Lung Cancer 101

Wallace Akerley

Huntsman Cancer Institute @
University of Utah

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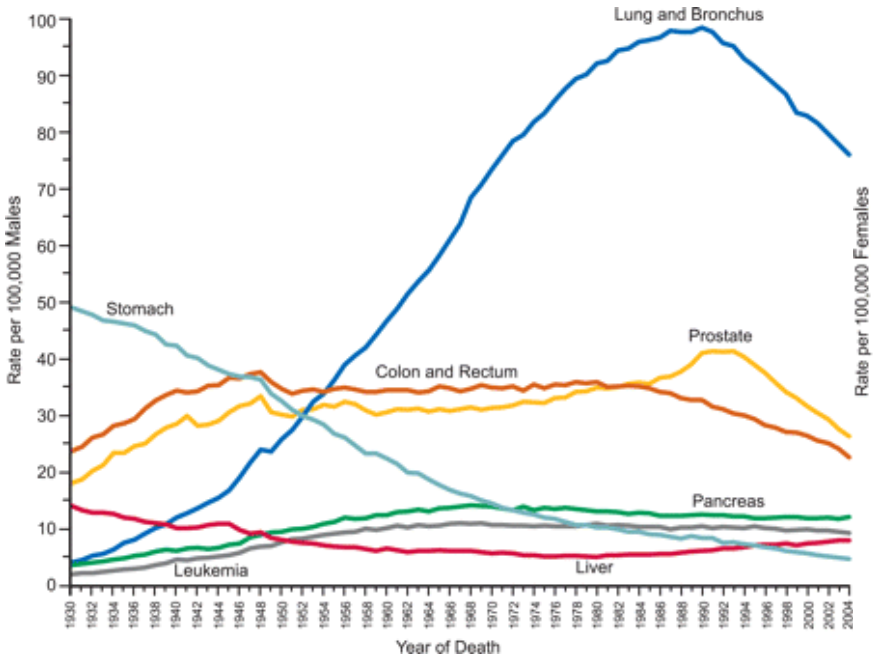
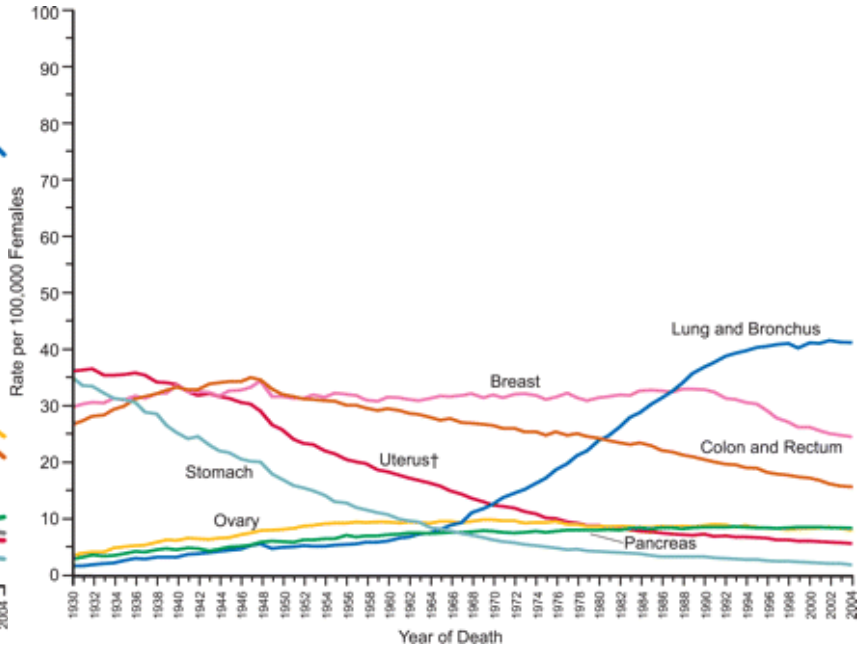
USA Cancer Death Rates





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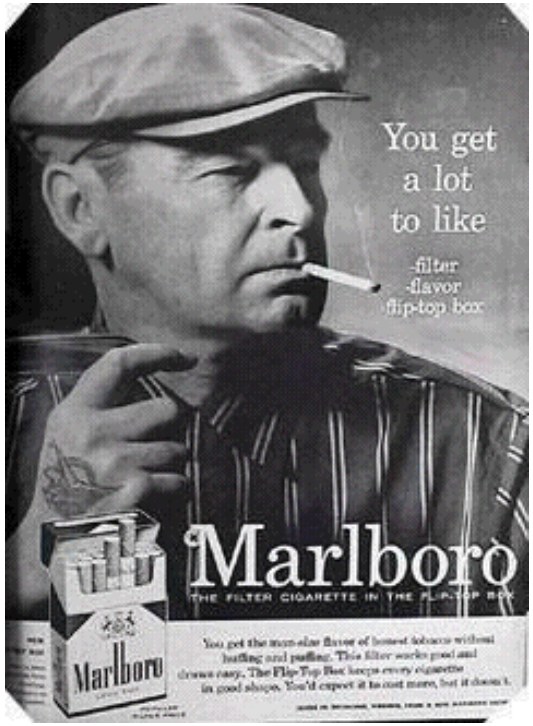
Invisible Ribbon

- Lung Cancer – Unrecognized
- Invisible Killer
- Number 1 Cancer Mortality in the USA
- Lacks Advocacy
- Guilt

A L C A S E


You get
a lot
to like
-filter
-flavor
-flip-top box
Marlboro
THE FILTER CIGARETTE IN THE FLIP-TOP BOX
Marlboro

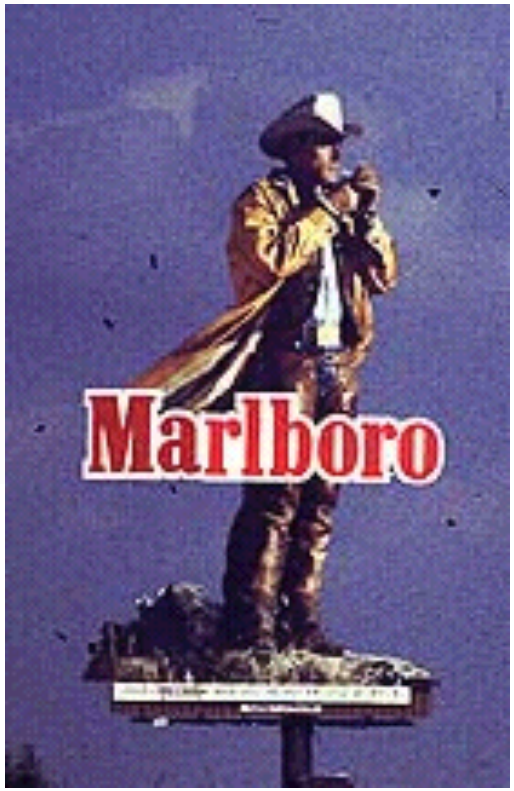
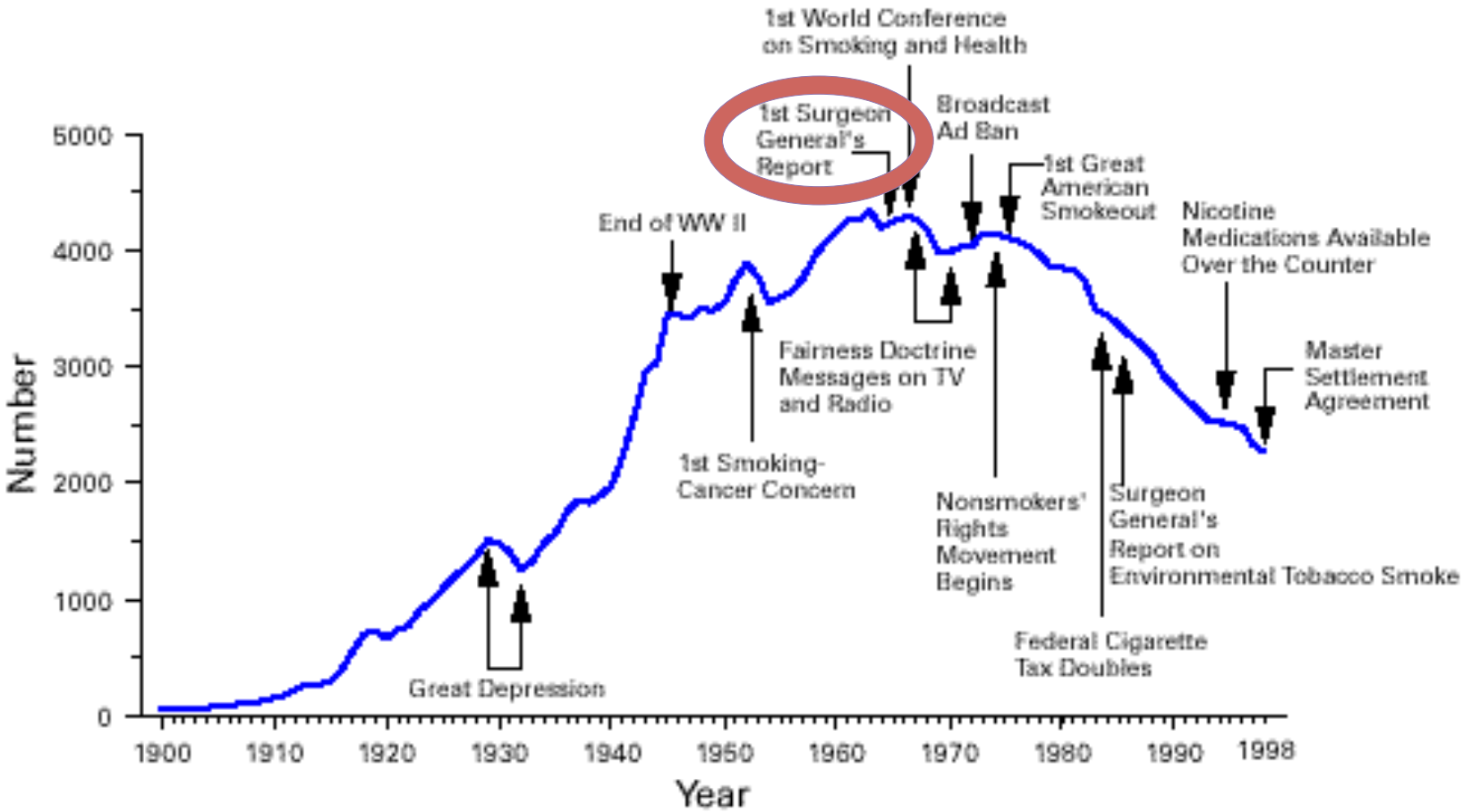

Marlboro

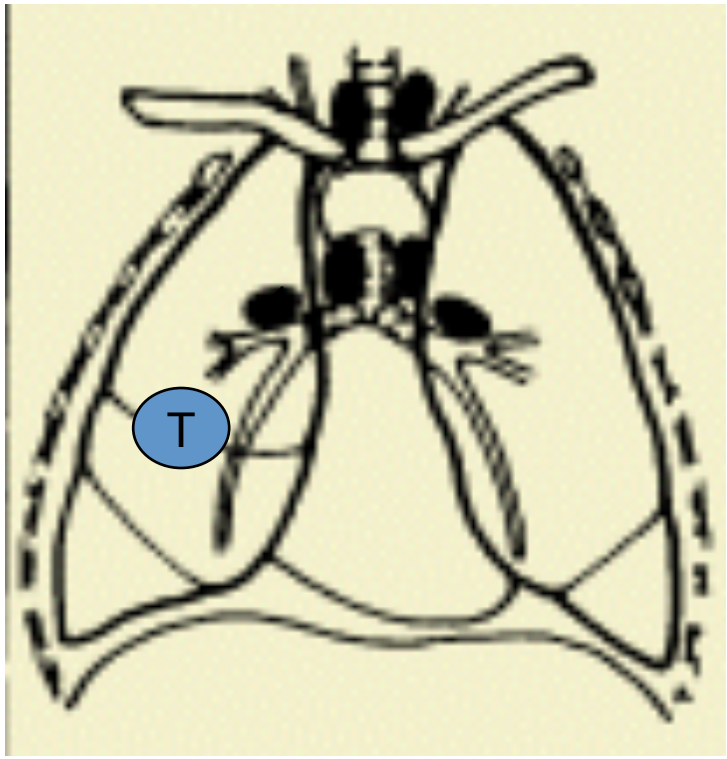
FIGURE 1. Annual adult per capita cigarette consumption and major smoking and health events — United States, 1900–1998



Sources: United States Department of Agriculture; 1986 Surgeon General's Report.

Staging and Treatment of Non-small Cell Cancer

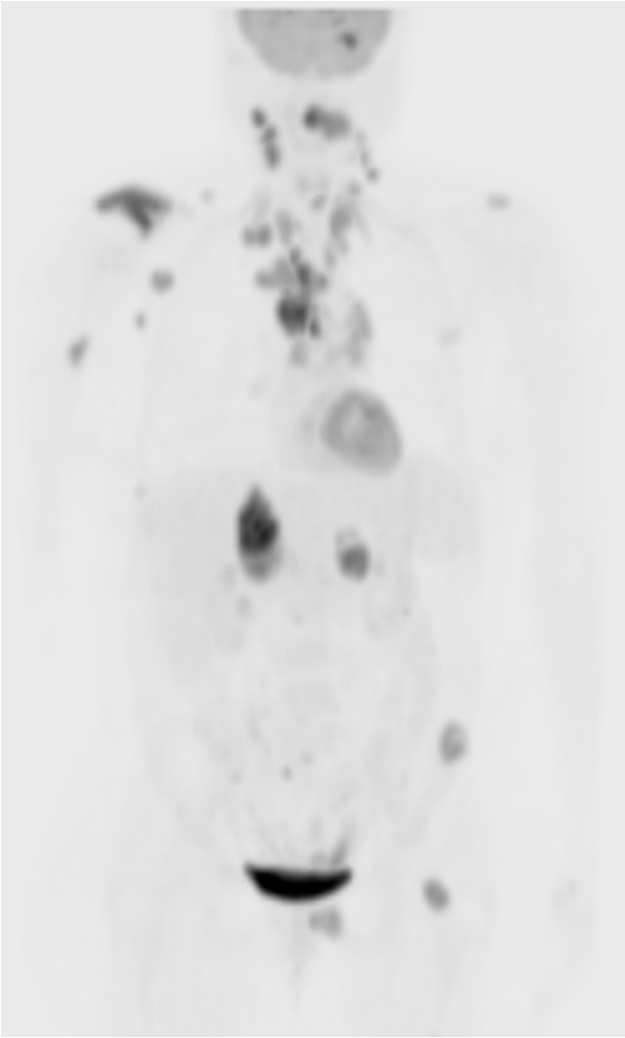
Non-Small Cell Lung Cancer
Simplified TNM Staging

