Lung Cancer-Progress and Promise

UNIVERSITÉ ST. JOSEPH ANNUAL SCIENTIFIC SYMPOSIUM

Fadlo R. Khuri, MD

June 21, 2018

Office of the President | American University of Beirut

Lung Cancer in 2018

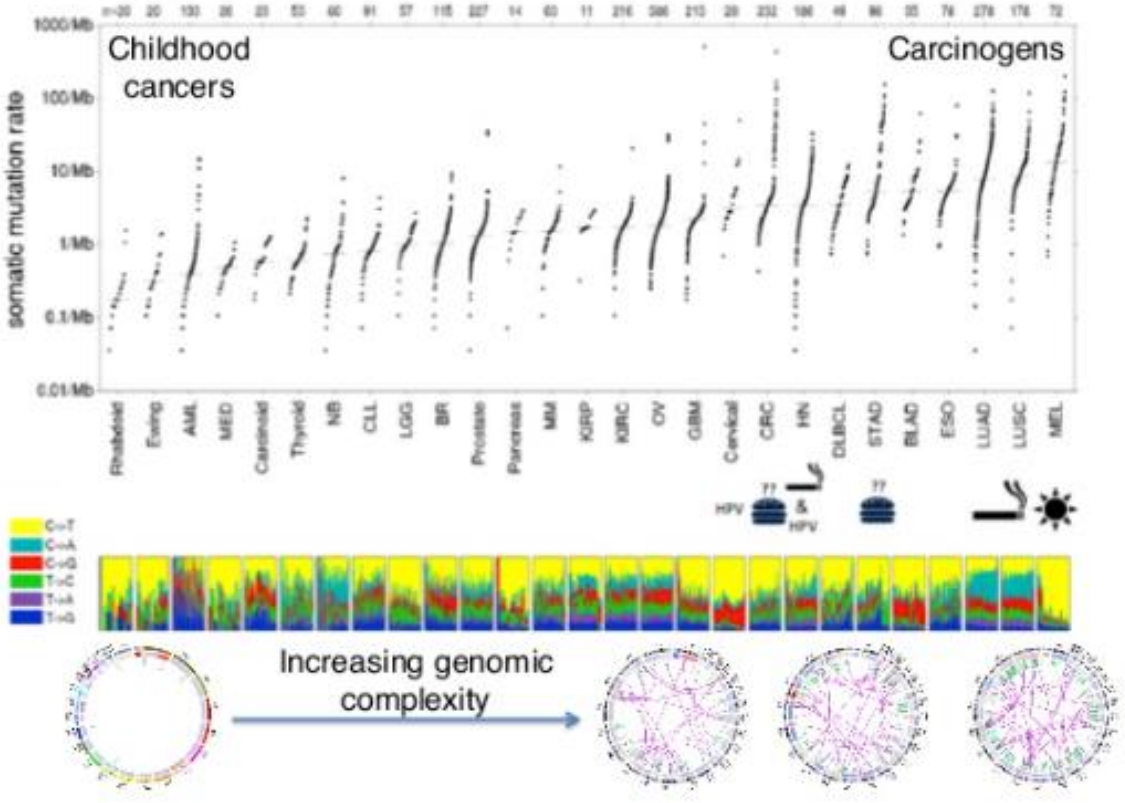
- Early detection by screening saves lives
- Distinct molecular subsets
- Targeted therapy improves outcomes
- Immunotherapy added to therapeutic armamentarium
- Individualized therapies under study in curative settings

MOLECULAR CLASSIFICATION

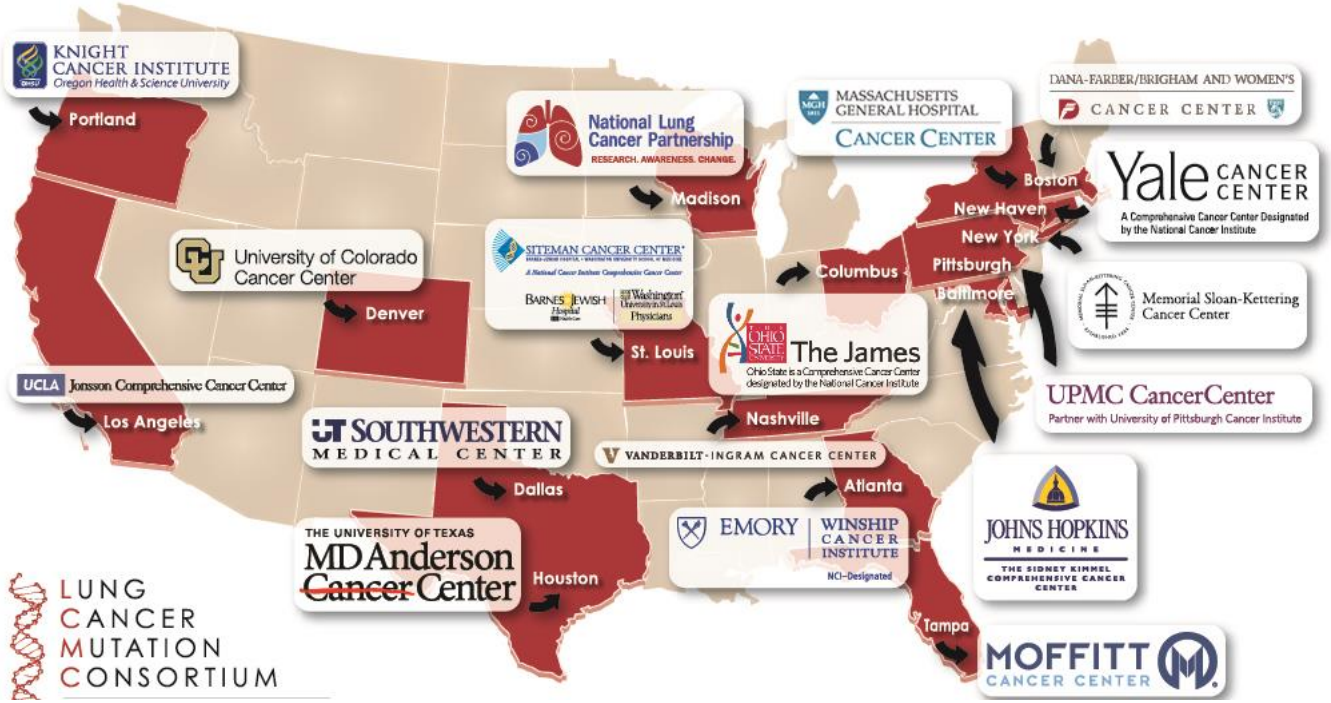
Non-small Cell Lung Cancer

- Every patient has a distinct disease course
- Response to a certain therapy varies from one patient to another
- Histology is used to understand behavior
  - Adenocarcinoma
  - Squamous cell carcinoma
  - Small cell lung cancer
- Various molecular pathways are in play across patients

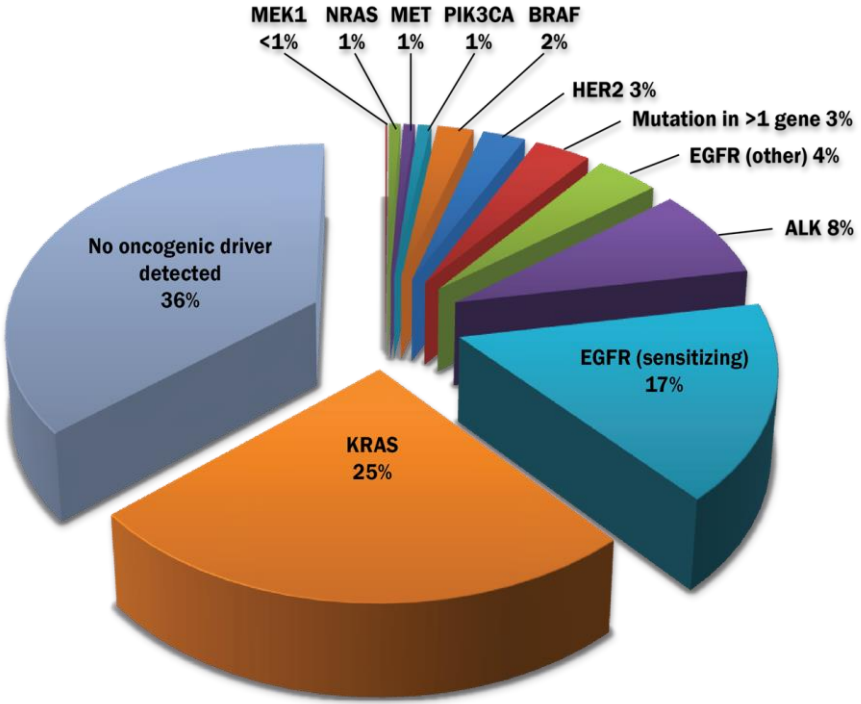
Mutational Burden in Cancer



Lung Cancer Mutation Consortium

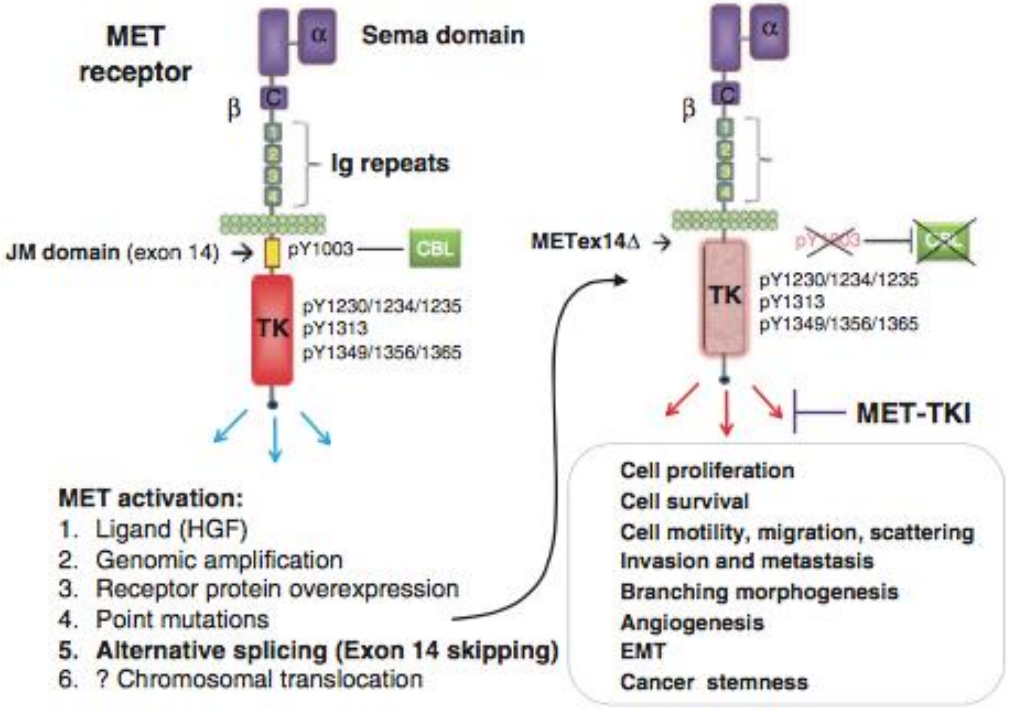


Lung Cancer Mutation Consortium: Incidence of Driver Mutations



Kris et al, JAMA, 2014

MET exon 14 splicing

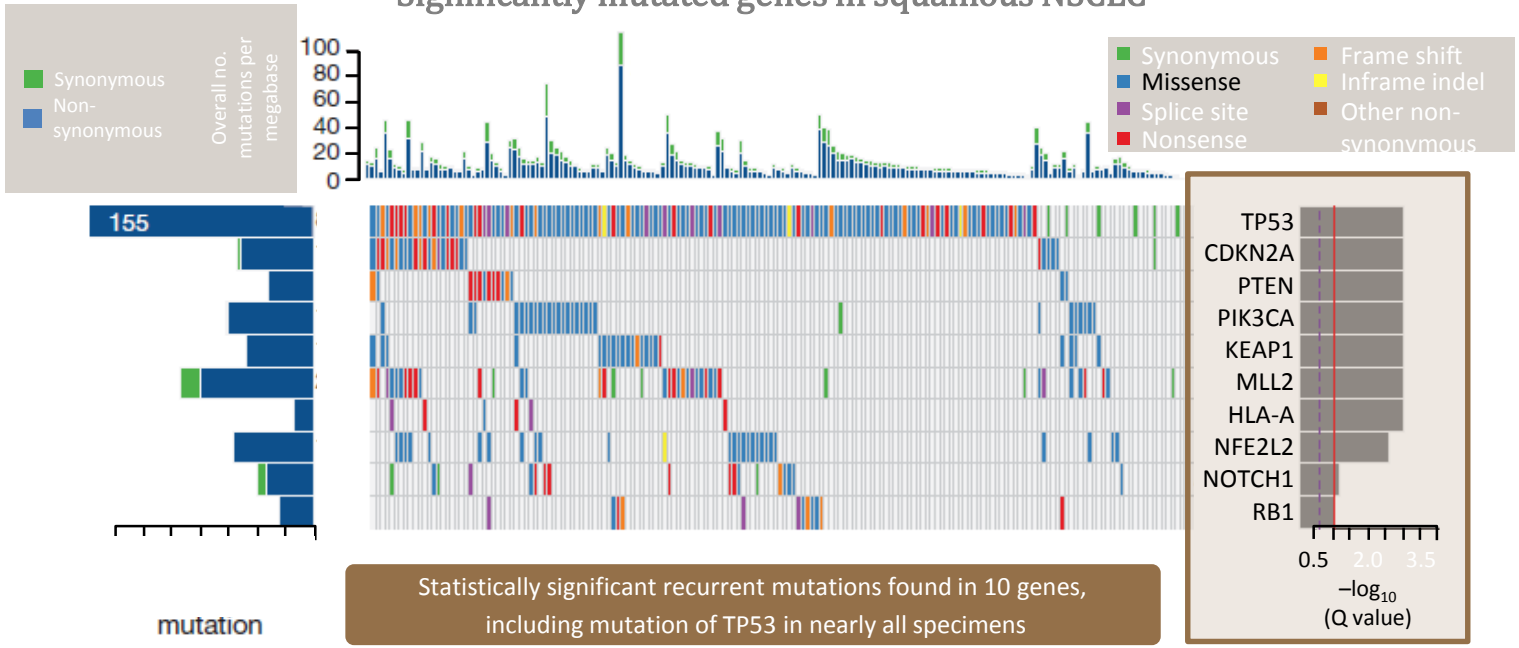


- 2-3% of lung adenocarcinoma
- 8/36 (23%) tumors with pulmonary sarcomatoid carcinoma

Ma et al, Cancer Discovery, 2015
Paik et al Cancer Discovery 2015
Liu et al, ASCO 2015

