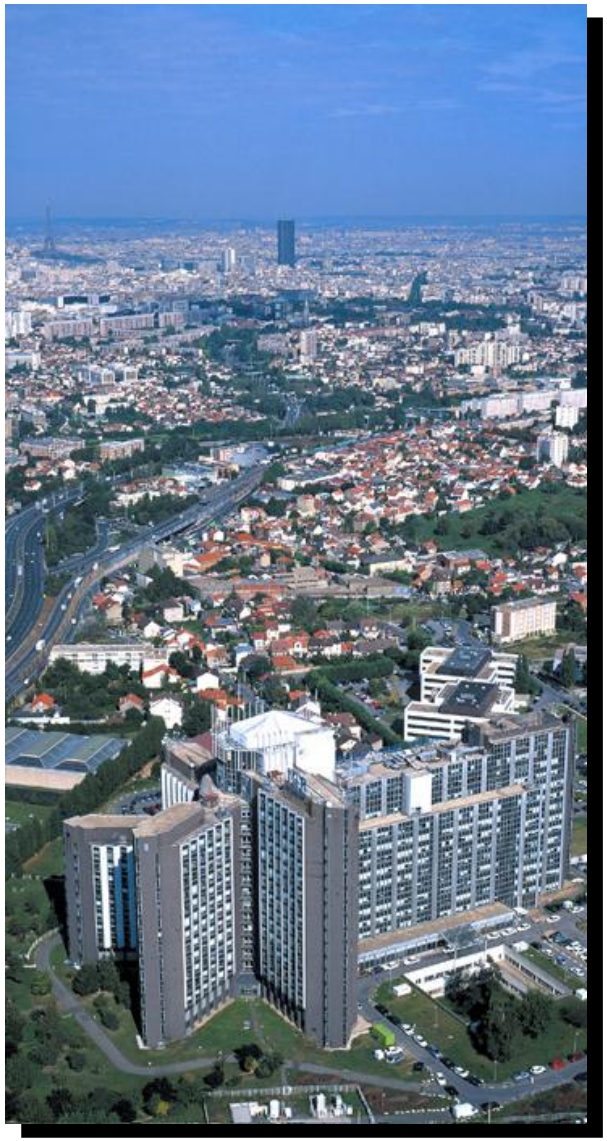
VIENNA 2012 ESMO congress



ESMO 2012 Presidential Symposium I

DISCUSSANT
LBA1: Profile 1007 phase III trial

Jean-Charles SORIA

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Inserm U981
French Institute of Health and Medical Research

IOT

UNIVERSITÉ PARIS SUD

Disclosure Slide

Consultancy fees from :

Abbott, Amgen, AstraZeneca, BMS, GSK, Lilly, Merck-Serono, MSD, Pfizer, Roche-Genentech, Sanofi

Steering committee activities :

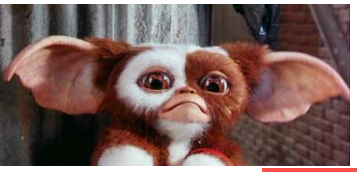
AstraZeneca, Boehringer-Ingelheim, Pfizer, Roche-Genentech, Servier

Discussion goals

- Background on metastatic NSCLC
- Putting efficacy and survival data into context
- Toxicity data
- Defining a molecular segment for drug development
- Optimal strategy in ALK patients
- Availability of targeted agents EU vs USA

NSCLC

no clear driver
or oncogenic event



NSCLC
Oncogene Addicted

LARGE CELL

ADENOCARCINOMAS

SQUAMOUS

cisplatin + pemetrexed

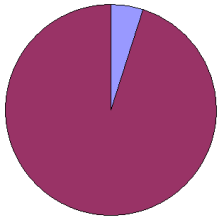
doublet + bevacizumab

platinum doublet

EGFR mutants
- Intrinsic better prognosis
- Predictive marker of efficacy for EGFR TKI

ALK translocated
crizotinib

The ALK entity

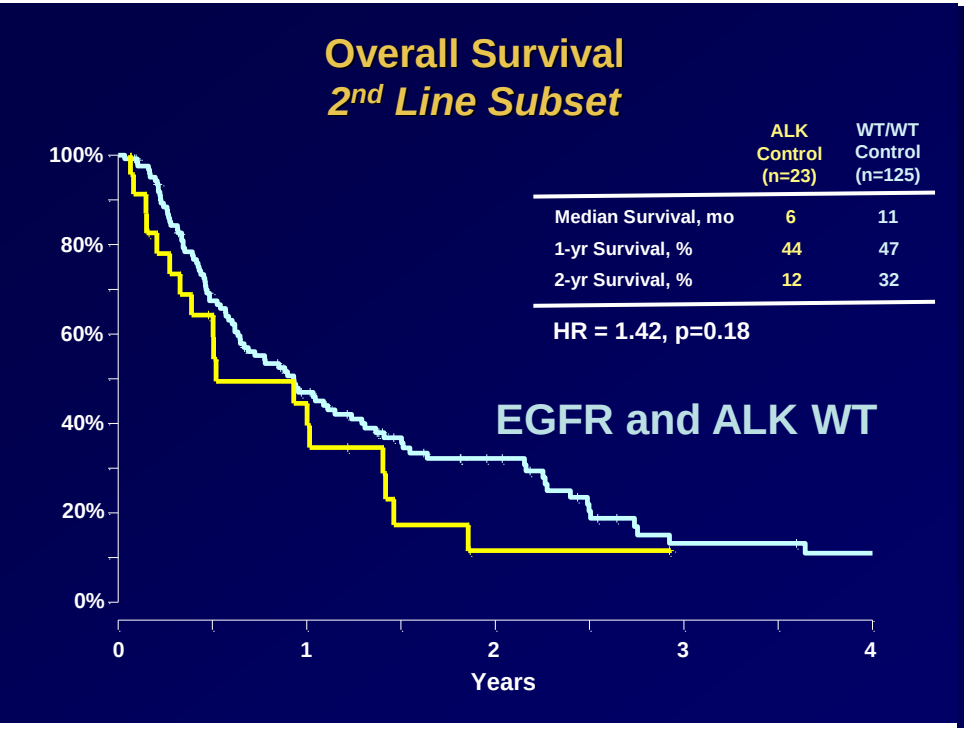


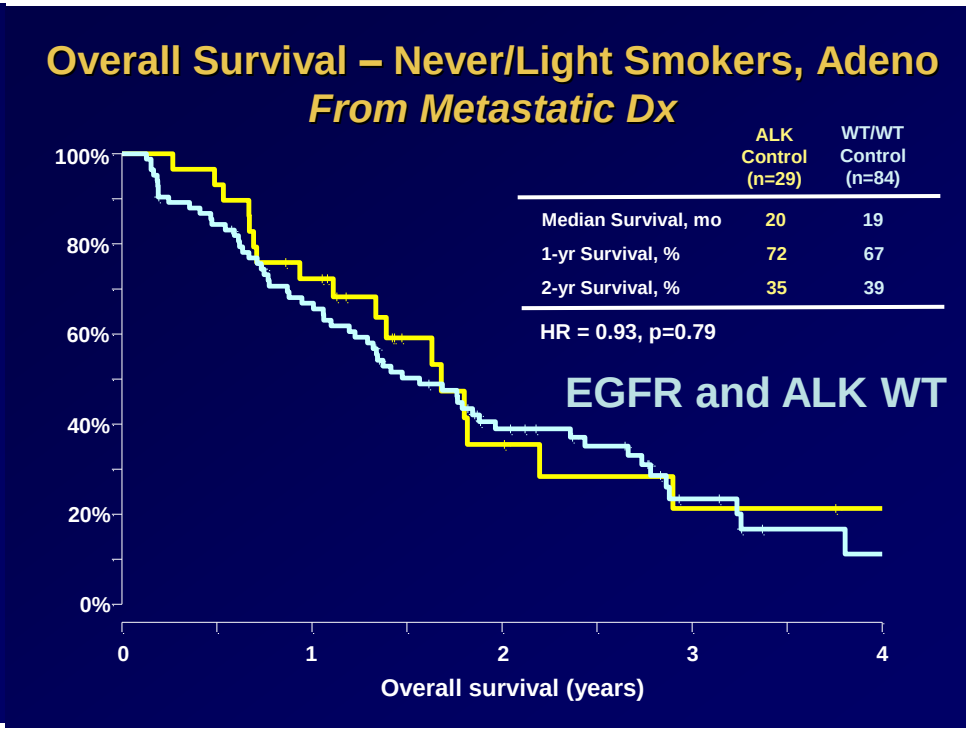
5% of NSCLC (range 3-7)

- 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

Camidge Nat. Rev. Clin. Oncol 2012

Prognostic value of ALK translocation





- HR 1.42, p =0.18
- HR 0.83, p =0.78

- ALK gene fusion does not appear to be a favorable prognostic factor BUT no randomized data

