Discussion Proffered Papers Abstract 1225O, Dae Ho Lee & Abstract 929LBA, Rafael Rosell

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Disclosures

- Member of the advisory board: Roche, Lilly, Daichi-Sankyo, BMS, AstraZeneca
- Honoraria for lectures: Roche ,Lilly, Daichi-Sankyo, AstraZeneca

Study Design

Multicenter, Open-label, Parallel, Phase II Study

Eligibility:

- Locally advanced or metastatic nonsquamous NSCLC
- Never-smokers*
- ECOG PS 0-2
- Failed one prior chemotherapy regimen

Stratification Facto

- ECOG PS: 0-1 vs 2
- Tumor histology: Adenocarcinoma vs non-adenocarcinoma

No TKI allowed

1:1:1 Randomization (237 pts)

- Pem (500 mg/m^2, d1)$^+$ + Erl (150mg, d2-d14), q21d
- Erl (150mg, d1-d21), q21d
- Pem (500 mg/m^2, d1)$^+$, q21d

Cycles continued until one of the criteria for discontinuation was met.

$^+$*Vitamin B_{12}, folate, and dexamethasone given in both Pem containing arms*

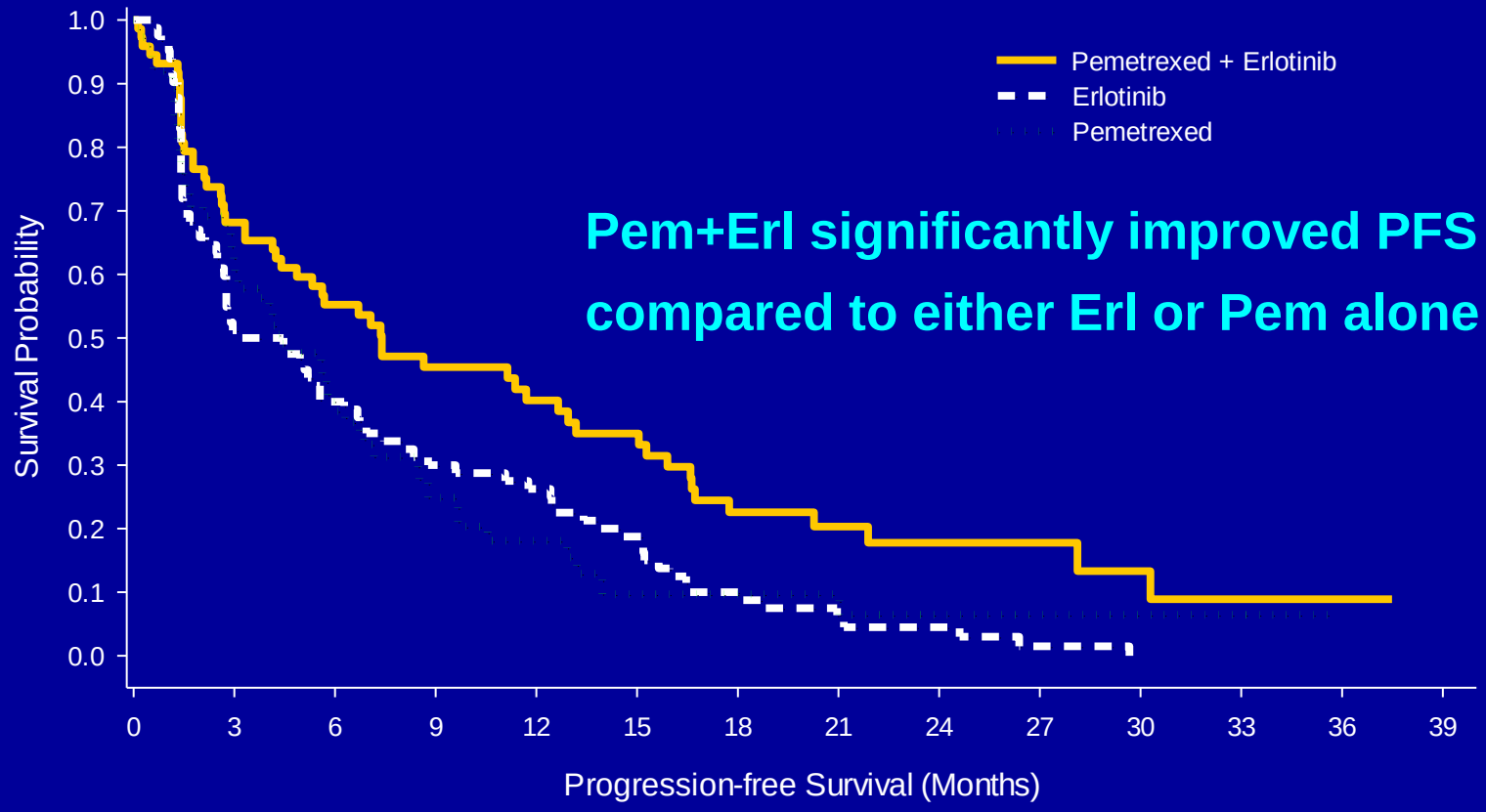
ECOG PS = Eastern Cooperative Oncology Group Performance Status

*Patients having smoked <100 cigarettes in their lifetime

Primary Analysis: PFS (Q-ITT Population)

Global p=0.003

		HR(95% CI):	Median (95% CI) Months
Pem+Erl vs. Erl	p=0.002	0.57 (0.40-0.81)	7.4 (4.4-12.9)
Pem+Erl vs. Pem	p=0.005	0.58 (0.39-0.85)	3.8 (2.7-6.3)
Pem vs. Erl	p=0.959	0.99 (0.70-1.40)	4.4 (3.0-6.0)



Pem+Erl significantly improved PFS compared to either Erl or Pem alone

How to interpret this trial?

In an unselected population….

	Pem + Erl.	Pem	Erl.	Erl. (BR.21)[1]	Pem (Hanna-Trial)[2]
PFS (m)	7.4	4.4	3.8	2.2	2.9

Is this an unselected population?