Squamous cell carcinomas frequently have genetic mutations in multiple pathways

Significantly mutated genes in squamous NSCLC[1]

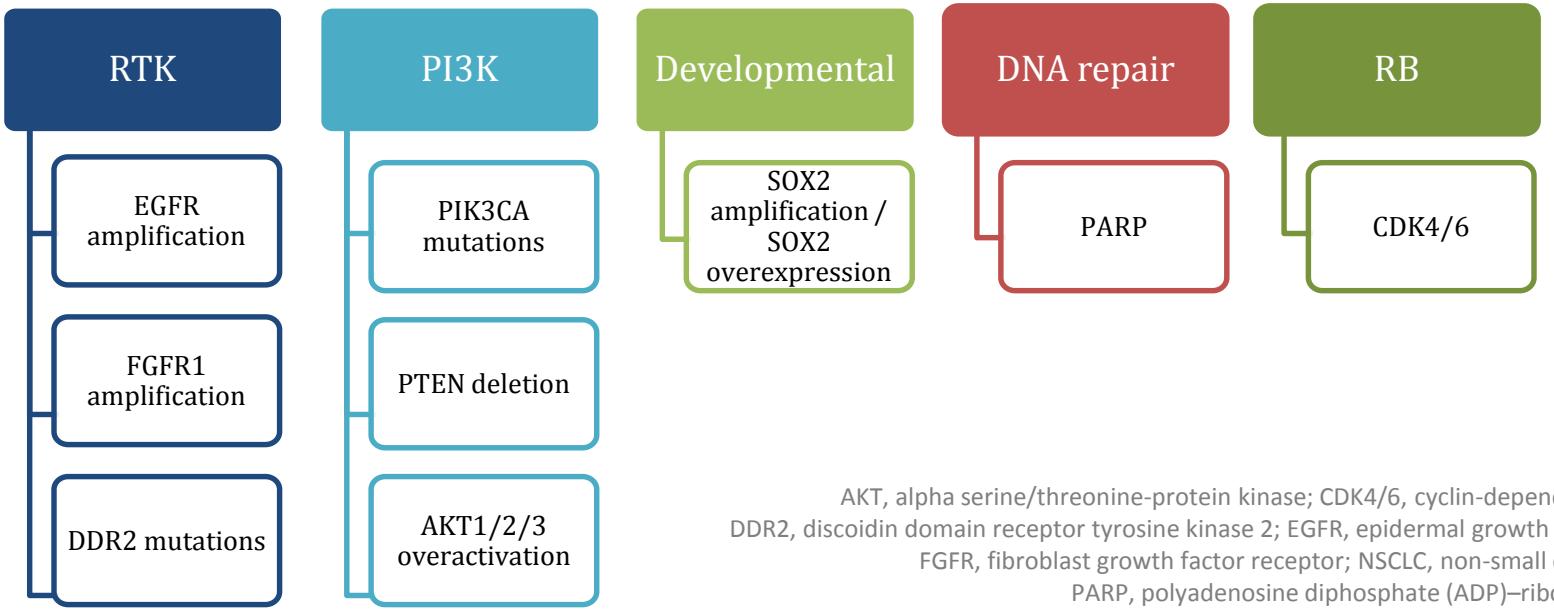


Statistically significant recurrent mutations found in 10 genes, including mutation of TP53 in nearly all specimens

CDKN2A, cyclin-dependent kinase inhibitor 2A; HLA-A, human leukocyte antigen A; KEAP1, kelch-like ECH-associated protein 1; MLL2, mixed lineage leukemia 2; NFE2L2, nuclear factor (erythroid derived 2)-like 2; NOTCH1, neurogenic locus notch homolog protein 1; NSCLC, non-small cell lung cancer; PIK3CA, phosphatidylinositol 3-kinase catalytic subunit; PTEN, phosphatase and tensin homolog; RB1, retinoblastoma 1; TP53, tumor protein 53

1. Cancer Genome Atlas Research Network. *Nature* 2012;489:519–25

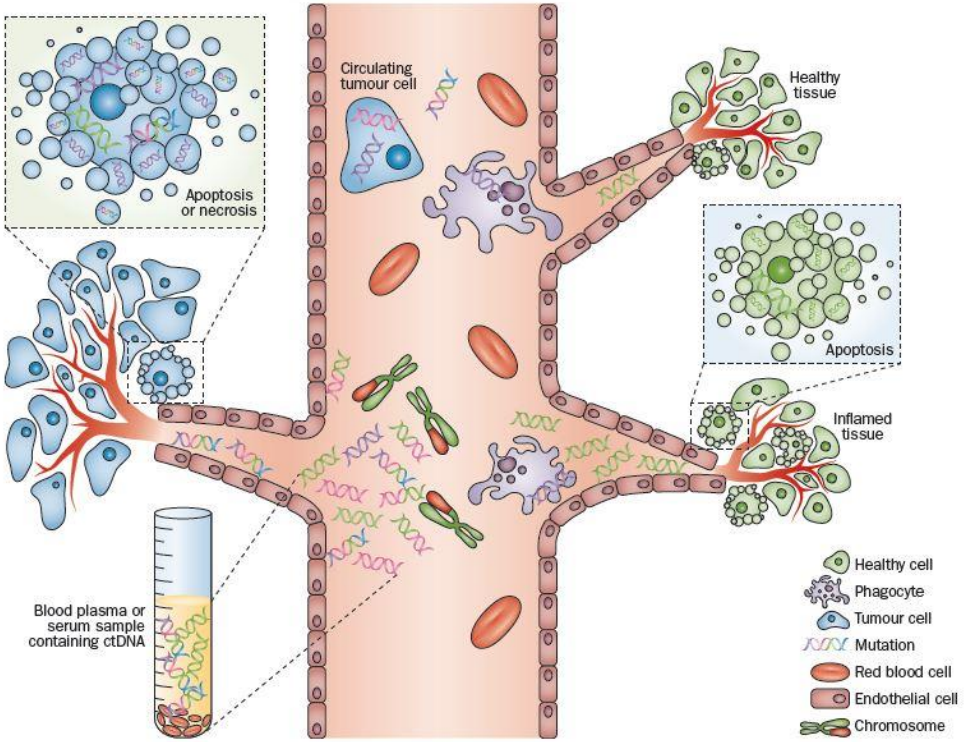
Selected potential target pathways in squamous NSCLC



AKT, alpha serine/threonine-protein kinase; CDK4/6, cyclin-dependent kinase 4/6; DDR2, discoidin domain receptor tyrosine kinase 2; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; NSCLC, non-small cell lung cancer; PARP, polyadenosine diphosphate (ADP)–ribose polymerase; PIK3CA, phosphatidylinositol 3-kinase catalytic subunit; PI3K, phosphoinositide-3-kinase; PTEN, phosphatase and tensin homolog; RB, retinoblastoma; RTK, receptor tyrosine kinase; SOX, SRY-related HMG box

1. Shtivelman E et al. *Oncotarget* 2014;5:1392–433; 2. Stead LF et al. *PLoS One* 2013;8:e78823

Blood-Based Testing with cfDNA

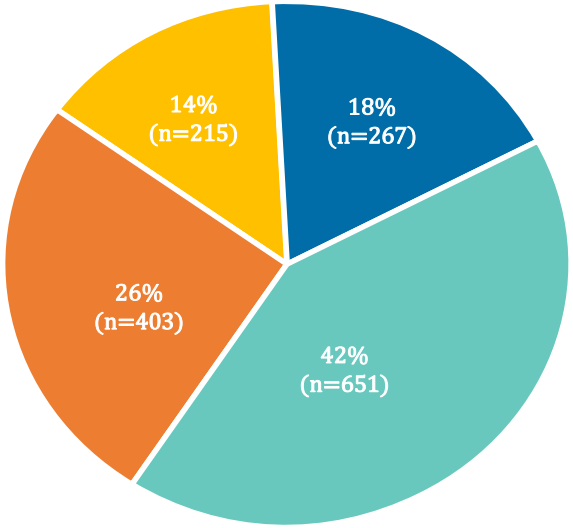


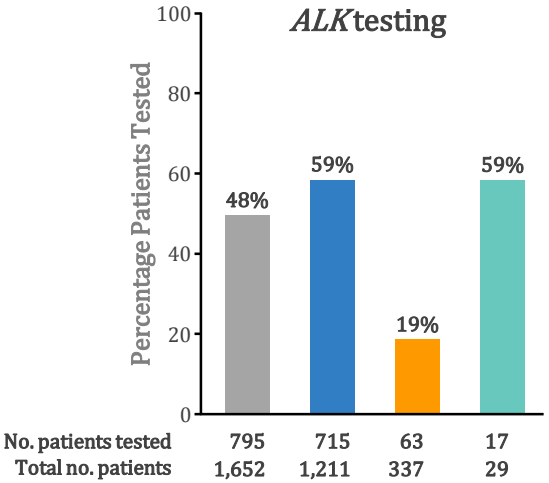
Crowley E et al. Nat Rev Clin Oncol. 2013;10(8):472-84.

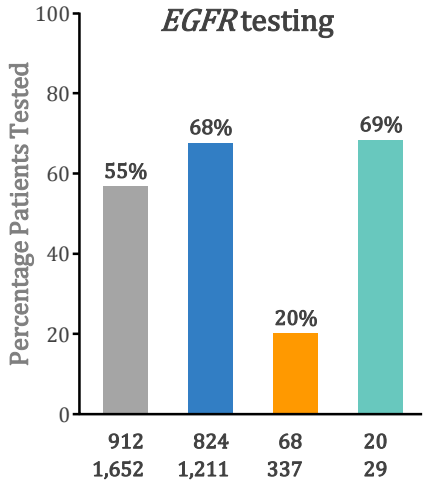
Technologies Utilized for cfDNA Analysis

Company	Platform	Panel
Biodesix	Droplet Digital PCR	EGFR, KRAS, BRAF
Sysmex Inostics	BD LSR II, LSRFortessa (FLOW)	22 gene panel
Roche	Cobas 4800 (RT-PCR)	EGFR
Natera	Massively-multiplexed PCR (mmPCR)	Unknown
Guardant Health	Illumina (NGS)	68 genes
Trovagene	Illumina (NGS)	EGFR, KRAS, BRAF

Biomarker Testing for NSCLC in the Community







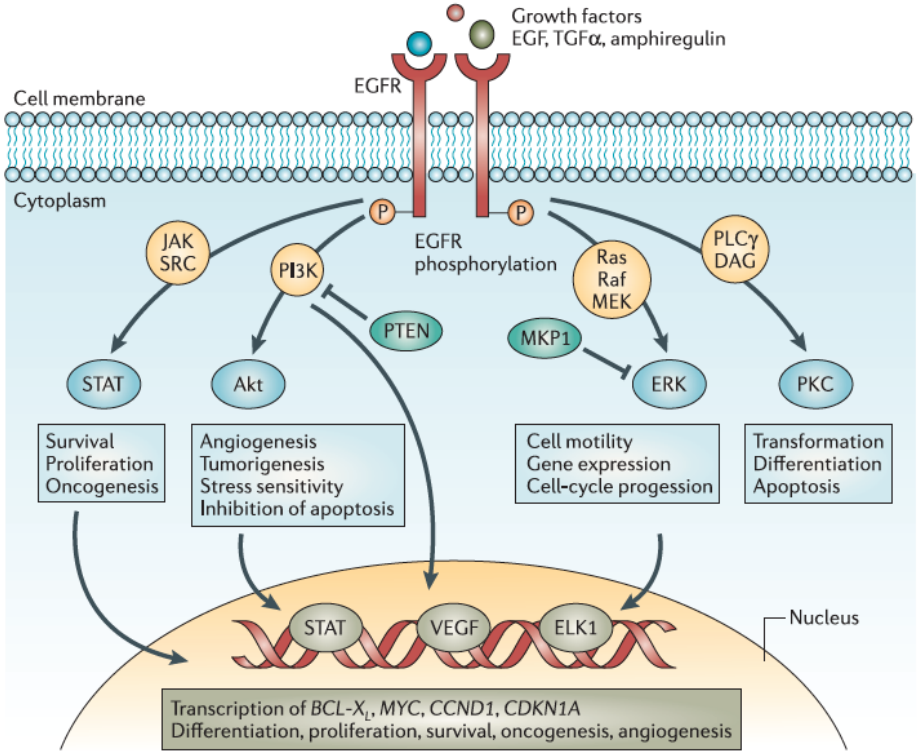
Overall | Adenocarcinoma | Squamous | Adeno/squamous

Other genes widely tested in this population included *KRAS* (13%, 216/1,652), *ROS1* (10%, n=161/1,652), and *BRAF* (5%, n=80/1,652)

Richards et al., CMSTO 2016

EGFR as a Therapeutic Target

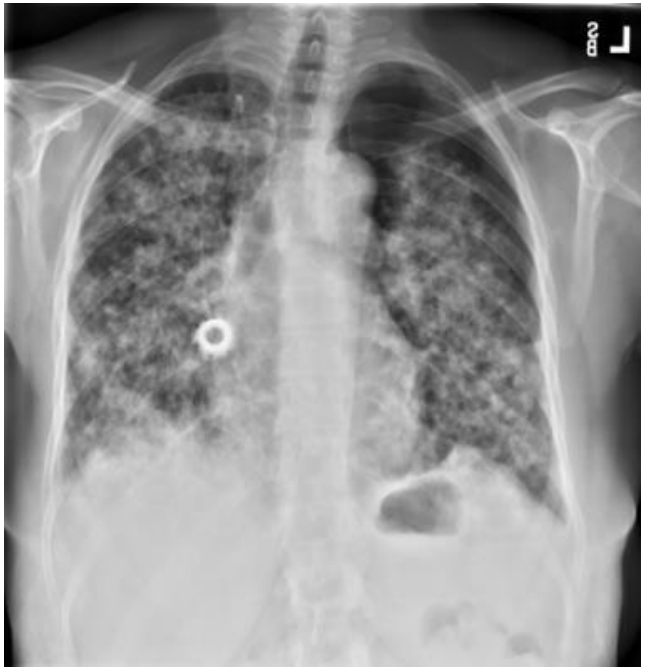
EGFR Pathway



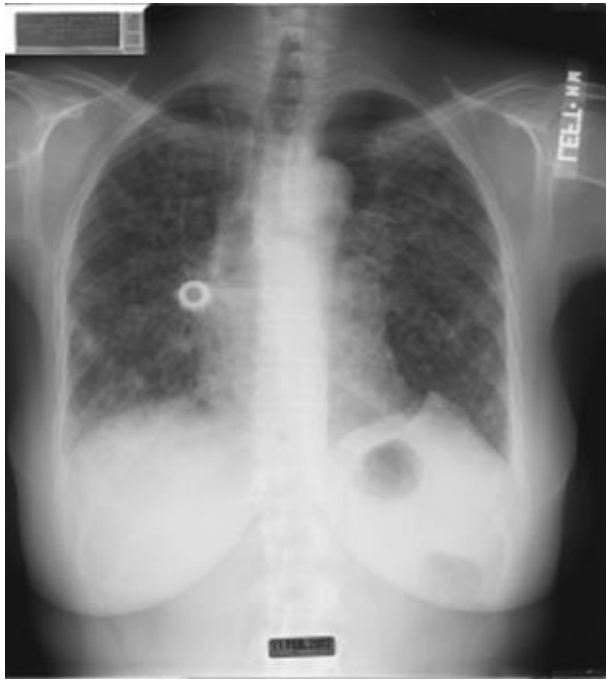
CCND1, gene encoding cyclin D1; *CDKN1A*, gene encoding p21; JAK, Janus kinase; TGFα, tranforming growth factor-α.

