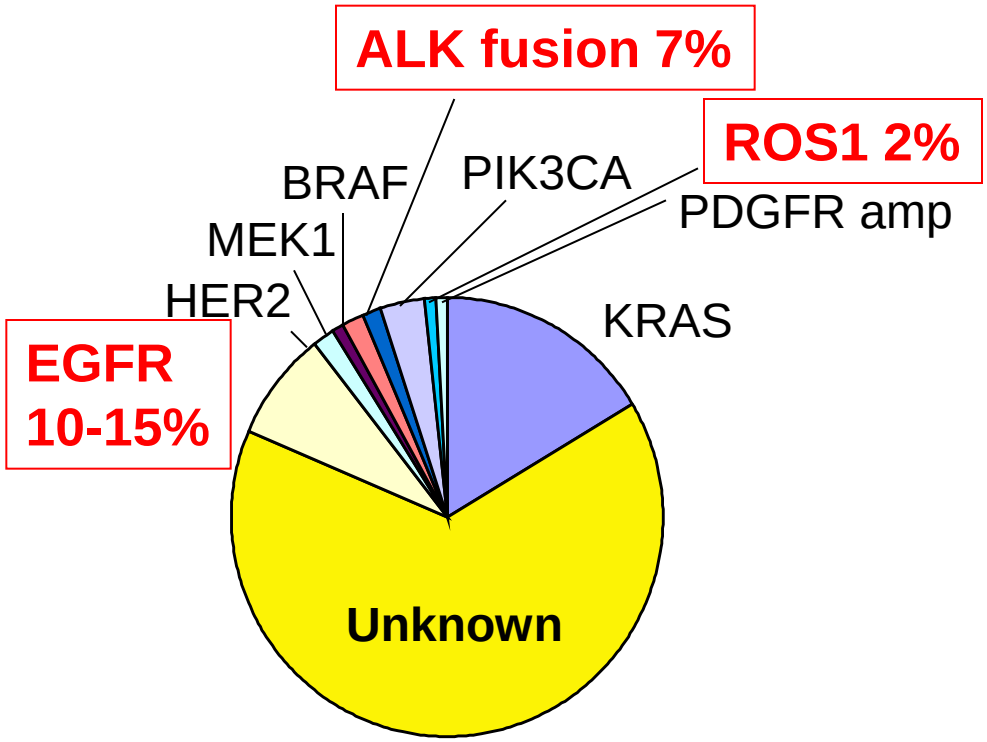
NSCLC adenocarcinoma subsets by molecular changes





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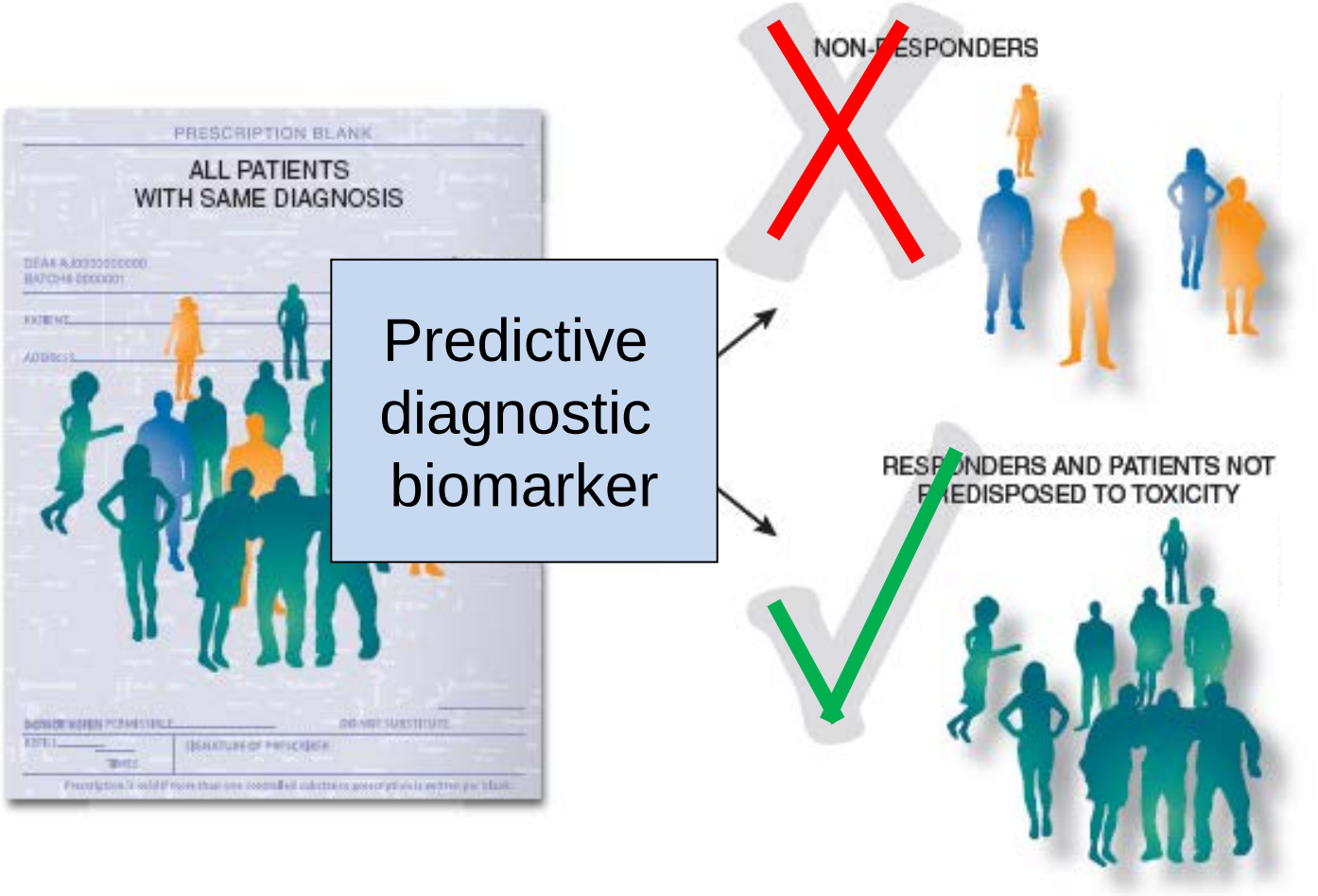
Personalized medicine