Shepherd F et al, NEJM 2005, Nasser H et al, J Clin Oncol 2004

Clinical selection

- Never smoking patients
- Non squamous histology
- 52.6 – 59.8% Asian patients (how to count Indians?)
- 55.8% EGFR mutations (18% samples available)
- No Pretreatment with EGFR-TKIs permitted

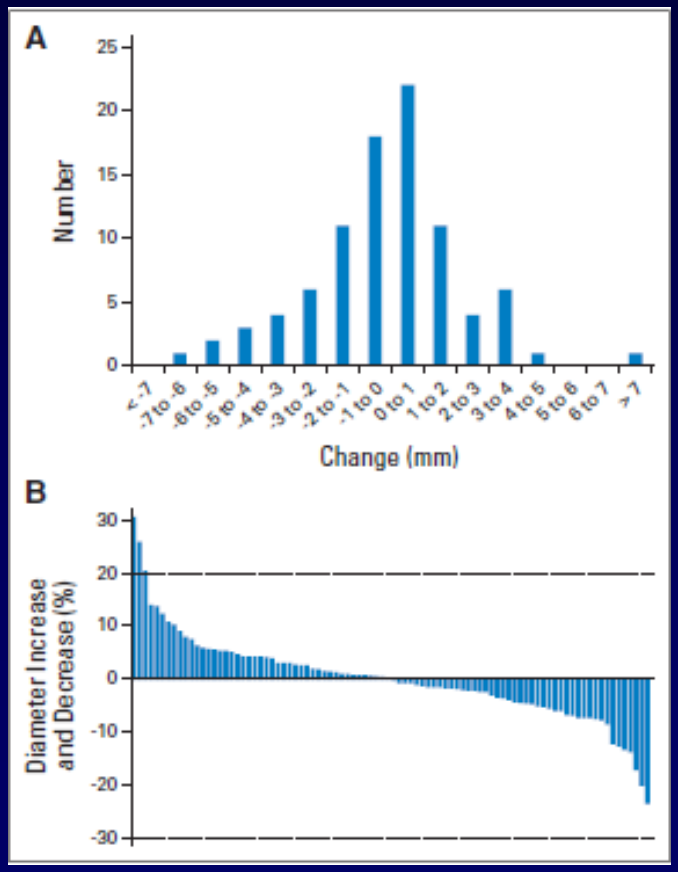
Results didn´t appear to be too overwhelming…

Conclusions?

- Chemo + EGFR TKI > Chemo in an patient with an wild type tumor?
- Maybe…
- Chemo + EGFR TKI > EGFR TKI in an patient with an EGFR mutant tumor?
- Maybe….
- ⇨ we do need an appropriate clinical and molecular classification in these specialised population with high rate of EGFR mutations!!

The issue of PFS

1. How appropriate can PFS be assessed?



Changes up to 30% of tumor size in two CT scans performed with the same machine within 15 minutes

Oxnard JR, J Clin Oncol 2011

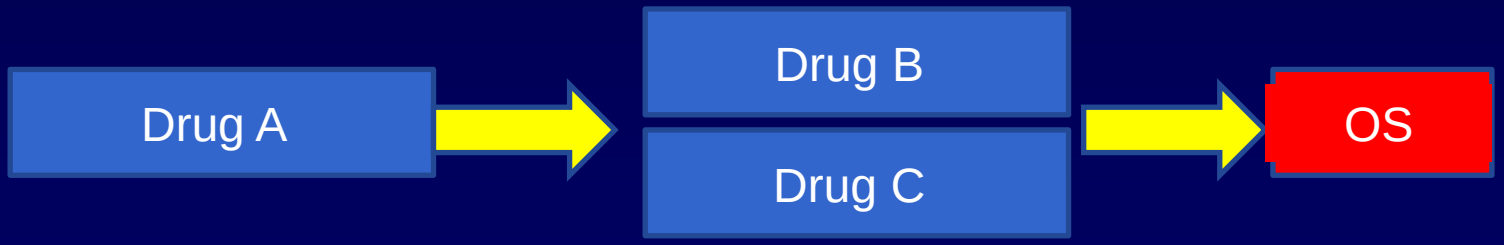
PFS alone?

- PFS Improvement was achieved by increase of toxicity
  - Drug related CTC ¾ side effects: 60% (combination) v 12% (E) v 28.9% (Pem)
- PFS Improvement in correlation with symptomatic benefit?
  - Unfortunately no Quality of life or Symptom relief data reported
- PFS Improvement in correlation with prognostical benefit?
  - No (based on highly censored analysis)
  - The old story: Improve PFS but not OS by adding a drug?

How to move forward in the setting of pretreated patients with NSCLC?

- Second/Third Line Treatment clearly defined by tolerability of treatment.
- In some patients long periods of treatment are to be expected.
- What might the best way to improve efficacy?