Niyati et al, Nature Reviews, 2006

NSCLC Patient Treated With an EGFR Inhibitor



6 FEB 2002



11 FEB 2002

The Driver

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 20, 2004 VOL. 350 NO. 21

Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

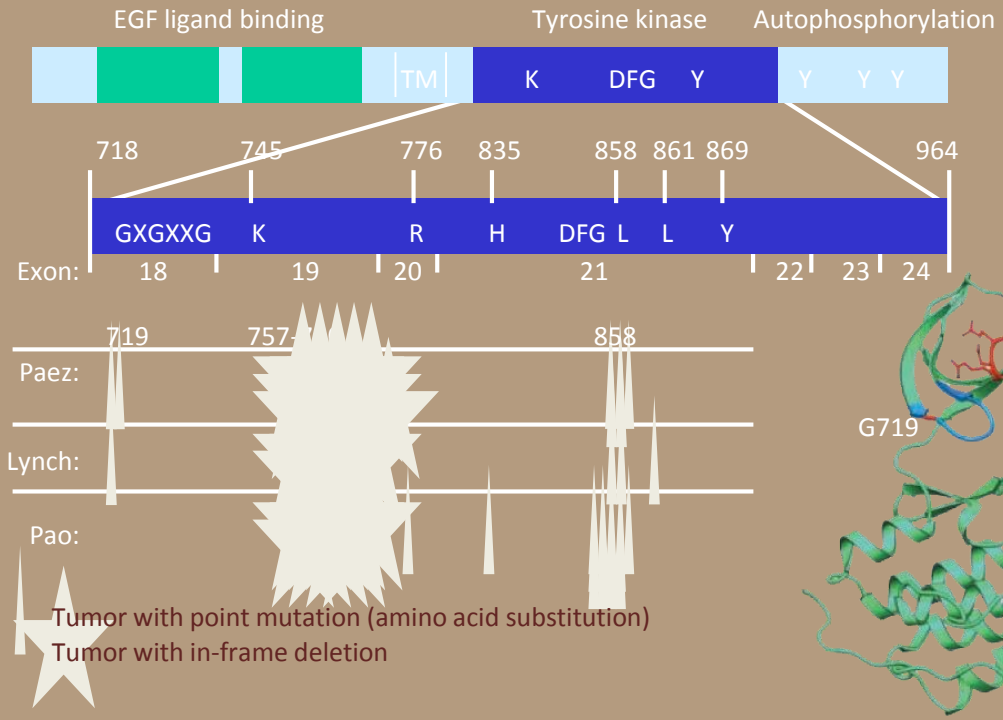
Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.

Sciencexpress Report

EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy

J. Guillermo Paez,[1,2*] Pasi A. Jänne,[1,2*] Jeffrey C. Lee,[1,3*] Sean Tracy,[1] Heidi Greulich,[1,2] Stacey Gabriel,[4] Paula Herman,[1] Frederic J. Kaye,[5] Neal Lindeman,[6] Titus J. Boggon,[1,3] Katsuhiko Naoki,[1] Hidefumi Sasaki,[7] Yoshitaka Fujii,[7] Michael J. Eck,[1,3] William R. Sellers,[1,2,4†] Bruce E. Johnson,[1,2†] Matthew Meyerson[1,3,4†]

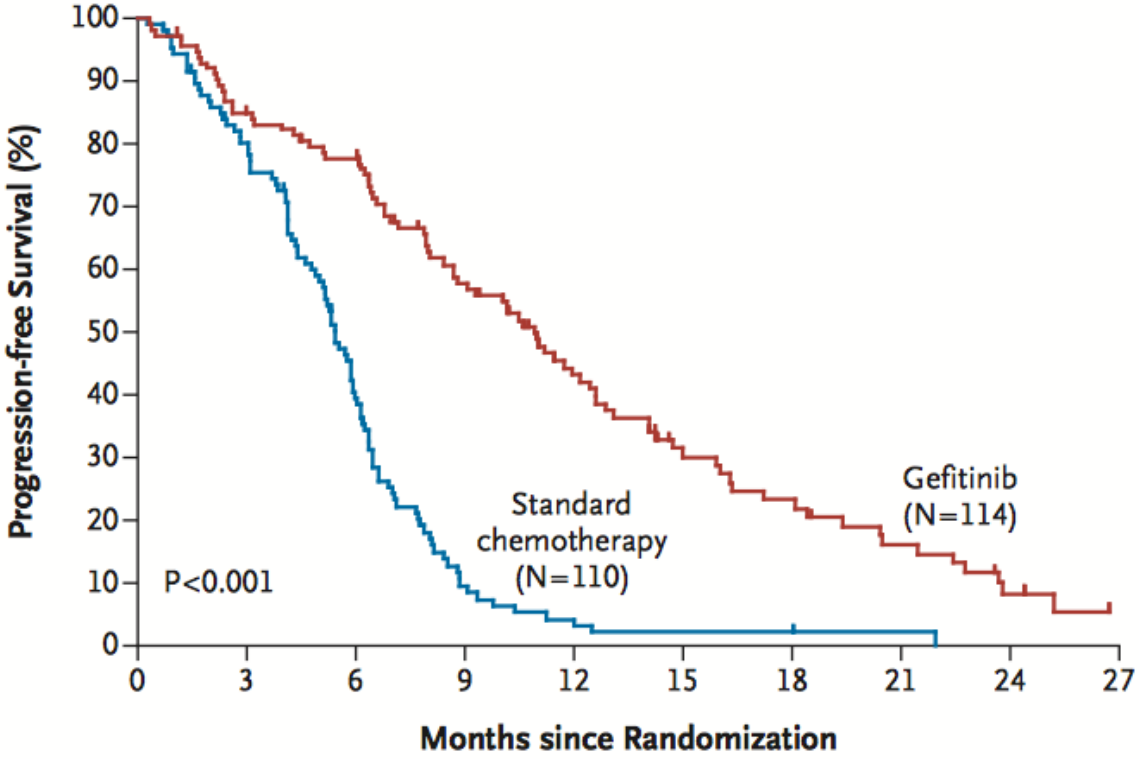
Positions of Mutations Detected in EGFR Tyrosine Kinase Domain in NSCLC



EGF=endothelial growth factor; TM=transmembrane.

Adapted from Pao et al. *Proc Natl Acad Sci U S A.* 2004;101:13306.
Lynch et al. *N Engl J Med*. 2004;350:2129.
Paez et al. *Science*. 2004;304:1497.

Targeted Therapy in EGFR Mut+ NSCLC



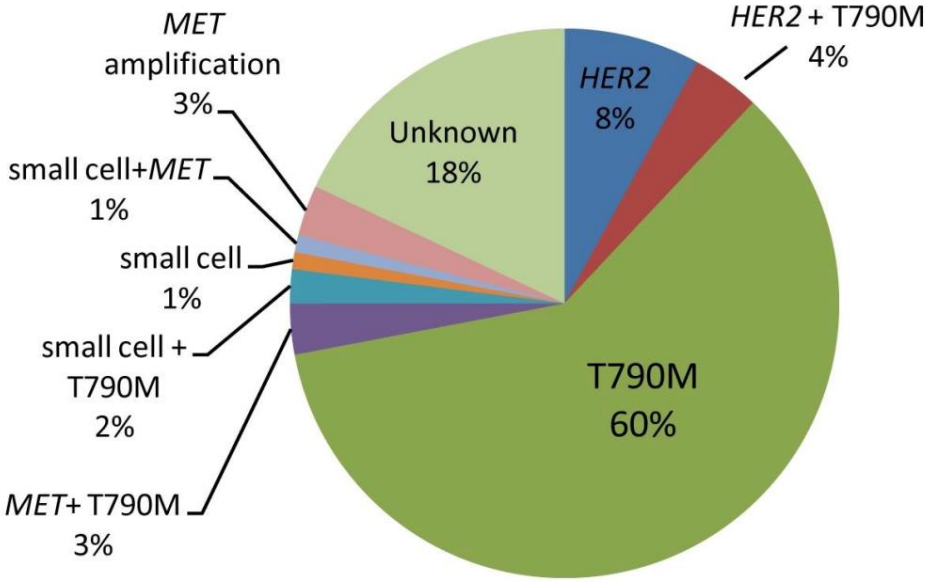
Maemondo et al, N Engl J Med, 2010

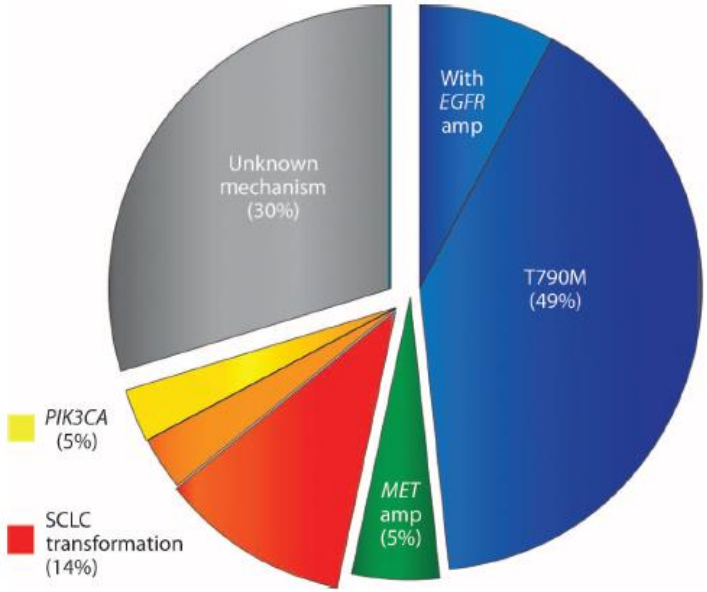
First- Line TKI Therapy in EGFR Mutated NSCLC—Randomized Phase III Trials

Study	N	Treatment Arm	Control Arm	Stage	Median PFS	Median OS	Indication
IPASS (Mok TS, et al. N Engl J Med. 2009;361:947-957.)	1217	Gefitinib	Carboplatin/ Placitaxel	IIIB/IV	5.7 vs 5.8 months (HR for EGFR mutated pts 0.48; HR for nonmutated pts 2.84)	18.6 vs 17.3 months (P = NS)	First-line
WJTOG3405 (Mitsudomi T, et al. Lancet Oncol. 2010; 11:121-128.)	177 (M+)	Gefitinib	Cisplatin, Docetaxel	IIIB/IV	9.2 vs 6.3 months (P < 0.001)		First-line
Maemondo M, et al. N Engl J Med. 2010; 362:2380-2388.	230 (M+)	Gefitinib	Carboplatin, Paclitaxel	IIIB/IV	10.8 vs 5.4 months (HR 0.3, P < 0.0001)	30.5 vs 23.6 months (P = NS)	First-line
OPTIMAL (Zhou C, et al. Lancet Oncol. 2011;12:735-742.)	165 (M+)	Erlotinib	Carboplatin/ Gemcitabine	IIIB/IV	13.6 vs 4.6 months (HR 0.16, P < 0.0001)		First-line
EURTAC (Rosell R, et al. Lancet Oncol. Jan 25, 2012 [Epub ahead of print].)	153 (M+)	Erlotinib	Platinum-based chemotherapy	IIIB/IV	9.4 vs 5.2 months (HR, 0.42, P < 0.0001)	22.9 vs 18.8 months (P = 0.42)	First-line

PFS is superior, no survival advantage for first line TKI- effect of cross-over

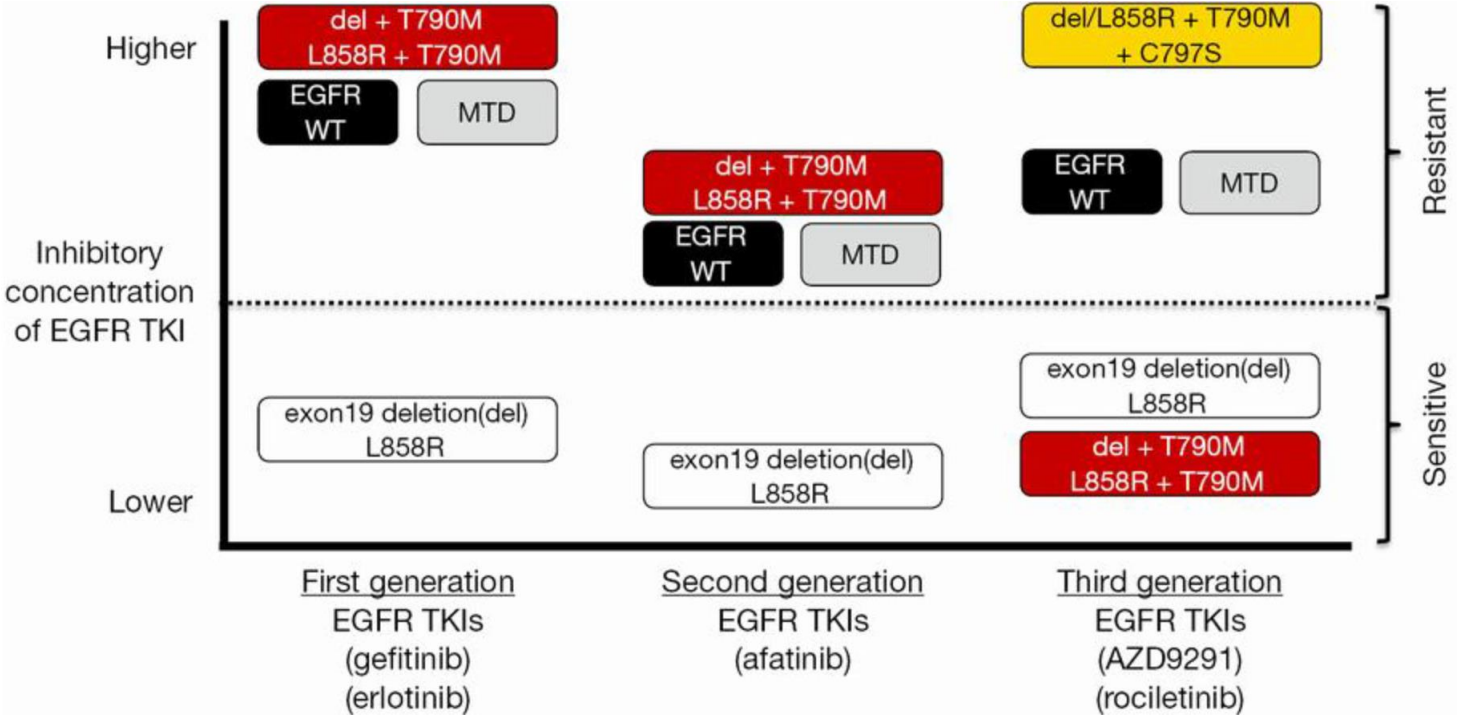
T790M is the Most Common Mechanism of Resistance to EGFR TKI





