The Changing Landscape of Lung Cancer and its Treatment

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Lung Cancer 2011

- **USA – 190,000 new cases**
  - **165,000 deaths**
  - **165,300 cases of NSCLC**
  - **115,000 cases of adenocarcinoma**
  - **28,500 cases of lung cancer in never smokers**
- **Global**
  - **550,000 deaths from lung cancer**

LUNG CANCER
Histological Types

- **Non-small cell lung cancer (85%)**
  - **Adenocarcinoma**
  - **Squamous cell carcinoma**
  - **Large cell carcinoma**
- **Small cell lung cancer (15%)**

LUNG CANCER
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Median survivals in SCLC

Very-limited disease	~5 years
Limited disease	18-24 months
Extensive disease	10 months
SCLC without treatment	<3 months

Major advances in treatment of SCLC in the last 2 decades

- Combined modality concomitant chemo-radiotherapy in limited disease
- Prophylactic cranial irradiation in limited and extensive disease
- Standard systemic therapy not changed in the last two decades: platinum plus etoposide
- No new systemic treatment approved after the registration of topotecan for second-line treatment (FDA 1998; EMEA 2006)

Teniposide in the Treatment of Small-Cell Lung Cancer: The Influence of Prior Chemotherapy

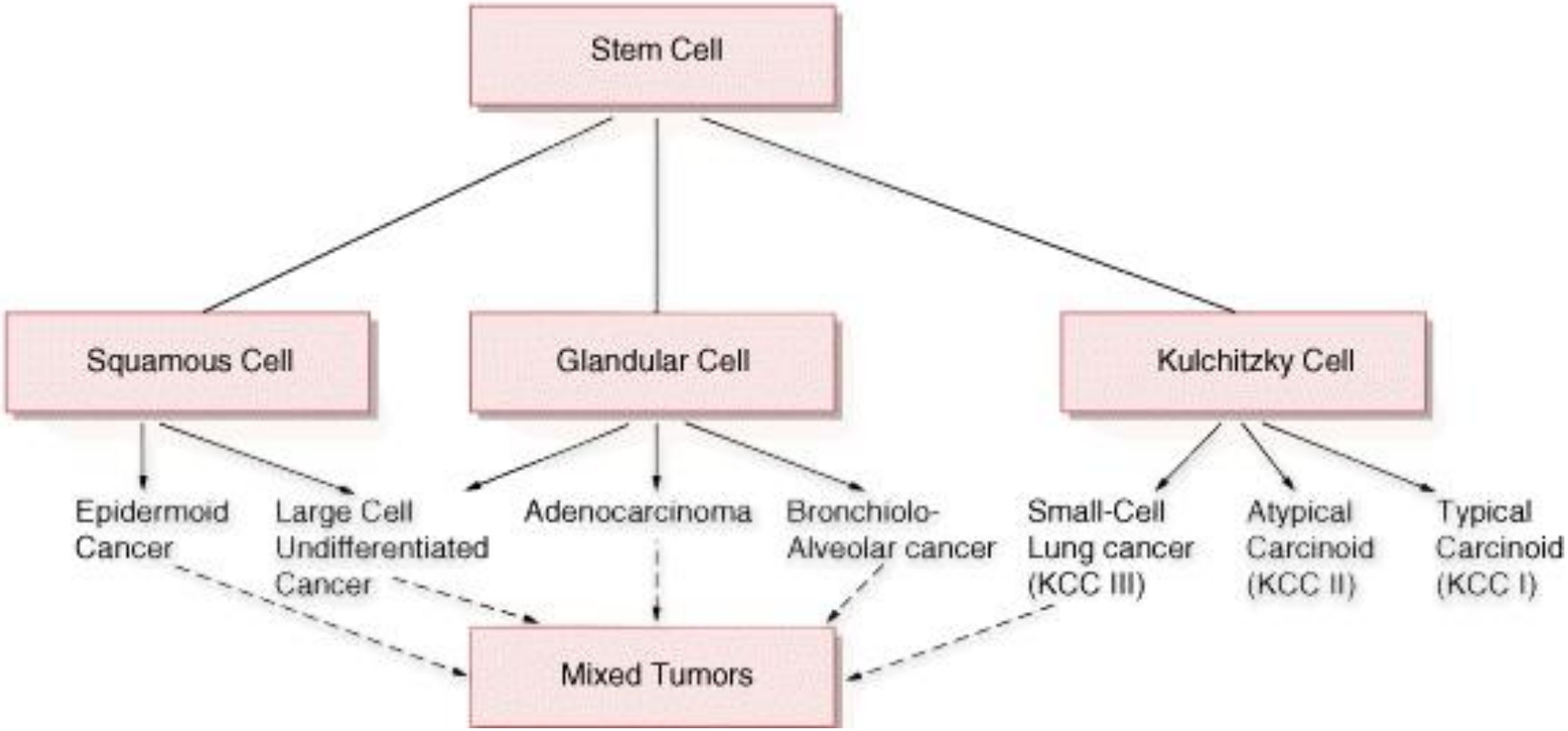
By Giuseppe Giaccone, Michela Donadio, Gianmaria Bonardi, Franco Testore, and Alessandro Calciati

Fifty patients with small-cell lung cancer (SCLC) were treated with teniposide (VM26) at 120 to 140 mg/m^2 on days 1, 3, and 5, every 3 weeks. Twelve elderly patients were administered VM26 as first-line chemotherapy. Toxicity was manageable, myelosuppression being the major side effect. The response rate for 44 evaluable patients was 34% (36% for untreated patients); the median durations of response and survival were 230 and 208 days, respectively. Effectiveness of prior chemotherapy and time from last administration was found to influence patient response to VM26: 42% of responders to prior chemotherapy responded to VM26, while 0% of the nonresponders to prior chemotherapy responded to the new agent. Moreover, among patients pretreated with chemotherapy, 12% of those recently treated (earlier chemotherapy ending ≤ 2.6 months before administration of VM26) responded to VM26, while 53% of patients treated > 2.6 months earlier responded to VM26. Survival was influenced by common prognostic factors (performance status, weight loss, prior chemotherapy exposure). Selection of pretreated patients by type of exposure to prior chemotherapy may help in the testing of new drugs in this disease.

J Clin Oncol 6:1264-1270.

Time from prior Chemotherapy	Response to teniposide	
≤ 2.6 m	12%	
> 2.6 m	53%	(p=0.016)

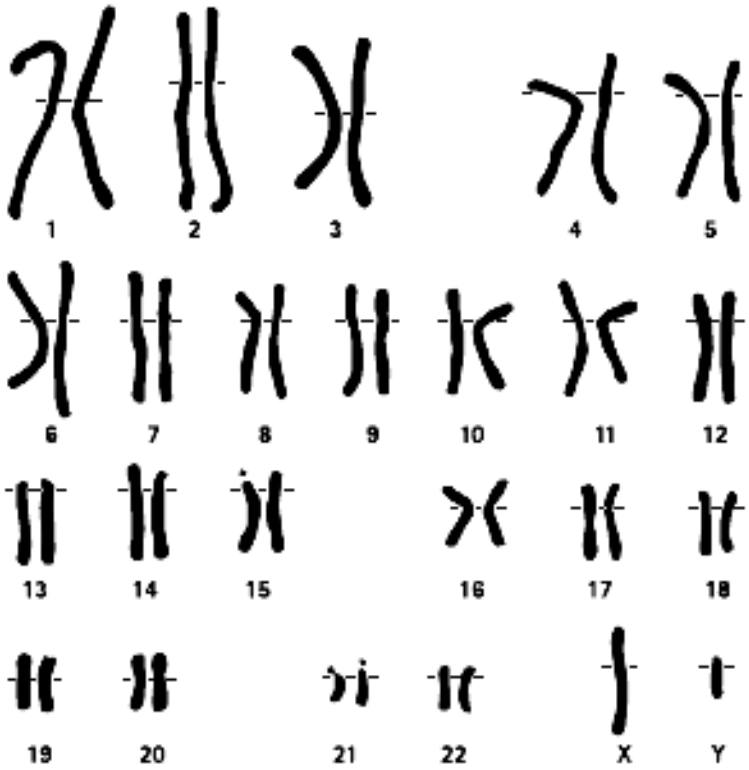
Hypothesized model of origin of lung tumors



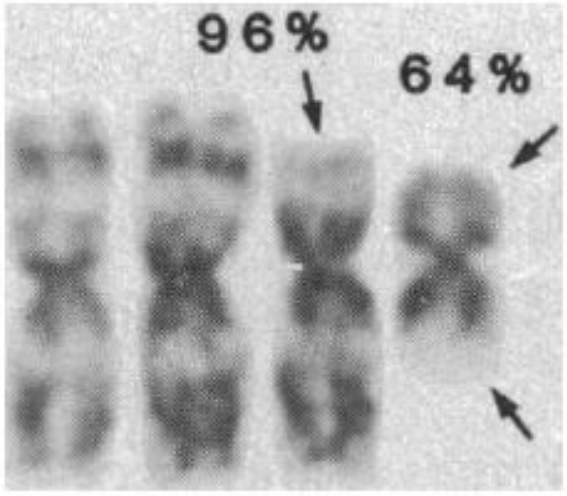
Cancer Medicine 2003

Copy number change in SCLC

- Cytogenetic study
  - Establishment of cell line → triggered into metaphase



Chr 3 deletion in SCLC



H69

J WHANG-PENG

Science 1982;215:181-2

SCLC, a forgotten disease ?

- Difficulty in obtaining fresh material has hampered large genomic studies
- Novel technologies may allow use of FFPE material
- Better understanding the biology will help identify new targets and develop novel strategies

Array-based comparative genomic hybridization of pulmonary neuroendocrine tumors

Goals of the project

- To what extent are SCLCs and carcinoids genetically connected ?
- Can we identify potential treatment targets for SCLC?
- Are SCLC cell lines representative of SCLC tumors?

Voortman et al. PNAS USA 2010,107(29):13040-5

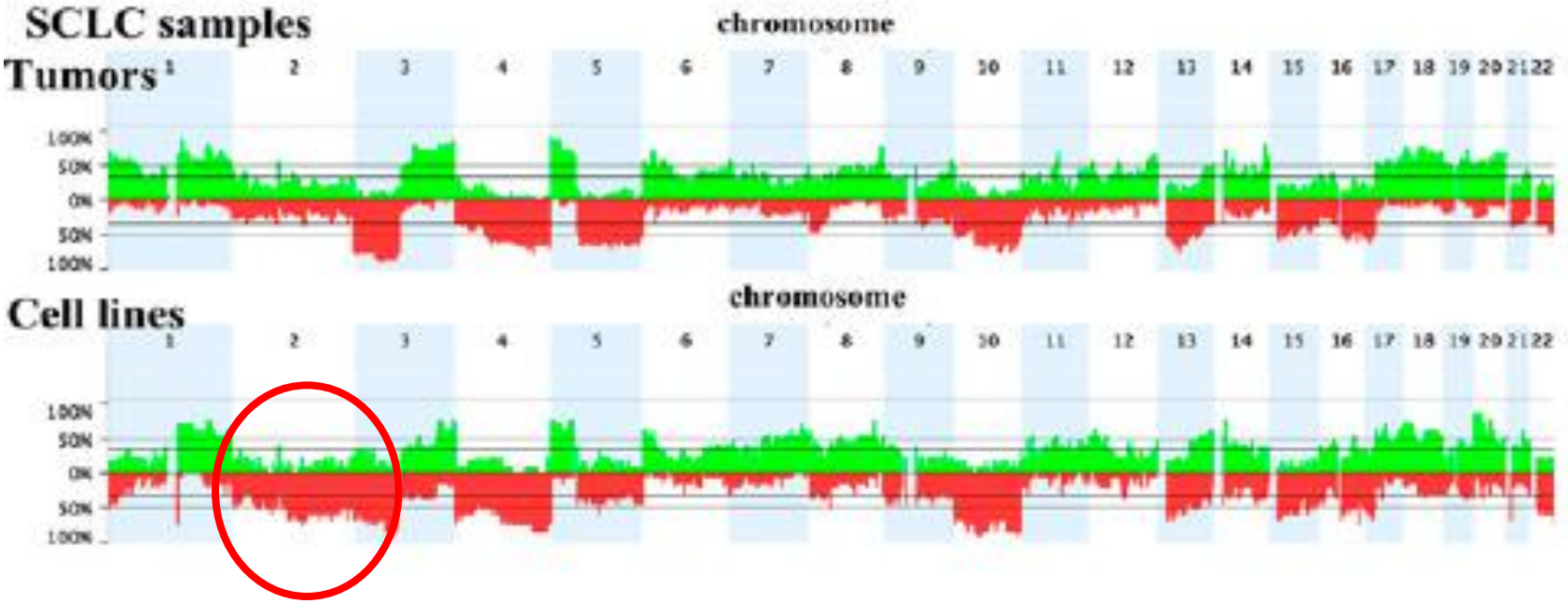
Array CGH study of lung neuroendocrine tumors

	SCLC tumors	SCLC cell lines	Bronchial carcinoids	GI carcinoids
Number	33	13	19	9
Cytogenetic bands with recurrent CN aberrancy				
gains	122	98	86	92
losses	48	71	45	89
Genes in cytogenetic bands with recurrent CN aberrancy				
gains	8459	6851	536	3406
losses	5085	7232	1022	1178
Cytogenetic bands with very high CN gain[&]				
	4	11	0	0
Genes in cytogenetic bands with very high CN gain[&]				
	41	39	0	0

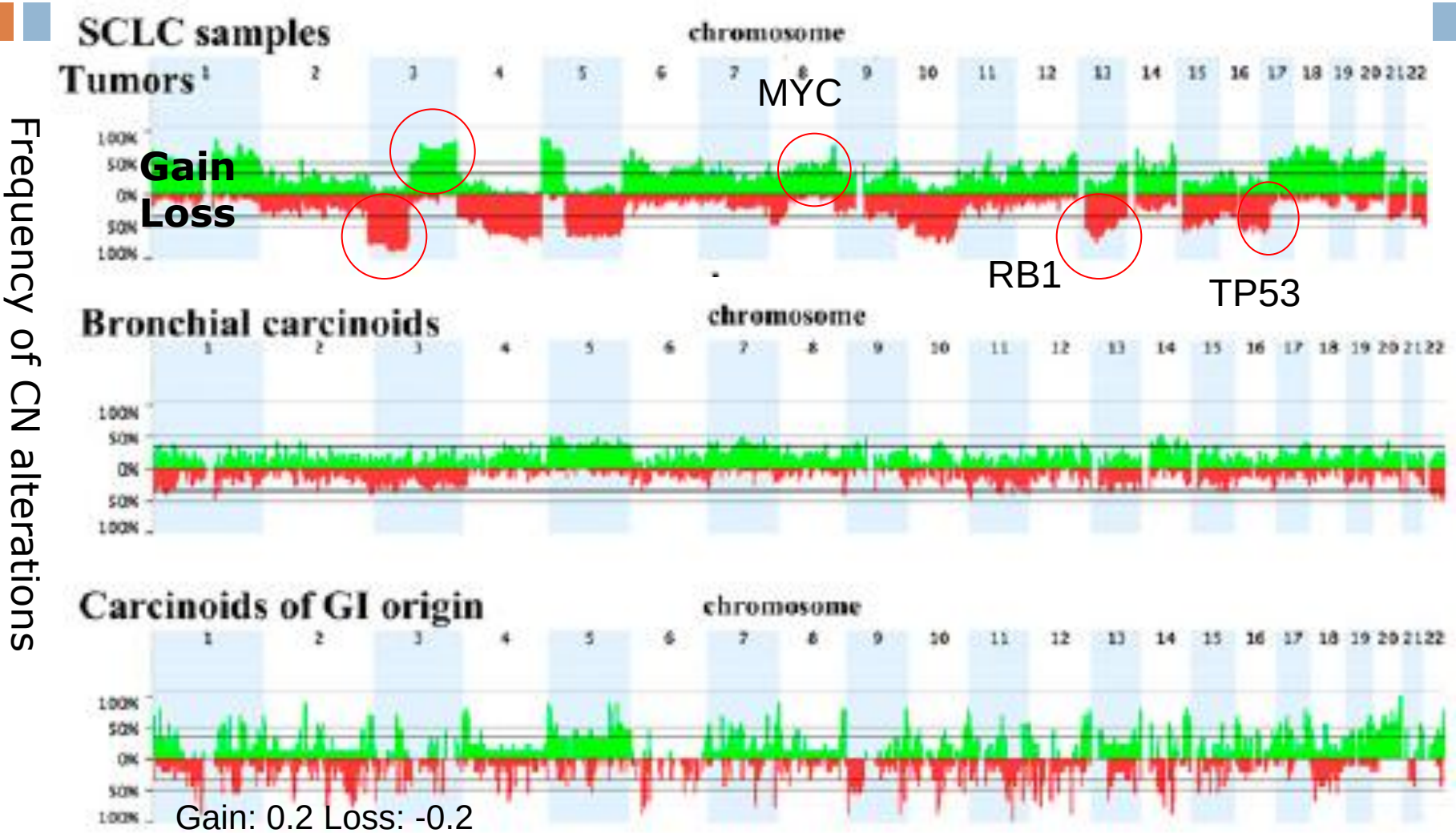
[&] 2-log ratio >3.0

SCLC cell lines may be representative of SCLC tumors genomically

- SCLC cell lines have more losses in chr. 2
- Only 74 genes were in cytogenetic bands in which the difference of frequencies of CNA between SCLC tumors and cell lines was > 50% and statistically significant



