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Cancer Centre

Patient selection for kinase inhibition in cancer

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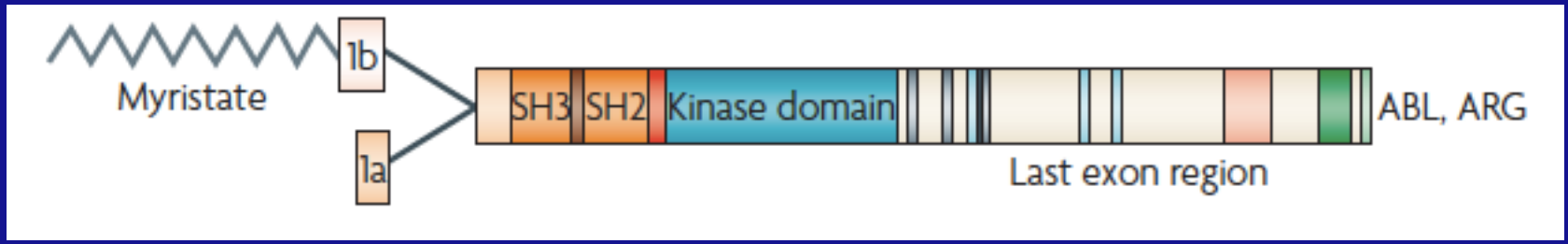
Summary

- Cancer as a genetic disease
  - oncogene activation; tumour suppressor gene inactivation
  - many oncogenes are kinases
    ~ so are readily drugable
- Advances in cancer biology continue to identify novel kinase targets
  – hence new agents
  – often striking activity in genetically selected patients
  – resistance becoming the next problem – mechanisms
- Diseases already tractable
  – CML
  – GIST
  – NSCLC
  – melanoma
- Patient selection improves: i) efficacy, ii) cost-effectiveness