Sequist Sci Transl Med 2011; Yu H et al. Clin Cancer Res. 2013 Apr 15;19(8):2240-7; Piotrowska The Cancer Journal 2015; Camidge Nat Rev Clin Oncol 2014

EGFR TKIs



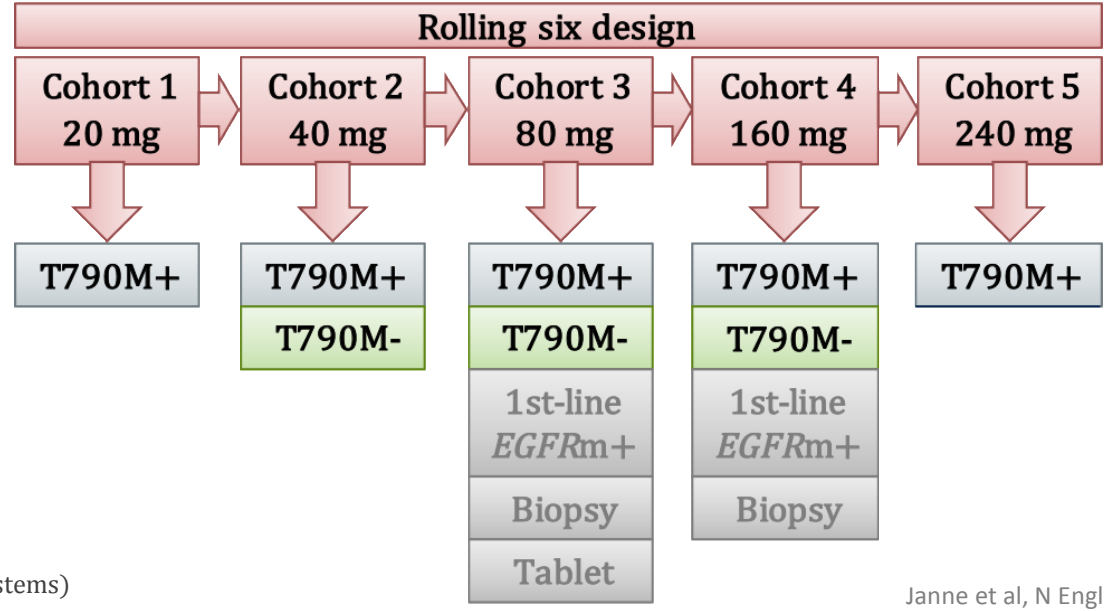
Costa et al, Transl Lung Cancer Res, 2015

Osimertinib: AURA Study

- Phase I, open-label, multicenter study of AZD9291 administered once daily in Asian and Western patients with advanced NSCLC who have documented radiological progression while on prior therapy with an EGFR-TKI (AURA; NCT01802632)

Escalation
Not preselected by T790M status

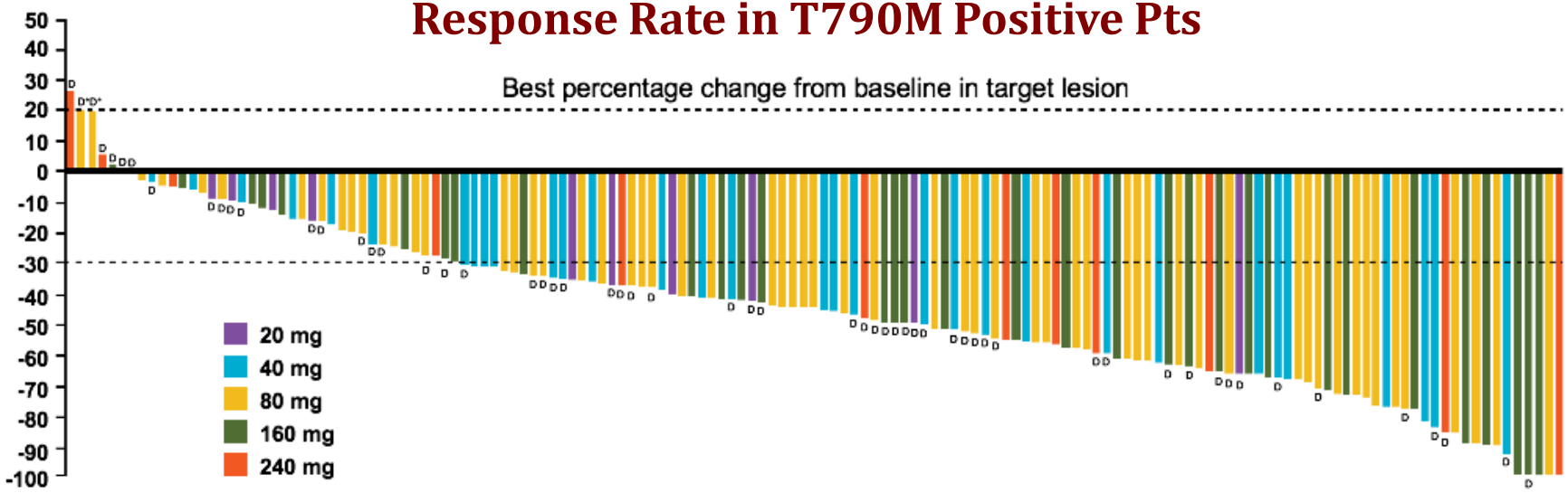
Expansion
Enrollment by local testing followed by central laboratory confirmation* of T790M status or by central laboratory testing alone



*cobas® EGFR Mutation Test (Roche Molecular Systems)

Janne et al, N Engl J Med, 2015

Response Rate in T790M Positive Pts



- DCR (CR+PR+SD) in patients with centrally tested T790M positive tumours was 90% (141 / 157; 95% CI 84, 94)

	20 mg	40 mg	80 mg	160 mg	240 mg	Total
N (157)	10	32	61	41	13	157
ORR (95% CI)	50% (19, 81)	59% (41, 76)	66% (52, 77)	51% (35, 67)	54% (25, 81)	59% (51, 66)

Osimertinib is Superior to Chemotherapy (AURA 3)

Key eligibility criteria

- ≥18 years (≥20 years in Japan)
- Locally advanced or metastatic NSCLC
- Evidence of disease progression following first-line EGFR-TKI therapy
- Documented EGFRm and central confirmation of tumour *EGFR* T790M mutation from a tissue biopsy taken after disease progression on first-line EGFR-TKI treatment
- WHO performance status of 0 or 1
- No more than one prior line of treatment for advanced NSCLC
- No prior neo-adjuvant or adjuvant chemotherapy treatment within 6 months prior to starting first EGFR-TKI treatment
- Stable* asymptomatic CNS metastases allowed

R 2:1

Osimertinib (n=279)
80 mg orally
QD

Platinum-pemetrexed (n=140)
Pemetrexed 500 mg/m^2 +
carboplatin AUC5 *or*
cisplatin 75 mg/m^2
Q3W for up to 6 cycles
+ optional maintenance
pemetrexed#

Endpoints

Primary:

- PFS by investigator assessment (RECIST 1.1)

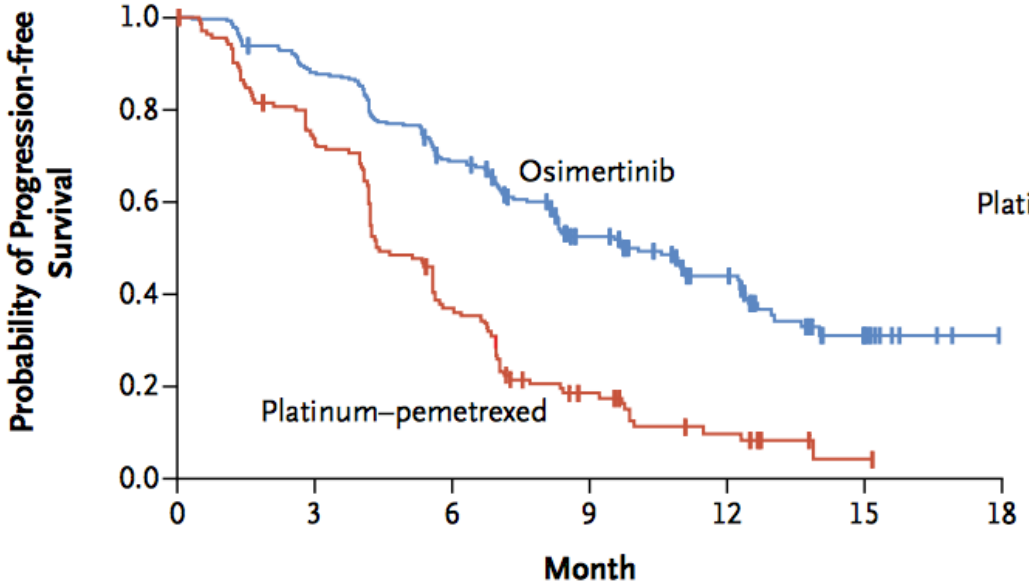
Secondary and exploratory:

- Overall survival
- Objective response rate
- Duration of response
- Disease control rate
- Tumour shrinkage
- BICR-assessed PFS
- Patient reported outcomes
- Safety and tolerability

Optional crossover
Protocol amendment allowed patients on chemotherapy to begin post-BICR confirmed progression open-label osimertinib treatment

- RECIST 1.1 assessments performed every 6 weeks until objective disease progression

Progression-free Survival

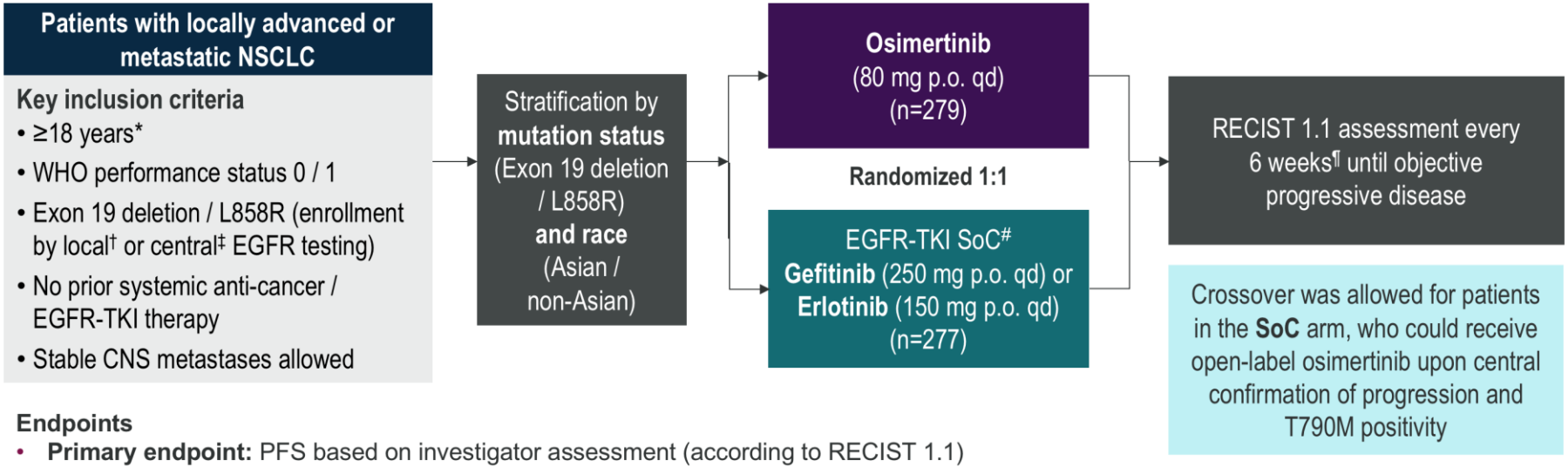


No. at Risk							
Osimertinib	279	240	162	88	50	13	0
Platinum–pemetrexed	140	93	44	17	7	1	0

	No. of Patients	Median Progression-free Survival
		mo (95% CI)
Osimertinib	279	10.1 (8.3–12.3)
Platinum–pemetrexed	140	4.4 (4.2–5.6)

Hazard ratio for disease progression or death, 0.30 (95% CI, 0.23–0.41)
P<0.001

FLAURA Study Design



Endpoints

- **Primary endpoint:** PFS based on investigator assessment (according to RECIST 1.1)
  - The study had a 90% power to detect a hazard ratio of 0.71 (representing an improvement in median PFS from 10 months to 14.1 months) at a two-sided alpha-level of 5%
- **Secondary endpoints:** objective response rate, duration of response, disease control rate, depth of response, overall survival, patient reported outcomes, safety

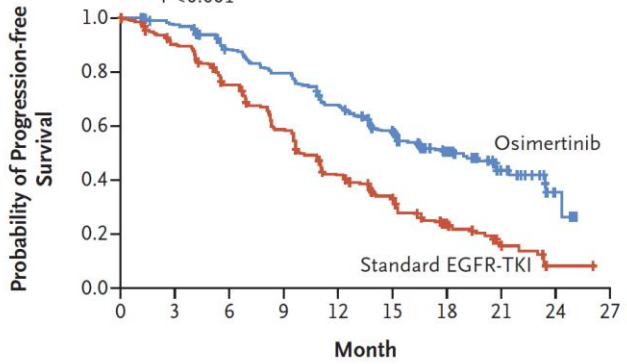
Soria et al, N Engl J Med, 2018

FLAURA: Efficacy

Progression-free Survival in Full Analysis Set

	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Osimertinib	279	18.9 (15.2–21.4)
Standard EGFR-TKI	277	10.2 (9.6–11.1)

