



Ospedale  
Sacro Cuore - Don Calabria  
Negrar (Verona)

## INCONTRI DI AGGIORNAMENTO DEL DIPARTIMENTO ONCOLOGICO TRATTAMENTO del NSCLC IV STADIO

Caso Clinico n. 1 – A.P.

# Beyond EGFR: a '*molecular mosaic*'



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Universitaria Integrata, Verona

**Negrar, 12 Marzo 2014**

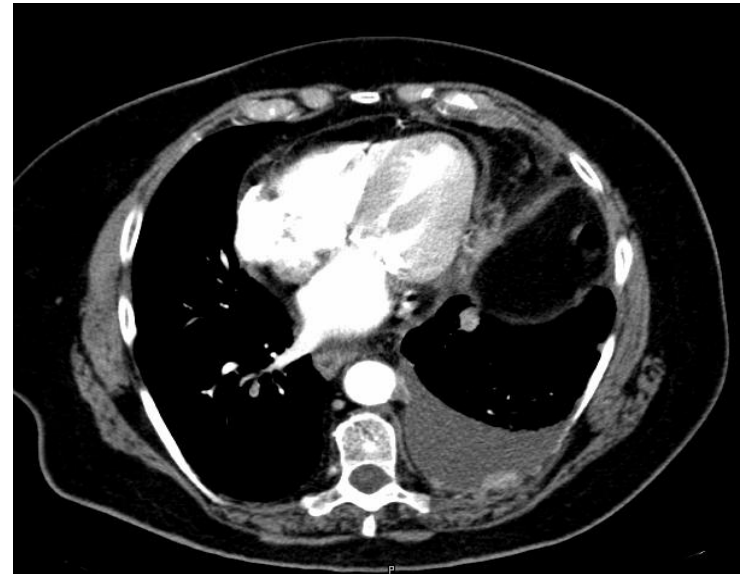
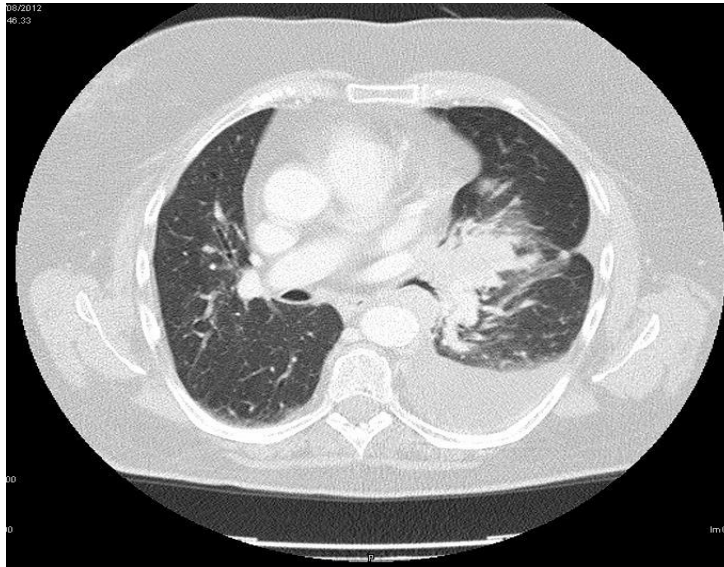
# Case Report - A.P.



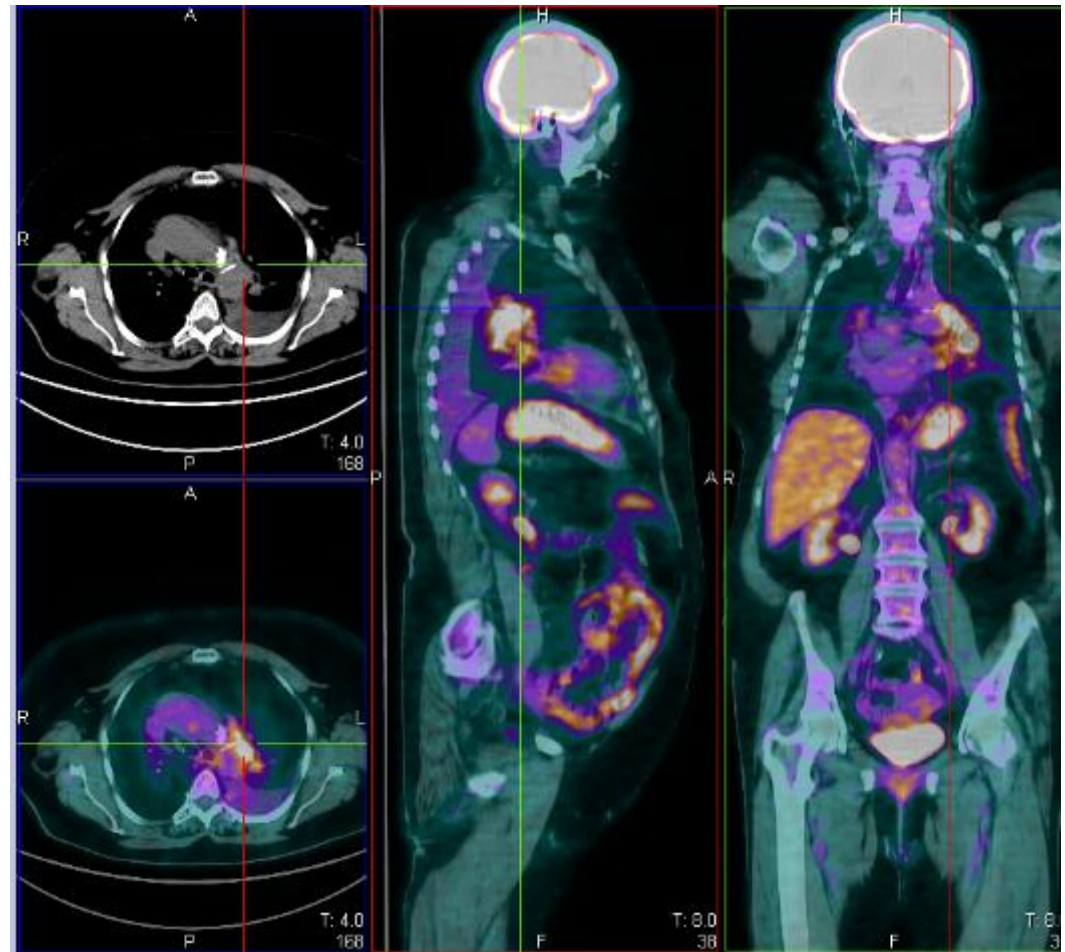
- Female patient, 77 year-old
- Never smoker
- Performance Status 2
- Comorbidities **[CLINICALLY SIGNIFICANT]**
  - ✓ ischemic-hypertensive cardiopathy ***[NYHA class II]***
  - ✓ diabetes mellitus
  - ✓ gastro-oesophageal reflux
- Persistent cough and dyspnea for about 1 month

# Case Report - A.P.

- Total-body CT-scan: large left hilar pulmonary mass with infiltration of the mediastinum and extension to both lobes; ipsilateral parenchymal and pleural nodules associated with pleural effusion; right pulmonary thromboembolism.



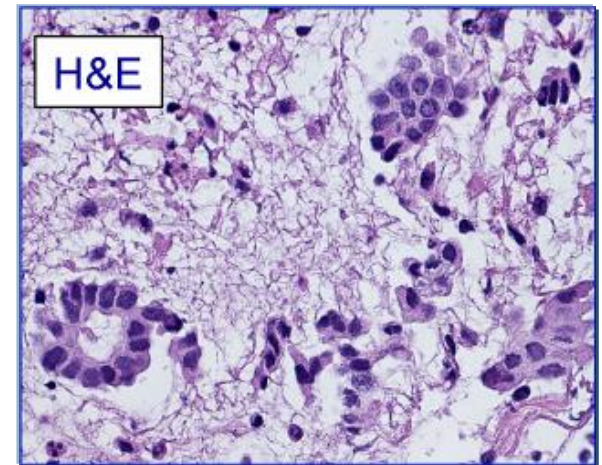
- Total-body PET-CT:  
intense pathological uptake in correspondence of the known pulmonary lesions in the left hilar and para-hilar region, lingula and of the pleural thickening (parietal pleura before the arch back of the V coast and coast between XI and X)



# Case Report - A.P.

- Bronchoscopy: hyperemia of the mucosa of the left main bronchus and enlargement of the spur between top and bottom, with no evidence of intraluminal disease; performed TBNA of the left main bronchus