Imatinib in CML: the paradigm

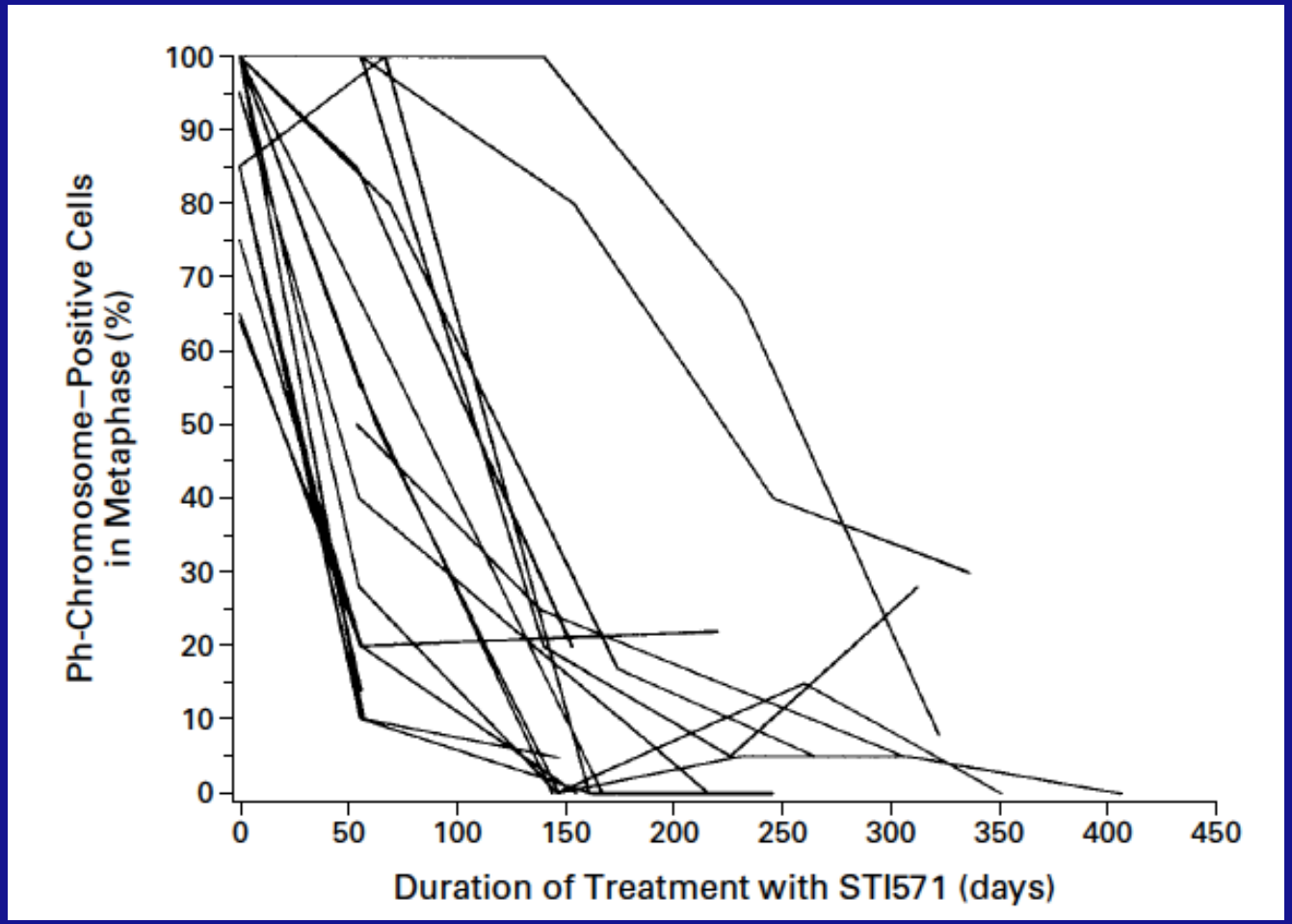


translocation between chromosomes 9 & 22

Philadelphia chromosome

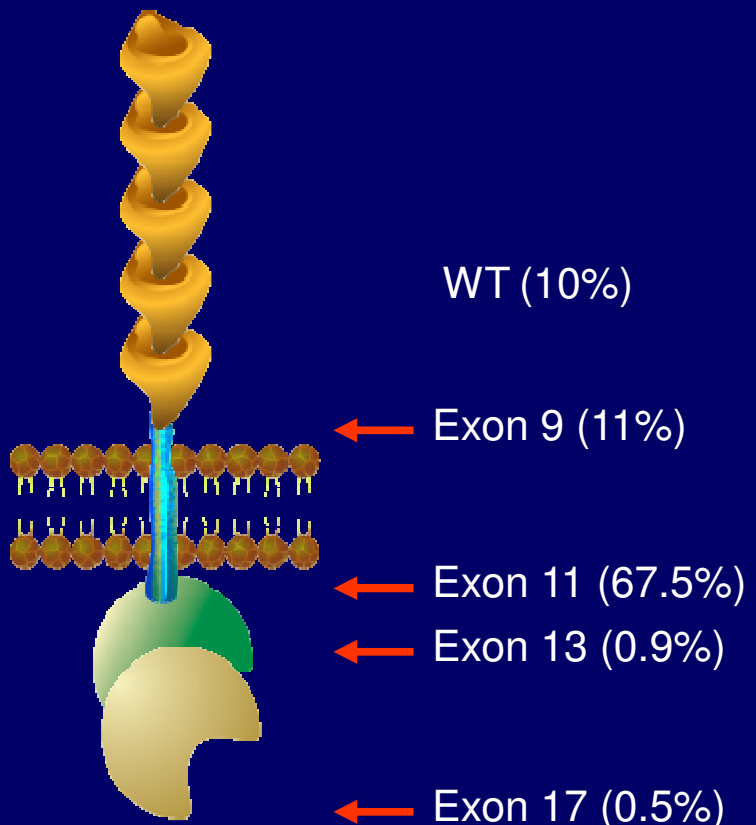
Imatinib in CML

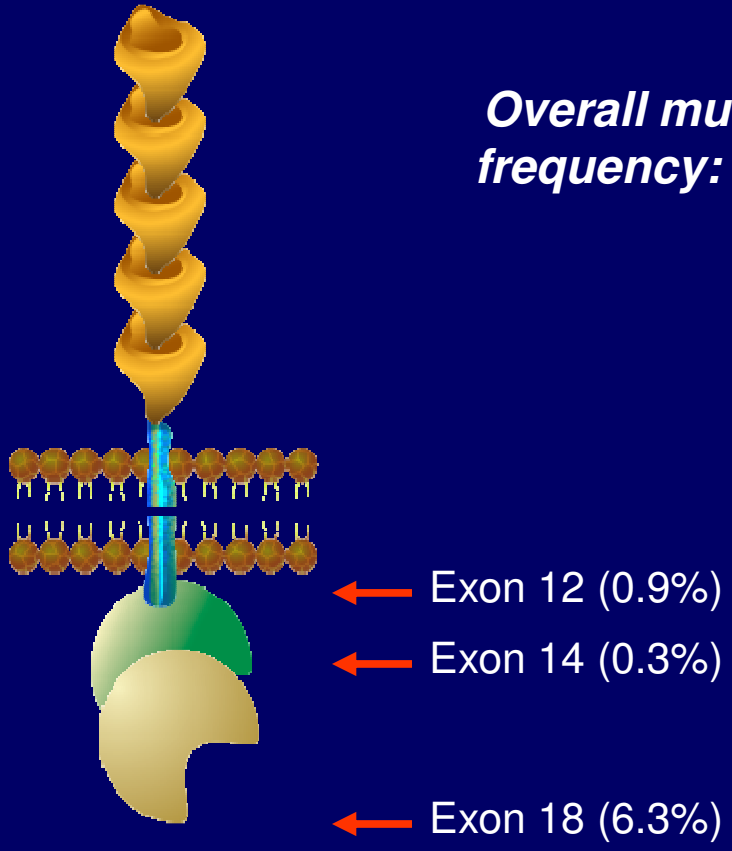
- efficacy of imatinib



Druker et al. NEJM 2001

cKIT and PDGFRα mutations in GIST

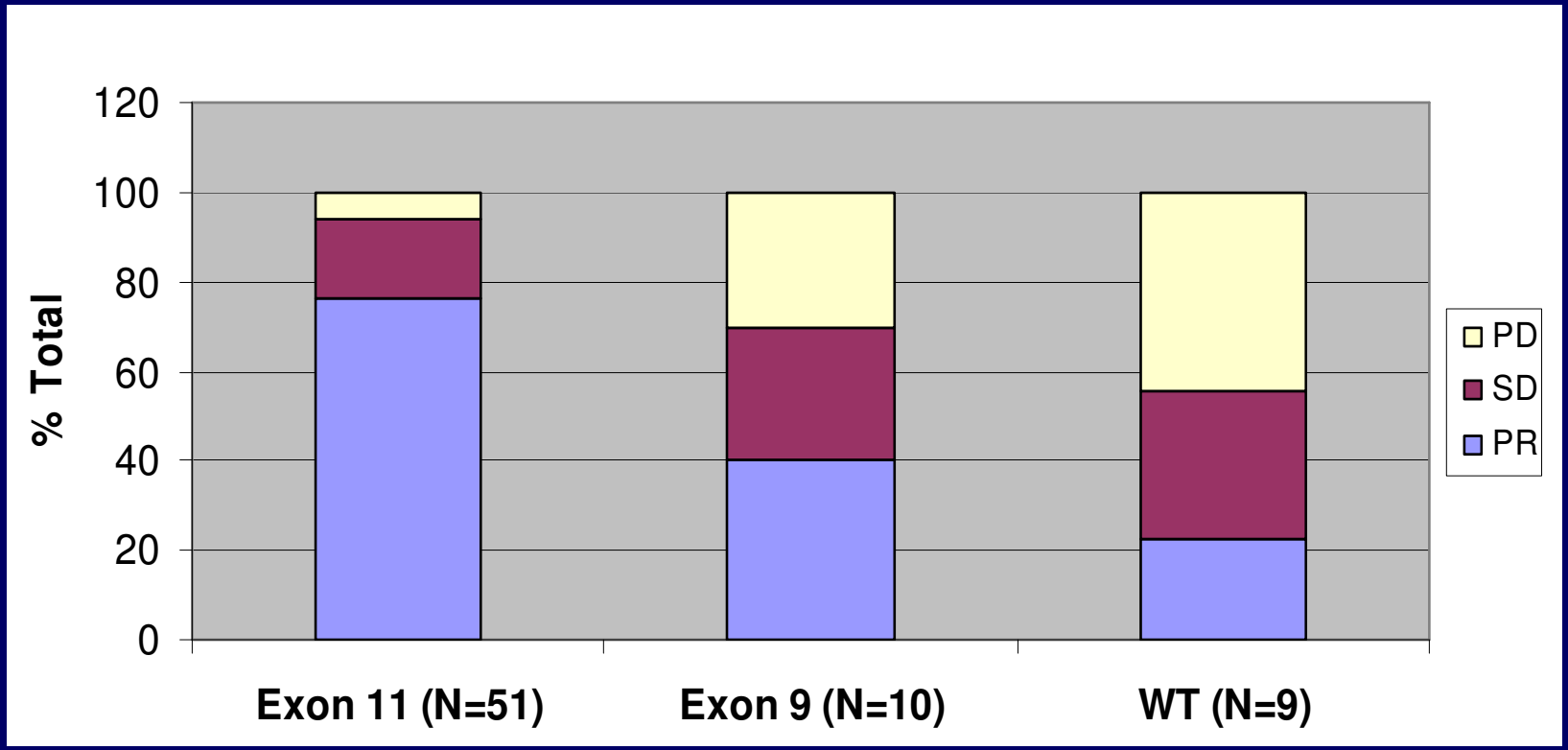




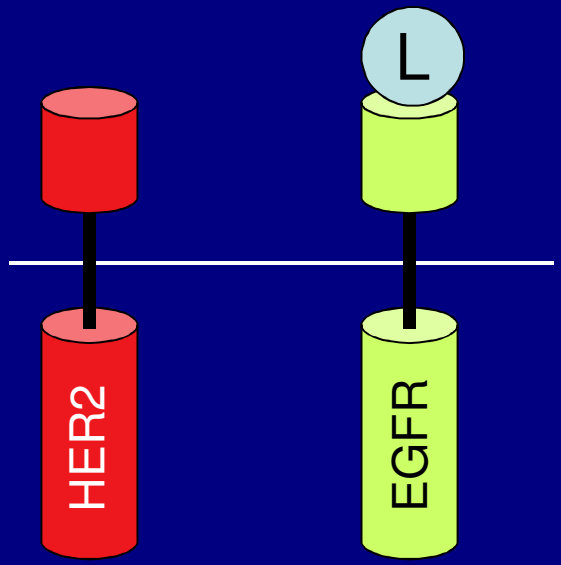
Overall mutation frequency: 87.4%

Heinrich et al. *Hum Pathol.* 2002;33:484.
Corless et al. *Proc Am Assoc Cancer Res.* 2003;44. Abstract R4447.