Hazard ratio for disease progression or death, 0.46 (95% CI, 0.37–0.57)
P<0.001



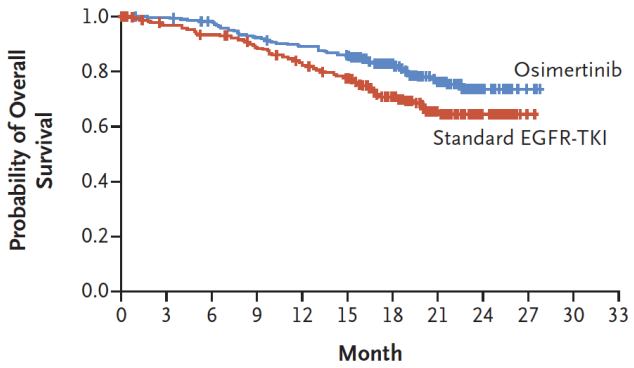
No. at Risk

Osimertinib	279	262	233	210	178	139	71	26	4	0
Standard EGFR-TKI	277	239	197	152	107	78	37	10	2	0

Overall Survival

	No. of Patients	Median Overall Survival (95% CI)
		mo
Osimertinib	279	NC (NC–NC)
Standard EGFR-TKI	277	NC (NC–NC)

Hazard ratio for death, 0.63 (95% CI, 0.45–0.88)
P=0.007



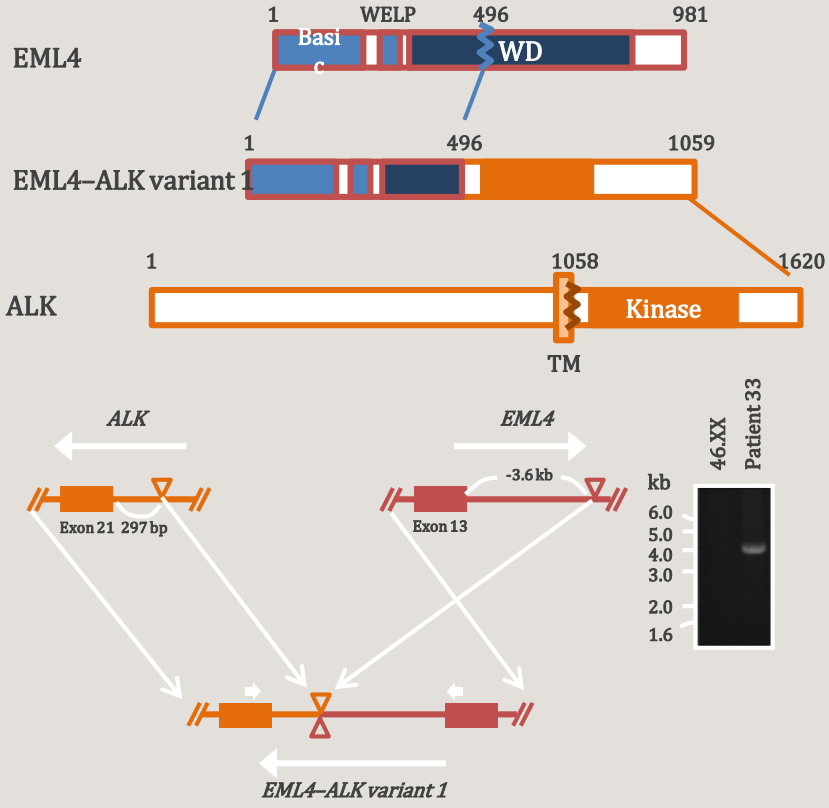
No. at Risk

Osimertinib	279	276	269	253	243	232	154	87	29	4	0	0
Standard EGFR-TKI	277	263	252	237	218	200	126	64	24	1	0	0

Soria et al, N Engl J Med, 2018

ALK Signaling in NSCLC

ALK Fusion Gene



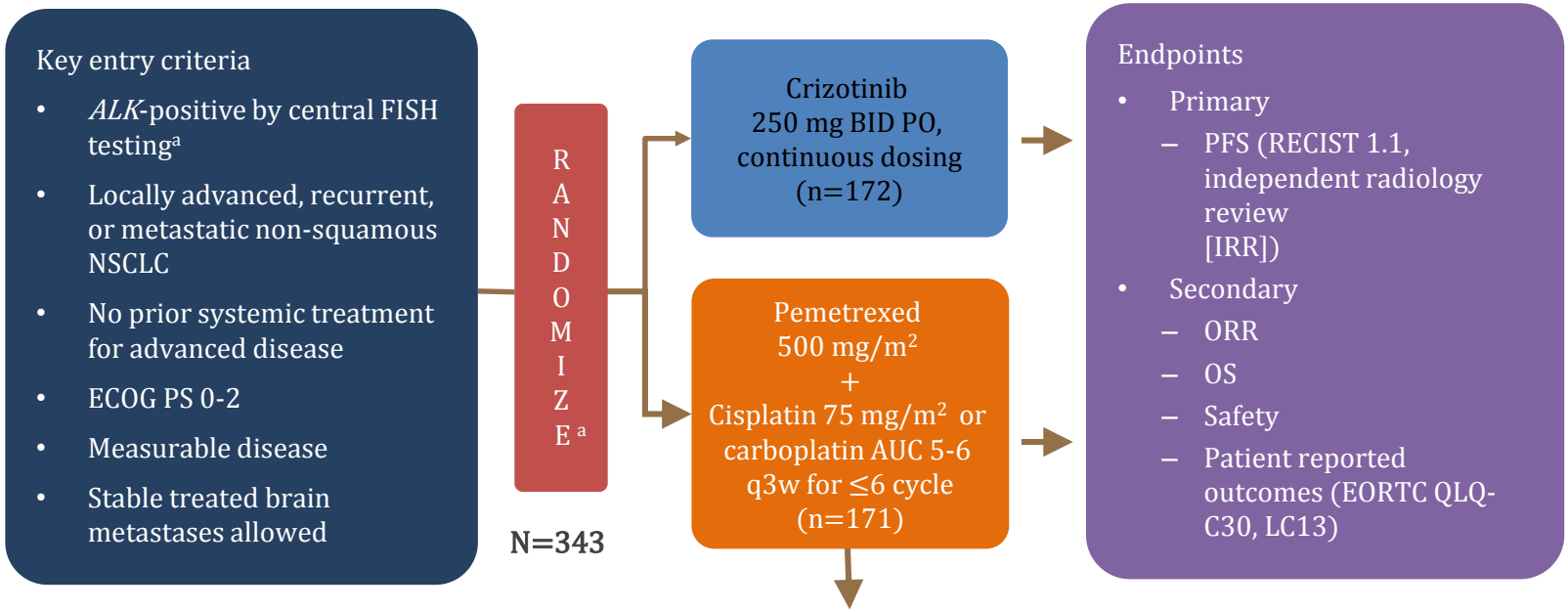
- Potent oncogenic activity
- Present in approximately 4-5% of NSCLC
- Detection by FISH or IHC

Soda et al, *Nature*, 2007; Shaw et al, *J Clin Oncol*, 2009.

ALK+ve NSCLC

- Observed in ~ 5% of lung adenocarcinoma
- Brain metastasis is a common clinical problem
- Predilection for pleural and pericardia metastasis
- Crizotinib is superior to chemotherapy for ALK +ve disease
- Acquired resistance develops in approximately 10 months

PROFILE 1014 Study Design

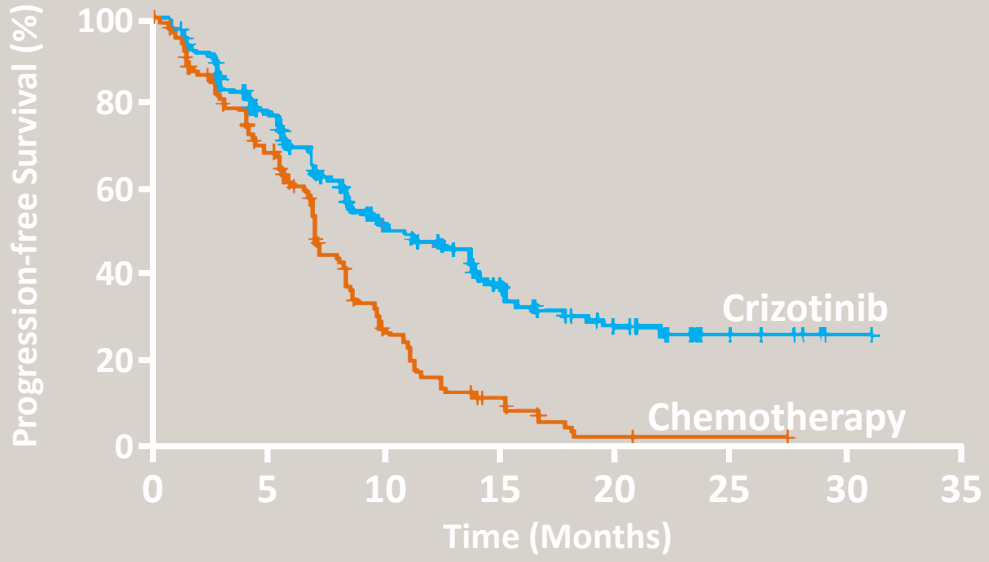


[a]ALK ststus determined using standard ALK break-apart FISH assay. [b]Stratification factors: ECOG PS (0/1 vs. 2), Asian vs. non-Asian race, and brain metastases (present vs. absent).

Mok et al, ASCO 2014; Solomon et al, N Engl J Med, 2014.

PROFILE 1014: NCT01154140

Crizotinib is Superior to Chemotherapy



No. at Risk

Crizotinib	172	120	65	38	19	7	1	0
Chemotherapy	171	105	36	12	2	1	0	0

	Crizotinibp (N=172)	Chemotherapy (N=172)
Events, n (%)	100 (58)	137 (80)
Median, months	10.9	7.0
HR (95% CI)	0.45 (0.35-0.60)	
P[b]	<0.0001	

Data cutoff: November 30, 2013. [a]Assessed by IRR; [b]1-sided stratified log-rank test

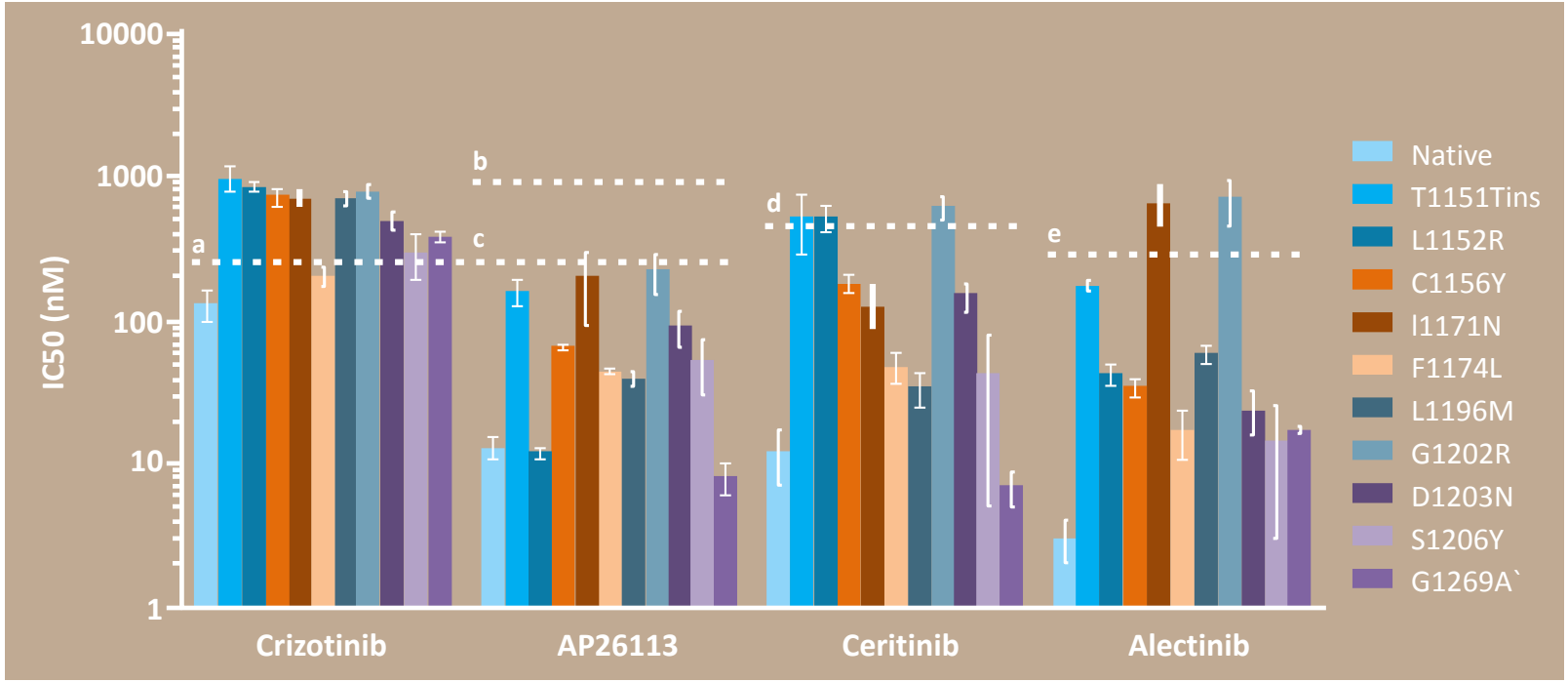
Solomon B, et al. *N Engl J Med* 2014;371; 2167-77.