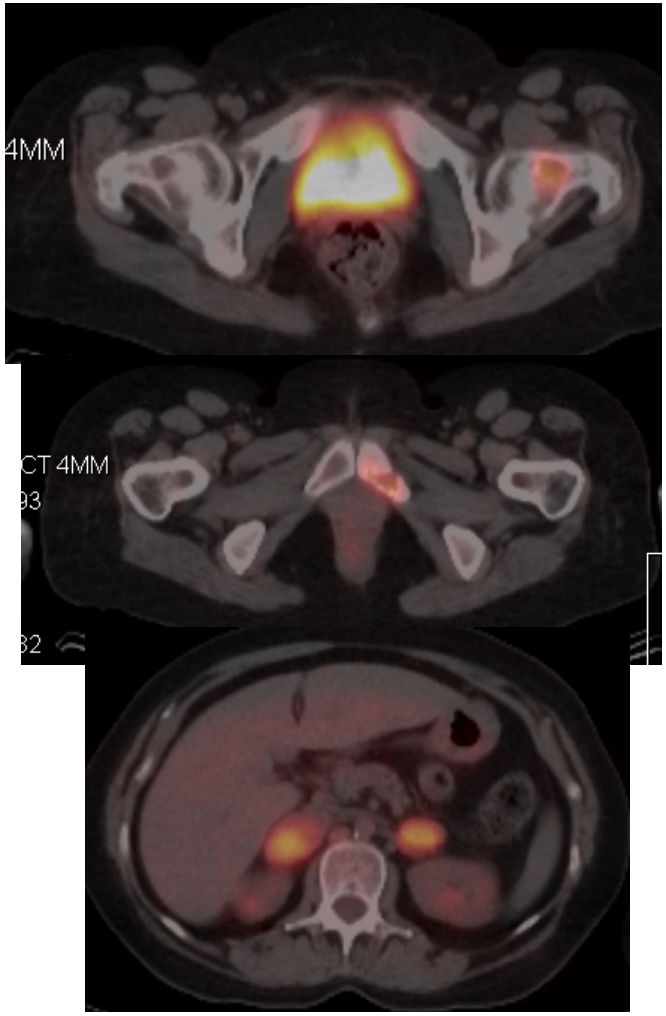


Stage		
I	T only	
II	N1	Local
III	N2	Regional
IV	M	Distant

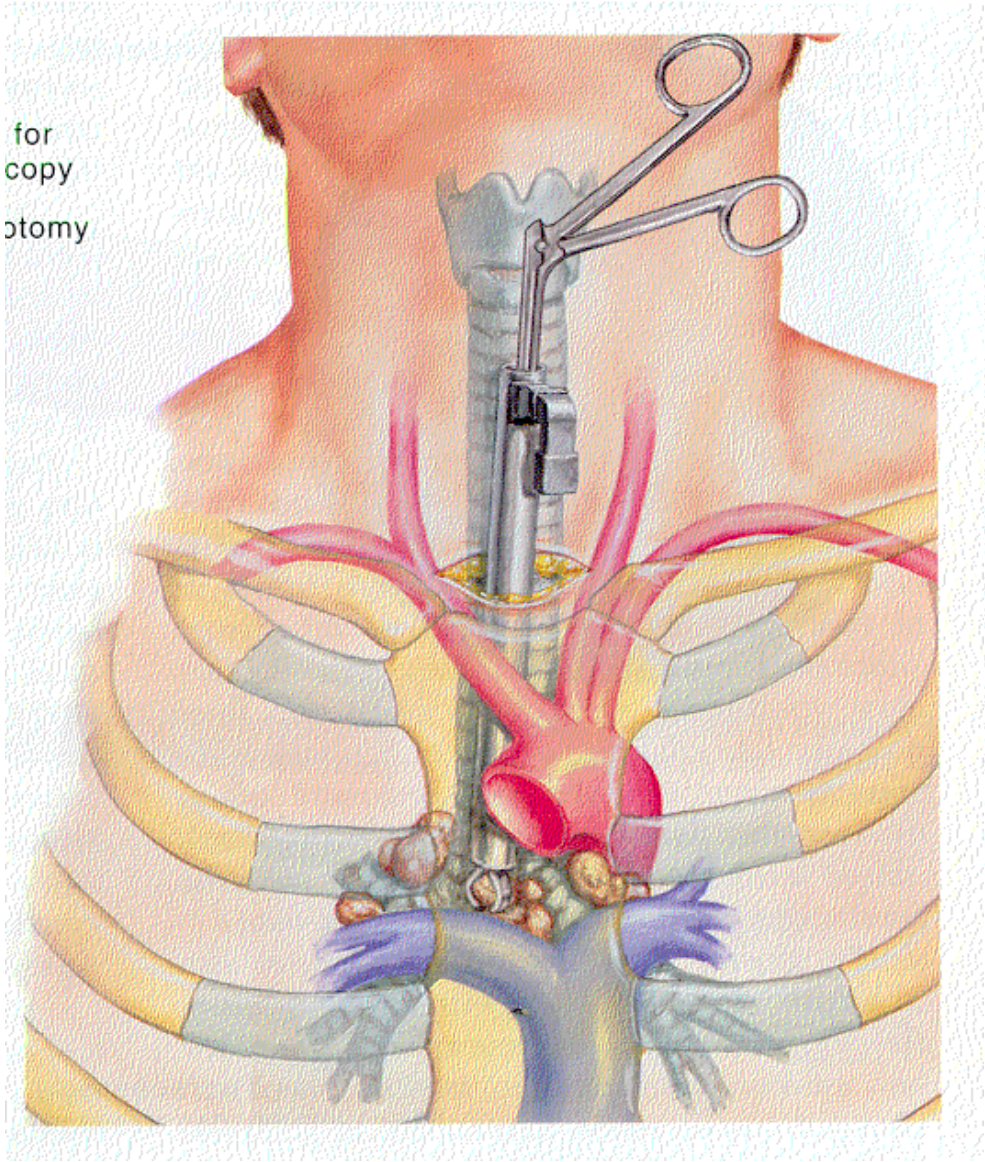
Tumor Node Metastasis

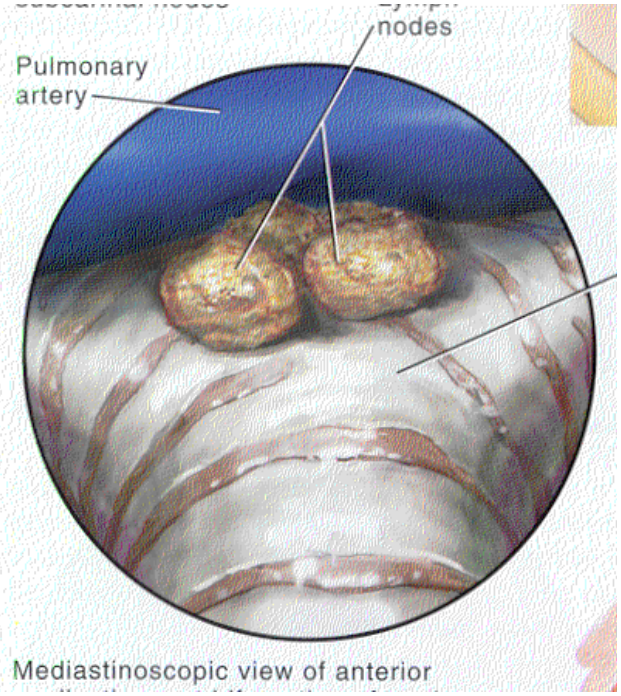
Positron Emission Tomography





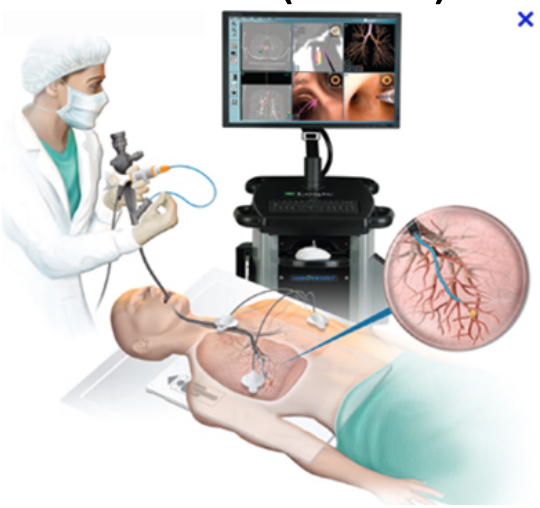
Mediastinoscopy

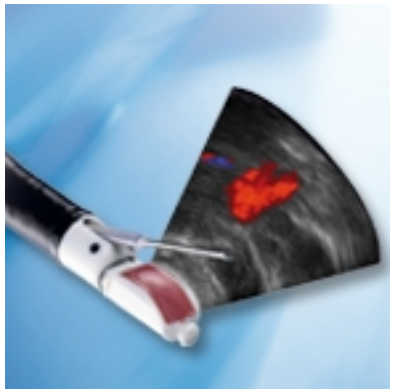




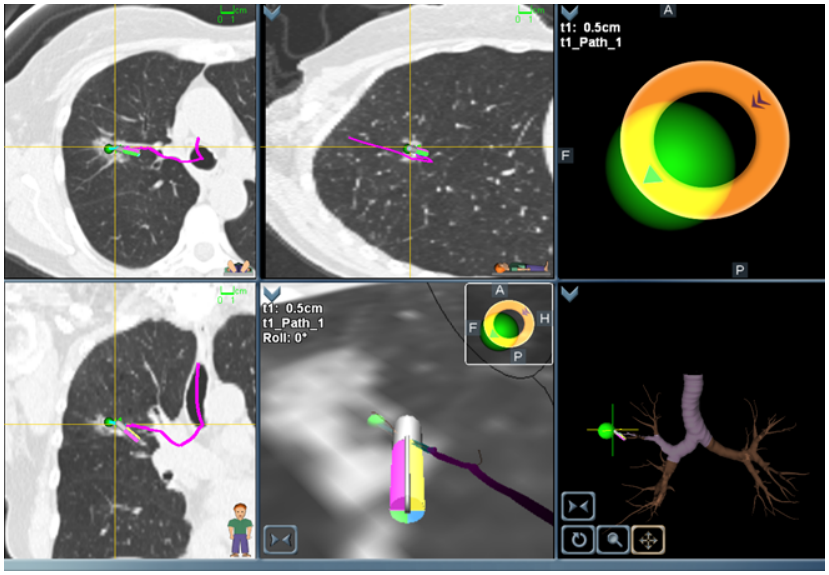
Bronchoscopy

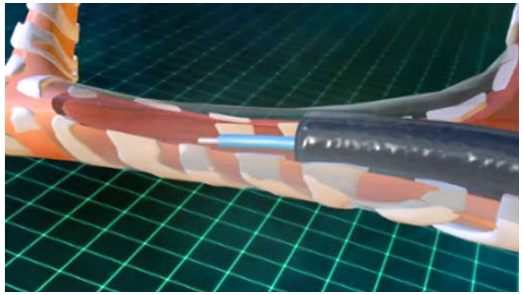
Endobronchial Utrasound (EBUS)



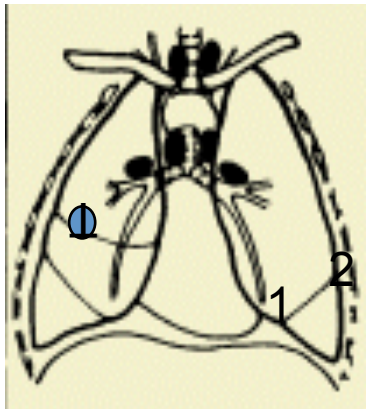


Navigational Bronchoscopy





Non-Small Cell Lung Cancer
Treatment = Surgery



Stage

I	T only	
II	N1	Local
III	N2	Regional

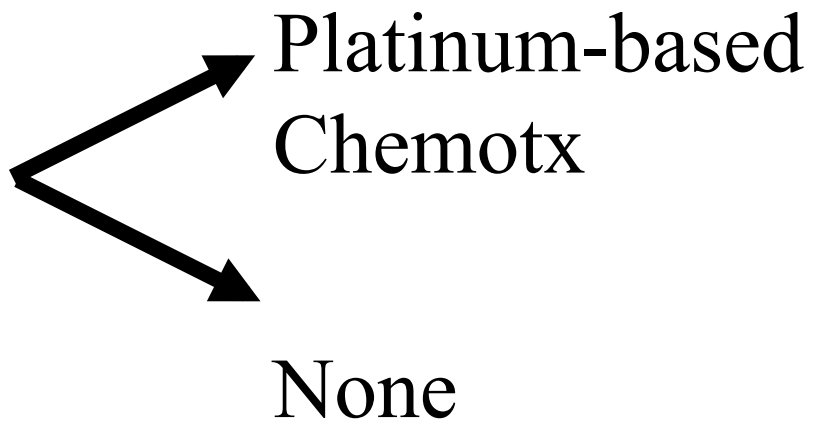
Surgery
Consider Adjuvant!

Tumor Node Metastasis

Adjuvant Therapy in NSCLC

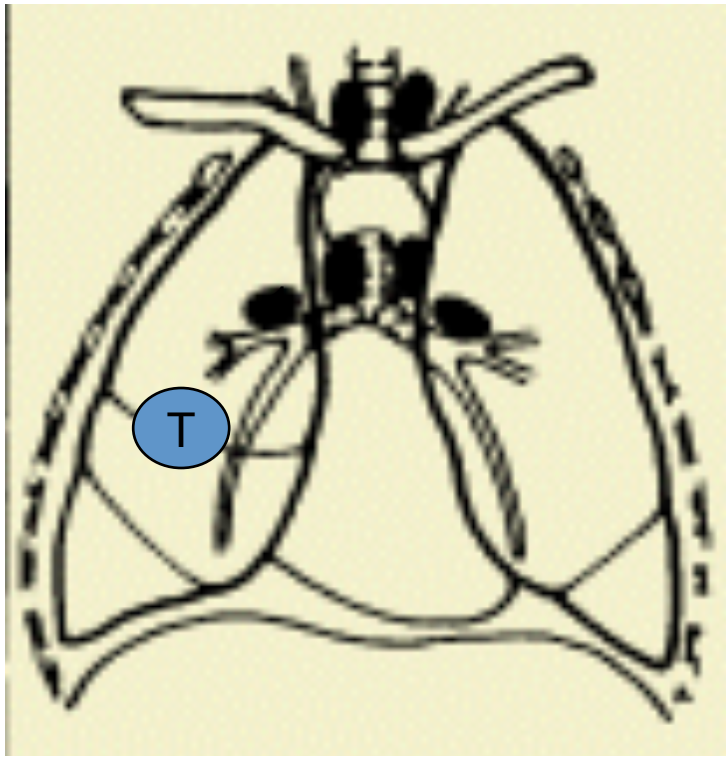
Resected NSCLC

Stage I-III



IALT

Non-Small Cell Lung Cancer
Simplified TNM Staging



Stage

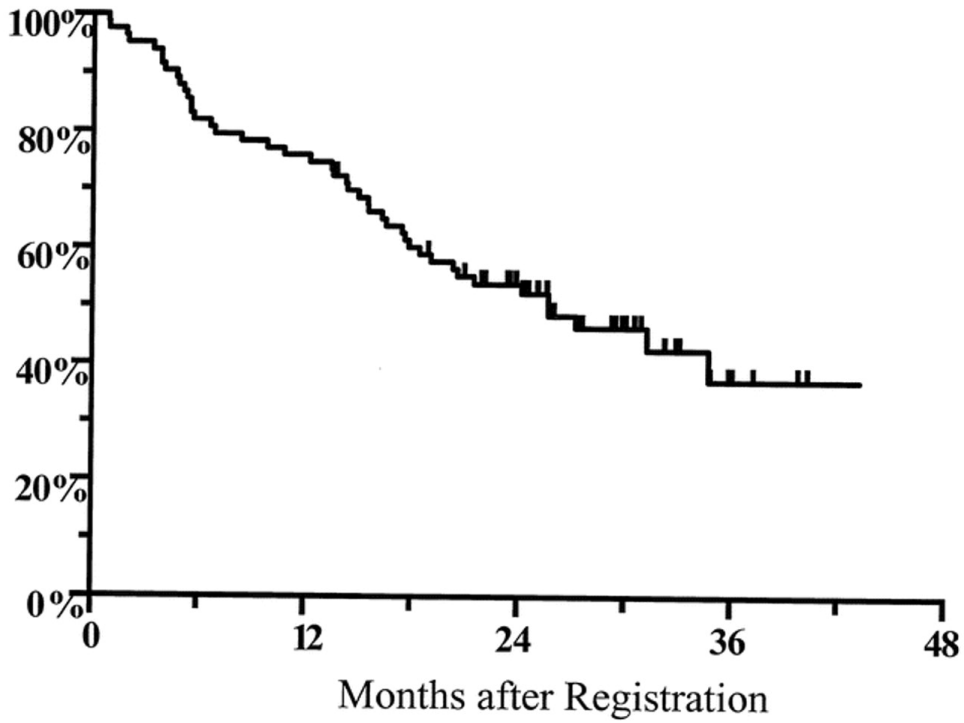
III	N2	Regional

Tumor Node Metastasis

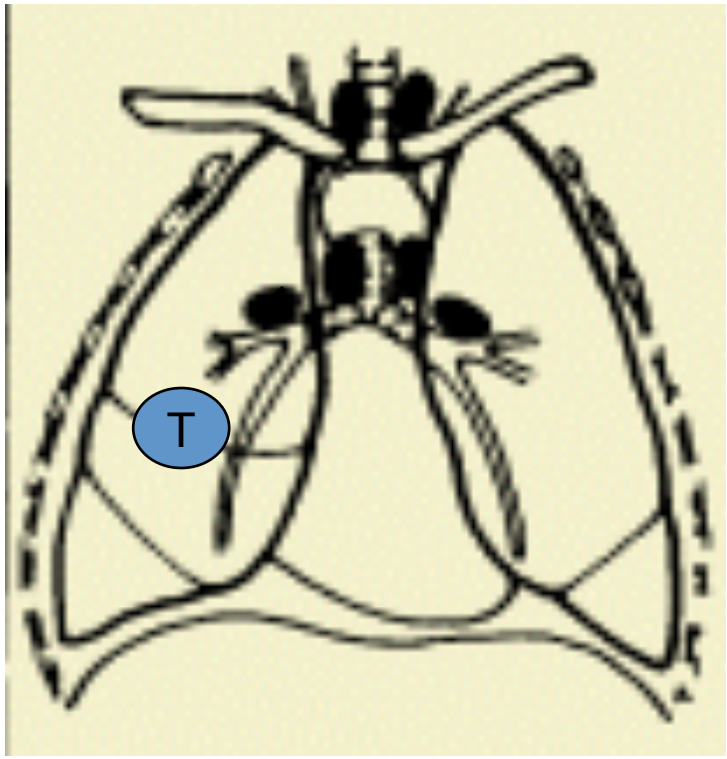
SWOG 9504
Gandara JCO 21:2004, 2003

Study	N	MST	2-YS	3-YS
S9504 (PE/RT ->D)	83	26m	54%	37%

Cure is Possible



Non-Small Cell Lung Cancer
Simplified TNM Staging



Stage

IV	M	Distant

Tumor Node Metastasis

Distant/Metastatic NSCLC

- Systemic Chemotherapy
  - 1st Line
  - 3rd Line
- Personalized- Precision Oncolgy
  - EGFR, ALK mutated
- Immunotherapy
  - 2nd Line

NSCLC Therapy

- Past
  - Non-small Cell Lung Cancer – One Group
  - Organ based Therapy
- Present
  - NSCLC - Many types
    - Defined by Histology, Genetics and Immune Profiles
    - Tissue and Blood Profiling
  - Precision Medicine
    - EGFR, ALK, PD-1, Squamous, BRAF, HER2, ROS, RET, MET
    - Plasticity - Serial Biopsy
  - Immunotherapy
    - Biomarker (PD1, PD-L1)