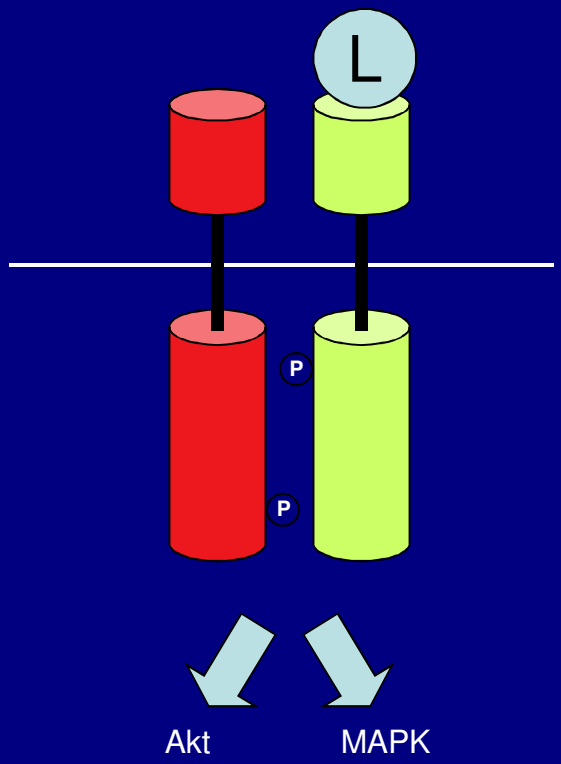
GIST: clinical response to imatinib according to mutational status