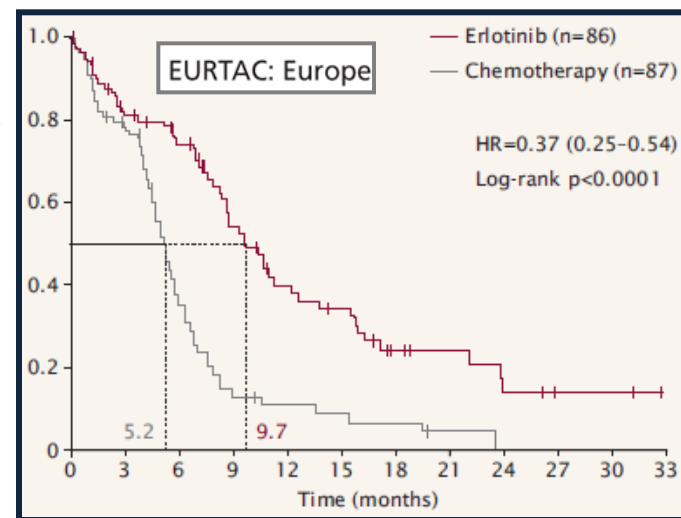
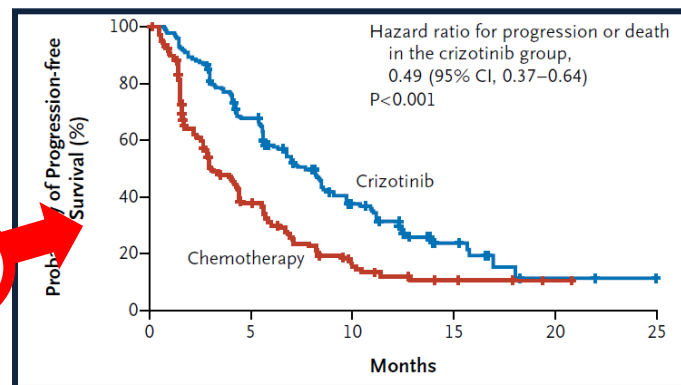
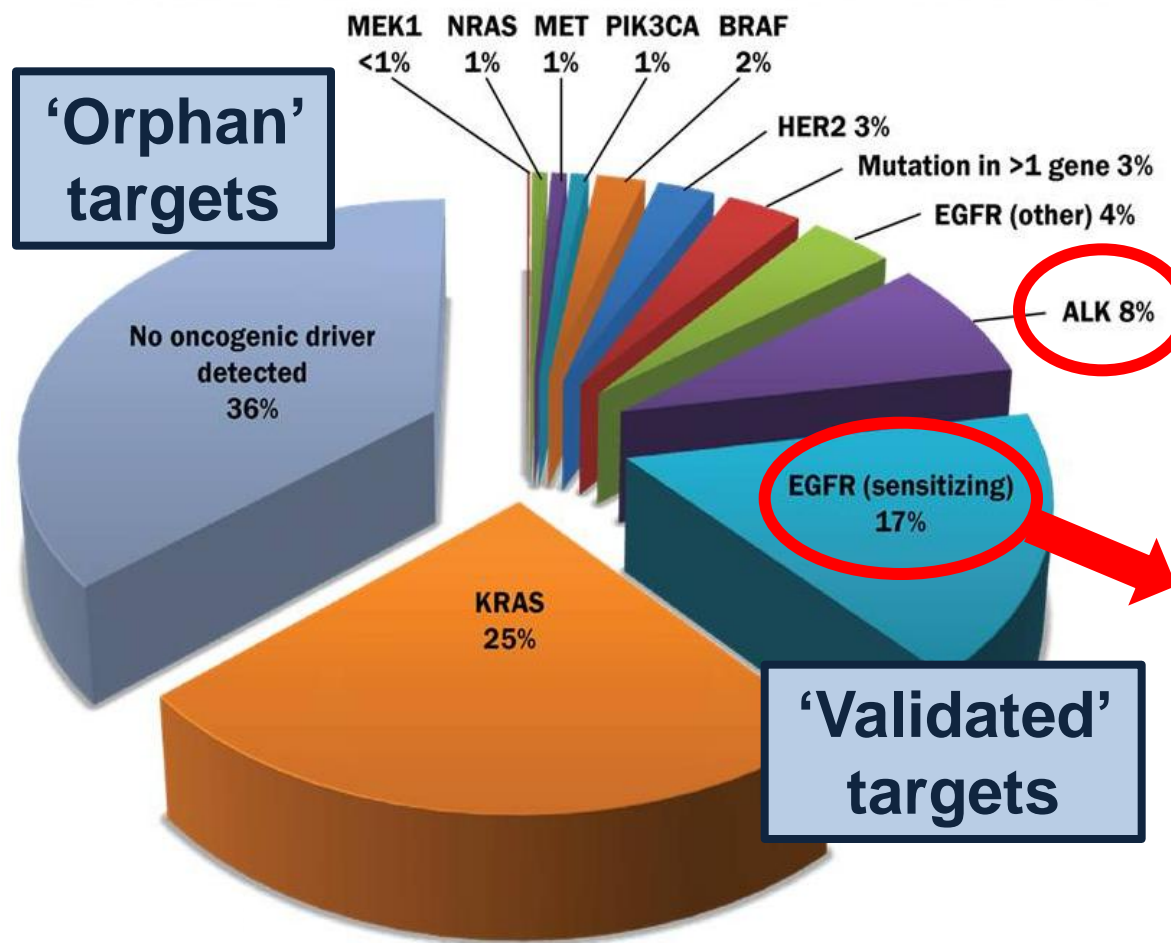
- Histology: lung adenocarcinoma



- Sequencing analysis of EGFR exons 18 to 21: **CTA-CAG point mutation in exon 21 [L861Q]**



# ..going beyond 'adenocarcinoma'..



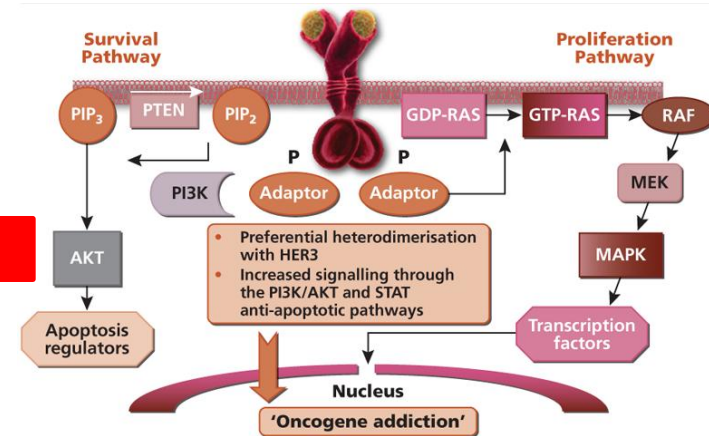
Lung Cancer Mutation Consortium: Incidence of Driver Mutations

Modified By Paul A. Bunn, MD at 2013 ASCO Annual Meeting

# Clinical Relevance of the 'Oncogene Addiction'

- In patients with solid malignancies in which a dominant mutation or gene amplification drives tumor growth, targeted therapies are highly effective but rarely curative...

- cKit mutations in GIST
- HER2 amplification in breast cancer
- **EGFR mutation in NSCLC**
- ALK traslocation in NSCLC



GENETICS

DEPENDENCY

PHARMACOLOGIC  
VULNERABILITY

# Medical Treatment for NSCLC – Molecular Selection [ *Validated* ] Biomolecular Predictors

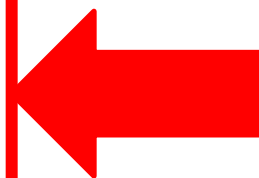
## Evidences for Drugs' Registration:

- Randomized Studies:

- **EGFR Sensitizing Mutations**

- Gefitinib [EMA, FDA?]

- Erlotinib [EMA]



- Early Phases Studies → Randomized Studies:

- EML4-Alk Traslocation

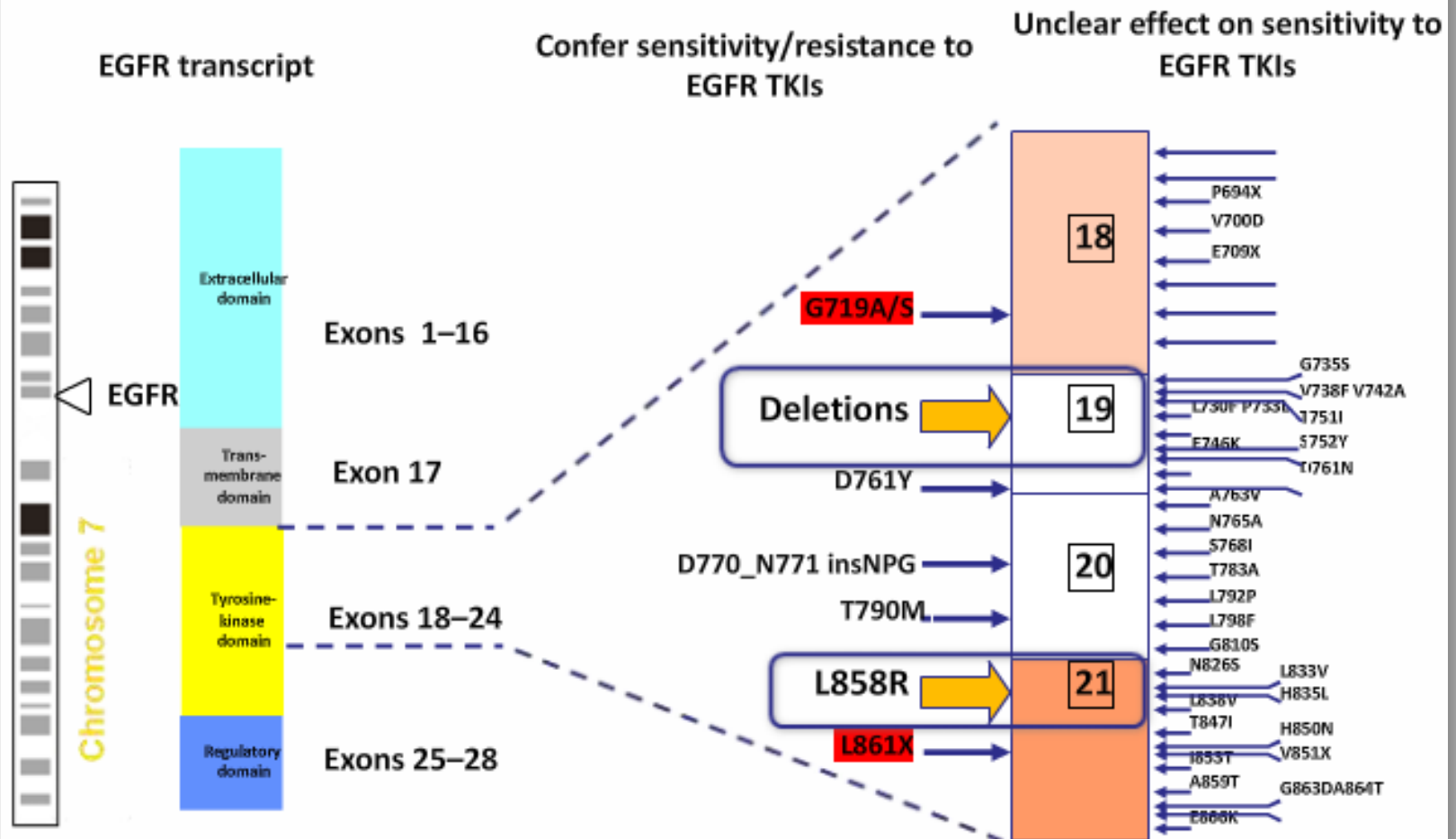
- Crizotinib [EMA, FDA]