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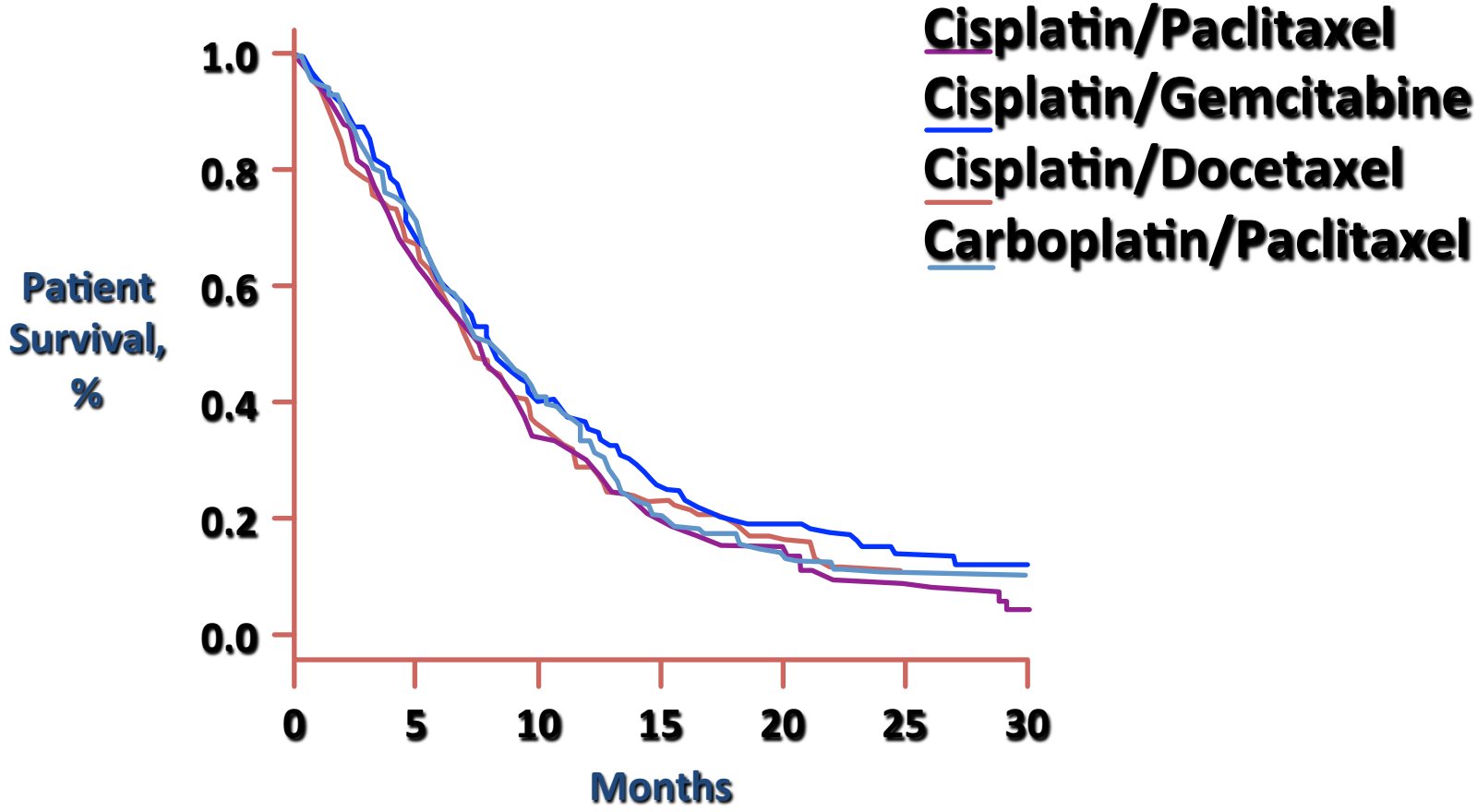
ECOG 1594
Survival by Treatment Arm



Reprinted with permission from Schiller JH et al. *N Engl J Med*. 2002;346:92-98.

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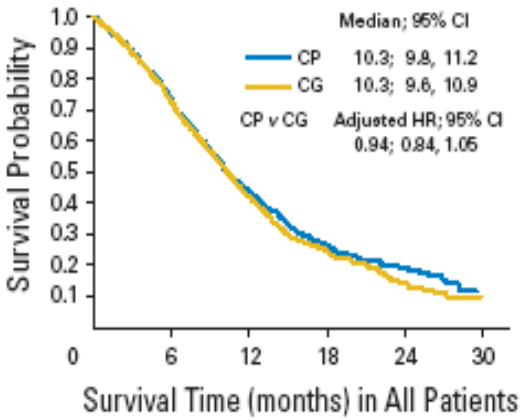
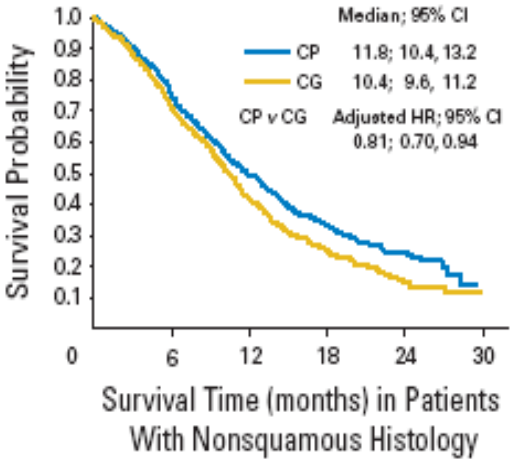
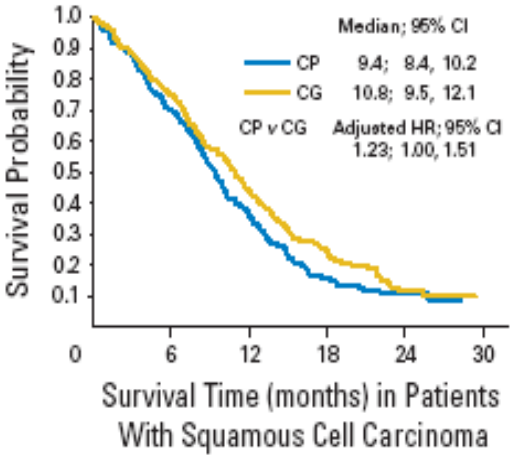
Gem/Cis vs Pemetrexed/Cis in NSCLC







<u>NSCLC inappropriate</u>

1.5 m improvement

Pem superior in Non-Sq
and Gem superior in Sq

Scagliotti. J Clin Oncol. 2008 Jul 20;26(21):3543-51.

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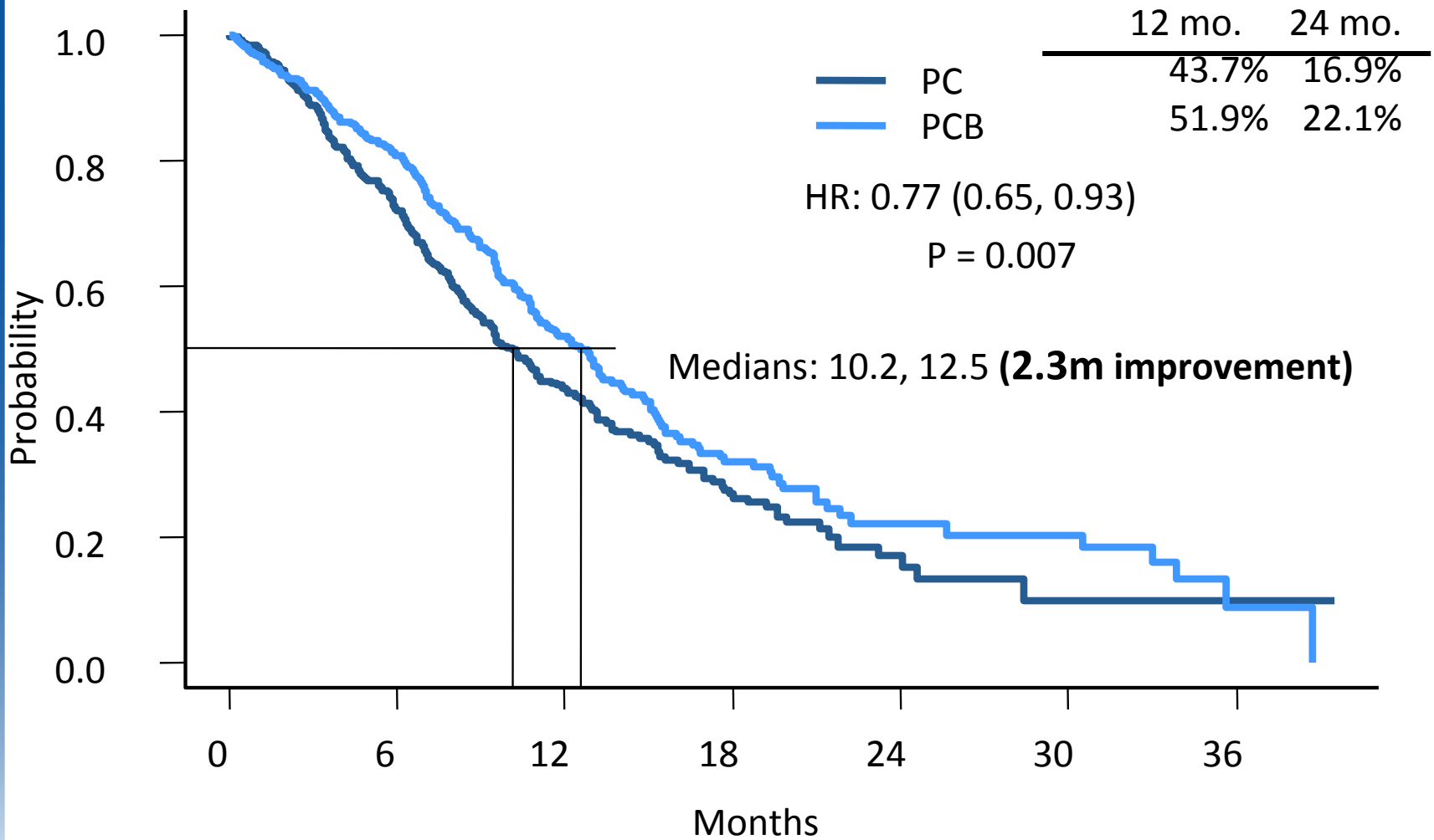
Phase III of Bevacizumab in Non-Squamous NSCLC: ECOG 4599



Sandler NEJM 355:2542-2550, 2006

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Cancer Systemic Therapy: Conventional, Targeted, Personalized

Anti-Proliferation

Any Targets other than Proliferation

Tumor targets define therapy

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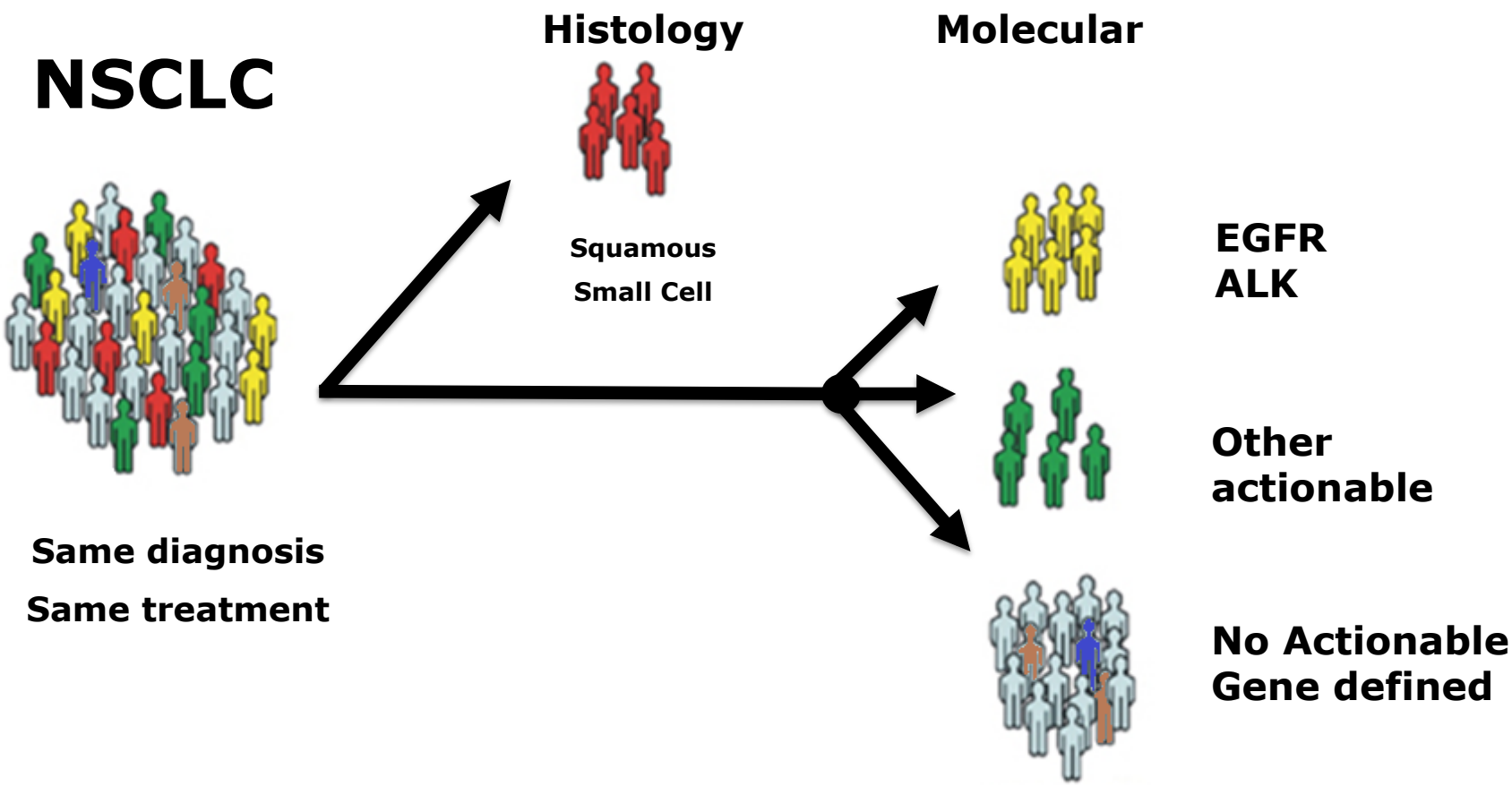
Personalized Oncology



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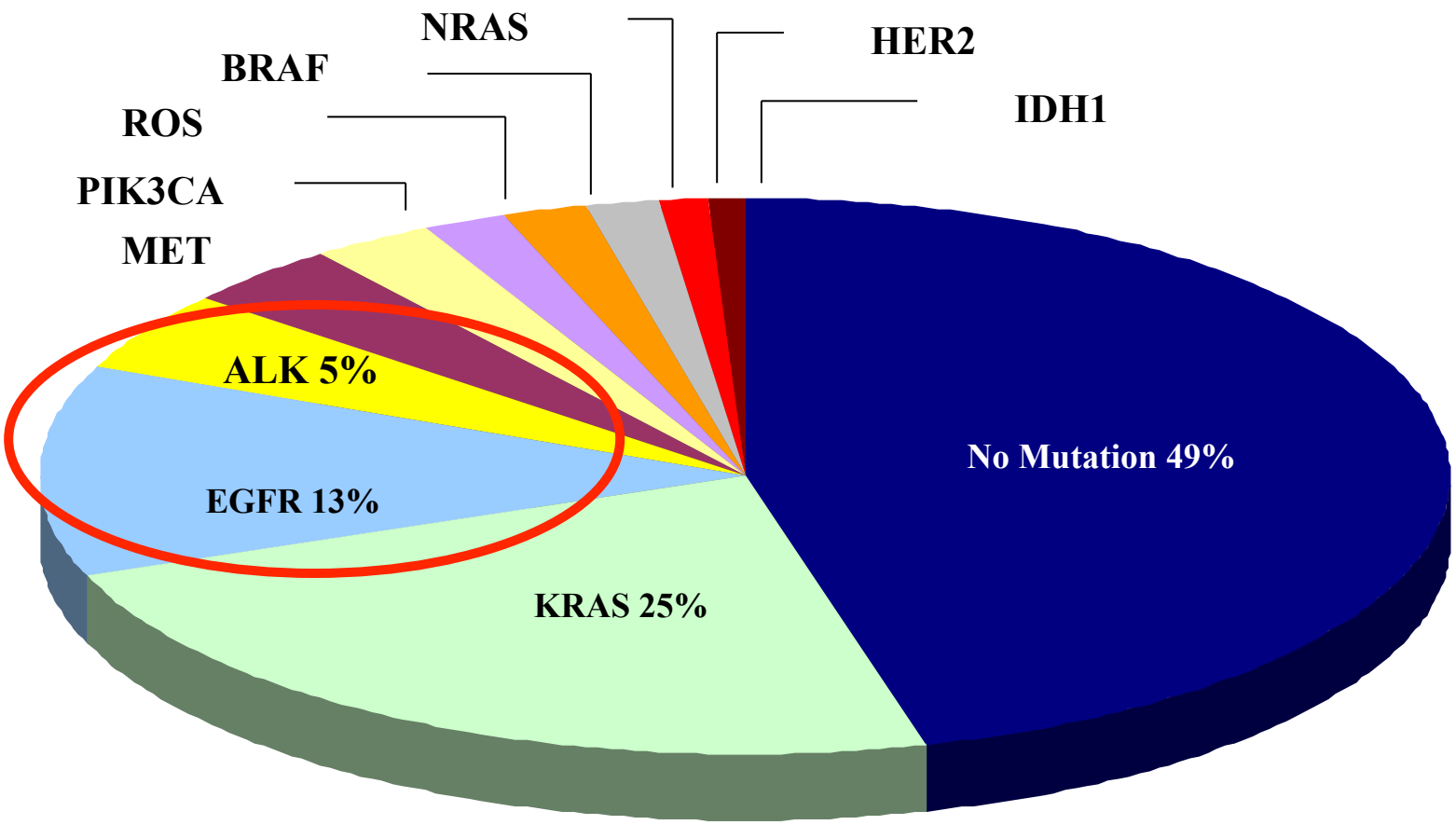
Over 50% of NSCLC have an Identifiable Driver Mutation



