Lung Cancer: Biomarker

Driver Mutations in Lung Cancer
- Beyond the EGFR

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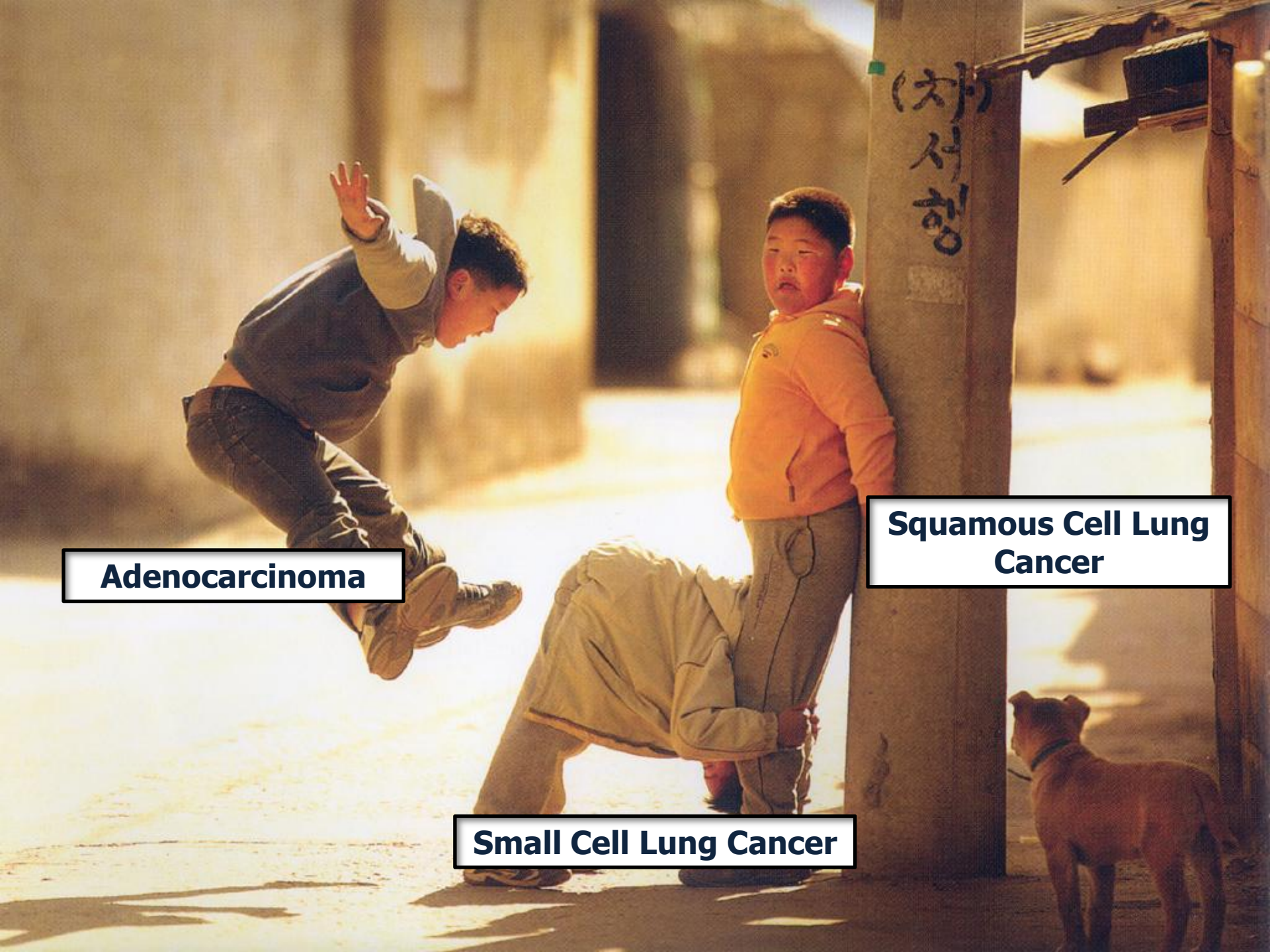
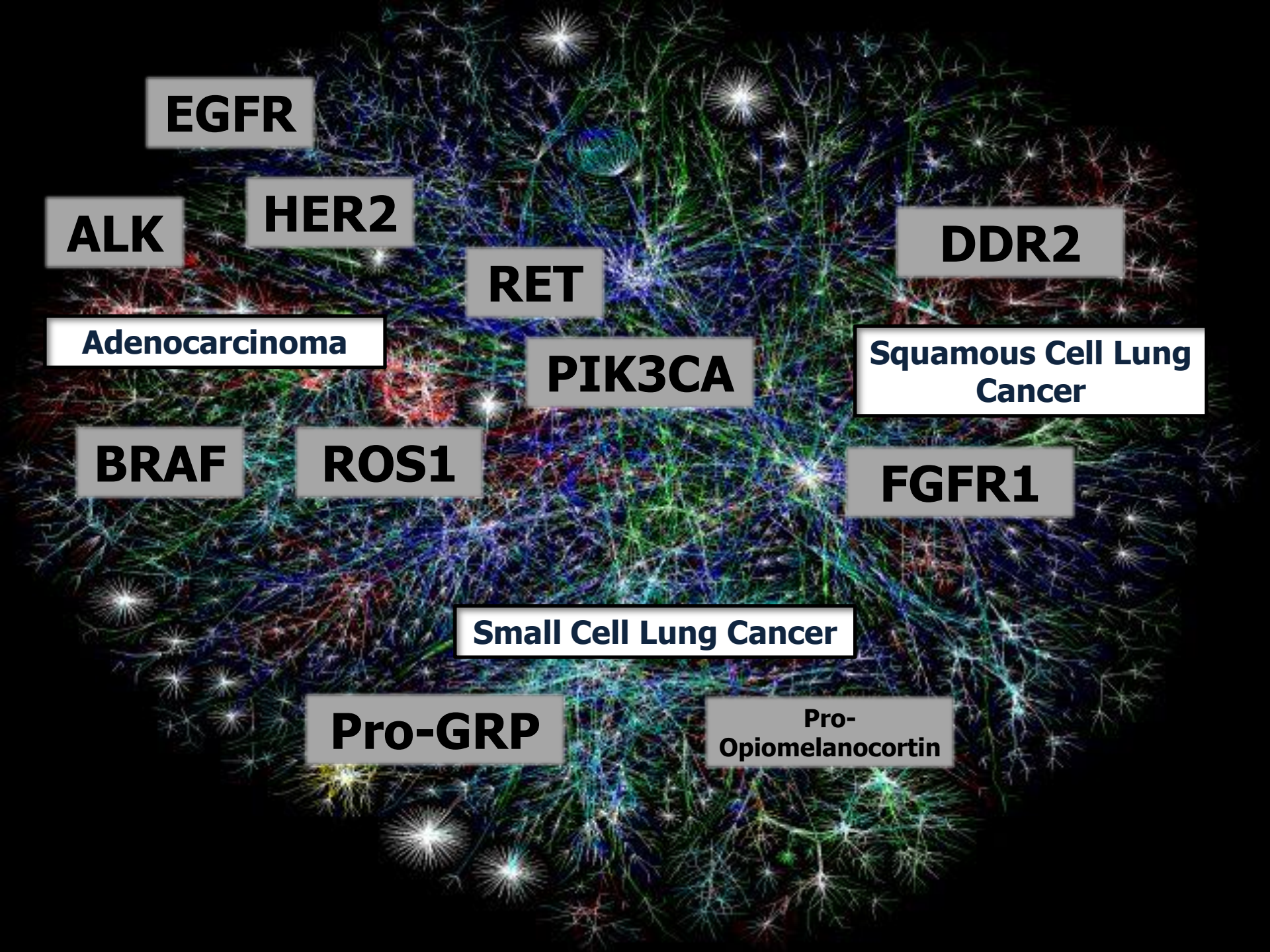

Adenocarcinoma
Squamous Cell Lung Cancer
Small Cell Lung Cancer


EGFR
ALK
HER2
RET
DDR2
Adenocarcinoma
PIK3CA
Squamous Cell Lung Cancer
BRAF
ROS1
FGFR1
Small Cell Lung Cancer
Pro-GRP
Pro-Opiomelanocortin

New Targetable Oncogenes in Lung Adenocarcinoma

Oncogenic Target	Prevalence	Reported Clinical Associations	Potential Kinase Inhibitors
HER2 insertions	2.8	Never-smokers Asian race Female sex	Afatinib (BIBW-2992) Neratinib (HKI-272) Dacomitinib (Pan-HER)
BRAF mutations	2 ~ 4.9	Ever-Smokers White race V600E:never-smokers V600E:female sex	Vemurafenib GSK2118436
PIK3CA mutations	1.5 ~ 2.6	No association	GDC-0941 XL147 BKM120
ROS1 Rearrangement	1.2 ~ 2.6	Never-smokers Asian race Younger age	Crizotinib
ALK fusion gene	3 ~ 7	Younger age Never/Light smoker	Crizotinb AP26113 (ALK/EGFR)

Geoffery RO, et al. JCO.2013:31(8);1097-1104

New Targetable Oncogenes in Squamous Cell Lung Carcinoma

Oncogenic Target	Prevalence	Reported Clinical Associations	Potential Kinase Inhibitors
PIK3CA mutations	3.6 ~ 6.5	No association	GDC-0941 XL147 BKM120
FGFR1 amplification	9.7 ~ 21	Ever-Smokers	Brivanib (BMS-582664) Dovitinib (TKI258) Ponatinib (AP24534) E3810
DDR2 mutations	2.2	No association seen	Dasatinib Imatinib Nilotinib

Geoffery RO, et al. JCO.2013:31(8);1097-1104

Median overall survival in first-line NSCLC studies

Bevacizumab triplet (AVAIL)

Cetuximab triplet (FLEX)

Cetuximab triplet (BMS099)

Erlotinib maintenance (SATURN)

Erlotinib (poor PS) (TOPICAL)

Erlotinib (TORCH)

Pemetrexed cisplatin (non-sqc.)

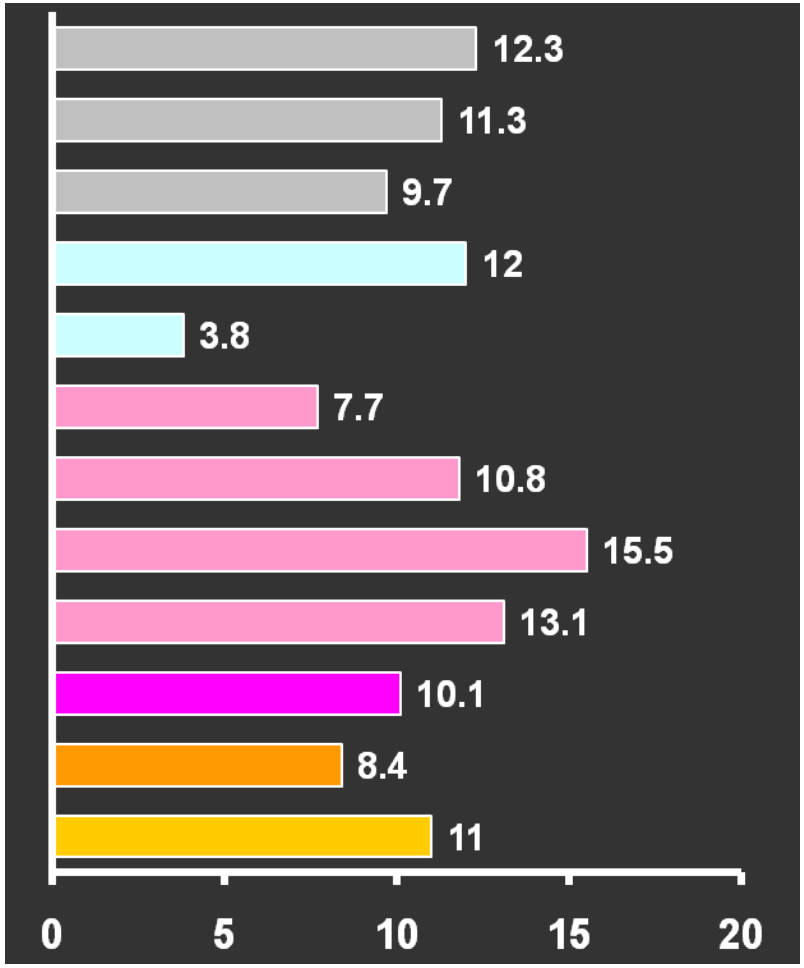
Pemetrexed maintenance (non-sqc.)