# EGFR TKIs versus chemotherapy as first-line therapy in EGFR mutant

Study [ref.]	Patients treated with TKI n	PFS	ORR %	Overall survival
NEJ002 [12, 23]	114	10.8 months versus 5.4 months; HR 0.32 [95% CI 0.24–0.44], $p < 0.001$	74 versus 31; $p < 0.001$	27.7 months versus 26.6 months; HR 0.89 [95% CI 0.63–1.24], $p = 0.483$
WJTOG3405 [13, 25]	51 for PFS (stage IIIb/IV subgroup) 86 for overall survival	8.4 months versus 5.3 months; HR 0.33 [95% CI 0.21–0.54], $p < 0.0001$ (stage IIIb/IV subgroup)	62 versus 32 <sup>++</sup> ; $p < 0.0001$	36 months versus 39 months; HR 1.19 [95% CI 0.771.83], $p = 0.443$
IPASS <sup>+</sup> [8, 14]	132	9.5 months versus 6.3 months; HR 0.48 [95% CI 0.36–0.64], $p < 0.001$	71 versus 47; $p < 0.001$	21.6 months versus 21.9 months; HR 1.00 [95% CI 0.76–1.33], $p = 0.990$
EURTAC <sup>5</sup> [9, 19]	86	9.7 months versus 5.2 months; HR 0.37 [95% CI 0.25–0.54], $p < 0.0001$	58 versus 15; $p$ -value not reported	19.3 months versus 19.5 months; HR 1.04 [95% CI 0.65–1.68], $p = 0.87$
EURTAC <sup>7</sup> [9, 19]	86	10.4 months versus 5.4 months; HR 0.47 [95% CI 0.28–0.78], $p = 0.0030$		
LUX-Lung 3 <sup>##</sup>	230	11.1 months versus 6.9 months; HR 0.58 [95% CI 0.43–0.78]; $p = 0.001$	56 versus 23; $p = 0.001$	28.1 months versus 28.2 months; HR 0.91 [95% CI 0.66–1.25], $p = 0.55$ (yet immature)
LUX-Lung 3 <sup>5</sup> [15]	230	11.1 months versus 6.7 months; HR 0.49 [95% CI 0.37–0.65]; $p = 0.001$	69 versus 44; $p = 0.001$	
OPTIMAL [10, 11]	82	13.1 months versus 4.6 months; HR 0.16 [95% CI 0.10–0.26], $p < 0.0001$	83 versus 36; $p < 0.0001$	22.7 months versus 28.9 months; HR 1.04 [95% CI 0.69–1.58], $p = 0.69$ (yet immature)
LUX-Lung 6 <sup>††</sup> [16]	242	11.0 months versus 5.6 months; HR 0.28 [95% CI 0.20–0.39], $p < 0.0001$	67 versus 23; $p < 0.0001$	Not reported; immature
LUX-Lung 6 <sup>5</sup> [16]	242	13.7 months versus 5.6 months; HR 0.26 [95% CI 0.19–0.36], $p < 0.0001$	74 versus 31; $p$ -value not reported	

# Mutations in the *EGFR* gene



TKI = tyrosine-kinase inhibitor

Riely, et al. Clin Cancer Res 2006

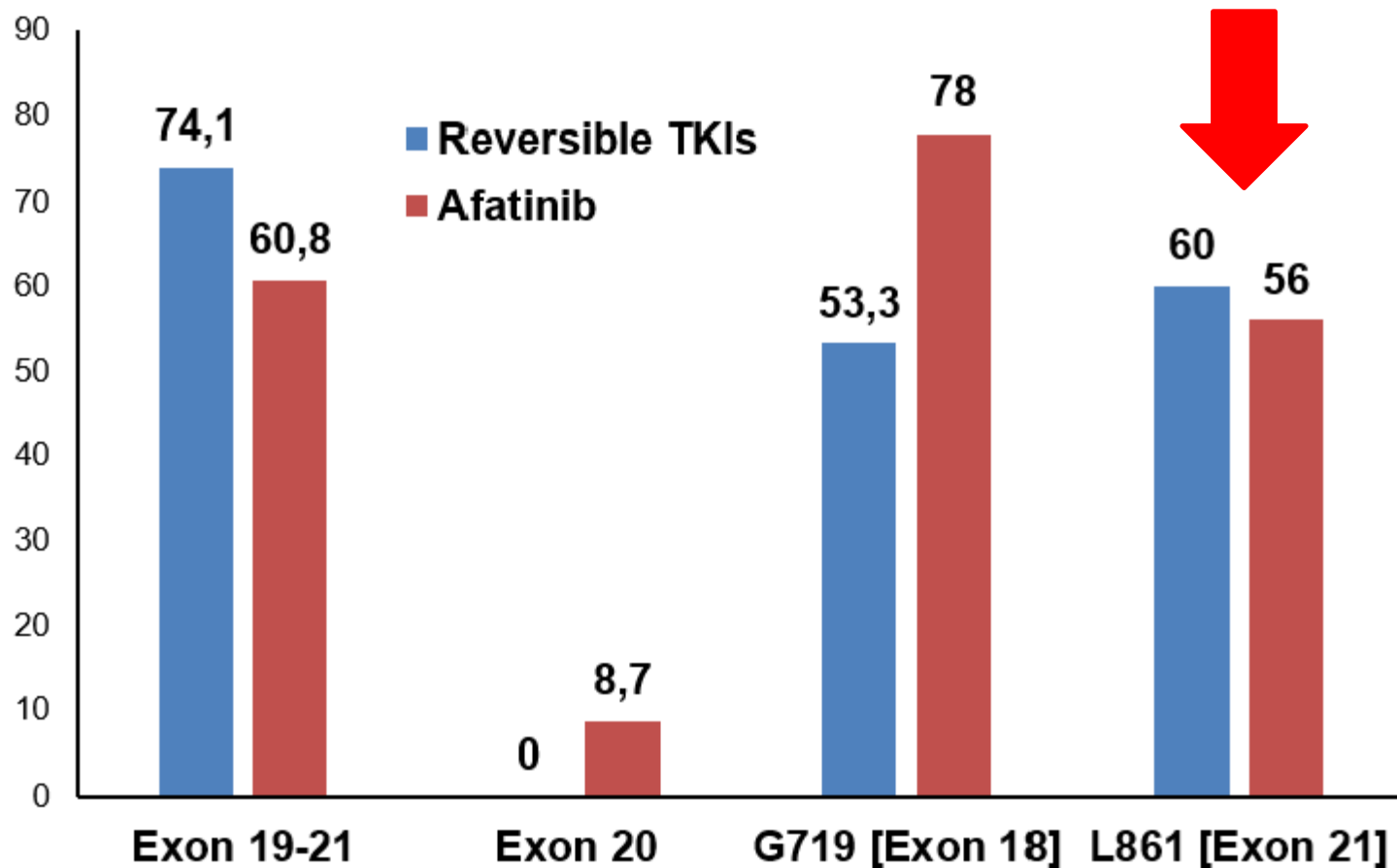
# ..but what about uncommon EGFR alterations?

EGFR	Reversible EGFR-TKIs <sup>1</sup>				Afatinib <sup>2,3,4</sup>			
	N	RR (%)	PFS (months)	OS (months)	N	RR (%)	PFS (months)	OS (months)
Exon 19-21	278	74.1	8.5	19.6	308 <sup>4</sup>	60.8	13.6	-
Wild-type	272	16.5	2.0	10.4	42 <sup>3</sup>	0	1.0	7.2
Exon 20 insertion	11	0	1.4	4.8	20 <sup>2</sup>	8.7	2.7	9.4
G719	15	53.3	8.1	16.4	18 <sup>2</sup>	78.0	13.8	26.9
L861	15	60.0	6.0	15.2	16 <sup>2</sup>	56.0	8.2	16.9
Other	15	20.0	1.6	11.1	1	100	-	-