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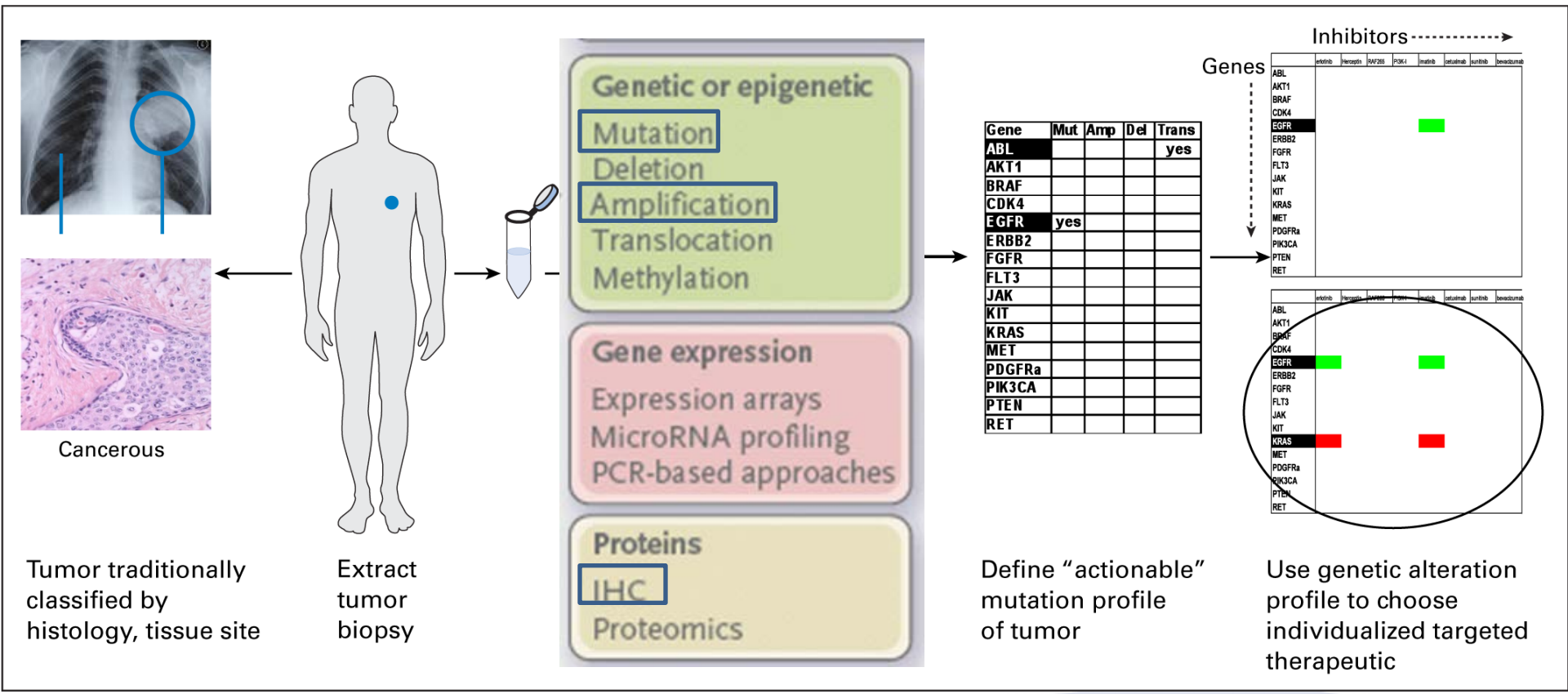
Principles of personalized medicine



MacConaill LE, Garraway LA. J Clin Oncol 2010;28:5219-5228.

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First line and maintenance therapy for NSCLC

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First line and maintenance therapy options for non-squamous NSCLC, wildtype for EGFR, ALK & ROS1

1. Paclitaxel & carboplatin + bevacizumab -> bevacizumab (E4599)
2. Pemetrexed & cisplatin -> pemetrexed
3. Pemetrexed & carboplatin/cisplatin + bevacizumab -> pemetrexed & bevacizumab
4. Vinorelbine & cisplatin + cetuximab -> cetuximab (FLEX)
5. Gemcitabine (J Clin Oncol. 2012 Oct 1;30(28):3516-24) (category 2)
6. Switch maintenance with erlotinib or pemetrexed (category 2)

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Targeting angiogenesis in NSCLC: VEGF inhibitors

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Angiogenesis inhibition the beginnings

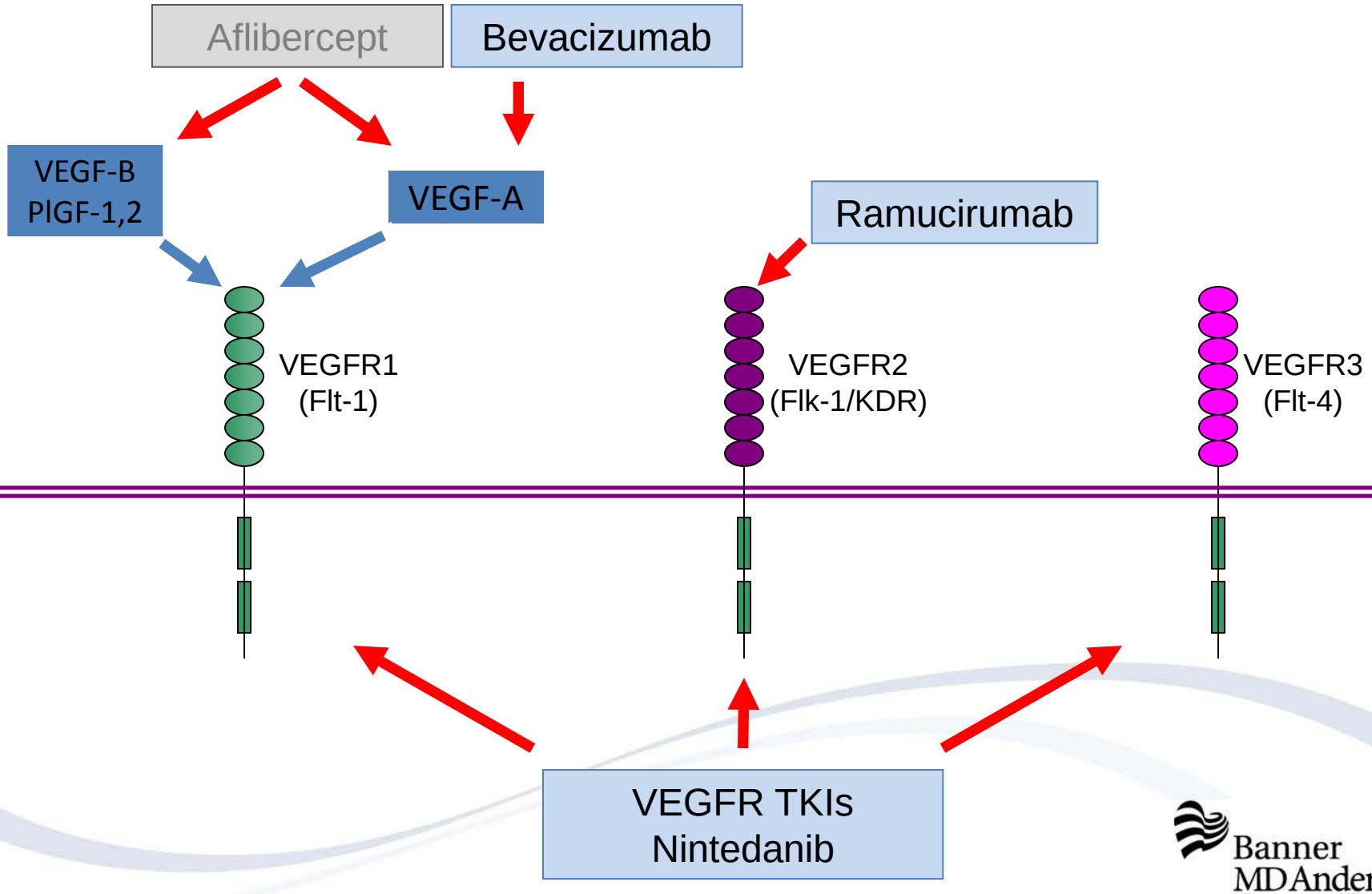
New England Journal of Medicine,
285:1182-1186, ***1971***

TUMOR ANGIOGENESIS: THERAPEUTIC IMPLICATIONS

JUDAH FOLKMAN, M.D.

1. "Solid tumors are **dependent** upon **new** capillary sprouts…"
2. "Without neovascularization solid tumors might become completely **dormant**…"
3. "The term **anti-angiogenesis** is proposed to mean the prevention of new vessel sprouts from penetrating into an early tumor implant."
4. "This hypothesis predicts the possible future discovery of **angiogenesis inhibitors**,.."
5. "An **antibody** to a tumor angiogenic factor (TAF) could be therapeutic."