Comparison of SCLC tumors, bronchial carcinoids, and carcinoids of GI origin

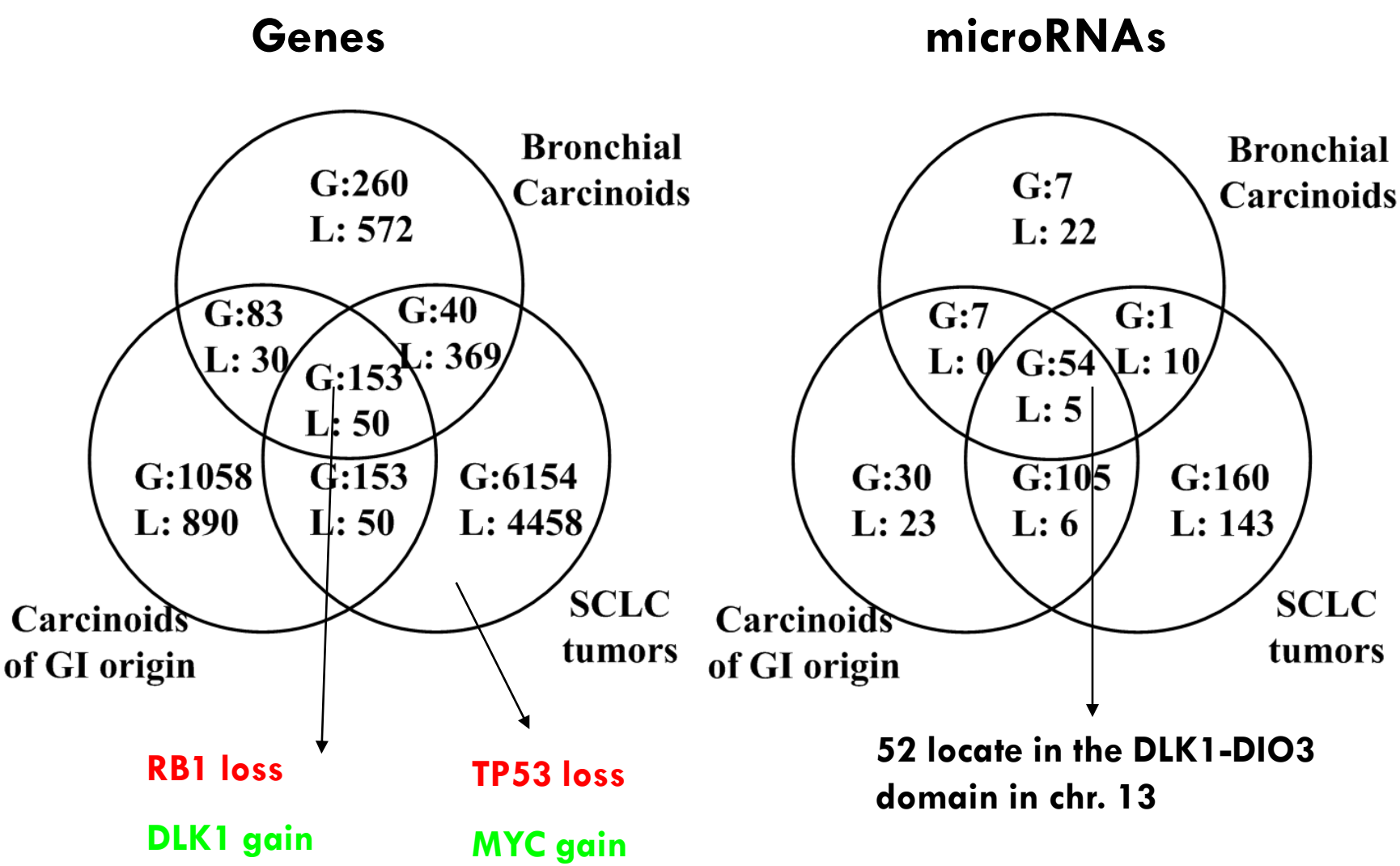


Gain: 0.2 Loss: -0.2

Recurrent alteration: 35%

Voortman and Lee PNAS 2010

Common copy number alterations of neuroendocrine tumors



Potential drug targets for SCLC

Genes with high frequencies of copy number alterations

	Tumorscape		Our series		Tumorscape		Our series
Genes	All cancers	SCLC	SCLC tumors	Genes	All cancers	SCLC	SCLC tumors
PIK3CA gain	21.6%	57.5%	75.8%	BCL2 gain	11.9%	47.5%	51.5%
AKT1 gain	16.3%	47.5%	63.6%	MCL1 gain	36.5%	57.5%	76.8%
PTEN loss	24.2%	62.5%	75.8%	PMAIP1 (Noxa) gain	11.7%	45%	66.8%
FRAP1 (mTOR) gain	13.4%	45.5%	54.5%	VHL loss	23.6%	80%	75.8%

Cytogenetic bands with very high copy number gain[&] in SCLC tumors

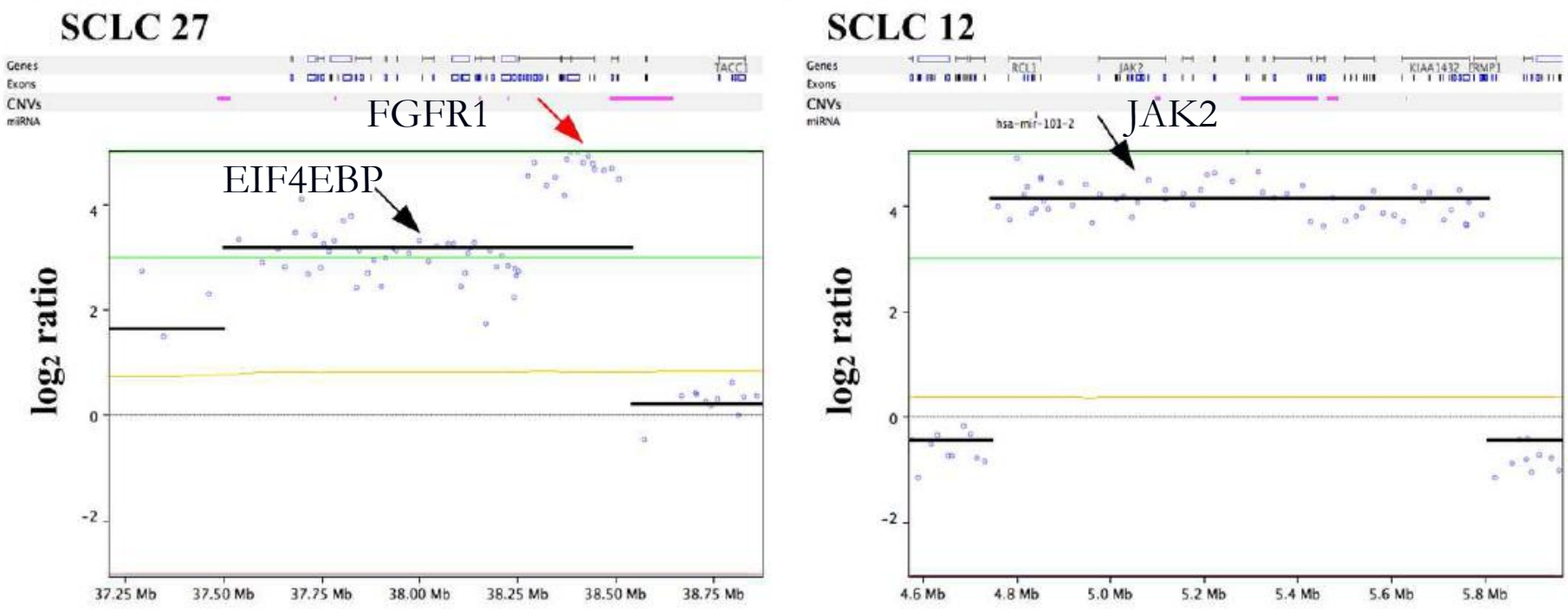
Cytogenetic band	Genes encoded	Candidate genes
8 p12 - p11.23	20	EIF4EBP1, FGFR1
9 p24.1	10	JAK2
9 p23 - p22.3	1	MPDZ
19 q13.12 - q13.13	10	*

[&]2-log ratio >3.0

*chr. 19 encodes 10 transcription factors

Potential drug targets

High copy number gain



A $\log_2$ ratio >4 means that the copy number may be more than $2^{(4+1)}=32$ copies

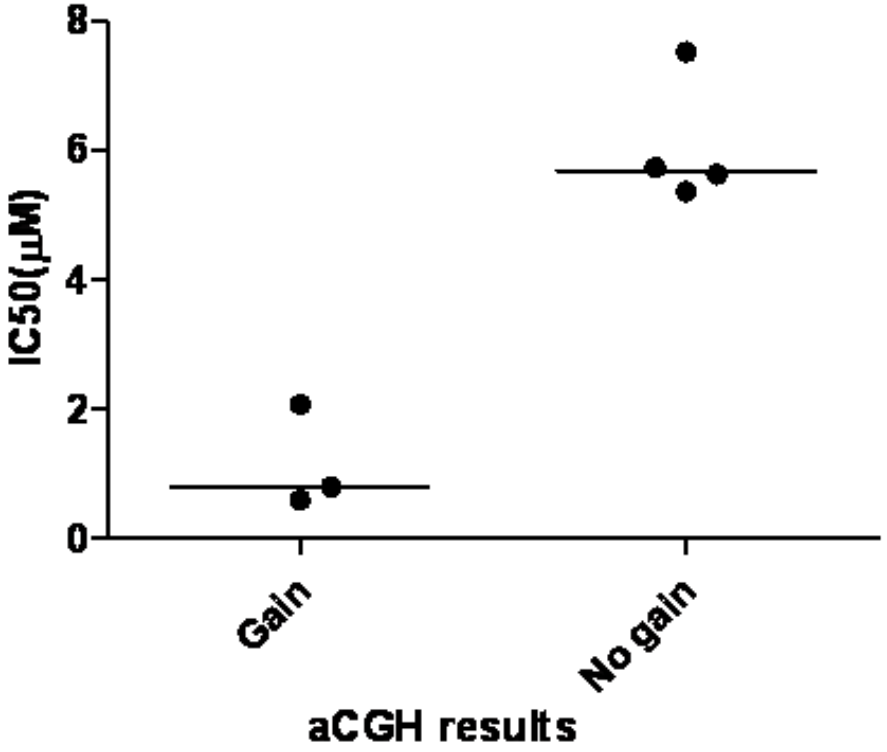
Copy number gain of the JAK2 gene and the FGFR1 gene in SCLC tumors and cells

	Tumorscape	Our series	
		SCLC tumors	SCLC cell lines
JAK2	42.5%	27.8%	30.8%
FGFR1	27.5%	33.3%	30.8%

JAK2 and FGFR1 are potential targets in subgroups of SCLC

Tumorscape: aCGH data of 26 cancer types and >3000 specimens
http://www.broadinstitute.org/tumorscape/pages/portalHome.jsf