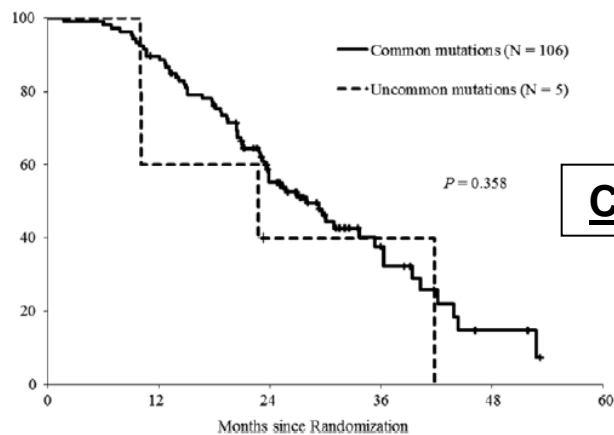
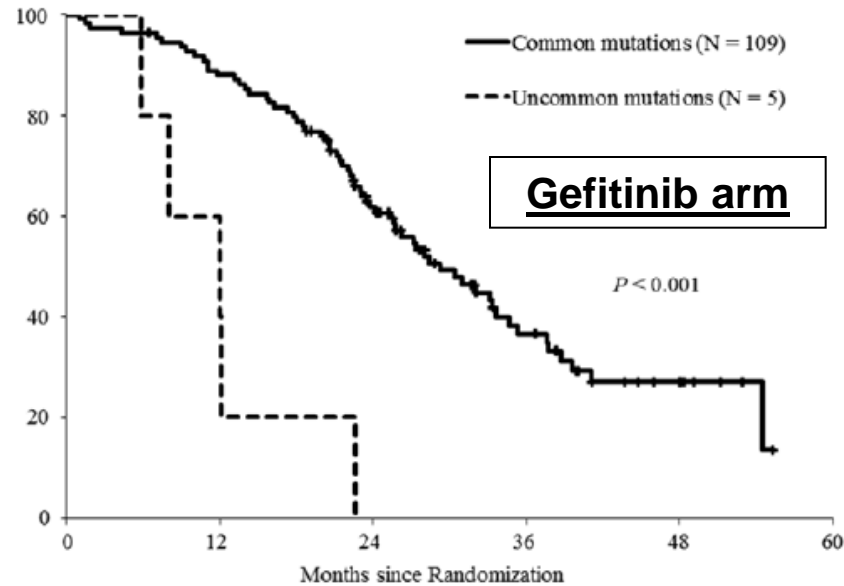
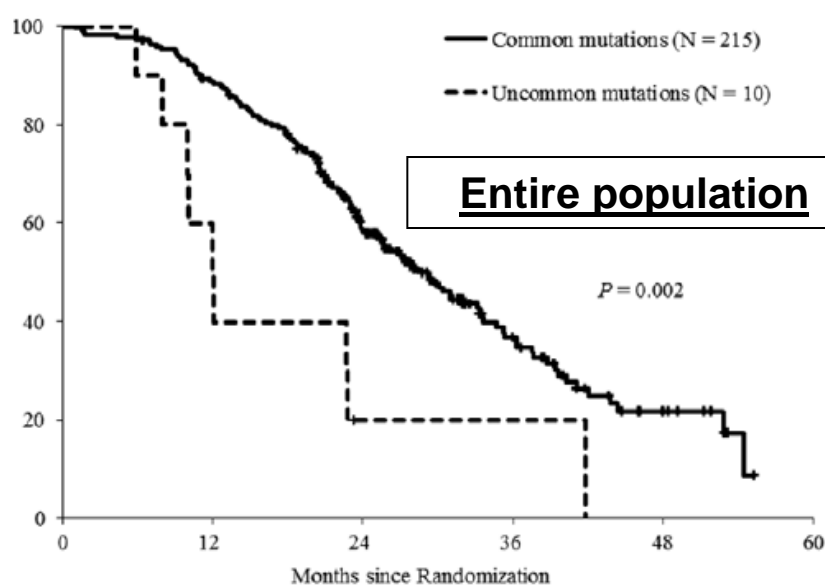
<sup>1</sup>Wu J et al. Clin Cancer Res 2011;17:3812-3821; <sup>2</sup>Yang Y et al. WCLC 2013; <sup>3</sup> Ahn et al, ESMO 2012; <sup>4</sup>Sequist et al JCO 2013

*Modified by Cappuzzo WCLC 2014*

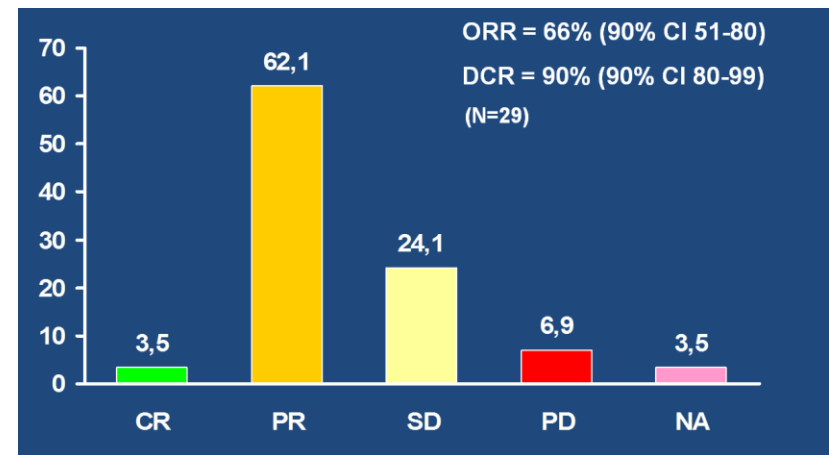
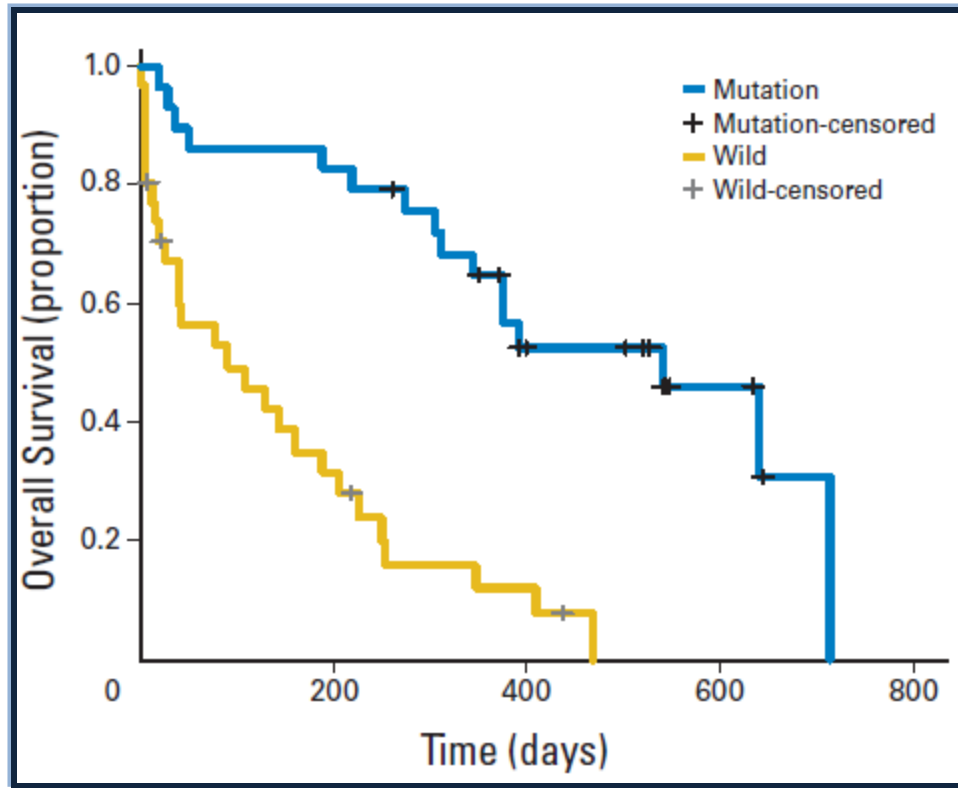
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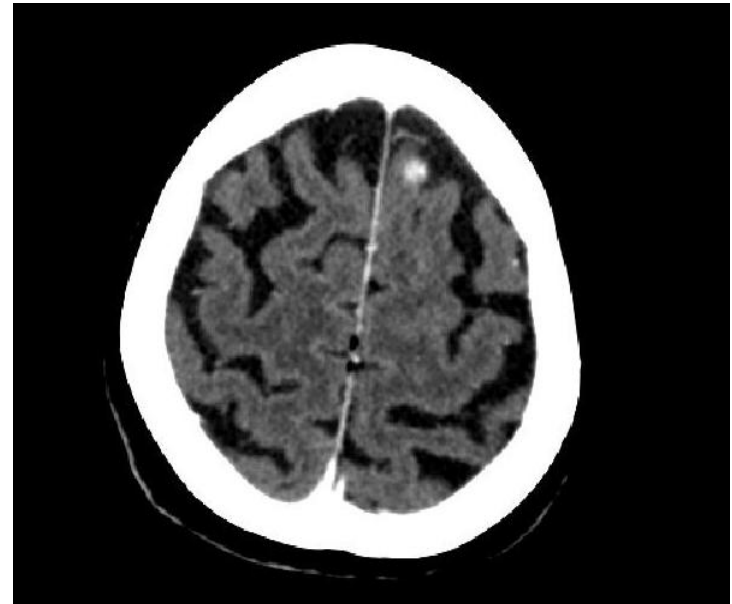
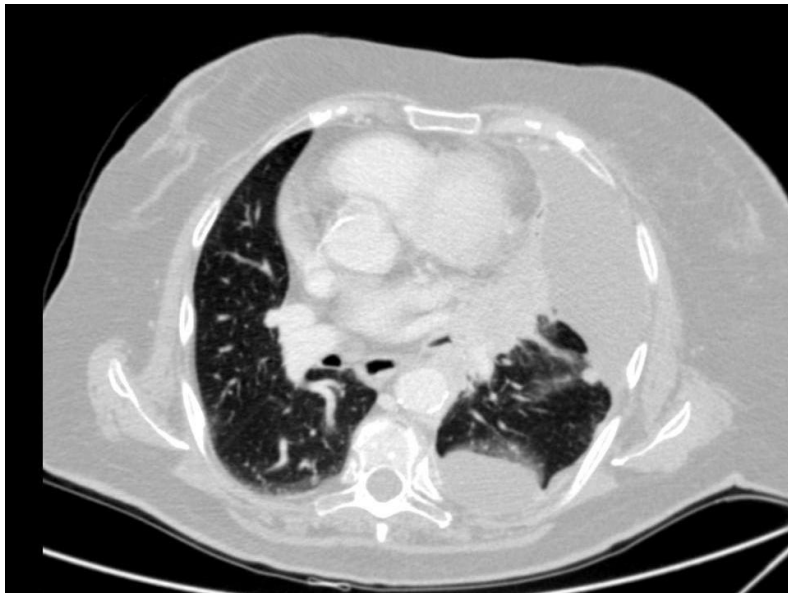
# ..and what about Gefitinib in EGFR mutant patients unsuitable for chemotherapy?





