L'innovazione tecnologica in farmacologia oncologica al servizio del paziente

CRIZOTINIB NELLA NEOPLASIA POLMONARE

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Recent advances in cancer biology

- The genomic map are redesigning the tumor taxonomy by moving from a histology to a genetic based level
- Somatic genetic alterations are legitimate targets for therapy
- Tumor specific DNA alterations represent highly sensitive biomarkers for disease detection and monitoring
- Tumor genotyping allows to individualize treatments by matching patients with the best treatment for their tumors

"Target and Control" **based on Biology**

CANCER

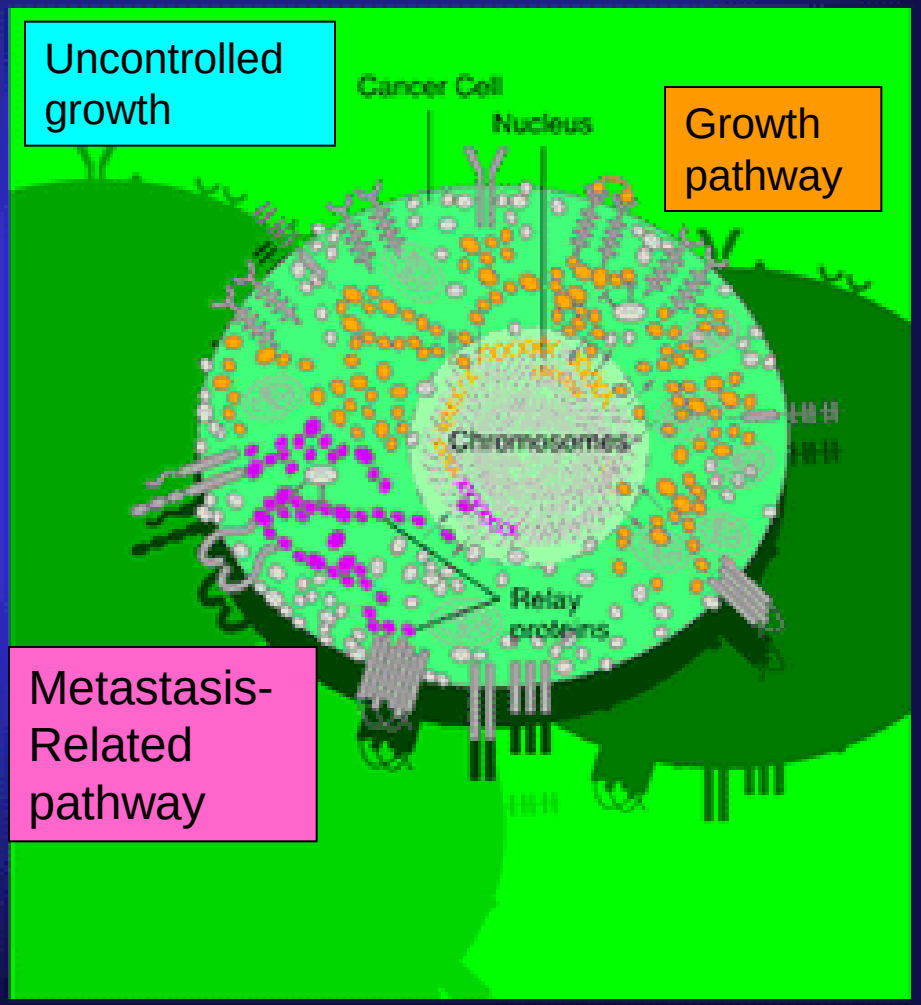
Discovery of:

Genetic

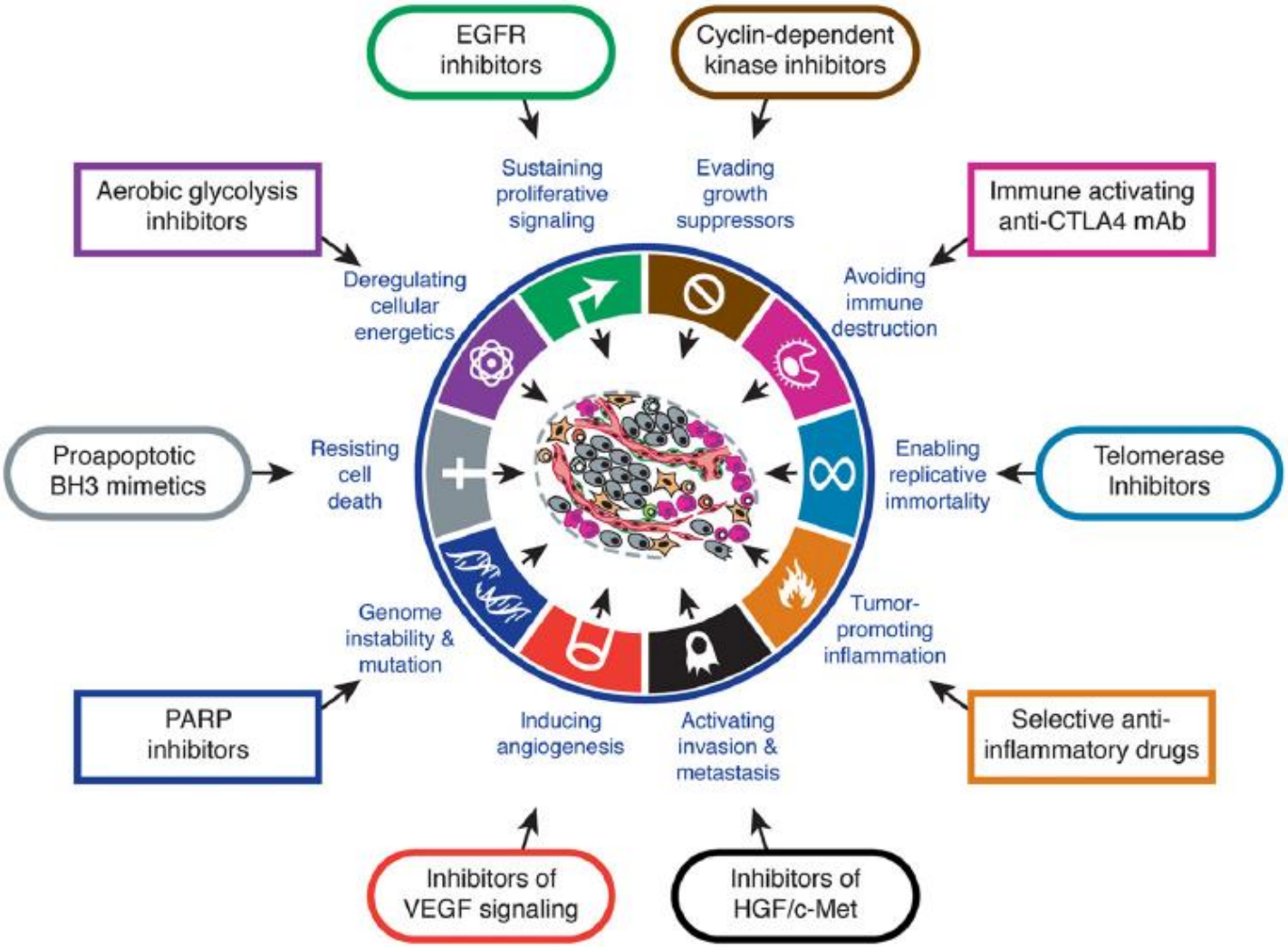
Molecular

Cellular

Mechanisms



Therapeutic targeting of the hallmarks of cancer

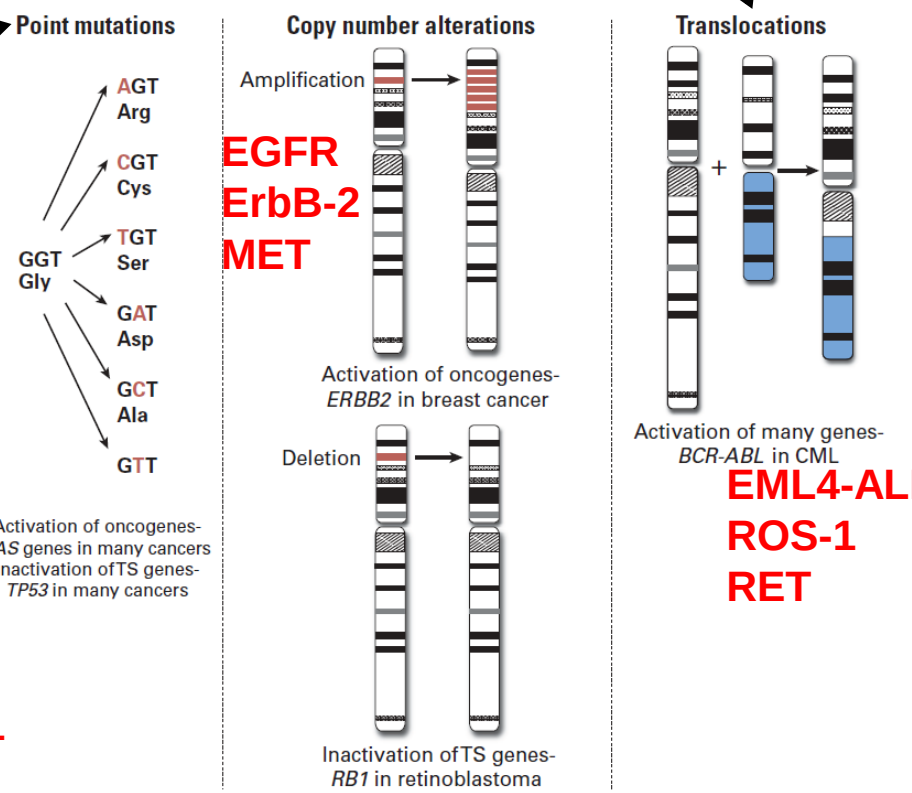


Hanahan D, Weinberg RA. Cell 2011; 144:646

The major classes of genomic alterations that give rise to cancer

FISH, Immunohistochemistry

Sequencing, Real Time PCR etc.