Option 1



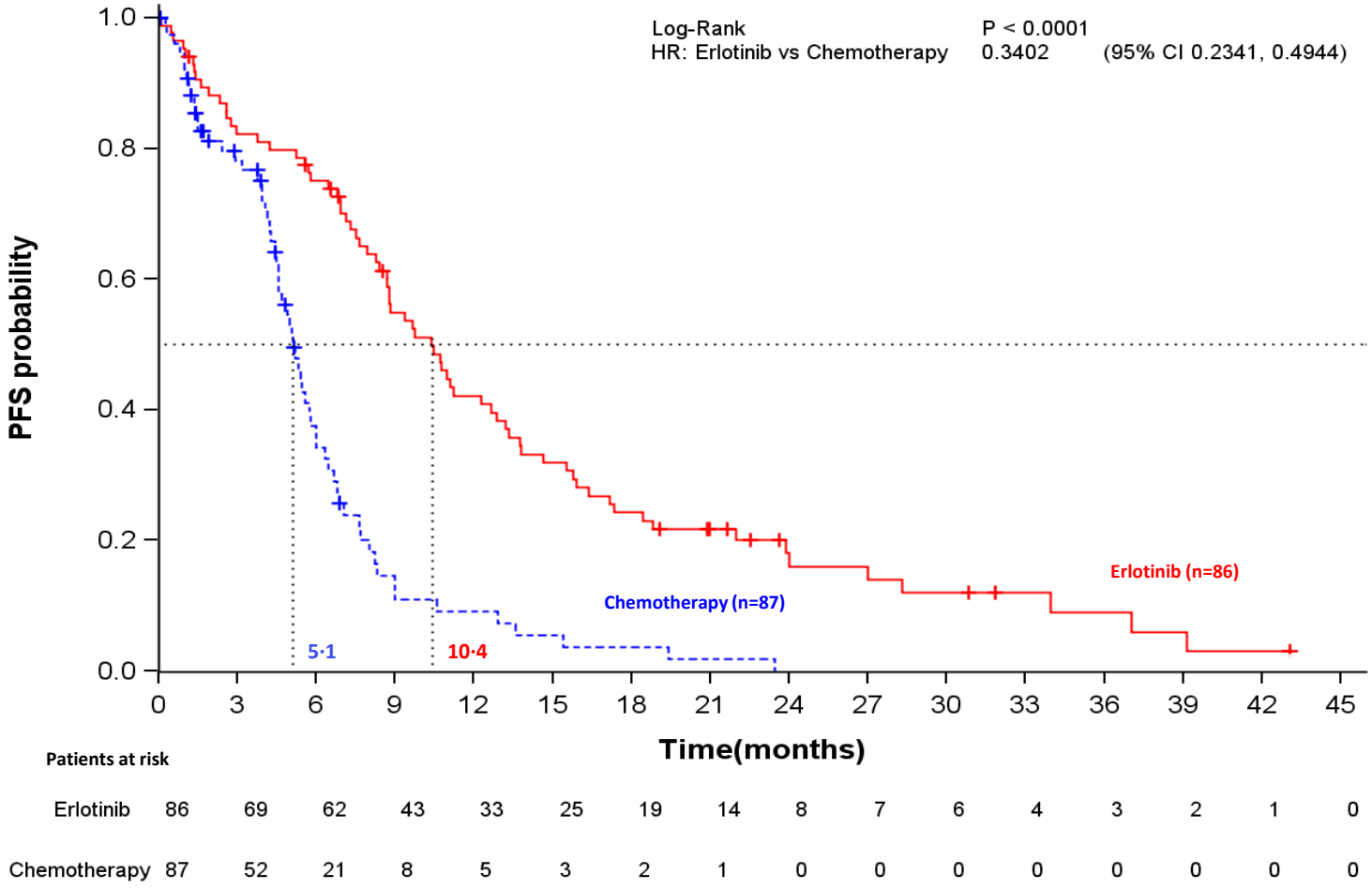
Option 2

- …adequate clinical and molecular classification for interpretation of data
- lessons from the EURTAC trial?

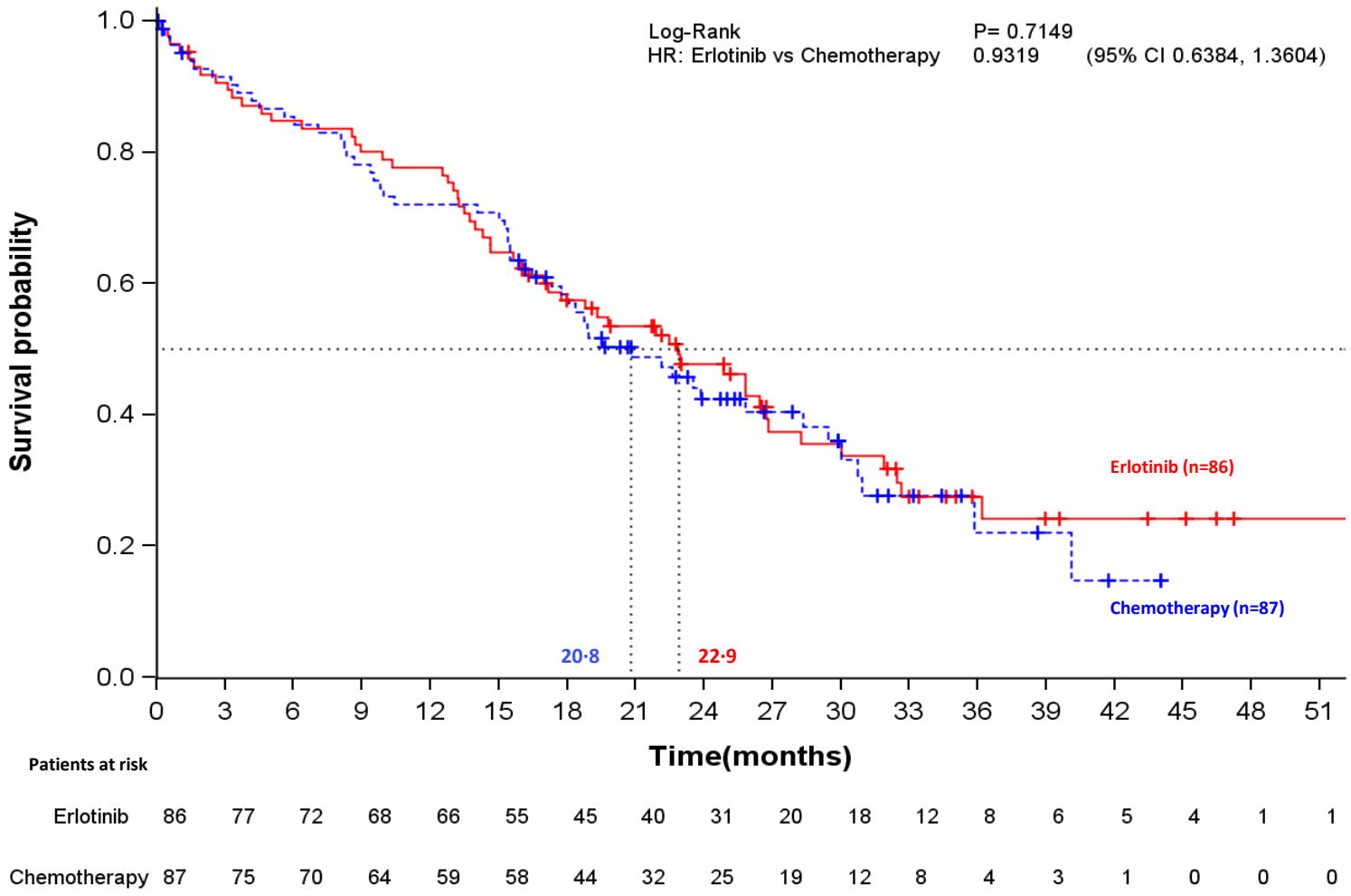
Concomitant actionable mutations and overall survival (OS) in EGFR-mutant non-small-cell lung cancer (NSCLC) patients (p) included in the EURTAC trial: EGFR exon 19 del/L858R w/ or w/out EGFR T790M, TP53, EML4-ALK and BIM mRNA expression