Shaw et al ASCO 2011 #7507; Lancet Oncol 2011

Courtesy F Blachall

Discussion goals

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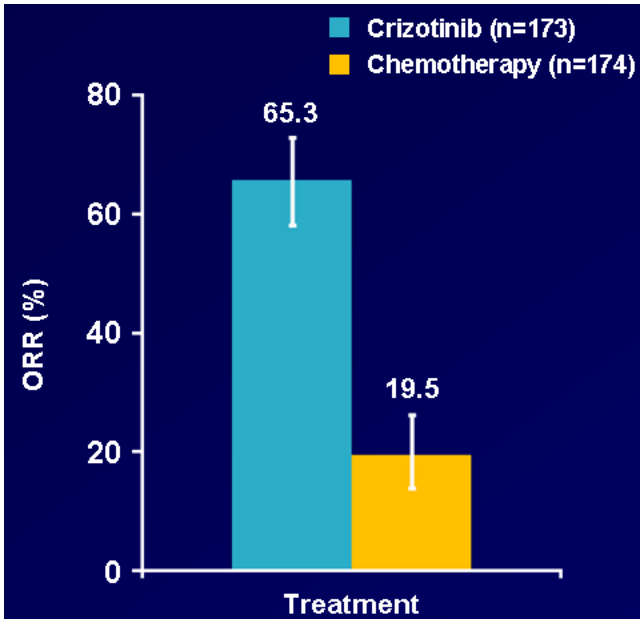
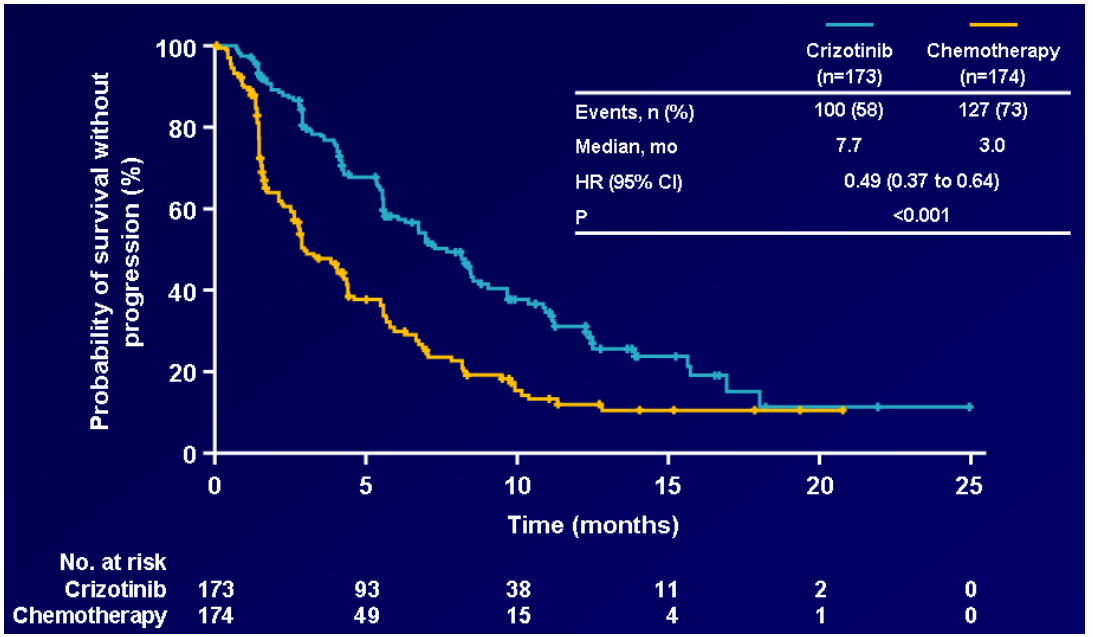
Activity

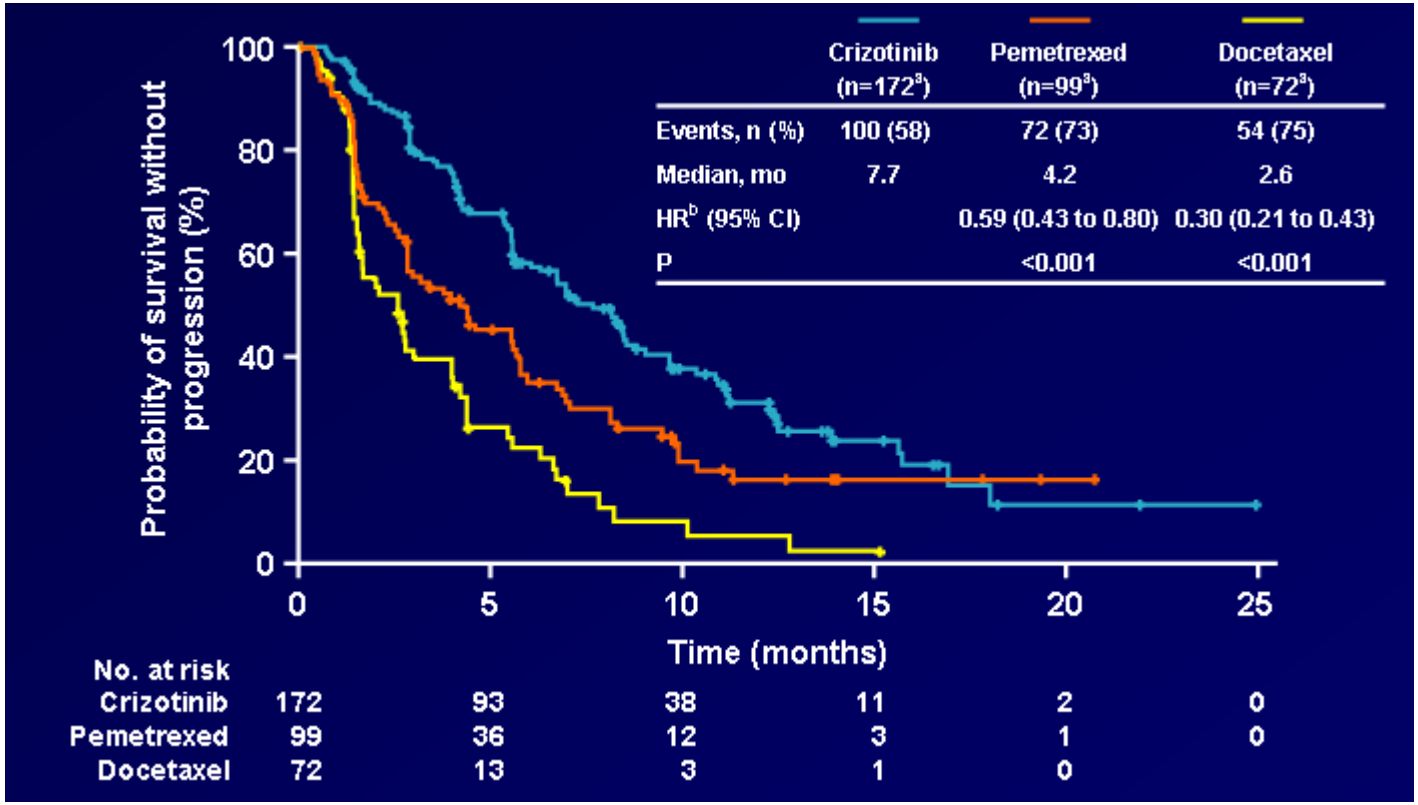




- Clear and strong signal of activity
  - → Objective response **is tripled**
  - → PFS is improved by **4,7 months** (**HR of 0,49**)
  - → Improvement of PFS in almost all subgroups
  - → Improvement of lung cancer-related symptoms and global QOL

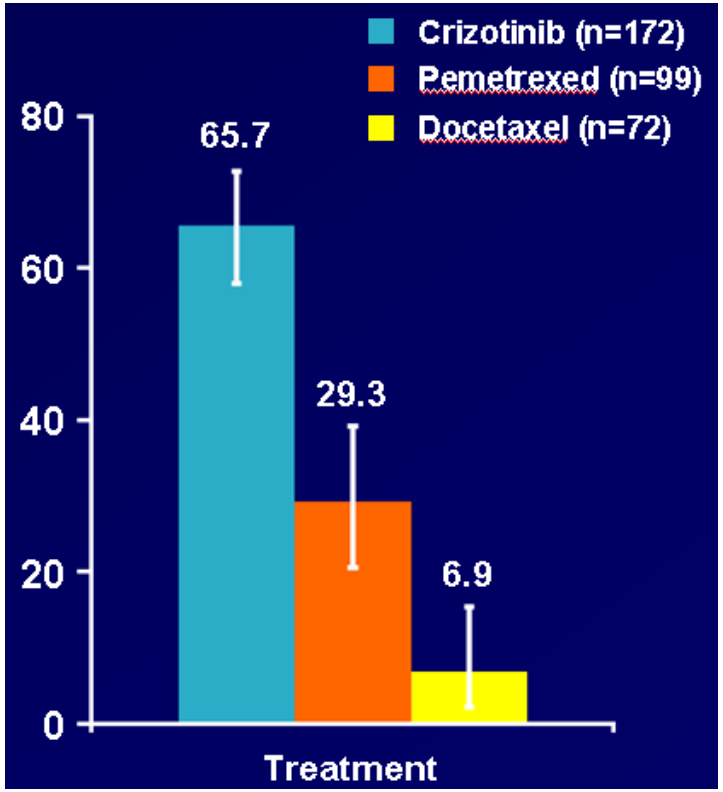
Efficacy data

- Pemetrexed vs docetaxel
  - → No formal randomization between these 2 arms
  - → Choice based on previous therapy and histology
  - → PFS advantage remains even when comparing to pemetrexed alone