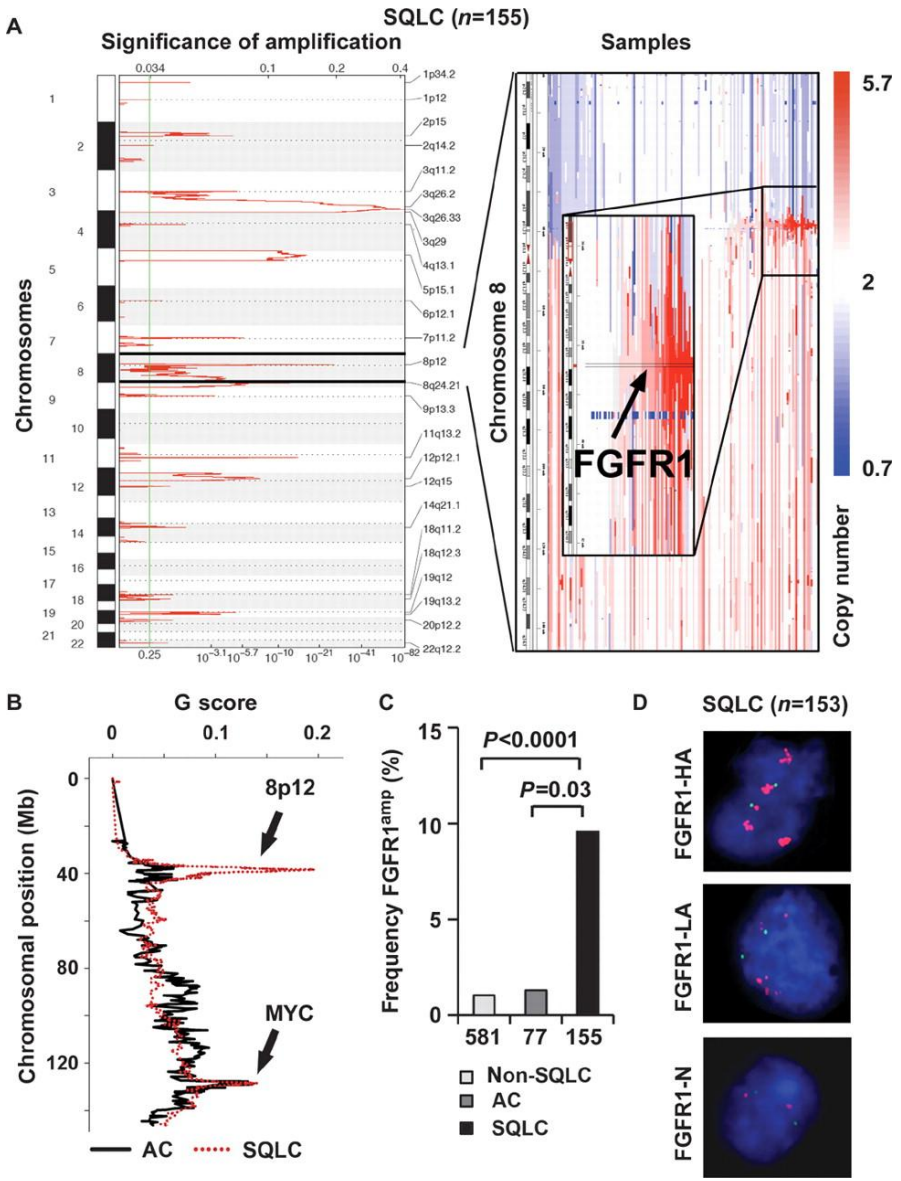
Targeting FGFR1 in SCLC



PD173074, a pan-FGFR inhibitor, on 7 SCLC cell lines

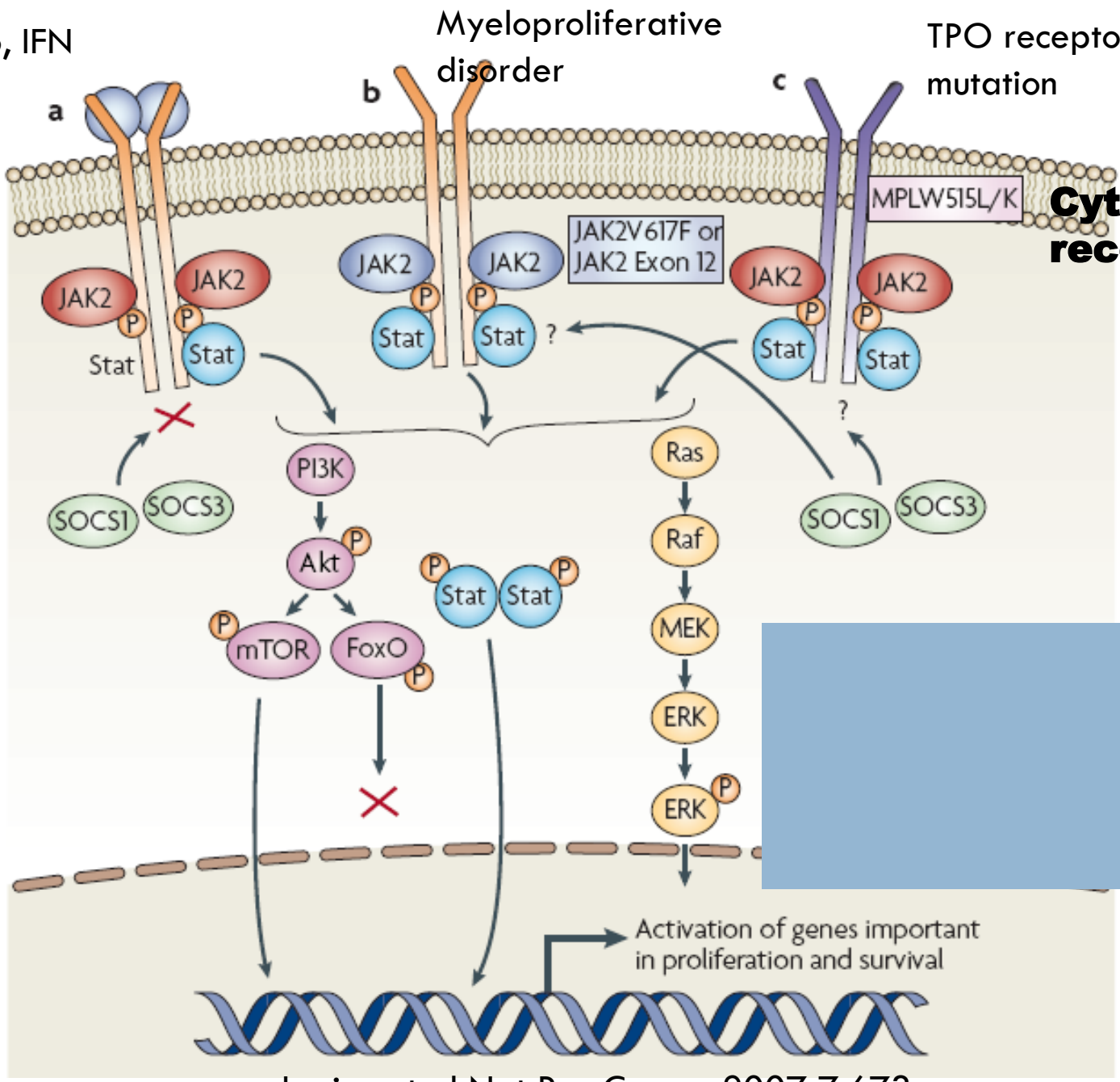
J-H Lee unpublished data

FGFR1 is amplified in squamous cell lung cancer



Weiss J et al. Sci Transl Med 2010;2:62ra93-62ra93

Cytokine receptors

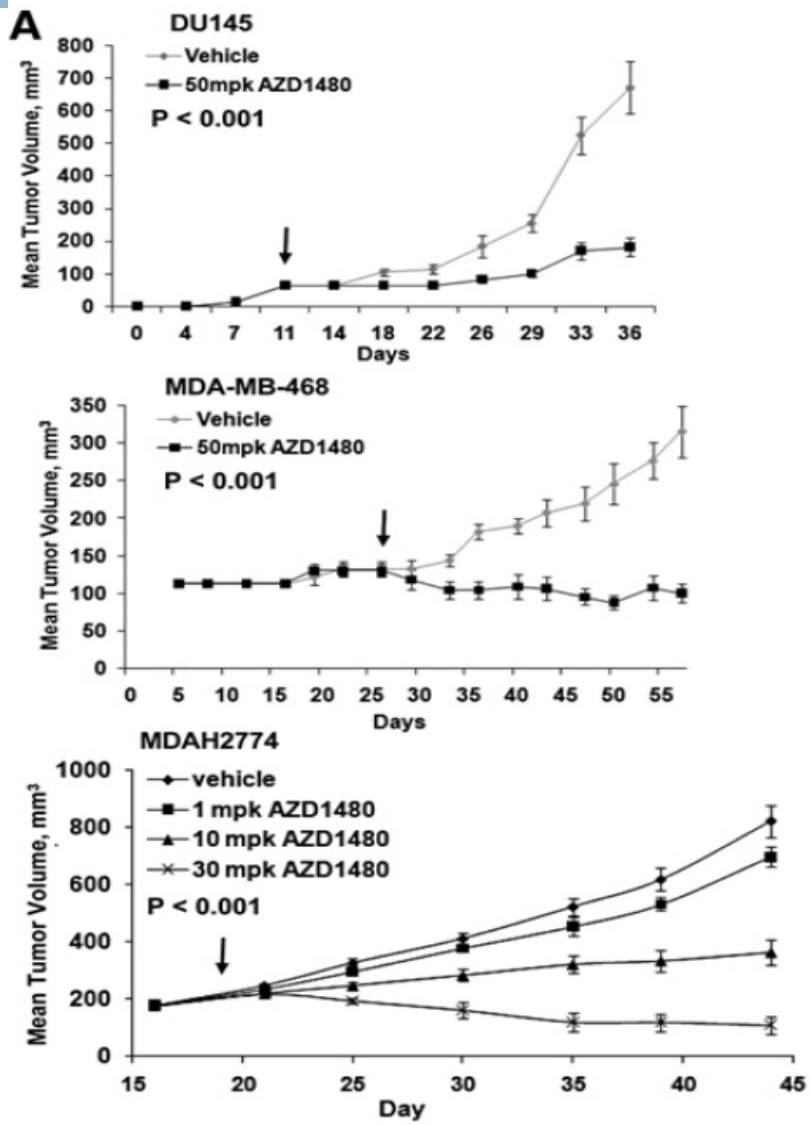


Levine et al Nat Rev Cancer 2007;7:673

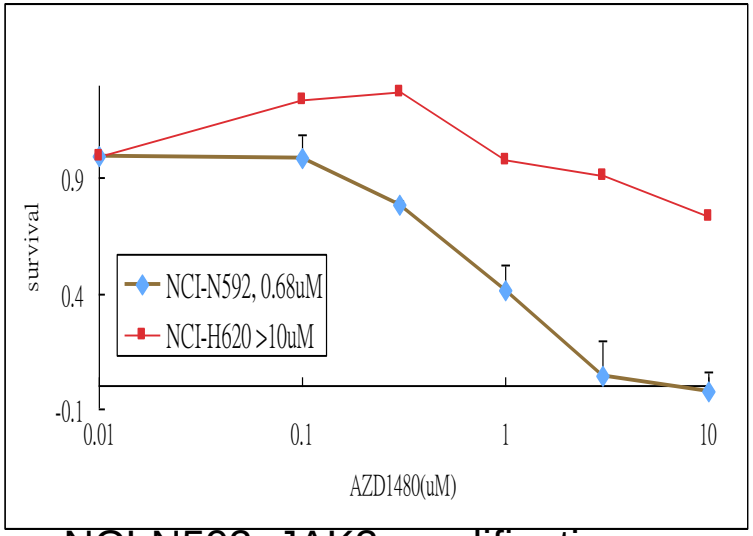
Targeting JAK2 in SCLC

- AZD1480, a JAK1/JAK2 inhibitor
- AZD1480 slows cancer xenograft growth of many solid tumors
- AZD1480 shows little cytotoxicity in cell culture systems

Cancer Cell 2009;16:487

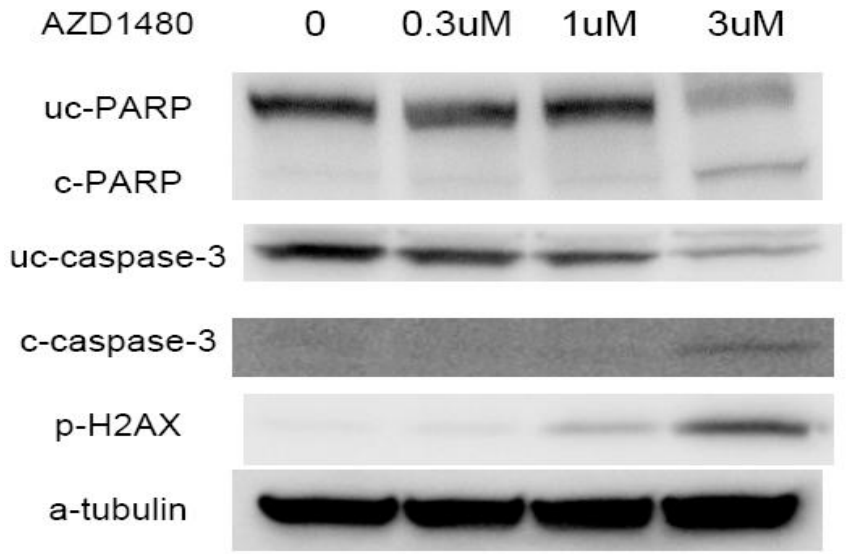


AZD1480 kills a SCLC cell line carrying JAK2 gene amplification and induces G2/M arrest and apoptosis

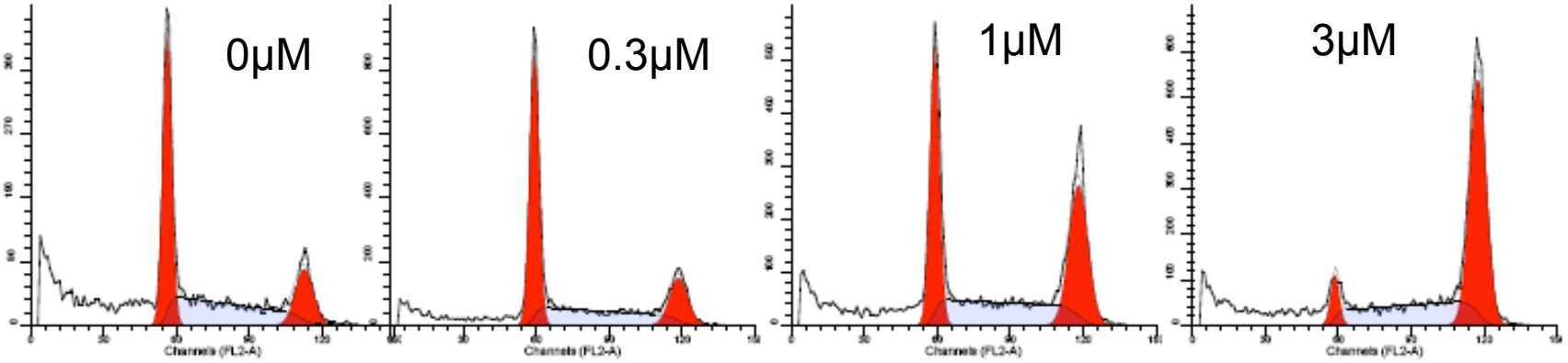


NCI-N592: JAK2 amplification

NCI-H620: JAK2 deletion



NCI-N592 Treated with drug for 48 hours



NCI-N592 Treated with drug for 24 hours

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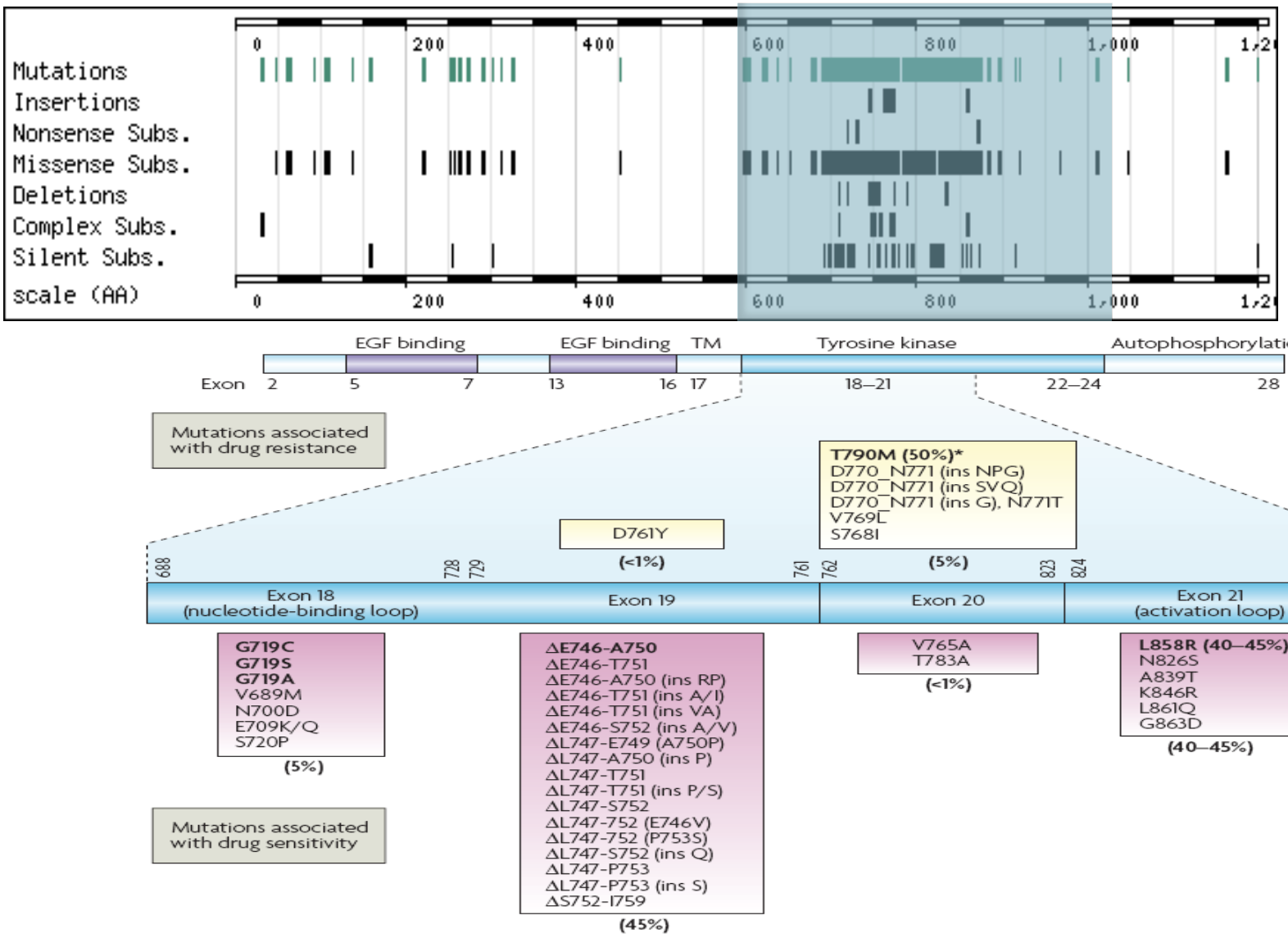
  - **Adenocarcinoma**
  - **Squamous cell carcinoma**
  - **Large cell carcinoma**
- **Small cell lung cancer (15%)**

EGFR mutations



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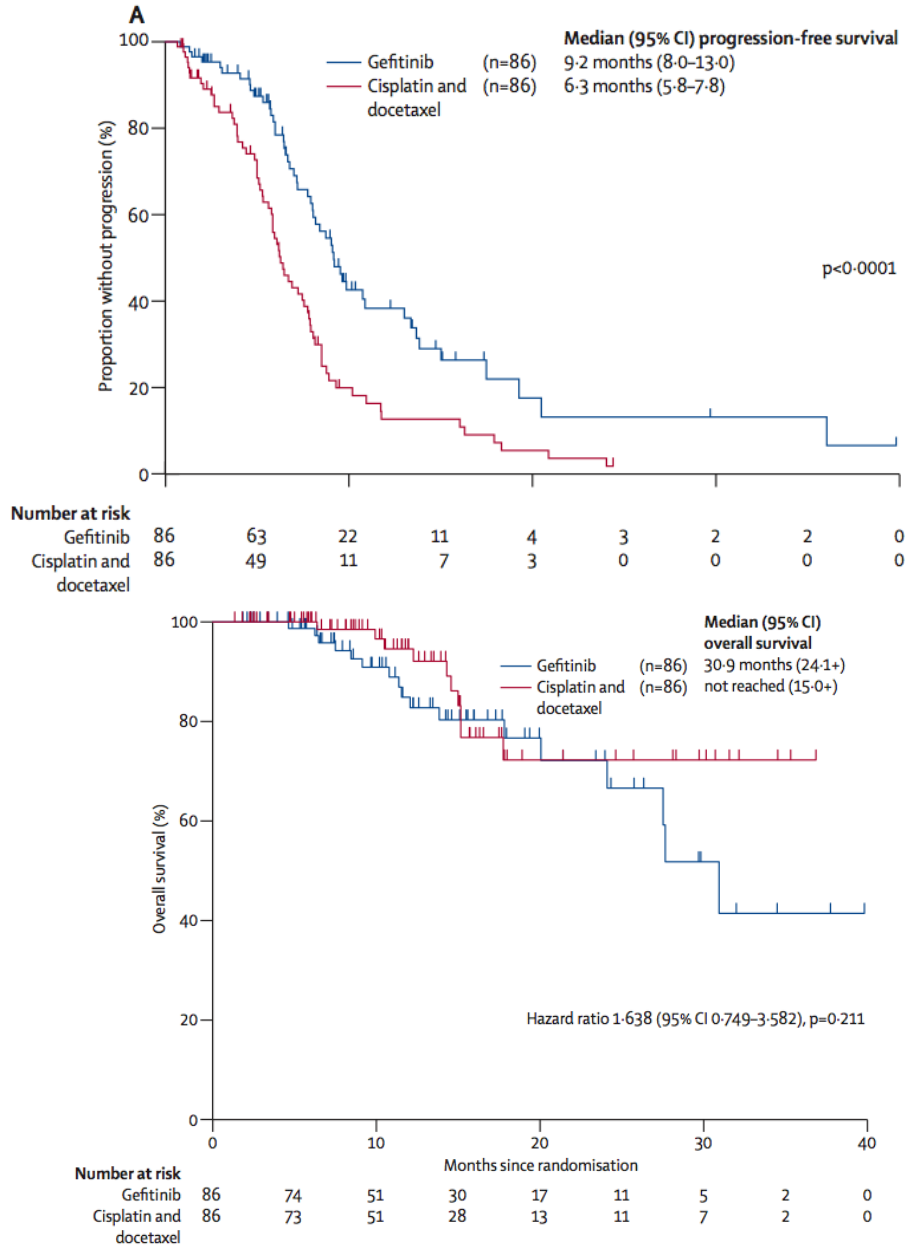
2. Sharma et al Nature Rev Cancer 7, 169, 2007

Prospective clinical trials comparing EGFR-TKIs to chemotherapy in first-line in advanced NSCLC with EGFR mutations