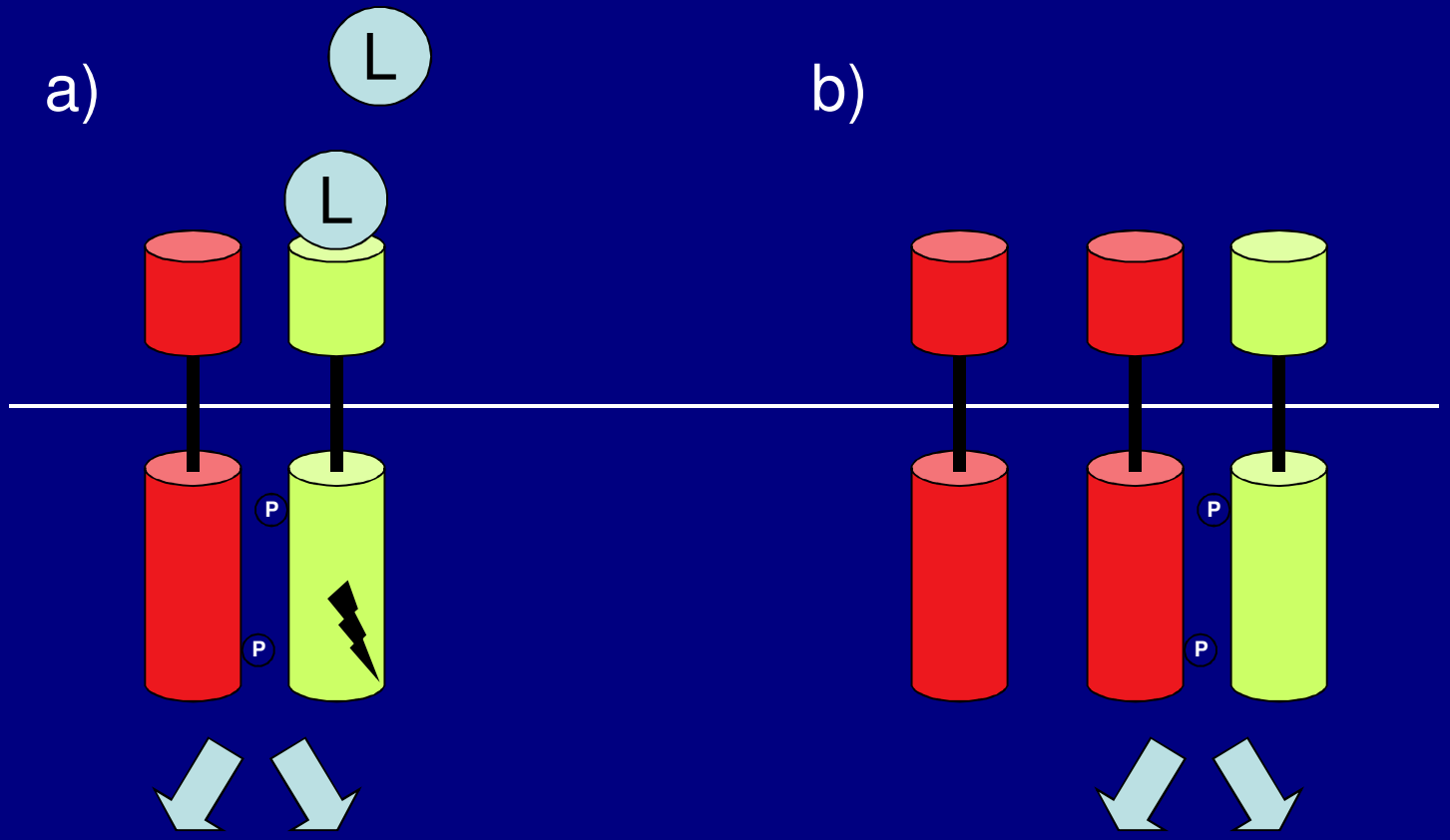
Physiological TK regulation by ligand



Physiological TK regulation by ligand

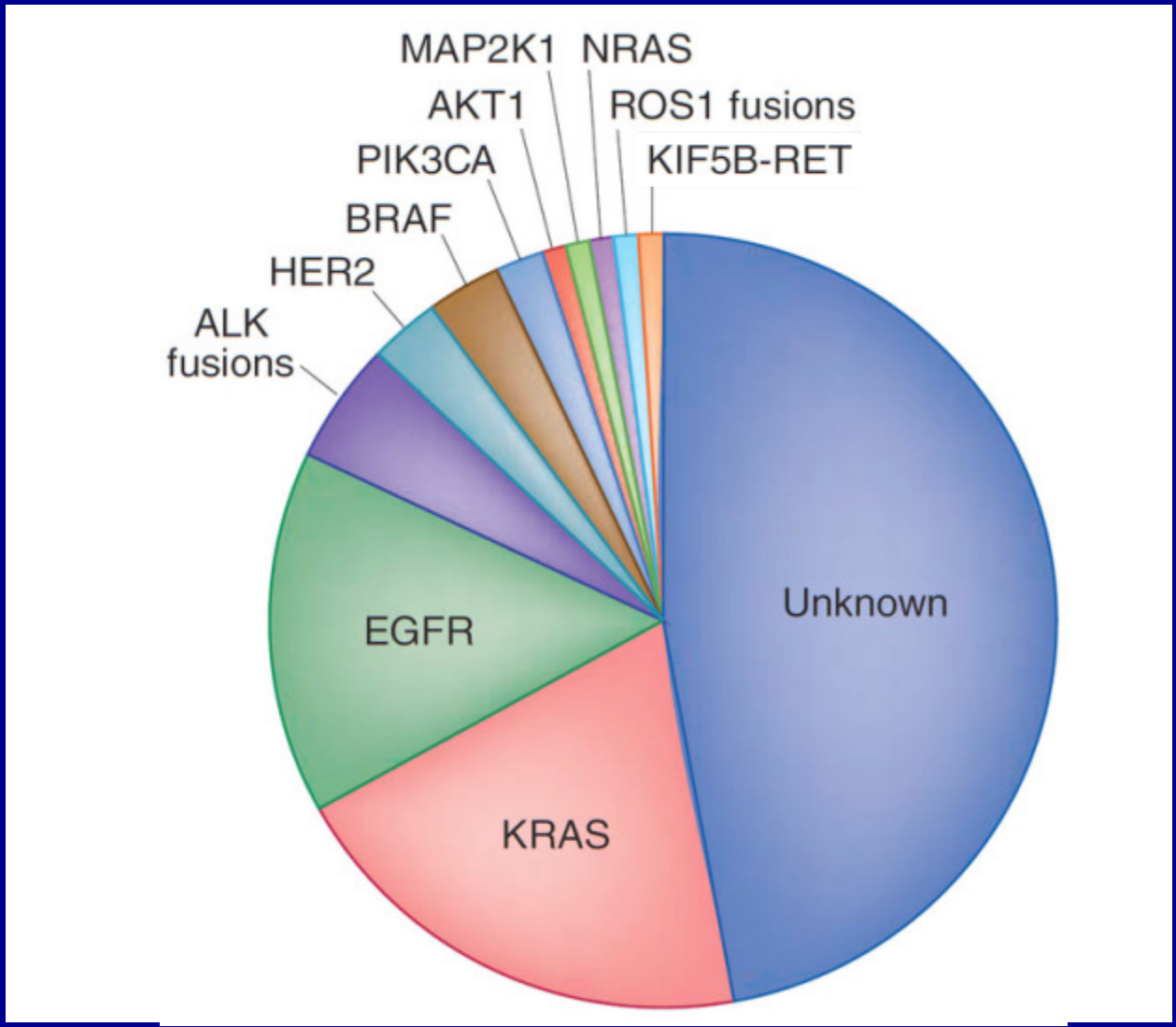


TK dysregulation in tumours



Molecular drivers in NSCLC

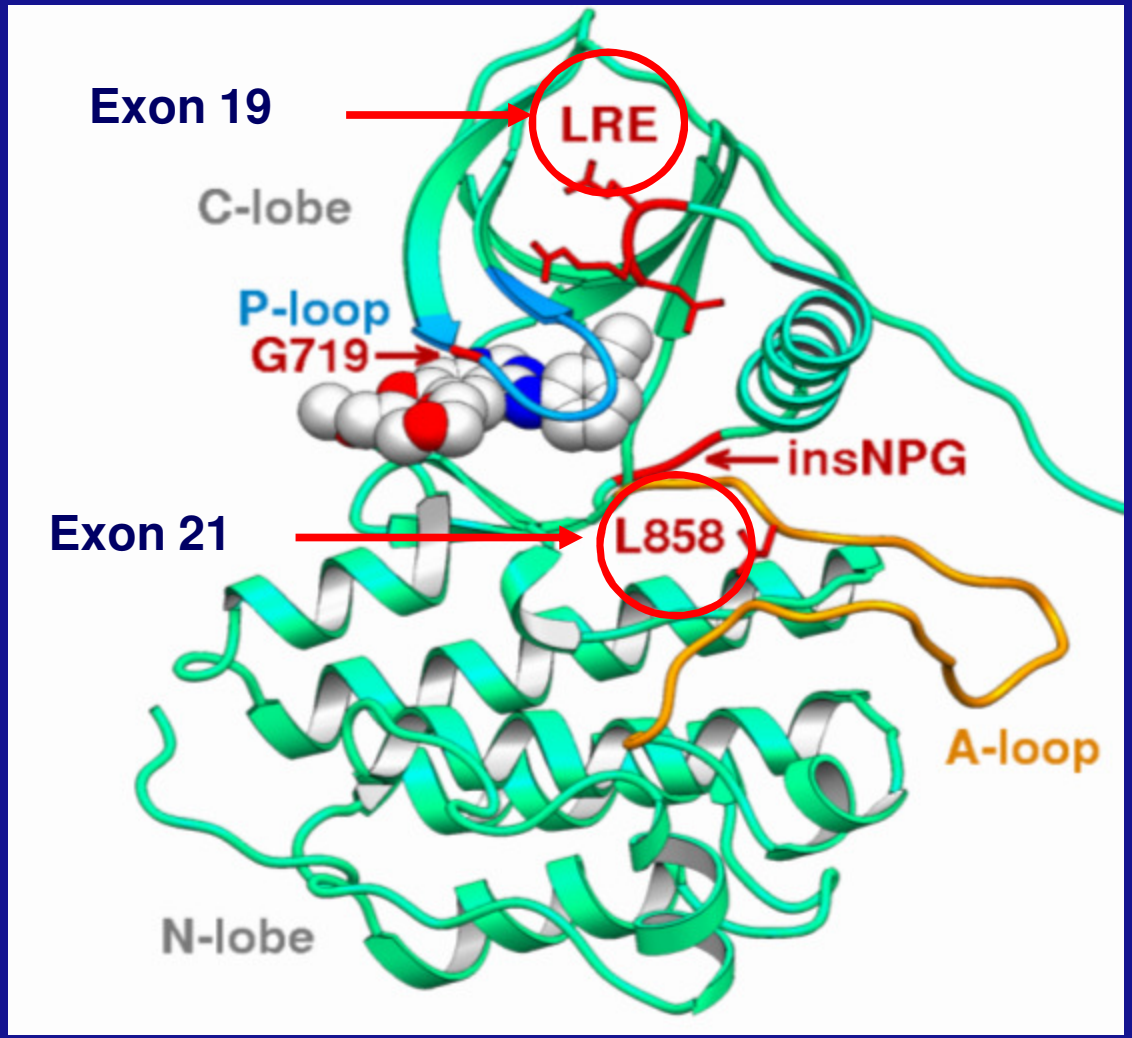
- Majority of adenocarcinomas driven by kinase upregulation



Pao & Hutchinson
Nature Medicine 2012

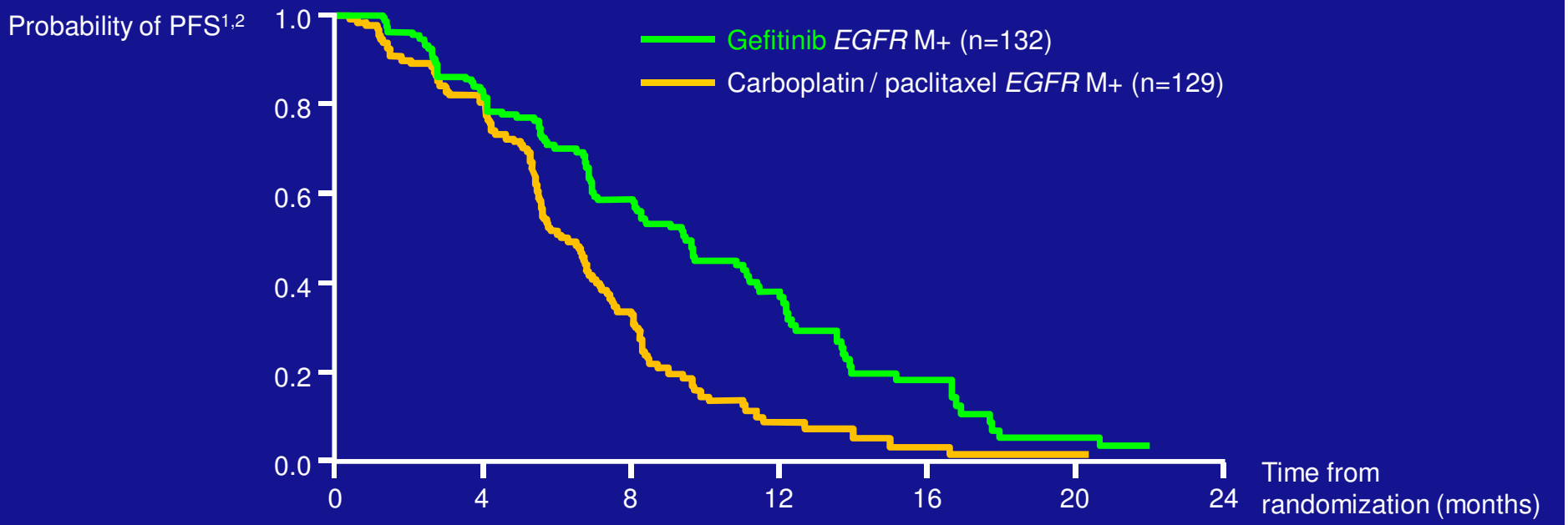
Mutations in EGFR

- More common in:
  - E Asian ethnicity[1]
  - Never or light smokers[2,3]
  - Non-SCC histology[3]
  - Women vs men[3]
- Associated with favourable response to erlotinib or gefitinib[4–6]