VEGF family signaling pathways and inhibitors



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ECOG-E4599: Improved overall survival for PC+Bevacizumab vs PC in non-squamous NSCLC

Endpoint	Car Tax (n = 433)	Car Tax Bev (n = 417)	HR	*p*-value
Median OS	**10.3 mo**	**12.3 mo**	0.79	0.003
Two-year OS	15%	23%	—	—
Median PFS	**4.5 mo**	**6.2 mo**	0.66	<0.001
Overall response	**15%**	**35%**	—	<0.001

Tax = paclitaxel 200 mg/m^2 q3wk x 6; Car = carboplatin AUC 6 mg/mL per minute q3wk x 6;
B = bevacizumab 15 mg/kg q3wk to progression
HR = hazard ratio
OS = overall survival
PFS = progression-free survival

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Summary of selected phase III trials with bevacizumab and/or pemetrexed maintenance therapy

Year	Treatment arms	PFS in mo		OS in mo	
2006 ECOG4599	Car Tax	4.5		10.3	
	Car Tax Bev -> Bev	6.2	p<0.001	12.3	**p=0.003**
2013 JCO PARAMOUNT	Cis Pem	2.8		11	
	Cis Pem -> Pem	4.1		13.9	**0=0.0195**
2013 JCO PointBreak	Car Tax Bev -> Bev	5.6		13.4	
	Car Pem Bev -> Pem + Bev	6	p=0.012	12.6	p=0.95
2015 J Thor Onc PRONOUN(	Car Pem -> Pem	4.4		10.5	
	Car Tax Bev -> Bev	5.5	p=0.61	11.7	p=0.616
2014 Ann Oncol AVAPERL	Cis Pem Bev -> Bev*	3.7		13.2	
	Cis Pem Bev -> Pem + Bev*	7.4	p<0.001	17.1	p=0.29
Ongoing ECOG5508	Car Tax Bev -> Bev	NR		NR	
	Car Tax Bev -> Pem	NR		NR	
	Car Tax Bev -> Pem + Bev	NR		NR	

Car = carboplatin, Cis= cisplatin, Tax = paclitaxel, Bev = bevacizumab, Pem = pemetrexed
Bev 15 mg/kg q3wk, except *7.5 mg/kg
PFS = progression-free survival
OS = overall survival

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1 st line and maintenance therapy options for NSCLC squamous cell carcinoma

1. Paclitaxel & carboplatin + bevacizumab -> bevacizumab (E4599)
2. Pemetrexed & cisplatin -> pemetrexed (pos ph-III data)
3. Pemetrexed & carboplatin/cisplatin + bevacizumab -> pemetrexed & bevacizumab
4. **Carboplatin/cisplatin & taxol/Abraxane, carboplatin/cisplatin & gemcitabine**
5. Vinorelbine & cisplatin + cetuximab -> cetuximab (Phase III, FLEX)
6. Gemcitabine (J Clin Oncol. 2012 Oct 1;30(28):3516-24) (category 2)
7. Switch maintenance with erlotinib or pemetrexed (category 2)

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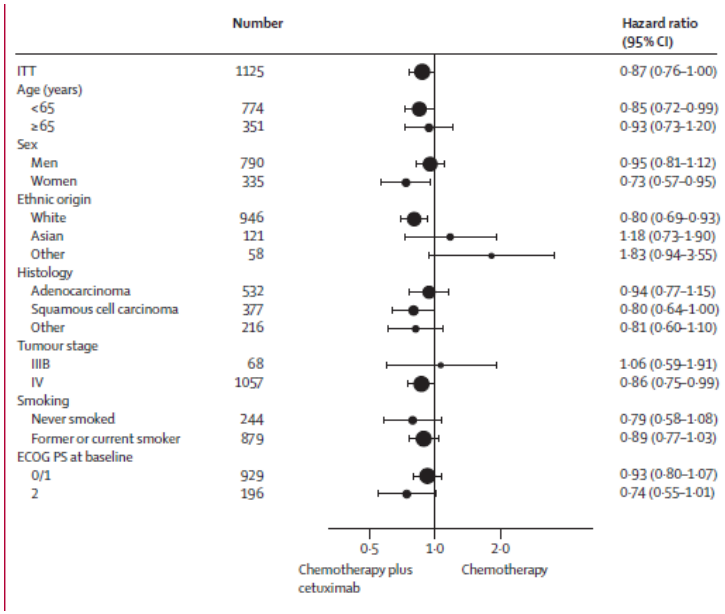
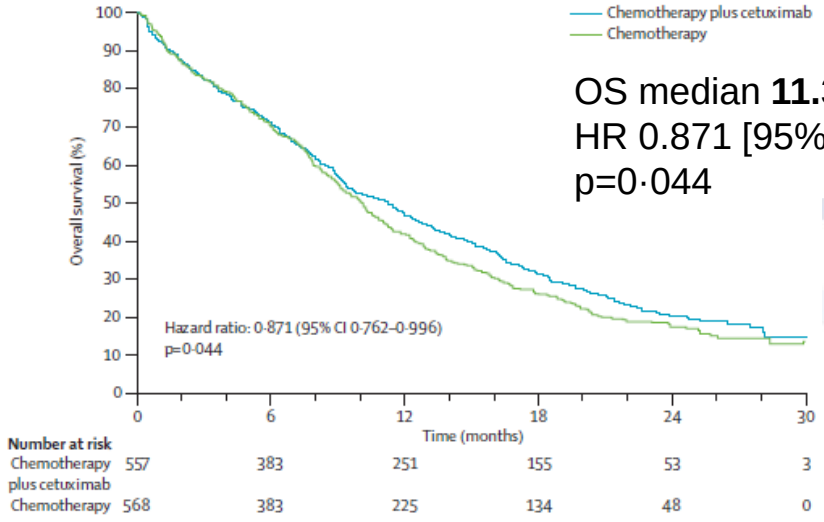
Cetuximab plus cisplatin/vinorelbine in advanced NSCLC (FLEX trial)

	Cisplatin and vinorelbine plus cetuximab (N=557)	Cisplatin and vinorelbine (N=568)
Age (years)		
Median (range)	59 (18–78)	60 (20–83)
≥65	172 (31%)	179 (32%)
Sex		
Men	385 (69%)	405 (71%)
Women	172 (31%)	163 (29%)
Ethnic origin		
White	466 (84%)	480 (85%)
Asian	62 (11%)	59 (10%)
Other	29 (5%)	29 (5%)
ECOG performance status		
0	132 (24%)	121 (21%)
1	333 (60%)	343 (60%)
2	92 (17%)	104 (18%)
Tumour stage		
IIIB	35 (6%)	33 (6%)
IV	522 (94%)	535 (94%)
Histology		
Adenocarcinoma	255 (46%)	277 (49%)
Squamous cell carcinoma	190 (34%)	187 (33%)
Other*	112 (20%)	104 (18%)
Never smoked	121 (22%)	123 (22%)

Data are number (%), unless otherwise indicated. ECOG=Eastern Cooperative Oncology Group. *Includes large cell, adenosquamous, and undifferentiated carcinomas.

Table 1: **Baseline characteristics**





OS median **11.3** mo vs **10.1** mo;
HR 0.871 [95% CI 0.762–0.996];
p=0·044

Pirker et al. Lancet. 2009 May 2;373(9674):1525-31.

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SECOND LINE THERAPY

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Principles of second line therapy

- Depend on first line and maintenance therapy choice.
- Chemotherapies based on pathologic subtype:
  - Non-squamous: Alimta, docetaxel, Erlotinib/Afatinib.
  - Squamous: Docetaxel, gemcitabine, Erlotinib/Afatinib.
  - Other NCCN listed: Vinorelbine, vinblastine, irinotecan, etoposide, mitomycin, ifosfamide.
- Anti-angiogenesis: Ramucirumab (anti-VEGFR2), Nintedanib (TKI against VEGFR, FGFR and PDGFR).
- Nivolumab anti-PD1, approved 03/04/2015 (Histology: Squamous only…so far)
- EGFR mutant patients:
  - T790M testing "3rd generation" EGFR TKI: Rociletinib (CO-1686), AZD9291 (irreversible).
- ALK translocated patients: Ceritinib, Alectinib.
- Clinical trials.