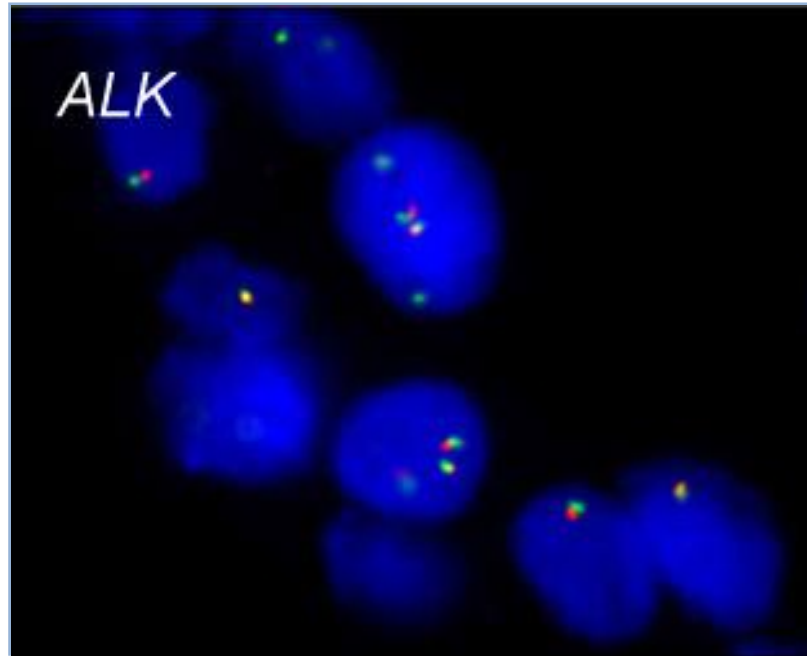
# Case Report - A.P.

- September 2012: the patient started **Gefitinib** 250 mg/day
- November 2012: symptoms rapidly worsen in the 5<sup>th</sup> – 7<sup>th</sup> week and the CT-scan showed progressive pleural disease and two brain metastasis (7 and 3 mm)



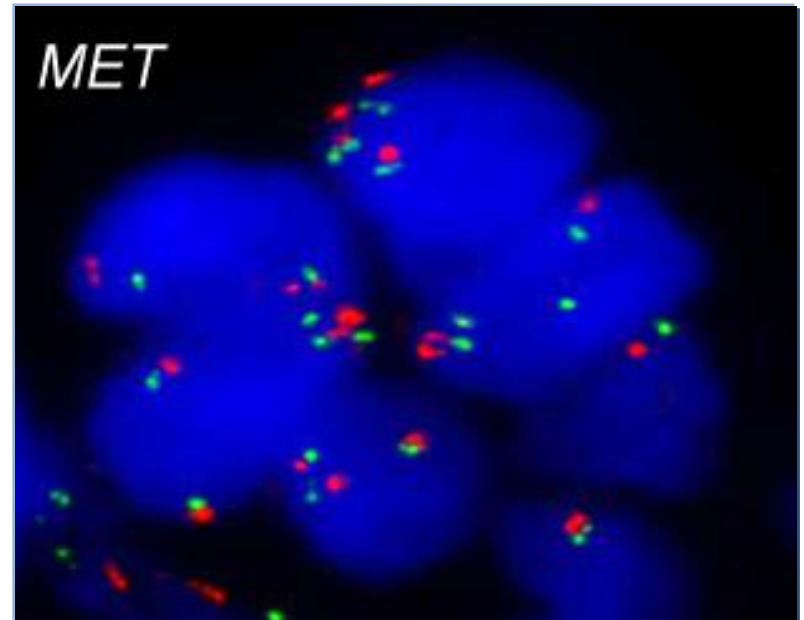
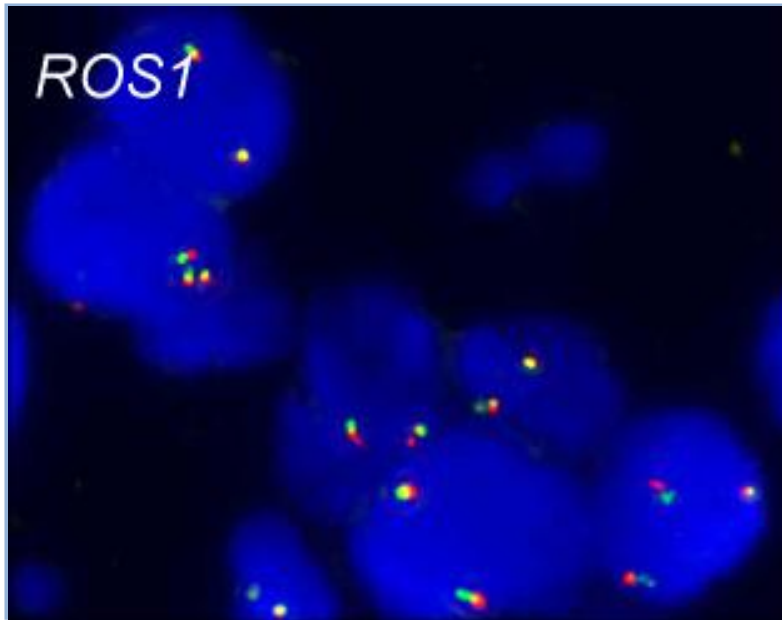
# Case Report - A.P.

- November 2012: stereotactic radiosurgery on brain metastasis
- FISH analysis for ALK: did not show any rearrangement, but an **increased gene copy number** was observed in 61% of cancer cells, with 2.6 mean signals per cell



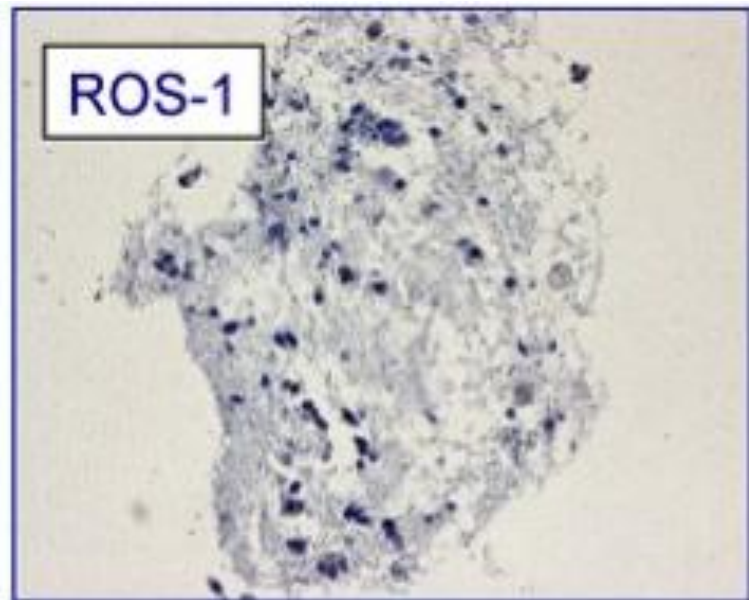
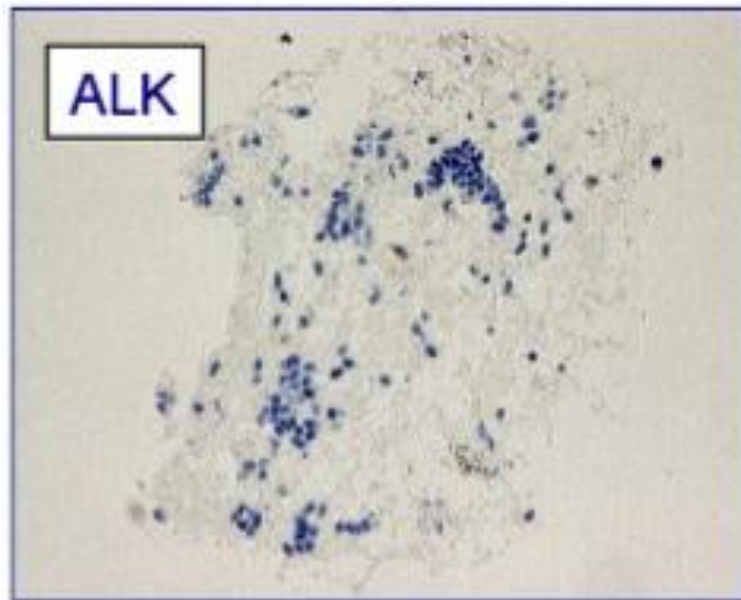
# Case Report - A.P.

- FISH analysis for ROS1 and MET: did not show any rearrangement, but an **increased gene copy number** was observed in the 67% and 72% cancer cells, with 2.6 and 2.9 mean signals per cell, respectively



# Case Report - A.P.

- IHC analysis for ROS1 and ALK: did not show any expression.