Rafael Rosell, Bartomeu Massuti, Carlota Costa, Miguel Angel Molina, Ana Gimenez-Capitan, Niki Karachaliou, Jia Wei, Alain Vergnenegre, Filippo De Marinis, Enriqueta Felip, Teresa Moran, Radj Gervais, Mariacarmela Santarpia, Margarita Majem, Joaquim Bosch, Petros Giannikopoulos, Craig Mermel, Trever Bivona, Ana Drozdowskyj, Luis Paz-Ares

PFS at final cutoff



OS at final cutoff



Molecular findings in 95 patients from the EURTAC trial

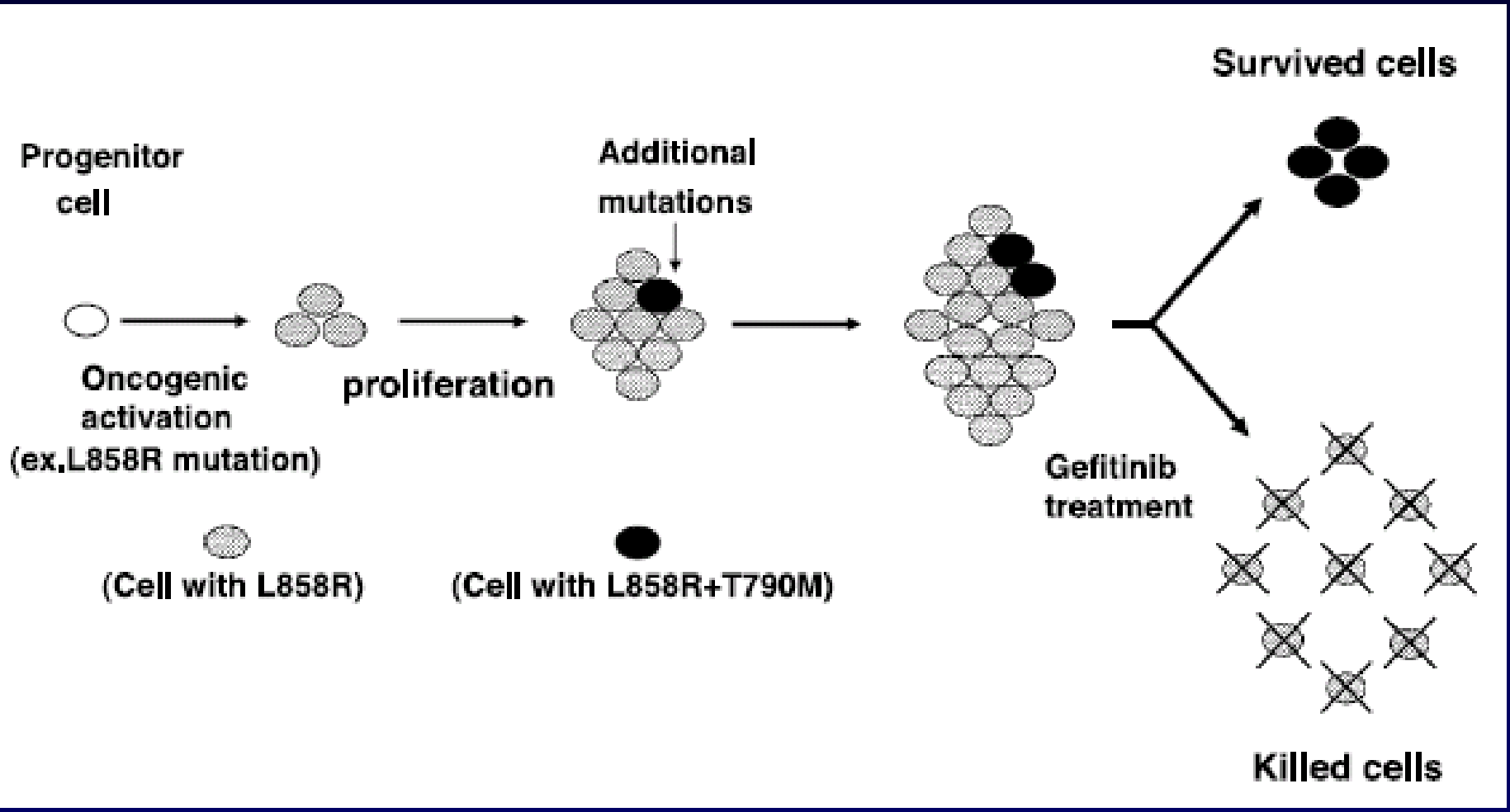
	Total (N=95) N (%)	Erlotinib (N=50) N (%)	Chemotherapy (N=45) N (%)	P-value
EML4-ALK				0.0968
Detected	15 (15.79)	11 (22.00)	4 (8.89)	
Not detected	79 (83.16)	39 (78.00)	40 (88.89)	
No data	1 (1.05)	0 (0.00)	1 (2.22)	
T790M mutation				0.6882
Not detected	59 (62.11)	32 (64.00)	27 (60.00)	
Detected	36 (37.89)	18 (36.00)	18 (40.00)	
TP53 mutation status				0.5953
Mutated	23 (24.21)	10 (20.00)	13 (28.89)	
Wild-type	58 (61.05)	33 (66.00)	26 (57.78)	
No data	13 (13.68)	7 (14.00)	6 (13.33)	
BIM expression				0.5418
Low/intermediate	53 (55.79)	26 (52.00)	27 (60.00)	
High	30 (31.58)	16 (32.00)	14 (31.11)	
No data	12 (12.63)	8 (16.00)	4 (8.89)	

A closer look….

…four earthquakes in Thoracic Oncology?