Sequist et al, Ann Oncol 2011; Kris et al, ASCO 2011

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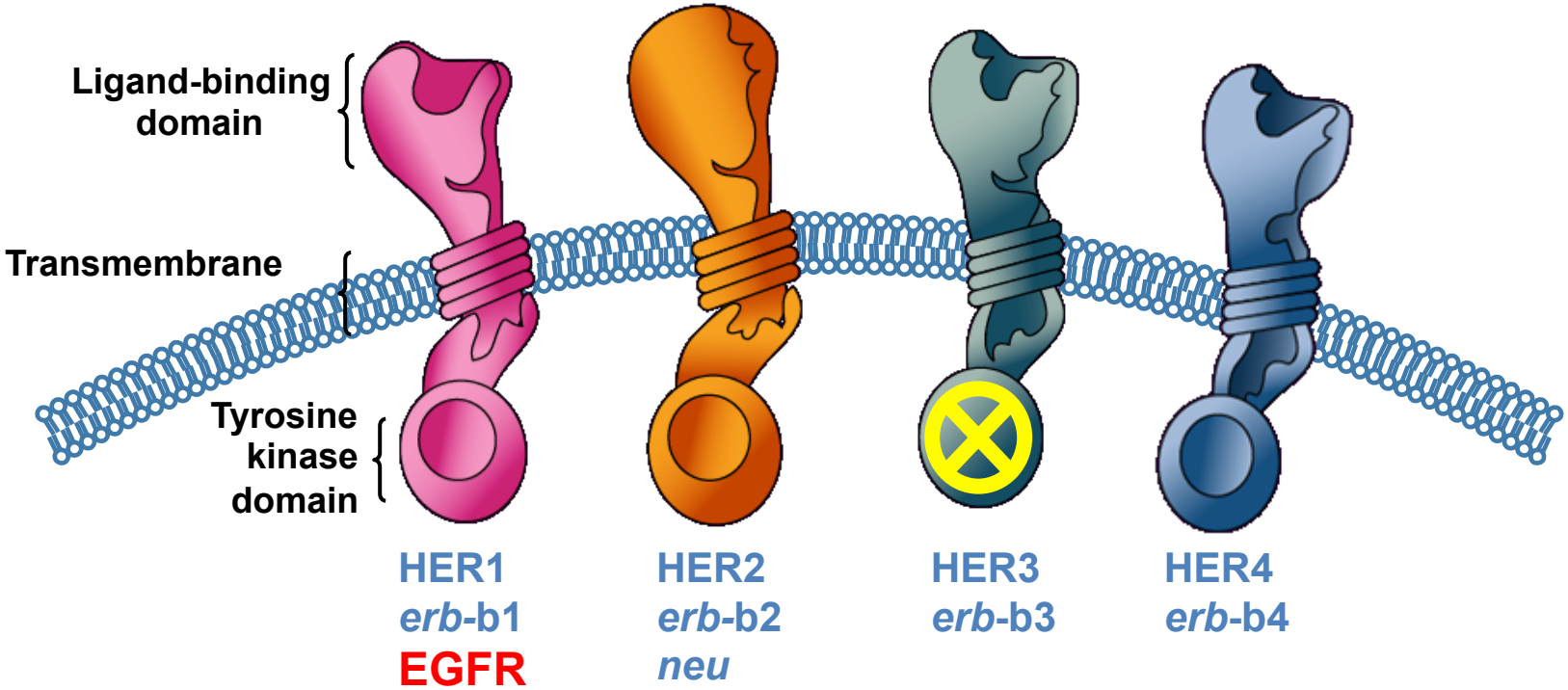
EGFR (epidermal growth factor receptor)
HER (human epidermal receptor 2)



Roskoski. *Biochem Biophys Res Commun*. 2004;319:1.
Rowinsky. *Annu Rev Med*. 2004;55:433.

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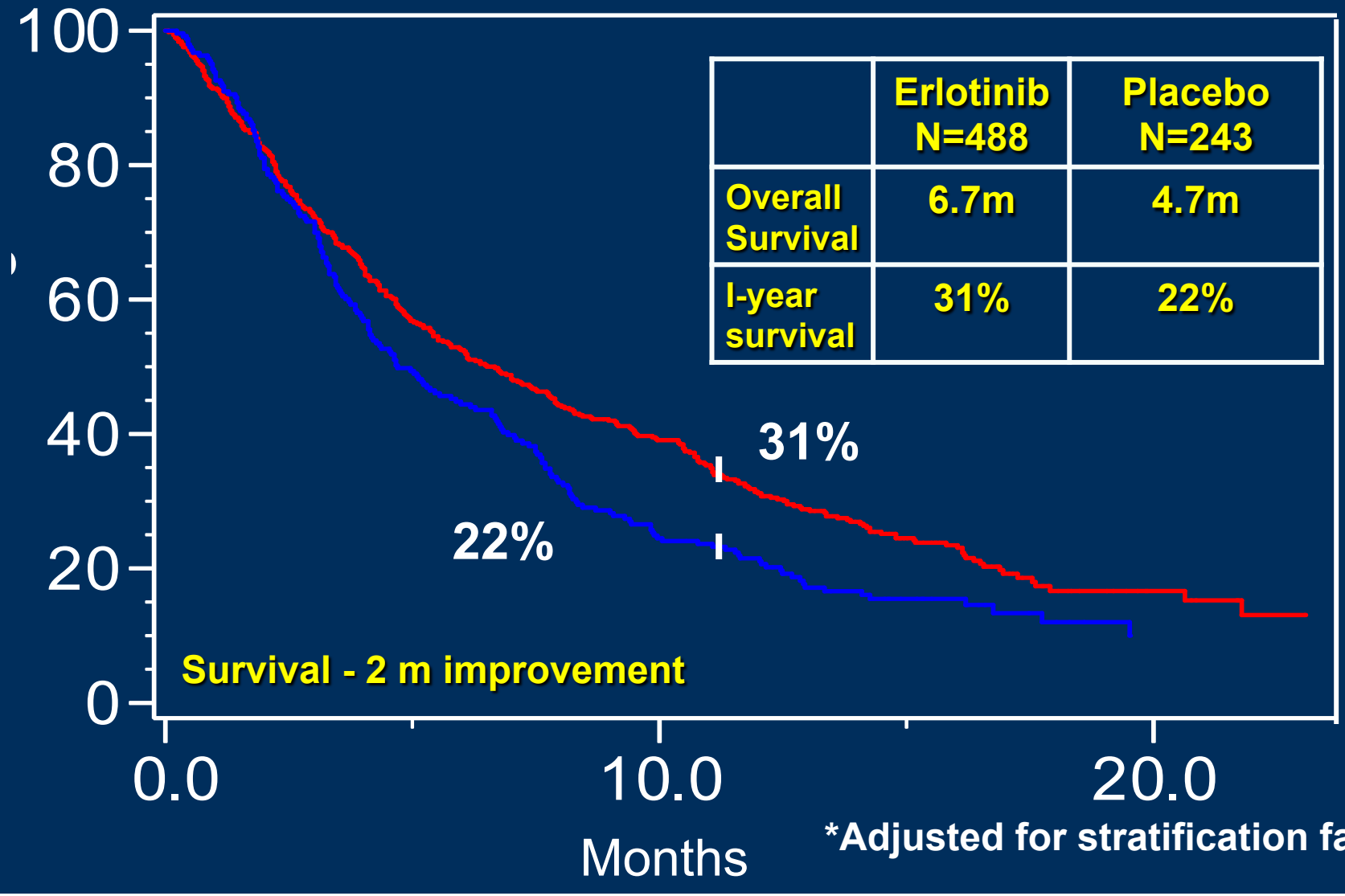
BR.21 Overall Survival



	Erlotinib N=488	Placebo N=243
Overall Survival	6.7m	4.7m
I-year survival	31%	22%

*Adjusted for stratification factors

IPASS (Iressa Pan Asian Study) 1st Line

- Paclitaxel-Carboplatin v Gefitinib
- Non smoker or light
  (quit >15y + <10 Pk-Yr)
- N=1217, 261 of 437 (60% mut+)
- Mut (del 19 54%, L858R 43%, ex 20 4%)

	Gefitinb	PC
Overall RR	43%	32%
Mut(+)	71%	47%
Mut (-)	1%	24%
Survival	18.6m	17.3m

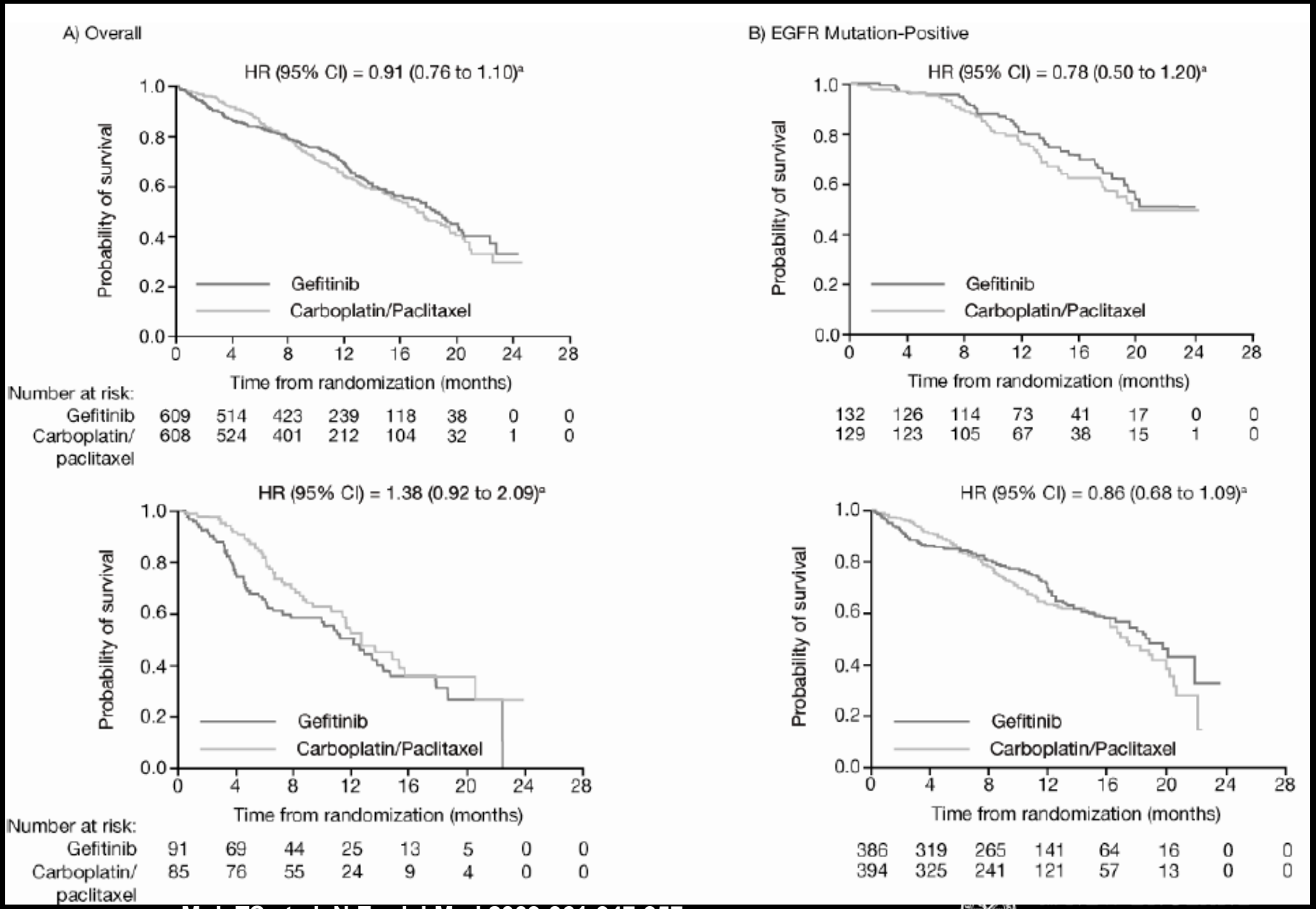
Characteristic	Gefitinib (N=609)	Carboplatin–Paclitaxel (N=608)
Age — yr		
Median	57	57
Range	24–84	25–84
Sex — no. (%)		
Male	125 (20.5)	127 (20.9)
Female	484 (79.5)	481 (79.1)
Ethnic group — no. (%)†		
Chinese	314 (51.6)	304 (50.0)
Japanese	114 (18.7)	119 (19.6)
Other East Asian‡	179 (29.4)	184 (30.3)
Other	2 (0.3)	1 (0.2)
Smoking history — no. (%)		
Never smoked	571 (93.8)	569 (93.6)
Former light smoker	37 (6.1)	38 (6.2)
Former non–light smoker	1 (0.2)	1 (0.2)
WHO performance status — no. (%)§		
0	157 (25.8)	161 (26.5)
1	391 (64.2)	382 (62.8)
2	61 (10.0)	65 (10.7)
Histologic feature of tumor — no. (%)		
Adenocarcinoma	581 (95.4)	591 (97.2)
Bronchoalveolar carcinoma	27 (4.4)	15 (2.5)
Unknown	1 (0.2)	2 (0.3)
Disease stage at entry — no. (%)		
IIIB	150 (24.6)	144 (23.7)
IV	459 (75.4)	463 (76.2)
Unknown	0	1 (0.2)