1. Shigematsu H, et al. J Natl Cancer Inst 2005;97(5):339–46; 2. Pham D, et al. J Clin Oncol 2006;24(11):1700–4; 3. Clark GM. Mol Oncol 2008;1:406–12; 4. Lynch TJ, et al. N Engl J Med 2004;350(21):2129–39; 5. Paez JG, et al. Science 2004;304(5676):1497–1500; 6. Pao W, et al. Proc Natl Acad Sci USA 2004;101(36):13306–11.

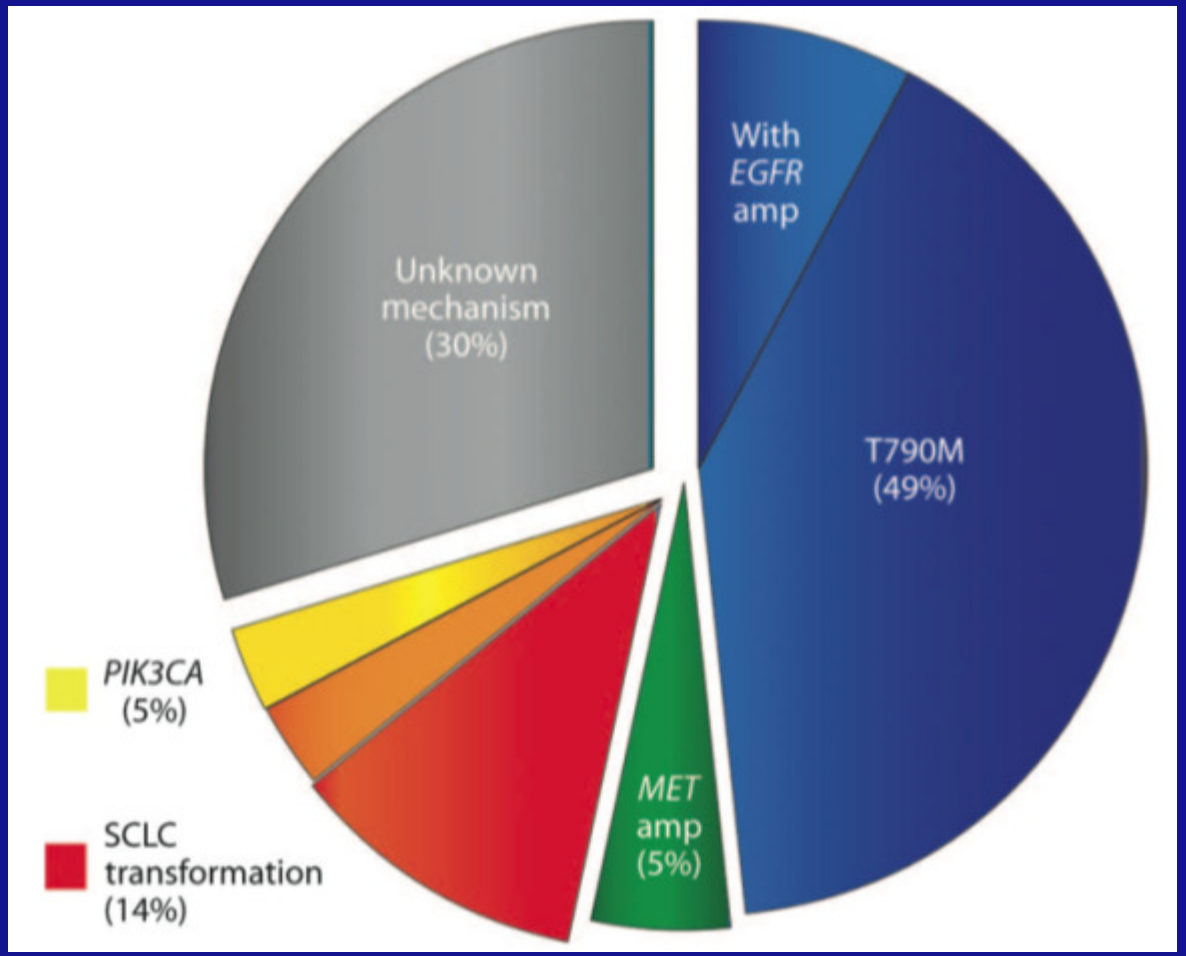
Randomised phase 3 trials of first-line EGFR TKIs



Study	n	RR (%)	Median PFS (mo)	Median OS (mo)
IPASS	261	71 vs 47	10 vs 6	22 vs 22
WJTOG 3405	172*	62 vs 32	8 vs 5	36 vs 39
NEJGSG002	230	74 vs 31	11 vs 5	31 vs 24
OPTIMAL	165	83 vs 36	13 vs 5	immature
EURTAC	174	58 vs 15	9.7 vs 5.2	19 vs 19
LUX-Lung 3	345	56 vs 23	11 vs 7	28 vs 28
LUX-Lung 6	364	67 vs 23	11 vs 6	immature

Mechanisms of acquired resistance to first-generation EGFR inhibitors

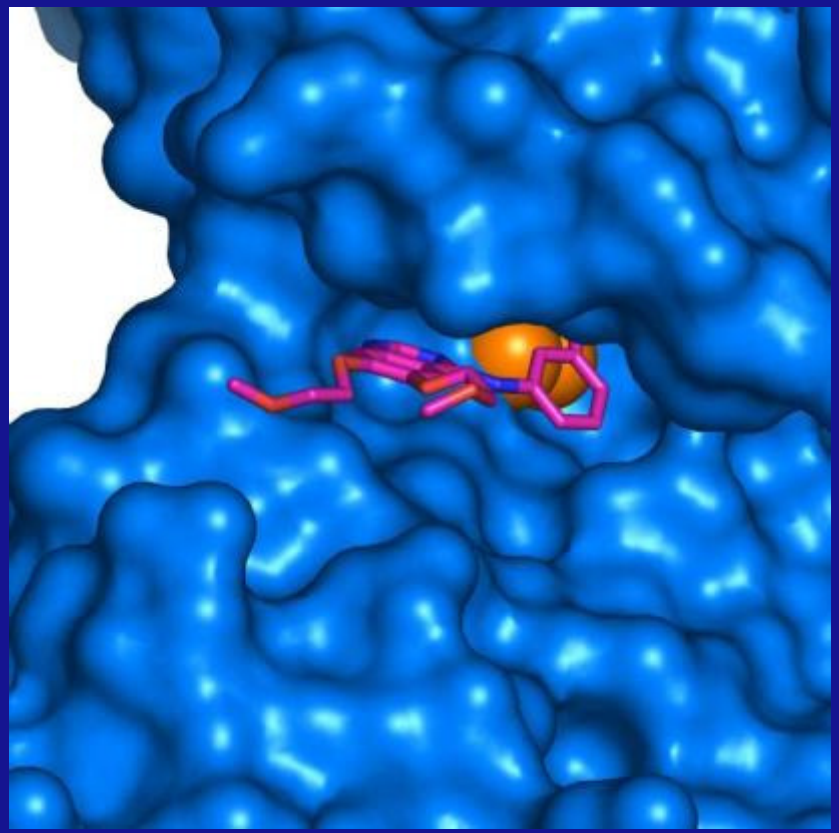
- All patients who initially respond to treatment with first-generation EGFR TKIs eventually progress due to acquired resistance:



Sequist LV, et al. Sci Transl Med 2011;3:75ra26.