Chemosensitivity

- Pemetrexed has prominent activity in ALK+ NSCLC



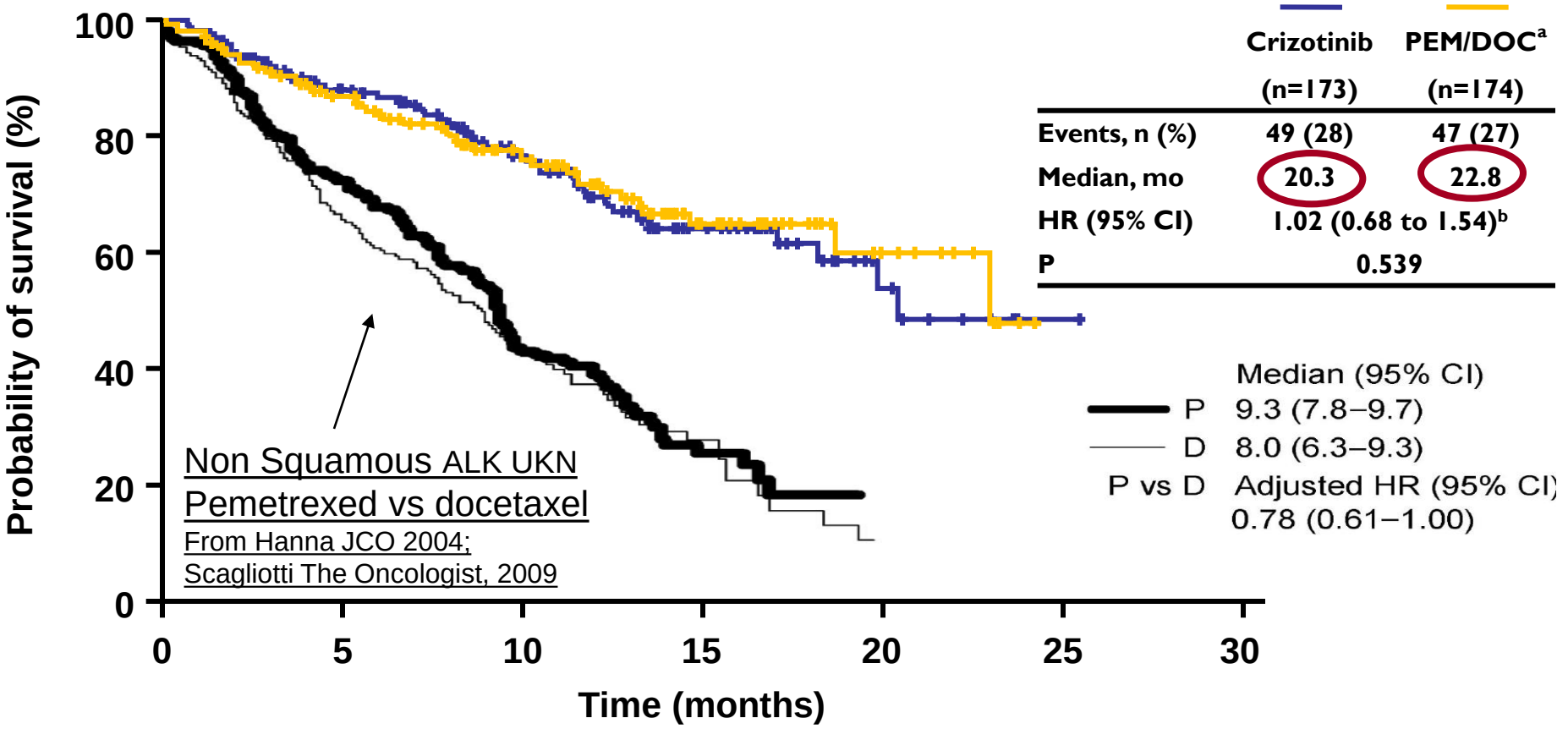
	Hanna Pem vs docetaxel		1007 Pem arm
Median PFS (months)	3,5 (ADK)	3,1 (non-SCC)	4,2
ORR	12,8 %	11,5 %	29,3 %

Hanna et al, JCO 2004

Scagliotti et al ,The Oncologist 2009

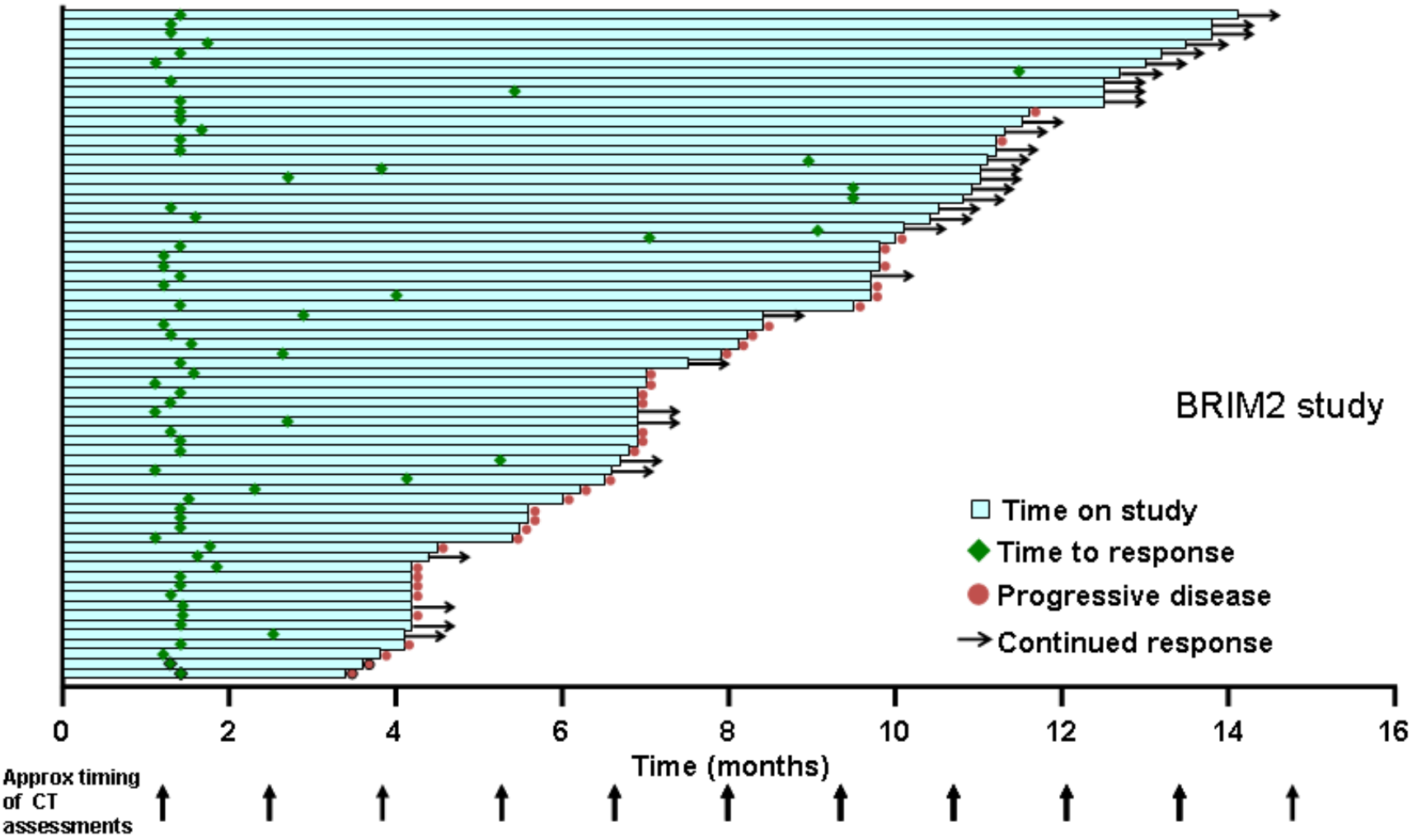
Camidge, Nat. Rev. Clin. Oncol 2012

Overall survival



- Lack of overall survival advantage:
  - → Cross-over +++ (87% of PD-patients on Chemo crossed to crizotinib)
  - → Data is immature: only 40% of 241 expected OS events occurred
  - → 49% of patients on crizo arm are still on treatment vs 16%
- Impressive median OS of 22 months in the 2nd line setting +++

Efficacy data



Sosman NEJM 2012

Discussion goals

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Tolerability of crizotinib

- Visual disorders

  light trails, flashes,

  image persistence at edge of visual field

  light adaptation

- Liver toxicity

  transaminases increase 38% (ALAT)

  grade ¾ is 16%

- Other

  renal cysts (rare)

  pneumonitis (rare)

  asymptomatic bradycardia (unknown)

  low testosterone (common) but real impact on sexual life?

Weickhardt et al. Cancer 2012

Discussion goals

- Background on metastatic NSCLC
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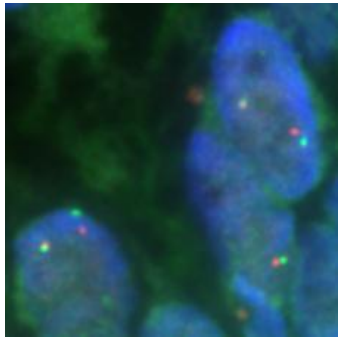
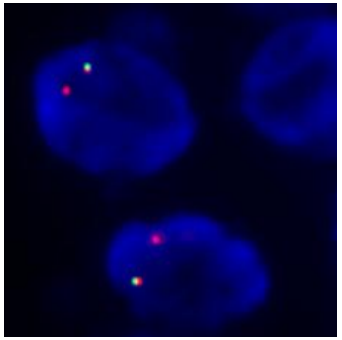
How do we define ALK positivity ?