39%in each arm have crossed over to alt

Mok TS et al. N Engl J Med 2009;361:947-957

The NEW ENGLAND JOURNAL of MEDICINE

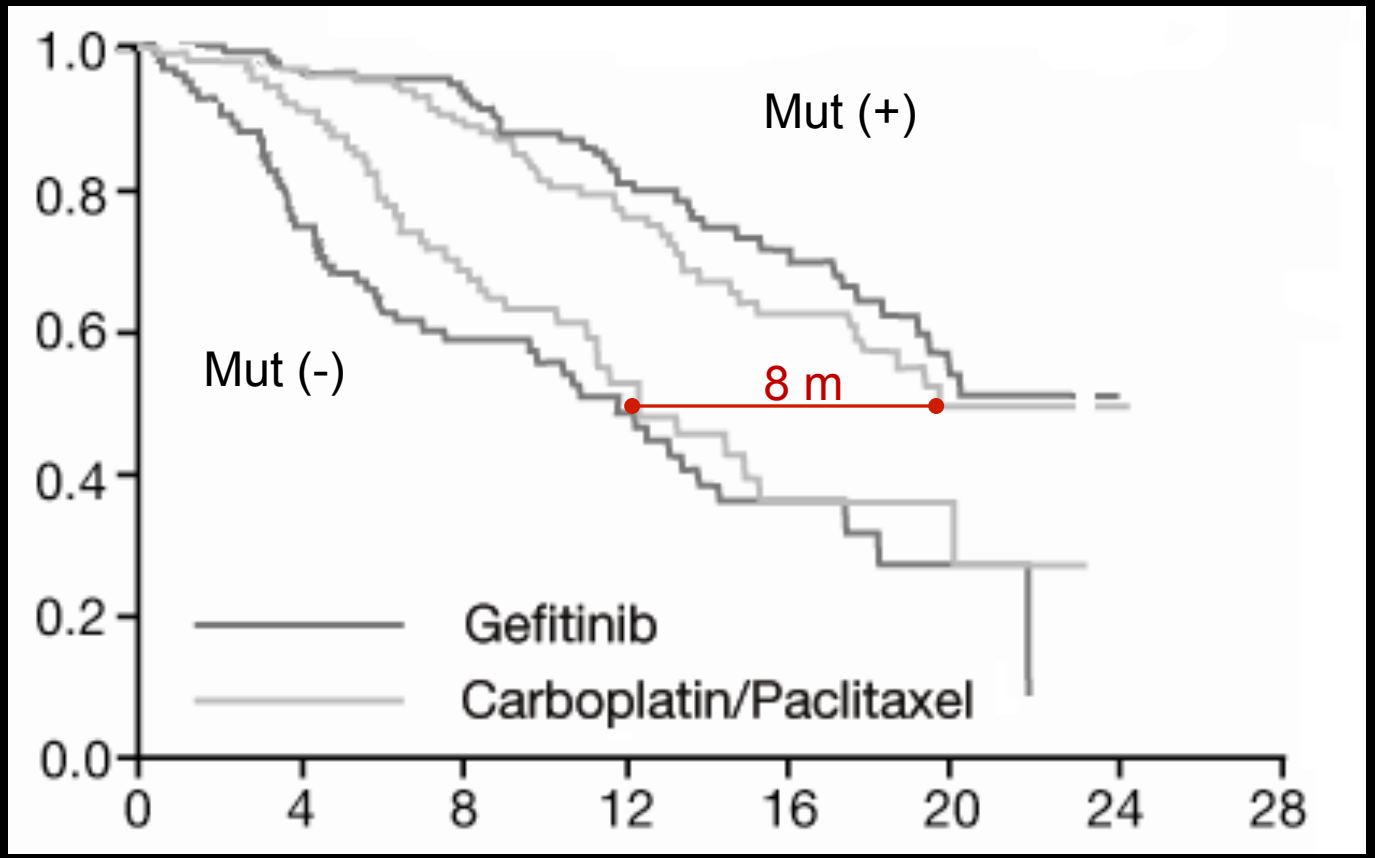
IPASS Survival



Mok TS et al. N Engl J Med 2009;361:947-957

JOURNAL of MEDICINE

IPASS: EGFR Mutation Status Prognostic, but NOT Predictive for Survival



Mok TS et al. N Engl J Med 2009;361:947-957

The NEW ENGLAND JOURNAL of MEDICINE

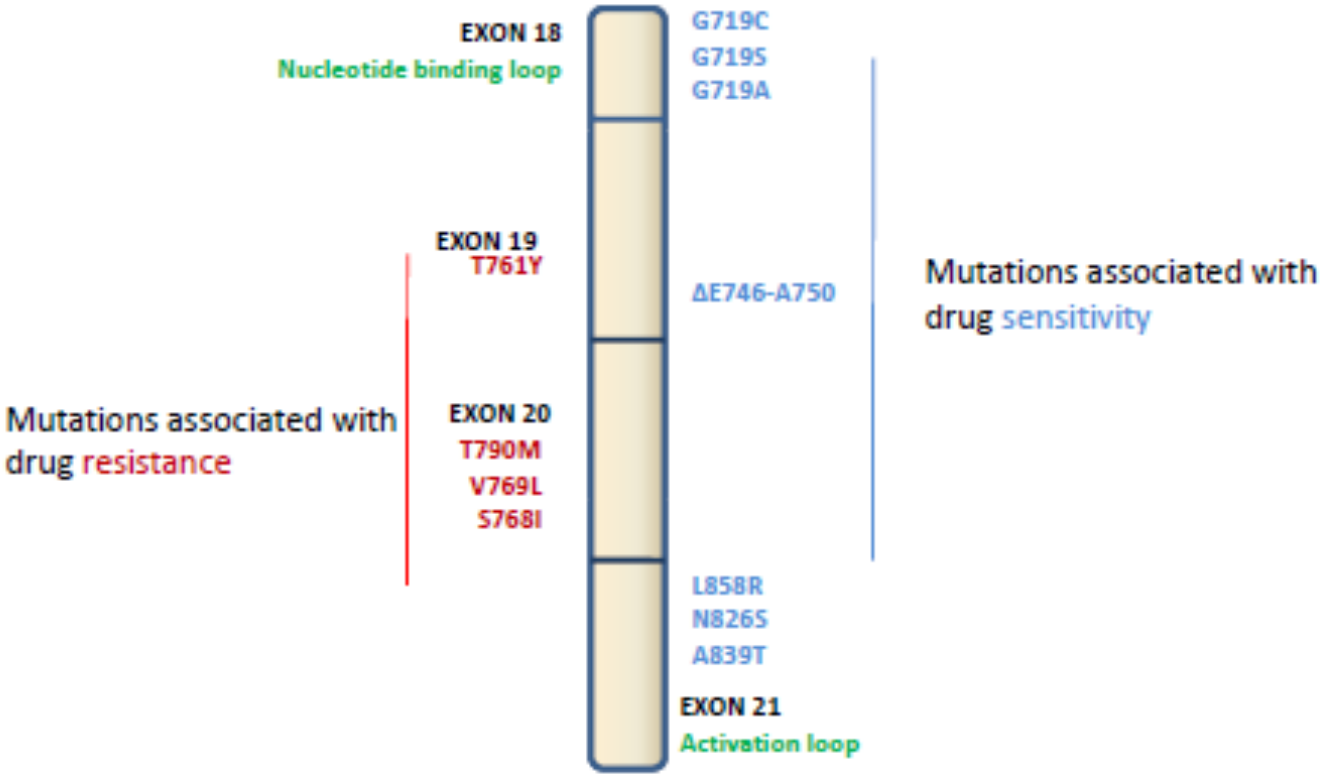
Currently 5 RCTs Confirm PFS Benefit of 1st line TKI

Study	N	Arms	Response Rate (%)	Med PFS (mo)	HR
IPASS NEJM '09	261	Gefitinib Carbo/paclitaxel	71% 47%	9.6 6.3	0.48 (.36, .64)
WJTOG 3405 Lan Onc '10	228	Gefitinib Cis/docetaxel	62% 31%	9.2 6.3	0.49 (.35, .71)
NEJ 002 NEJM '09	194	Gefitinib Carbo/paclitaxel	74% 31%	10.4 5.5	0.36 (.25, .51)
OPTIMAL Lan Onc'11	165	Erlotinib Carbo/gem	83% 36%	13.1 4.6	0.16 (.10, .26)
EURTAC ASCO '11	174	Erlotinib Cis or carbo + doce or gem	58% 15%	9.7 5.2	0.37 (.25, .54)

Note: none of these are expected to show an OS benefit due to effectiveness of EGFR TKIs in later lines

EGFR Mutations

Not all created equal



Adapted from Sharma SV et al, *Nat Rev Cancer*:7:169-81, 2007

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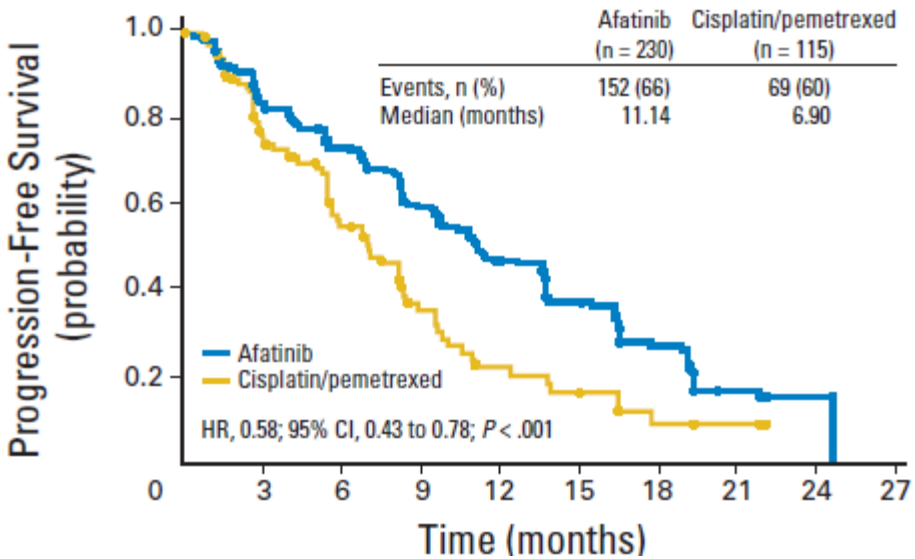
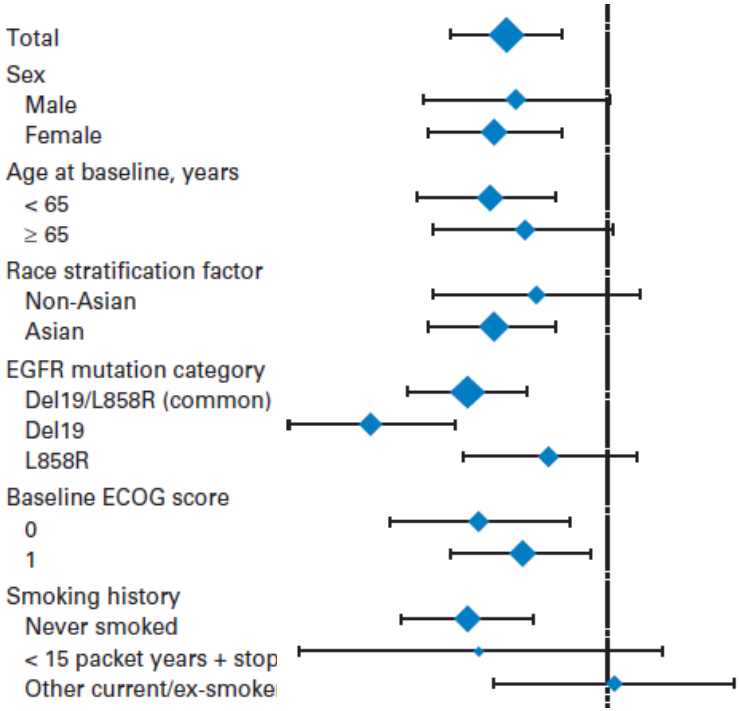
Afatinib vs Pem-Cis in EGFR (+) Lux Lung 3





HER 1,2,4, dimers, T790M inhibitor
N=345, 75% Asian
PFS 11.1 v 6.9 m HR = 0.58
Ex19/21 13.6 6.9 m HR=0.47

Sequist, et al. JCO, 2013

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Third Generation (mutant specific) EGFR TKIs

- A (relatively) new class of drugs irreversibly inhibits mutant EGFR, in particular EGFR T790M, with much less activity against wild-type EGFR.
- Effective in preclinical tumor models with both EGFR-TKI-sensitizing and T790M resistance mutations.
- References: Cross, D Cancer Discovery 2014; Tjin Tham Sjin R Molecular Cancer Therapeutics 2014,

	Drug	Target	Reversible/ Irreversible	Company
3rd generation (mutant specific)	AP26113	EGFR/ALK	Reversible	Ariad
	CO-1686	Mutant EGFR	Irreversible	Clovis
	AZD9291	Mutant EGFR	Irreversible	Astra Zeneca
	EGF816	Mutant EGFR	Irreversible	Novartis
	ASP8273	Mutant EGFR	Irreversible	Astellas

Ref: Yu, Riely, and Lovly Clinical Cancer Research in press

	WT	Sensitivity (18,19,21)	Resistance
1st	X	X	0
2nd	X	X	?
3rd	0	X	X

Inhibition of WT = Rash, GI

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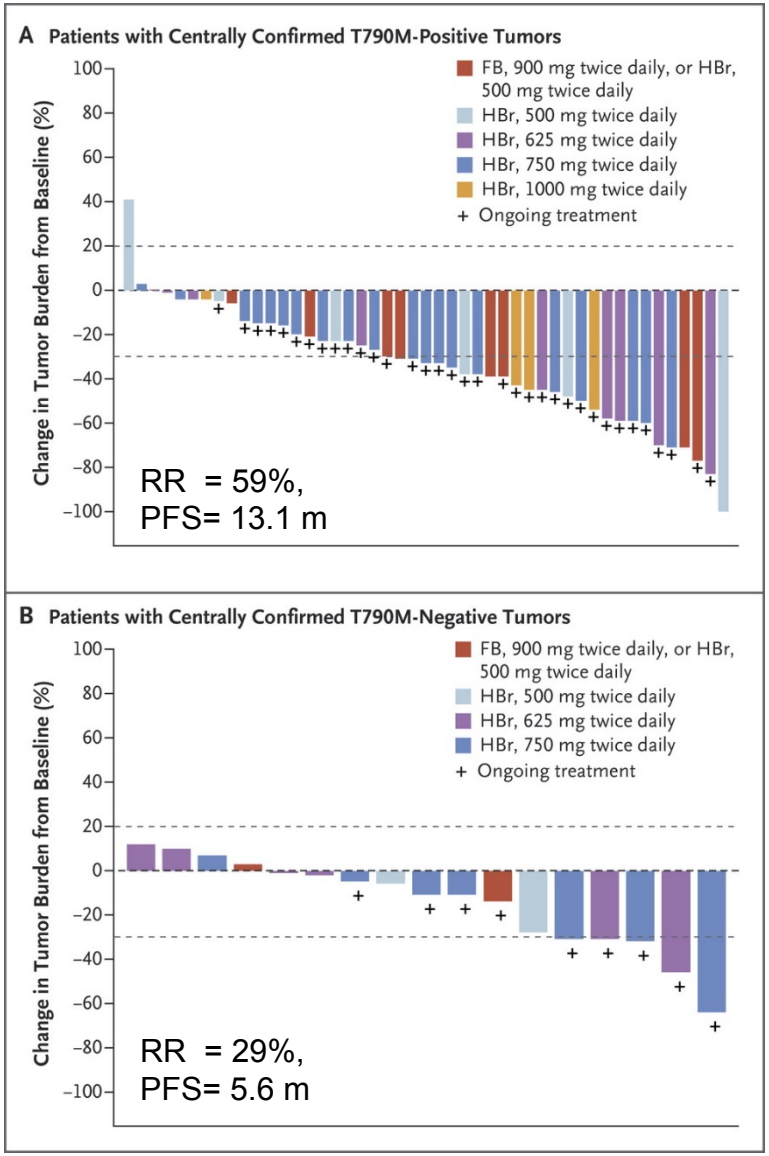
Rocelitinib in T790 +/-



N=130

Hyperglycemia: 38% on hypoglycemic
IGF-1R blocked by metabolite

Sequist LV et al. N Engl J Med 2015;372:1700-1709

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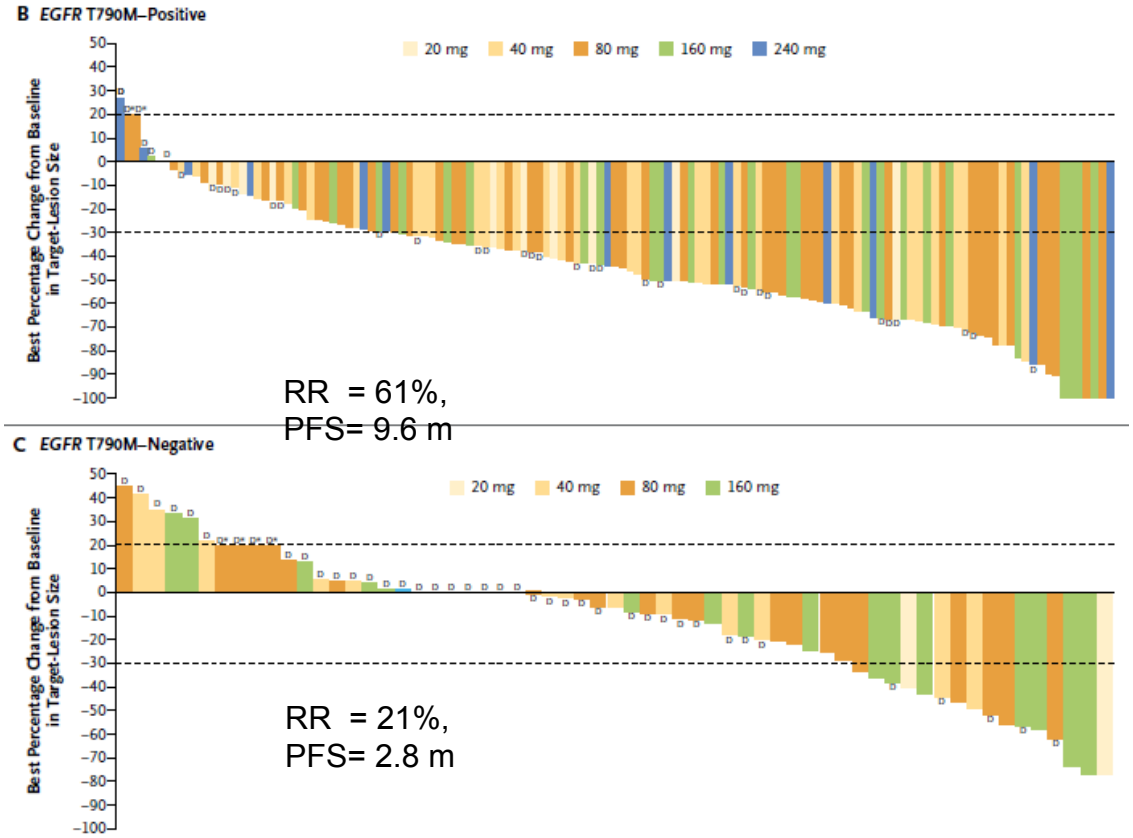
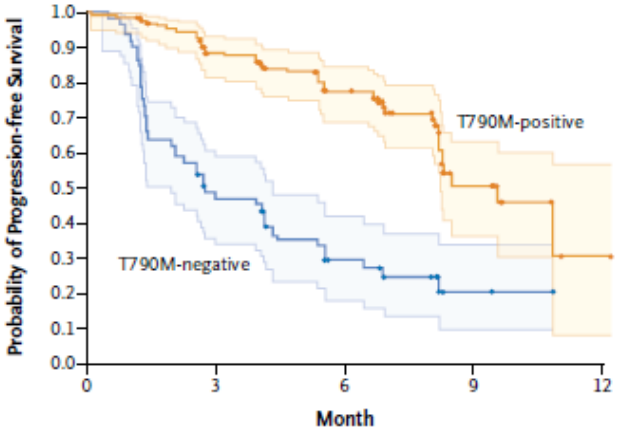
AZD9291 in T790 +/-





N=253

Osimertinib approved November 15, 2015

Janne et al. NEJM. 372: 1689, 2015.