'NEXT-GENERATION' ALK INHIBITORS

TKI	COMPANY	OTHER TARGETS	STATUS
Alectinib (CH5424802)	Genentech/ Roche	LTK	Accelerated approval for the treatment of people with ALK+ metastatic NSCLC who have progressed on or are intolerant to crizotinib
Brigatinib (AP26113)	Ariad	ROS1	Phase 2
Ceritinib (LDK378)	Novartis	IGF-1R, IR	Accelerated approval for the treatment of people with ALK+ metastatic NSCLC who have progressed on or are intolerant to crizotinib
Lorlatinib (PF-06463922)	Pfizer	ROS1	Phase 1/2
ASP3026	Astellas	ROS1	Discontinued
TSR-011	Tesaro	Trk	Phase 1/2
X-396	Xcovery	MET	Phase 1/2
Entrectinib (RXDX-101)	Ignyta	Trk, ROS1	Phase 2

Adapted from Awad and Shaw 2014 Clin Adv Hematol Oncol

Inhibitory Profiles of ALK Inhibitors in Cellular Models



50% maximal inhibitory concentration (IC-50) values of Ba/F3 cells depemdent onexpresion of EML4-ALK (naïve) or kinase domain mutated EML4-ALK variants (n-10). Data for each cell derived from at least 4 independent experiments (error bars – standard deviation). Dashed horizontal lines indicate the mean steady-state exposure concentrations of each drug corrected for the functional effects of protein binding at the recommended phase 2 doses. [a]Crizotinib: 250 mg BID, 250 nM[2], AP26113: [b]180 mg QD, 899 nM and [c]90 mg QD, 264 nM2, [d]Certinib: 750 mg QD, 458 nM11, Alectinib: 600 mg BID, 277 nM[12], [e]n=2

1. Gettinger, et al. Presented at: ESMO. 2014 (abstr 439O). 2. Squillace, et al. Presented at: AACR. 2013 (abstr 5655).

J-ALEX Phase III Study Design

Key Entry Criteria

- Stage IIIB/IV or recurrent *ALK*-positive NSCLC
- ALK centralized testing (IHC and FISH or RT-PCR)
- ECOG PS 0-2
- ≥1 measurable lesion assessed by investigator
- Treated/asymptomatic brain metastases allowed
- ≤1 prior chemotherapy

R
1:1

**Alectinib 300 mg BID PO,
28-day cycle
(N=100)**

**Crizotinib 250 mg BID PO,
28-day cycle
(N=100)**

Endpoints

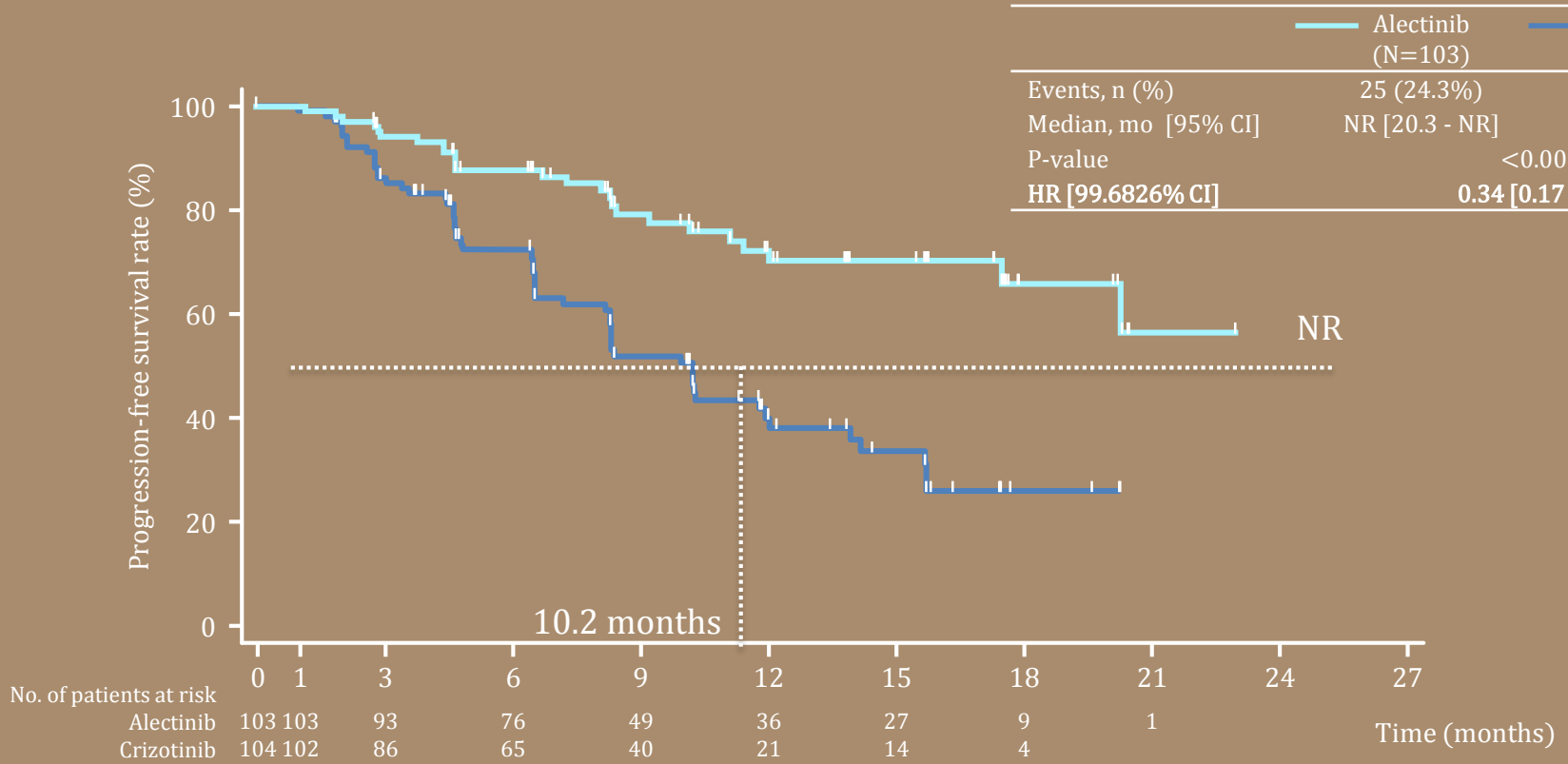
- Primary
  - PFS assessed by IRF*
- Secondary
  - OS
  - ORR
  - PK
  - QOL
  - CNS PFS
  - Safety

*IRF Independent Review Facility

Stratification factors: Clinical stage (IIIB/IV vs. Recurrent)
Prior chemotherapy (0 vs. 1)
ECOG PS (0/1 vs. 2)

Nokihara et al, ASCO 2016

Inhibitory Profiles of ALK Inhibitors in Cellular Models



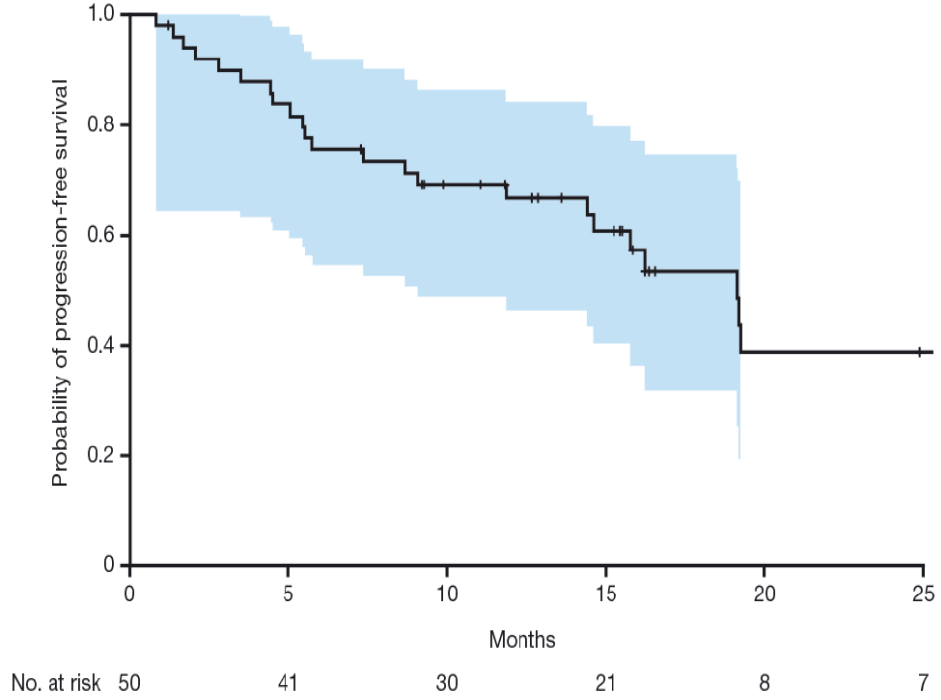
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Crizotinib in *ROS1*-Rearranged Non–Small-Cell Lung Cancer

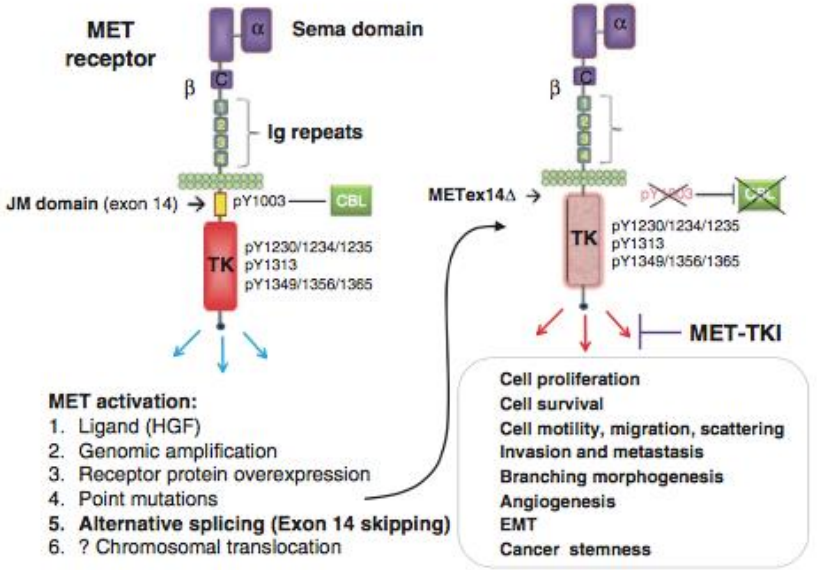
Alice T. Shaw, M.D., Ph.D., Sai-Hong I. Ou, M.D., Ph.D., Yung-Jue Bang, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D., Benjamin J. Solomon, M.B., B.S., Ph.D., Ravi Salgia, M.D., Ph.D., Gregory J. Riely, M.D., Ph.D., Marileila Varella-Garcia, Ph.D., Geoffrey I. Shapiro, M.D., Ph.D., Daniel B. Costa, M.D., Ph.D., Robert C. Doebele, M.D., Ph.D., Long Phi Le, M.D., Ph.D., Zongli Zheng, Ph.D., Weiwei Tan, Ph.D., Patricia Stephenson, Sc.D., S. Martin Shreeve, M.D., Ph.D., Lesley M. Tye, Ph.D., James G. Christensen, Ph.D., Keith D. Wilner, Ph.D., Jeffrey W. Clark, M.D., and A. John Iafrate, M.D., Ph.D.

Prolonged Progression-Free Survival with Crizotinib



MET exon 14 splicing

- 2-3% of lung adenocarcinoma
- 8/36 (23%) tumors with pulmonary sarcomatoid carcinoma

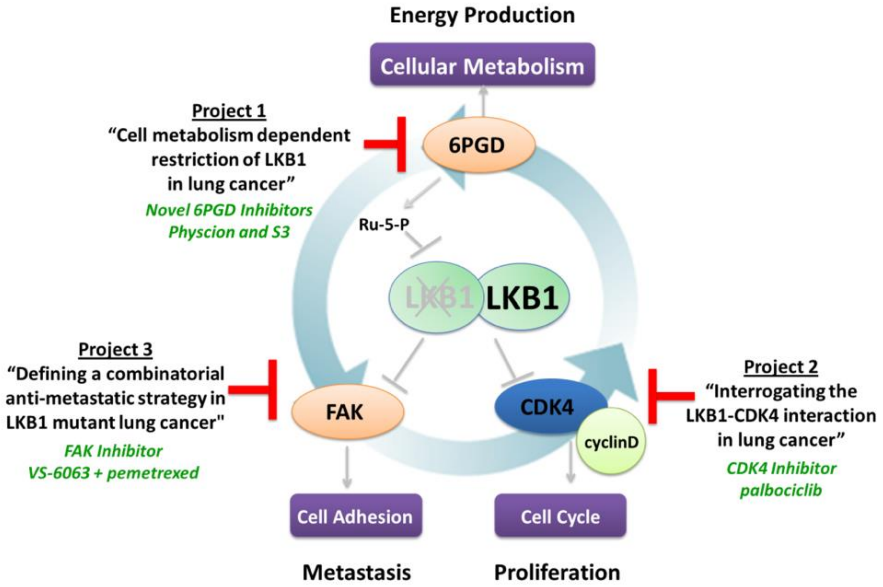


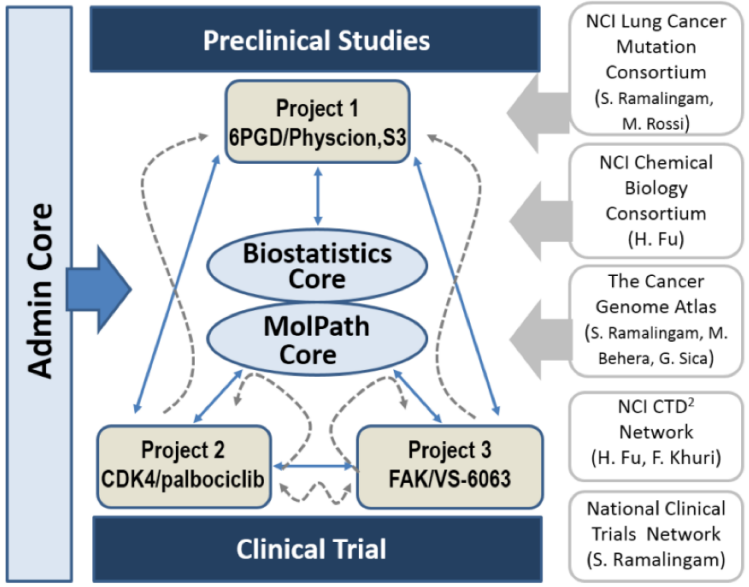
Ma et al, Cancer Discovery, 2015
Paik et al Cancer Discovery 2015
Liu et al, ASCO 2015

Other Treatable Mutations

Target	Treatment	Results	Status
RET gene rearrangement	Carbozantinib Vandetanib	RR 15-40% mPFS 3-7 m	In development
MET exon 14 mutation	Crizotinib	RR 44%	In development
BRAF V600E mutation	Dabrafenib + Trametinib	RR 65% mPFS 9.5 m	Breakthrough status from FDA