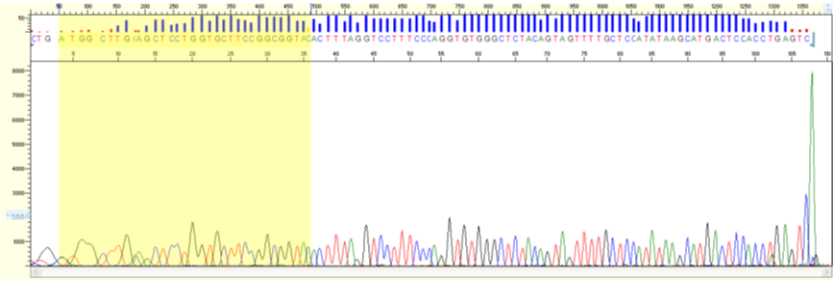
- FISH break-apart
  - → Why the 15% threshold ?
  - → 15% is 2 SD above the average number of split or isolated red signals in FFPE non-tumor control tissues
- RT-PCR
  - → Allows detection of variants
- IHC

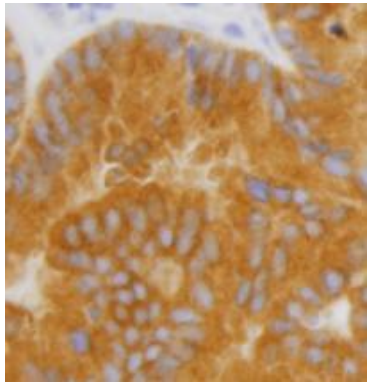
split red & green signals



Isolated red signals







Kwak NEJM 2012; Camidge Nat. Rev. Clin. Oncol 2012, Sasaki et al 2010; Sanders et al. 2011

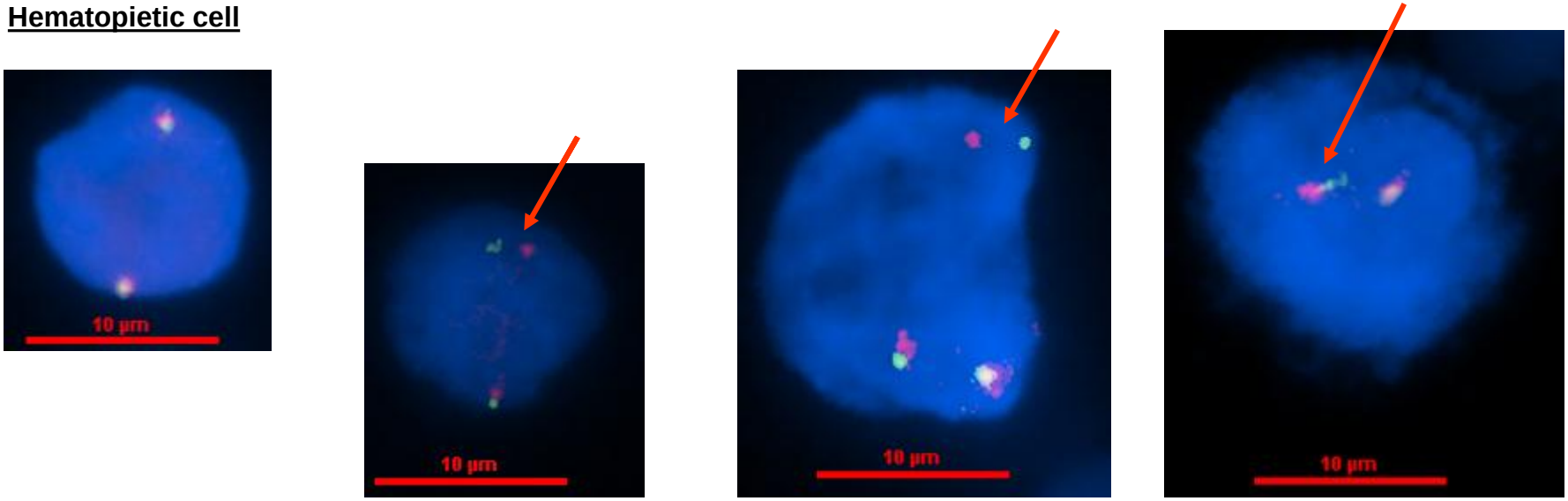
Detection of ALK-fusion gene in CTCs

Françoise Farace, Benjamin Besse, Philippe Vielh and Jean Charles Soria

Translational research Laboratory & INSERM U981

Examples of translocated CTCs

Hematopietic cell



Patient with 25 translocated CTCs/ml

Ilie Annals Oncol 2012

Molecular predictors of efficacy

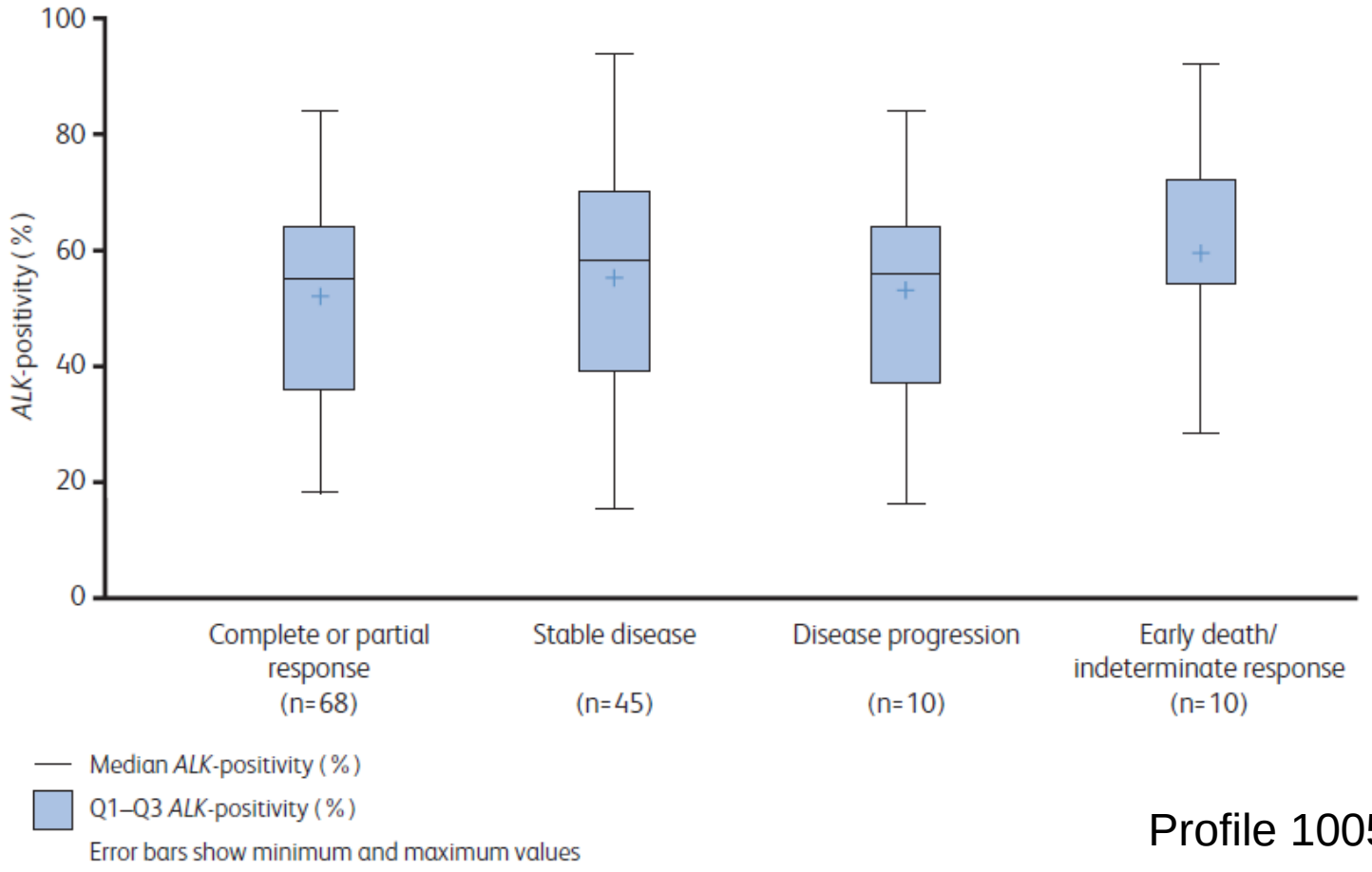
- Variable responses are seen among ALK + patients in this trial !

- Is the % of ALK translocated cells a predictor of crizotinib benefit ?

- Are the different ALK variant fusions predictors of crizotinib benefit ?
  → EML4-ALK (11 variants), KIF5B-ALK, TFG-ALK, KLC1-ALK…

Heuckmann et al CCR 2012

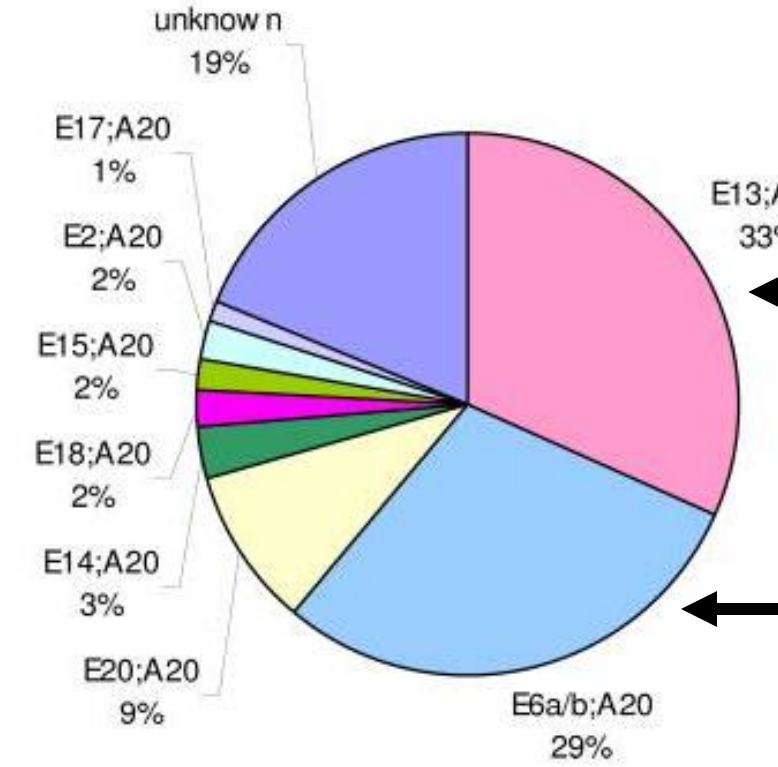
Figure 2. Box plot showing distribution of percent *ALK*-positivity (FISH) by best overall response.