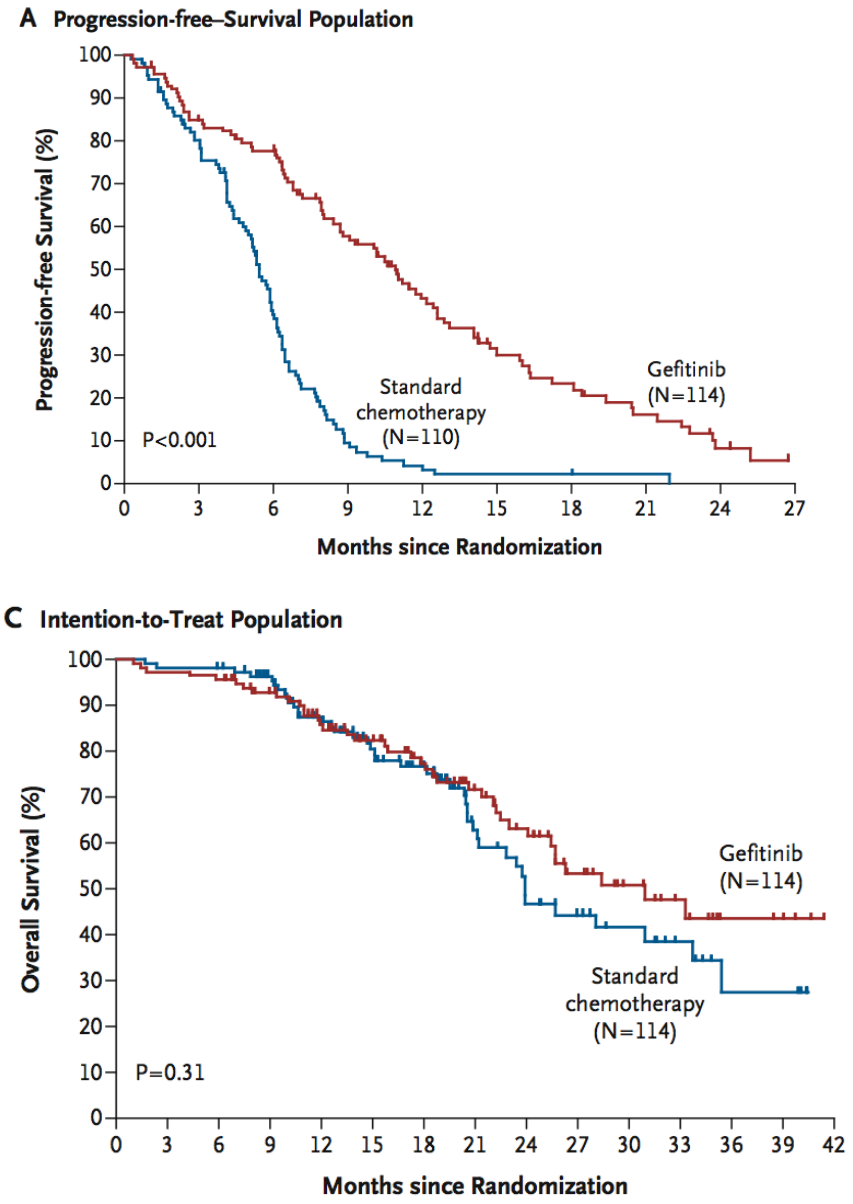
Author	Treatments	# patients	Response rate	PFS (m)	OS (m)
Mitsudomi (Lancet Oncol 2010)	Gefitinib DDP/DXL	86 86	62.1 23.2 (p<.001)	9.2 6.3 (p<.001)	30.9 NR (p=NS)
Maemondo (NEJM 2010)	Gefitinib CRB/PXL	114 110	73.7 30.7 (p<.001)	10.8 5.4 (p<.001)	30.5 23.6 (p=NS)
Zhou (ESMO 2010)	Erlotinib CRB/GEM	82 72	83 36 (p<.0001)	13.1 4.6 (p<.0001)	NA NA
EURTAC	Erlotinib CRB/GEM DDP/DXL				

NR=not reached; NA=not availble; NS=not significant

EGFR mutant selected

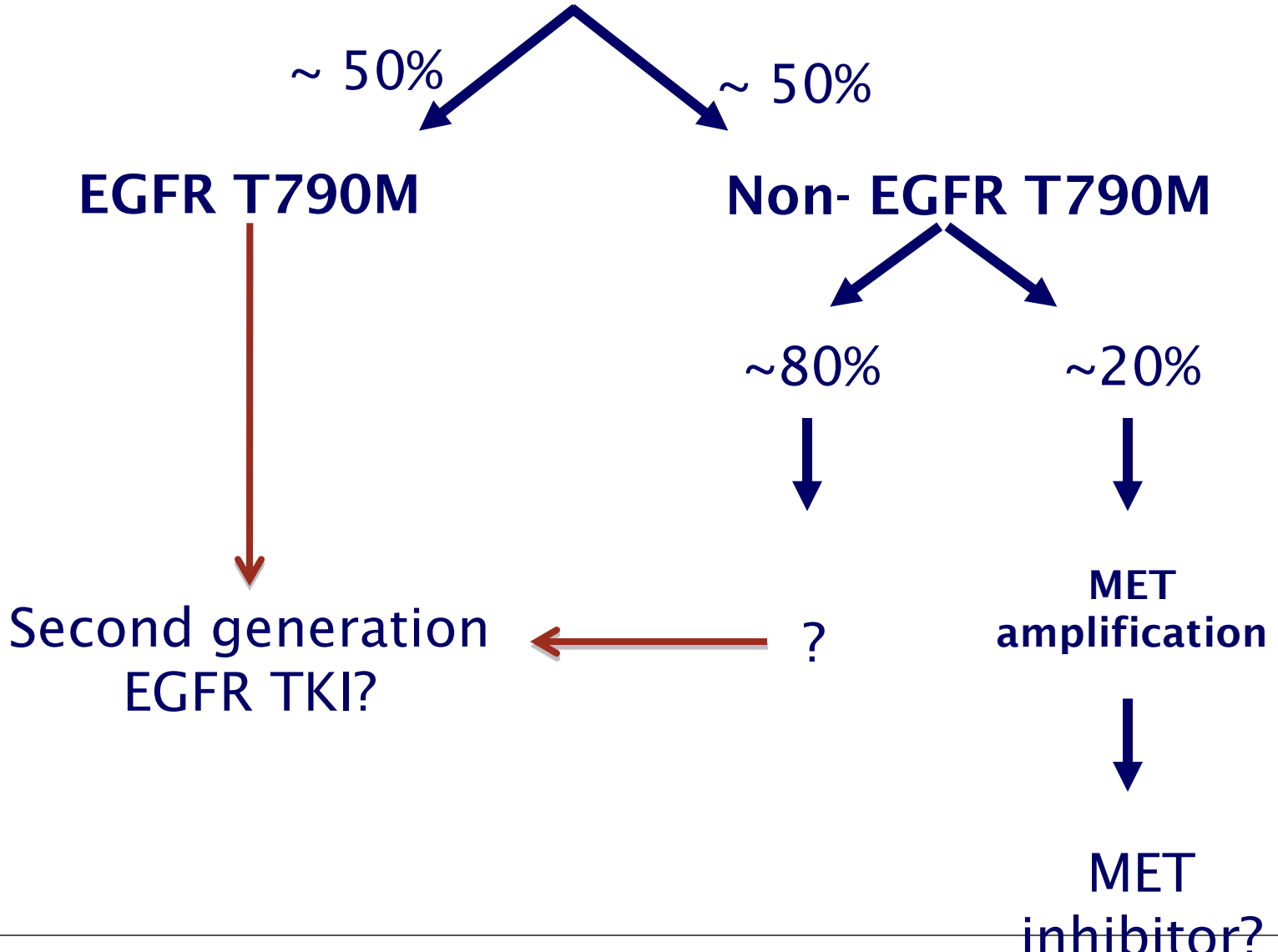


Mitsudomi et al. Lancet Oncol 11,121, 2010



Maemondo et al. NEJM 362, 25, 2010

Mechanisms of Acquired Resistance to EGFR TKIs



PF-00299804

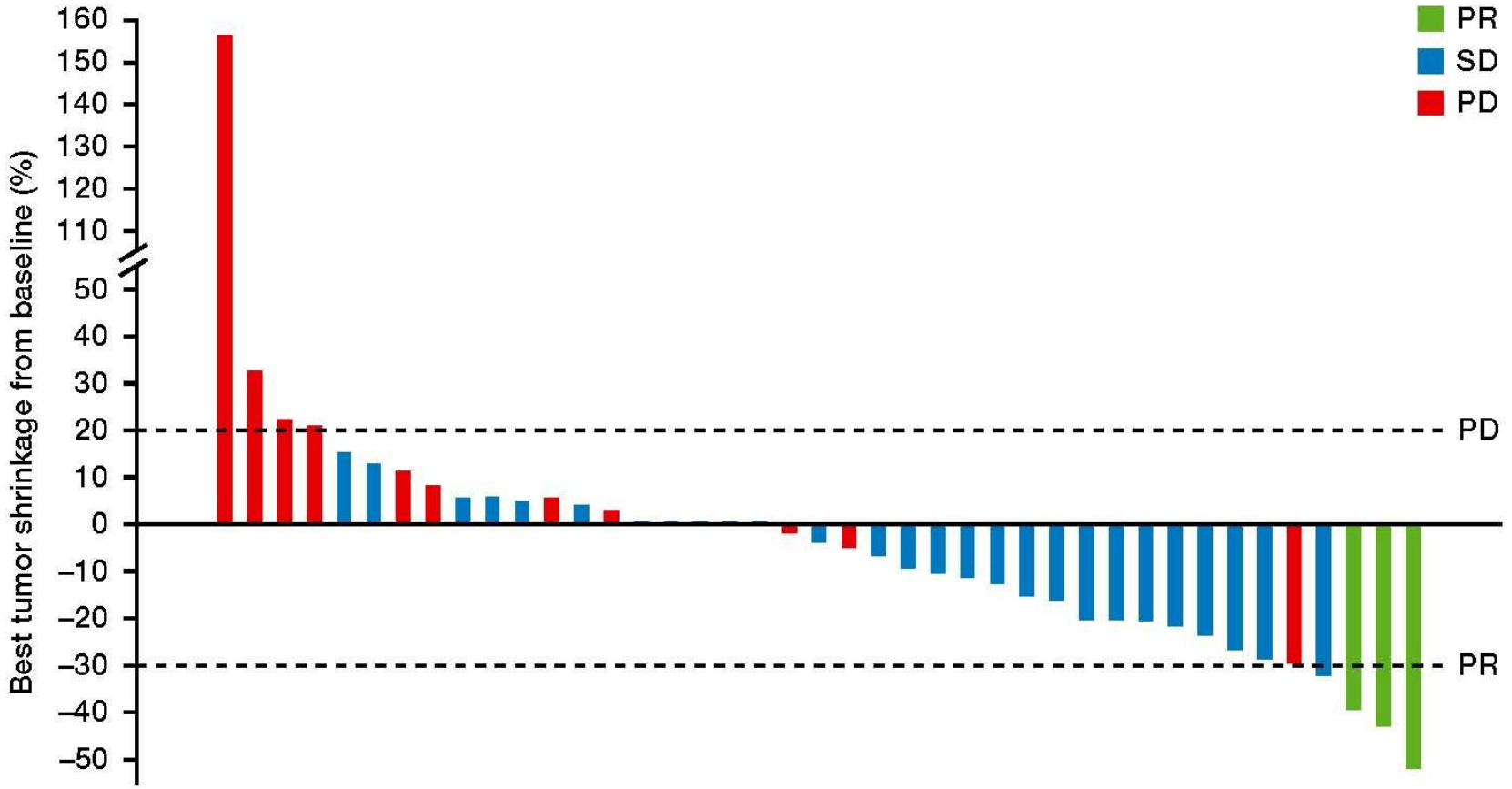
in vitro Activity against EGFR, HER2 and KRASmut NSCLC Cell Lines

Cell Line	EGFR mutation	ERBB2 mutation	K-ras mutation	Gefitinib IC_{50}	PF00299804 IC_{50}
A549	WT	WT	G12S	> 10 μM	> 10 μM
H441	WT	WT	G12V	> 10 μM	4 μM
Calu-3	WT	WT HER2 +++	WT	1.4 μM	0.063 μM
H1819	WT	WT HER2 +++	WT	0.42 μM	0.029 μM
H1781	WT	Ins G776V, C	WT	> 10 μM	0.275 μM
HCC 827	Del E746_A750	WT	WT	0.008 μM	0.002 μM
HCC 4006	Del L747 _E749	WT	WT	0.050 μM	0.004 μM
PC-9	Del E746_A750	WT	WT	0.023 μM	0.002 μM
H3255	L858R	WT	WT	0.075 μM	0.007 μM
H3255 GR	L858R/T790M	WT	WT	> 10 μM	0.119 μM
H1975	L858R/T790M	WT	WT	> 10 μM	0.44 μM

• MTS 72-Hour Proliferation Assay; 6-12 wells per assay; all experiments repeated at least 3X

Engelman et al. *Cancer Res*. 2007;67:11924.

PF-00299804 - response



PD = progressive disease; PR = partial response; SD = stable disease.

P. Janne….G.Giaccone, ASCO 2009

Case Presentation

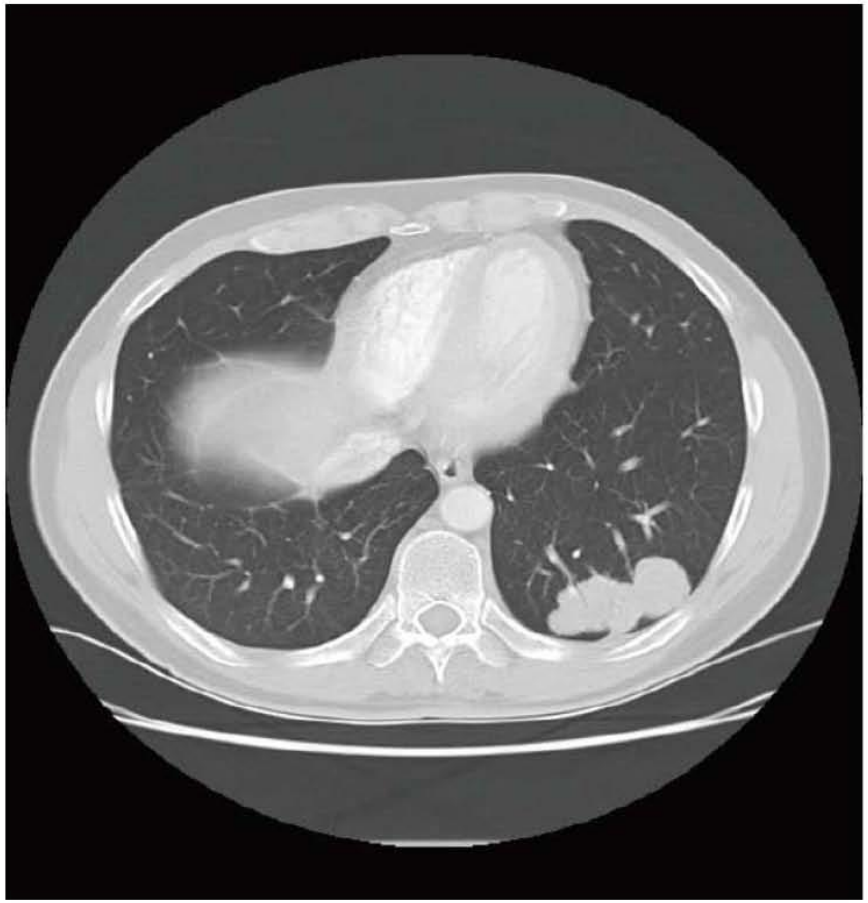
- 52 y/o AA male
  - Never smoker
  - Diagnosed with NSCLC adenocarcinoma
  - Stage IV, multiple lesions in LLL and RUL
- No Past Medical History
- No Family History

- Treatment:
  - carboplatin/paclitaxel/bevacizumab
    - 8 cycles, initial Partial Response (PR) then Progressive Disease (PD)
  - erlotinib 150 mg PO daily, (6 weeks) PD
  - Referred for evaluation at NCI

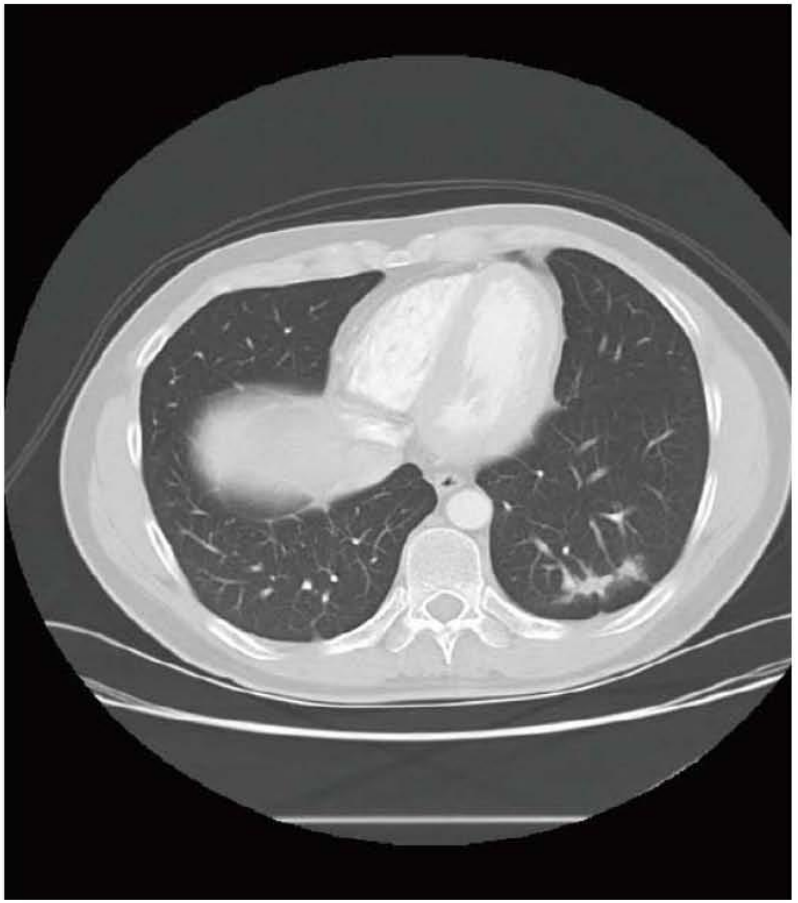
Treatment Course

- Screened for PF-00299804 trial:
  - KRAS wild type (wt)
  - [EGFR wt]
- Enrolled on trial PF-00299804 for patients who have failed EGFR TKIs
- Started on PF-00299804
  - 45 mg PO daily