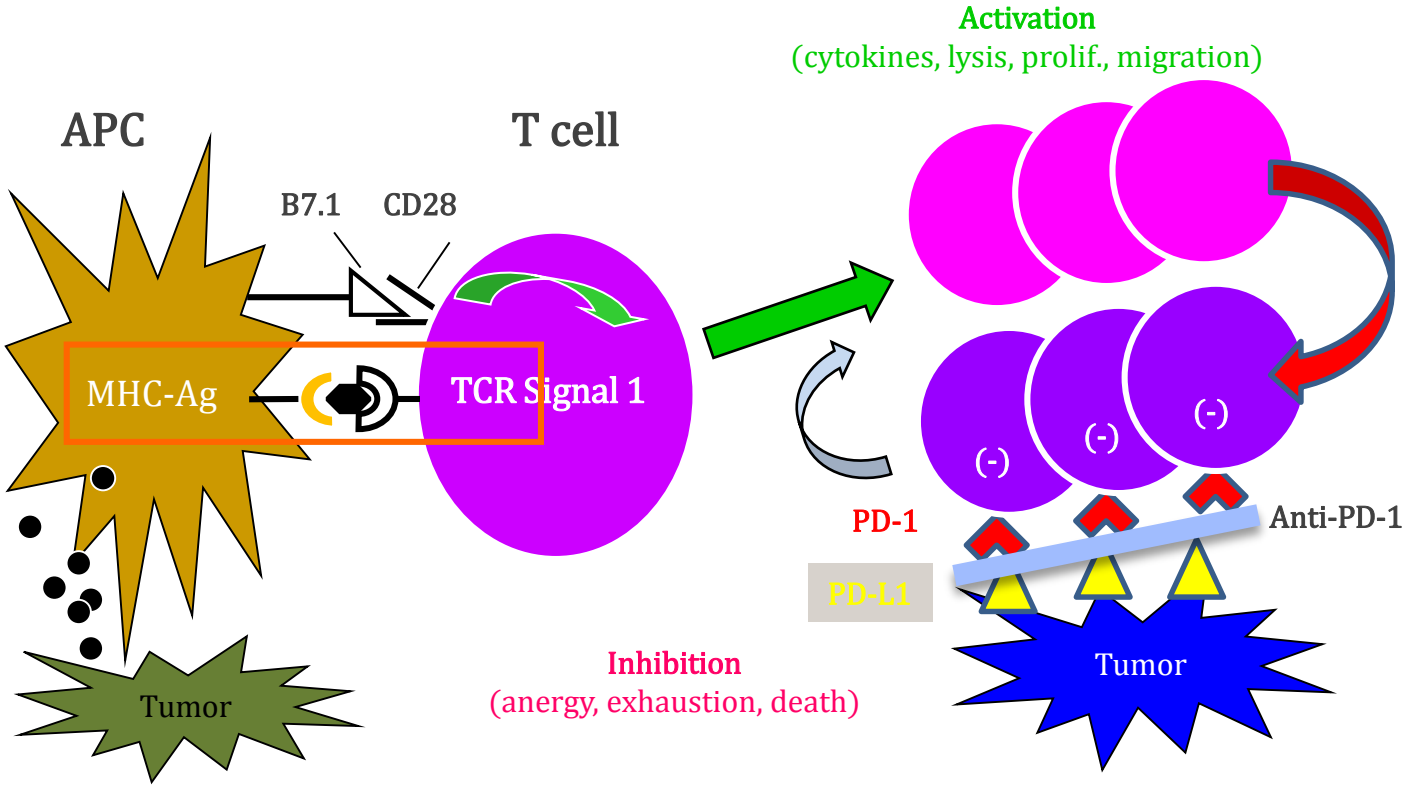
Emory Lung Cancer Program Project





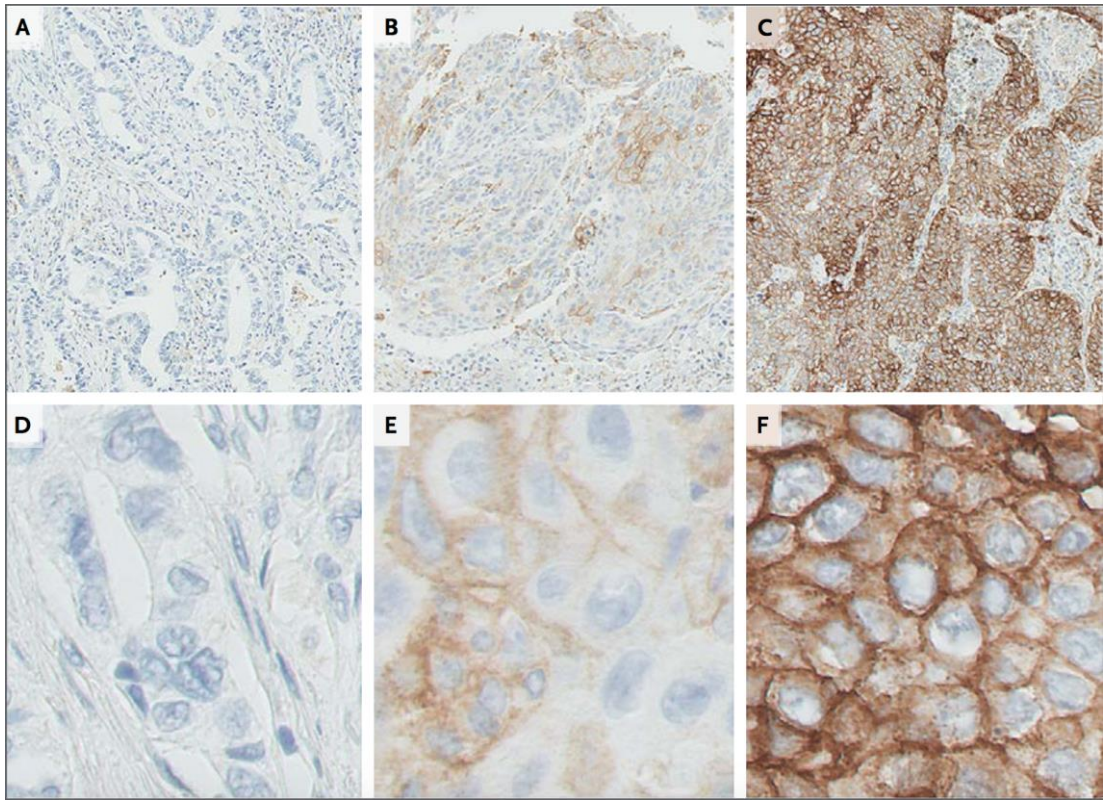
Immune Checkpoint Inhibition

Role of PD-1 in Suppressing Antitumor Immunity



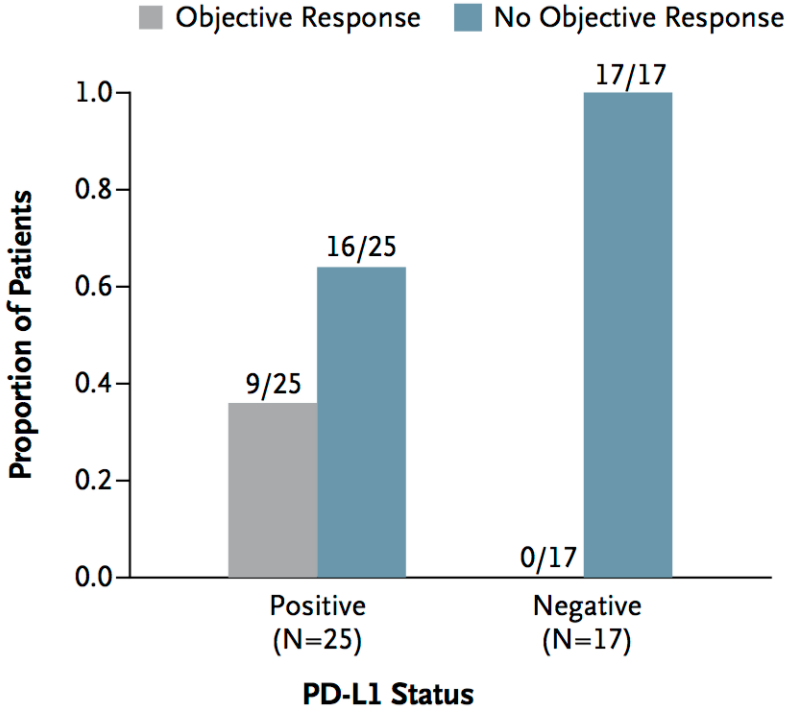
Keir ME et al, Annu Rev Immunol 2008; Pardoll DM, Nat Rev Cancer 2012

PD-L1 Expression in NSCLC



Garon et al, N Engl J Med, 2015

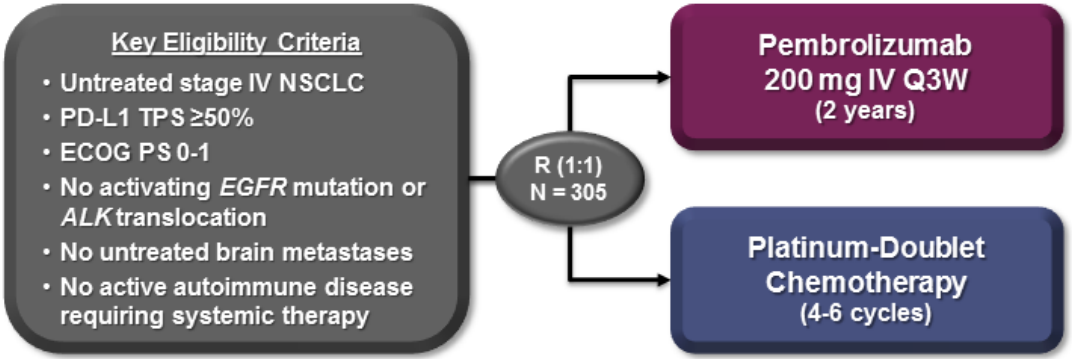
PDL-1 Expression as a Predictive Marker



Topalian et al, N Engl J Med, 2012

M Reck. ESMO 2016.

KEYNOTE-024 Study Design (NCT02142738)



Key End Points

Primary: PFS (RECIST v1.1 per blinded, independent central review)

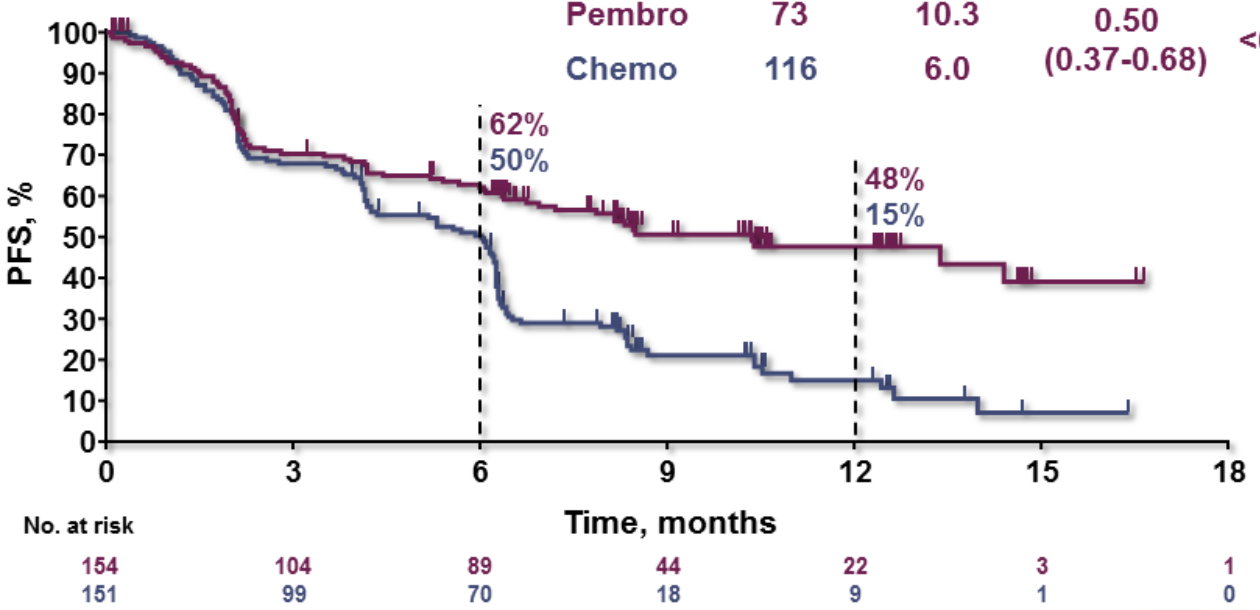
Secondary: OS, ORR, safety

Exploratory: DOR

M Reck. ESMO 2016.

Progression-Free Survival

	Events, n	Median, mo	HR (95% CI)	*P*
Pembro	73	10.3	0.50 (0.37-0.68)	<0.001
Chemo	116	6.0		



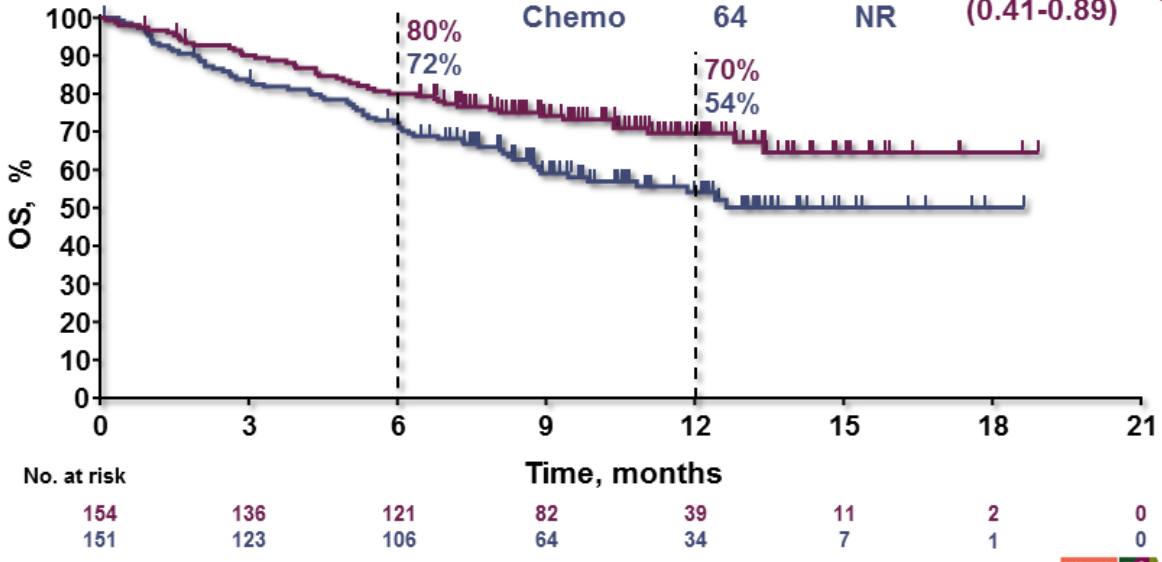
Assessed per RECIST v1.1 by blinded, independent central review.
Data cut-off: May 9, 2016.

COPENHAGEN 2016 ESMO congress

M Reck. ESMO 2016.