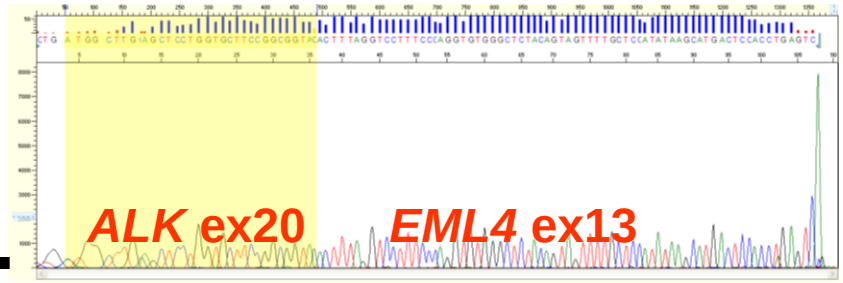


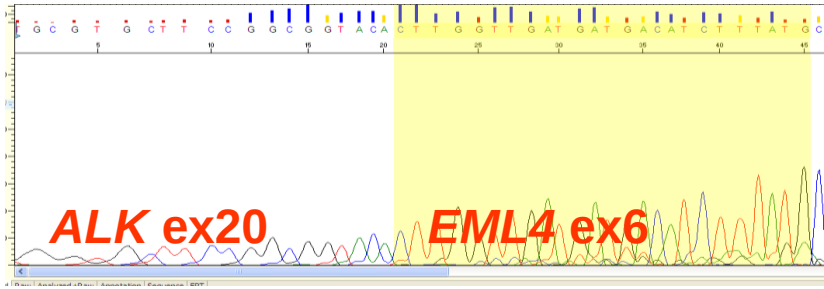
Profile 1005

Kim ECCO-ESMO 2011, Abs 9084

At least 11 EML4-ALK variants..
as well as KIF5B, TFG, and KLC1 fusion partners







EML4-ALK Variants

E13;A20	E13;A20 (variant 1), E13;ins69 A20
E6;A20	E6a/b;A20 (variant 3a/b)
E20;A20	E20;A20 (variant 2), E20;ins18A20
E14;A20	E14;ins11del49A20(variant 4'), E14;del12A20 (variant 7)
E18;A20	E18;A20 (variant 5')
E15;A20	E15 del19;del20A20 (variant 4)
E2;A20	E2;A20 &E2;ins117A20 (variant 5a/b)
E17;A20	E17;ins68A20

Heuckmann et al CCR 2012

Sasaki et al 2010; Sanders et al. 2011; Courtesy F Blackhall

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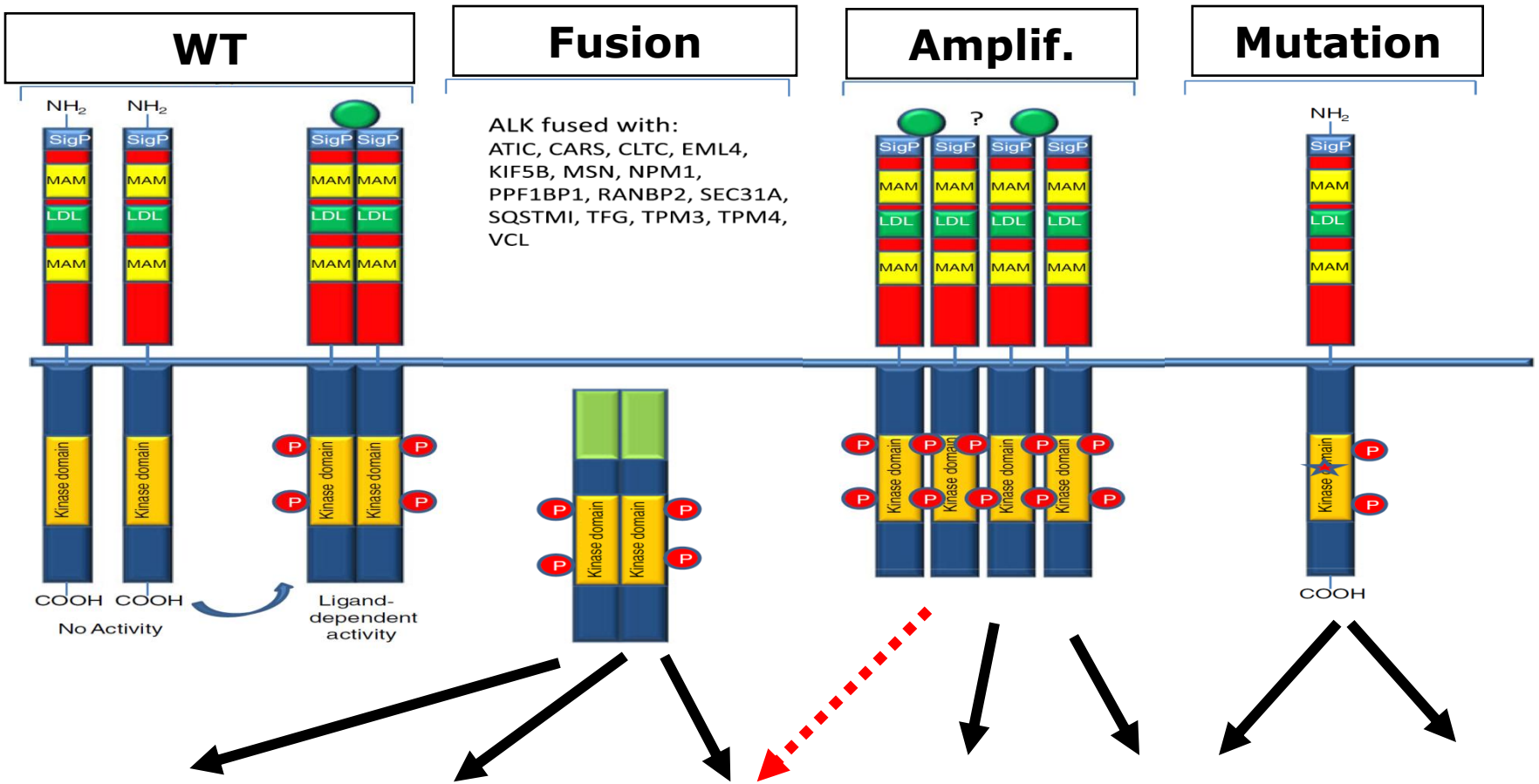
VIENNA 2012 ESMO congress

ALK across cancer field



Inflammatory Myoblastic Tumors — 3 PR / 7

ALCL Lymphoma — 7 CR / 8

Lung Cancer

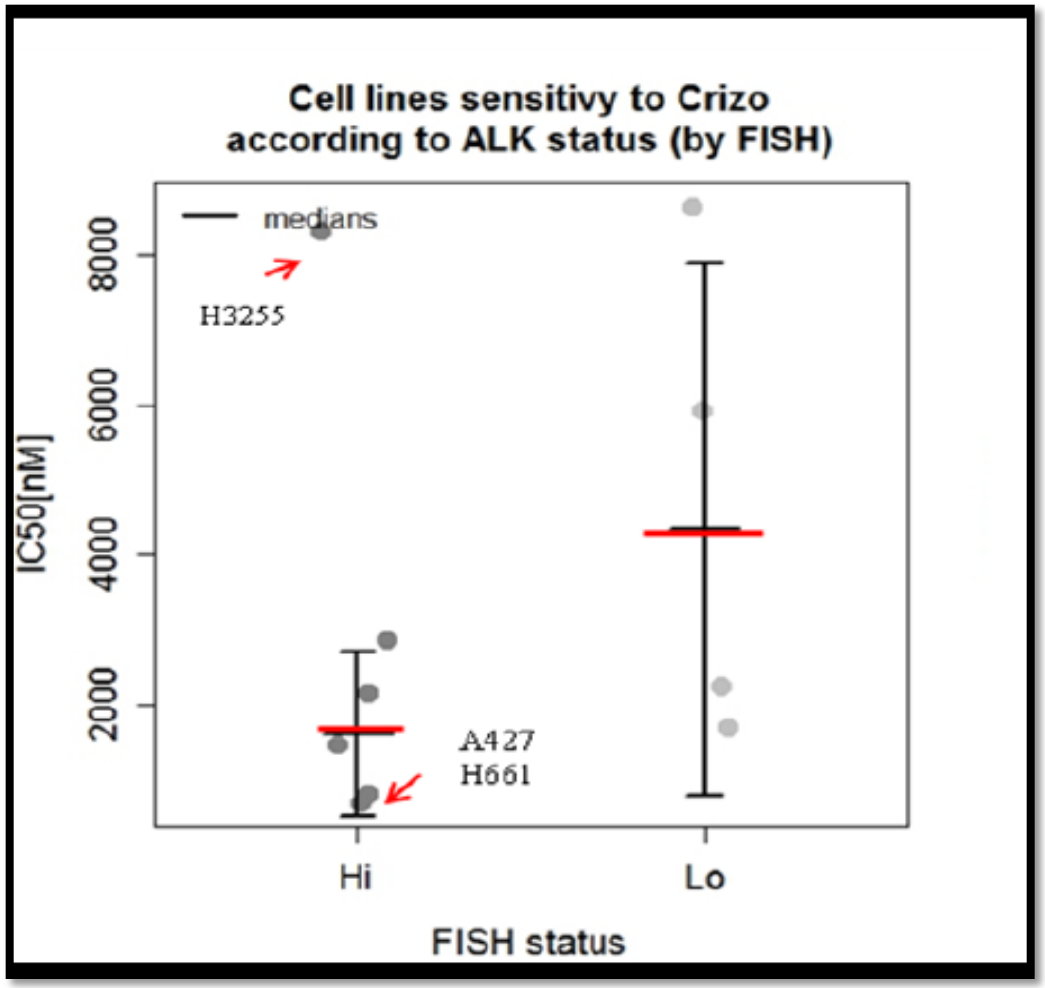
Breast Cancer *inflammatory*

Neuro-blastoma — 1 PR / 3

Rhabdo-myosarcoma

Phase I study

ALK amplification in vitro

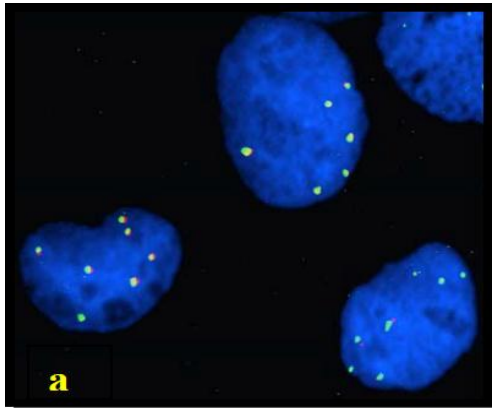


9 cell lines

Median IC50

Low ALK 1750 nM [300-2800nM]