T790M resistance mutation

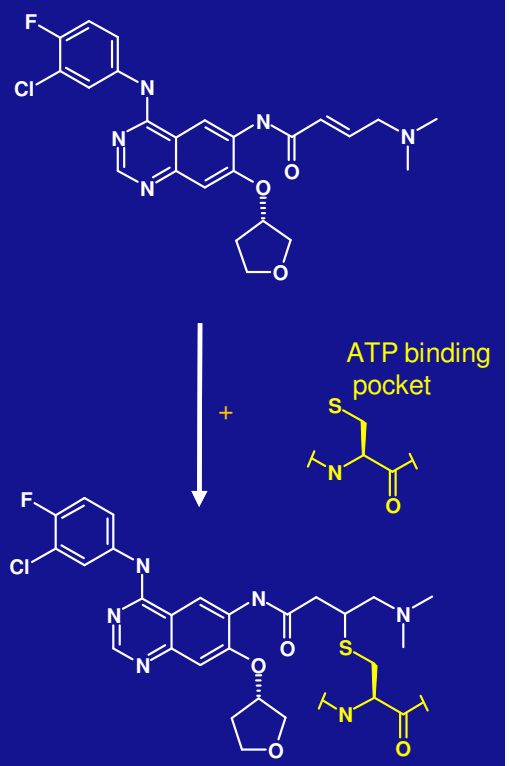
- Threonine substituted for methionine at codon 790
- T790M accounts for 50–68% of acquired resistance to EGFR TKIs[1–3]
- Presence of T790M before EGFR TKI treatment
  - Prevalence varies with detection method (6–38%)[4–5]



1. Arcila ME, et al. Clin Cancer Res 2011;Jan 19 [Epub ahead of print]. 2. Oxnard GR, et al. Clin Cancer Res 2010;December 6th [Epub ahead of print]; 3. Engelman JA, et al. Clin Cancer Res 2008;14:2895–9; 4. Maheswaran S, et al. N Engl J Med 2008;359:366–77; 5. Sequist L, et al. J Clin Oncol 2008; 26:2442–9.

Some ErbB inhibitors in development

Agent	EGFR IC_{50} (nM)	HER2 IC_{50} (nM)	HER4 IC_{50} (nM)
Dacomitinib	6	45	73
Afatinib	0.5	14	1
Neratinib	92	59	–



Spicer & Rudman. Targeted Oncol 2010;5(4):245–55; Yamamoto N, et al. 7524a ASCO 2011

Newer inhibitors specific for mutated EGFR, especially T790M

AZD9291[1]

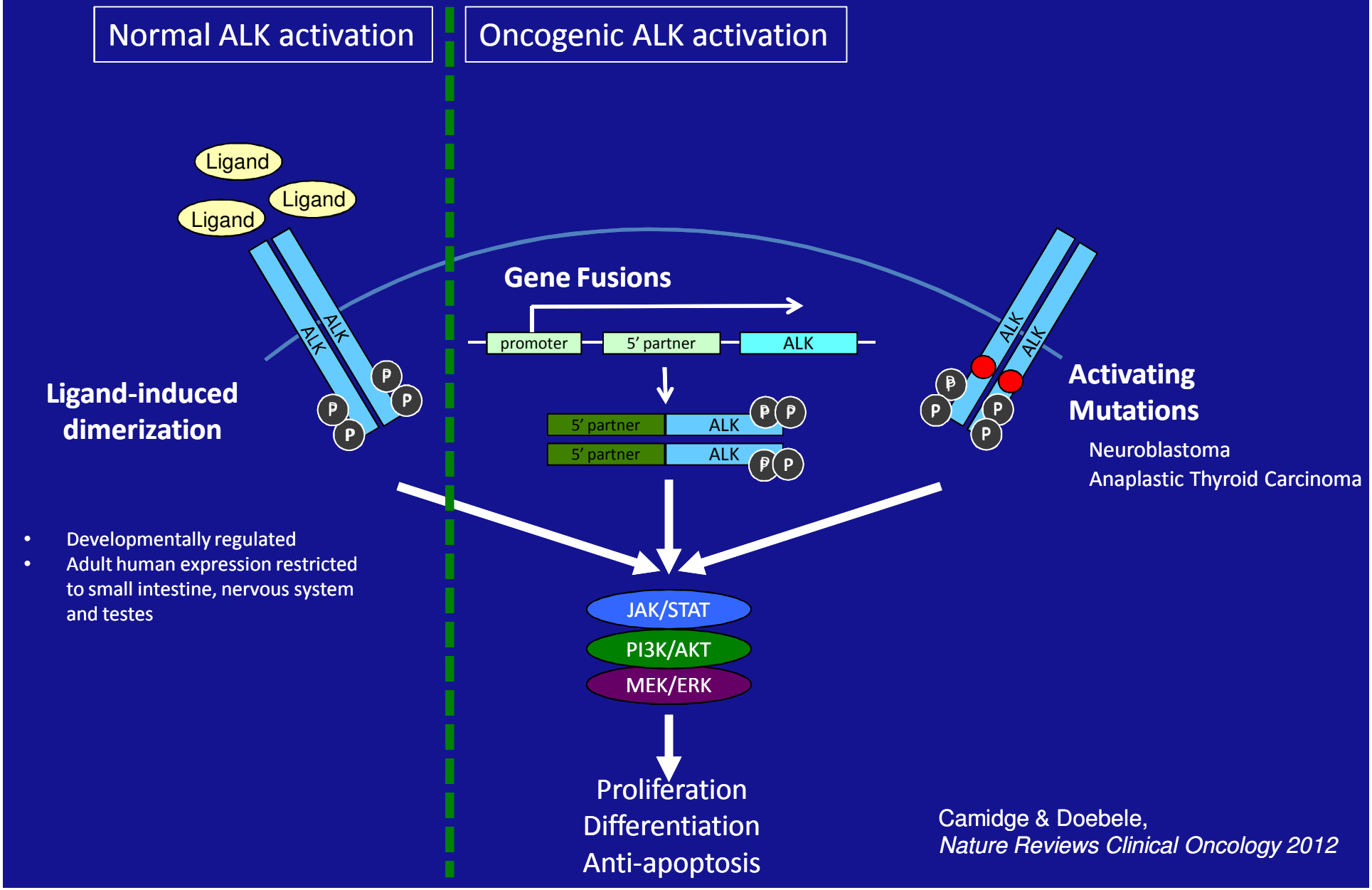
- Phase 1 dose escalation in any pre-treated EGFR+
- expansions at each dose level with proven T790M
- recruiting only 6 months (60 pts enrolled). Well tolerated so far, rash G1, D G2
- RR = 7/12 T790M