Pretreatment and after 4 cycles of PF-00299804

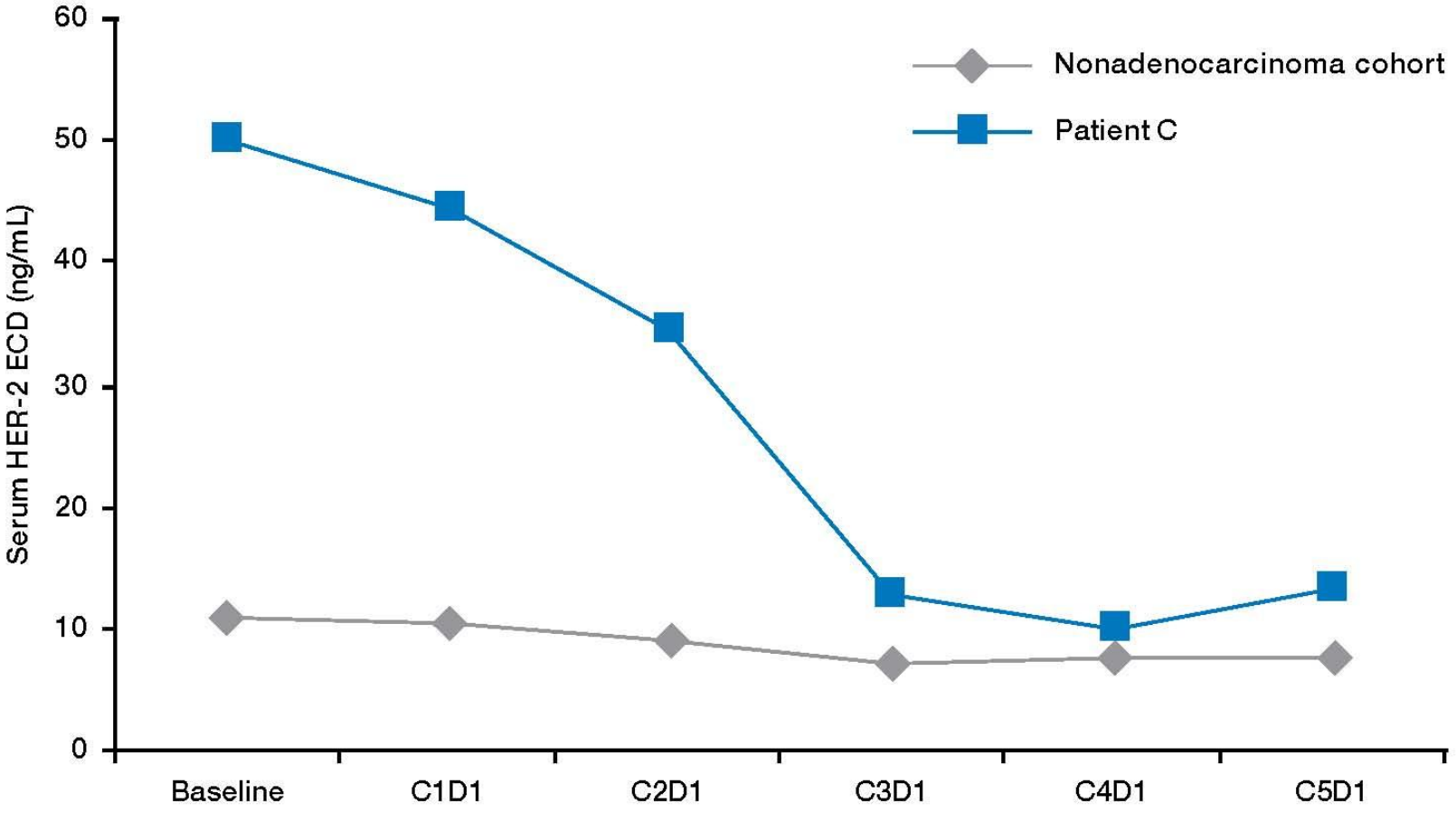


October 21, 2008



January 16, 2009

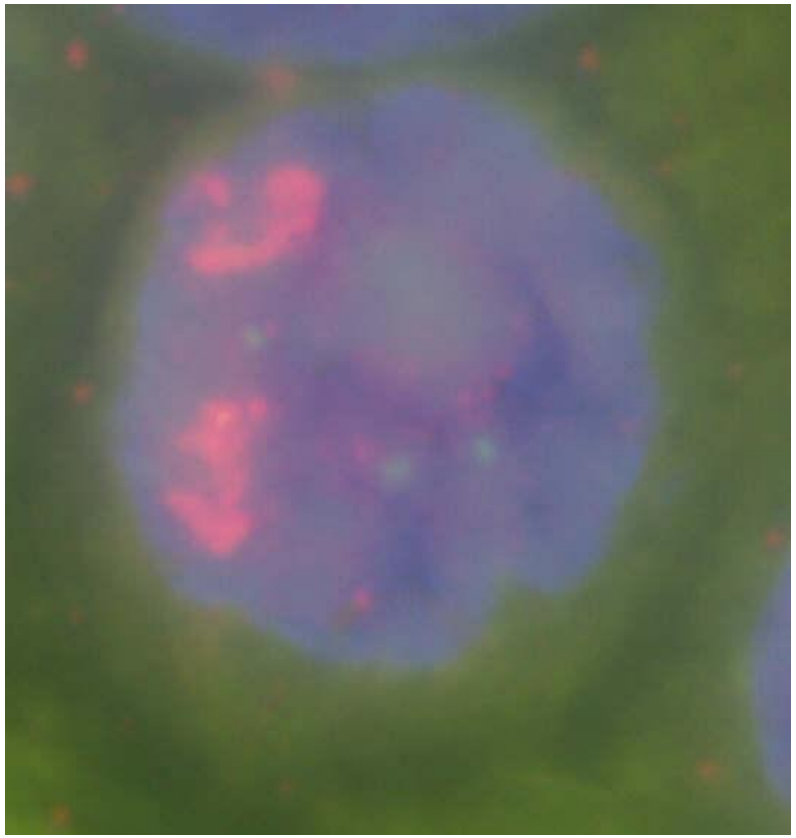
Serum HER-2 levels at baseline and through 4 cycles of PF-00299804 therapy



C = cycle; D = day; ECD = extracellular domain; EGFR = epidermal growth factor receptor; WT = wild type.

Stain Tumor for Her2/Neu

HER2/Neu FISH



PATHOLOGY

- IHC 2+
- Her2/Neu Amplified
  - Cells counted 20
  - HER2 = 10.3
  - CEP17 = 2.4
  - HER2/CEP17 Ratio: 4.3

Kelly R & Giaccone G JCO 2010 Oct 1;28(28):e507-10

EGFR mutations in African-Americans

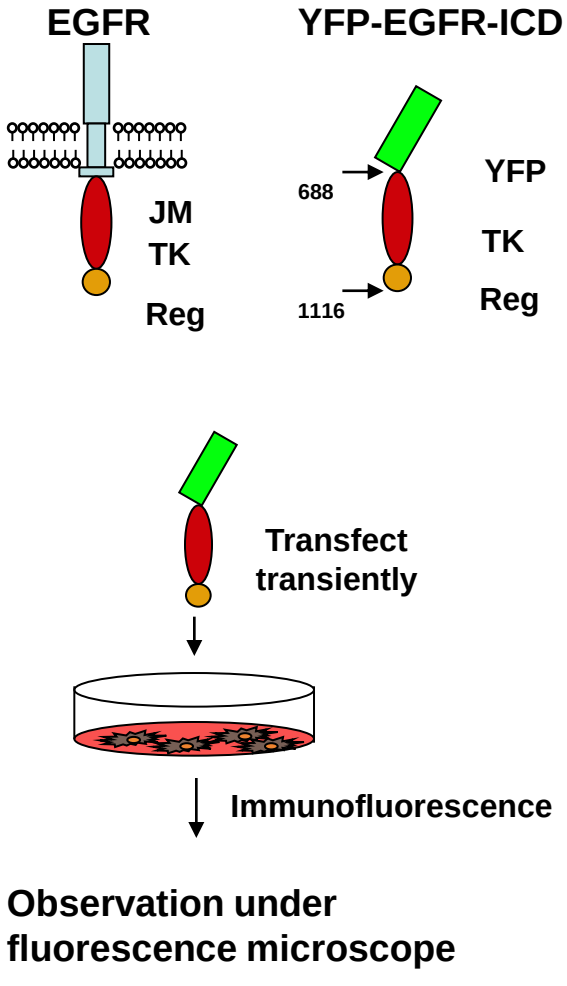
Patient number	*Gender*	*Histology*	*Age at diagnosis*	*Smoking history (PY)*	*Stage*	*EGFR mutation*	*EGFR (IHC)*	*KRAS mutation*	*Response to EGFR-TKI*
Non-smokers									
NS-001	Male	Ad	52	<1	IIIB	**N771GY**	WP	WT	PD
NS-002	Female	Ad	64	Never	IIIA	**L858R**	SP	WT	NA
NS-003	Male	Ad	50	Never	IV	**Del19**	NA	WT	PR
NS-004	Female	Ad	45	Never	IV	**WT**	NA	WT	PD
NS-005	Male	Ad	48	Never	IIIB	**767A–769V dup**	NA	WT	NA
NS-006	Male	Ad	49	Never	IV	**WT**	SP	WT	PD
NS-007	Female	Ad	71	Never	IV	**WT**	NA	WT	PR
NS-008	Female	Ad	58	Never	IV	**Del19**	NA	WT	PR
Smokers									
S-001	Female	NOS	54	30	IV	**WT**	WP	13 (GGC > GAC)	NA
S-002	Female	Ad	58	35	IV	**WT**	SP	WT	NA
S-003	Female	SCC	51	30	IB	**WT**	NA	WT	NA
S-004	Male	NOS	68	50	IV	**WT**	NA	WT	PD
S-005	Male	NOS	49	15	IV	**WT**	NA	WT	PD
S-006	Female	Ad	58	35	IV	**WT**	NA	WT	NA
S-007	Male	Ad	73	50	IIIB	**WT**	NA	NA	NA
S-008	Female	Ad	65	50	IIIB	**WT**	NA	12 (GGT > TGT)	NA

Harada T et al. Oncogene, 2010.

Mutated YFP-tagged EGFR intracellular domain activate the downstream signal

Harada T et al Oncogene 2010

A.



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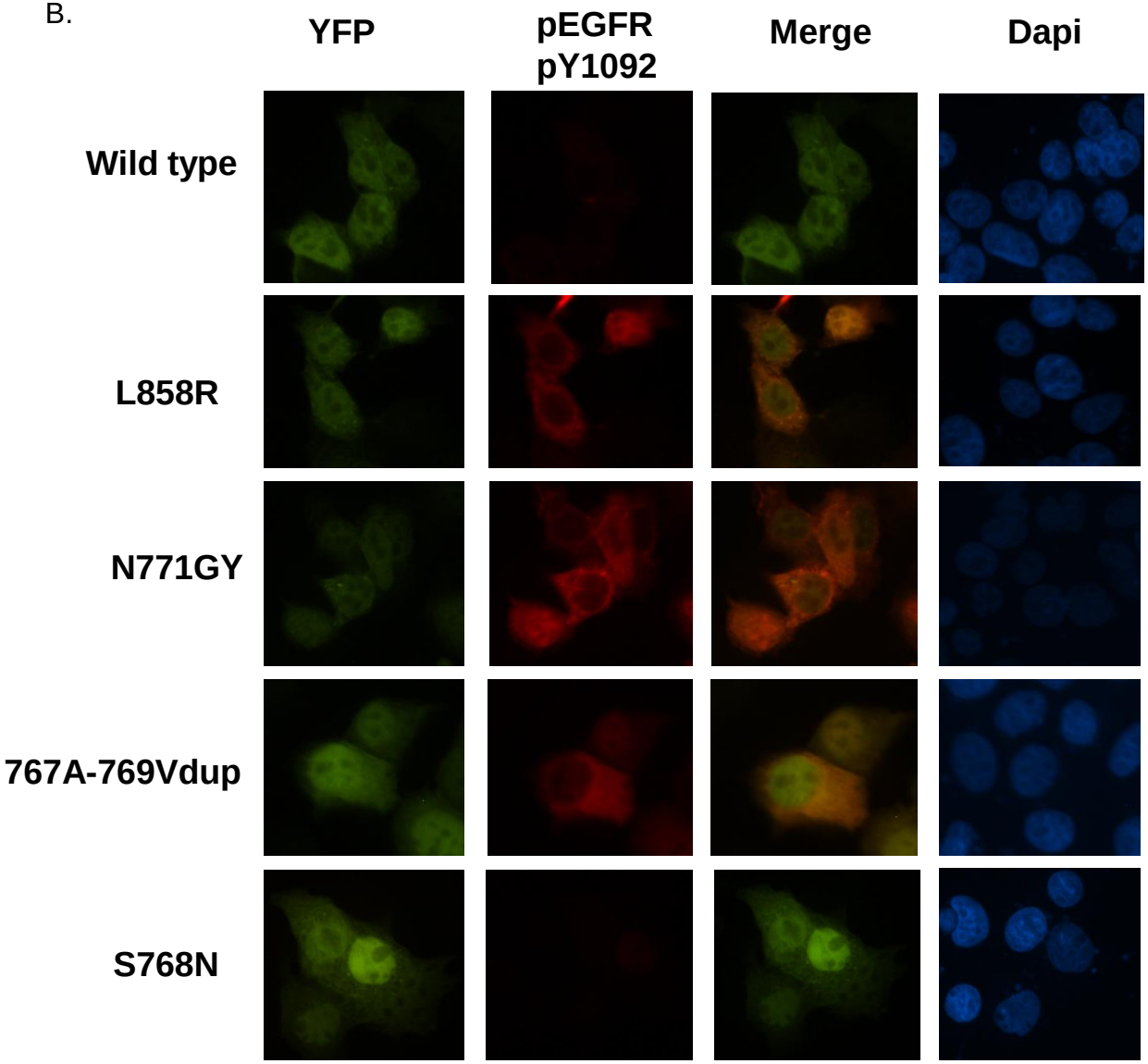
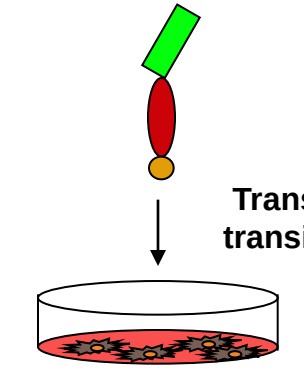
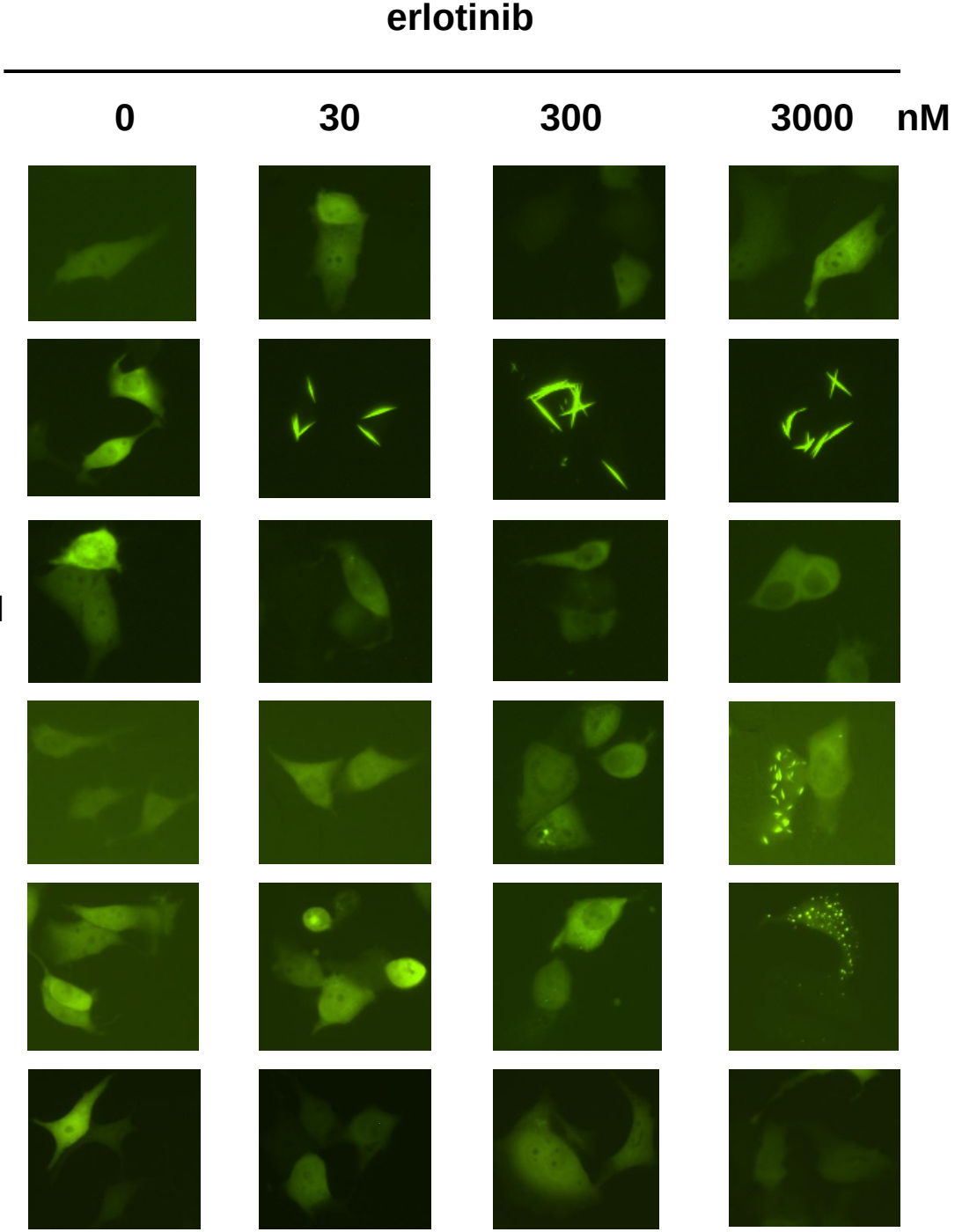