Cisplatin/gemcitabine (AVAIL)

Cisplatin/vinorelbine (FLEX)

Taxane/carboplatin (BMS099)

Platinum based doublets (SATURN)



Reck et al, 2010; Pirker et al, 2009; Lynch et al 2010; Cappuzzo et al 2010; Lee ASCO 2010 abtsr 7504; Gridelli ASCO 2010 abstr 7508; Scagliotti et al 2008; Sandler et al 2006

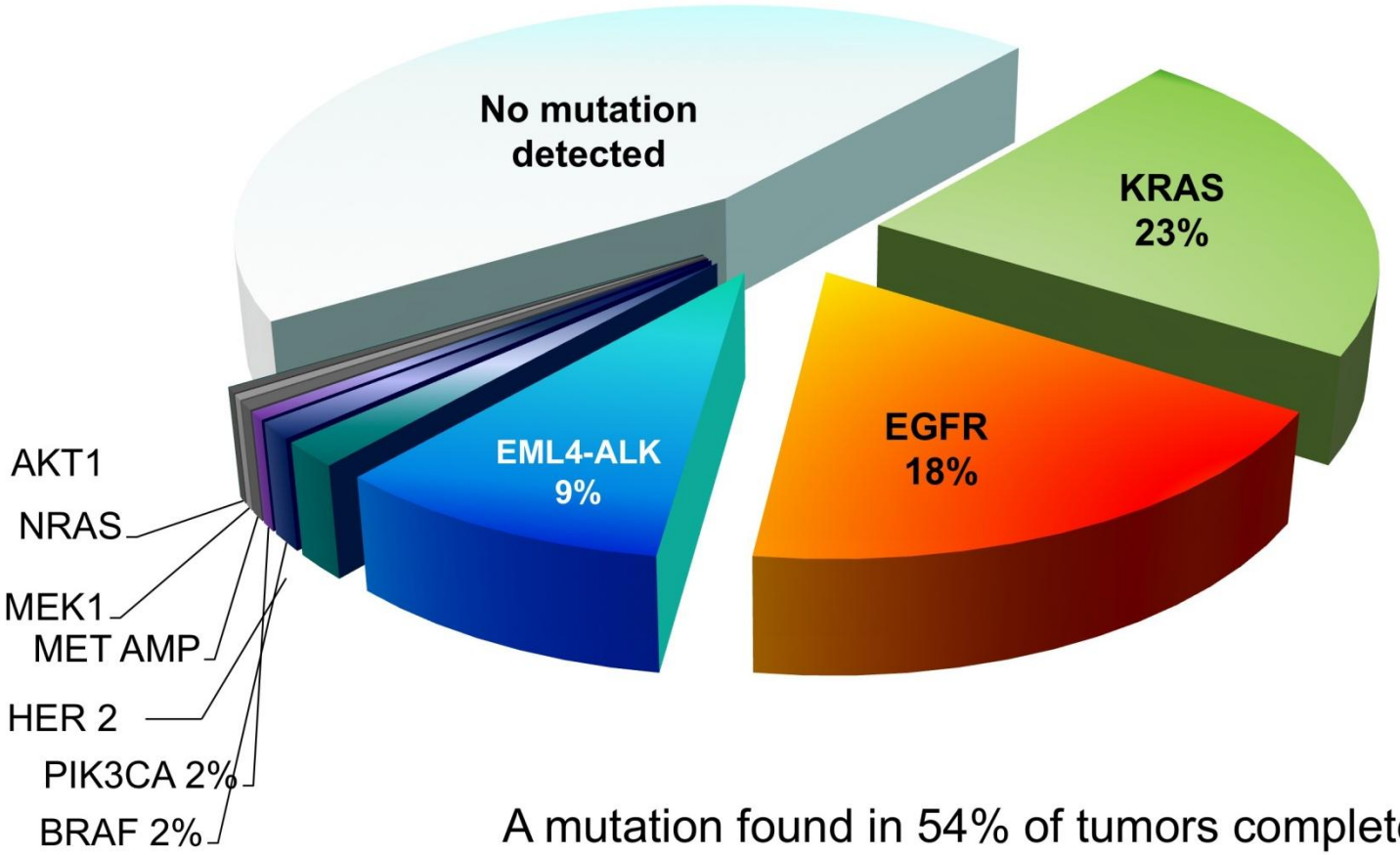
Molecular Analysis-Based Treatment

- **The development of individualized therapy as a strategy for increasing survival in patients with NSCLC**
  - Emerging research suggests that clinical characteristics alone are insufficient for selecting patients for therapies that may confer significant survival benefit

- **Techniques to analyze molecular biomarkers, such as IHC, FISH, PCR, gene microarray**

West H, et al. J Thorac Oncol 4(9 Suppl 2): S1029-1039

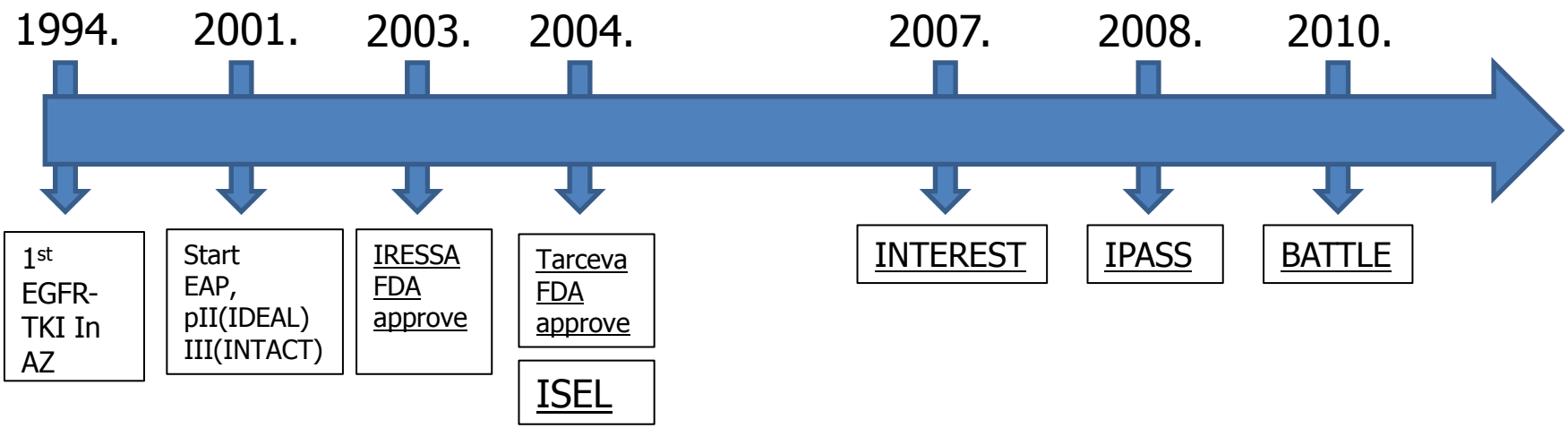
Lung Cancer Mutation Consortium
Incidence of Single Driver Mutations



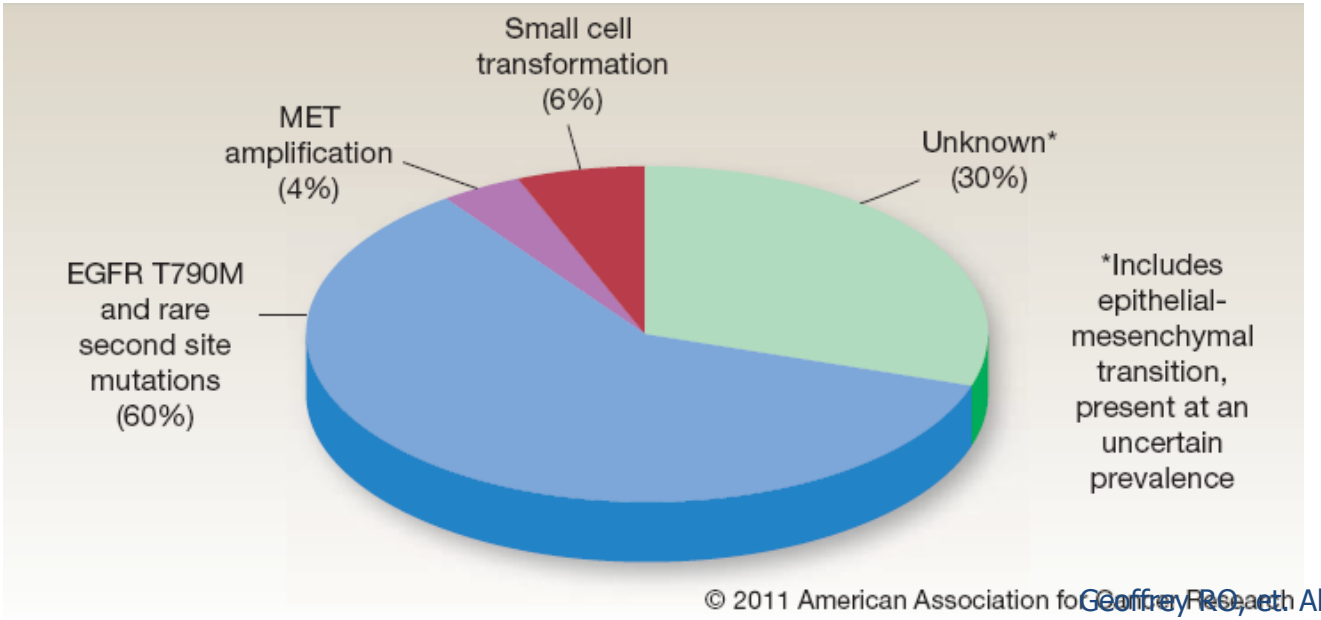
A mutation found in 54% of tumors completely tested

Kris M. et al. Proc. ASCO 2011

EGFR



- Frequency of acquired resistance mechanisms for EGFR-TKIs.

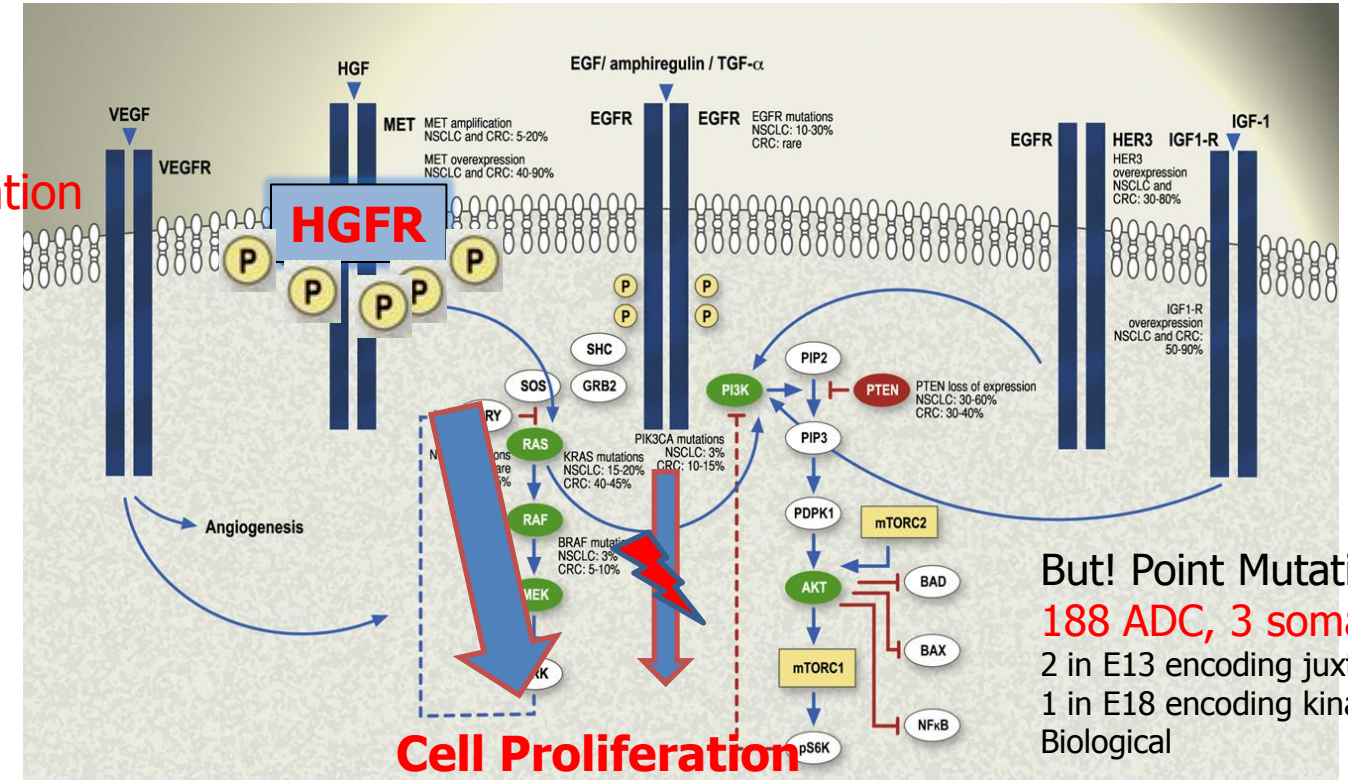


Geoffrey R. Oxnard et al. CCR.2011.17(17);1-8

MET amplification and point mutation

- Heptaocyte growth factor receptor is a receptor tyrosine kinase encoded by MET, which is located on chromosome 7q21-q31.
- Amplification of MET: Resistance of EGFR TKI through Kinase Switch.
- MET amplification is seen in 1.4 ~ 21.0 % of Patients.