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Relapsed NSCLC 2nd line therapies phase III trial data

Outcome	Erlotinib[1,2] 150 mg/day	Docetaxel[3,4] 75 mg/m^2	Pemetrexed[5] 500 mg/m^2
Response rate (%)	**8.9**	**7.1–8.8**	**9.1**
Median duration of response (months)	7.9	5.3–9.1	4.6
1-year survival rate (%)	31	30–37	30
Median survival in PS 0/1 patients with 1 prior regimen (months)	**9.42**	**9.15**	**9.45**
Median survival (months)	6.7	5.7–7.9	8.3

Results cannot be compared directly because of different patient populations

[1] *Shepherd F et al. N Engl J Med 2005;353:123–32.*
[2] *OSI and Roche data.*
[3] *Shepherd F et al. J Clin Oncol 2000;18:2095–103.*
[4] *Fossella F et al. J Clin Oncol 2000;18:2354–62.*
[5] *Hanna N et al. J Clin Oncol 2004;22:1589–97.*

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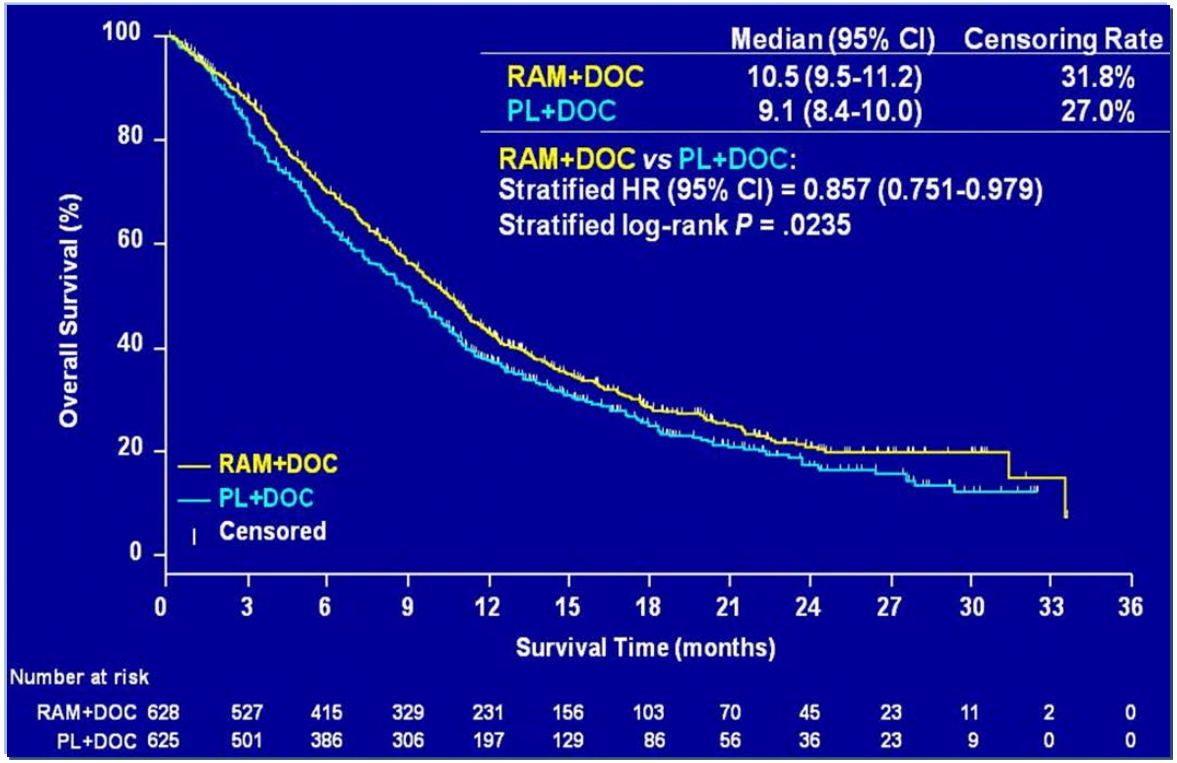
Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of st IV NSCLC (REVEL study, multicentre, double-blind, randomised ph-III)



N= 1253 patients
OS 10.5 vs 9.1 mo
Median PFS 4.5 vs 3.0 mo

Grade 3:
Neutropenia 49% vs 40%
Febrile neutropenia 16% vs 10%
Hypertension 6% vs 2%

Effect in all subtypes

Garon et al. Lancet. 2014 Aug 23;384(9944):665-73.

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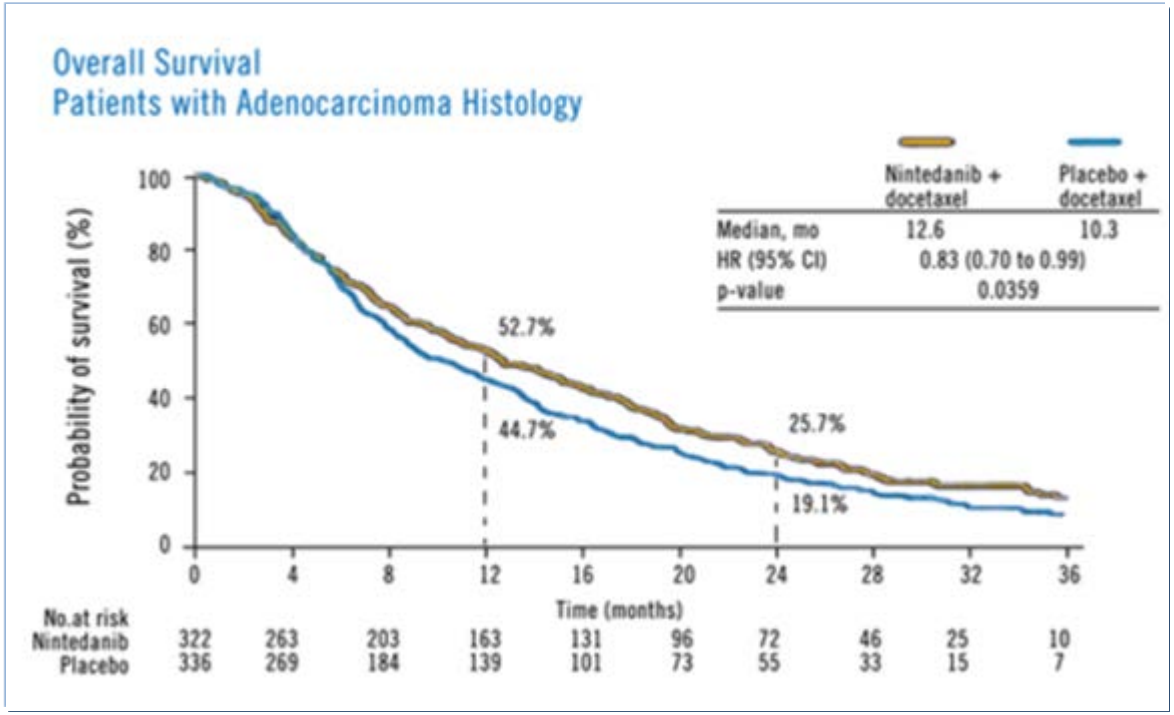
Docetaxel plus nintedanib versus docetaxel plus placebo in patients with NSCLC (LUME-1, ph-III, double-blind, randomised)



N= 1314

PFS median 3.4 vs 2.7 mo (HR 0.79, p=0.0019)

OS adenocarcinoma median 12.6 vs 10.3 mo (HR 0.83, 0.0359), not in total/SCC

Grade 3:
Diarrhea 6.6% vs 2.6%
Alanine aminotransferase 7.8% vs 0.9%

Reck et al. Lancet Oncol. 2014 Feb;15(2):143-55.