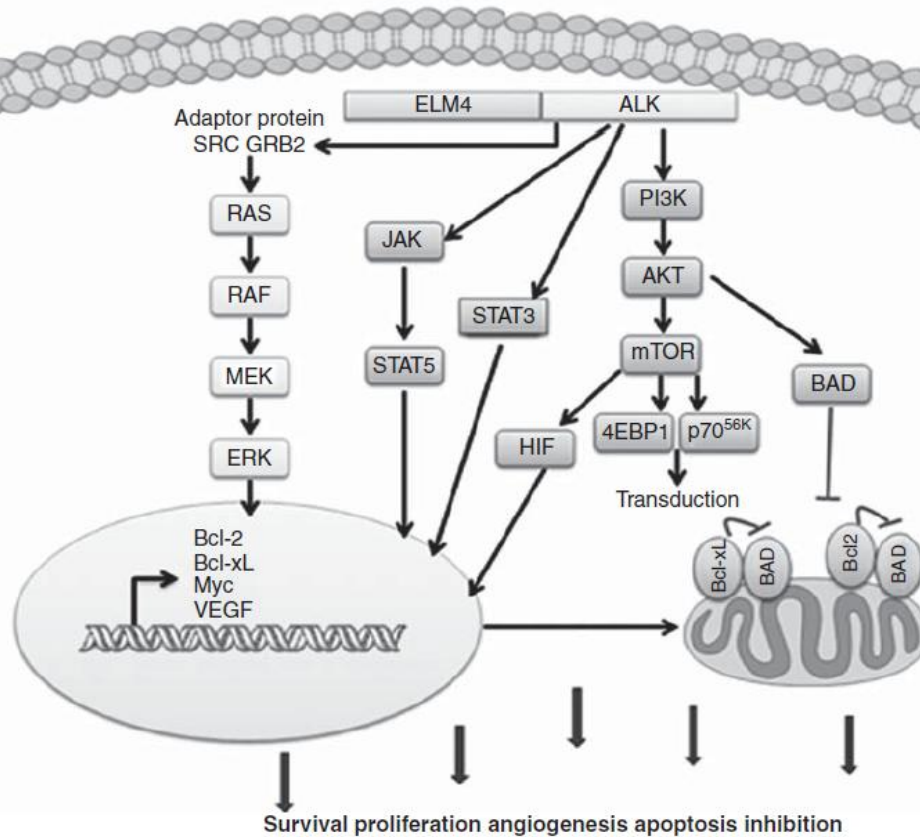
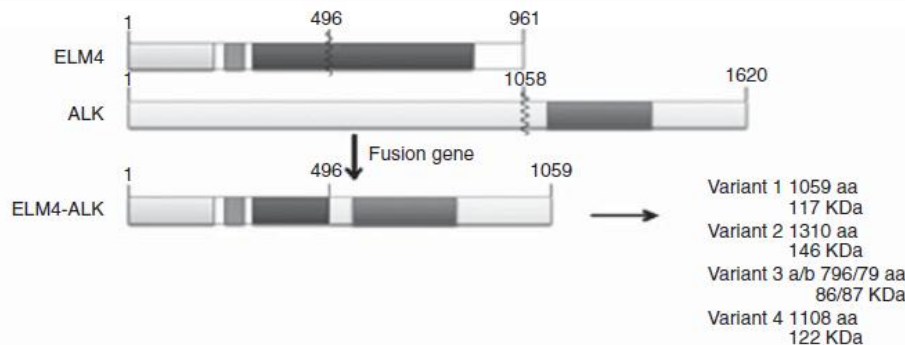
# PROFiling non-small-cell lung cancer patients for treatment with crizotinib according to anaplastic lymphoma kinase abnormalities: translating science into medicine

## The ALK entity



5% of NSCLC (range 3-7)

- ❖ Median age of onset ~ 50 (20-80s)
- ❖ Mainly adenocarcinoma histology (signet-ring histology)
- ❖ Never/light smoking status
- ❖ Excess of
  - hepatic metastases,
  - pleural and pericardial effusions
  - and probably brain metastasis (35% in this trial)
- ❖ Minimal overlap with other driver mutations
- ❖ Neutral prognosis vis à vis *EGFR* and ALK WT control groups



# Medical Treatment for NSCLC – Molecular Selection [ *Validated* ] Biomolecular Predictors

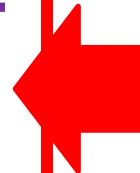
## Evidences for Drugs' Registration:

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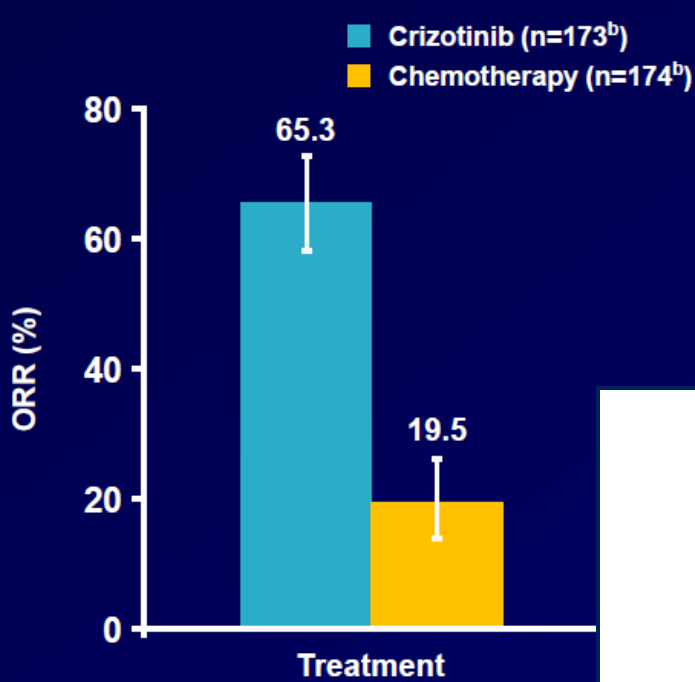
- EGFR Sensitizing Mutations
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- Early Phases Studies → Randomized Studies:

- EML4-Alk Traslocation
  - Crizotinib [EMA, FDA]



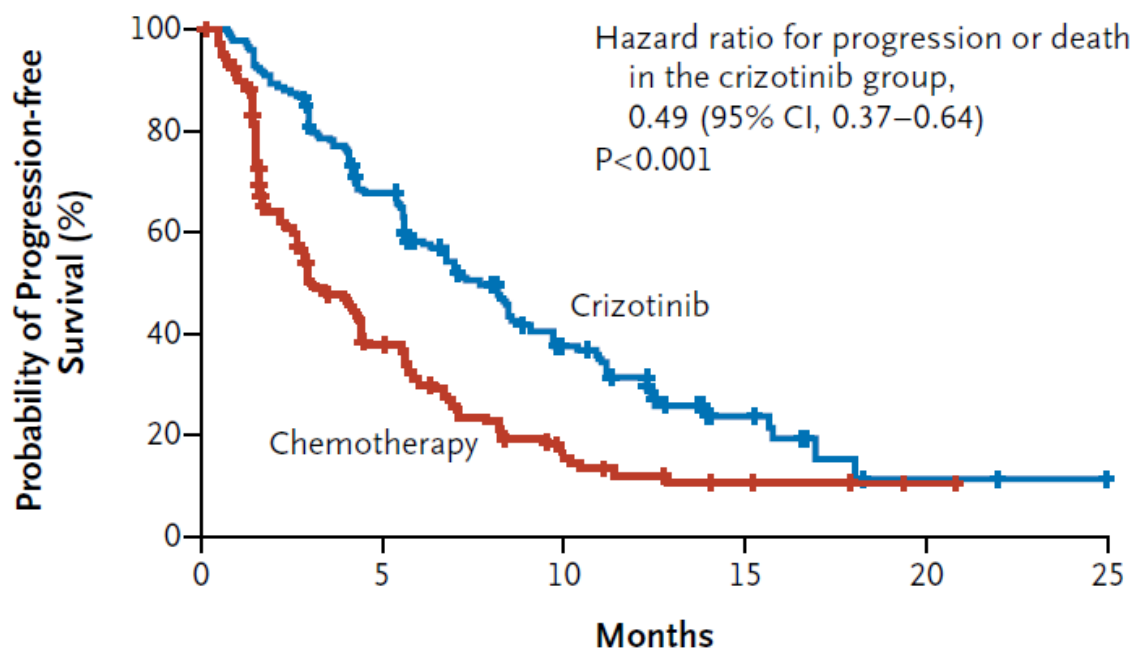




## Clear and strong signal of activity

- Objective response is **tripled**
- PFS is improved by **4,7 months (HR of 0,49)**
- Improvement of PFS in almost all subgroups
- Improvement of lung cancer-related symptoms and global QOL

Kinase	IC <sub>50</sub> (nM) mean <sup>*</sup>	Selectivity ratio
c-MET	8	—
ALK	40-60	5-8X
ROS1	60	7X



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Crizotinib versus Chemotherapy in Advanced  
ALK-Positive Lung Cancer

# Case Report - A.P.



- November 2012: the patient started Crizotinib 250 mg/BID/day
- After 4 weeks on crizotinib, a significant improvement of symptoms (cough and dyspnea) and Performance Status (0-1) was obtained. Treatment was well tolerated, except for a grade 1 skin rash and increase of transaminases
- July 2013: the last CT scan and clinical evaluation still confirm a stable disease after 8 months of crizotinib
- August 2013: the patient suddenly died for arrhythmia and heart failure

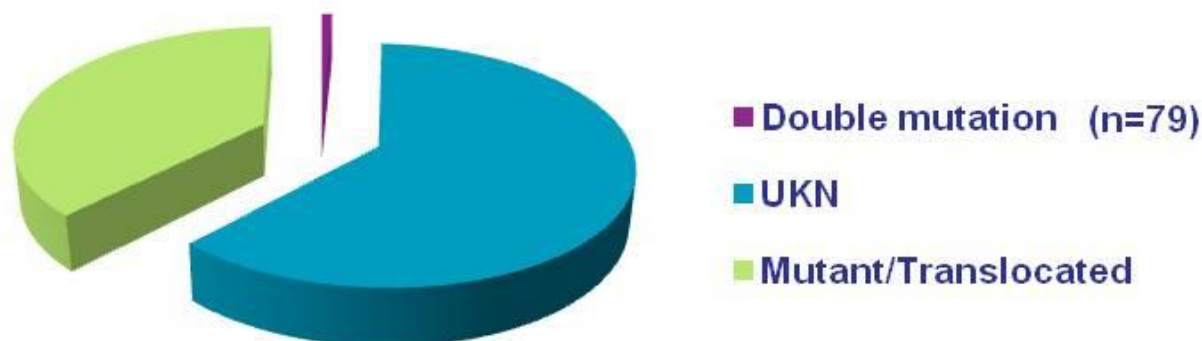
# Conclusions (Issues for Q&A)

- Emerging data about the potential **predictive** (and prognostic) role of the **uncommon EGFR mutations**
  - Very modest efficacy of currently available TKIs against T790M & exon 20 alterations
  - Similar efficacy in G719 and L861 mutations with reversible and irreversible TKIs
  - Waiting for new irreversible EGFR mutant selective agents (i.e. CO-1686)
- Who occurred **first in the pathogenesis**?
  - EGFR mutation as an 'escape' from ALK-driven addiction?
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- Which role as predictors of crizotinib for genetic **abnormalities 'other' than traslocations**?
  - Amplification
  - High GCN
    - In this case, what cut-offs?