In Vitro,
MET amplification



But! Point Mutation are Rare.
188 ADC, 3 somatic Mut (+)
2 in E13 encoding juxtamemb. domain
1 in E18 encoding kinase domain
Biological

Rodrigo D, et al. Molecular Oncology. 2013:6;15-26

MET amplification and point mutation

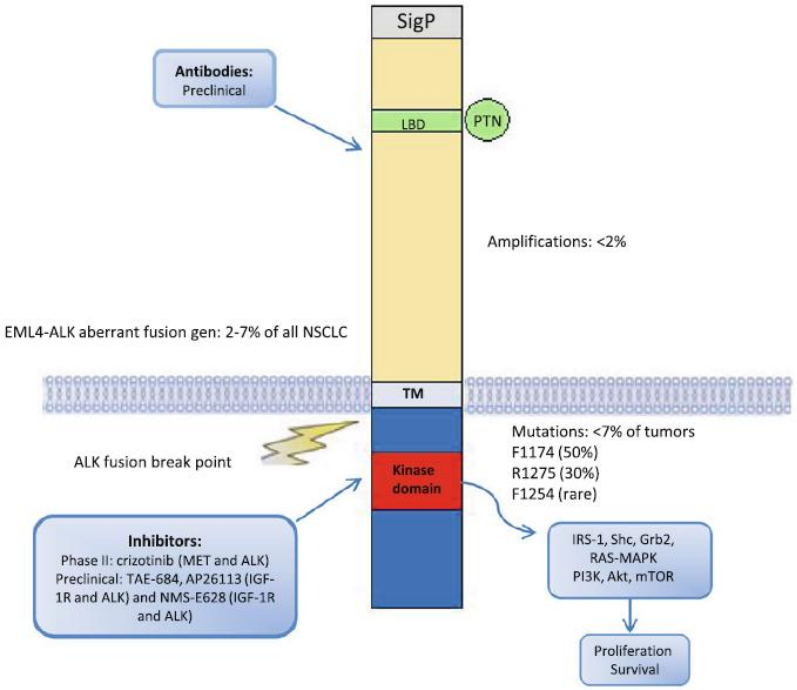
- Small-molecule inhibitors of HGFR are being developed.
- PF-02341066 is being developed as an ALK Inhibitor but also inhibits HGFR kinase activity in mutant MET cells.
- AMG102 is a fully humanised IgG2 monoclonal antibody that binds to and neutralises HGF.

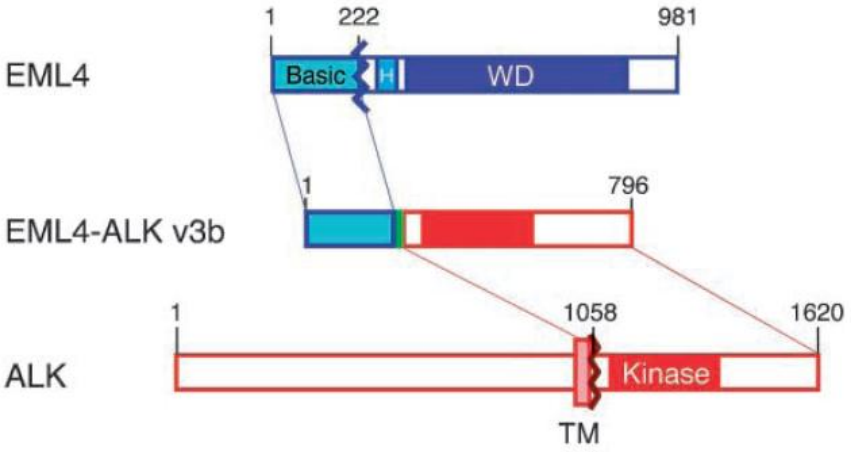
MET			
PF-02341066	1, 2	Yes	NCT00965731
GSK1363089, formerly known as XL880	1	No	NCT00742131
XL184	1, 2	Yes	NCT00596648
AMG 102	1, 2	No	NCT00791154
MetMAb	1, 2	No	NCT00854308
ARQ 197	1, 2	No	NCT00777309
SCH 900105	1, 2	No	NCT01039948

ALK fusion genes

- Anaplastic lymphoma kinase(ALK) was originally discovered from chromosomal translocations leading to the production of fusion proteins of the COOH-terminal kinase domain of ALK and the NH2-terminal portions of different genes.
- NPM(nucleophosmin gene) is the most common fusion partner of ALK(80% of translocation), but at least six other fusion partner have been identified.

- The fusion of the ALK gene with EML4: 6.7% of Japanese NSCLC (2007)

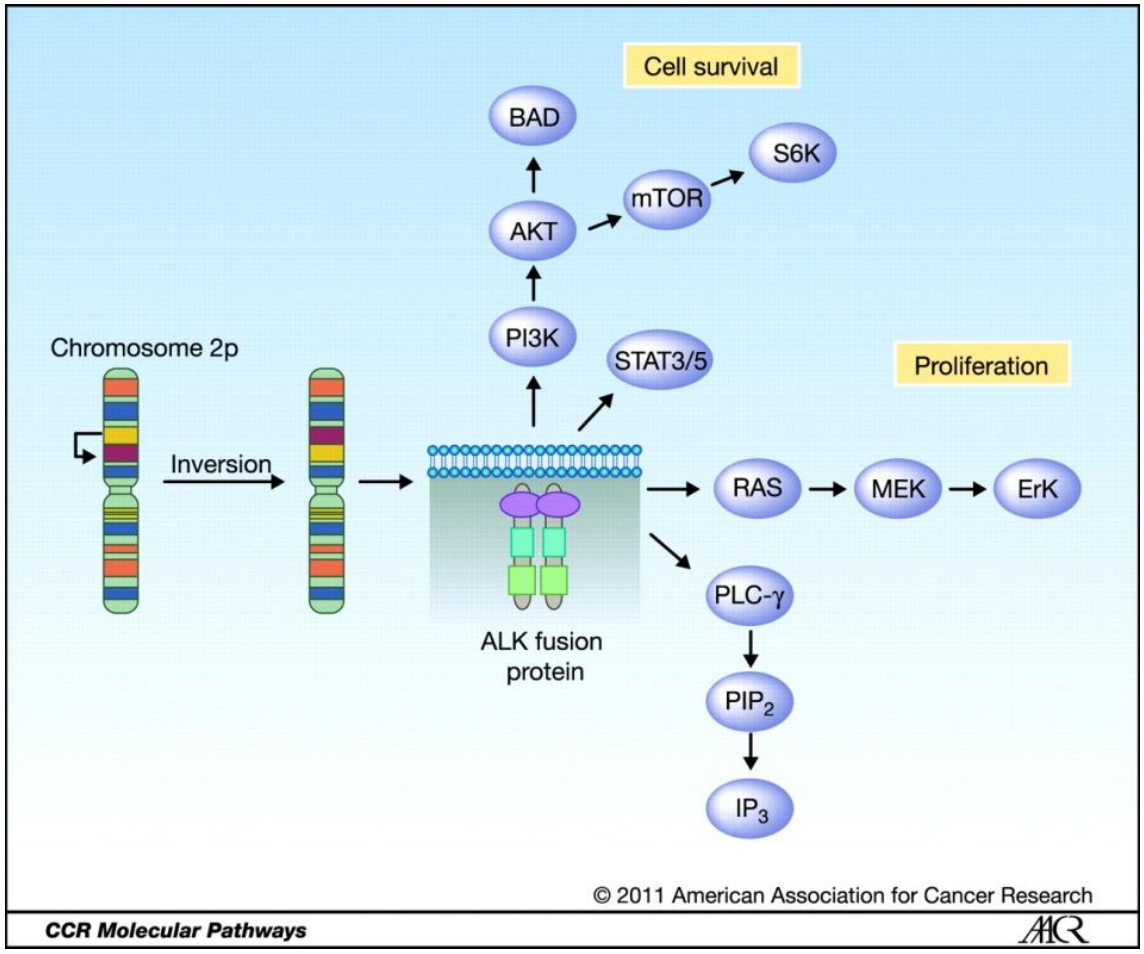




Soda M, et al. *Nature*. 2007;448(7153):561-566.
Luid Cabezon-Gutierrez, et al. Lung. 2012;190:381-388.

ALK fusion genes

- EML4-ALK fusions result in protein oligomerisation and constitutive activation of the kinases.

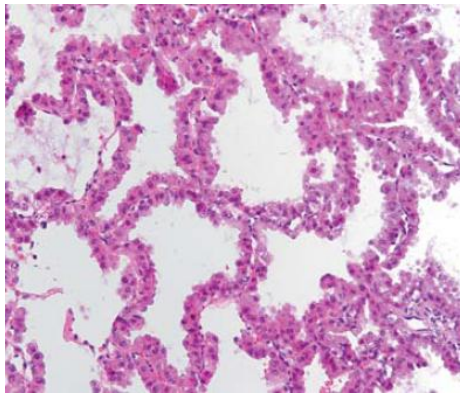


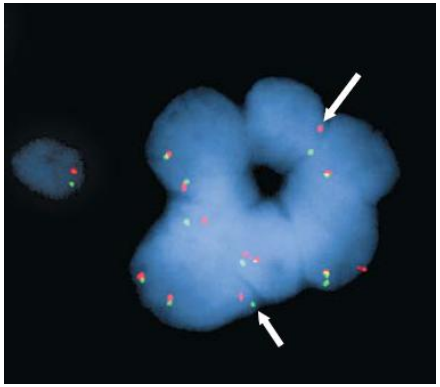
Luid Cabezon-Gutierrez, et al. Lung. 2012;190:381-388.

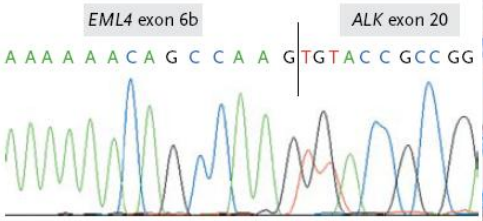
ALK fusion genes

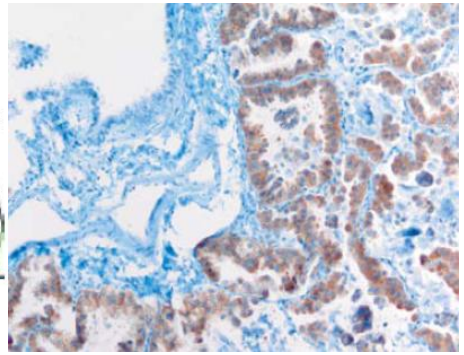
- Detection Method.
- Gold standard: Fluoresence in-situ hybridisation with break apart probes (orange-red telomeric signal and a green centromeric signal – overlapping to yellow signal)

- Immunohistochemistry: The IHC tests used to diagnose ALK-rearranged Aanplastic large cell lymphoma(ALCL) in clinical laboratories are inadequated for the detection of most ALK-rearranged lung ADC due to lower level of ALK expression [NCCN v2. 2013]









Soda M, et al. *Nature*. 2007;448(7153):561-566.
Luid Cabezon-Gutierrez, et al. Lung. 2012;190:381-388.
Eunice L, et al. NEJM. 2010;363(18):1693-1703

Clinical Characteristic features of ALK-positive NSCLC

- Patients were selected for genetic screening on the basis of two or more of the following clinical characteristics: female sex, Asian ethnicity, never/light smoking history, and adenocarcinoma histology