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CANCER IMMUNOTHERAPY

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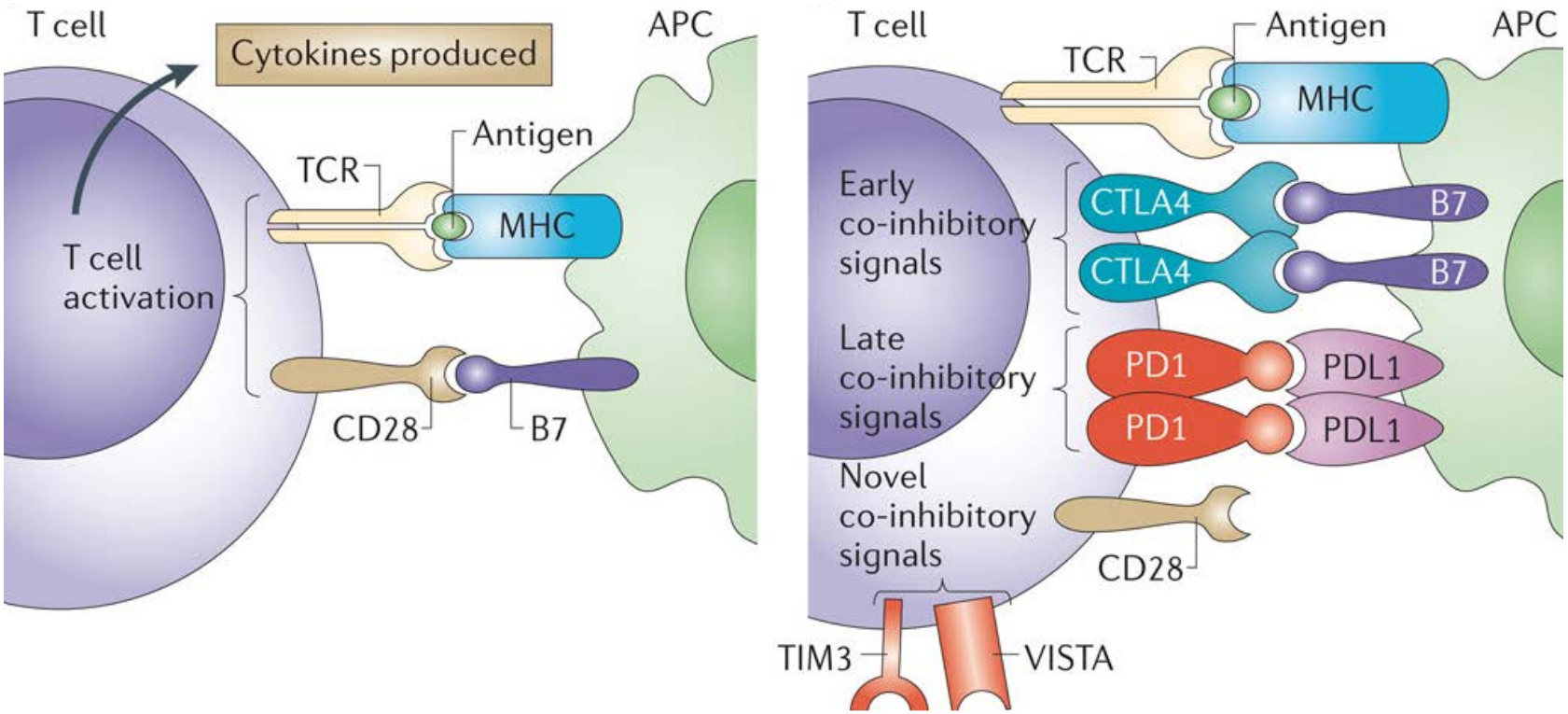
Cancer immunotherapy strategies

- Cell based immunotherapy (Allogeneic SCT, adoptive T-cell transfer etc.)
- Cytokines (for example, IL-2 or interferon-α)
- Enhancement of antigen presentation (for example, stimulation of Toll-like receptors 7, 8 or 9, dendritic cells or anti-CD40 agonistic antibody)
- Monoclonal antibody therapy (Passive, i.e. cetuximab)
- Vaccination (NSCLC: MAGE A3, MUC-1, EGFR, Belagenpumatucel-L)
- ***Checkpoint inhibitors (Anti-CTLA4, -PD-1, -PD-L1)***

Molecular mechanism of checkpoint inhibitors



Sharma, Wagner and Allison. Nature Reviews Cancer, Nov 2011.

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Nivolumab (Opdivo) for squamous NSCLC, 2nd line after platinum-based chemotherapy (CheckMate-017)

- The FDA has approved the anti–PD-1 agent nivolumab (Opdivo) for the treatment of patients with advanced squamous non–small cell lung cancer (NSCLC) who have progressed on or after platinum-based chemotherapy. The approval comes 3 months ahead of the FDA's scheduled decision date.

- The approval is based on data from the phase III CheckMate-017 trial:
  - N=272.
  - Nivolumab 3 mg/kg IV every 2 weeks (n = 135) or docetaxel 75 mg/m2 (n = 137) IV every 3 weeks.
  - Nivolumab versus docetaxel OS 9.2 vs 6.0 mo (HR = 0.59; 95% CI, 0.44-0.79; P=0.00025) -> Nivolumab improved overall survival by 3.2 months.

- Second trial: Single-arm, multinational, multicenter. Metastatic squamous NSCLC after platinum-based therapy and one additional systemic regimen.
  - N=117
  - ORR 15% (95% CI: 9, 22), all PR
  - 10 of 17 responding patients (59%) response durations of 6 months

- Immune-mediated AE: Pneumonitis, colitis, hepatitis, nephritis/renal dysfunction, hypothyroidism, and hyperthyroidism.

FDA announcement 03/04/2015.

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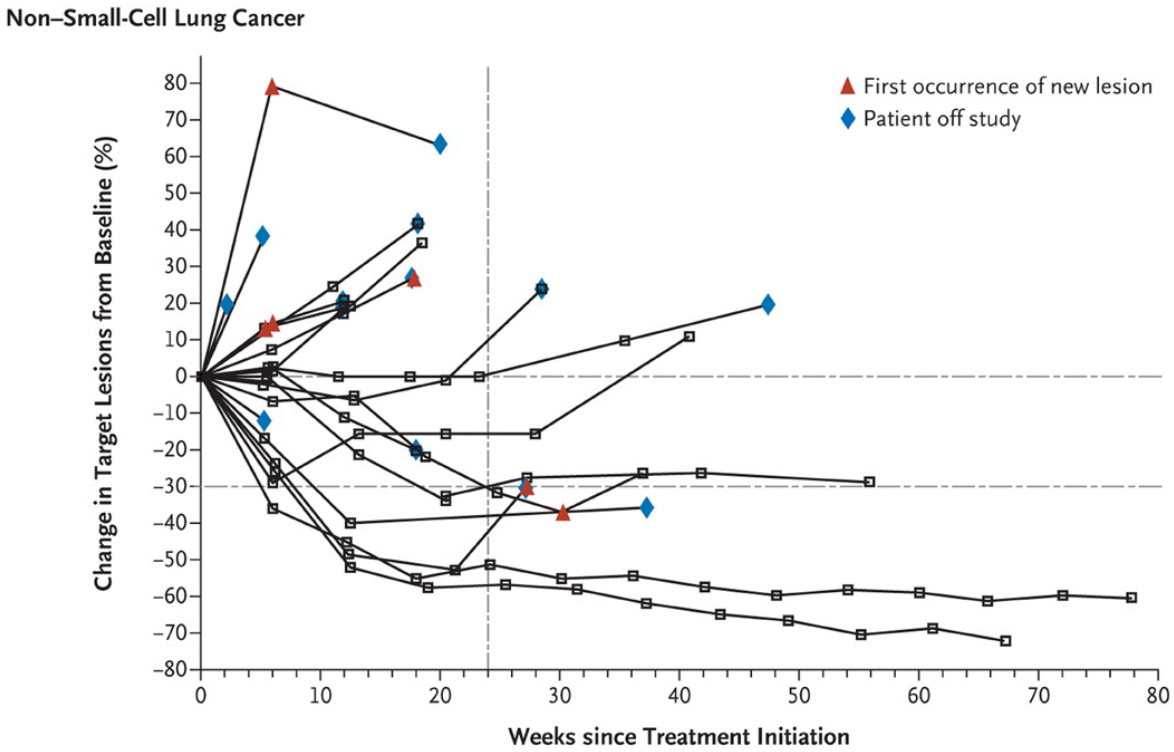
Activity of Anti-PD-L1 in NSCLC ph-I trial