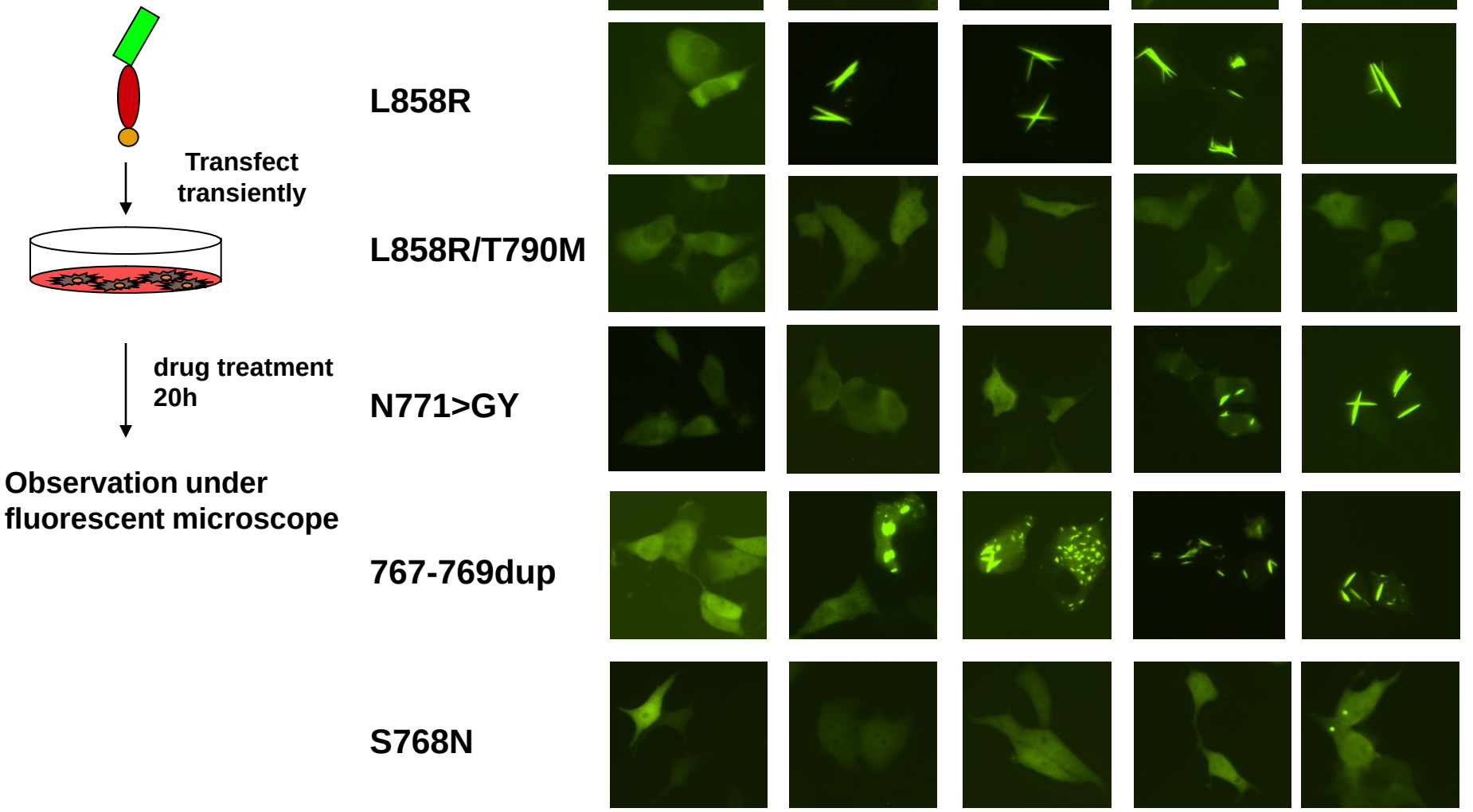


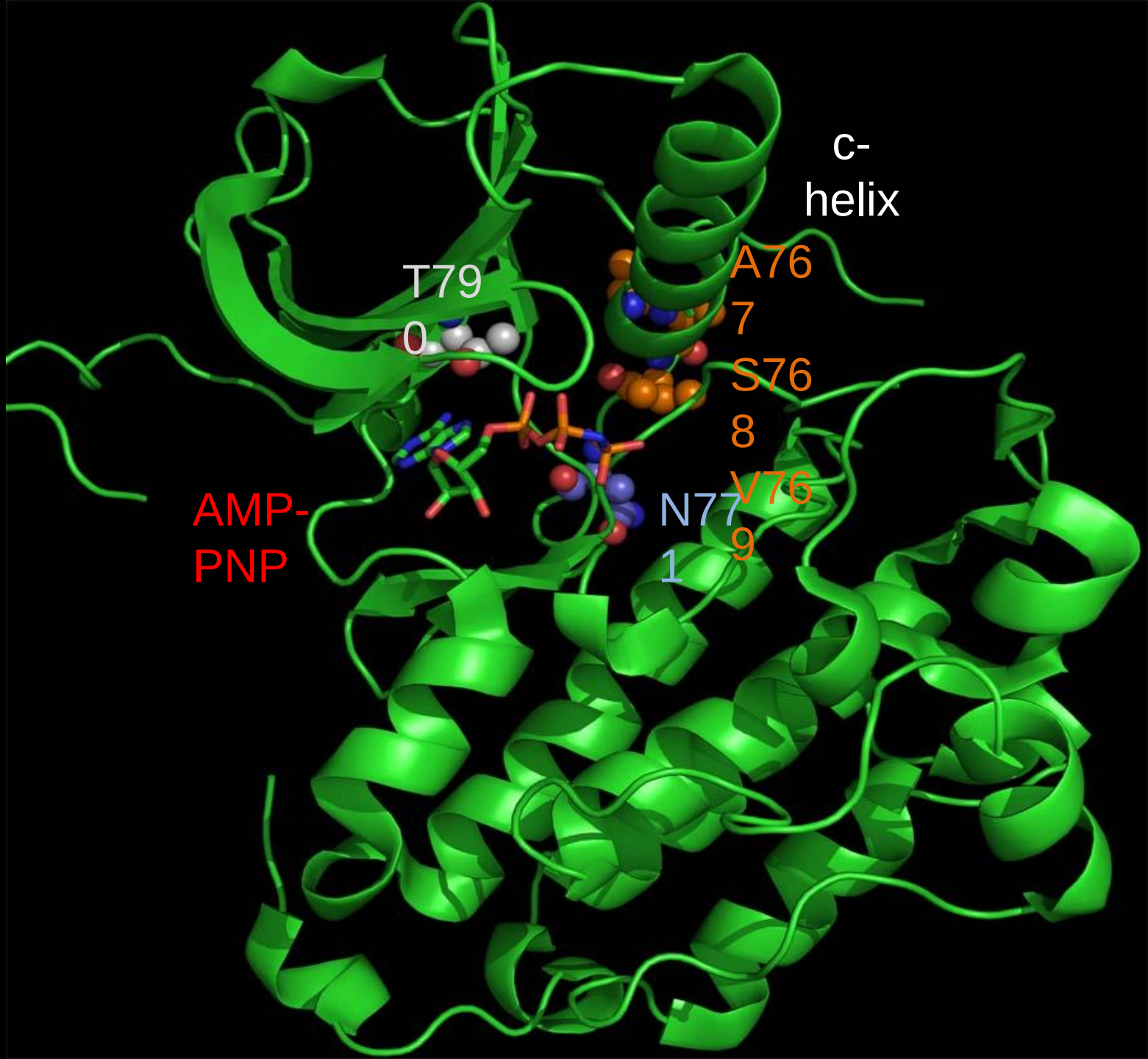
Transfect transiently

drug treatment 20h

Observation under fluorescent microscope




PF00299804
0
1
10
50
100
nM
Wild type
L858R
L858R/T790M
N771>GY
767-769dup
S768N
Transfect
transiently
drug treatment
20h
Observation under
fluorescent microscope


c-
helix
A76
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PNP
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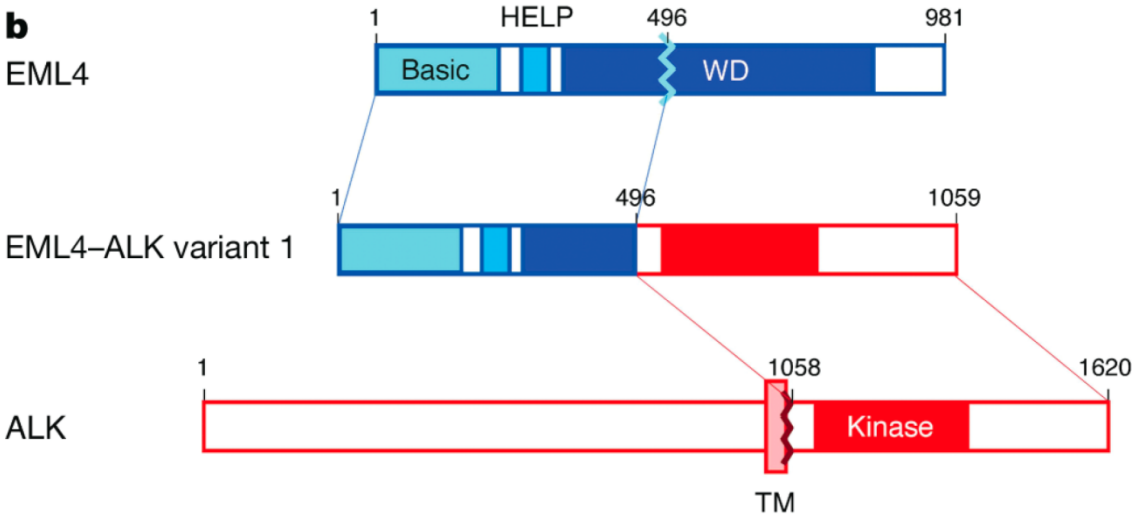
1

EML4-ALK Translocations in NSCLC

Vol 448|2 August 2007|doi:10.1038/nature05945 nature

Identification of the transforming *EML4–ALK* fusion gene in non-small-cell lung cancer

Manabu Soda[1,2], Young Lim Choi[1], Munehiro Enomoto[1,2], Shuji Takada[1], Yoshihiro Yamashita[1], Shunpei Ishikawa[5], Shin-ichiro Fujiwara[1], Hideki Watanabe[1], Kentaro Kurashina[1], Hisashi Hatanaka[1], Masashi Bando[2], Shoji Ohno[2], Yuichi Ishikawa[6], Hiroyuki Aburatani[5,7], Toshiro Niki[3], Yasunori Sohara[4], Yukihiko Sugiyama[2] & Hiroyuki Mano[1,7]



EML4-ALK frequency:

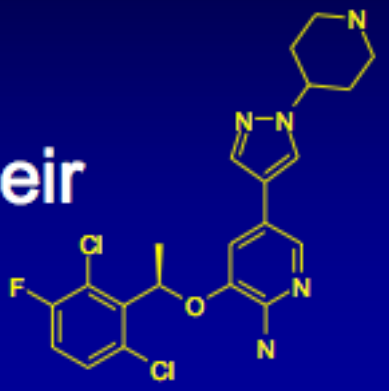
~4% (64/1709)

Primarily lung adenocarcinoma

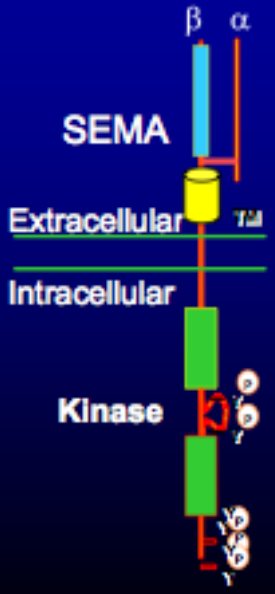
Soda et al., Nature 448: 561-566, 2007

PF-02341066

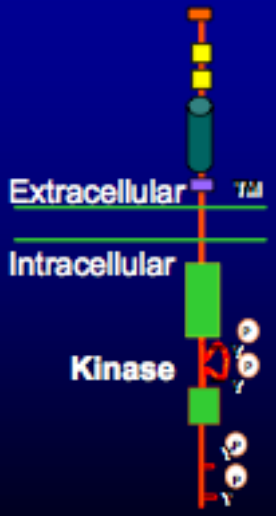
Potent & selective ATP competitive oral inhibitor of MET and ALK kinases and their oncogenic variants



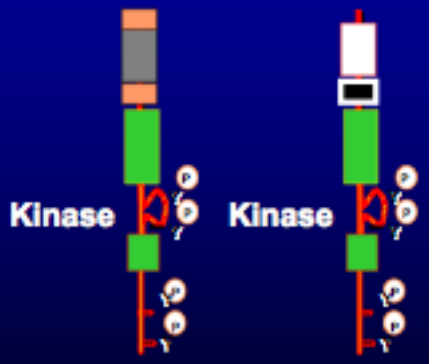
MET/HGFR



ALK



Cytoplasmic Fusion Variants of ALK



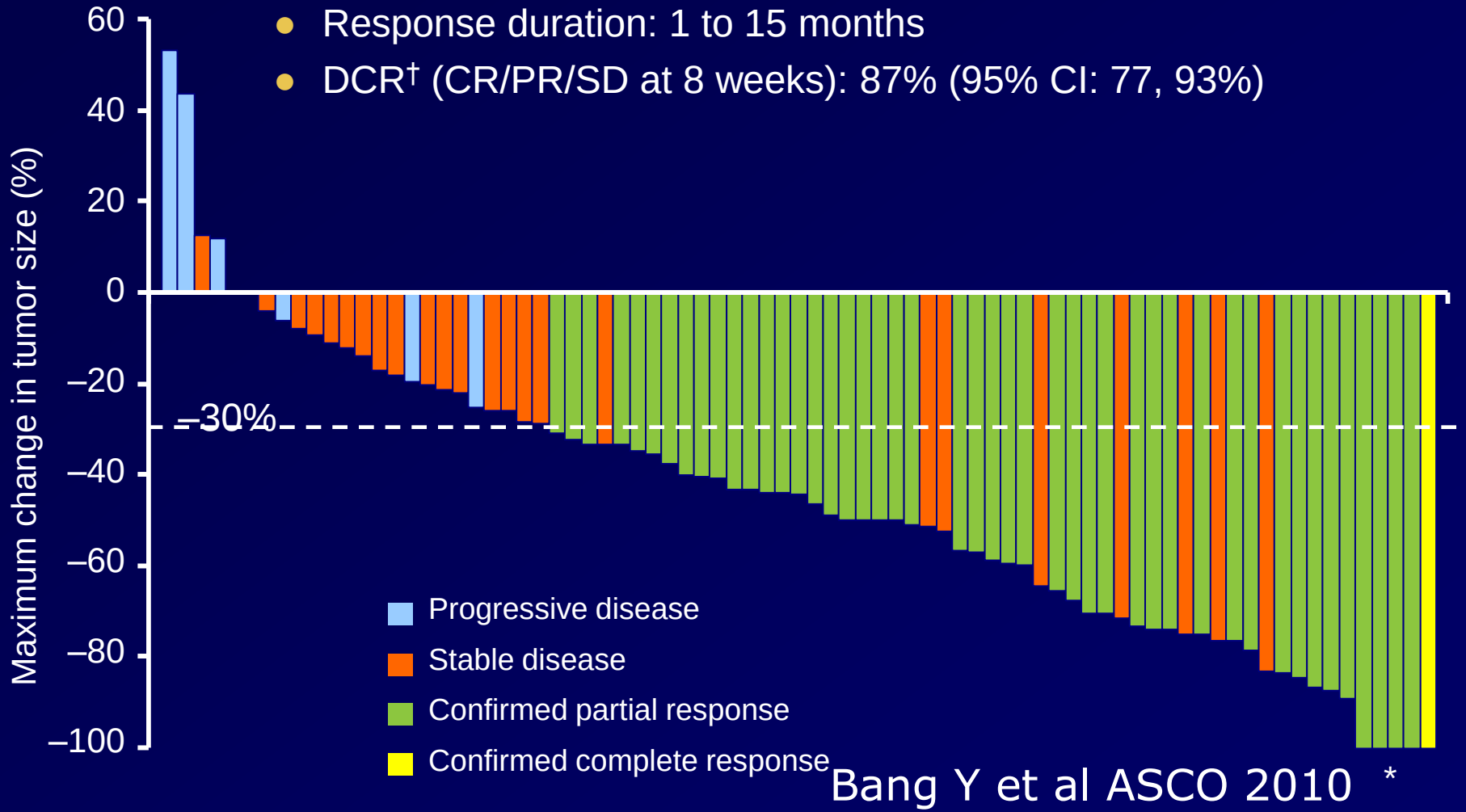
NPM-ALK EML4-ALK

Kinase	IC50 (nM) Mean	Selectivity Ratio[a]
c-Met	8	—
ALK	20	2X
RON	248	31X
Axl	308	39X
Tie-2	448	56X
Trk A	580	73X
Trk B	399	50X

PF2341066 was >100X selective for Met/ALK across a panel of 150 additional kinases.