Characteristic	Genotype: *ALK* (n = 19) No.	*ALK* (n = 19) %	*EGFR* (n = 31) No.	*EGFR* (n = 31) %	WT/WT (n = 91) No.	WT/WT (n = 91) %	*P*: *ALK* v *EGFR*	*P*: *ALK* v WT/WT
Age, years								
Median								.005
Range								
Sex								
Male								.039
Female								
Smoking history								
Never smoker								< .001
Light smoker								
Smoker								
Ethnicity								
Asian								.602
Non-Asian								
Pathology								
Adeno								.686*
BAC†								
Adenosquamous								
Squamous								
Large cell/NOS								
Stage								
IA								
IB								
IIA								
IIB								
IIIA								
IIIB								
IV								.051‡
Multifocal BAC	0	0	0	0	10	11		

Solid ty

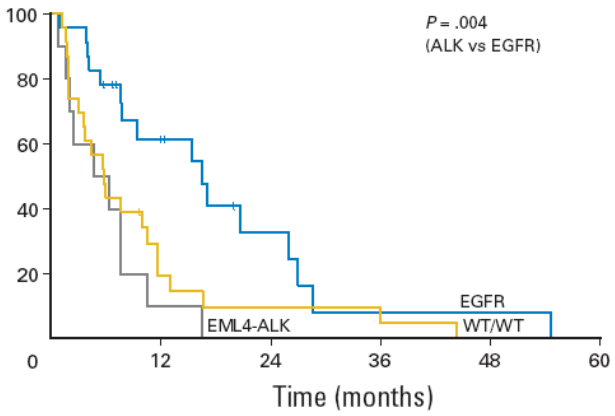
Analysis	Genotype: *ALK*	*EGFR*	WT/WT
ALK rearrangement			
Positive	19	0	0
Total	19	31	91
EGFR mutation			
Positive	0	31	0
Total	19	31	74
KRAS mutation*			
Positive	0	0	6
Total	11	10	23

Abbreviation: WT, wild type.
**KRAS* mutation testing was not performed on all patients because of limited amounts of tissue.

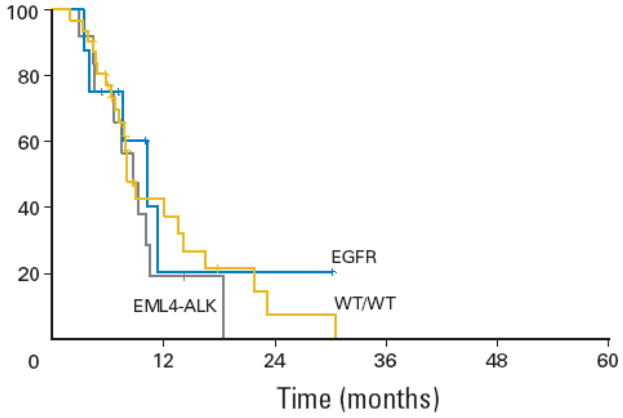
Abbreviations: WT, wild type; adeno, adenocarcinoma; BAC, bronchioloalveolar carcinoma; NOS, not otherwise specified.
*Adeno and BAC *v* all others.
†Adeno with any element of BAC is listed as BAC.
‡Stages I to III *v* IV.

Alice T. Shaw, et al. JCO. 2009.27(26);4247-4253.

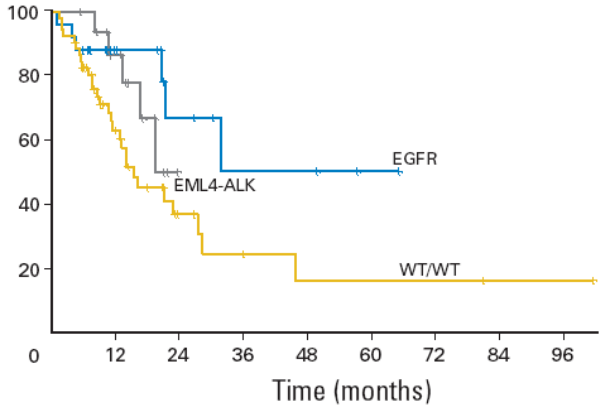
Clinical feature and outcome of patients with NSCLC who harbor EML4-ALK



TTP on EGFR TKI



TTP on any first-line, platinum-based, combination



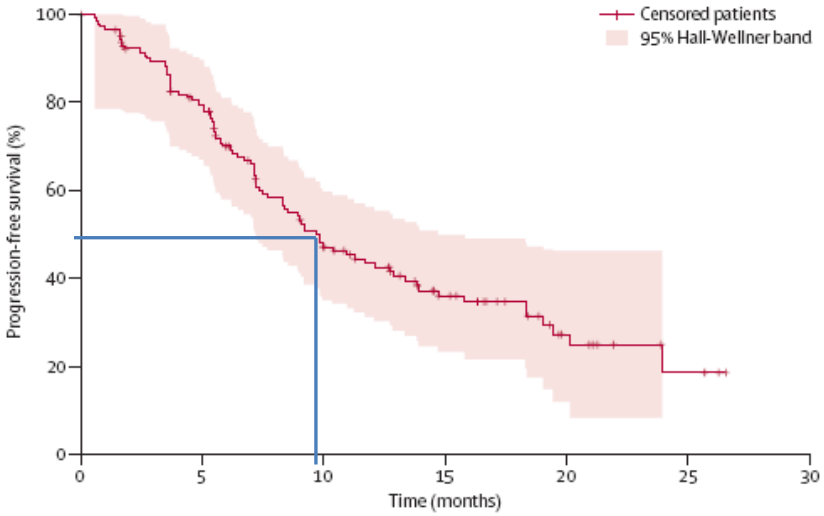
OS

- Time to progression (TTP) and overall survival (OS) of *EML4-ALK–positive* patients compared with patients who have EGFR mutant and wild-type (WT)/WT tumors.

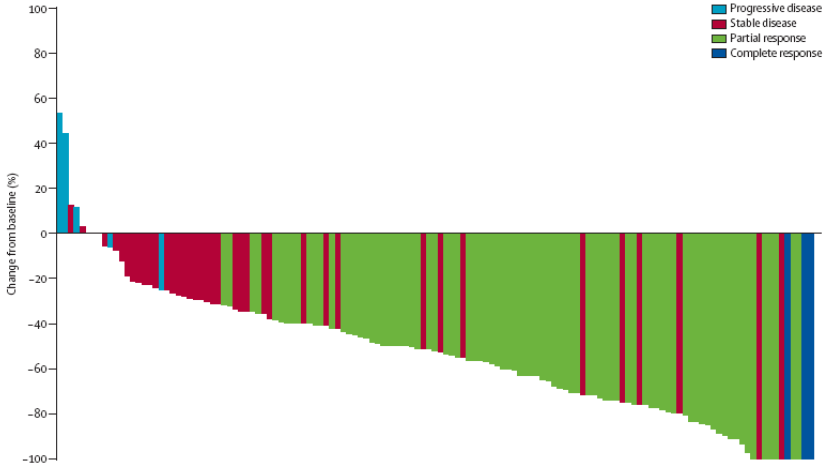
Alice T. Shaw, et al. JCO. 2009.27(26);4247-4253.

[Phase I]
Crizotinib in ALK-positive Lung Cancer

- Crizotinib: Most potent against c-MET but also against a handful of other RTKs including ALK and ROS1
- Phase I study, Patients with ALK-positive stage III or IV NSCLC received oral Crizotinib 250mg twice daily



PFS 9.7ms (95%CI 7.7-12.8ms)



ORR 60.8% (95%CI 52.3-68.9%, 3CR, 84PR)
Estimated Overall survival at 6m(87.9%) and 1y(74.8%)
Median duration of response 49.1wks

Eunice L. Kwak, M.D., et al. NEJM. 2010;363(18):1693-1703
Camidge, et al. Lancet 2012;13:1011-19

[Phase II]
Crizotinib in advanced ALK-positive NSCLC (PROFILE 1005)

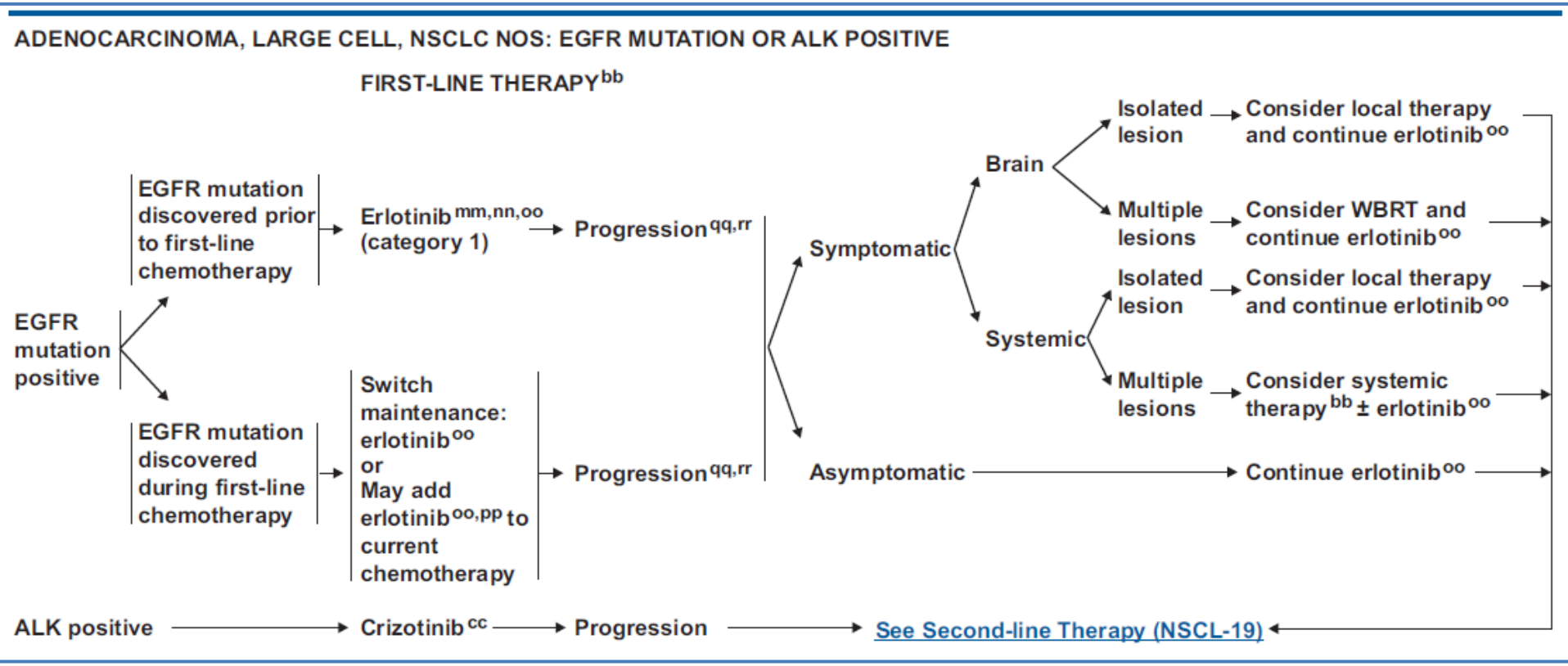
- Crizotinib 250mg bid in week cycles in patients with advanced ALK-positive NSCLC (who progressed after ≥1 chemotherapy)

- 439 patients
- Female(53%) / never-Smoker(65%) / ADC (92%)
- Median treatment duration was 25weeks (77% ongoing)
- ORR 53% (95%CI 47-60),
- Median duration of response 43eeks (96% CI: 36-50)
- Median PFS 8.5 ms(95%CI: 6.2-9.9)

- On the basis of the response rated demonstrated in the phase I and II studies, along with its safety profile, Crizotinib was granted accelerated approval by the FDA Aug, 2012.

Kim D-W, et al. JCO 30:488s 2012(suppl;abstr 7533)

Crizotinib in NCCN Guideline.