BMS-936559: Fully human, anti-PD-L1, IgG4 inhibits binding of PD-L1 to PD-1 and CD80

NSCLC:

- All doses: CR/PR 10% (N=5/49)
- 10mg/kg: CR/PR 16% (N=4/25), duration 3.5, 9.8, 12.6+, 16.6+ mo

Brahmer et al. N Engl J Med. 2012 Jun 28;366(26):2455-65.

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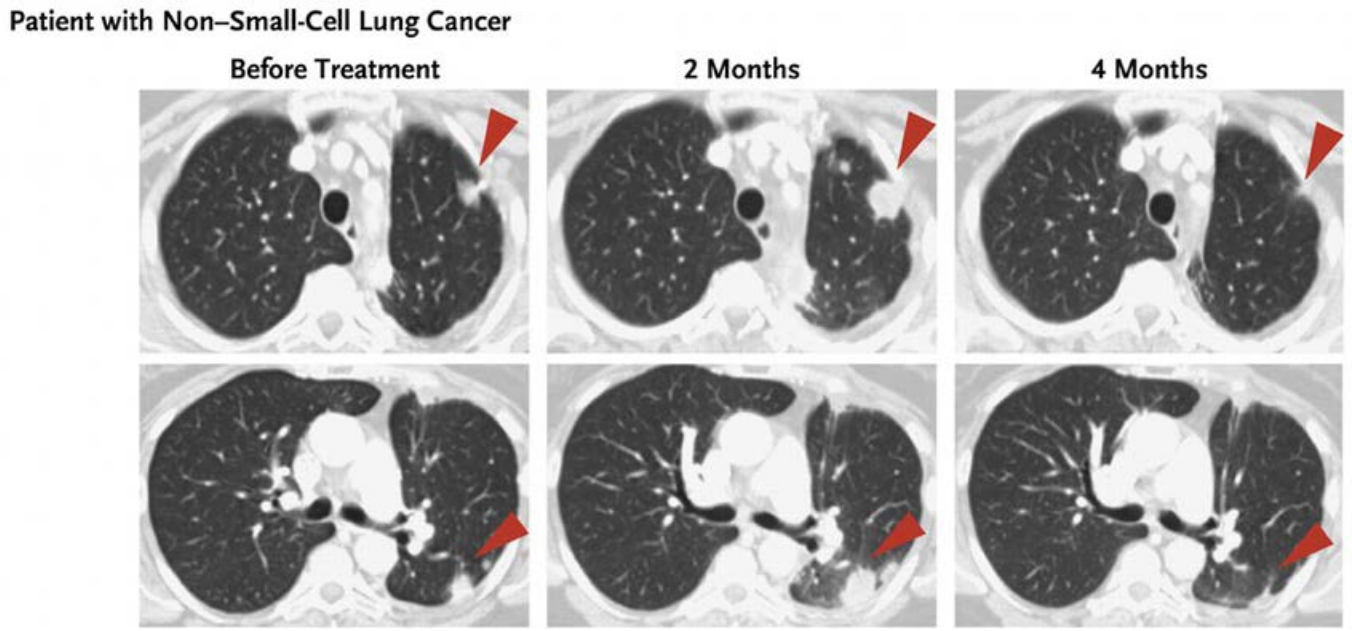
Activity of Anti-PD1 in NSCLC ph-I trial



BMS-936558 (MDX-1106 and ONO-4538) anti-PD1

NSCLC:

- PR/CR SCC **33%** (N=6/18)
- PR/CR Non-squamous **12%** (N=7/56)

Topalian et al. N Engl J Med. 2012 Jun 28;366(26):2443-54.

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Third-line and fourth-line chemotherapy outcomes for advanced NSCLC

- Asahina et al. Clin Lung Cancer. 2012 Jan;13(1):39-43:
  - N=599.
  - 2nd line 69%, 3rd line 38%, 4th line 18%.
  - Most frequently used (Japan): Docetaxel, gefitinib, and S-1.
  - 3rd line chemo: RR 17% and DCR 34%; 4th line chemo RR 11% and DCR 25%.

- Massarelli et al. Lung Cancer. 2003 Jan;39(1):55-61:
  - 43 patients between 1993 and 2000.
  - two prior chemotherapy regimens that included platinum and docetaxel.
  - RR 1st line 21%, 2nd line 16%, 3rd line 2%, 4th line 0%.
  - Median OS from last treatment (3rd or 4th line) 4 months.

EGFR AND EGFR INHIBITORS

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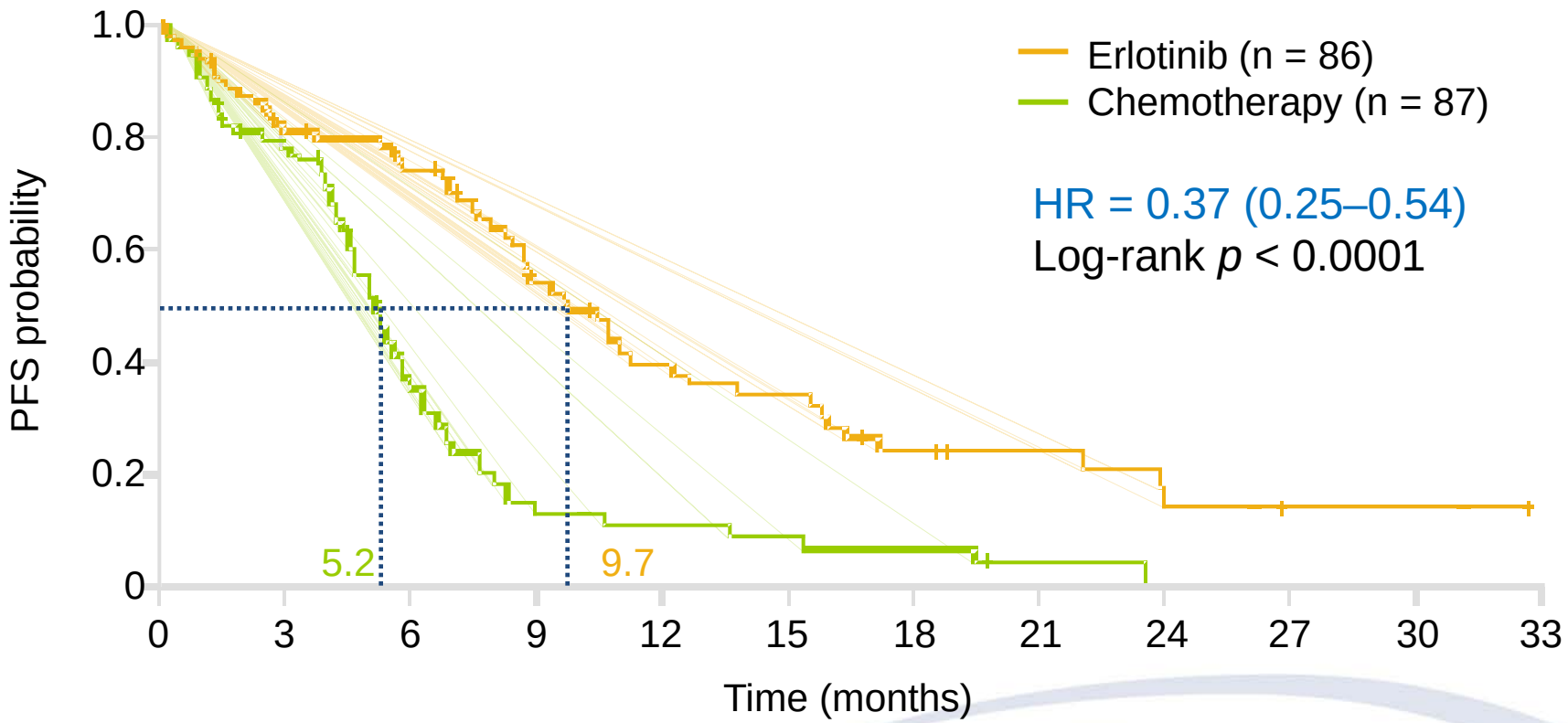
EGFR inhibitors for lung cancer patients with EGFR mutations