Overall Survival

	Events, n	Median, mo	HR (95% CI)	*P*
Pembro	44	NR	0.60 (0.41-0.89)	0.005
Chemo	64	NR		

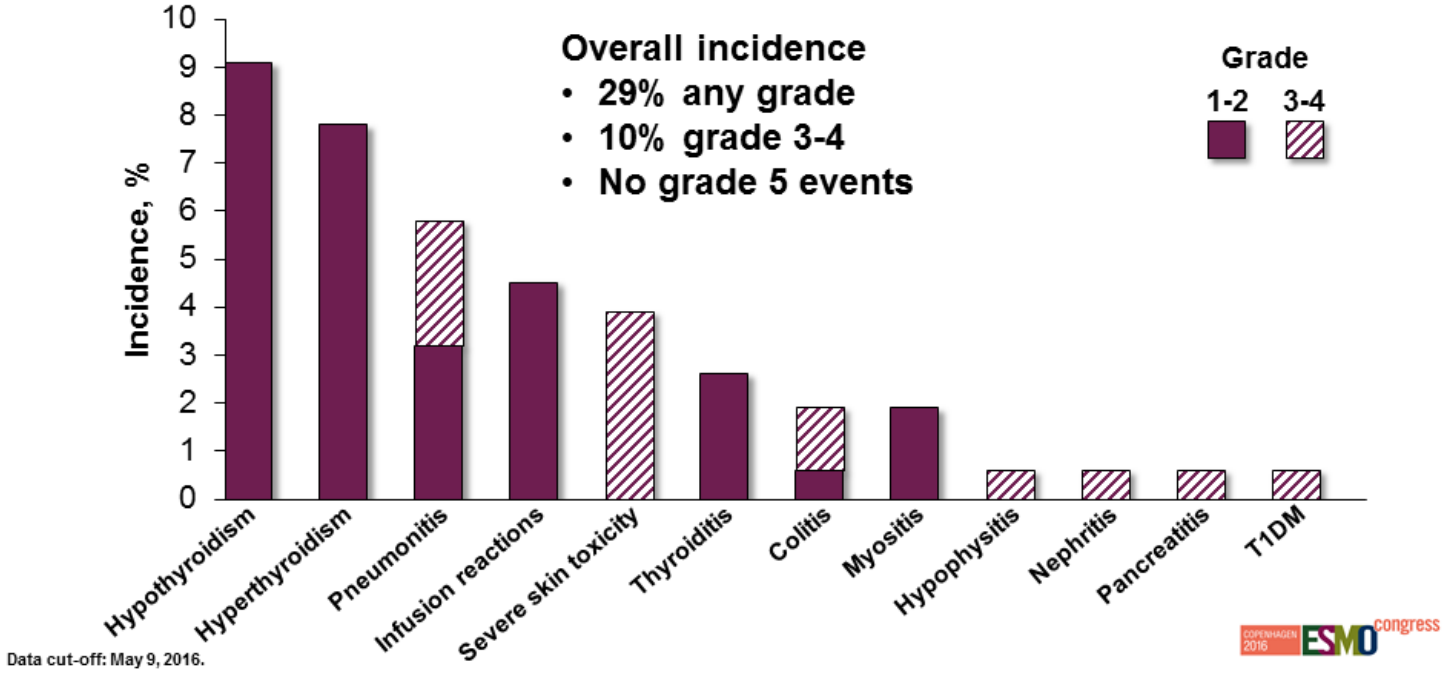


Data cut-off: May 9, 2016.

COPENHAGEN 2016 ESMO congress

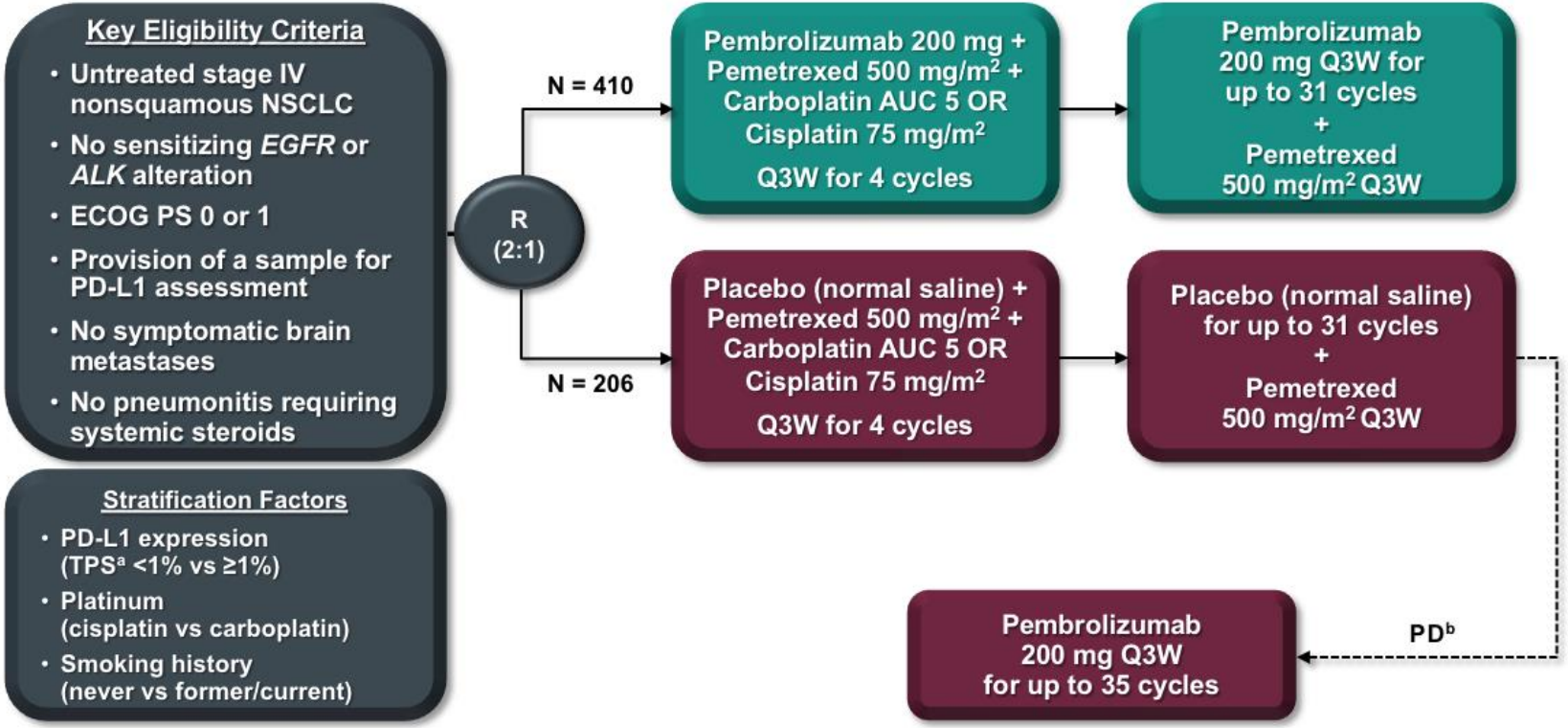
M Reck. ESMO 2016.

Immune-Mediated AEs With Pembrolizumab



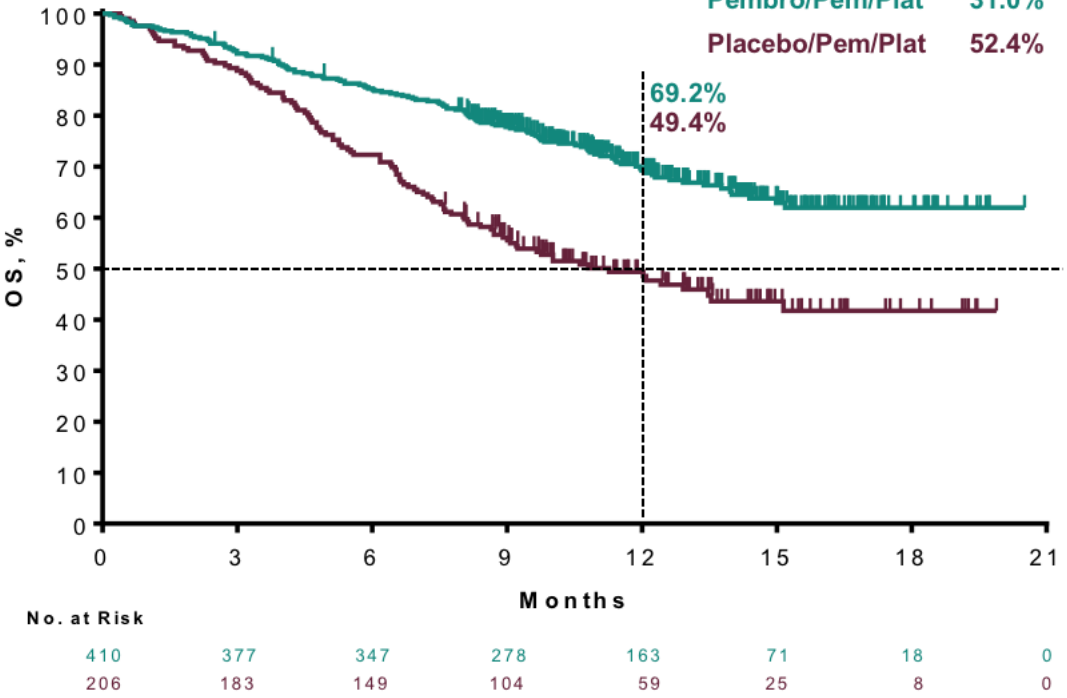
Data cut-off: May 9, 2016.

KEYNOTE 189 Study

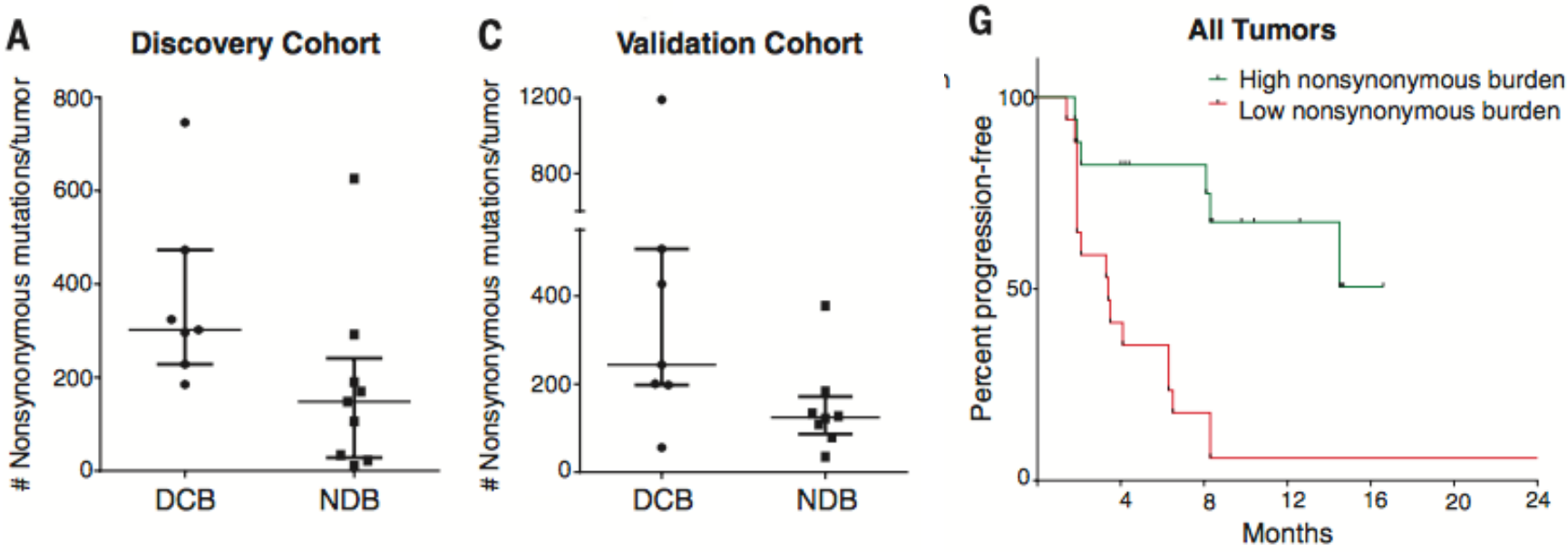


Gandhi et al, NEJM,2018

Overall Survival, ITT

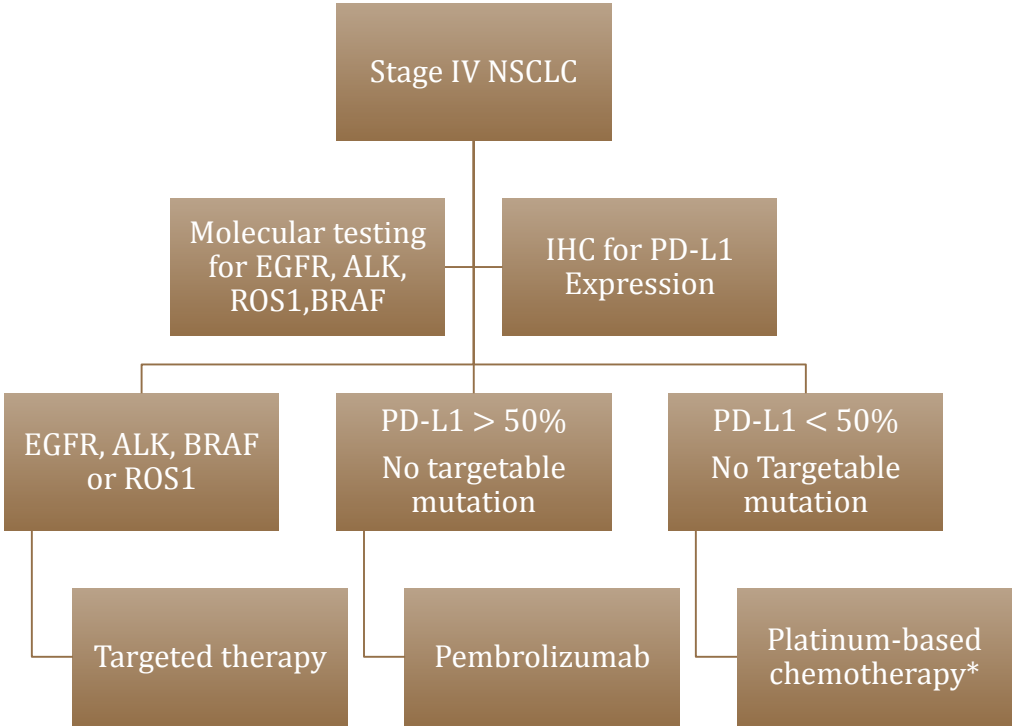


Mutational Burden as Biomarker



Rizvi et al, Science, 2015

Treatment Algorithm for Stage 4 NSCLC



* Bevacizumab/necitumumab added when appropriate

Treatment Algorithm for Stage 4 NSCLC

- Biomarkers are used to individualize therapy to patients
- EGFR, ALK and ROS1 are proven biomarkers in lung adenocarcinoma
- Other promising options under evaluation
- No proven treatment options for KRAS
- Molecular testing should be included as part of diagnostic work up for NSCLC

Thank you!

Fadlo R. Khuri, MD

June 21, 2018
Office of the President | American University of Beirut