Tumor Responses to Crizotinib for Patients with *ALK*-positive NSCLC

- Objective response rate : 57% (95% CI: 46, 68%)
- Response duration: 1 to 15 months
- DCR† (CR/PR/SD at 8 weeks): 87% (95% CI: 77, 93%)



Bang Y et al ASCO 2010 *

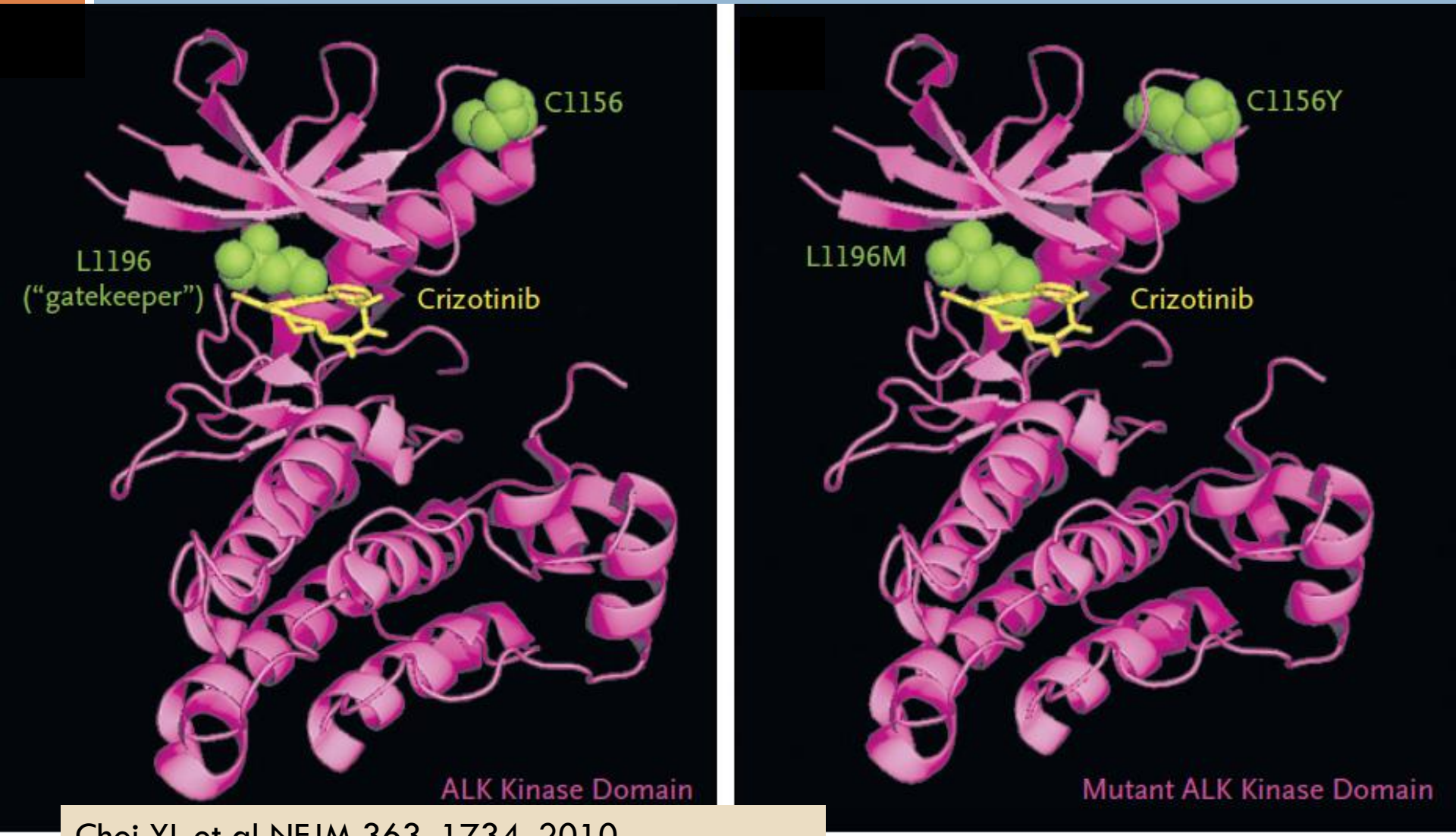
*Partial response patients with 100% change have non-target disease present

Main patient characteristics

- NSCLC screened = 1500
- NSCLC with Alk translocation = 82 + 2
- Male 52%
- White 56%, Asian 35%
- $\geq$ prior lines 41%
- Adenocarcinoma 96%
- Never-smoking 76%