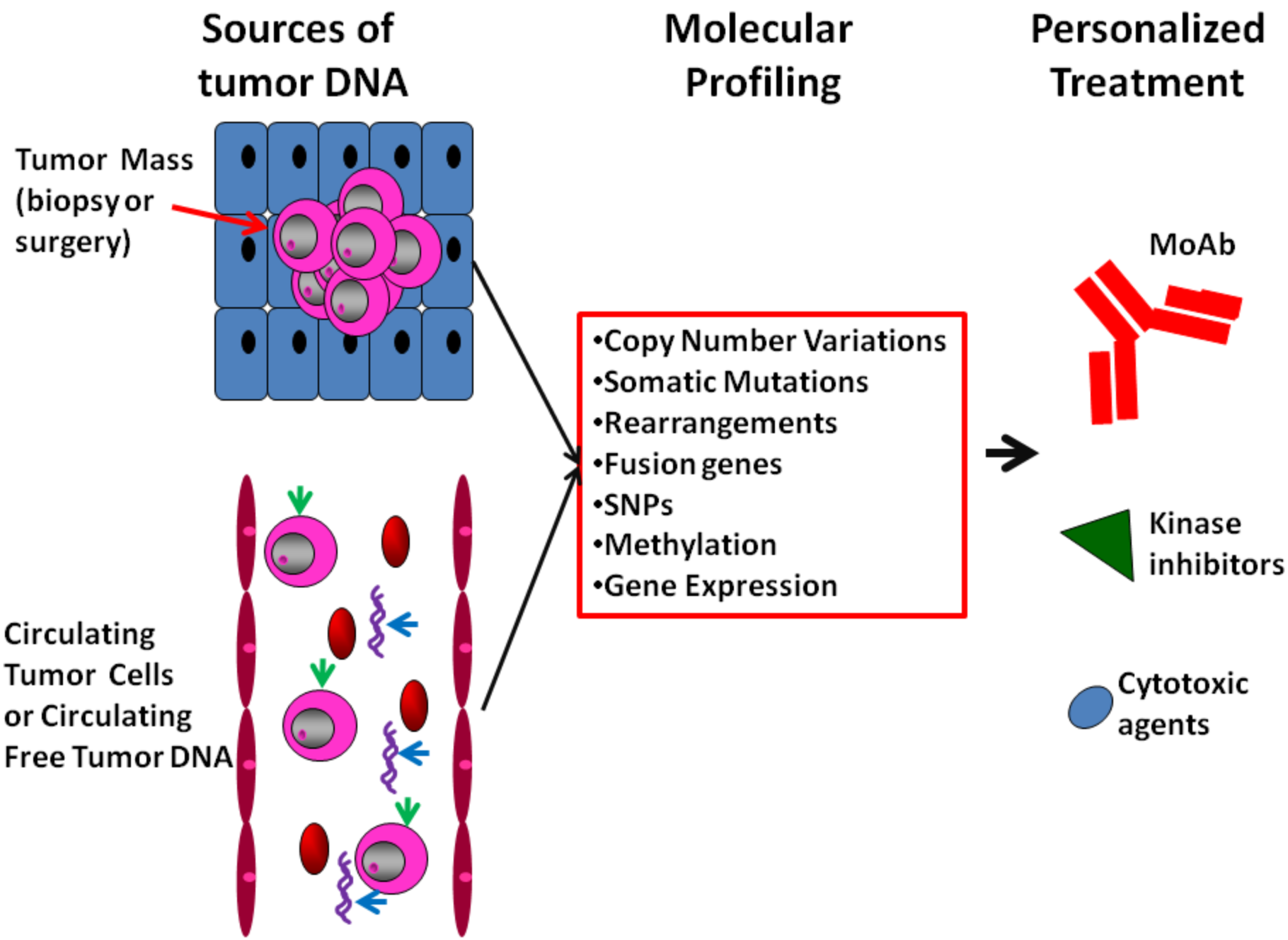


EGFR
ErbB-2
BRAF
PIK3CA
AKT1
MAP2K1

EGFR
ErbB-2
MET

EML4-ALK
ROS-1
RET

Modified from McConaill JCO 2010



Normanno J Cell Biochem 2012

ONCOGENE ADDICTION

Some cancers that contain multiple genetic, epigenetic and chromosomal abnormalities are dependent to one or a few genes for both maintenance of the malignant phenotype and cell survival

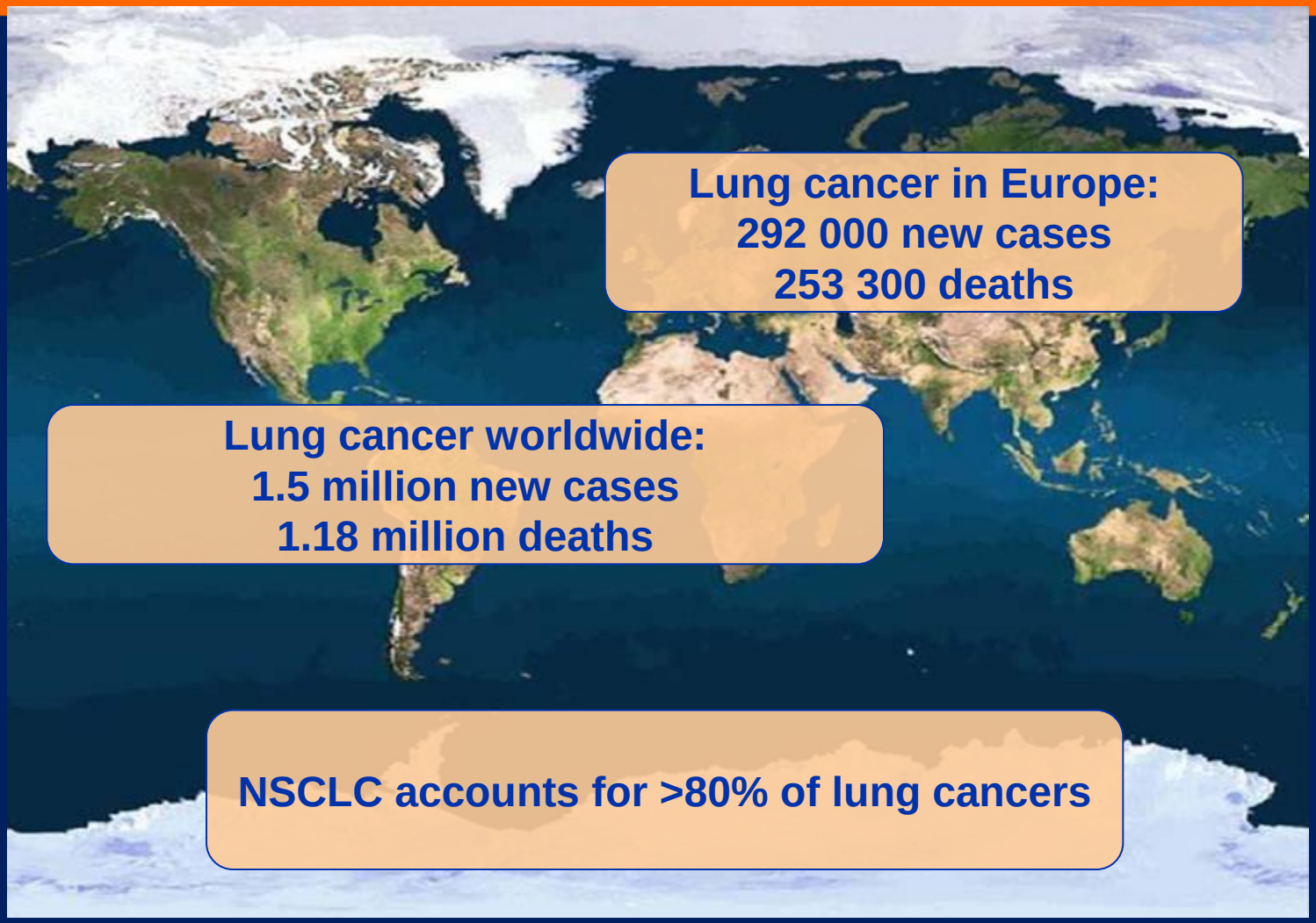
- **ERB-B2 in breast cancer**
- **EGFR in NSCLC**
- **EML4-ALK in NSCLC**
- **ROS1 in NSCLC**
- **BRAF in NSCLC and melanoma-KIT in GIST**
- **RET in medullary thyroid cancer**
- **RET in NSCLC**
- **HIF/VEGF in renal cancer**

Weinstein Science, 2002

WORLDWIDE APPROVED MOLECULAR DRUGS FOR CLINICAL PRACTICE

Targets	Diseases	Drugs
EGFR	Lung adenocr.	Gefitinib Erlotinib
C-KIT	LMC – GIST	Imatinib
ALK-Translocation ROS Rearrangement	Lung adenocr.	Crizotinib
B-RAF	Melanoma Lung adenocr.	Vemurafenib
HER-B2	Breast cancer Gastric cancer Lung adenocr.	Trastuzumab
VEGF-R	Lung, colorectal, ovarian, breast, gliomas and renal cancers	Bevacizumab Sorafenib Sunitinib
RET	Thyroid cancer	Vandetanib