NCCN Guideline v2.2013

Phase III studies for Crizotinib

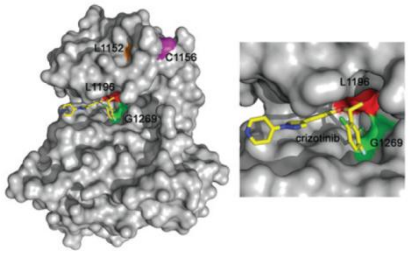
- [PROFILE 1007]

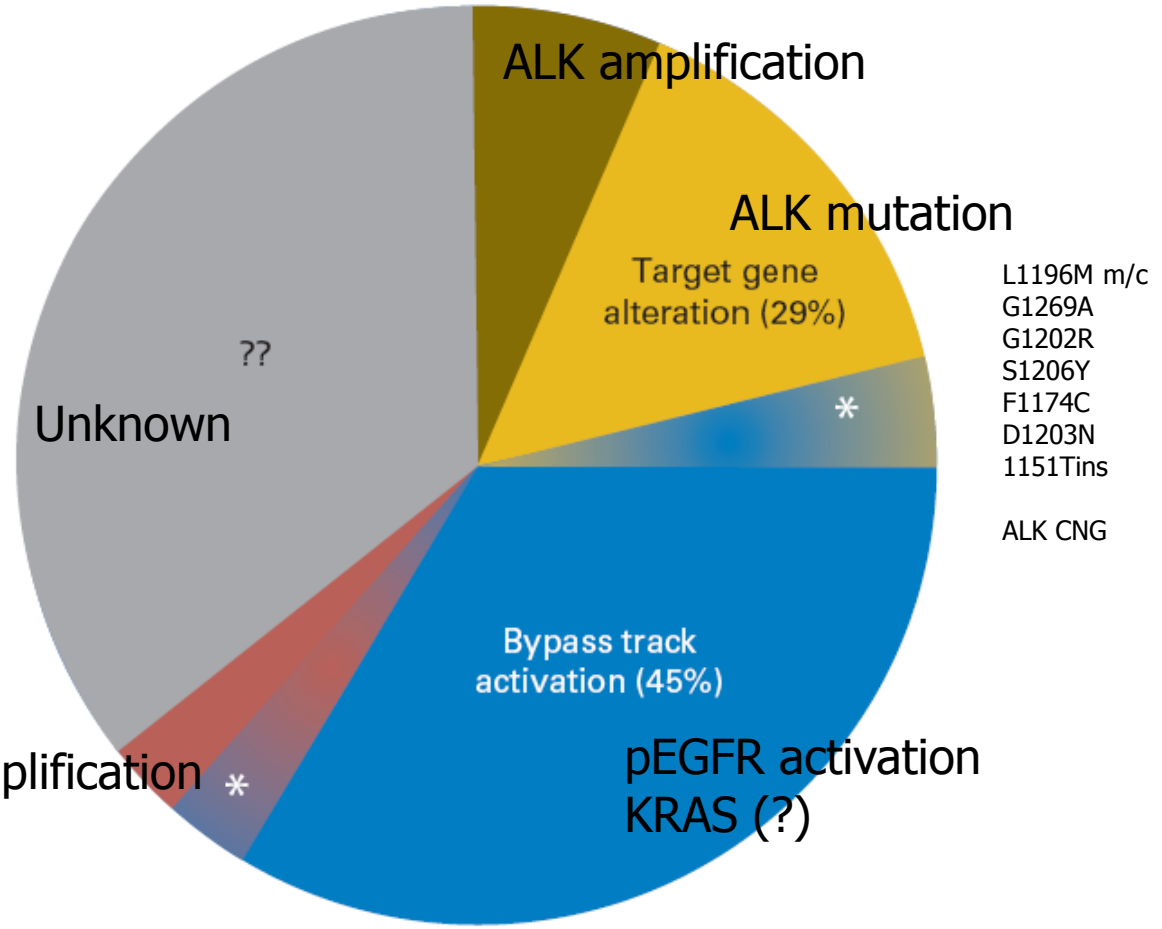
  Phase 3, Randomized, Open-Label Study Of The Efficacy And Safety Of PF-02341066 Vs. Standard Of Care Chemotherapy (Pemetrexed Or Docetaxel) In Patients With Non-Small Lung Cancer Harboring A Translocation Or Inversion Event Involving The Anaplastic Lymphoma Kinase (ALK) Gene Locus

- [PROFILE 1014]

  A Clinical Trial Testing The Efficacy Of Crizotinib Vs. Standard Chemotherapy Pemetrexed Plus Cisplatin Or Carboplatin In Patients With ALK Positive Non Squamous Cancer Of The Lung

Resistance Mechanism of ALK Inhibitor





Robert C. Doebele, et al. ASCO.2012;30(15)(suppl;abstr 7504)
Katayama R, et al. Sci Transl Med. 2012.4:120ra17

ROS1 rearrangements

- ROS1, like ALK, is a receptor tyrosine kinase of the insulin receptor family.

Comparison of RTK phosphorylation in Subgroups of NSCLC cell lines and Tumors

RTKs	Phosphopeptide Sum	Number of Cell Lines	Phospho Level/Cell Line	RTKs	Normalized Phosphopeptides Sum	Number of Samples	Phospho Level/Sample
ROS	43	1	43	MET	847	12	71
ALK	36	1	36	ALK	464	7	66
MET	233	11	21	DDR1	3136	63	50
PDGFRα	40	2	20	ROS	50	1	50
ErbB2	44	3	15	VEGFR-2	662	16	41
EGFR	132	11	12	IGF1R	675	18	37

1. Identified as a potential driver mutation in an NSCLC cell line and one NSCLC patient.
2. Translocations leading to ROS1 fusion transcripts were shown to lead to constitutive kinase activity and sensitivity to TKIs.

Rikova K, et al. Cell. 2007;131:1190-1203

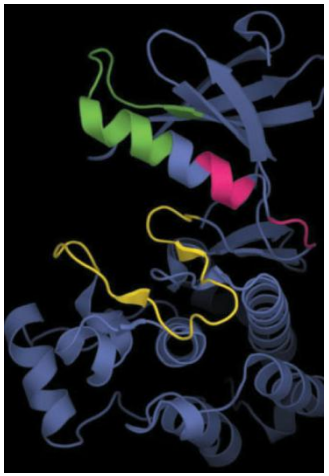
Demographics and Clinical Characteristics of patients with ROS1-positive NSCLC

Demographic or Clinical Characteristic	All Patients (n = 1,073) No.	%	*ROS1* Positive (n = 18) No.	%	*ALK* Positive (n = 31) No.	%	*ROS1* Negative (n = 1,055) No.	%	*P* (*ROS1* positive *v* *ROS1* negative)
Age, years									
Median	62.0		49.8		51.6		62.3		< .001
Range	32-87		32-79		29-73		32-87		
Sex									
Male	523	49	7	39	17	55	516	49	.480
Female	550	51	11	61	14	45	539	51	
Smoking history									
Never-smoker	239	22	14	78	13	42	225	21	< .001
Light smoker	62	6	1	6	1	3	61	6	
Smoker	695	65	2	11	3	10	693	66	
NA	77	7	1	6	14	45	76	7	
Ethnicity									
Asian	45	4	5	28	2	6	40	4	< .001
Non-Asian	942	88	13	72	18	58	929	88	
NA	86	8	0	0	11	35	86	8	
Pathology									
Adenocarcinoma	694	65	18	100	16	52	676	64	.019
Squamous	200	19	0	0	1	3	200	19	
NSCLC, NOS	59	5	0	0	0	0	59	6	
Adenosquamous	10	1	0	0	0	0	10	1	
Other	38	4	0	0	0	0	38	4	
NA	72	7	0	0	14	45	72	7	
Stage									
IA	218	20	1	6	1	3	217	21	NS
IB	140	13	1	6	1	3	139	13	NS
IIA	44	4	1	6	2	6	43	4	NS
IIB	87	8	0	0	1	3	87	8	NS
IIIA	139	13	2	11	5	16	137	13	NS
IIIB	73	7	2	11	2	6	71	7	NS
IV	327	30	11	61	12	39	316	30	.010
NA	45	4	0	0	7	23	45	4	

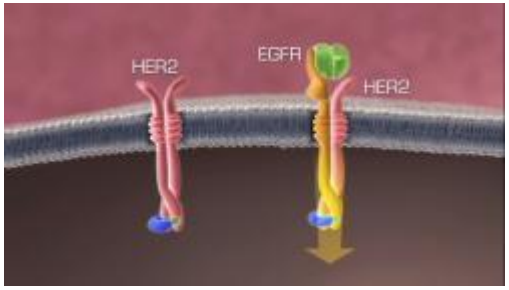
Bergethon, et al. JCO.2012.30(8);863-870

HER2 mutations

- HER2 protein (also known as ERBB-2) is a member of the HER family of receptor tyrosine kinases.



ERBB2 forms homodimers or heterodimers with other members of the HER family.
Similar positioning within the EGFR kinase domain of the EGFR and ERBB2 mutations



Stephens, et al. 2004. Nature.2004;431:525-26

- HER2 overexpression on IHC was shown to be a marker of poor prognosis in NSCLC (esp, ADC), but not in the HER2 amplification.
- In the lung cancer setting, amplification by FISH was found in 2-23% of the patients, while HER2 mutations were found in 2% of lung ADC.

A. IHC

IHC	No expression	Overexpression		
	0	1+	2+	3+
n = 410	241	86	76	7
	58.8%	21.0%	18.5%	1.7%

B. FISH

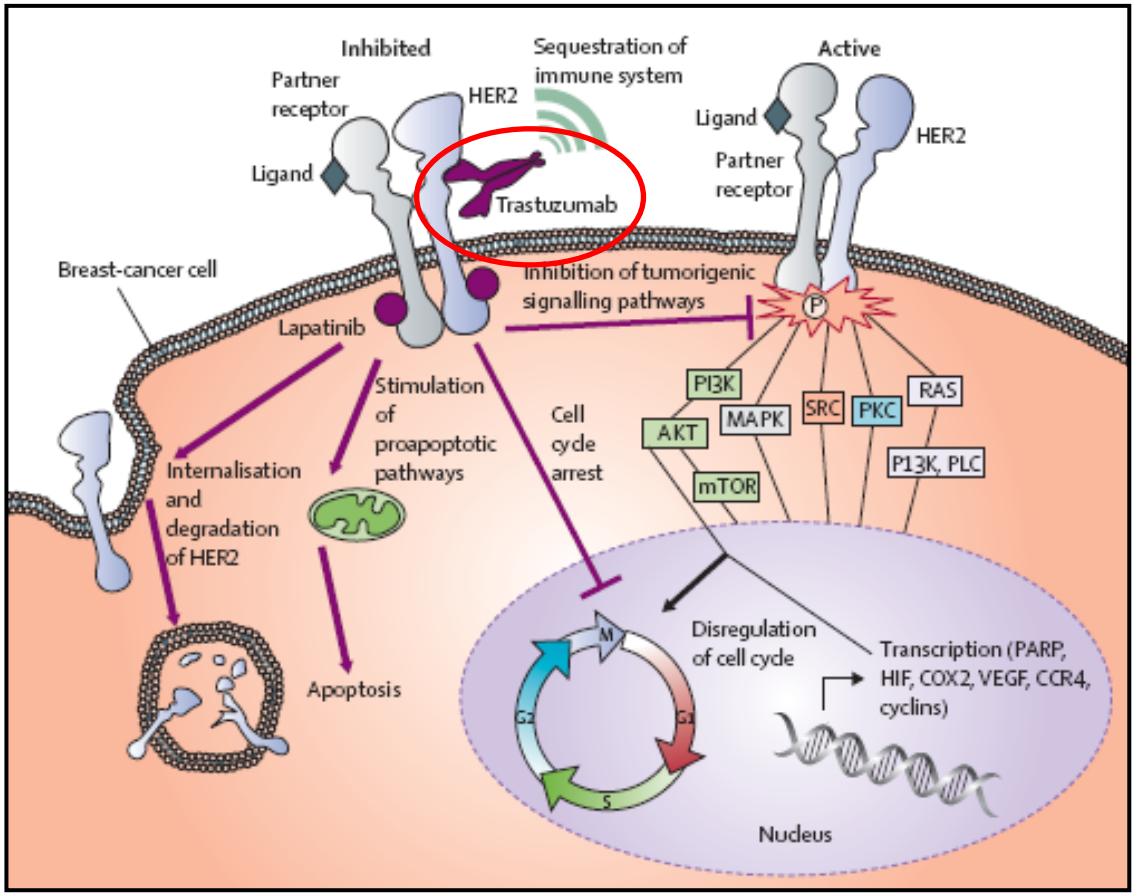
FISH	No amplification	Amplification	
	<2.0	2.0≤ × ≤4.0	>4.0
n = 378	371	5	2
	98.1%	1.3%	0.5%

Table. HER2 results by IHC and FISH

Liu L, et al. JTO. 2010;5:1922-1932.

HER2 mutations

- Early clinical trials with Trastuzumab, a humanized monoclonal antibody to HER2 that is active in breast cancer where HER2 is amplified.