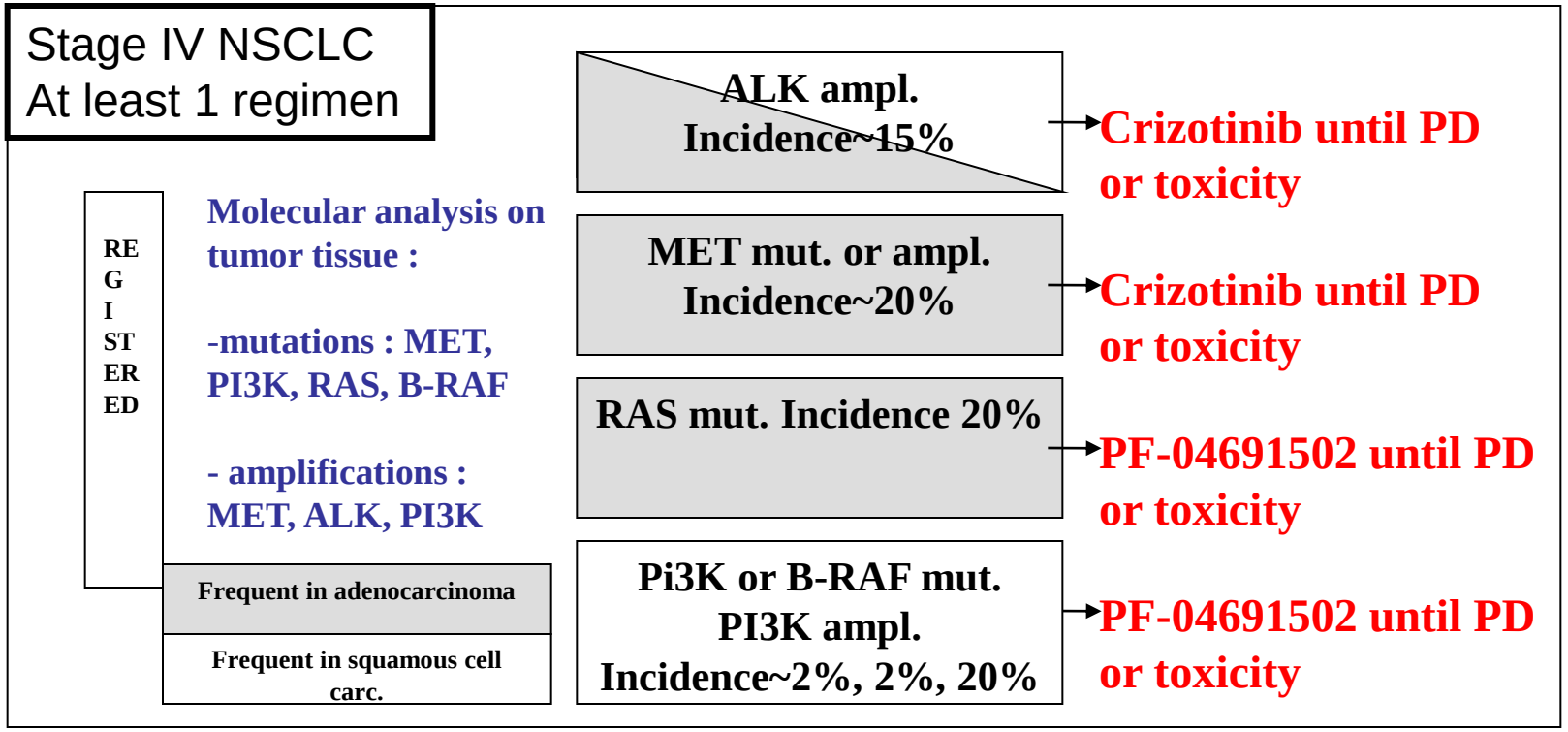
High ALK 4500 nM [800-8000nM]



Kalai ASCO 2012

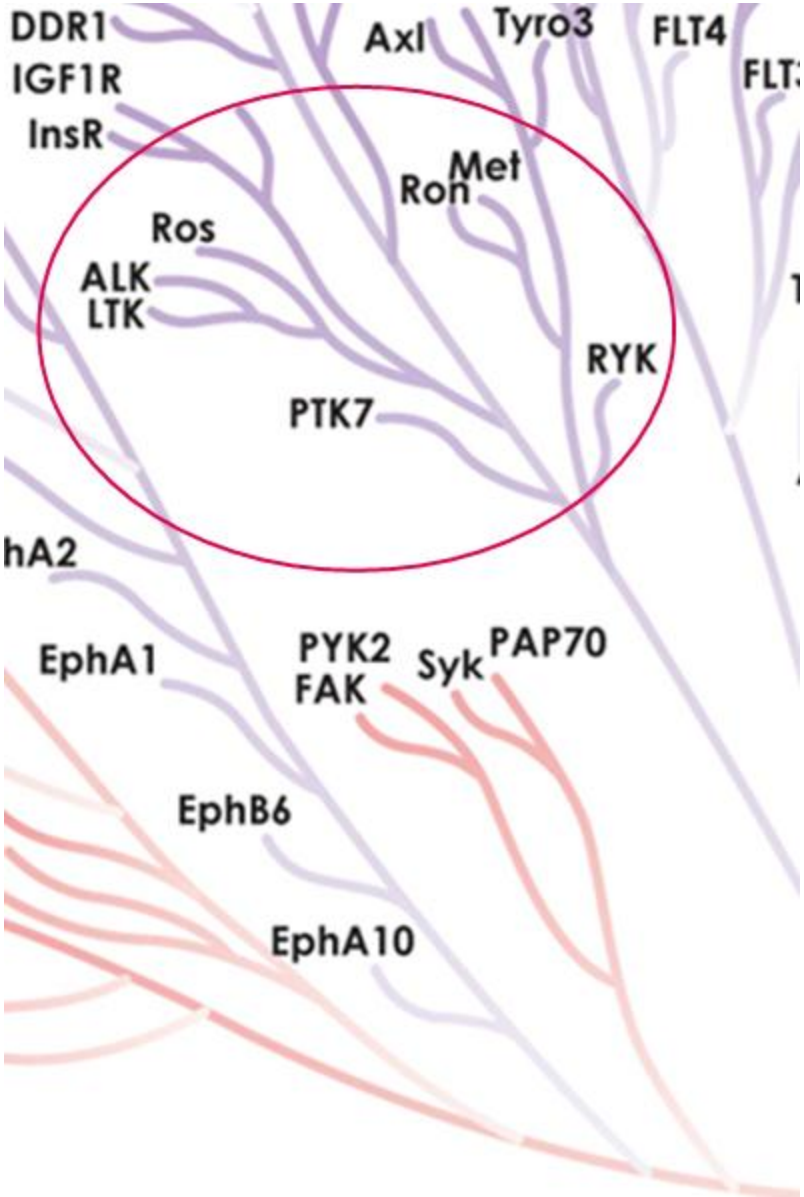
MATCHLUNG

Molecularly Adapted Treatment with Crizotinib or PF-04691502 in Heavily pretreated advanced non small cell LUNG cancer



Hypothesis : ratio PFS 2 (MATCHLUNG) / PFS 1 (PREVIOUS LINE) >1.3; in > 24% pts

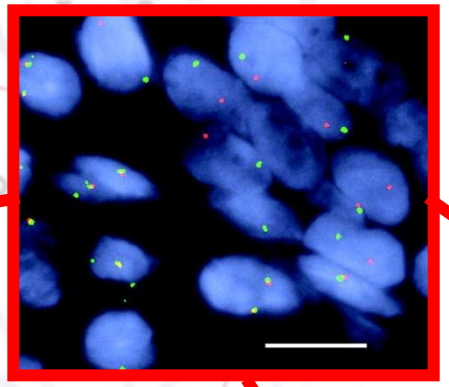
Crizotinib characteristics



Kinase	IC_{50} (nM) mean*	Selectivity ratio
c-MET	8	–
ALK	40-60	5-8X
ROS1	60	7X
RON	80	10X
Axl	294	34X
	322	37X
Tie-2	448	52X
Trk A	580	67X
Trk B	399	46X
Abl	1,159	166X
IRK	2,887	334X
Lck	2,741	283X
Sky	>10,000	>1,000X
VEGFR2	>10,000	>1,000X
PDGFRβ	>10,000	>1,000X