1. T790M Mutations appear at time of resistance and determine inefficacy of EGFR-TKIs?

The traditional view on T790M mutation-related resistance



Inukai M et al, Cancer Res 2006

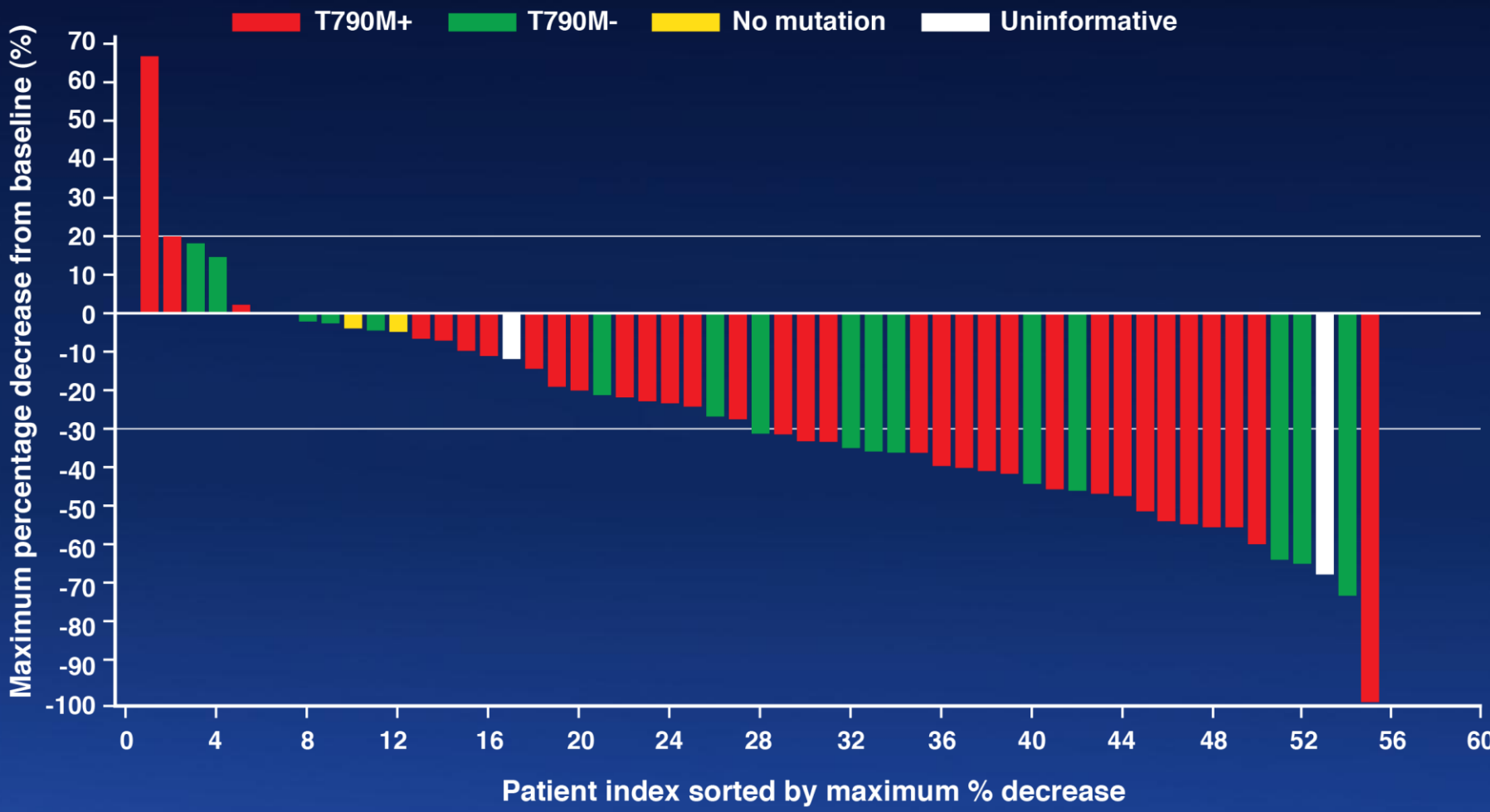
T790M Mutations at primary diagnosis

- 38% pretreatment incidence
- 35% previous report
  (Rossell et al, Clin Cancer Res 2011)
- 0.5% (8/845 patients) historical summary
  (Ma et al J Thor Dis 2010)
- Importance of appropriate testing:
  - PCR > Sanger Sequencing

Clinical implications…

- Do patients with pretreatment T790M mutation not benefit from erlotinib?
- Obviously they do
- PFS T790M+ patients: 12.3 months
- PFS T790M - patients: 9.7 months
- Do second generation TKIs work better in patients with T790M mutations?

Afatinib + Cetuximab
Tumor Regression by T790M Mutation Status



Horn L, WCLC 2011

Clinical implication…

- Do patients with pretreatment T790M mutation not benefit from erlotinib?
- Obviously no
- PFS T790M+ patients: 12.3 months
- PFS T790M - patients: 9.7 months
- Do second generation TKIs work better in patients with T790M mutations?
- Need for clinical data:
  - Importance of pretreatment T790M mutation
  - Importance of T790M mutation at progression