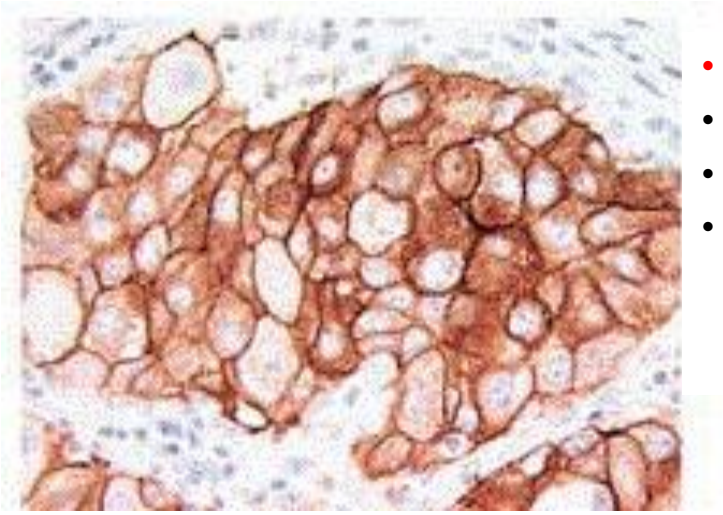


Kellie LJ, et al. Lancet.2009;10:1179-87.
Hirsch FR, et al. Semin Oncol 2004;31:75-82

HER2 mutations

[NCT00016367] Cisplatin and Gemcitabine Plus Trastuzumab in Treating Patients With Stage IIIB or Stage IV Non-Small Cell Lung Cancer

- Early clinical trials with Trastuzumab, a humanized monoclonal antibody to HER2 that is active in breast cancer where HER2 is amplified.
- Clinical studies with Trastuzumab single in patients with unselected patients with NSCLC have not shown a demonstrable advantage for the majority of patients.



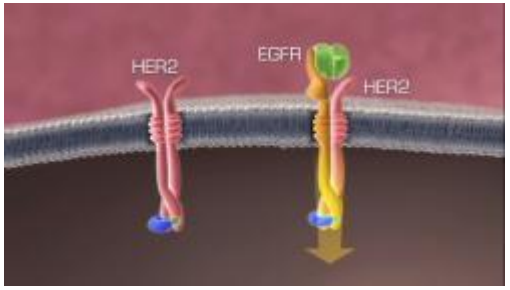
- HER2 overexpression or HER2 gene amplification (6 patients)
- 80% of the patients on treatment were still alive at 6-ms f/u.
- RR: 83%
- median PFS 8.5ms (Range 4.6-19.6) vs 6.1 (0.9-19.6)

Hirsch FR, et al. Semin Oncol 2004;31:75-82
Gatzemeier, et al. Ann of Onco. 2004;15:19-27

HER2 Mutations

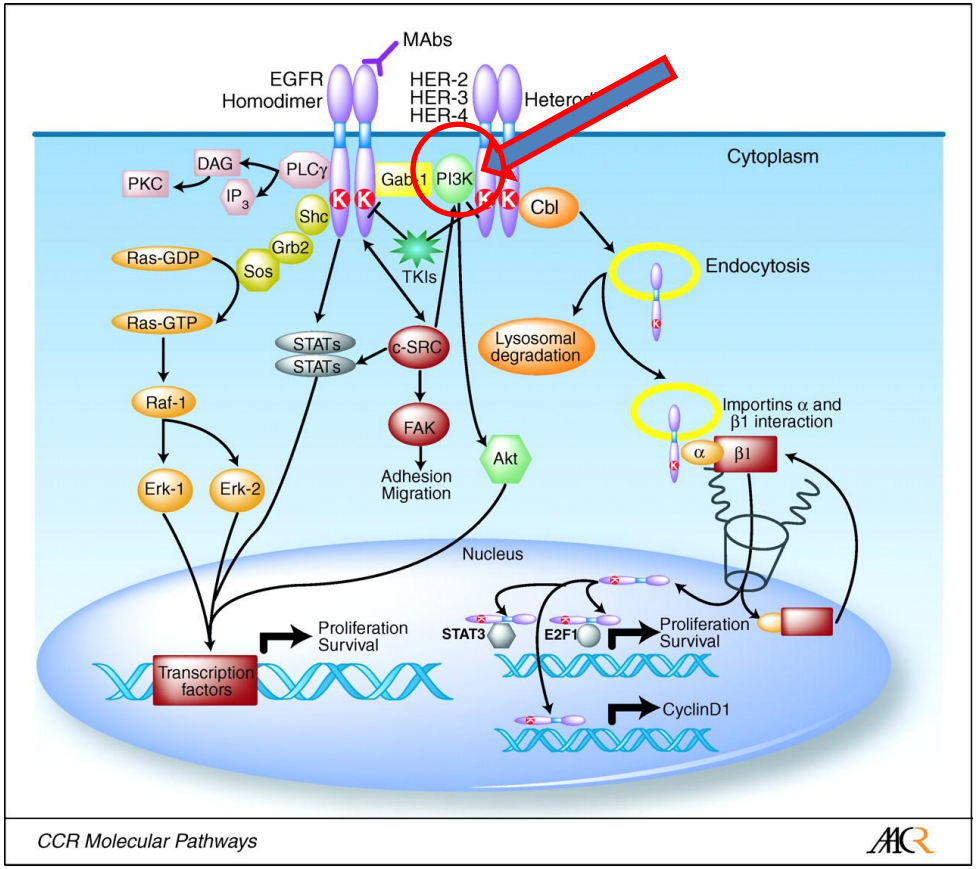
- Several kinase inhibitors are in development for *HER2*-dependant lung ADC.
- Irreversible TKIs targeting HER2 and EGFR

1. Neratinib (HKI-272)
2. Dacomitinib (PF-00299804)
3. Afatinib (BIBW-2992)



PIK3CA Mutations

PI3Ks are a family of lipid kinases that regenerate PIP3, which is key mediator between growth factor receptors and intracellular downstream signalling pathways.



- Mut (+) in PIK3CA 1.3 ~ 3.4% of NSCLC
- Higher in SQC than ADC
- In ADC, coexisting with another oncogenic Mut (+).

Geoffrey RO. et al , et al. JCO. 2013:31(8);1097-1104

PIK3CA inhibitors

[NCT01501604]

BKM120 in Cancers With PIK3CA Activating Mutations

[NCT00974584]

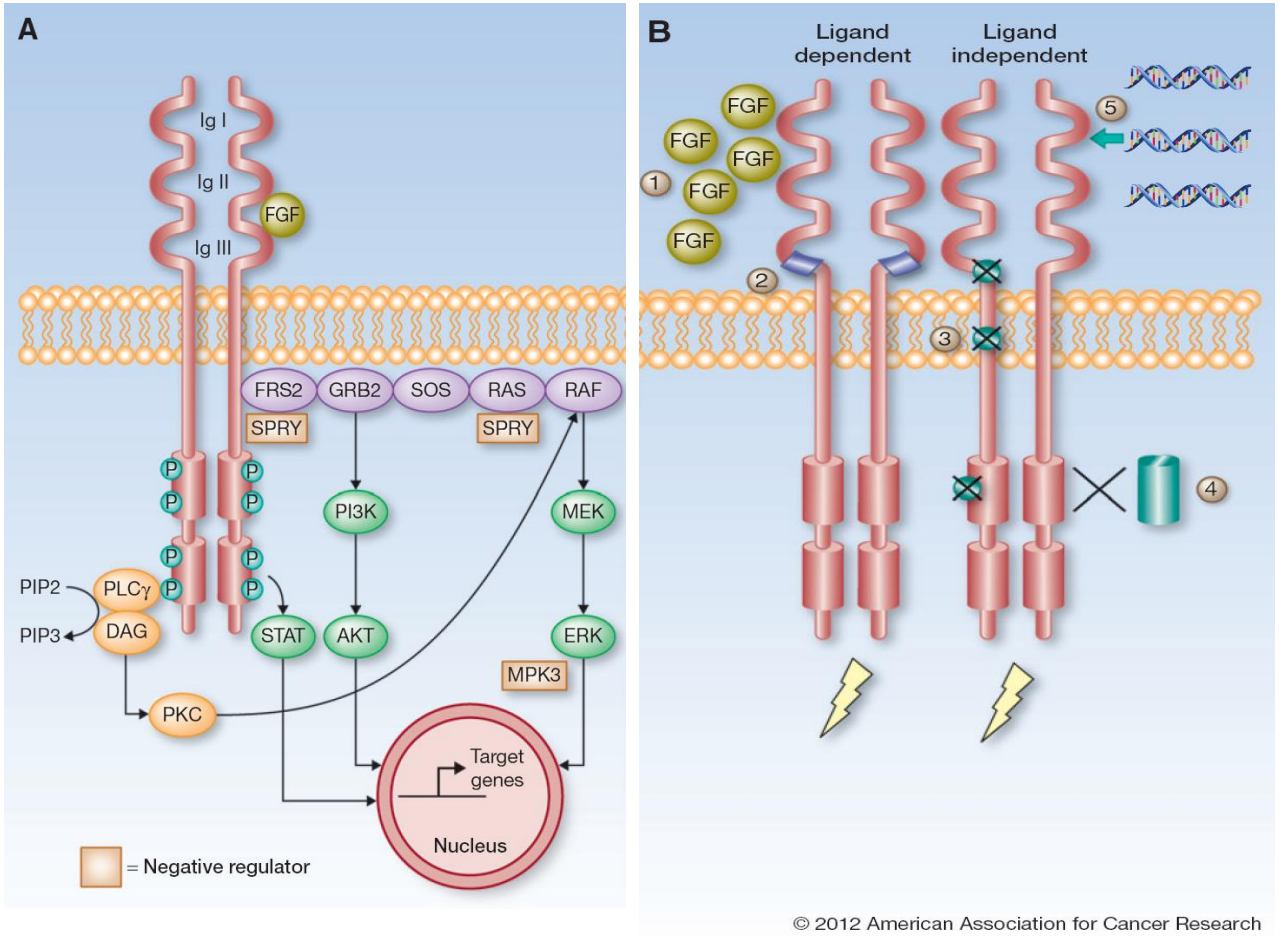
A Study of the Safety and Pharmacology Of PI3-Kinase Inhibitor GDC-0941 In Combination With Either Paclitaxel And Carboplatin (With or Without Bevacizumab) or Pemetrexed, Cisplatin, And Bevacizumab in Patients With Advanced Non Small Cell Lung Cancer

[NCT00756847]

Safety Study of XL147 (SAR245408), in Combination With Paclitaxel and Carboplatin in Adults With Solid Tumors

FGFR1 Amplification

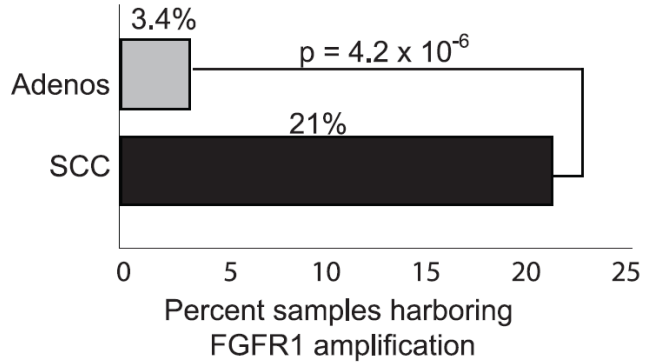
- Membrane-bound receptor tyrosine kinase that regulates proliferation via the MAPK and PI3K pathways.



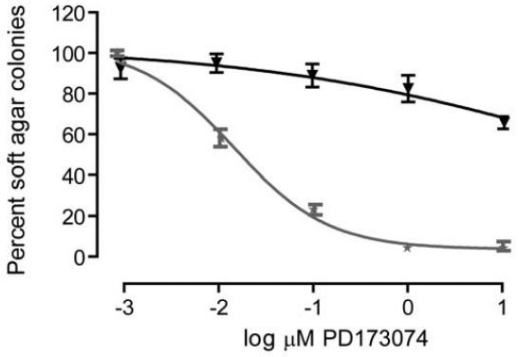
Brooks et al. CCR. 2012.18:1855-1862

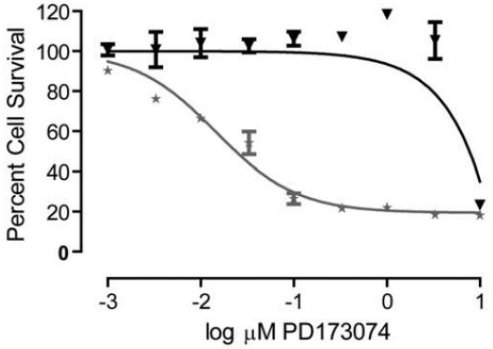
FGFR1 Amplification

- 732 NSCLC samples (628 primary tumors and 104 cell lines)



- Survival of FGFR1-amplified lung cancer cell lines was additionally shown to be dependent on overexpression of the FGFR1 kinase





Dutt A, et al. 2011. Plus One.2011. 6:e20351

Phase II of FGFR1 inhibitors

- Brivanib (dual VEGFR and FGFR inhibitor) in advanced solid tumors: Results of a phase II randomized discontinuation trial.