Rosell R et al. Proc ASCO 2011;Abstract 7503.

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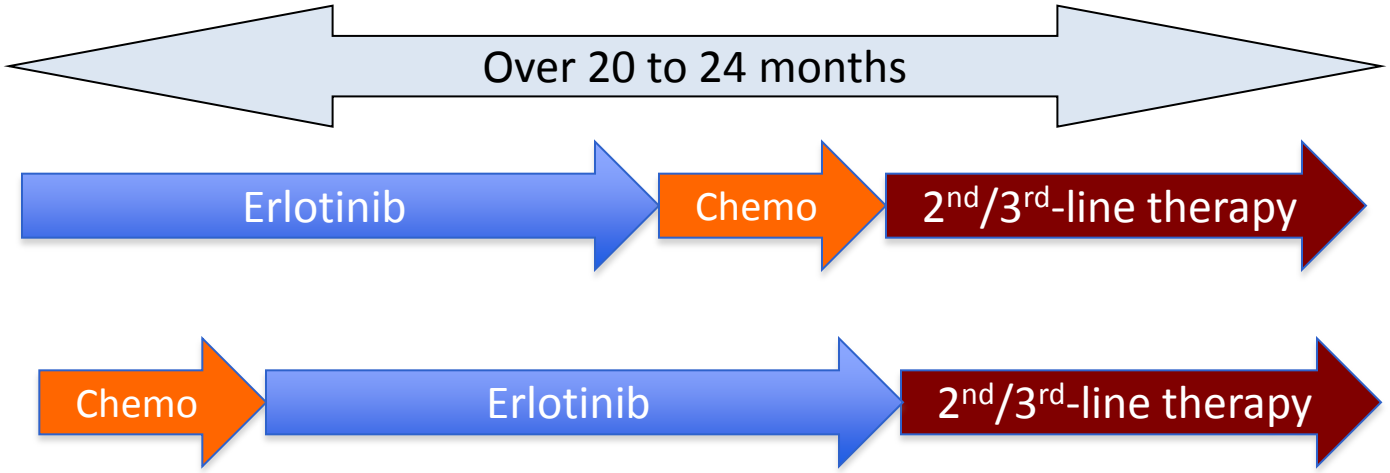
Crossover

Treatment sequence in patients with EGFR mutation



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New EGFR TKIs from Clovis and AZ targeting T790M

- Rociletinib (CO-1686) (irreversible)
  - 26th EORTC-NCI-AACR 2014
  - ph-I/II
  - 67% objective response rate (ORR) in pretreated T790M+ patients
  - 625mg or 500mg BID (clinical dose group)
  - Median PFS of 10.4 months; data continue to mature
  - Side effects: Hyperglycaemia, nausea and diarrhea (mostly grade 1 or 2), rash

- AZD9291 (irreversible)
  - ASCO 2014
  - ph-I
  - N=199 NSCLC EGFR pos patients, who progressed after one or more standard EGFR therapies
  - Overall RR 51%
  - T790M mutation pos (N=89) RR 64%
  - T790M neg RR 23%
  - Longest response lasting more than 8 months, data continue to mature

ALK (EML4-ALK) AND ALK INHIBITORS

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EML4-ALK is a potent cancer driver

- Expression plasmids generated for wild-type EML4 and ALK, wild-type and mutant EML4-ALK, and v-Ras were introduced into mouse 3T3 fibroblasts

- In vitro cell transformation and in vivo tumor formation in mice observed with only EML-4ALK, NPM-ALK or v-Ras expressing cells

- Inhibition of ALK leads to dramatic in vivo tumor regression

Soda M et al. Nature 2007;448:561-567.

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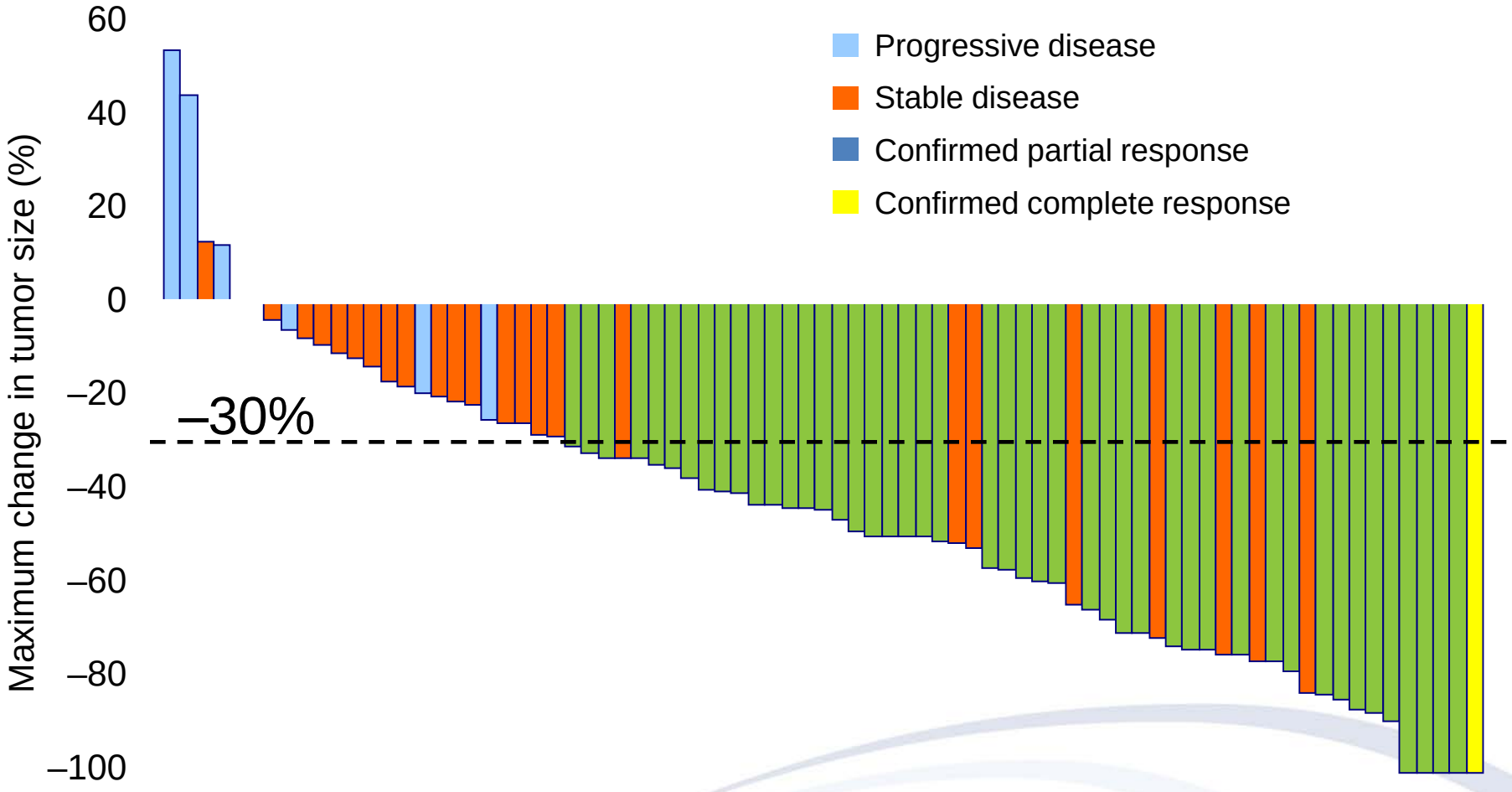
Tumor response to Crizotinib for patients with *ALK*-positive NSCLC