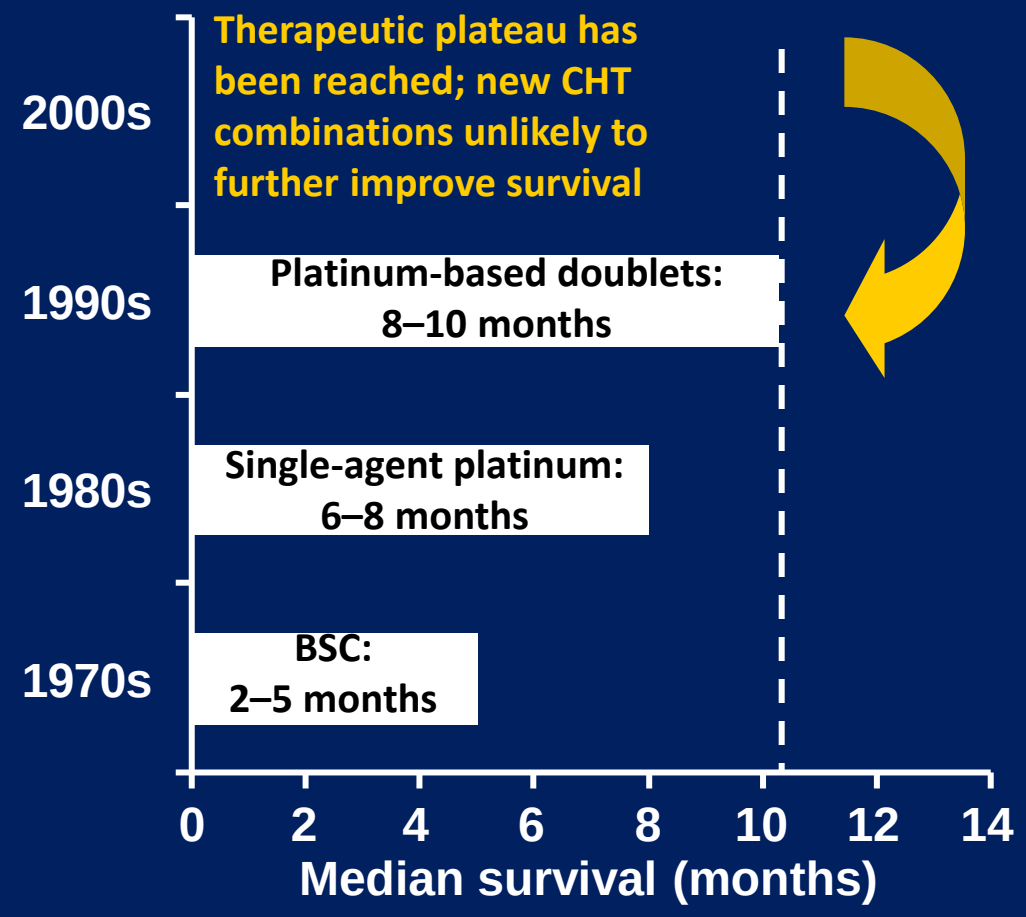
The burden of NSCLC



Parkin D, et al. CA Cancer J Clin 2005;55:74–108; Ferlay J, et al. Ann Oncol 2007;18:581–592

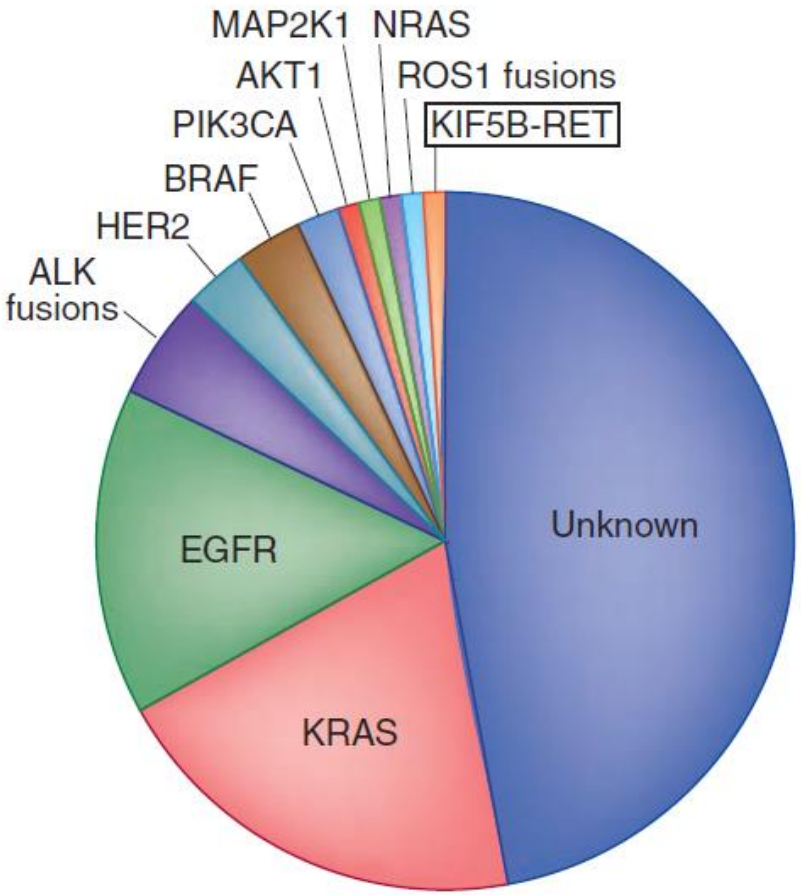
‘Longer life’ . . . are we meeting the objective?

Chemotherapy combinations have failed to substantially improve median OS beyond 8–10 months