Tumor type	N	2 prior regimens (%)	FGF(+) %	Status at 12 wks (%)	
				PR	**SD**
Sarcoma	251	52	65	3	27
NSCLC	42	93	79	0	24
Pancreatic Ca.	38	66	79	0	13
Gastric Ca.	34	71	97	9	9
Bladder Ca	31	52	88	0	16

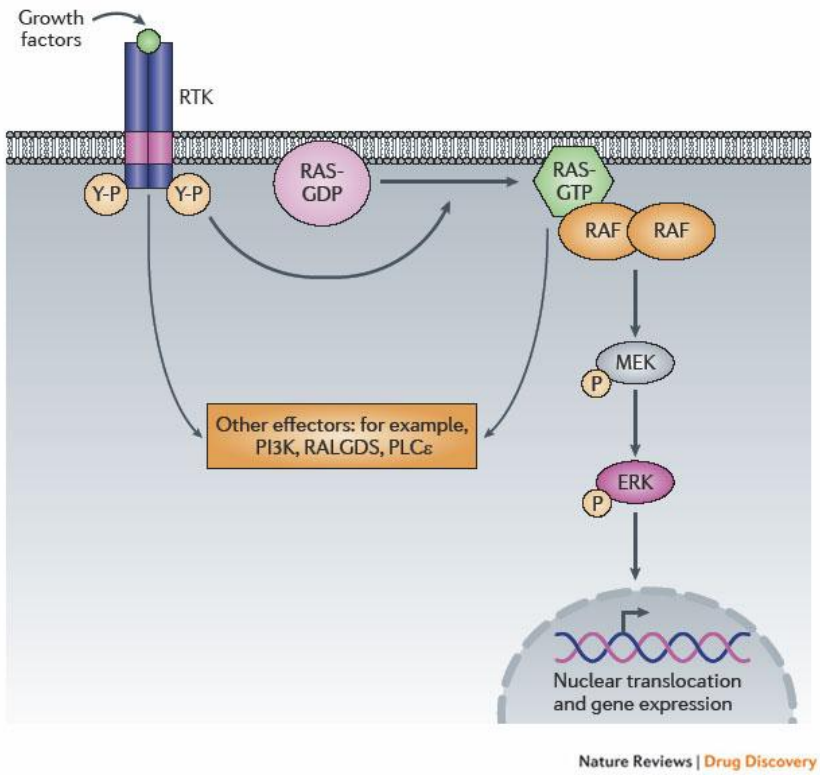
Ratain MJ, Et al. JCO.2011;29:213S(suppl;abstr 3079)
Jonker DJ, et al. 2011 Ann Oncol 22:1413-1419

Current development of FGF/FGFR targeting anticancer agents

Compound	Company	Target	Clinical development (indication)
Small-molecule tyrosine kinase inhibitors: mixed pharmacology			
Brivanib	Bristol-Myers Squibb	FGFR, VEGFR	Phase III (CRC, HCC, liver)
Dovitinib	Novartis	FGFR, PDGFR, VEGFR, FLT3, c-KIT	Phase III (RCC)
Lenvatinib	Eisai	FGFR, PDGFR, VEGFR	Phase III (melanoma, thyroid)
Masitinib	AB Science	FGFR3, PDGFR, c-KIT	Phase III (GIST, melanoma, MM, pancreatic)
Nintedanib	Boehringer Ingelheim	FGFR, PDGFR, VEGFR	Phase III (NSCLC, ovarian)
Pazopanib	GlaxoSmithKline	FGFR1, FGFR3, VEGFR, PDGFR, c-KIT	Phase III (breast, lung, ovarian, RCC, STS)
PI-88	Progen	FGF1, FGF2, VEGF	Phase III (HCC, liver)
Regorafenib	Bayer	FGFR, PDGFR, VEGFR, c-KIT, RET	Phase III (GIST, CRC)
TSU 68	Pfizer	FGFR, KDR, PDGFR, VEGFR2	Phase III (HCC)
ENMD-2076	Entremed	FGFR1, KDR, FGFR2, PDGFR, VEGFR, FLT3, c-KIT, Aurora K, FLT3	Phase II (ovarian)
Ponatinib	Ariad	FGFR, PDGFR, VEGFR	Phase II (AML, CML)
E3810	Eisai	FGFR1, VEGFR	Phase I (solid tumors)
PBI-05204	Phoenix Bio	FGF2, AKT, NF-κB, p70S6K	Phase I (solid tumors)
Small-molecule tyrosine kinase inhibitors: FGFR selective			
AZD4547	AstraZeneca	FGFR1–3	Phase II (breast, gastric)
BGJ398	Novartis	FGFR1–3	Phase I (solid tumors)
LY2874455	Eli Lilly	FGFR1–4	Phase I (solid tumors)
FGFR antibodies			
RG7444	Roche	FGFR3	Phase I (MM)
FGF-ligand traps			
FP-1039	Five Prime Therapeutics	FGF1, FGF2, FGF4	Phase II (endometrial)

BRAF Mutations

- BRAF is a Serine/Threonine kinase downstream from KRAS in the MAPK signaling cascade.
- RAF mutations were only first identified in 2002, with a particularly high prevalence in melanoma.



Gideon Bollag, et al. 2012. Nat Rev Drug Disc. 11:873-886

BRAF Mutations

- A retrospective series of 1,046 NSCLCs (739 of ADCs and 307 of SCCs) was investigated for BRAF mutations

BRAF Mutation	Change		Histologic Type		*P*
	Nucleotide	Aminoacid	ADC	SCC	
Exon					.001
15	T1799A	V600E	21	—	
	A1781G	D594G	2	—	
	T1790G	L597R	2	—	
	C1789G	L597V	1	—	
	T1790A	L597Q	1	—	
	G1798T	V600L	1	—	
	A1801G	K601E	1	—	
	A1803T	K601N	1	—	
	T1810A	W604R	—	1	
	G1817C	G606A	1	—	
	G1817T	G606V	1	—	
11	G1397T	G466V	2	—	
	G1406C	G469A	1	—	
	G1406T	G469V	1	—	
Total					.001
No.			36	1	
%			4.9	0.3	

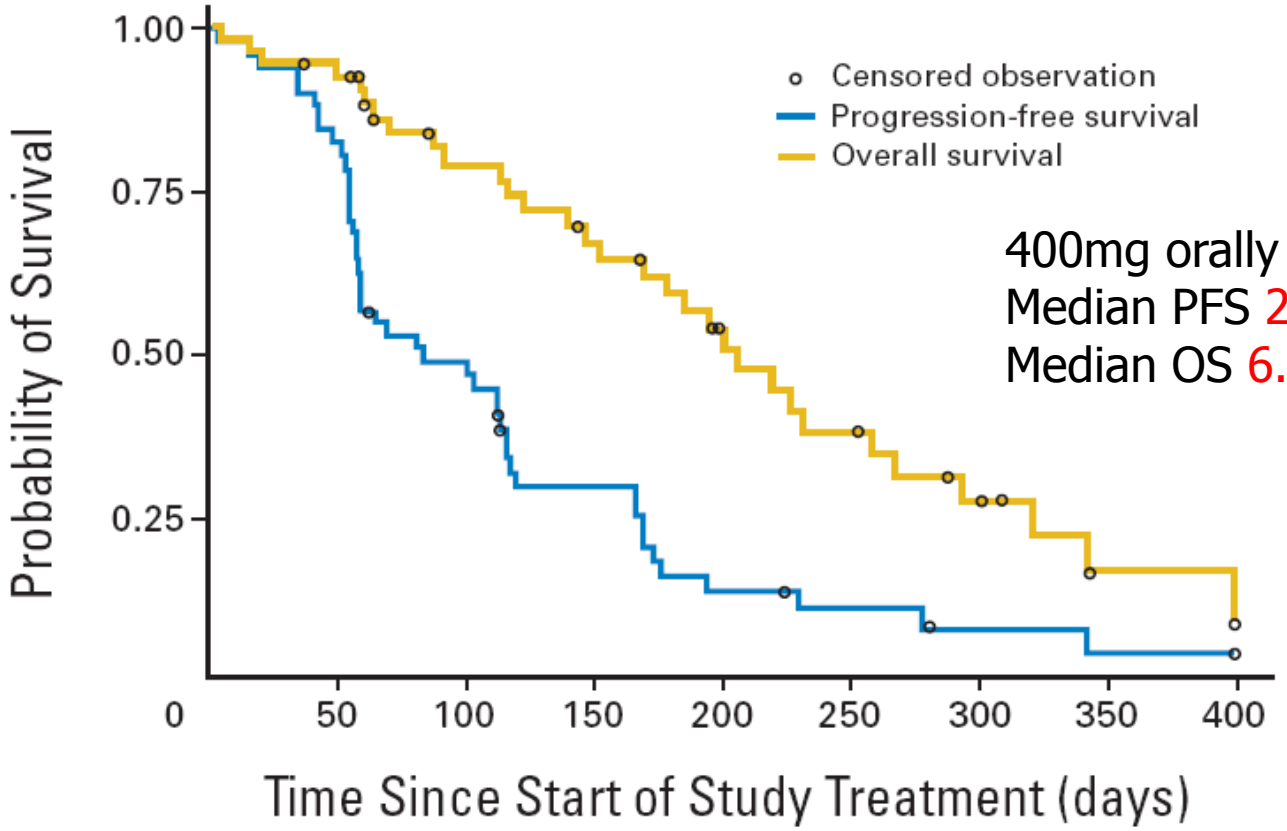
Marchetti A, et al. JCO. 2011;29:2046-2051

BRAF Mutations

Variable	Total No. of Patients (N = 739)	V600E					Non-V600E				
		Mutated (n = 21)		Wild Type (n = 718)			Mutated (n = 15)		Wild Type (n = 724)		
		No.	%	No.	%	*P*	No.	%	No.	%	*P*
Age, years						.19; NS					.72; NS
Mean		67.7		64.7			65.9		64.8		
SD		± 6.5		± 9.1			± 7.6		± 9.2		
Sex						< .001					.13; NS
Male	552	5	0.9	547	99.1		14	2.5	538	97.5	
Female	187	16	8.6	171	91.4		1	0.5	186	99.5	
Smoking history						.042					.015
Smoker/former smoker	542	11	2	531	98		15	2.8	527	97.2	
Never smoker	197	10	5.1	187	94.9		0	0	197	100	
Tumor size						.1; NS					.61; NS
T1	322	6	1.9	316	98.1		5	1.6	317	98.4	
T2	330	9	2.7	321	97.3		9	2.7	321	97.3	
T3	58	4	6.9	54	93.1		1	1.7	57	98.3	
T4	29	2	6.9	27	93.1		0	0	29	100	
N status						.13; NS					.97; NS
N0	457	8	1.8	449	98.2		10	2.2	447	97.8	
N1	111	5	4.5	106	95.5		2	1.8	109	98.2	
N2	166	8	4.8	158	95.2		3	1.8	163	98.2	
N3	5	0	0	5	100		0	0	5	100	
Stage						.11; NS					.79; NS
I	412	7	1.7	405	98.3		9	2.2	403	97.8	
II	109	4	3.7	105	96.3		3	2.8	106	97.2	
III	194	8	4.1	186	95.9		3	1.5	191	98.5	
IV	24	2	8.3	22	91.7		0	0	24	100	

Marchetti A, et al. JCO. 2011;29:2046-2051

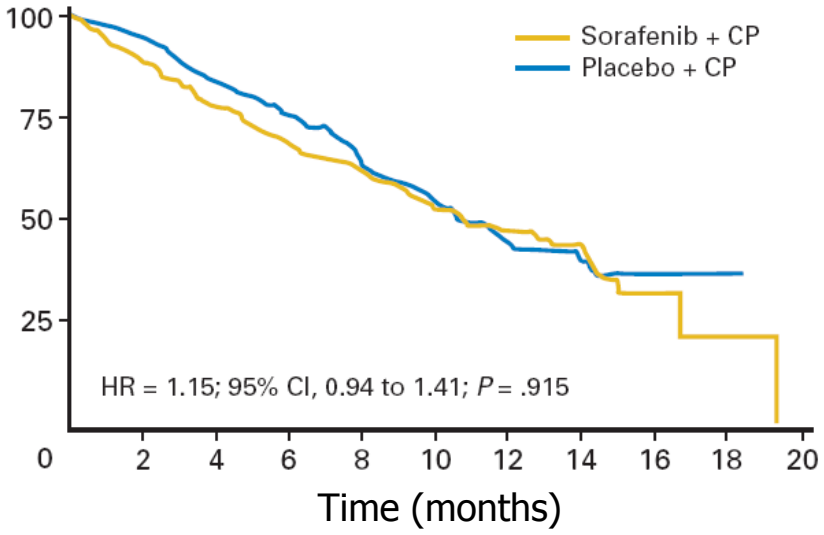
Phase II, multicenter, uncontrolled trial of single-agent sorafenib in patients with relapsed or refractory, advanced non-small-cell lung cancer.