Kwak EL et al. N Engl J Med 2010;363:1693-703.

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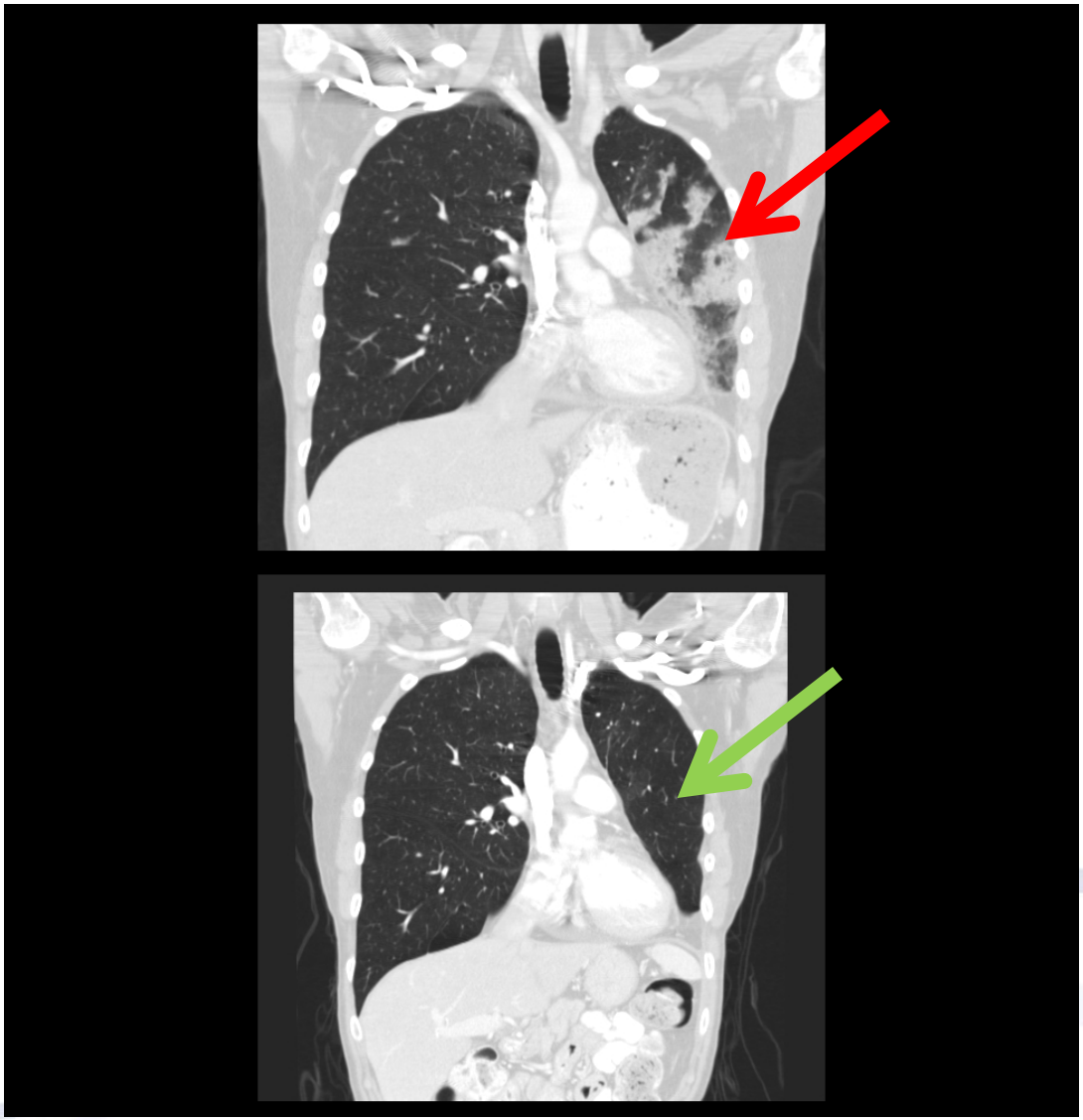
Crizotinib response example

Pre-treatment

After 2 cycles crizotinib



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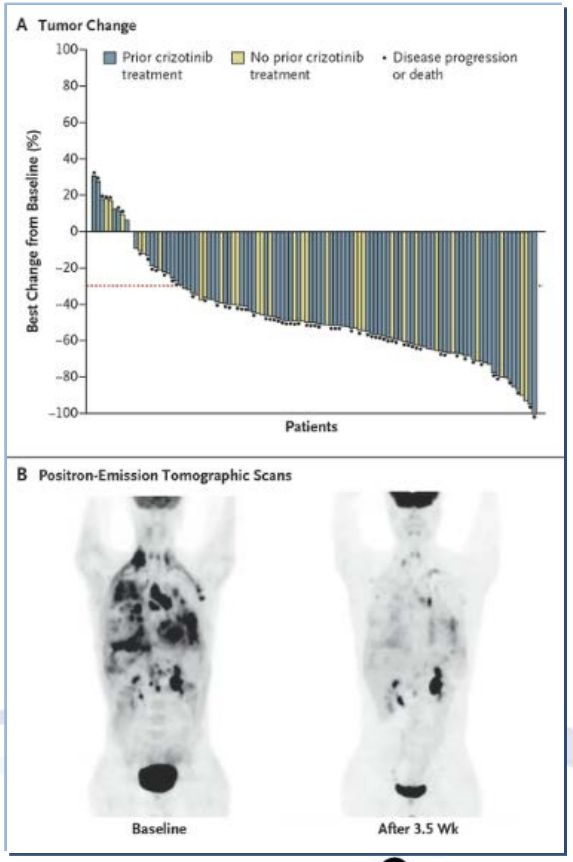
New ALK TKIs: Certinib and Alectinib

- Ceritinib
  - FDA approved.
  - Ceritinib in ALK-Rearranged Non–Small-Cell Lung Cancer. Shah et a. N Engl J Med. 2014 Mar 27;370(13):1189-97.
  - Activity in CNS metastasis, ASCO 2014.

- Alectinib
  - Not FDA approved, trials ongoing.
  - Activity in CNS metastasis.
  - Ph-I 47 patients, ALK positive, s/p crizotinib:
    - Alectinib 300 mg to 900 mg twice daily.
    - RR 55%, CR 2%.
    - CNS metastases 52% RR.



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QUESTIONS

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