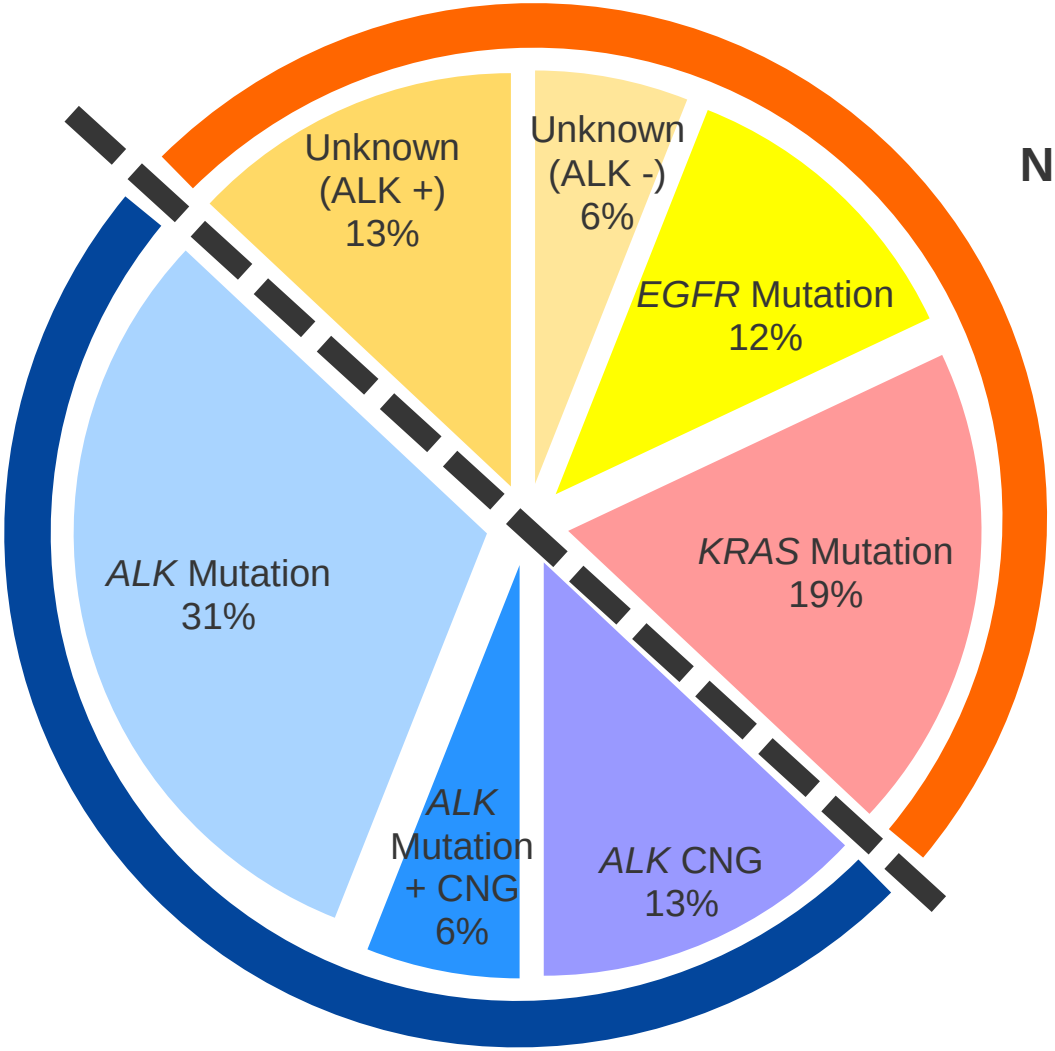
2. EML4 ALK Translocation and EGFR mutation do appear exclusively (death of the „Highlander“ mutation?)

3. The frequency of EML4 ALK Fusions does not exceed 8%

EML4 ALK Translocation

- Among 95 patients with confirmed EGFR mutation EML4 ALK was diagnosed in 15 patients (15.8%)
  - Prior reports?: 6% EGFR mutations in patients with EML4 ALK Translocation (Sasaki T et al, Cancer Research 2011)
  - EGFR Mutation as part of resistance mechanism after crizotinib?

Systematic resistance to ALK inhibitors



ALK Non-Dominant

ALK Dominant

Doebele et al. J Clin Oncol 30, 2012 (suppl; abstr 7504)

EML4 ALK Translocation

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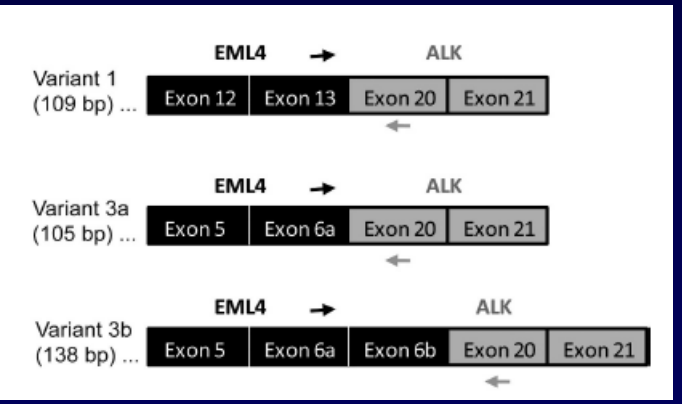
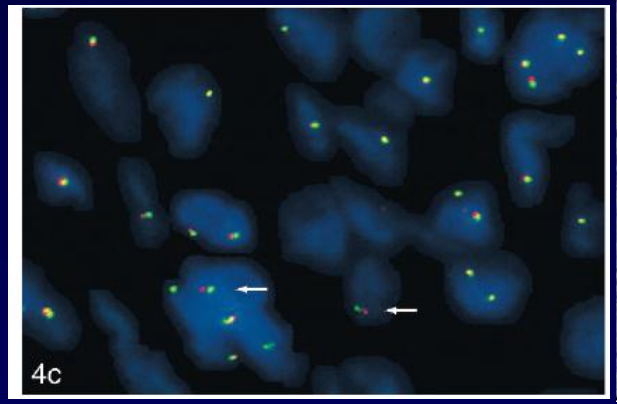
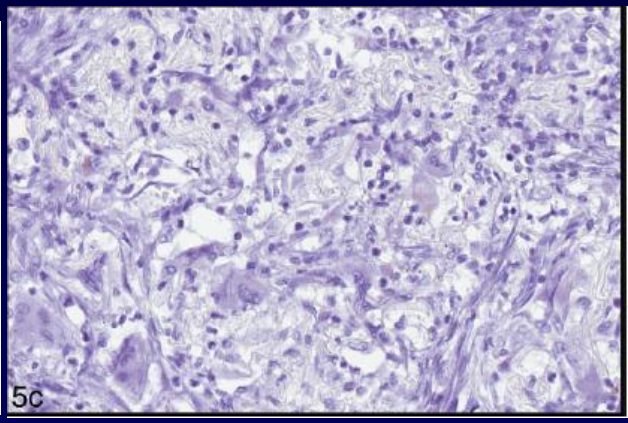
  - Prior reports?: 6% EGFR mutations in patients with EML4 ALK Translocation (Sasaki T et al, Cancer Research 2011)
  - EGFR Mutation as part of resistance mechanism after crizotinib?
- Method of diagnosis?