Schiller, et al. NEJM 2002
Sandler, et al. NEJM 2006

Molecular subsets of lung adenocarcinoma



Pao & Hutchinson Nat Med 2012

Pioneers and milestones: evidence that EGFR is important in NSCLC biology

1980

Isolation of human EGF receptor (EGFR) by Stanley Cohen

Cohen S, et al. J Biol Chem 1980

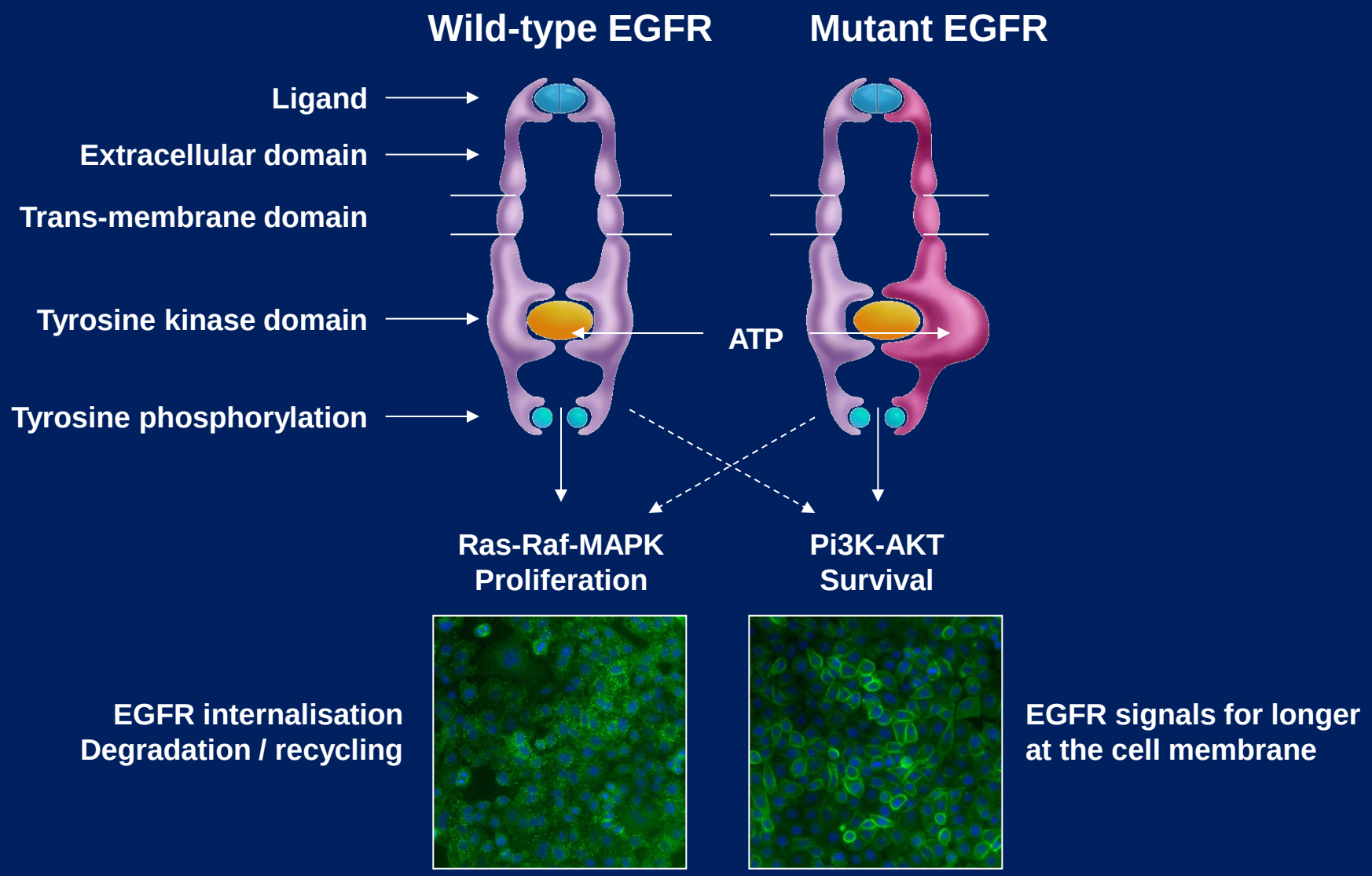
1984

Human EGFR gene cloned and sequenced

Ullrich A, et al. Nature 1984

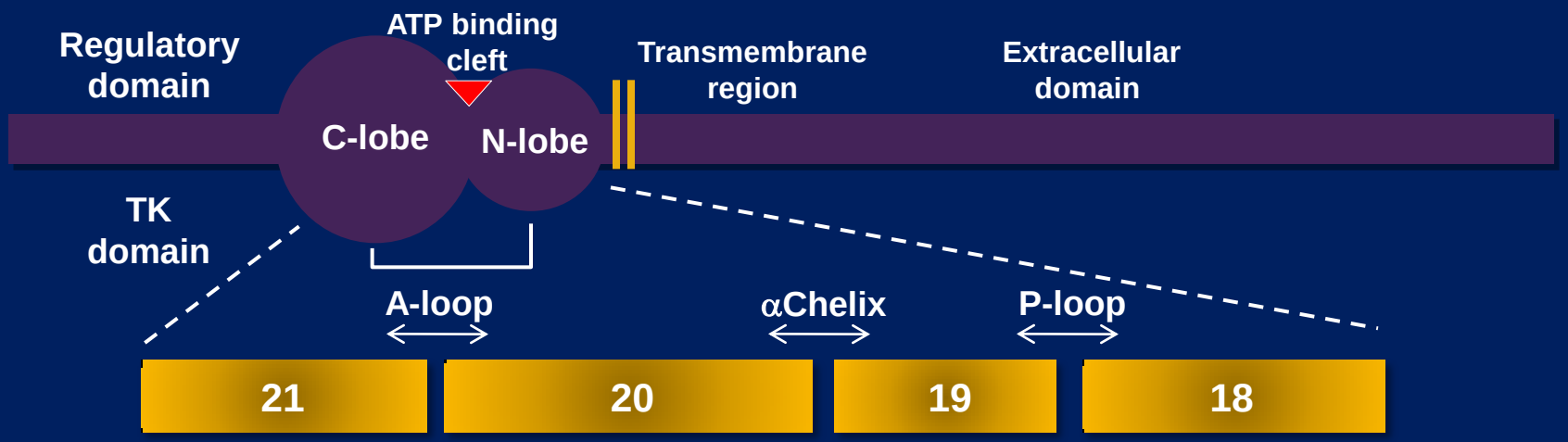
1930 1940 1950 1960 1970 1980 1990 2000 2010

EGFR mutation causes conformational change and increased activation



Arteaga 2006; Gadzar et al 2004; Hendricks et al 2006; Sordella et al 2004

Common mutation sites in the EGFR gene



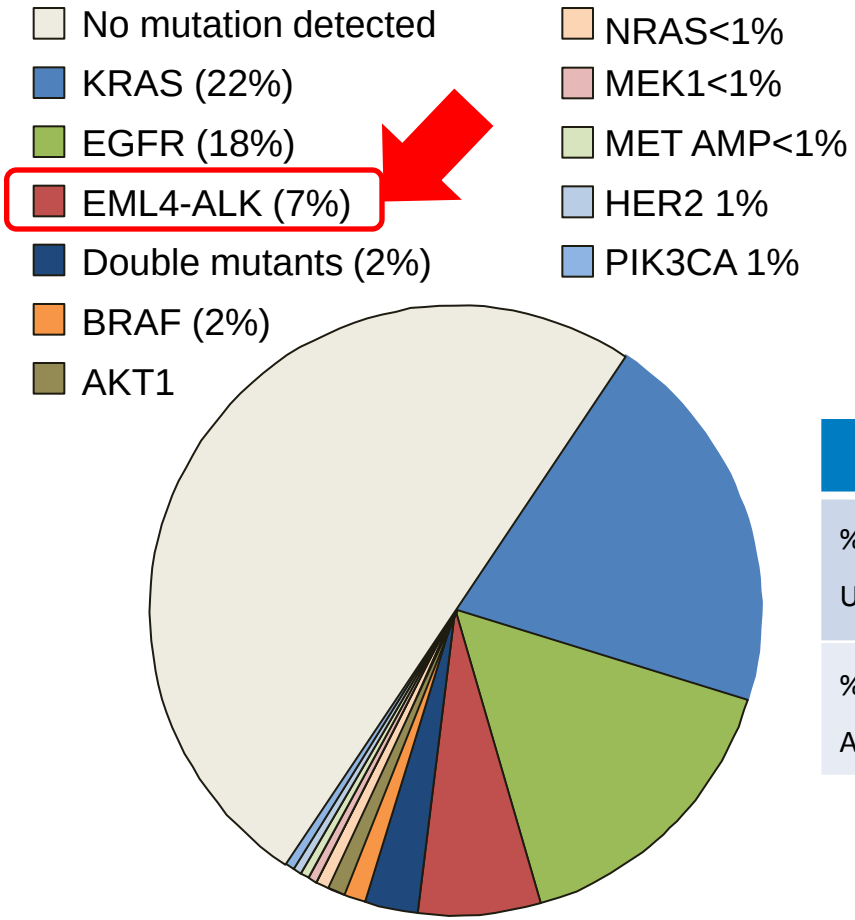
Lynch et al, 2004; Paez et al 2004

EGFR-TKI vs. chemotherapy for *EGFR*-mutant NSCLC

Study	EGFR-TKI	*EGFR* mut	Population	RR (EGFR-TKI vs chemo)	PFS (EGFR-TKI vs chemo)
WTOG 3405 (N=172)	Gefitinib	del 19 or L858R	Asiatic	62.1% vs. 32.2% *P*<.0001	9.2 vs. 6.3 months *P*<.0001 – HR=0.48
NEJ002 (N=224)	Gefitinib	All	Asiatic	73.7% vs. 30.7% *P*<.001	10.8 vs. 5.4 P<.001 – HR=0.32
OPTIMAL (N=154)	Erlotinib	del 19 or L858R	Asiatic	83% vs. 36% *P*<.0001	13.1 vs. 4.6 months *P*<.0001 – HR=0.16
EURTAC (N=173)	Erlotinib	del 19 or L858R	Caucasian	63.6% vs. 17.8% *P*<.0001	9.7 vs. 5.2 months *P*<.0001 – HR=0.37
LUX-Lung 3 (N=345) *72% Asiatic	Afatinib	All	Mixed*	56.1% vs. 22.6% *P*<.001	11.1 vs. 6.9 months *P*=.0004 – HR=0.58

WTOG 3405: Mitsudomi, et al. Lancet Oncol 2010
NEJ002: Maemondo, et al. NEJM 2010; Inoue, et al. ASCO 2012
OPTIMAL: Zhou, et al. Lancet Oncol 2011
EURTAC: Rosell et al. Lancet Oncol 2012
LUX-Lung 3: Yang, et al. ASCO 2012

Status of Actionable Driver Mutations in Lung Adenocarcinoma Tumor Specimens



Alk Fusion Prevalence in NSCLC: Retrospective Data

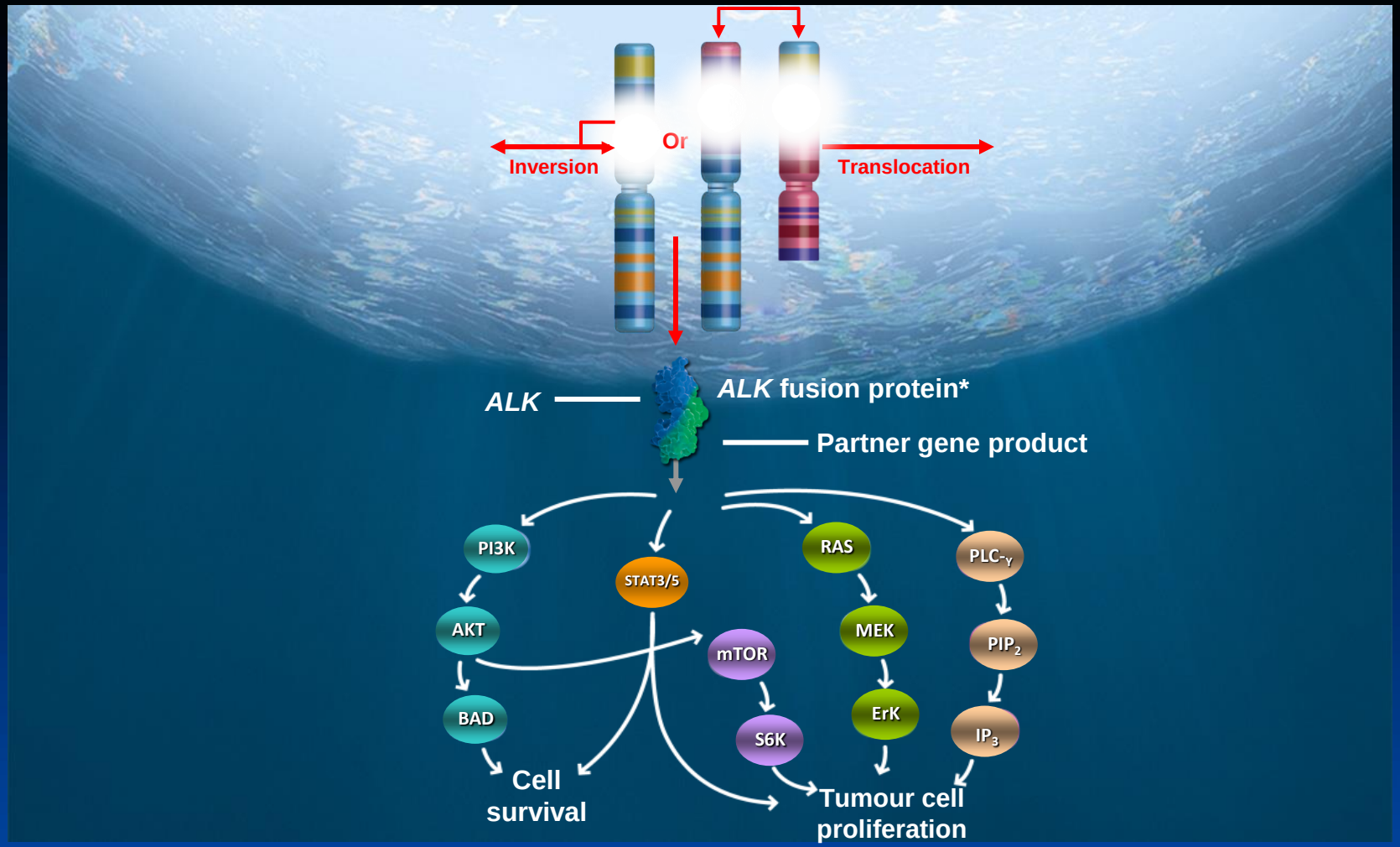
	RT-PCR	FISH	IHC
% *ALK*+ patients Unselected	1.6%[1] - 4.9%[2]	2.7%[3] - 4.2%[4]	1.7%[5] - 8.6%[6]
% *ALK*+ patients Adenocarcinoma	2.4%[7] - 4.9%[2]	5.6%[8]	2.7%[5]