Cui et al. J Med Chem 54: 6342-63, 2011 and Pfizer data on file

Crizotinib characteristics



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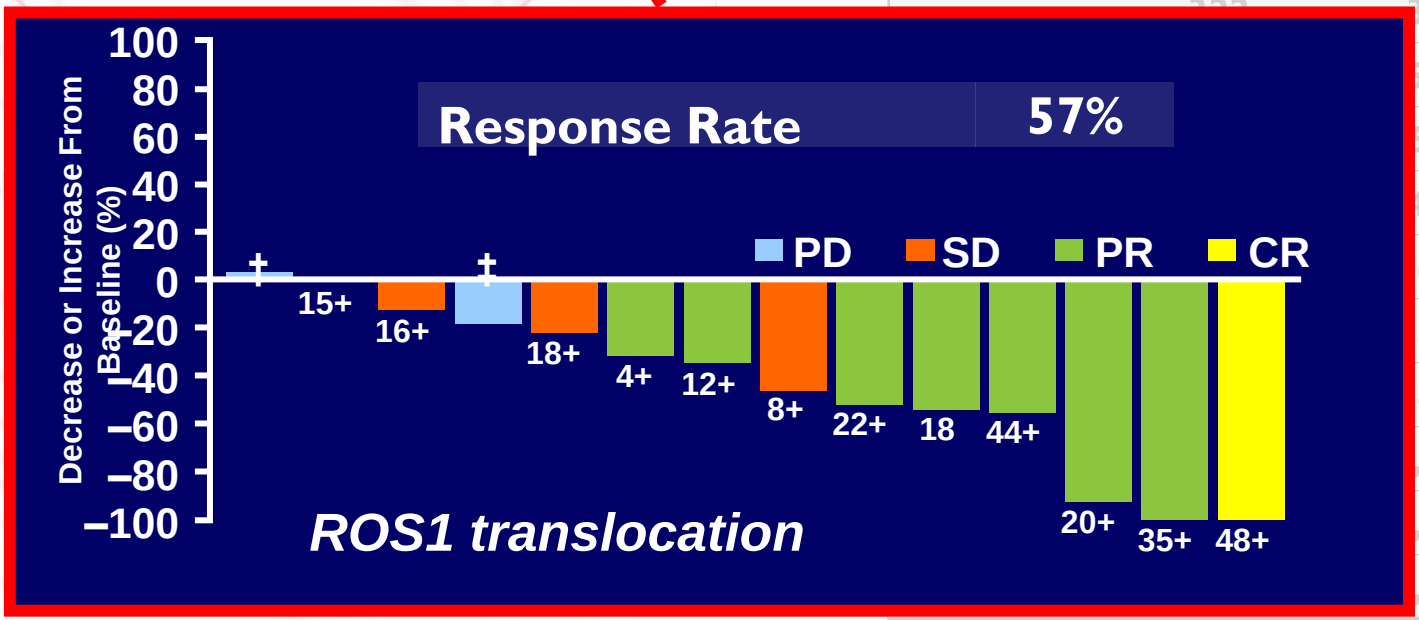


Shaw ASCO 2012

Cui et al. J Med Chem 54: 6342-63, 2011 and Pfizer data on file

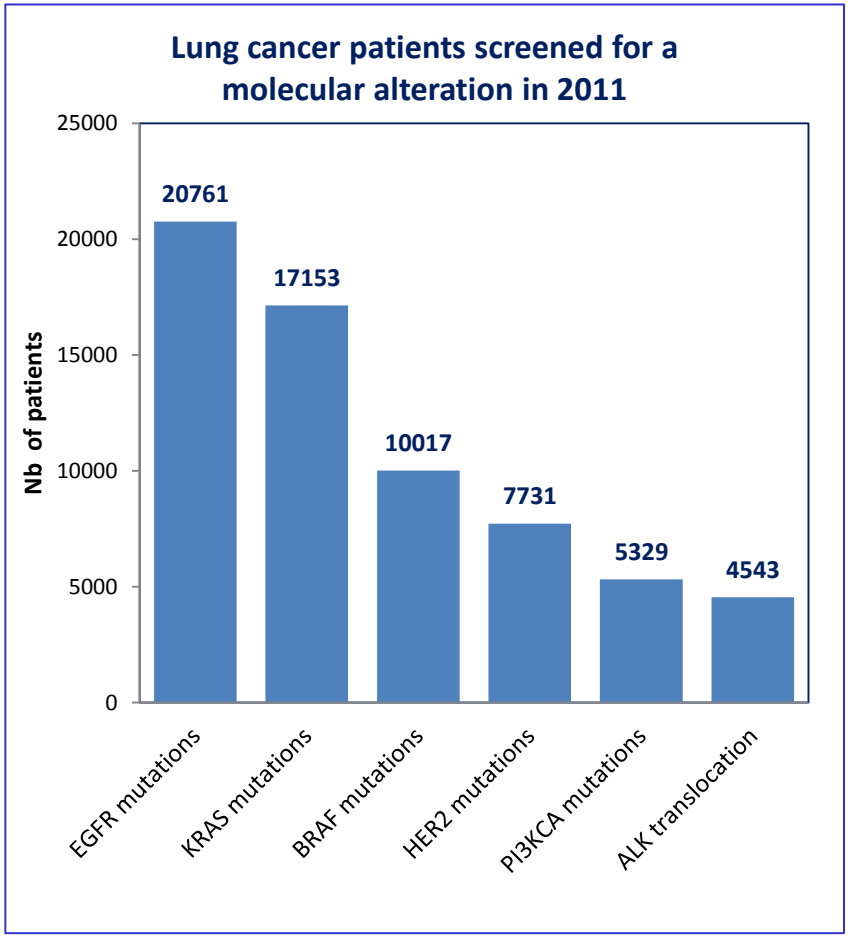
How to implement molecular testing in daily practice ?

- Financial issues
  - → Who should pay ?
  - → Pharma
  - → Insurance
  - → National Cancer plans (eg INCa)

- Practical issues
  - → Optimal technique: FISH vs RT-PCR vs IHC
  - → Optimal sample: tissue vs CTC vs free DNA
  - → Tissue availability: EGFR testing should not compete with ALK
    - Multiplexing strategies are key +++

Andre, JCO 2011

Tumor molecular profiling the french national initiative



INSTITUT NATIONAL DU CANCER

Nowak, Nat Rev Clin Oncol 2012

Discussion goals

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When and how to integrate crizotinib in the management of metastatic NSCLC ?

	Ph I (1001) n = 119	Ph II (1005) n= 136	Ph III (1007) n= 172 (crizo arm)
Line of therapy	Any line 32 % 2nd line	2nd and beyond 6,6 % 2nd line	2nd line only
ORR %	61	50	65,3
Median duration of response (range)	48.1 wks (4.1, 76.6)	41.9 wks (6.1, 42.1)	36 wks (2.1, 72.4)
Median duration of treatment	32 weeks	22 weeks	30 weeks

Kwak NEJM 2012

Camidge Lancet Oncol 2012

Kim , ESMO 2011, #9084

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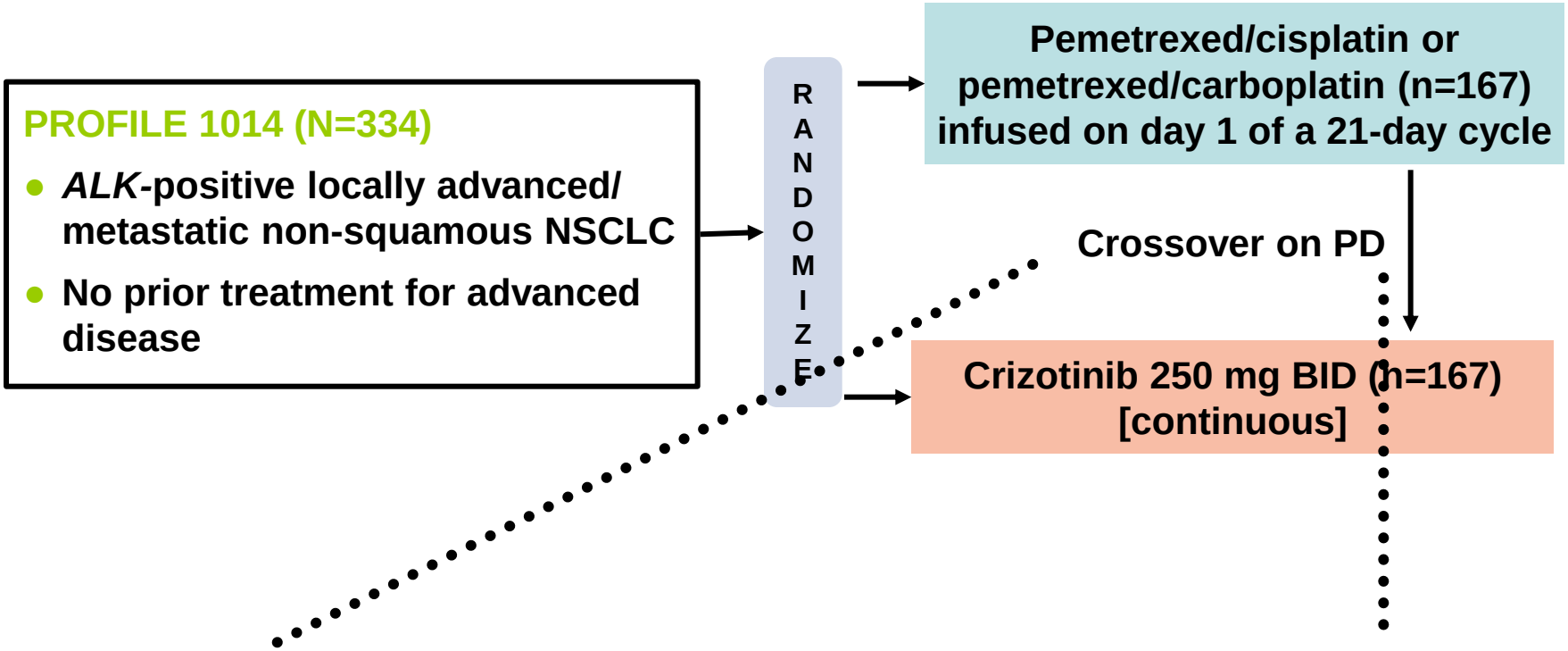
Median duration of treatment	32 weeks	22 weeks	30 weeks
Median PFS	10 months	NR	7,7 months
Survival probability At 6 months	90%	NR	87%
Survival probability At 12 months	81%	NR	70%