EML4 ALK ≠ EML4 ALK

46 pulmonary adenocarcinoma tested for EML4-ALK fusions







11/46 (24%) PCR
Variant 1 and 3a/b

7/46 (15%) FISH

9/46 (20%) IHC

Great variability of EML4 ALK fusions by different assessment methods

Eurtac: EML4-ALK fusions identified by PCR, 1/15 pat. Fish +, 0/15 pat ICH +

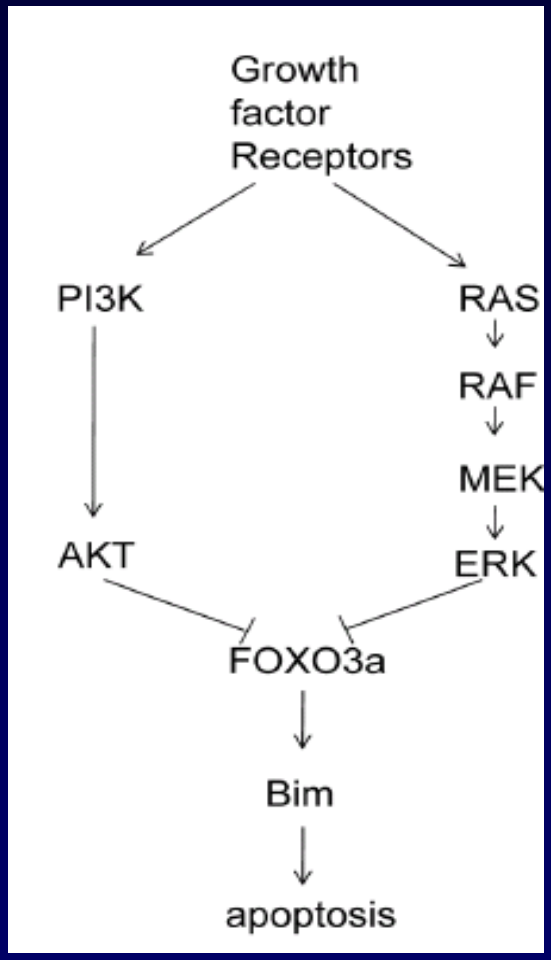
Wallander ML et al, Arch Pathol Lab Med 2012

Clinical implications..

- What is the most appropriate test to define EML4 ALK fusion?
- FISH has been proven, what about PCR?
- EGFR-TKI do not work in patients with EML4ALK fusions?
- Median survival not reached
- Combination of EGFR-TKI and Crizotinib better than Crizotinib?
- Interesting (particular for resistance following Crizotinib but we need clinical confirmation)

4. The book of EGFR mutations in NSCLC is to be closed.

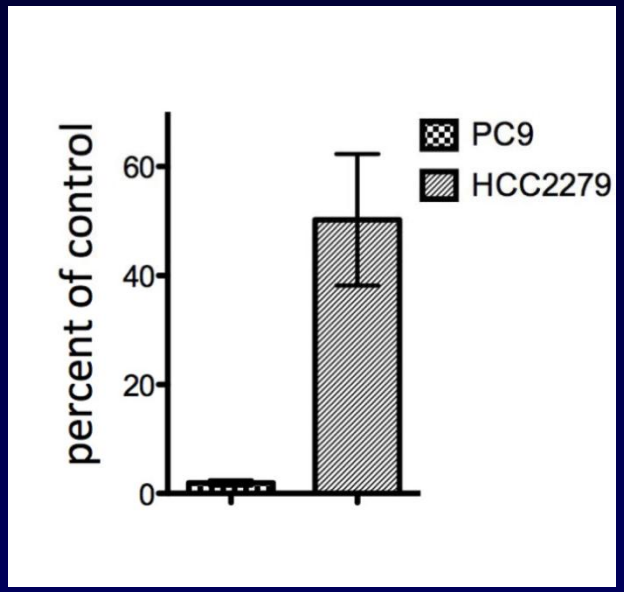
BIM and EGFR mutation



- 30% of patients with EGFR-mutant tumors do not respond to EGFR-TKI
- Evasion of Apoptosis – hallmark of cancer
- Bcl-2 like proteins connect growth factor signals with apoptosis (mitochondria)
- BIM pro apoptotic Bcl-2 protein
- BIM mediator of targeted therapy induced apoptosis