[1]Takahashi, et al. 2010. [2]Wong, et al. 2009. [3]Perner, et al. 2008. [4]Paik, et al. 2011. [5]Boland, et al. 2009. [6]Paik, et al 2011. [7]Takahashi, et al. 2010. [8]Rodig, et al. 2009.

Johnson D, et al. ECCO ESMO 2011. Abstract 9018.

See alternative slide in back-up (slide 28)

ALK Pathway



*Subcellular localisation of the *ALK* fusion gene, while likely to occur in the cytoplasm, is not confirmed.[1,2]

BAD, BCL2-associated agonist of death; STAT3, signal transducer and activator of transcription 3; S6K, ribosome protein S6 kinase; ERK, extracellular signal-regulated kinase.

[1]Inamura K, et al. *J Thorac Oncol.* 2008;3:13–17. [2]Soda M, et al. *Proc Natl Acad Sci. U S A.* 2008;105:19893–97.

Figure based on: Chiarle R, et al. *Nat Rev Cancer.* 2008;8(1):11–23. Mossé YP, et al. *Clin Cancer Res.* 2009;15(18):5609–14; and Pfizer Inc, data on file.

Clinical Features of NSCLC Patients with EML4/ALK Fusion*

EML4/ALK+	Med. Age	Male	Female	Never** Smoker	Smoker†	Adeno‡	Non-Adeno
129/3933 (3.3%)	59 (29-79)	56/1451 3.9%	51/1017 5.0%	83/762 10.8%	36/1534 2.3%	118/2168 5.4%	8/870 0.9%

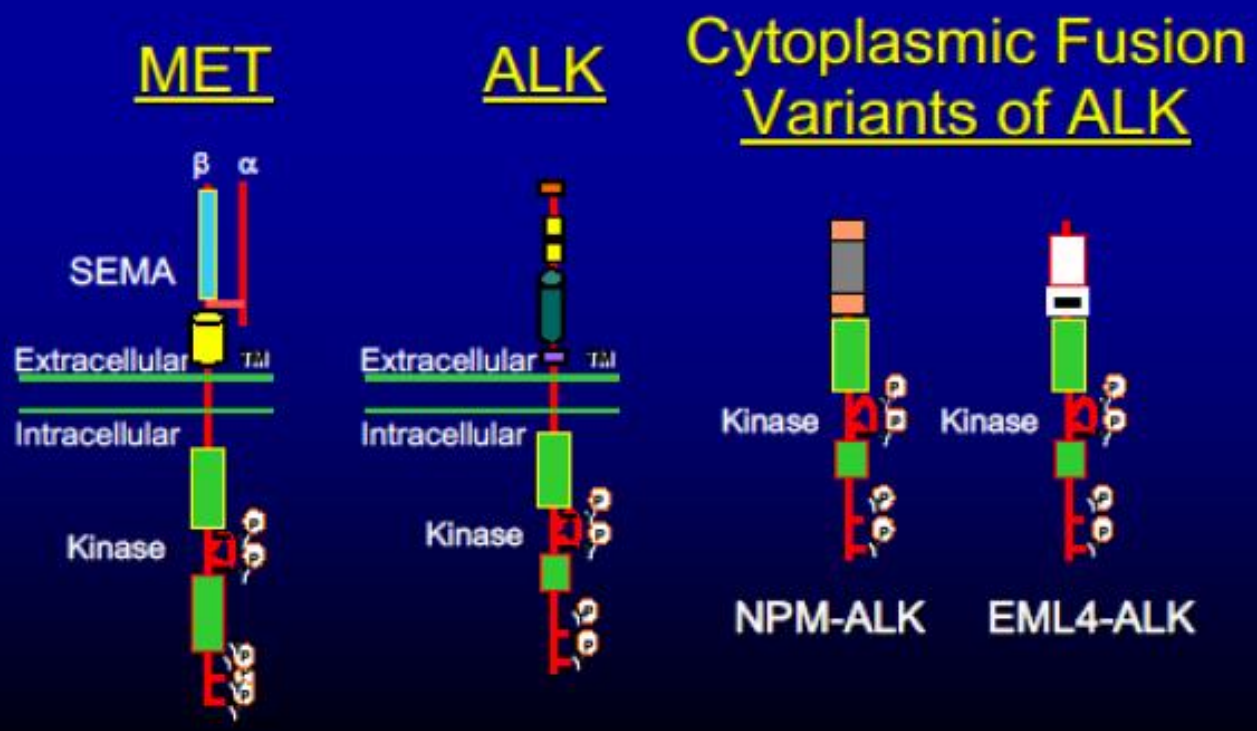
*From 14 literature studies. **includes never and light smokers. †includes current and former smokers. ‡includes all subtypes and adenosquamous

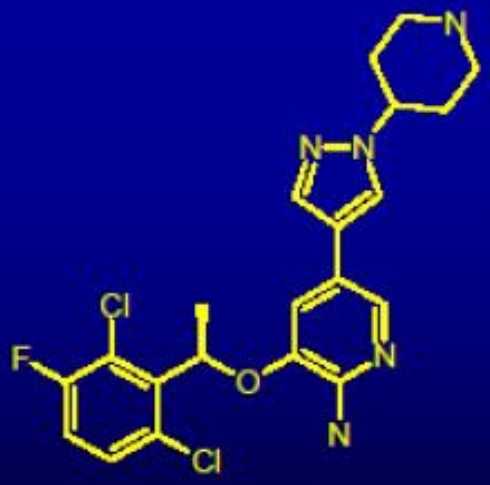
Conclusions:

- Median age is low but cannot order based on age.
- Frequency equivalent by sex, ethnicity and stage.
- More common in adenocarcinoma histology but occurs in squamous.
- More common in never/light smokers but may occur in smokers.

Crizotinib, PF-02341066

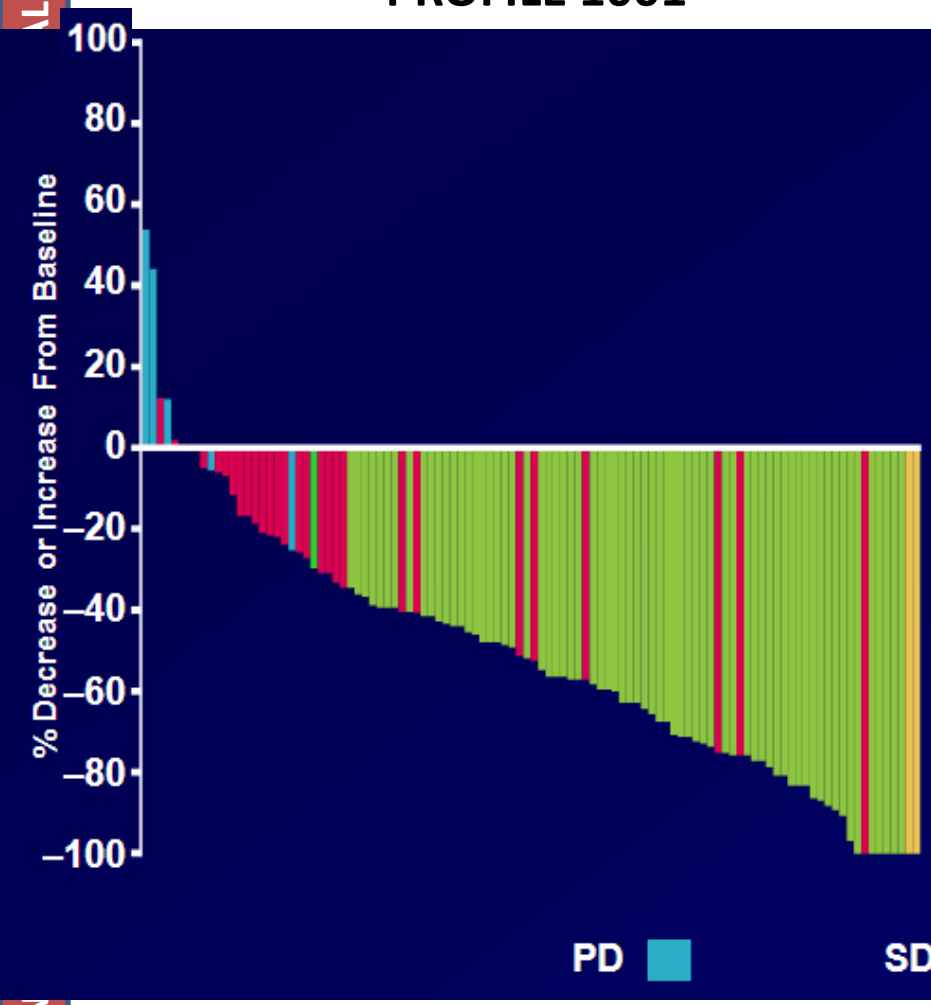
Potent & selective ATP competitive oral inhibitor of MET and ALK kinases and their oncogenic variants