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# Results: biomarkers assessment (n=9911)



	EGFR	ALK	KRAS	BRAF	PI3K	HER2
EGFR	-					
ALK	3	-				
KRAS	5	10	-			
BRAF	2	1	6	-		
PI3K	16	1	33	1	-	
HER2				1		-

Supported by:



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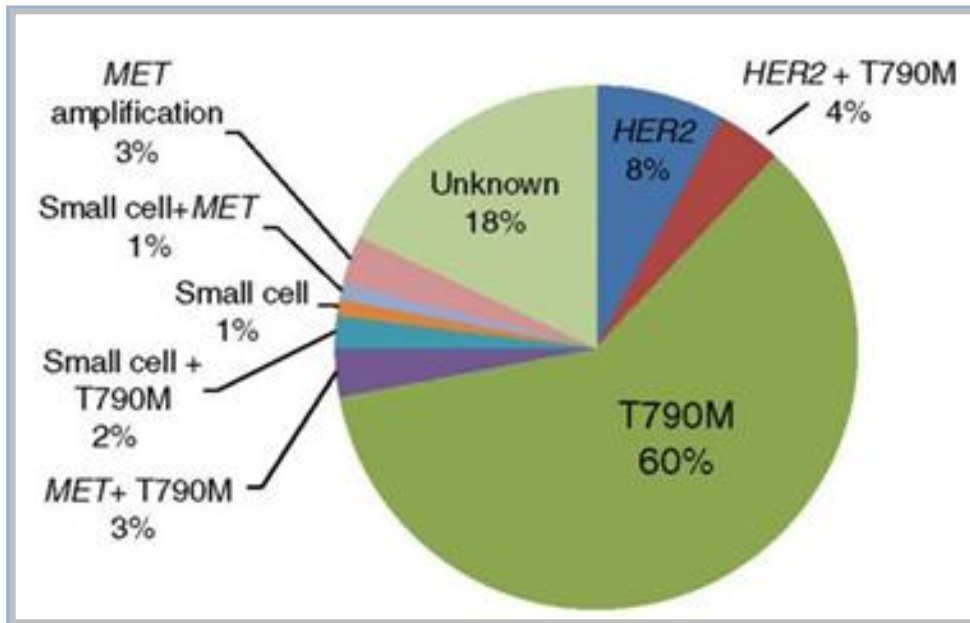


Annual '13  
Meeting

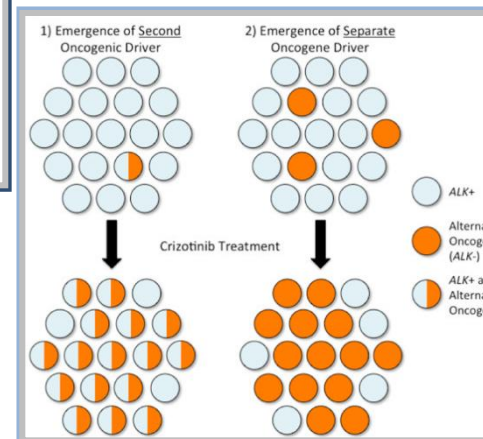
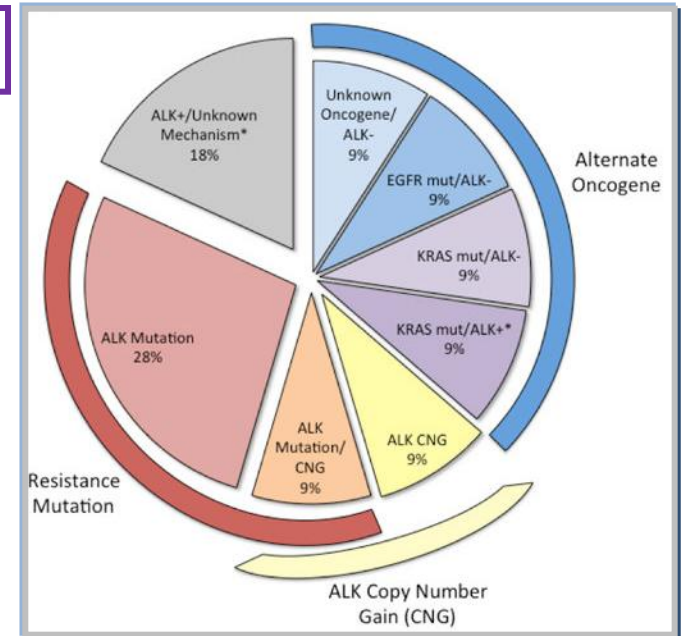
***Presented By Fabrice Barlesi, MD, PHD at 2013 ASCO Annual Meeting***

# The Issue of resistance to TKIs

## anti-EGFR TKIs



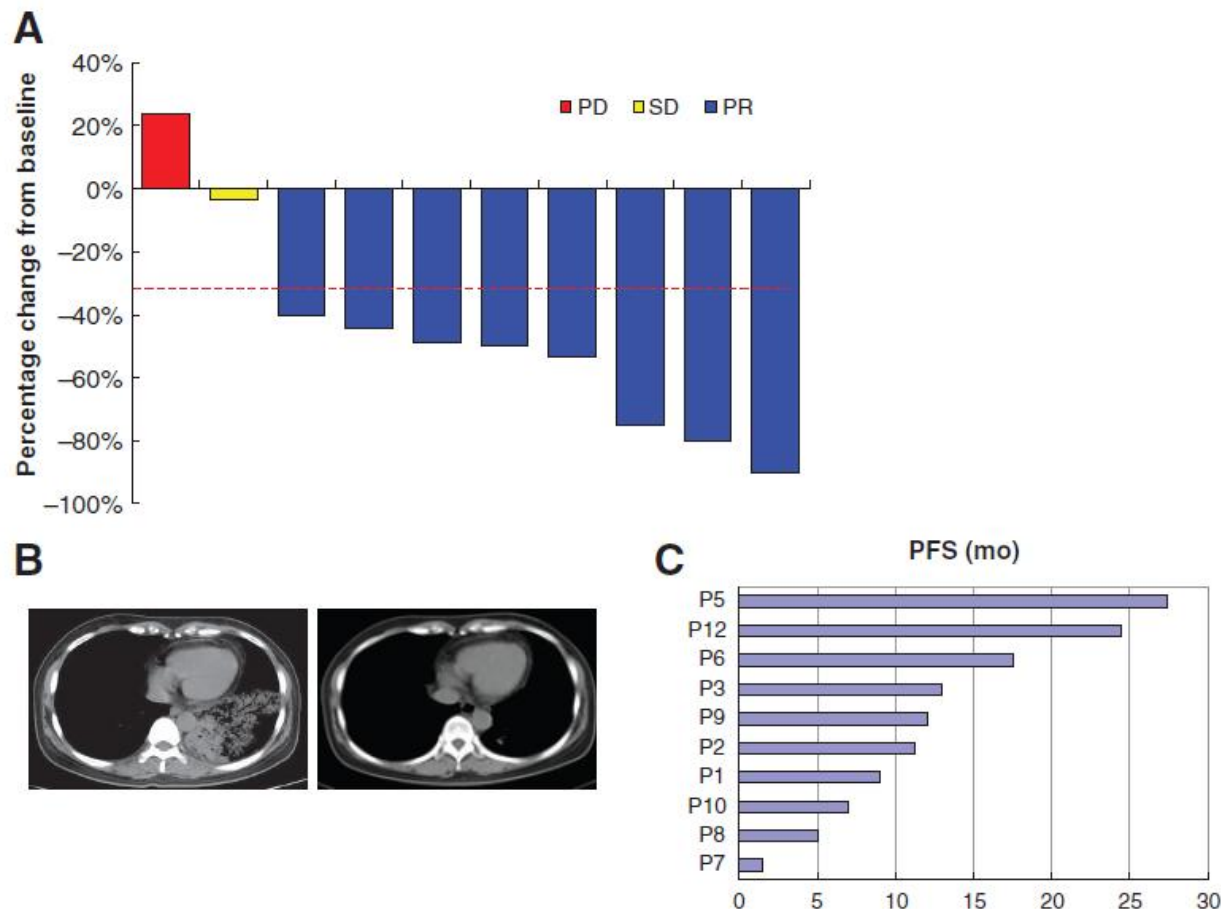
## crizotinib





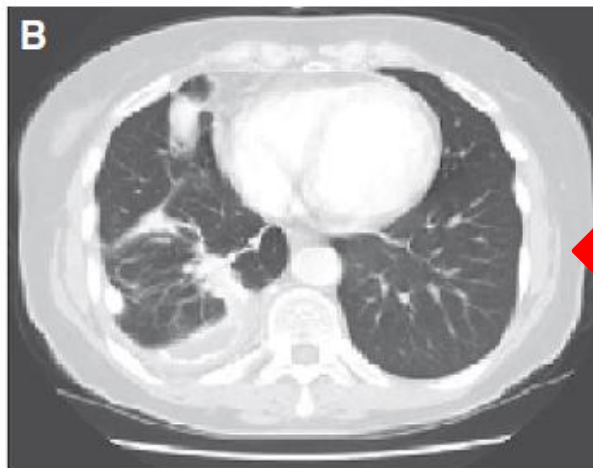
# Lung Cancers with Concomitant *EGFR* Mutations and *ALK* Rearrangements: Diverse Responses to EGFR-TKI and Crizotinib in Relation to Diverse Receptors Phosphorylation