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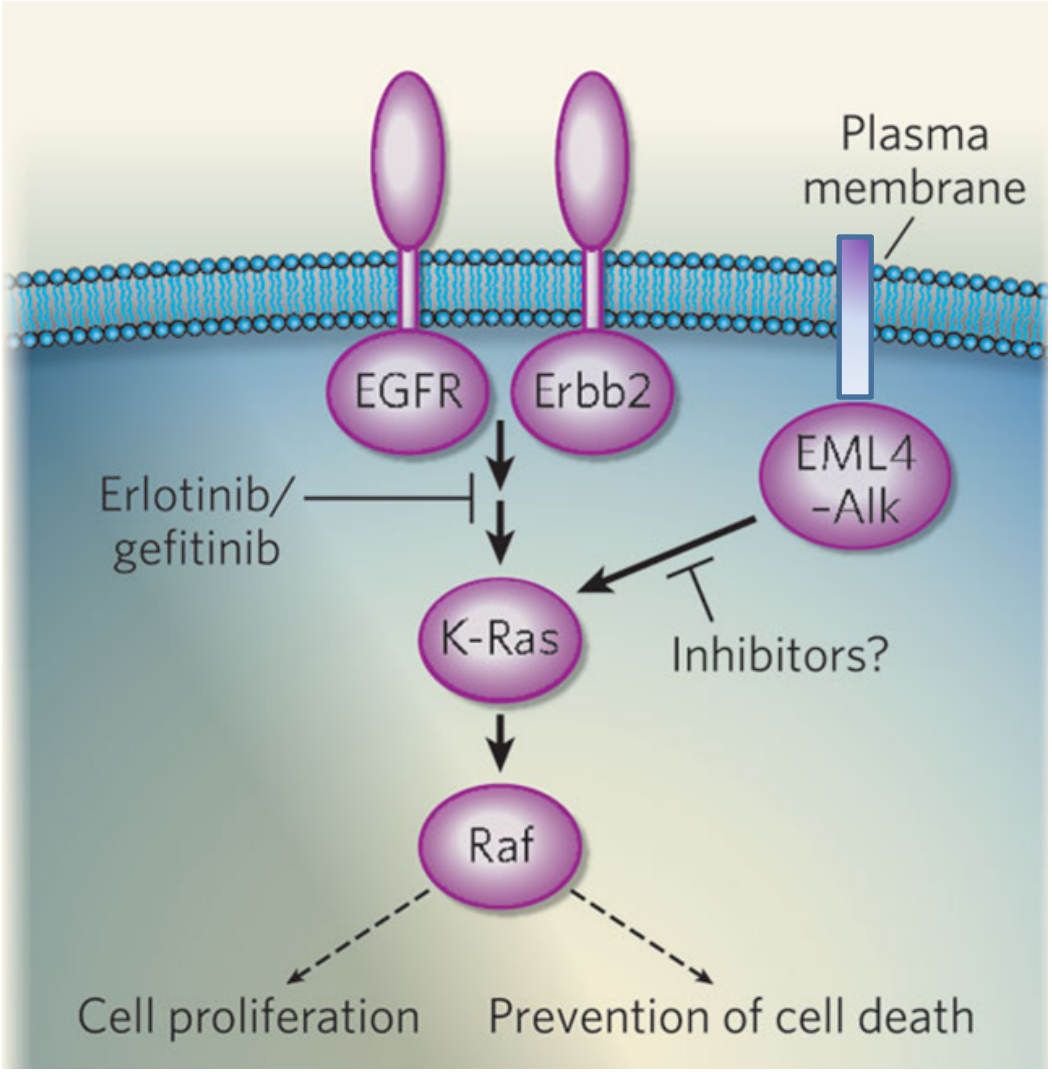
EML4-ALK



Cancer: Broken genes in solid tumours
Meyerson *Nature* **448**, 545, 2007

EML4-ALK Translocation
- Echinoderm Microtubule associated protein Like 4-anaplastic lymphoma kinase

Both on Chr 2
5% of NSCLC
Constitutive active kinase
Mutation:
- Lung, Lymph, Neuroblastoma

ALK
- Insulin superfamily
- Neurogenesis function

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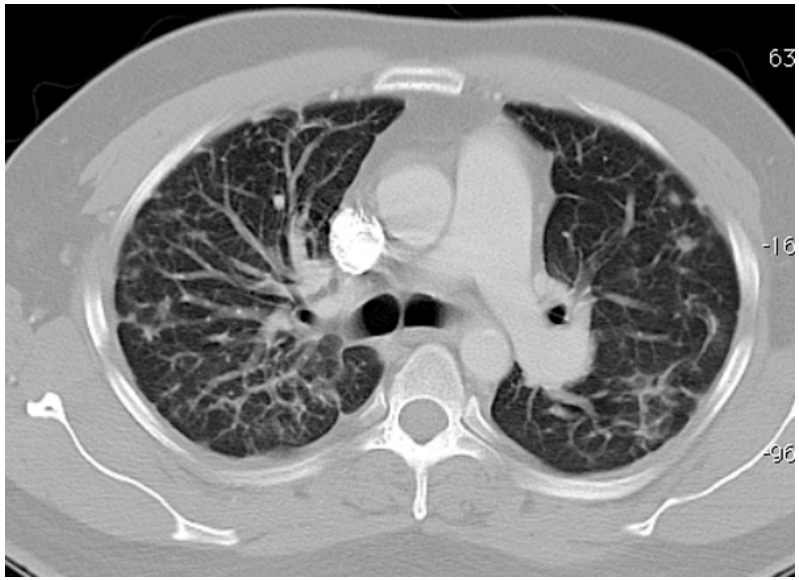
Response to Crizotinib



Pre-Treatment

Crizotinib x 12 weeks

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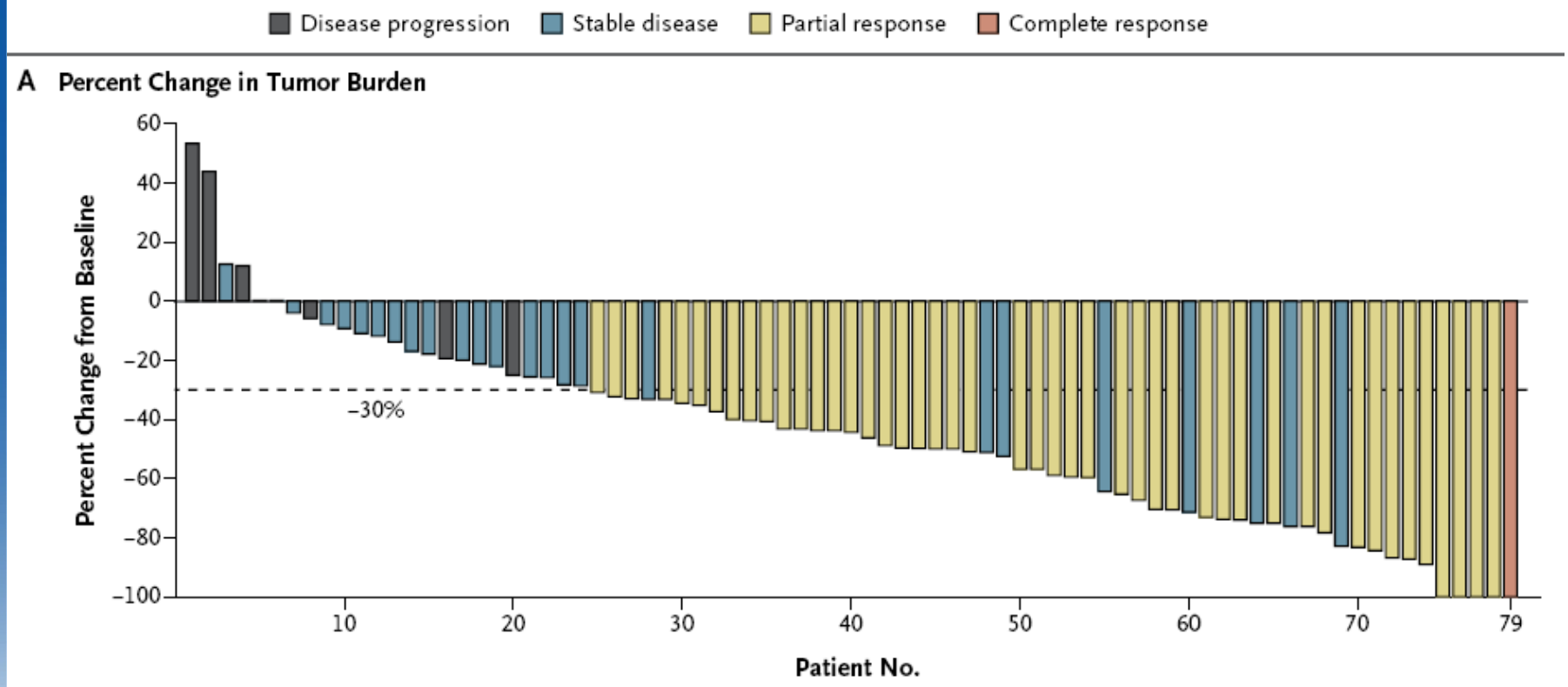
Crizotinib Response



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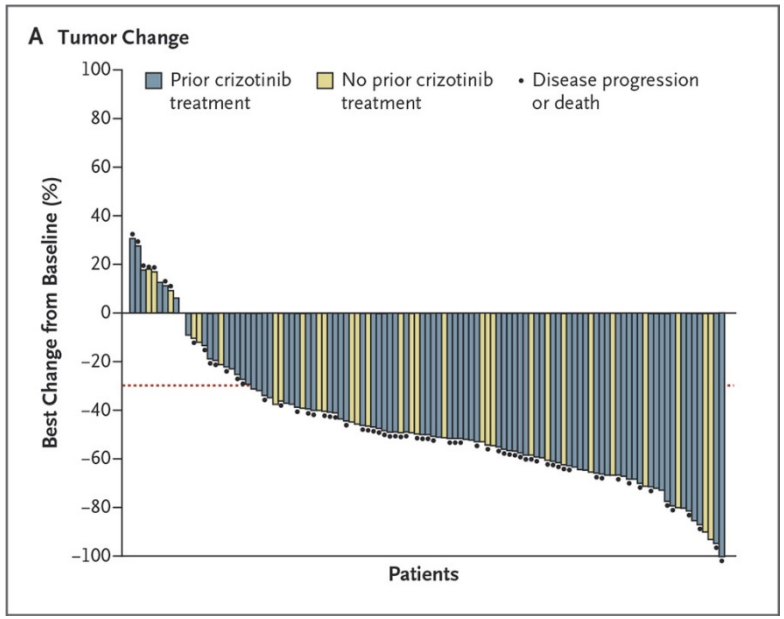
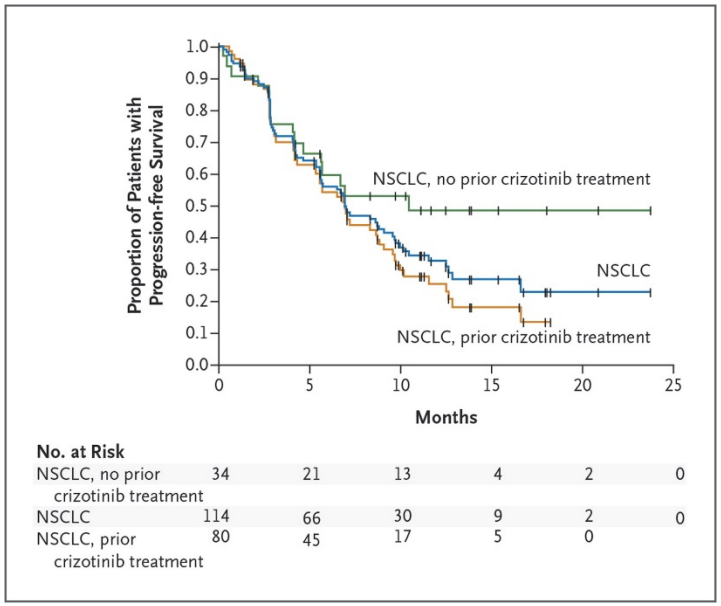
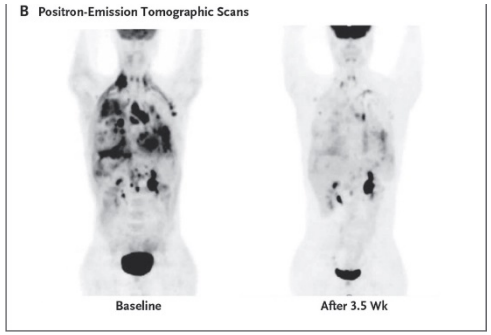
Ceritinib

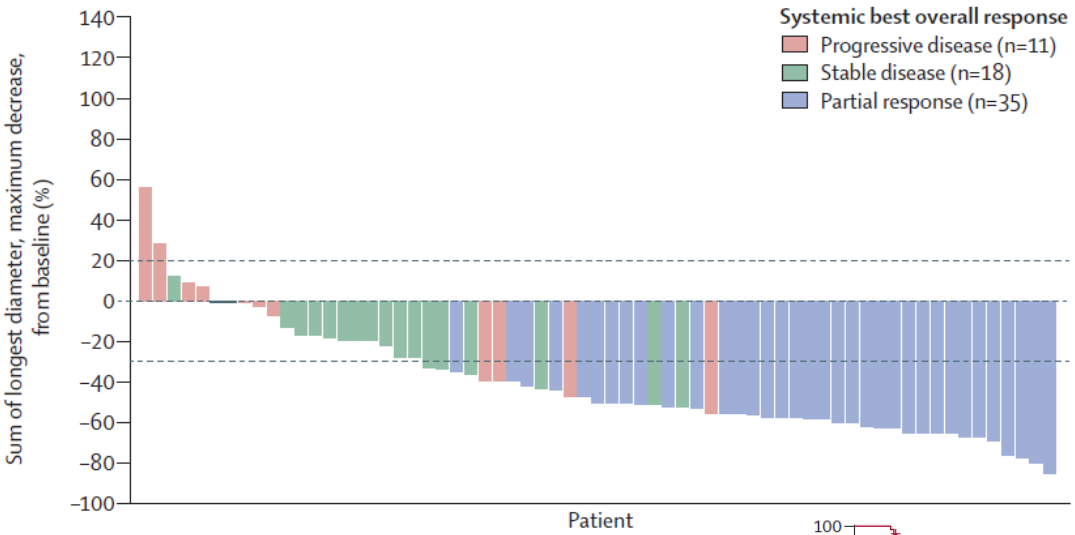




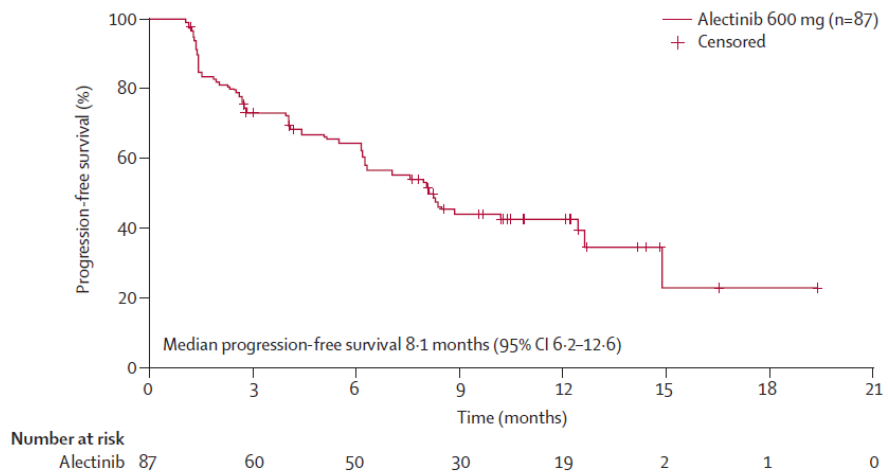


Shaw AT et al. N Engl J Med 2014;370:1189-1197. Approved May 2014

Alectinib



RR 48% updated to 55%
CNS penetration



Shaw Lancet 2015. Approved Dec 11,2015

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EMERGING TARGETED AGENTS FOR PATIENTS WITH GENETIC ALTERATIONS

Genetic Alteration (ie, Driver event)	Available Targeted Agents with Activity Against Driver Event in Lung Cancer
BRAF V600E mutation*	vemurafenib[1] dabrafenib[2]
MET amplification	crizotinib[3,4]
ROS1 rearrangements	crizotinib[5]
HER2 mutations	trastuzumab[6] (category 2B) afatinib[7] (category 2B)
RET rearrangements	cabozantinib[8] (category 2B)

*Non-V600E mutations have variable kinase activity and response to these agents.

[1]Gautschi O, Pauli C, Strobel K, et al. A patient with BRAF V600E lung adenocarcinoma responding to vemurafenib. J Thorac Oncol 2012;7:e23-24.
[2]Planchard D, Mazieres J, Riely GJ, et al. Interim results of phase II study BRF113928 of dabrafenib in BRAF V600E mutation-positive non-small cell lung cancer (NSCLC) patients [abstract]. J Clin Oncol 2013;31(Suppl 15): Abstract 8009.
[3]Ou SH, Kwak EL, Siwak-Tapp C, et al. Activity of crizotinib (PF02341066), a dual mesenchymal-epithelial transition (MET) and anaplastic lymphoma kinase (ALK) inhibitor, in a non-small cell lung cancer patient with de novo MET amplification. J Thorac Oncol 2011;6:942-946.
[4]Camidge RD, Ou S-HI, Shapiro G, et al. Efficacy and safety of crizotinib in patients with advanced c-MET-amplified non-small cell lung cancer. J Clin Oncol 2014;32(Suppl 5): Abstract 8001.
[5]Shaw AT, Ou S-HI, Bang Y-J, et al. Crizotinib in *ROS1*-rearranged non-small cell lung cancer. N Engl J Med 2014;371:1963-1971.
[6]Cappuzzo F, Bemis L, Varella-Garcia M. HER2 mutation and response to trastuzumab therapy in non-small-cell lung cancer. N Engl J Med 2006;354:2619-2621.
[7]Mazieres J, Peters S, Lepage B, et al. Lung cancer that harbors an HER2 mutation: epidemiologic characteristics and therapeutic perspectives. J Clin Oncol 2013;31:1997-2003.
[8]Drilon A, Wang L, Hasanovic A, et al. Response to cabozantinib in patients with RET fusion-positive lung adenocarcinomas. Cancer Discov 2013; 3:630-635.