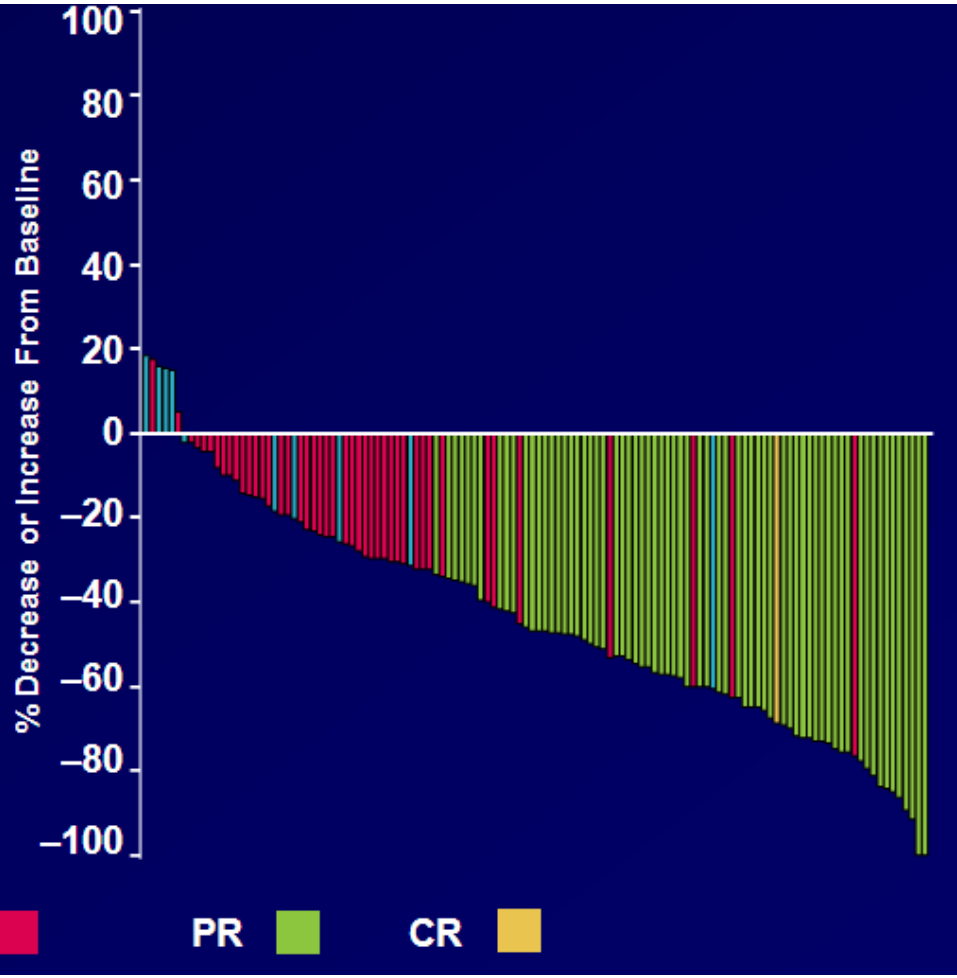


Tumor responses to crizotinib by patient

PROFILE 1001[1]



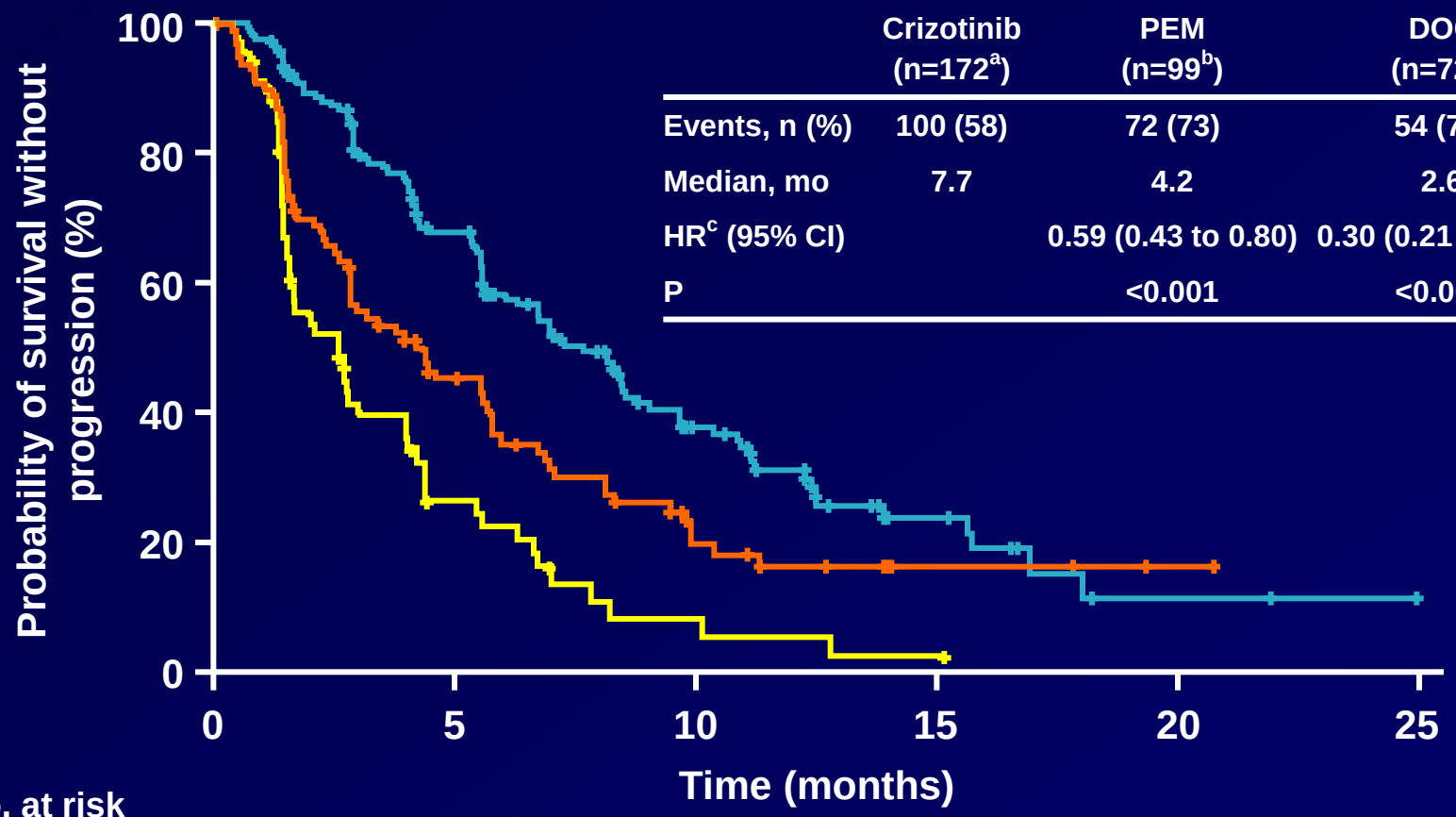
PROFILE 1005[2]