Clovis CO-1686[2] Phase 1: PR in 4/31 T790M+

- entering Phase 2

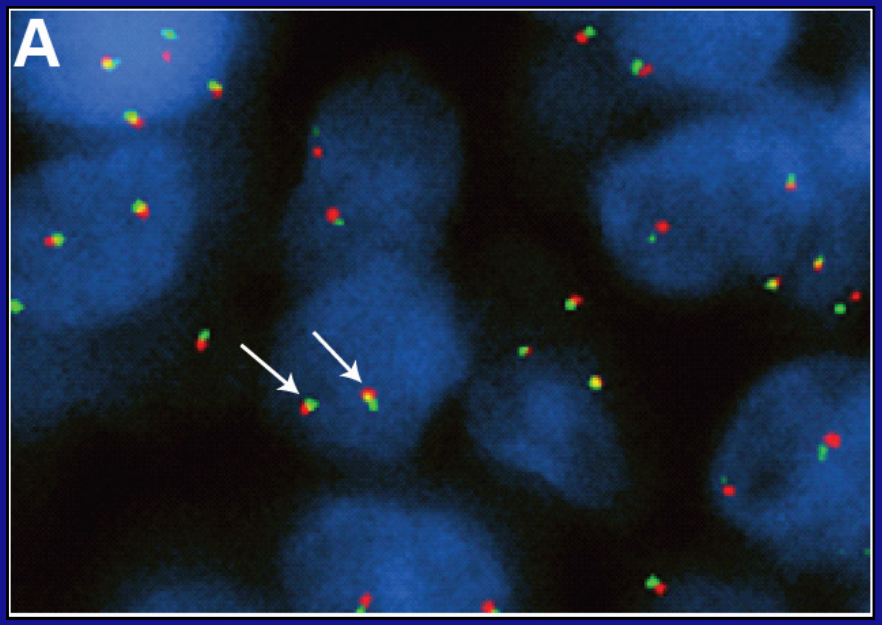
[1] Ransom ECC 2013
[2] Sequist ASCO 2013

ALK translocation

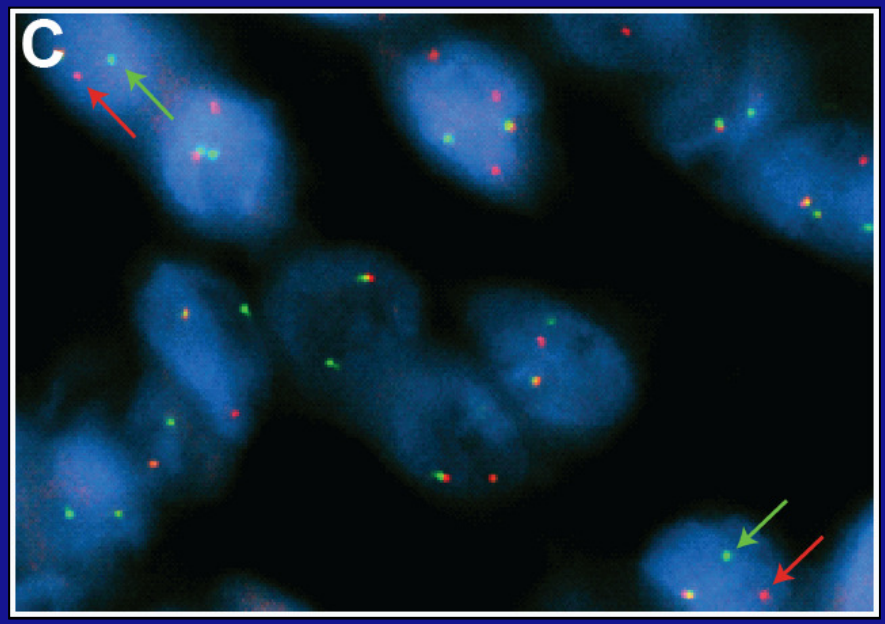


Camidge & Doebele,
Nature Reviews Clinical Oncology 2012

Break-apart FISH detects all potential *ALK* fusion partners in NSCLC



Negative



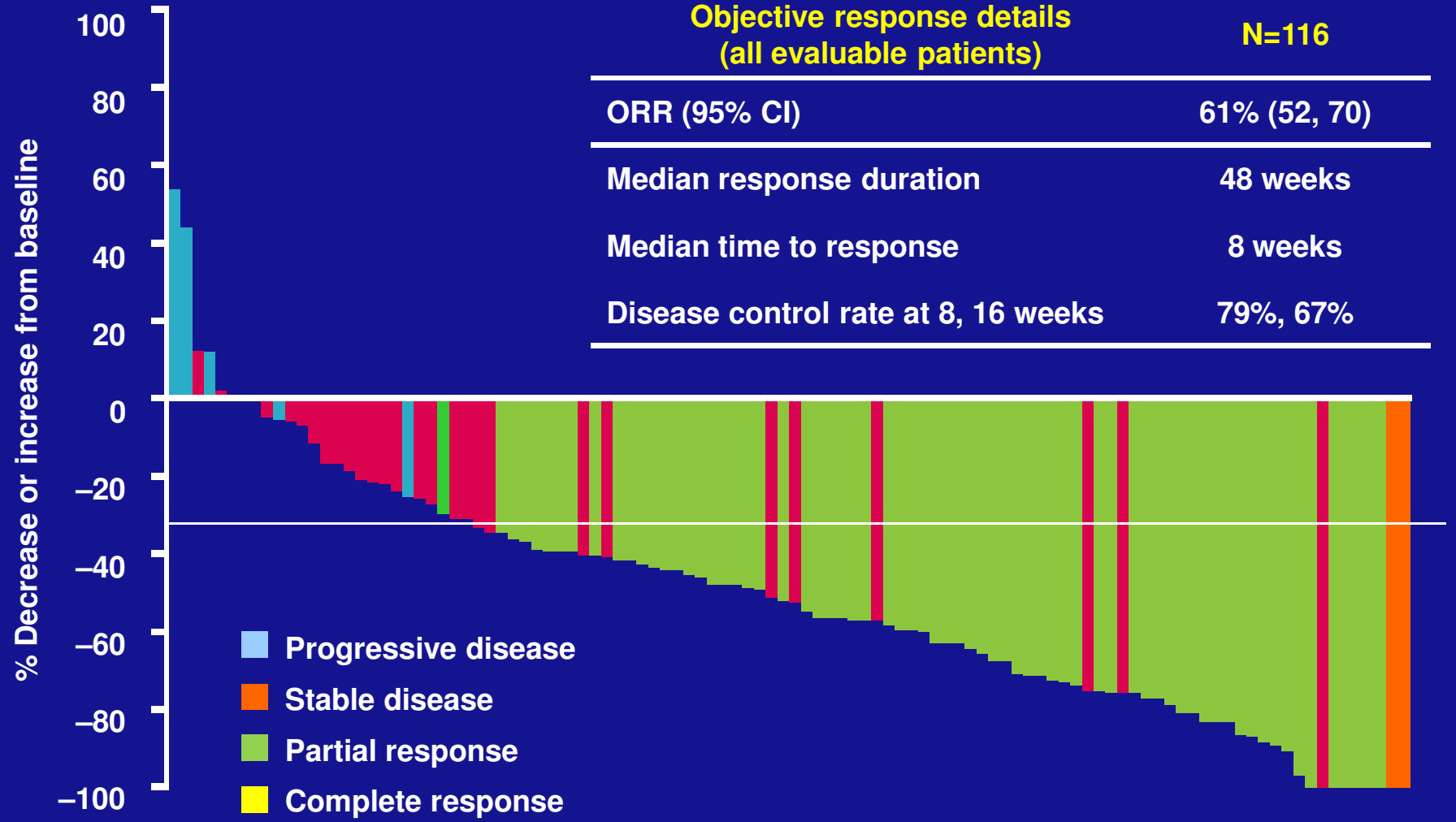
Positive

Varella-Garcia M et al.
American Society of Clinical Oncology
Annual Meeting 2010. Abstract 10533
Chicago, IL, USA.