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

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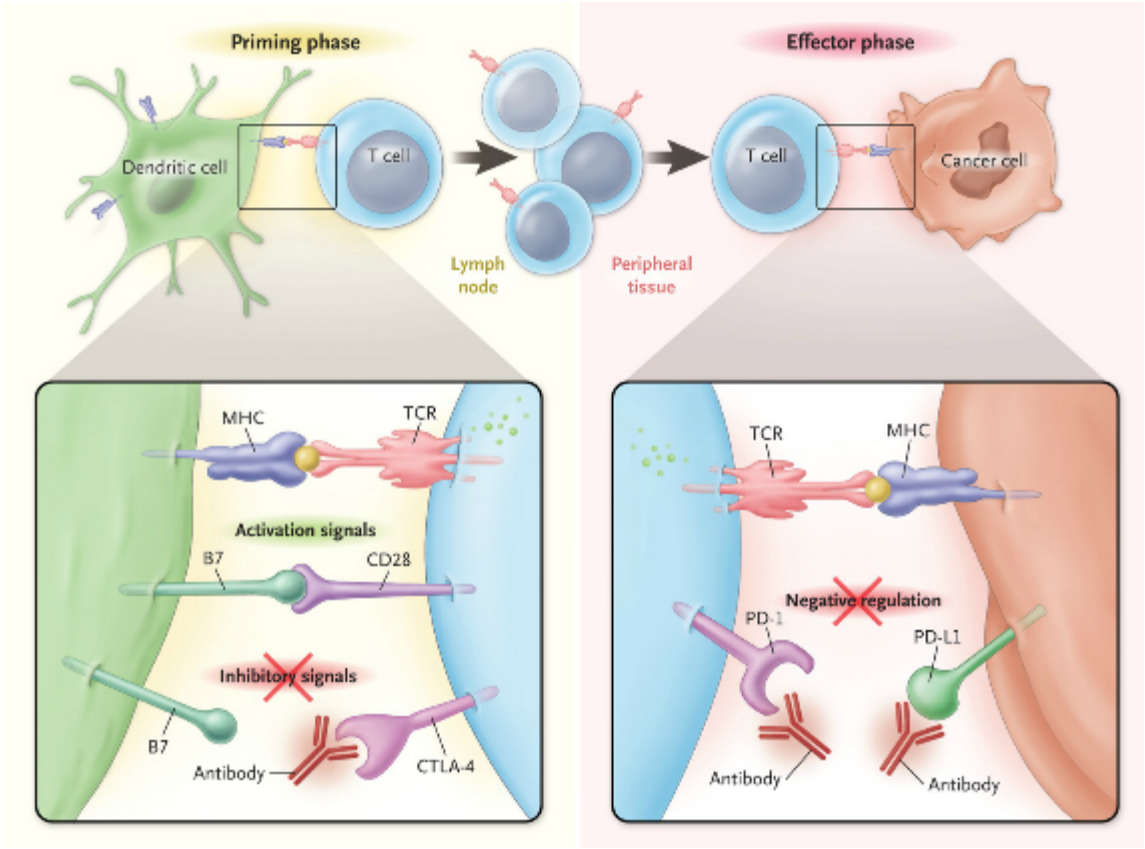
Immune checkpoint Regulation



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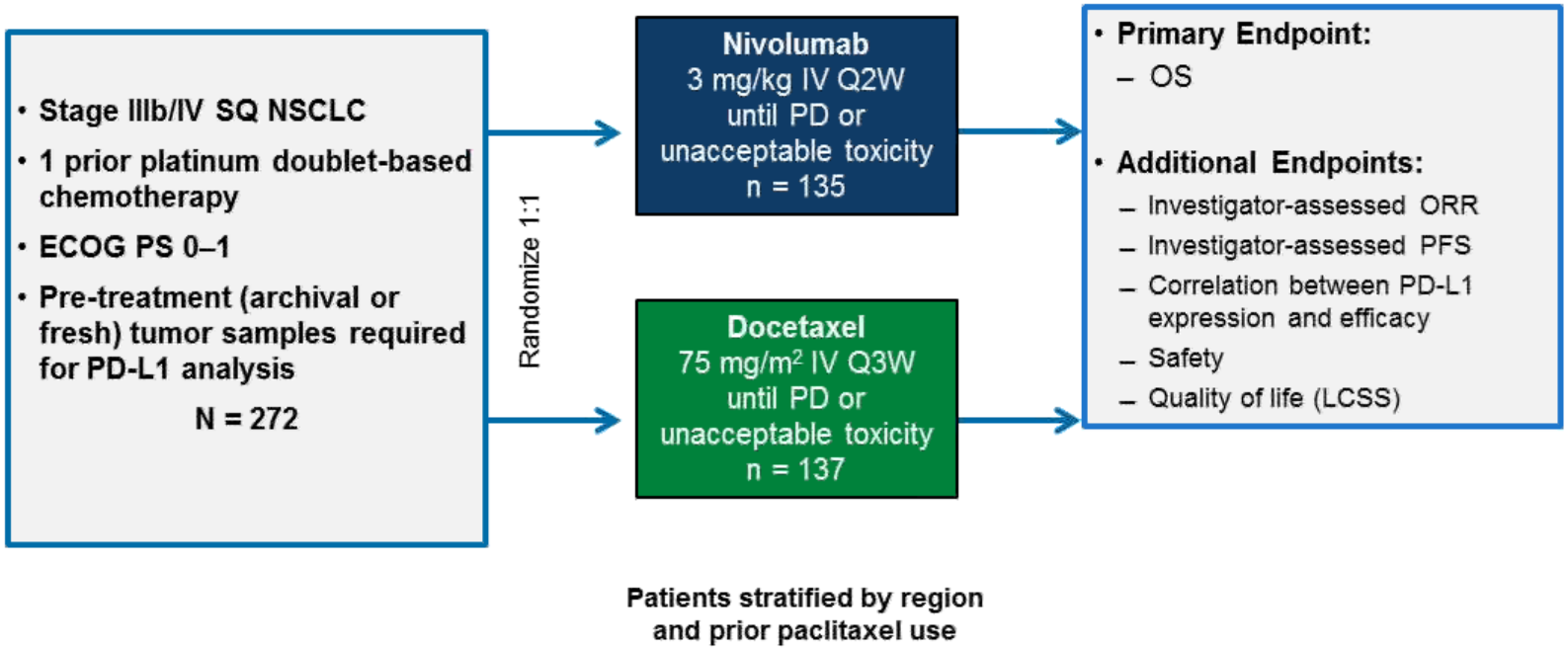
PD-1, PD-L1

- PD-L1 (Personalized)
  - Medimmune/AZ
  - Genentech
- PD-1 (Targeted and Personalized)
  - Pembrolizumab
  - Nivolumab

CheckMate 017 (NCT01642004) - Study Design



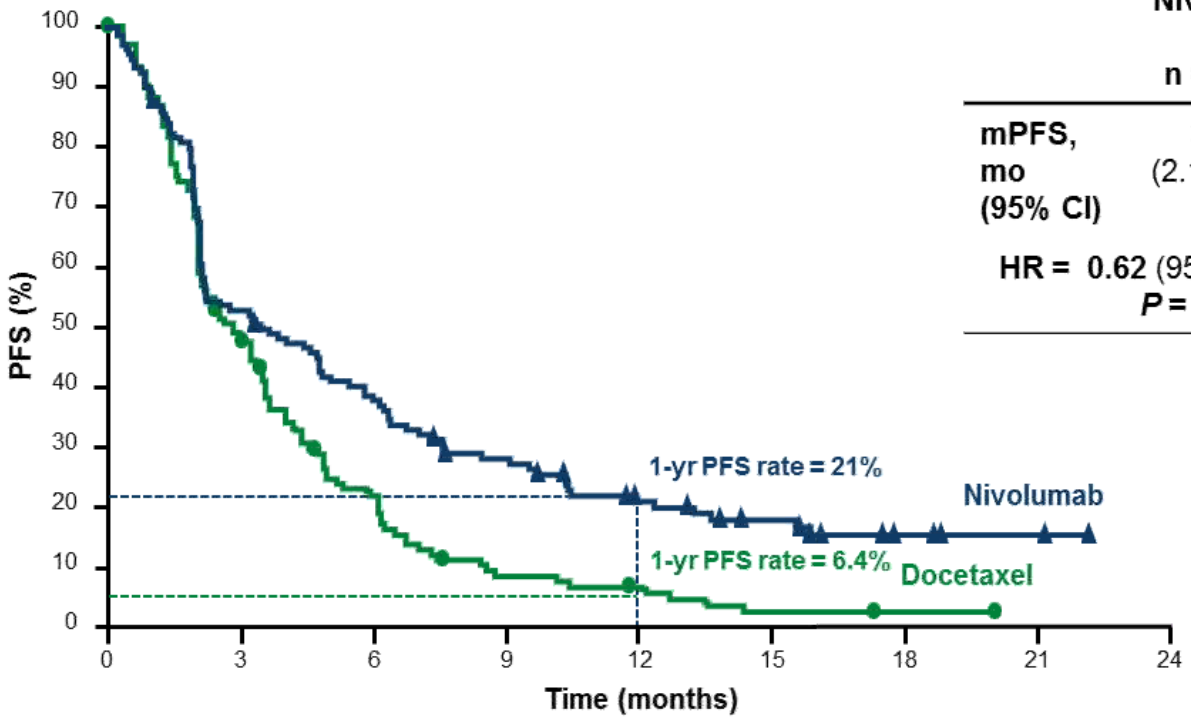
Objective Response Rate

	Nivolumab n = 135	Docetaxel n = 137
ORR, % (95% CI)	**20** (14, 28)	**9** (5, 15)
***P*-value[a]**	**0.0083**	
Best overall response, %		
Complete response	1[b]	0
Partial response	19	9
Stable disease	29	34
Progressive disease	41	35
Unable to determine	10	22
Median DOR,[c] mo (range)	NR (2.9, 21+)	8.4 (1.4+, 15+)
Median time to response,[c] mo (range)	2.2 (1.6, 12)	2.1 (1.8, 9.5)

- 28 patients in the nivolumab arm were treated beyond RECIST v1.1-defined progression
- Non-conventional benefit was observed in 9 patients (not included in ORR)

Squamous Cell Lung Cancer

Progression-free Survival



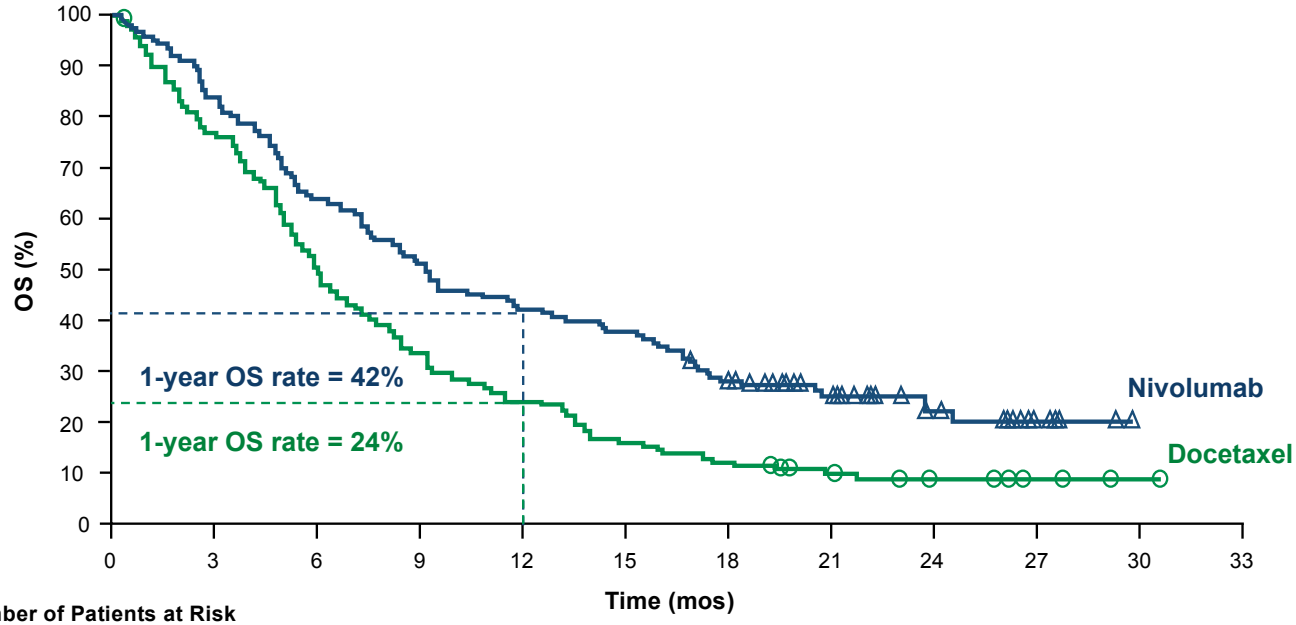
	Nivolumab n = 135	Docetaxel n = 137
mPFS, mo (95% CI)	3.5 (2.1, 4.9)	2.8 (2.1, 3.5)

HR = 0.62 (95% CI: 0.47, 0.81); ***P* = 0.0004**

Number of Patients at Risk

Nivolumab	135	68	48	33	21	15	6	2	0
Docetaxel	137	62	26	9	6	2	1	0	0

Nivolumab vs Docetaxel in Squamous NSCLC



Number of Patients at Risk

Nivolumab	135	113	86	69	57	51	37	25	14	6	0	0
Docetaxel	137	104	69	46	33	22	17	11	7	3	1	0

Paz-Ares L, et al. ASCO 2015, Abstract LBA109.

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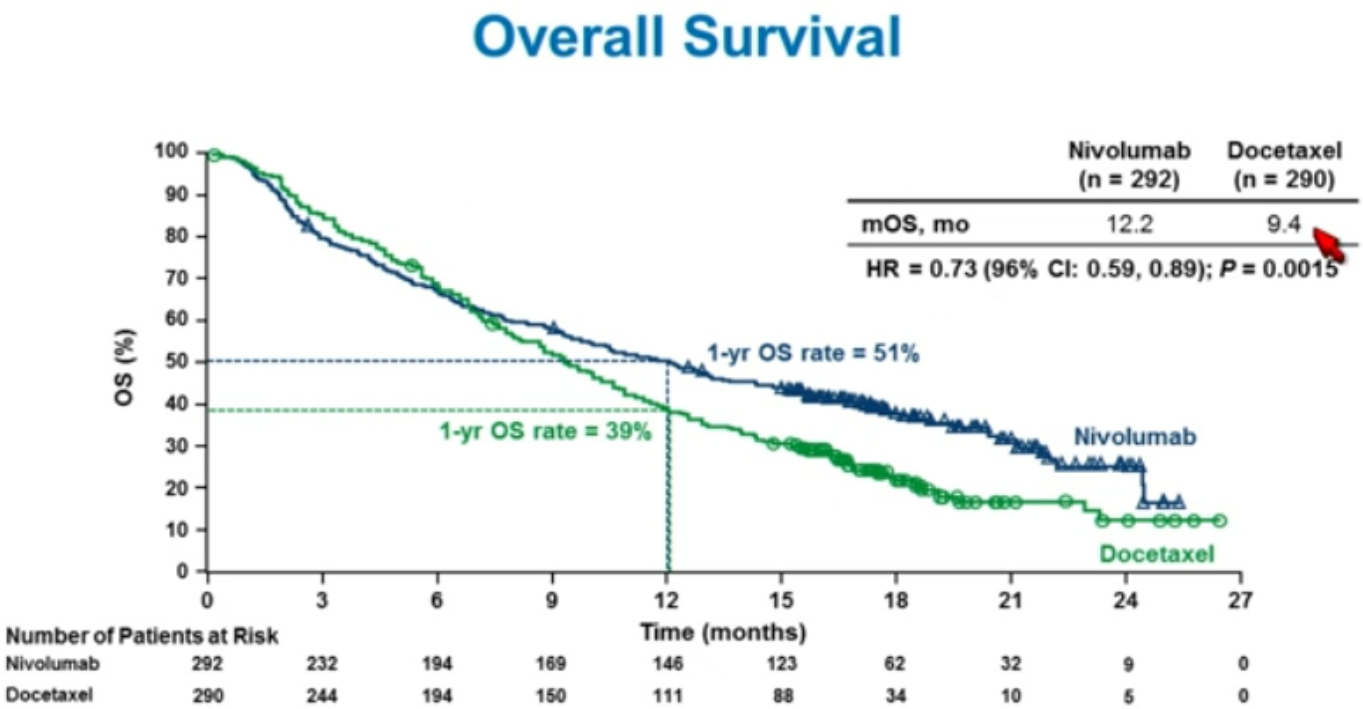
Non-Sq Lung Cancer

Objective Response Rate

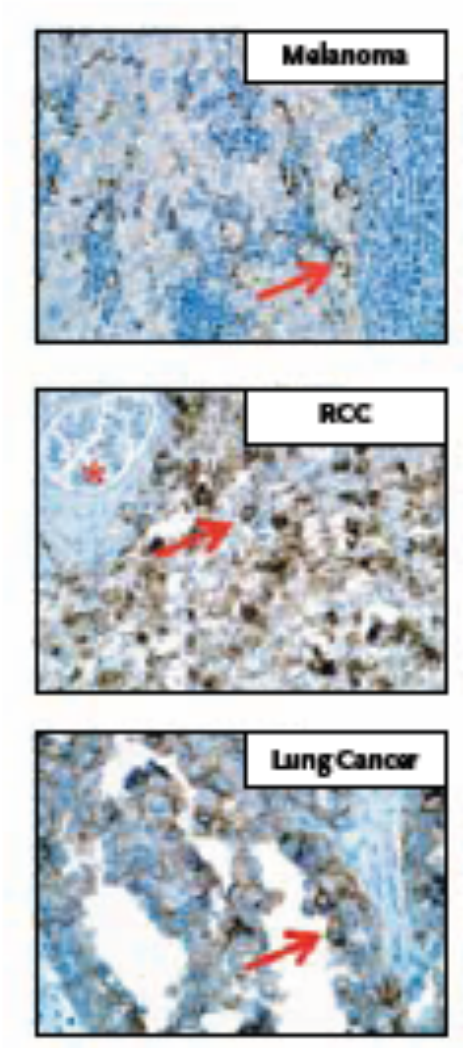
	Nivolumab (n = 292)	Docetaxel (n = 290)
ORR (95% CI)	**19%** (15, 24)	**12%** (9, 17)
***Odds Ratio* (95% CI)** ***P*-value[a]**	1.72 (1.1, 2.6) 0.0246	
Best overall response, %		
Complete response	1	<1
Partial response	18	12
Stable disease	25	42
Progressive disease	44	29
Unable to determine	11	16
Median time to response,[b] mo (range)	2.1 (1.2, 8.6)	2.6 (1.4, 6.3)
Median DOR,[b] mo (range)	**17.2** (1.8, 22.6+)	**5.6** (1.2+, 15.2+)
Ongoing response,[c] %	52	14