Jin-Ji Yang<sup>1</sup>, Xu-Chao Zhang<sup>1,2</sup>, Jian Su<sup>2</sup>, Chong-Rui Xu<sup>1</sup>, Qing Zhou<sup>1</sup>, Hong-Xia Tian<sup>2</sup>, Zhi Xie<sup>2</sup>, Hua-Jun Chen<sup>1</sup>, Yi-Sheng Huang<sup>1</sup>, Ben-Yuan Jiang<sup>1</sup>, Zhen Wang<sup>1</sup>, Bin-Chao Wang<sup>1</sup>, Xue-Ning Yang<sup>1</sup>, Wen-Zhao Zhong<sup>1</sup>, Qiang Nie<sup>1</sup>, Ri-Qiang Liao<sup>1</sup>, Tony S. Mok<sup>3</sup>, and Yi-Long Wu<sup>1,2</sup>

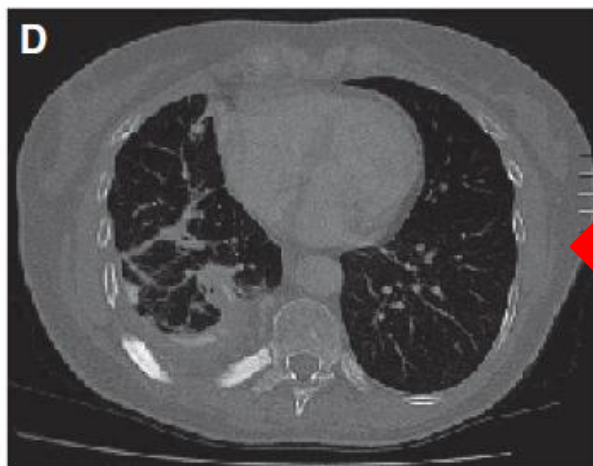


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**Response  
during gefitinib  
[PFS 24 ms]**



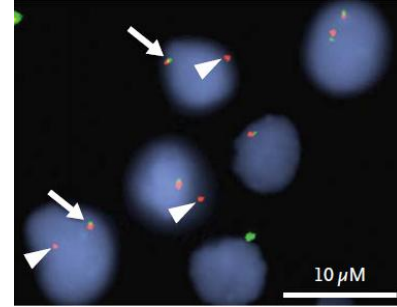
**Response  
during crizotinib  
[PFS 25 ms]**

Long-Term Response to Gefitinib and Crizotinib in Lung Adenocarcinoma Harboring Both Epidermal Growth Factor Receptor Mutation and *EML4-ALK* Fusion Gene

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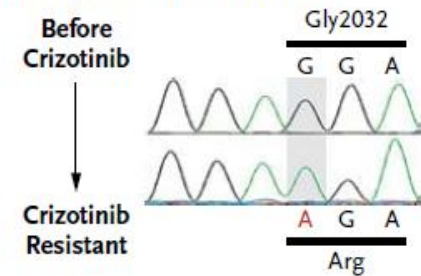
# Acquired Resistance to Crizotinib from a Mutation in *CD74-ROS1*



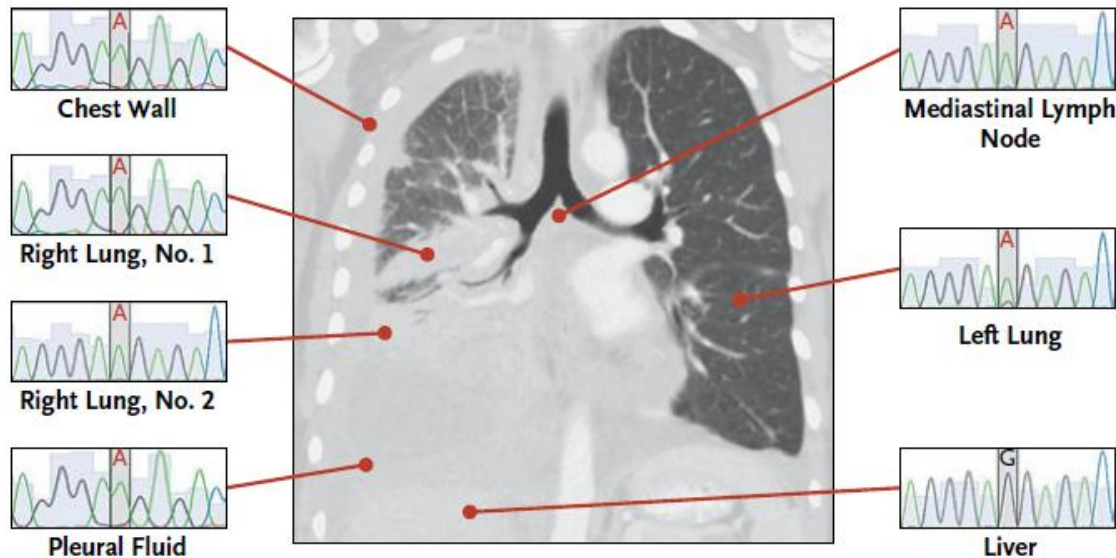
## A CT Scans of the Chest



## B Acquired G2032R Mutation



## C Detection of the G2032R *ROS1* Mutation in Autopsy Specimens



Autopsy Site	G2032R
Liver (normal)	–
Chest wall tumor	+
Right lung tumor no. 1	+
Right lung tumor no. 2	+
Malignant pleural effusion	+
Mediastinal lymph-node tumor	+
Left lung (microscopic disease)	+

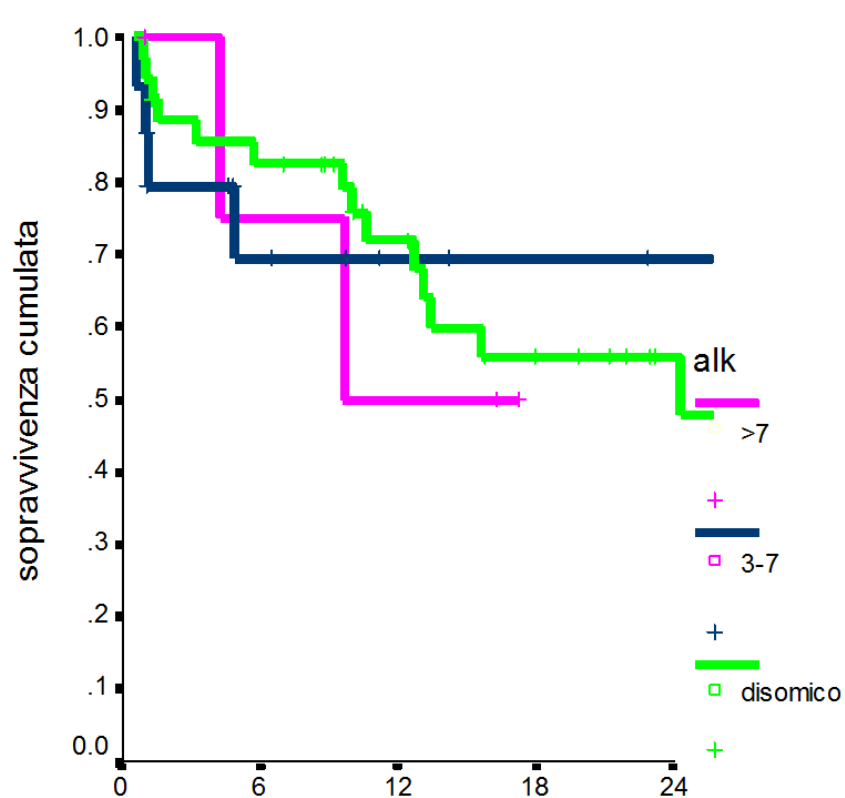


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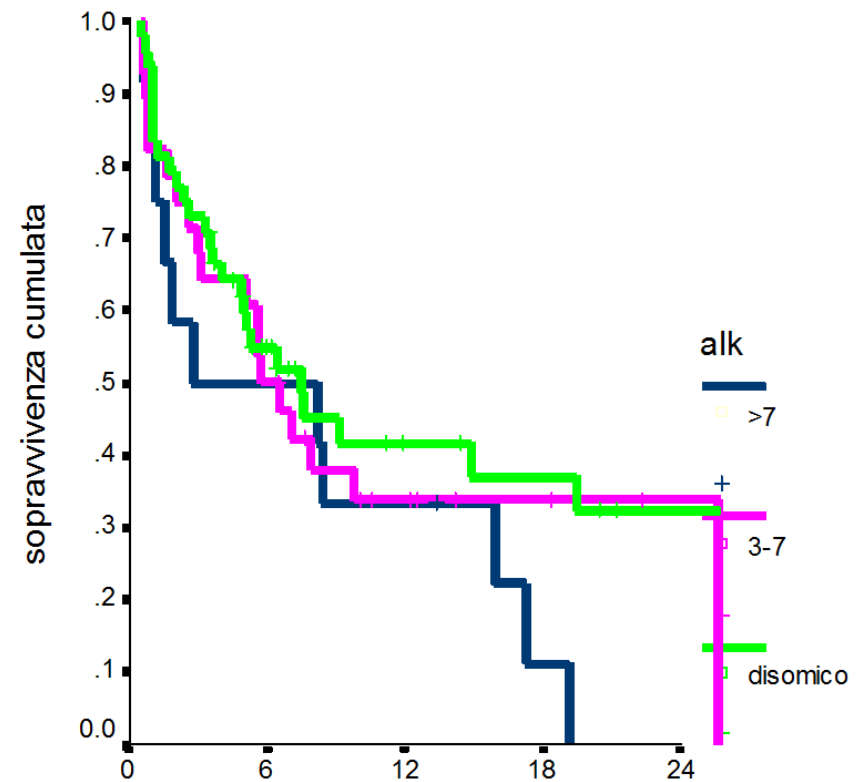
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# Prognostic value of *ALK* gene copy number (GCN) status for resected and metastatic Non-Small-Cell Lung Cancer (NSCLC): a retrospective analysis of 205 patients (pts)



**Resected**



**Metastatic**