PD SD PR CR

1. Camidge et al., ASCO 2011; Abs #2501
2. Riely et al., IASLC 2011; Abs #O31.05

PFS of Crizotinib vs Pemetrexed or Docetaxel

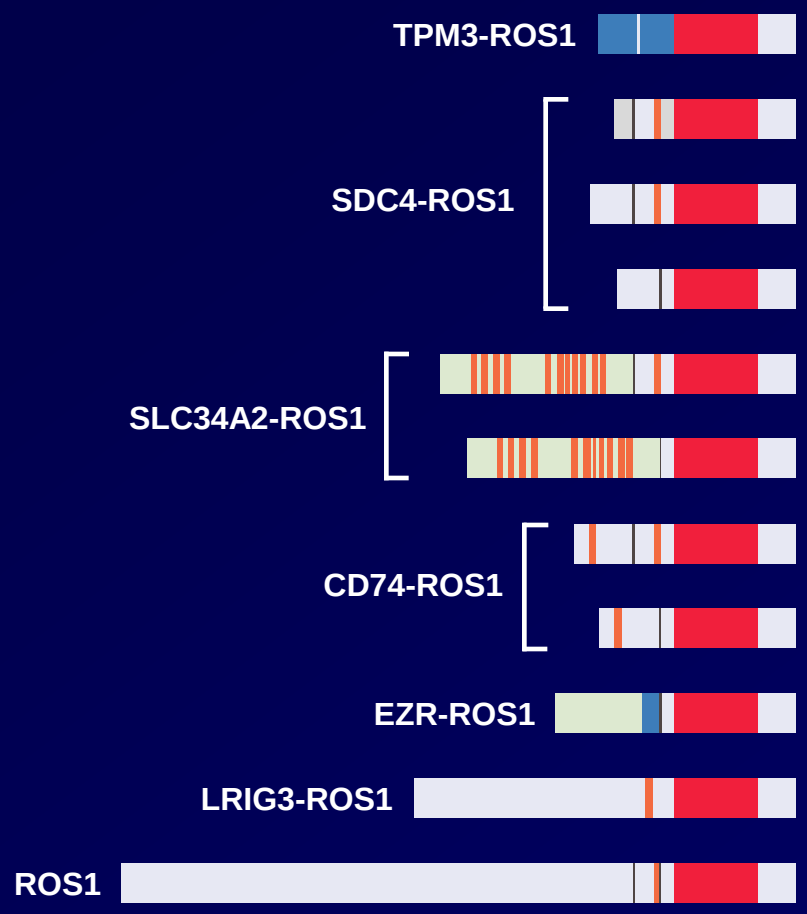


	Crizotinib (n=172[a])	PEM (n=99[b])	DOC (n=72[b])
Events, n (%)	100 (58)	72 (73)	54 (75)
Median, mo	7.7	4.2	2.6
HR[c] (95% CI)		0.59 (0.43 to 0.80)	0.30 (0.21 to 0.43)
P		<0.001	<0.001

No. at risk						
Crizotinib	172	93	38	11	2	0
PEM	99	36	12	3	1	0
DOC	72	13	3	1	0	

[a]Excludes 1 patient who did not receive study treatment; [b]excludes 3 patients in chemotherapy arm who did not receive study treatment; [c]vs crizotinib

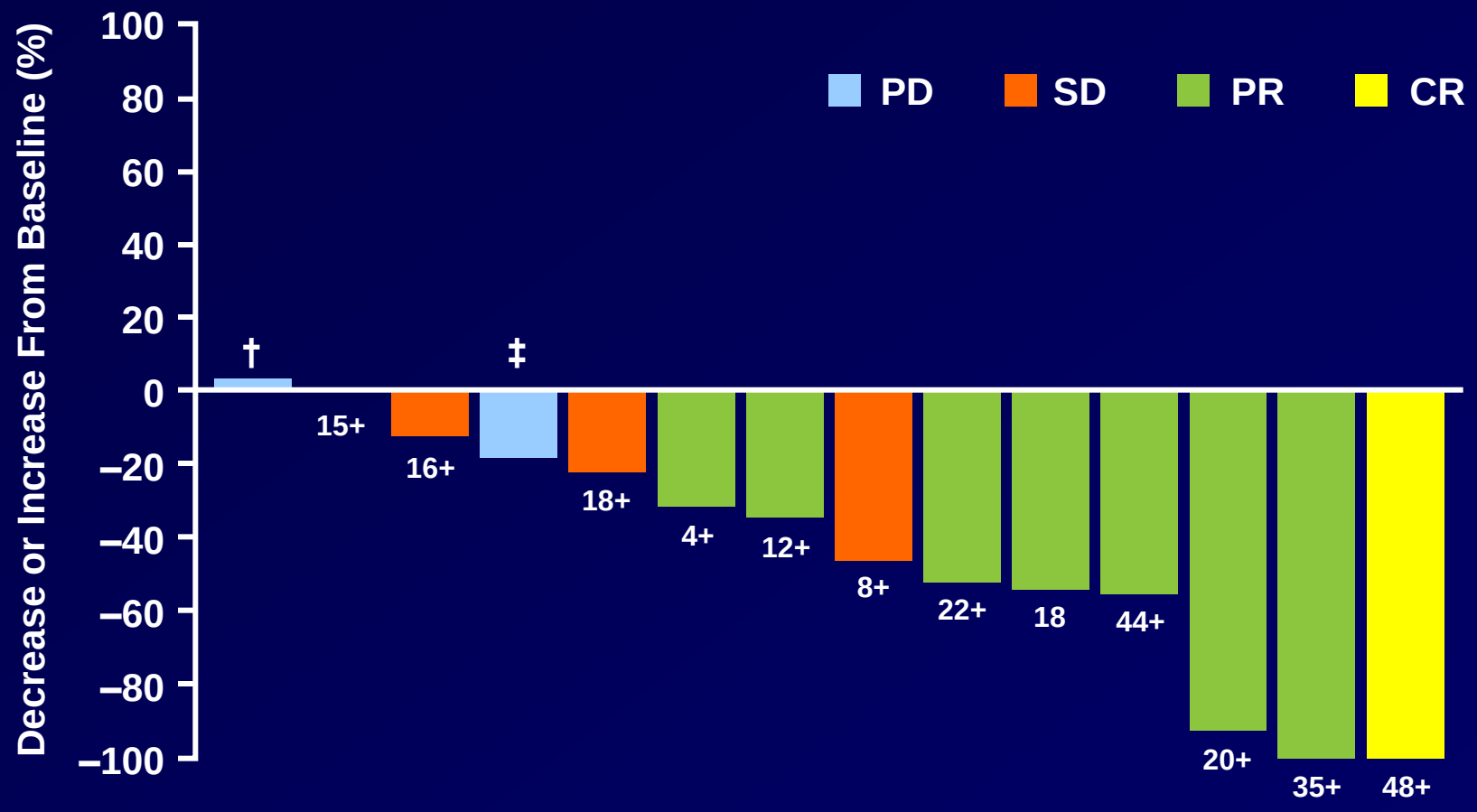
ROS1 Rearrangements in NSCLC



- **Present in ~1% of NSCLC cases (also found in some GBMs and cholangiocarcinomas)**
- **Enriched in younger never or light smokers with adenocarcinoma histology**
- **No overlap with other oncogenic drivers**

Bergethon et al., JCO 30(8): 863-70, 2012; Takeuchi et al., Nat Med 18(3): 378-81, 2012

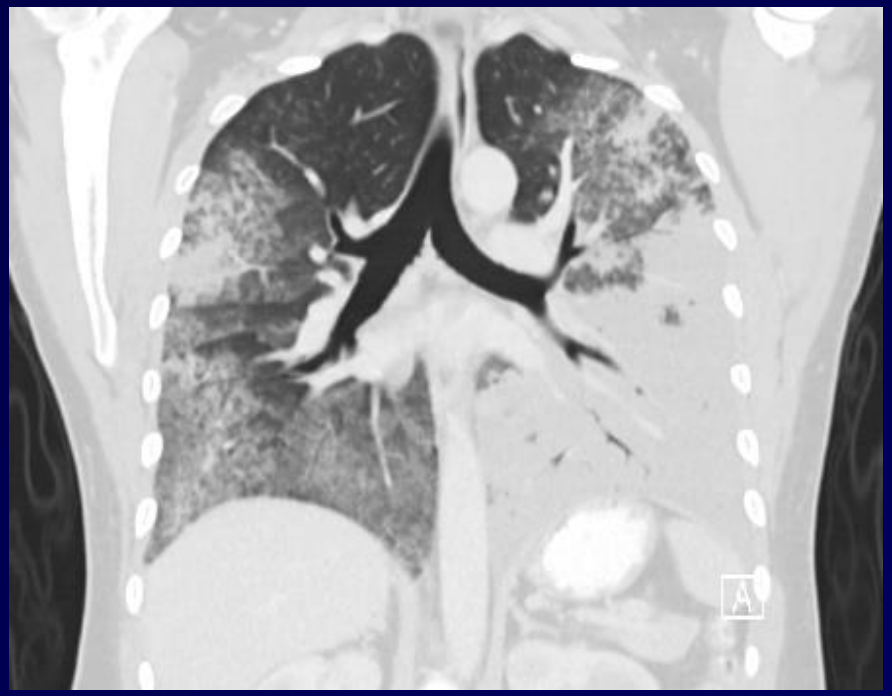
Summary of Tumor Responses in Patients with Advanced ROS1+ NSCLC (N=14*)



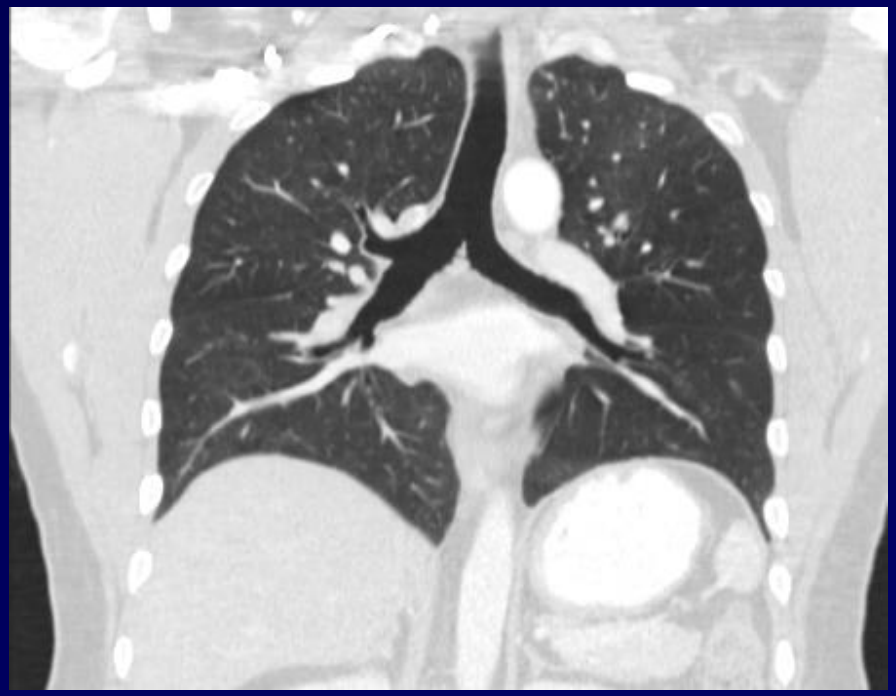
*Response-evaluable population. †Tumor ROS1 FISH-positive, but negative for ROS1 fusion gene expression. ‡Crizotinib held for >6 wks prior to first scans which showed PD. +, Treatment ongoing. For ongoing patients, duration of response/SD is the time from first documentation of tumor response/first dose to last available on treatment scan. For discontinued patients, duration is to the time of PD or death. Duration is in weeks.