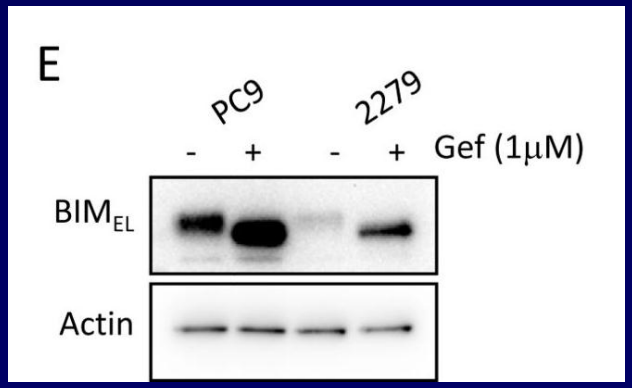
Faber A et al, Cancer Discov 2011

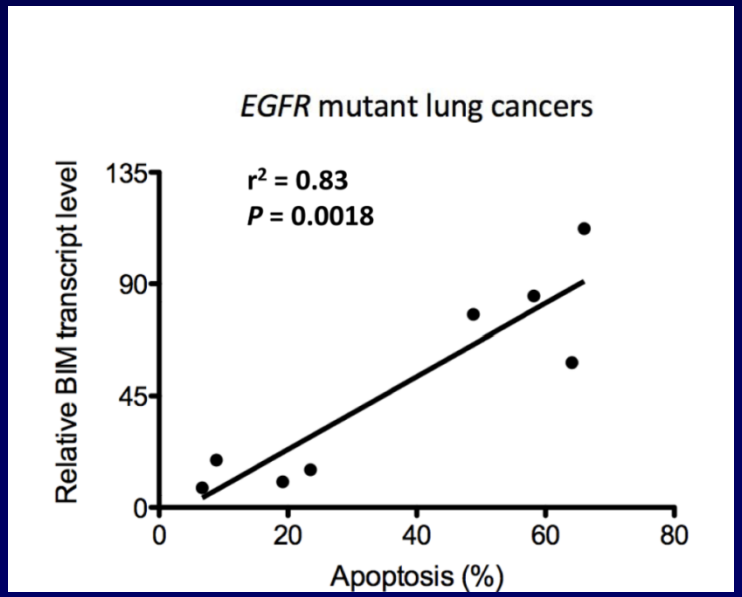
BIM and EGFR mutation



Exon 19 mutation

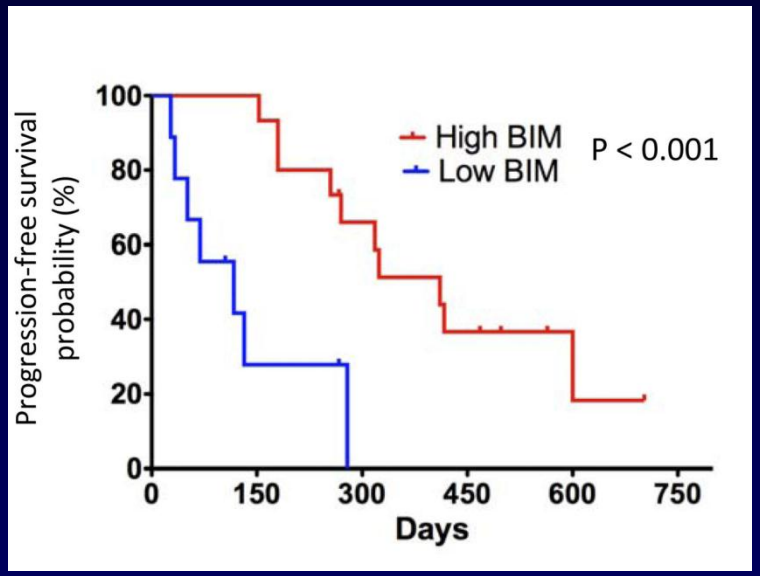
- PC9: Apoptotic response ≈ 65%
- HCC2279: Apoptotic response < 10%



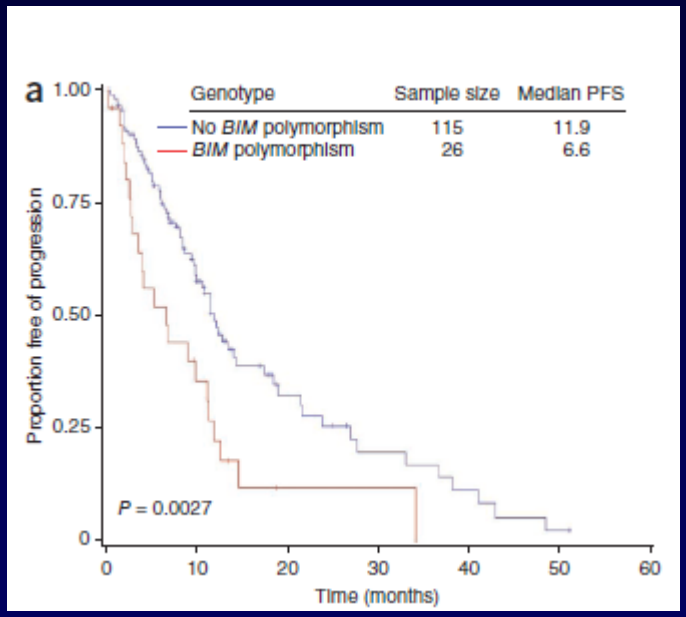


Faber A et al, Cancer Discov 2011

BIM and EGFR mutation



24 patients, metastatic NSCLC
No T790M, KRAS, PIK3CA mutation.



141 Asian patients, metastatic NSCLC, confirmed EGFR mutation.

Faber A et al, Cancer Discov 2011; Ng KP et al Nature Medicine 2012

Multivariate analyses

- Multivariate analyses included sex, smoking status, PS, treatment group, brain mets, bone mets, type of EGFR mutation, T790M, BIM, TP53 and EML4-ALK
- Markers of longer PFS
  - erlotinib (HR, 0.36; P=0.0005)
  - high BIM expression (HR, 0.55; P=0.033)
- Markers of longer OS
  - high BIM expression (HR, 0.47; P=0.025)

EGFR del 19 / L858R
w/ or w/out

- **T790M**
- **BIM mRNA**
- **TP53**
- **EML4/ALK**

erlotinib

PFS
12.3 mo

T790M +

MS
40.1 mo
16 pts ↑ **BIM**

HR = 2.46 (p=0.04)

15.4 mo
17 pts ↓ **BIM**

9.7 mo

T790M -

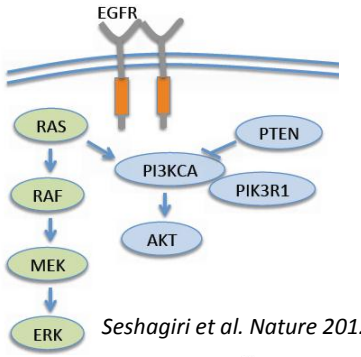
MS
25.8 mo
↑ **BIM**

22.1 mo,
↓ **BIM**

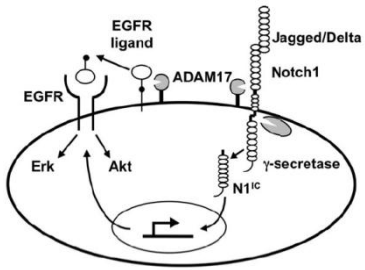
15 pts EML4-ALK
MS= NR

Compensatory survival pathways that can inhibit **BIM**

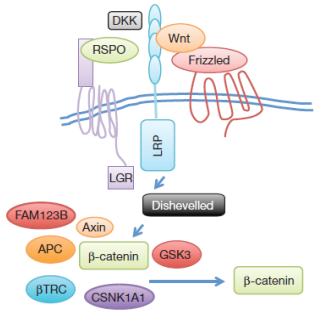
- ROR1(Pan-HER i)
- ZNF217(β-TGF i)
- GATA2/STAT5/BCL2
- NOTCH3 (Gsi), HES1, Numb
- ADAM17 (MEK i)
- Tankyrases 1&2 (TNKS)



Seshagiri et al. Nature 2012



Baumgart et al. Cancer Res 2010



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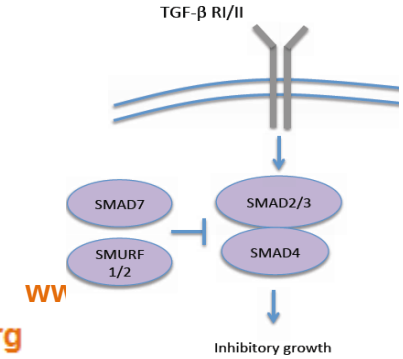

Seshagiri et al. Nature 2012

VIENNA 2012 ESMO congress

www.esmo2012.org

Clinical implications…

- Additional assessments besides EGFR mutation test might be useful because
- There might be therapeutic options to impact BIM regulation:
  - Upregulation of BIM expression (e.g. by HDAC inhibitors or demethylating agents)
  - Upregulation of unbound BIM (BH3 mimetics)
  - BIM independent upregulation of BIM (chemotherapy)

Thank you for keep us thinking!!