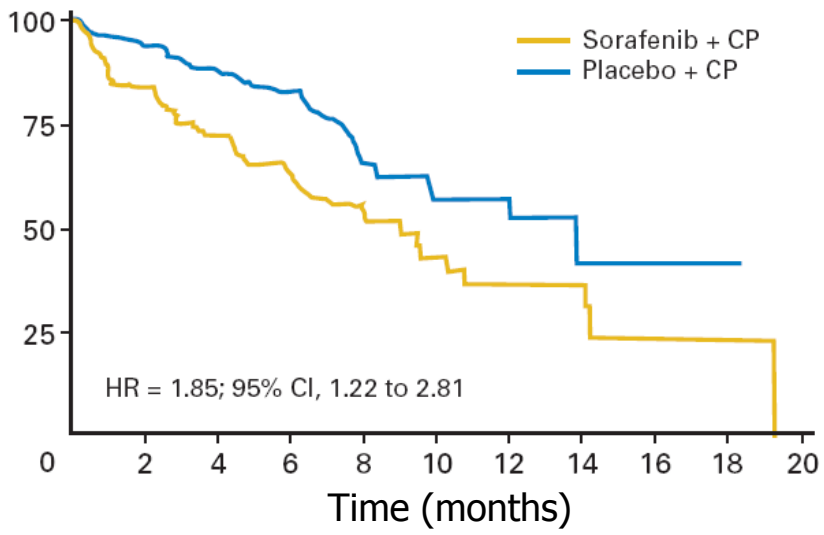
400mg orally twice daily
Median PFS 2.7ms
Median OS 6.7ms

George R. B. et al. JCO. 2009:27(26);4274-4280

Phase III study of carboplatin and paclitaxel alone or with sorafenib in advanced non-small-cell lung cancer.



Overall patient population



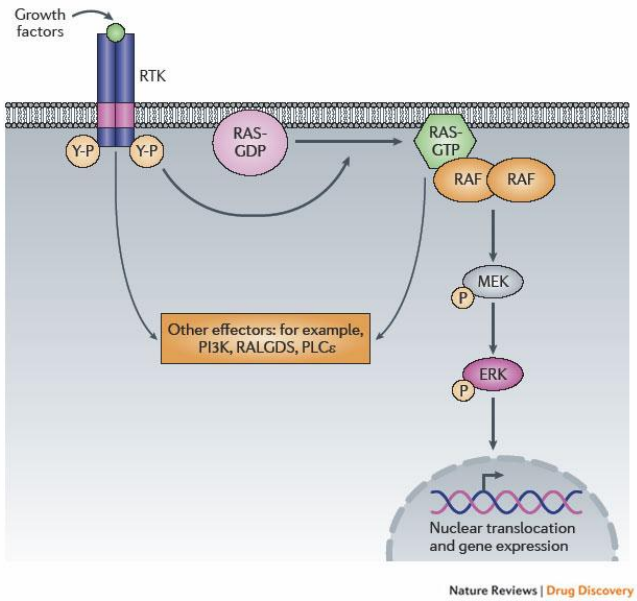
Patients with SQC

Scagliotti G, et al. JCO. 2010:28(11);1835-1842

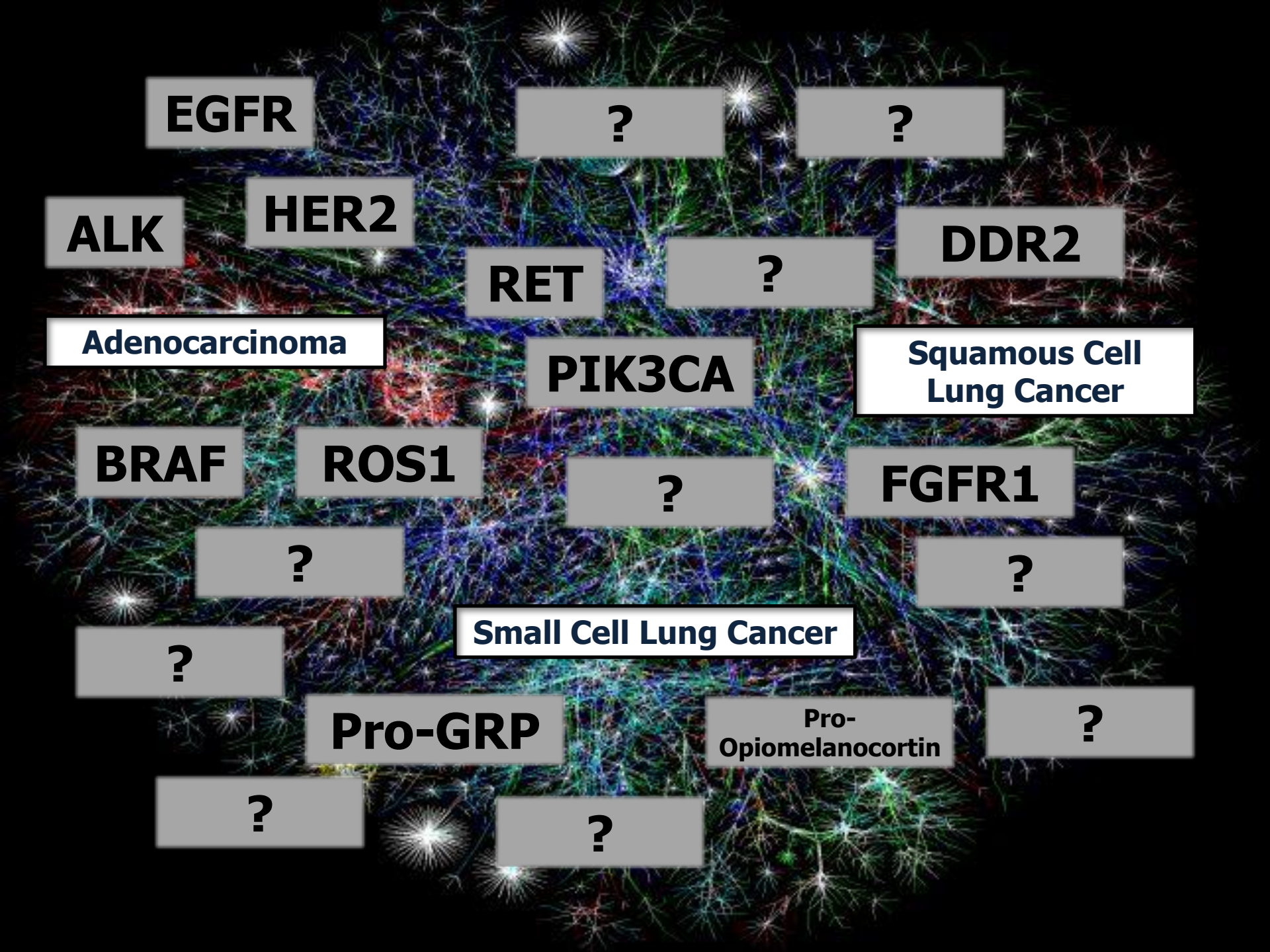
BRAF Mutations

- [NCT01336634]
  A Phase II Study of the Selective BRAF Kinase Inhibitor GSK2118436 in Subjects With Advanced Non-small Cell Lung Cancer and BRAF Mutations (V600E mutant)

- [NCT00888134]
  AZD6244 in Cancers With BRAF Mutations
  Drug that works by blocking the MEK.



Geoffrey RO. et al , et al. JCO. 2013:31(8);1097-1104


EGFR
?
?
ALK
HER2
DDR2
RET
?
Adenocarcinoma
PIK3CA
Squamous Cell Lung Cancer
BRAF
ROS1
?
FGFR1
?
?
Small Cell Lung Cancer
?
Pro-GRP
Pro-Opiomelanocortin
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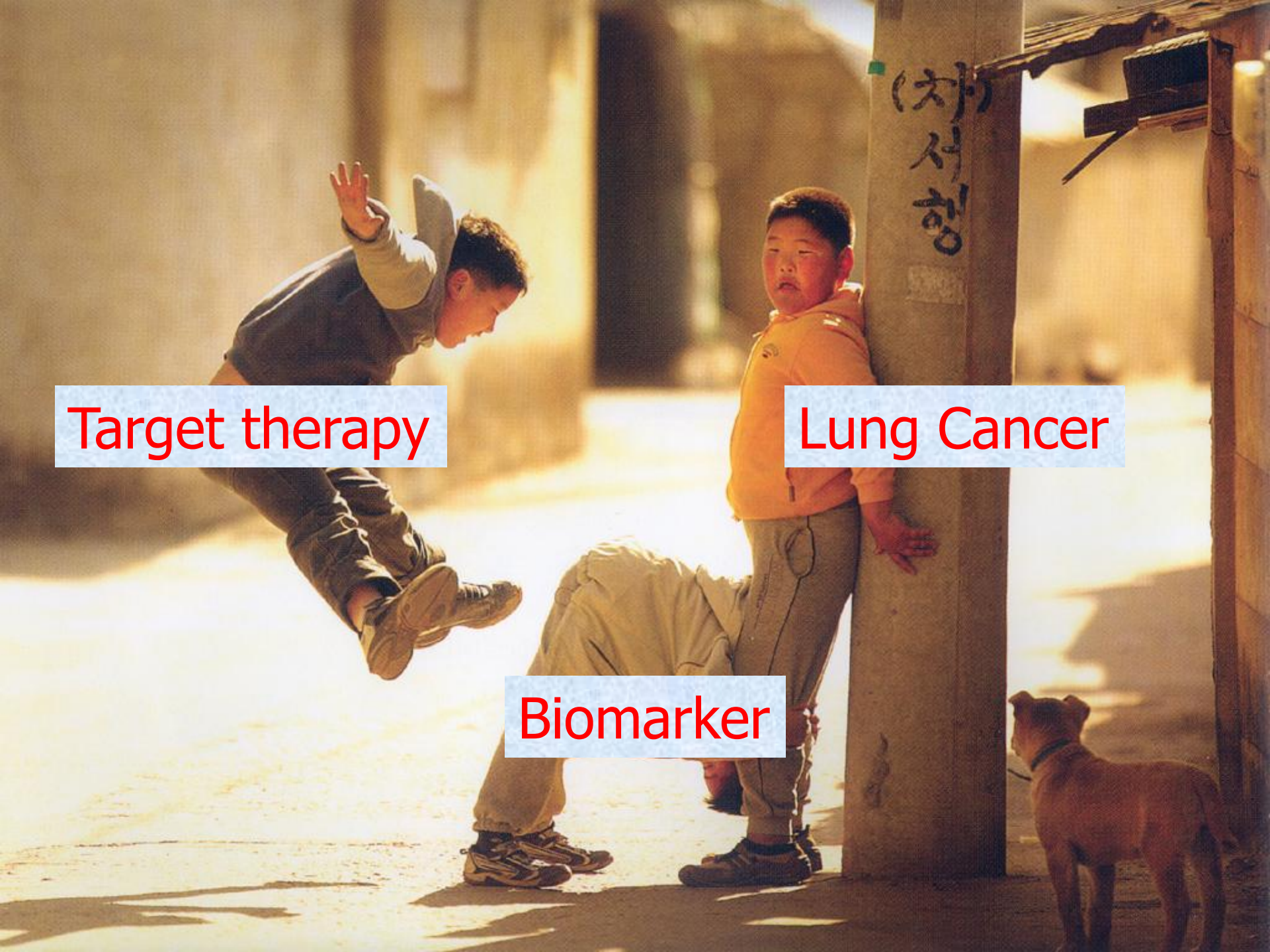
Target therapy
Lung Cancer
Biomarker