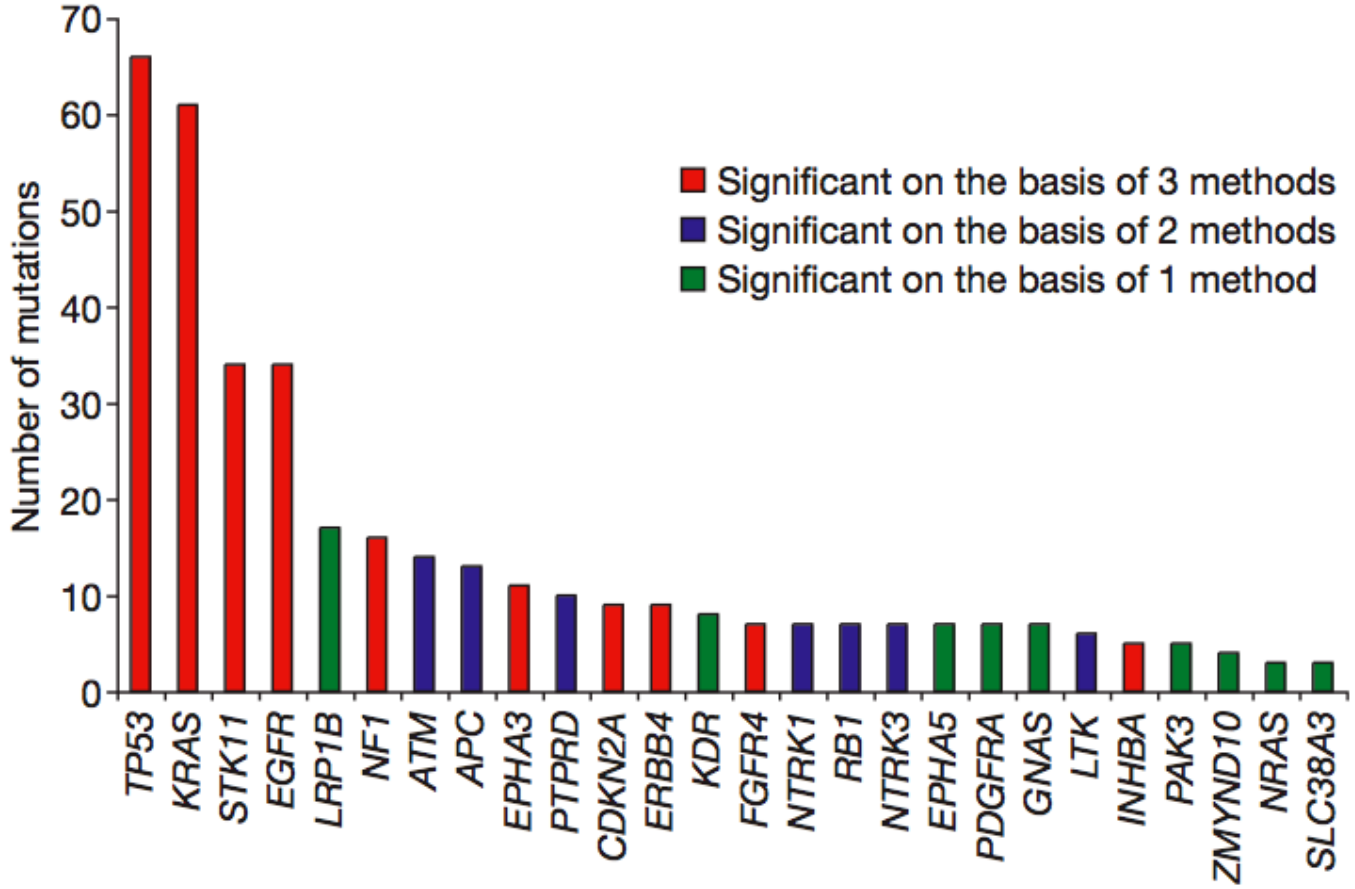
Kwak EL et al NEJM 363, 1693, 2010

Predicted Crystal Structure of the Kinase Domain of ALK and Resistant Mutants



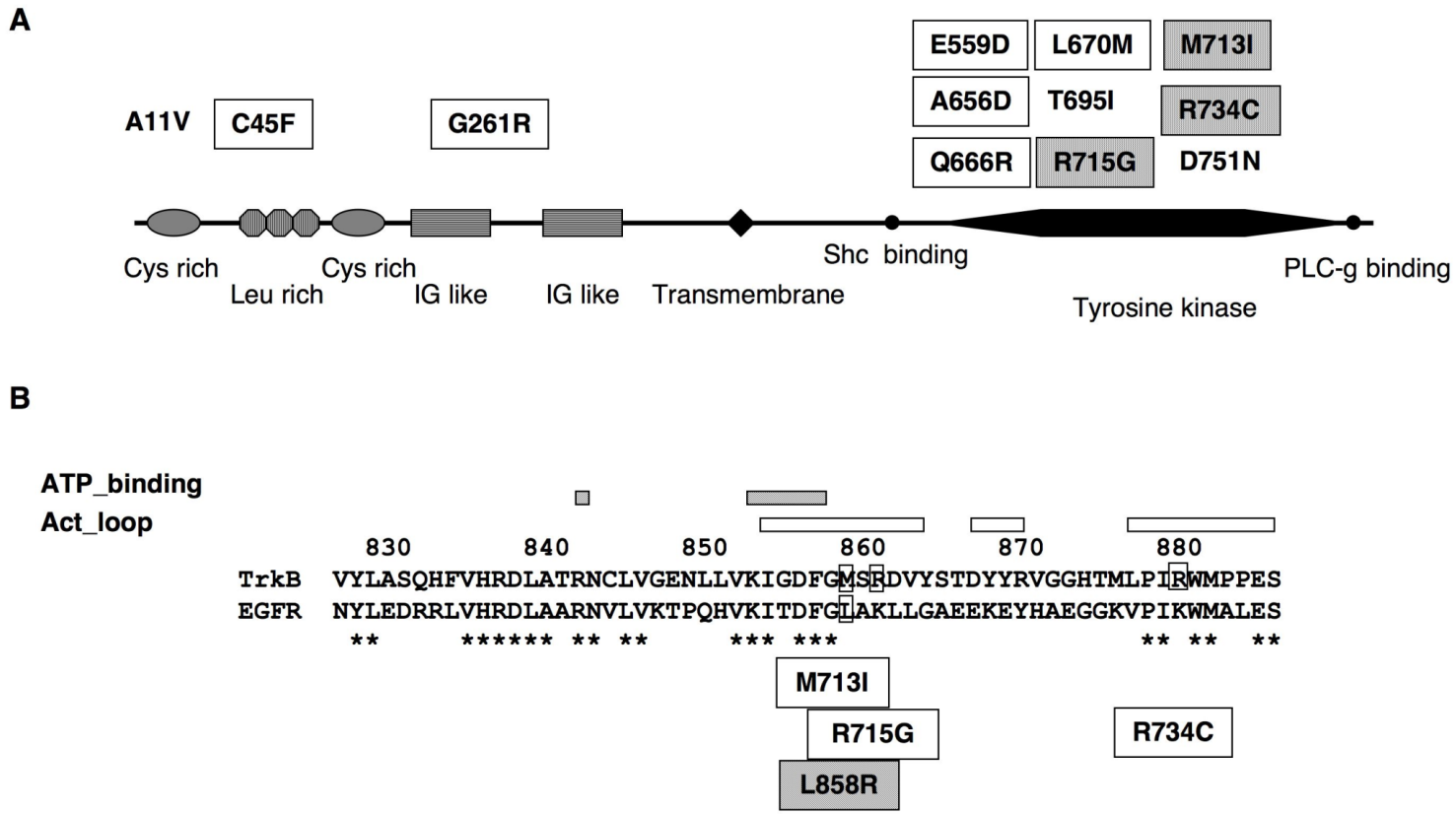
Choi YL et al NEJM 363, 1734, 2010

Significantly mutated genes in adenocarcinoma of the lung

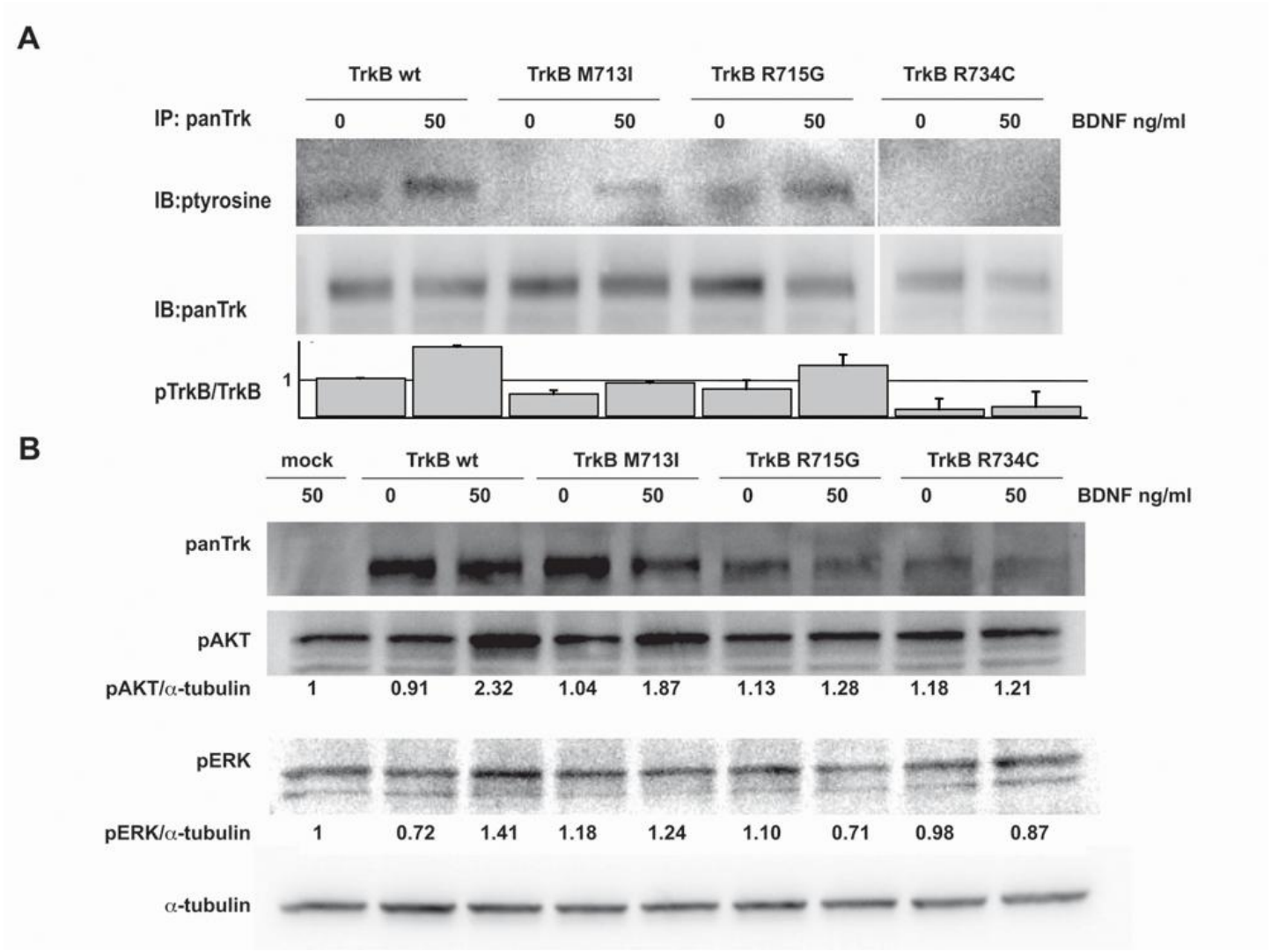


Ding et al. Nature 455, 1069, 2008

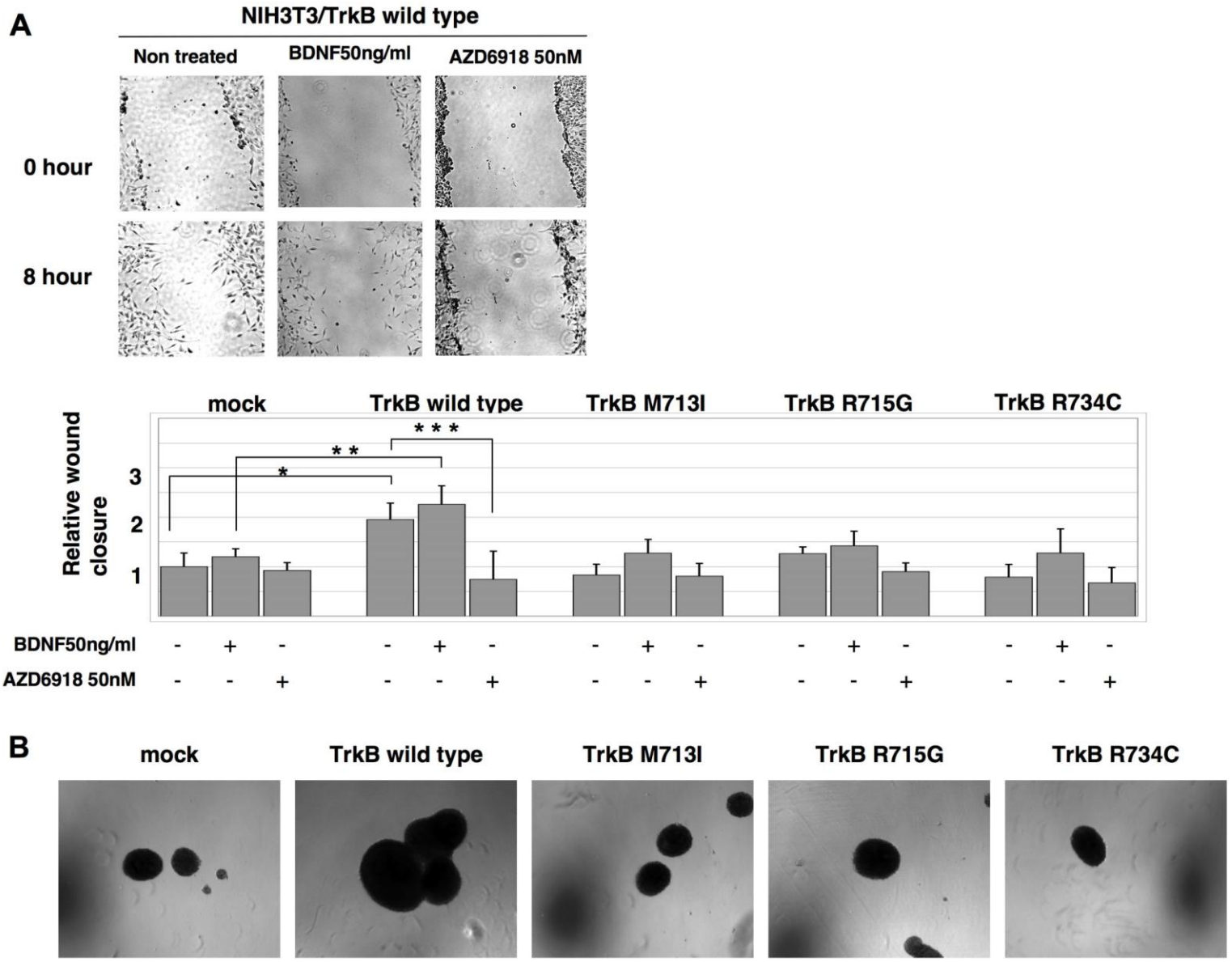
TRKB domain and reported mutations



TRKB in NIH3T3 transfected cells

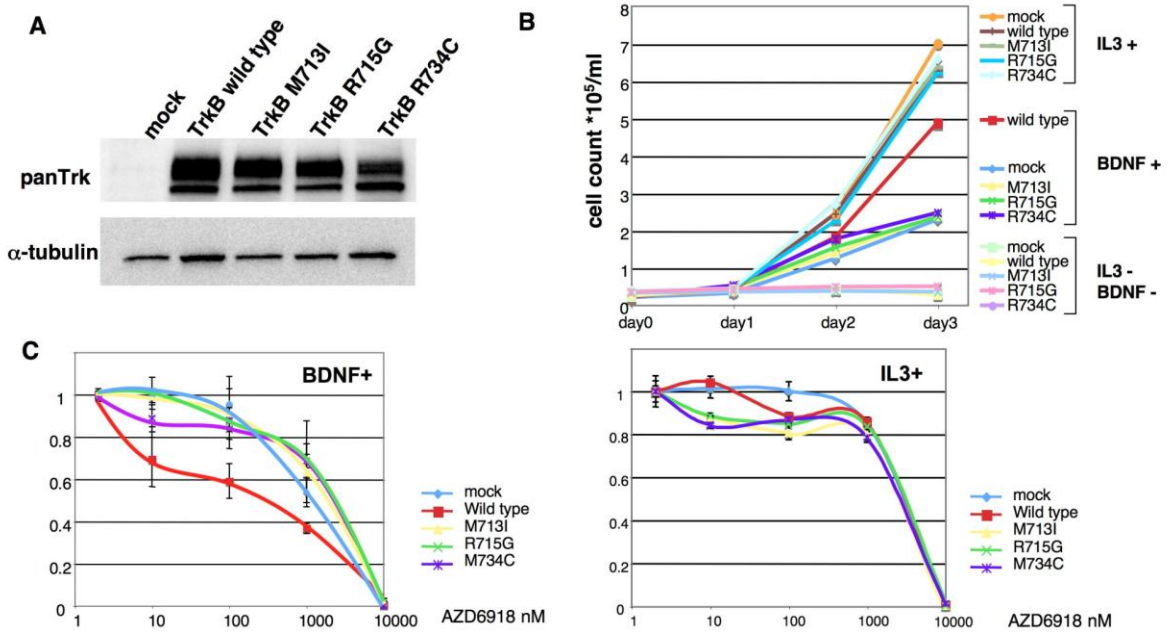


Cell migration and anchorage independent growth

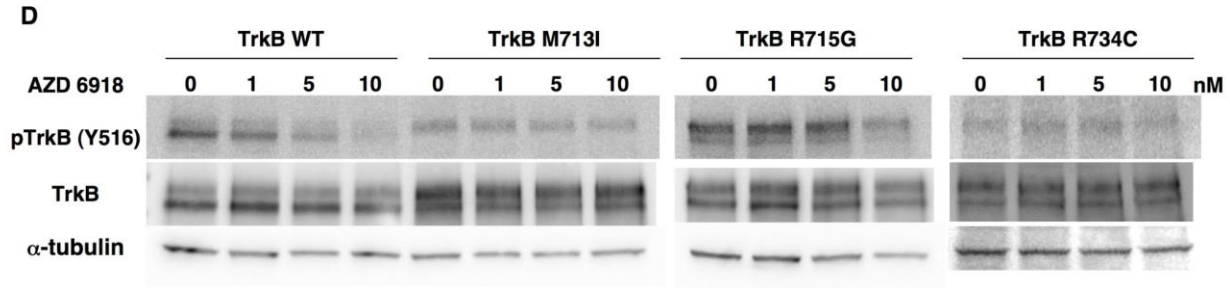


Functional characterization of TrkB

Baf3



MCF7



Summary of TRKB mutations in lung cancer

	Histology	Pt.No.	mutations	country
This study	ADC	17	ND	Asia
	LCNEC	28	ND	(Japan)
	SCLC	10	ND	
	ADC	12	ND	Europe
	SCC	6	ND	(Netherland)
	LCC	5	ND	
	Cell lines			
	ADC	17	ND	
	SCC	1	ND	
	LCC	3	ND	
	SCLC	8	ND	
	TC	1	ND	
Marchetti et al.	ADC	228	ND	Europe
	SCC	184	ND	(Italy)
	LCC	31	ND	
	LCNEC	29	4(13.8%)	
	SCLC	39	ND	
	TC	17	ND	
	AC	10	ND	
Ding et al.	ADC	188	6(3.2%)	USA
total	NSCLC(without cell lines)	728	10(1.39%)	
	SCLC(without cell lines)	49	ND	

ADC=adenocarcinoma; LCC=large cell carcinoma; LCNEC=large cell neuroendocrine carcinoma; SCC＝squamous cell carcinoma; SCLC=small cell carcinoma; TC=typical carcinoid; AC=atypical carcinoid; ND=not detected; NSCLC=non-small cell lung cancer

Harada et al. Clin Cancer Res (in press)

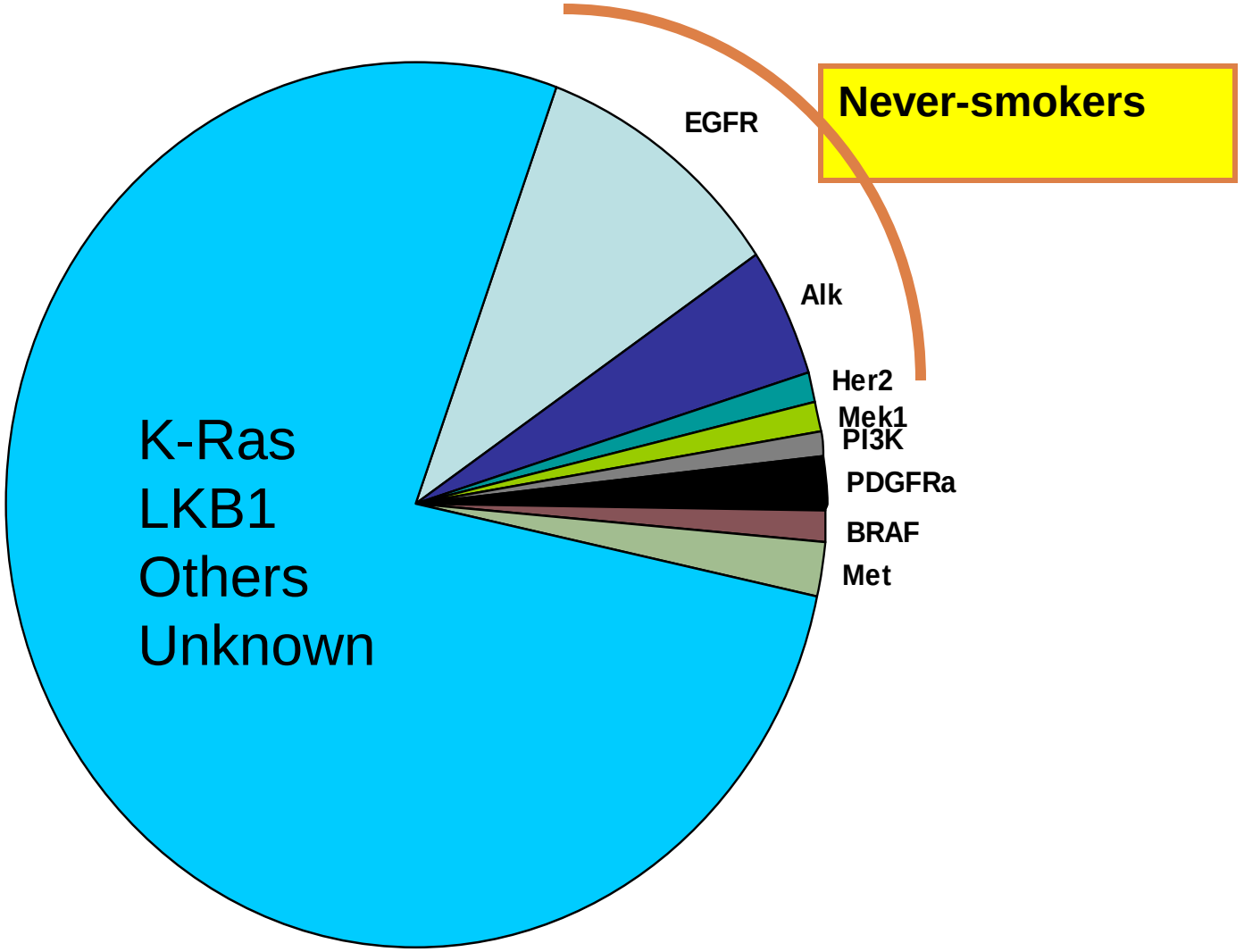
“Oncogene addiction” may explain clinical responses to many kinase-targeted therapeutics

Tumor type	Mutated/amplified kinase	Drug
NSCLC	EGFR	gefitinib/erlotinib
NSCLC	Alk	PF-02341066
CML	BCR-ABL	imatinib/dasatanib
GIST	c-Kit/PDGFR	imatinib/sunitinib
CMML	PDGFR-b	imatinib
Breast cancer	Her2	trastuzumab/lapatanib
Gastric cancer	c-MET	PHA-665752*
Gastric cancer	FGFR2	AZD2171*
Melanoma	B-Raf	PLX4032
Melanoma	Her4	lapatinib *
Basal cell carcinoma	PTCH1/SMO	GDC-0449

*Pre-clinical data only

”Addiction” to mutationally activated kinases can be faithfully modeled in cell culture.

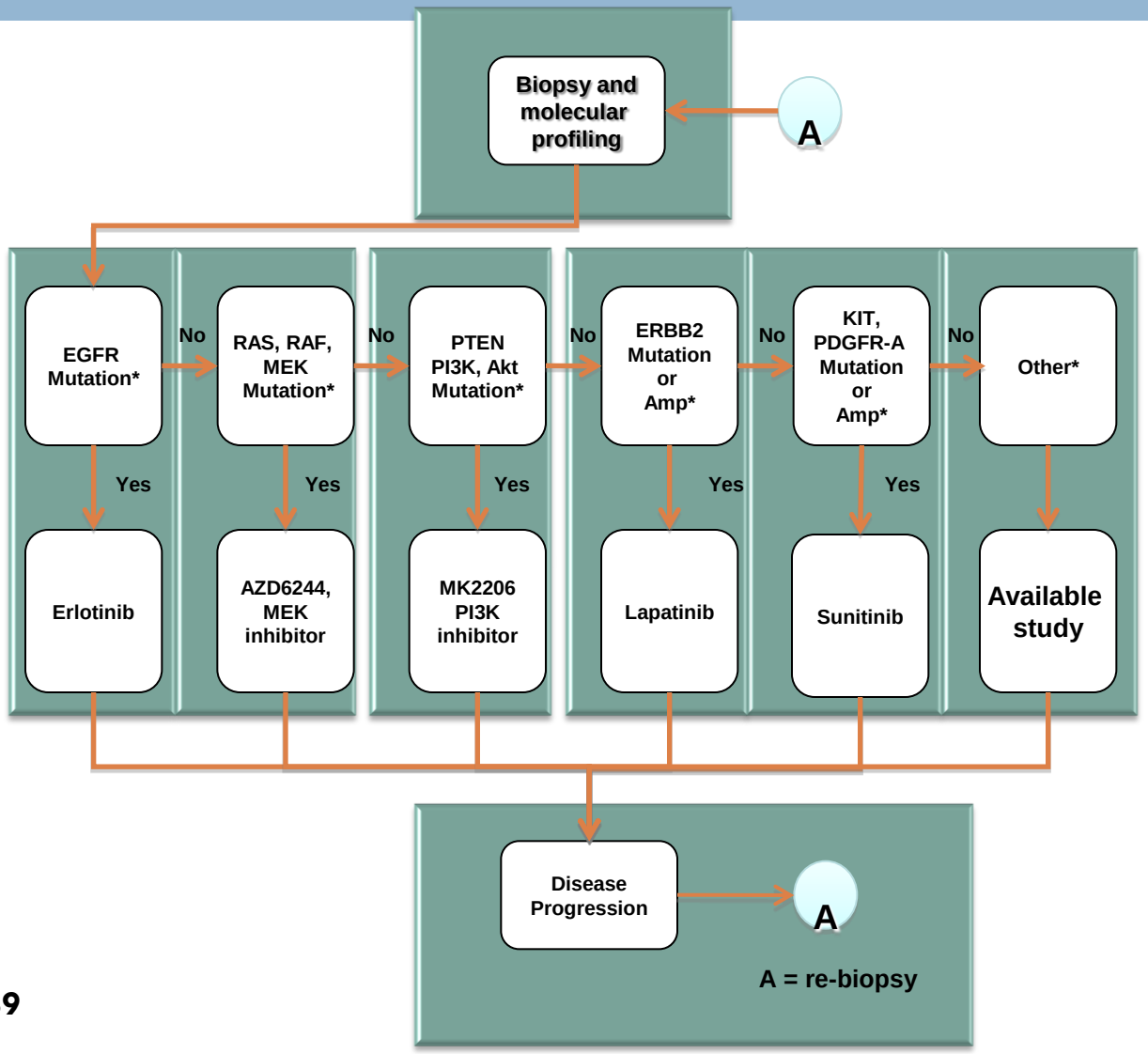
“Drugging” the genome in NSCLC



Molecularly Targeted Treatment of Advanced Thoracic Malignancies

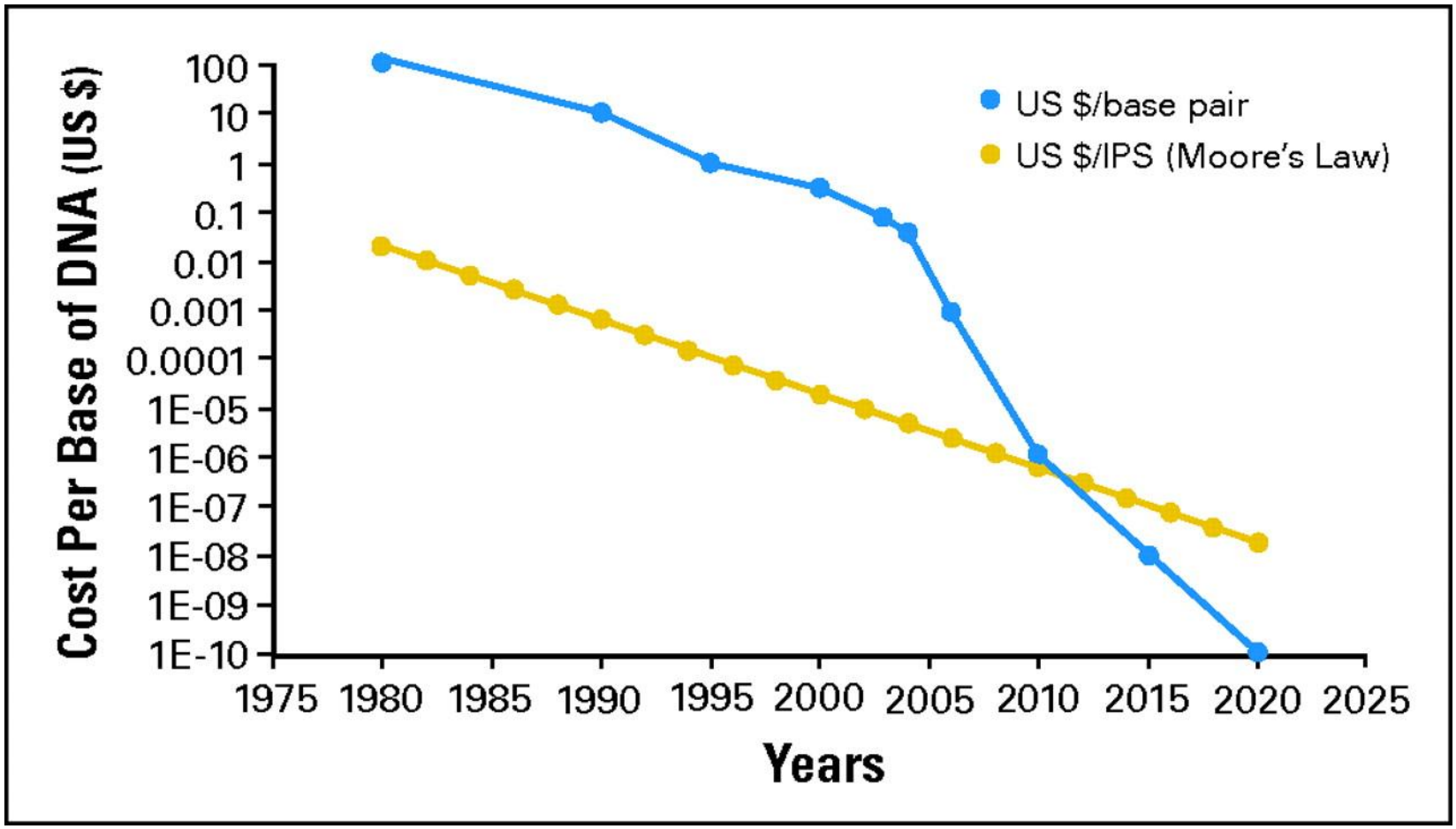
Patient selection:
Molecular +
NSCLC, SCLC and
thymic malignancies

Treatment:
Targeted therapies



NCI / CTEP protocol 8639

Advances in massively parallel technologies have dramatically reduced the cost of sequencing.



MacConaill L E , Garraway L A JCO 2010;28:5219-5228

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The Changing Landscape of Lung Cancer and its Treatment