Kwak NEJM 2012 Camidge Lancet Oncol 2012 Kim , ESMO 2011, #9084

Implications for front-line trial

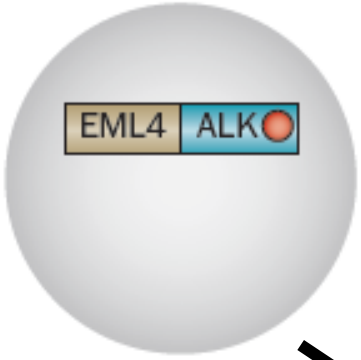


❖At least 13% of patients will not access crizotinib…

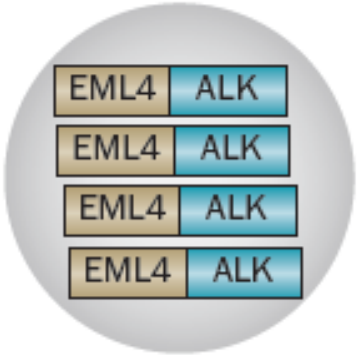
(16 pts out of 127 pts who progressed on chemotherapy never got crizotinib on Profile 1007)

ALK dominant mechanisms of resistance

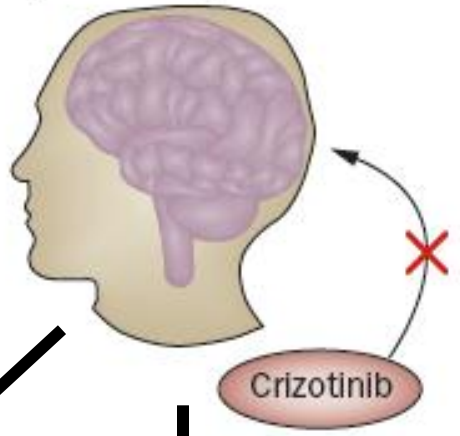
Resistance mutations



Copy number gain



Inadequate CNS penetration?



2nd generation ALKi

- **LDK378**

ORR 81% in 26 crizo-R pts

R.Mehra ASCO #3007

Combinations with crizotinib ?

Increase dose of crizotinib ?

HSP90 inhibitors

Camidge NRCO 2012

Wong et al. ASCO 2011

Crizotinib + Local ablative therapy

- **Adds 6 months PFS**

A. Weickhardt, #7526 ASCO 2012

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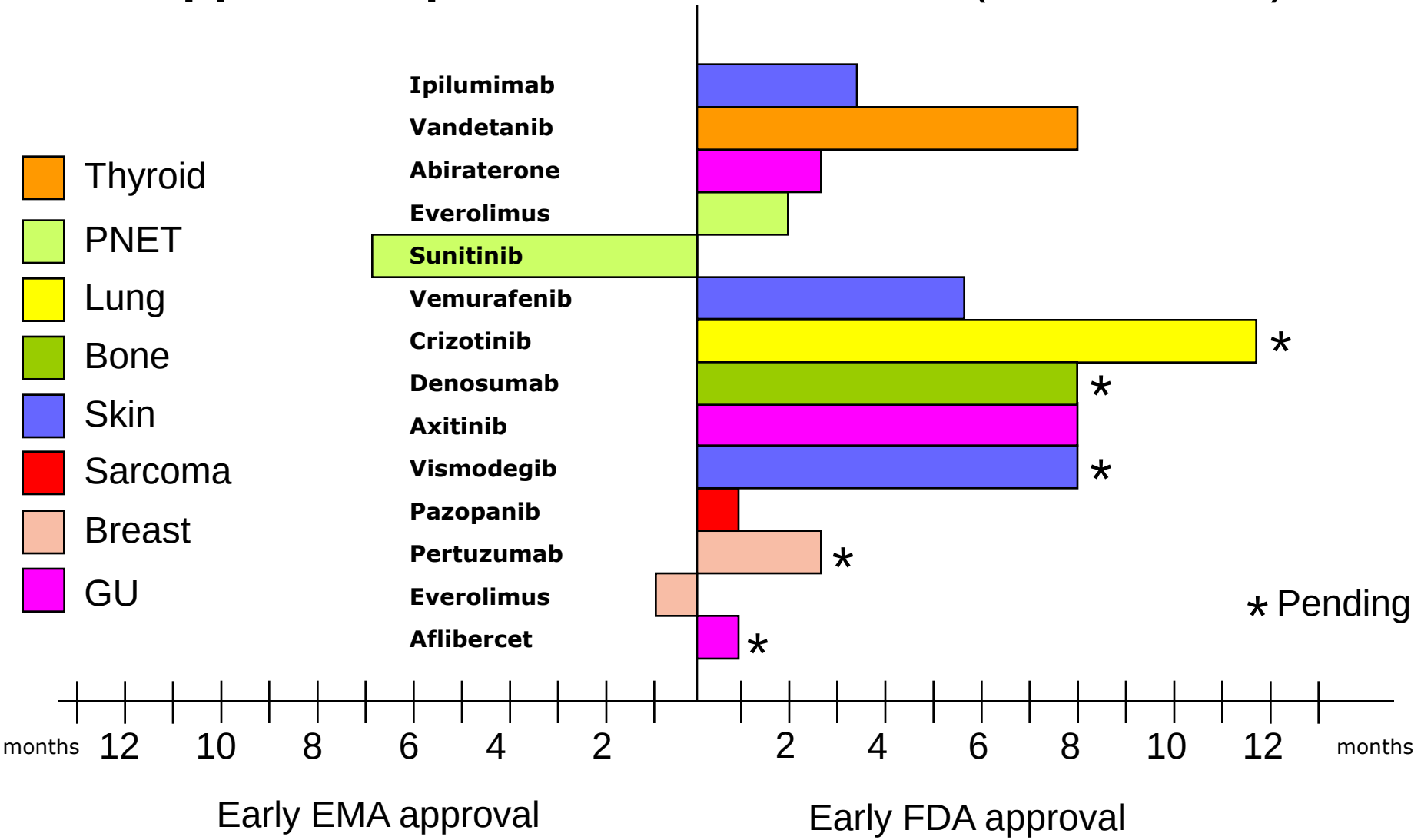
Reasons for EMA reluctance for approval

Fow chart	FDA	EMA
Pre-meeting	Welcomed filing of single arm data for accelerated approval	Conditional approval can only be granted on an **established** positive benefit/risk assessment
Submission Single arm data April 2010	4.9 months review Agreement on single arm data	14 months review Required randomized data
Approval	**August 26, 2011**	**Estimated late Oct. 2012**

US treats, EU randomizes !

Approval speed : FDA vs EMA (2011-2012)



Conclusions for ALK+ patients

- Crizotinib offers better QoL, increased response and longer PFS as compared to second line chemotherapy

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- Comparison with historical data suggests that crizotinib has changed the natural history of the disease (median OS 22 months vs 9 months)
- Crizotinib AE profile is mild (liver to be monitored)

Conclusions for ALK+ patients

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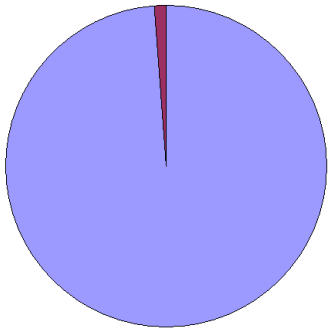
- Crizotinib AE profile is mild (liver to be monitored)
- Crizotinib has more to offer to cancer patients and the oncology community than its activity in ALK + NSCLC
- Will randomization remain mandatory for conditional approval in very rare molecularly defined subgroups of patients ?



Is 1% still amenable to randomization?

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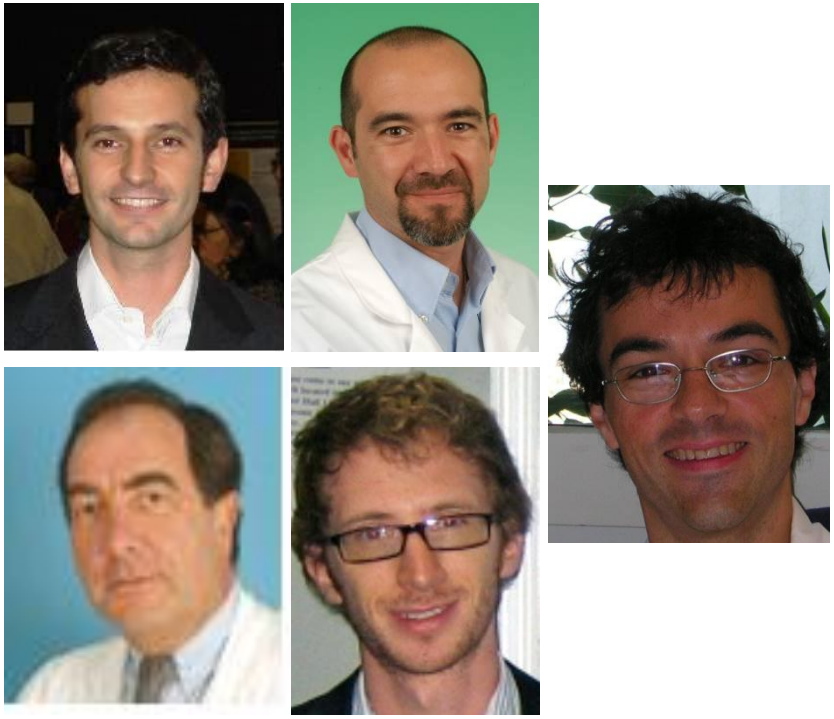

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