Data in the database as of April 19, 2012

Significant Responses to Crizotinib in Patients with ROS1-Positive NSCLC



Baseline



After 3 months of crizotinib

Bergethon et al., JCO 30(8): 863-70, 2012

Case Report

46-ys-old **light ex-smoker** woman

- **June 2011** superior right lobectomy + lymphadenectomy for G3 lung adenocarcinoma Stage IA (pT1aN0MO, TMN 7° edition). The subsequent radiological controls were negative until June 2012.

- **June 2012:** A CT scan showed disease recurrence with multiple bilateral mediastinal nodes

Molecular Analysis: EGFR and K-RAS wild type, FISH for EML4-ALK negative, ERCC1 high, TS low; **ROS1 rearrangement positive**

- **June-July 2012:** After 2 cycles of ciplatin + pemetrexed → nodal disease progression and appearance of pericardial effusion

- **20 August 2012:** Patient was started on crizotinib 250 mg x 2

University of Colorado Cancer Center

A NATIONAL CANCER INSTITUTE-DESIGNATED CONSORTIUM COMPREHENSIVE CANCER CENTER

Molecular Pathology Shared Resource
Cytogenetics
Anschutz Medical Campus, RC1 South, room 8401A
Aurora CO 80045
Phone 303-724-3147

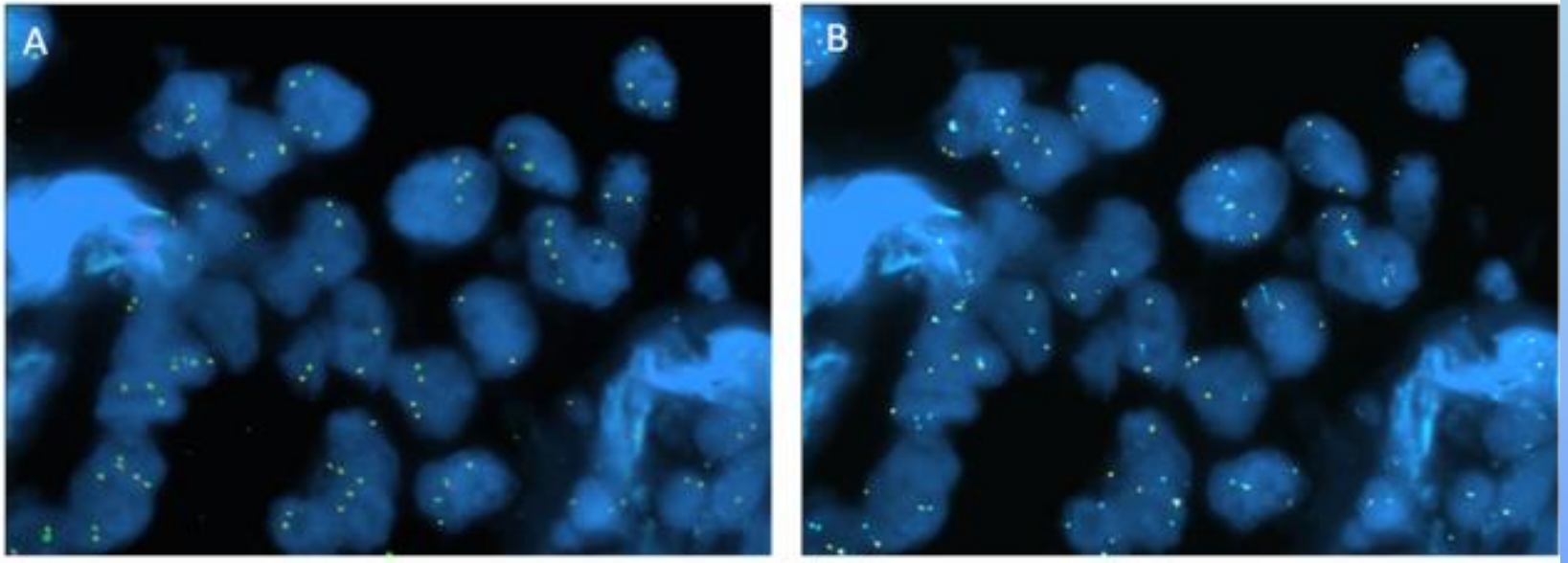
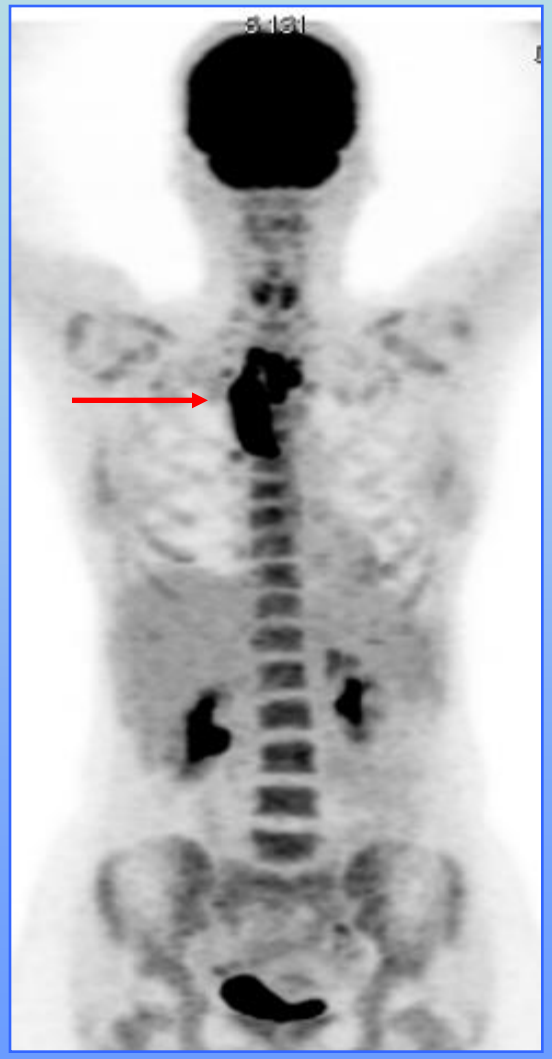
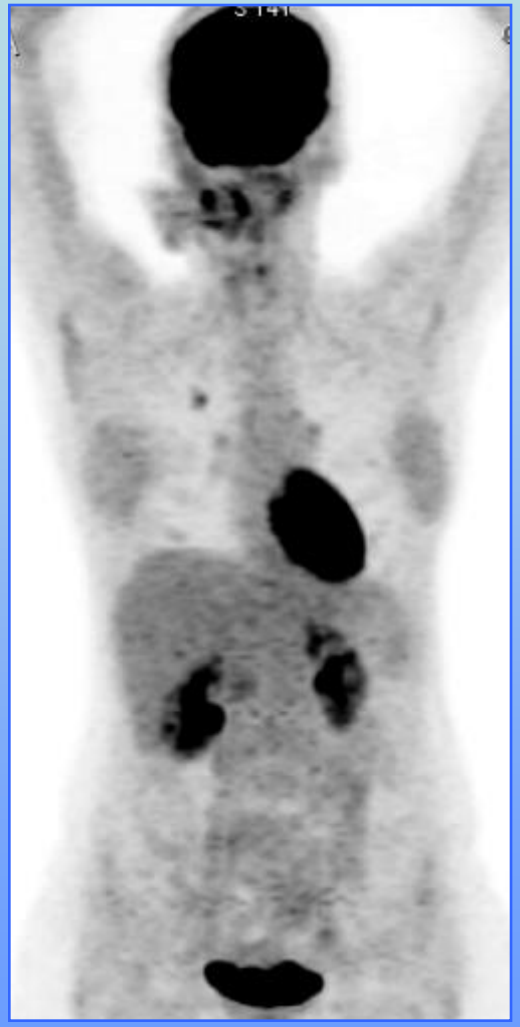


Figure 1: Specimen 8456 hybridized with the *ALK/ROS1* Break Apart (BA) probe showing patterns compatible with no *ALK* rearrangement (A) and rearrangement in the *ROS1* gene (B)

August 2012: Start crizotinib



After 1 month of crizotinib



Almost disappeared

Cancer research at the roundabout

- Cancer is a genetic somatic disease (5% inherited)
- It originates from stem cells
- It is caused by genetic alterations of a handful of genes
- It is often possible to identify these genetic lesions by molecular diagnosis
- “Target” therapy is only effective when aimed at the alteration of the driver gene (s)