- 71 (24%) patients on nivolumab were treated beyond RECIST v1.1-defined progression
- Non-conventional benefit was observed in 16 patients (not included in best overall response)

Non-Sq Lung Cancer



PD-1 Expression in Tumors



Immune Panels

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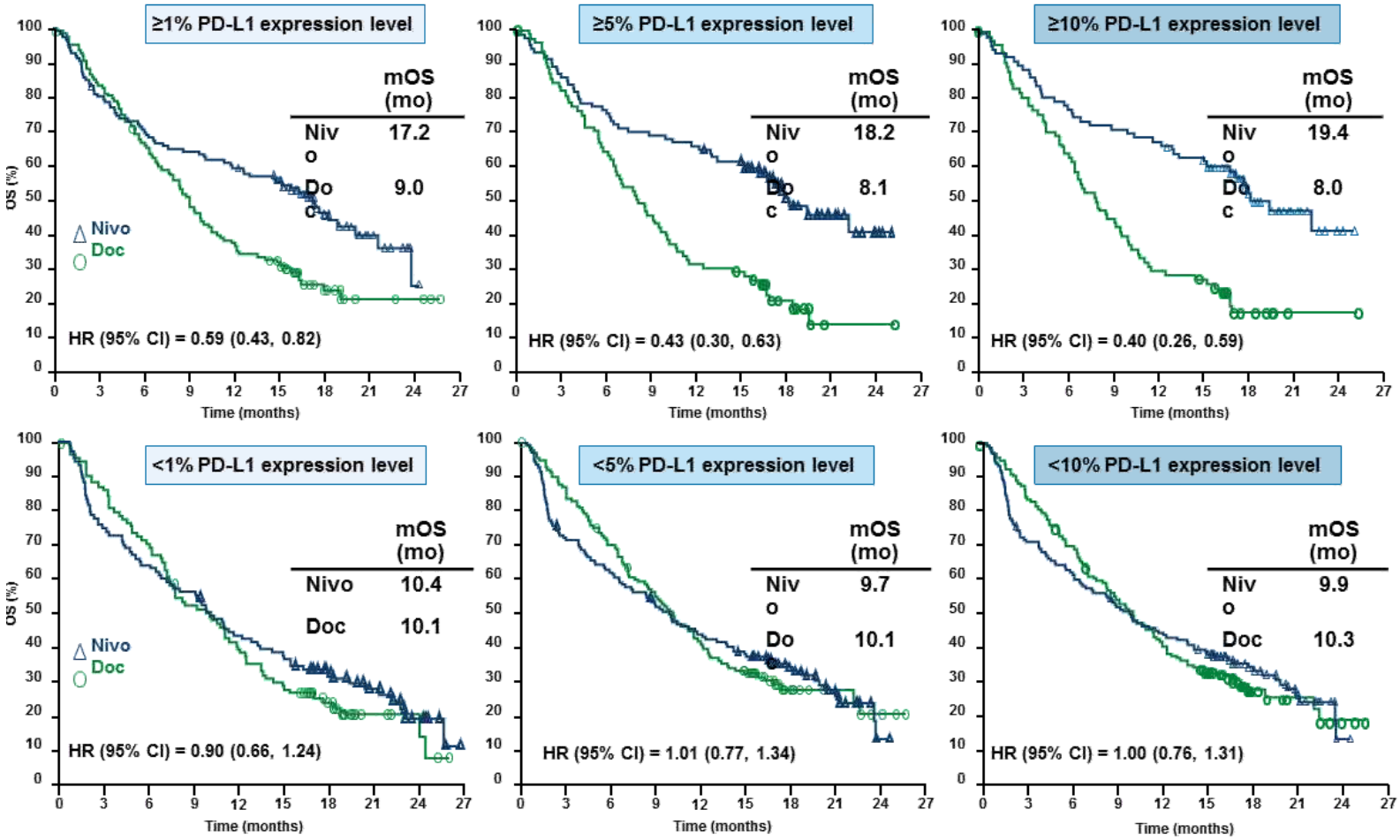
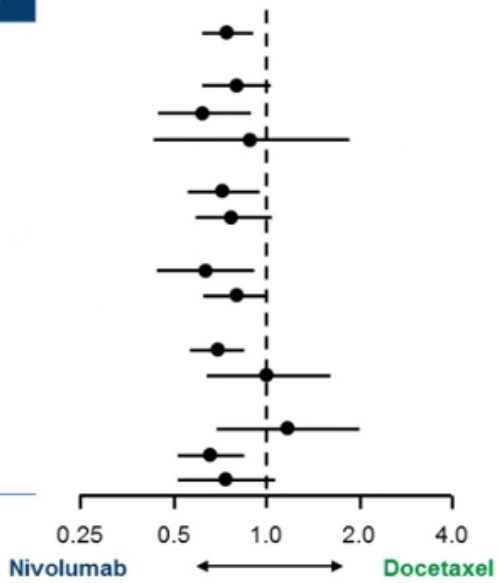
OS by PD-L1 Expression

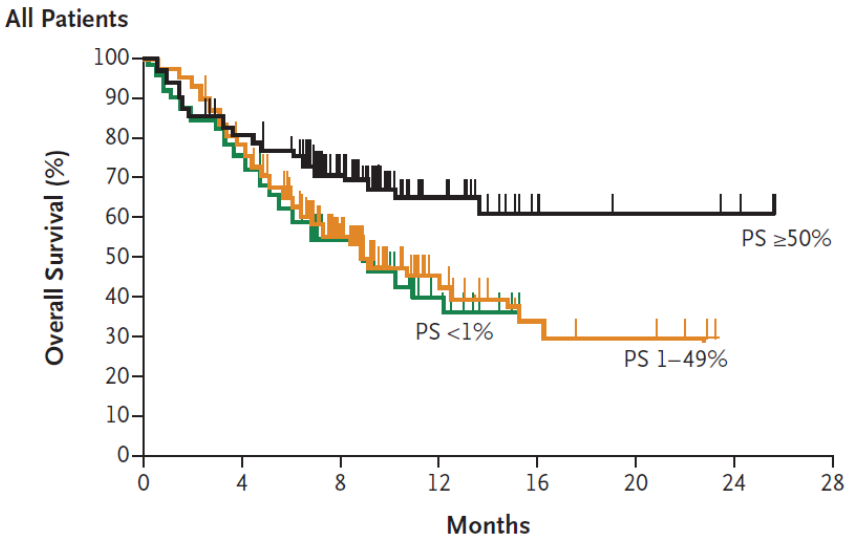


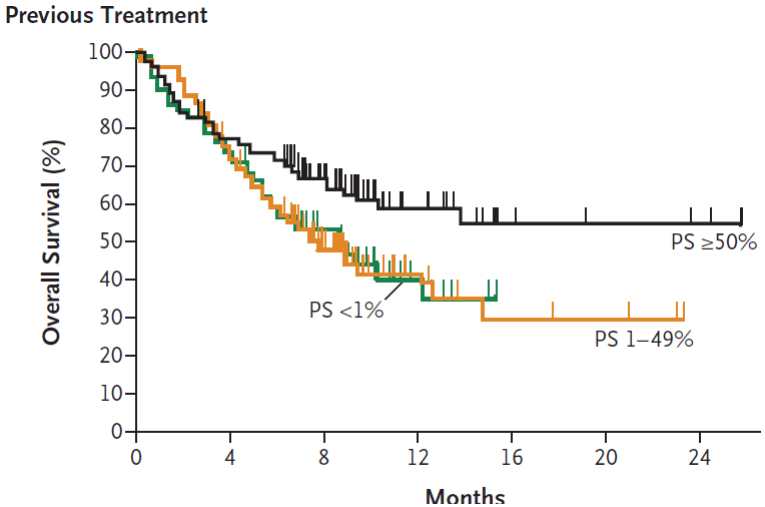
Treatment Effect on OS in Predefined Subgroups

	N	Unstratified HR (95% CI)
Overall	582	0.75 (0.62, 0.91)
Age Categorization (years)		
<65	339	0.81 (0.62, 1.04)
≥65 and <75	200	0.63 (0.45, 0.89)
≥75	43	0.90 (0.43, 1.87)
Gender		
Male	319	0.73 (0.56, 0.96)
Female	263	0.78 (0.58, 1.04)
Baseline ECOG PS		
0	179	0.64 (0.44, 0.93)
≥1	402	0.80 (0.63, 1.00)
Smoking Status		
Current/Former Smoker	458	0.70 (0.56, 0.86)
Never Smoked	118	1.02 (0.64, 1.61)
***EGFR* Mutation Status**		
Positive	82	1.18 (0.69, 2.00)
Not Detected	340	0.66 (0.51, 0.86)
Not Reported	160	0.74 (0.51, 1.06)

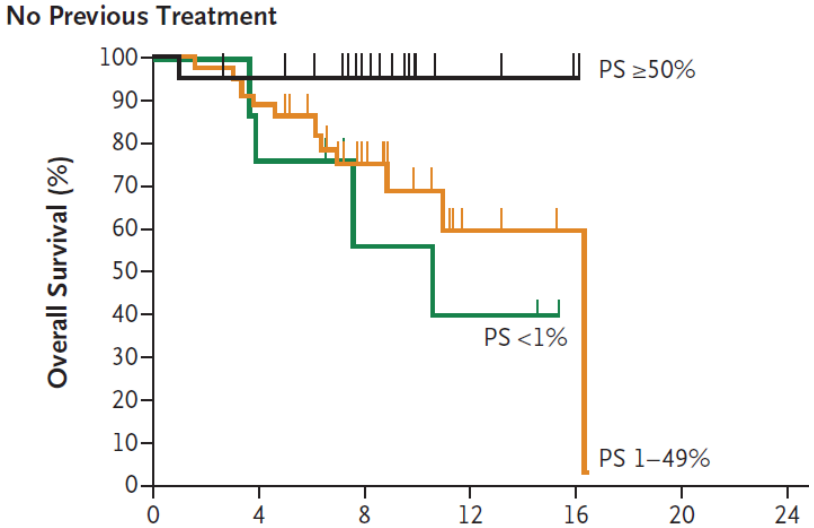


Pembrolizumab in NSCLC





25% are Good (> 50%) PD-L1



Garon EB et al. N Engl J Med 2015. DOI: 10.1056/NEJMoa1501824

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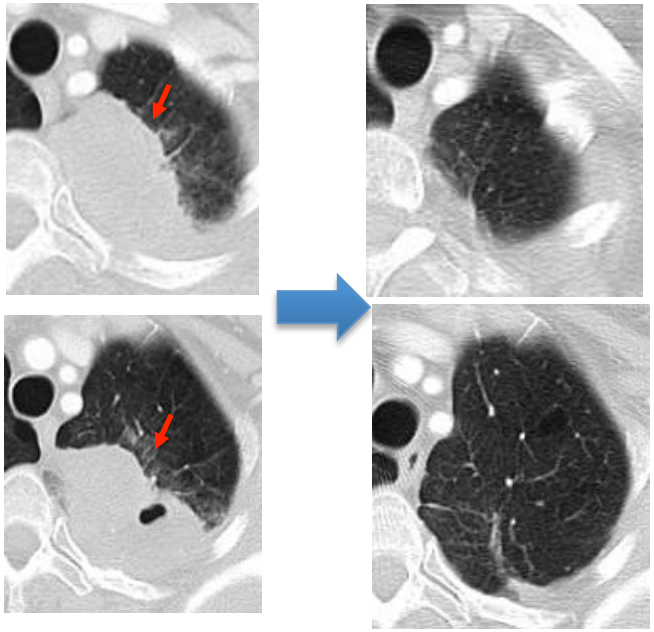
Patient CB

57 yo F smoker

- 1/10/2014
  - Squamous cell lung cancer with mets to lungs, adrenal
  - Taxol, carboplatin,
  - gemcitabine carboplatin,
- 9/1/2014
  - PD-L1 positive
  - Atezolizumab started 10/7/14



Smoker, Squamous response

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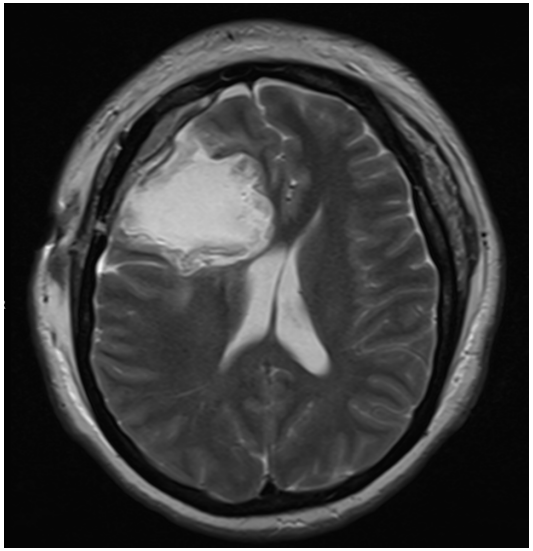
Patient LM



43 yo F never smoker

- 2/16/2008
  - Brain metastasis resected, WBRTX
  - Taxol, cisplatin, pemetrexed, erlotinib, cMet
- 8/1/2011
  - Phase I trial of LDK378 (ceritinib)for ALK translocated NSCLC
  - Complete response on sub-recommended dose
  - SRS for Brain relapses (3/14, 4/15, 1/16)

Long term benefit possible

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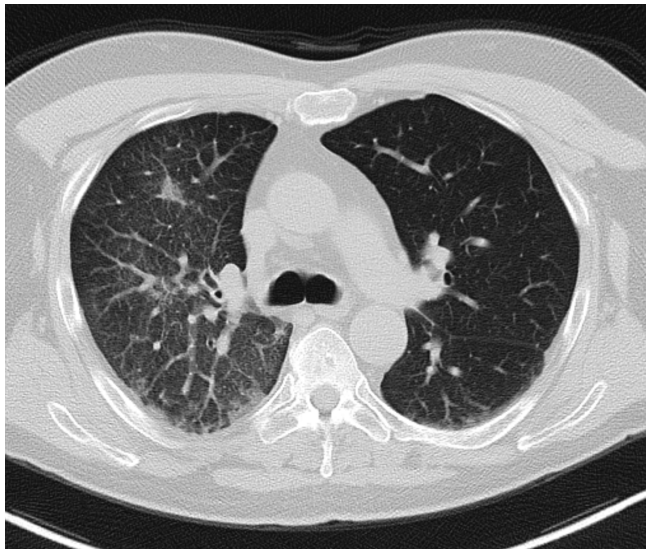
Patient AS



65 yo M never smoker

- Jan 2010
  - Bilateral lymphangitic,
  - EGFR del 19, Erlotinib bevacizumab
- Sept 2011 Pemetrexed carbo
- April 2014 retreatment erlotinib
- June 2014 BRAF V600E dabrafenib
- January 2015 new biopsy BRAF V600E darafenib trametinib
- Brain Mets: SRS 5/13, WBRTX 7/2015

Mutations may change

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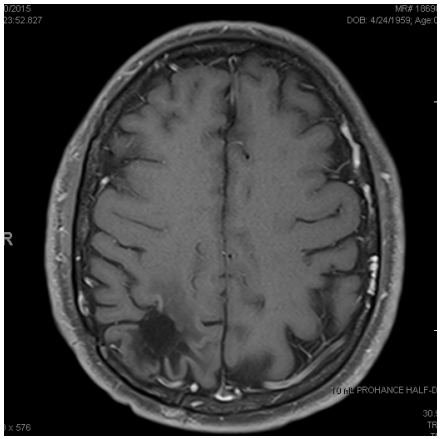
Patient JB



43 yo M light former smoker

- 2003
  - Stage I lung Cancer
  - Resected, adjuvant chemotherapy
- 2008 Relapse in Brain
  - SRS for Brain relapses (6/08, 4/11, 7/12,8/12)
- 9/11/12
  - ALK identified and Ceritinib started
  - CR in mediastinum
  - no further brain mets

Brain metastases control

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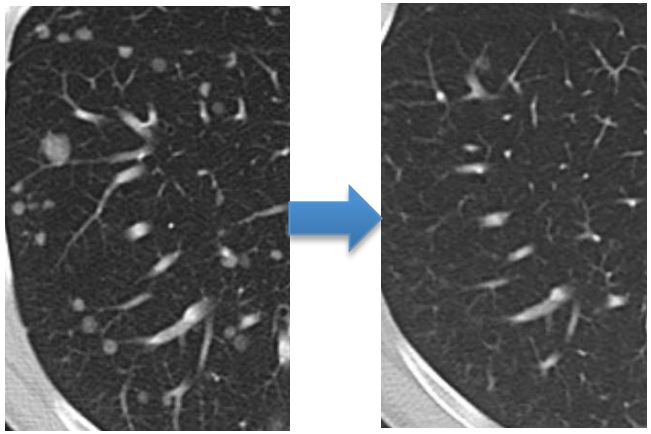
Patient SL

51 yo F never smoker

- 4/30/2014
  - Path Fx hip, arthroplasty, RTX
  - Mets to bones, lung, brain
  - EGFR exon 19 del, erlotinib
- 4/15/2015
  - New small lesion in chest, RTX to spine, CK153 nivolumab
- 10/9/15
  - Guardant T790M identified
  - AZD9291 (osimertinib)



Cf DNA predicts Progression; Brain w/o RTX

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Summary

- NSCLC is no longer an adequate diagnosis
- EGFR and ALK testing in all lung cancer
  - ROS1, RET, BRAF, HER-2, MET-amplified
  - T790M
- PD-1/PD-L1 changing Landscape
  - Next wave - Combination Immune Tx

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