Courtesy Ross Camidge

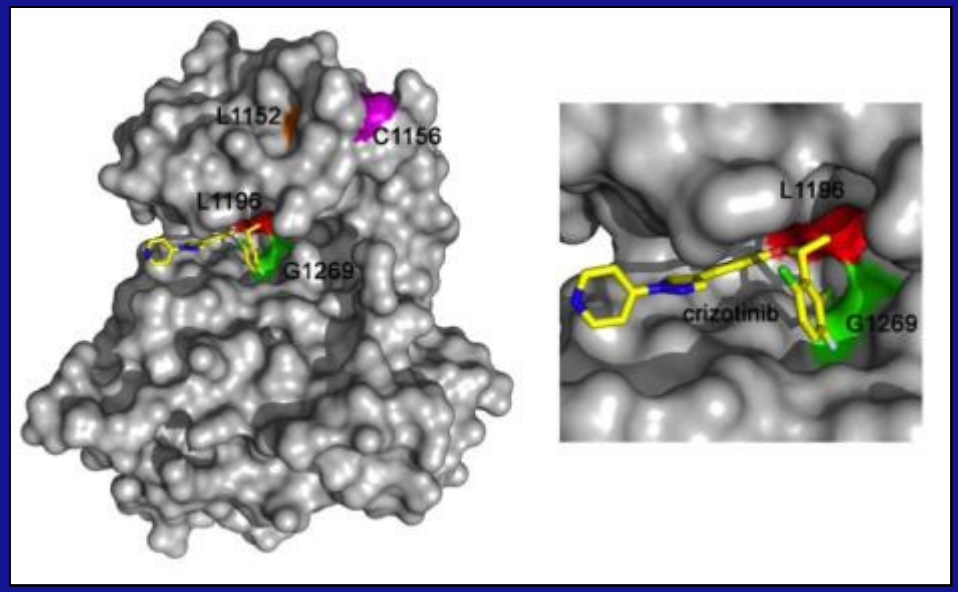
Crizotinib: best % change from baseline in target lesions

Objective response details (all evaluable patients)	N=116
ORR (95% CI)	61% (52, 70)
Median response duration	48 weeks
Median time to response	8 weeks
Disease control rate at 8, 16 weeks	79%, 67%



Camidge et al, ASCO 2011

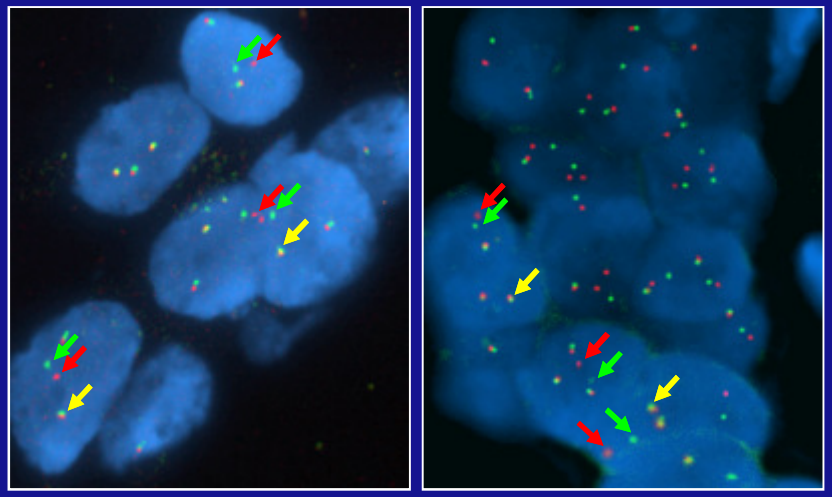
ALK: mechanisms of resistance



ALK mutations[1]

Pre-criz

Post-PD [2]



ALK Exon 21-25 WT

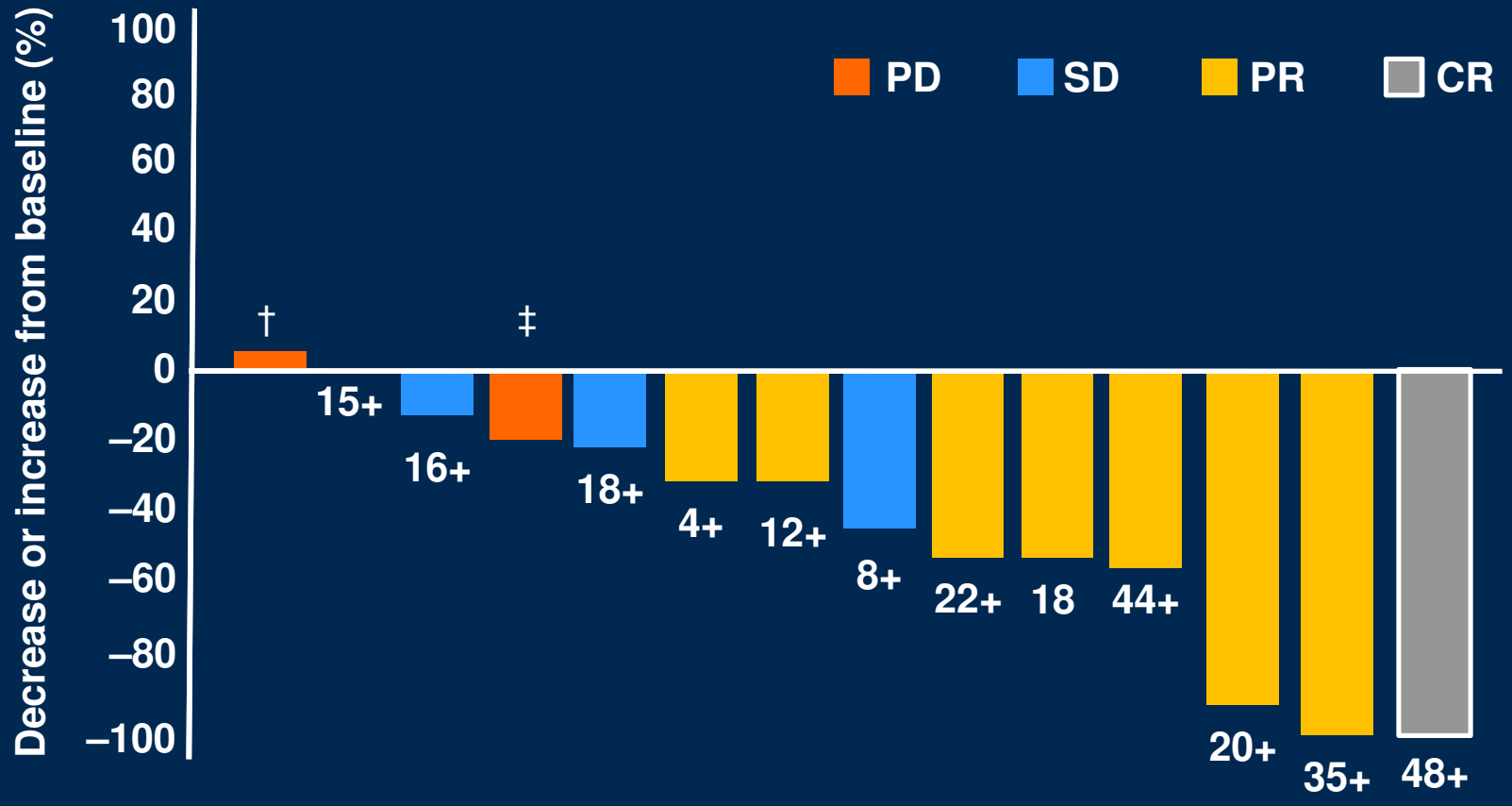
ALK FISH copy number gain
4.4-fold increase

- New generation ALK inhibitors in development

LDK378 RR = 81% in patients resistant to crizotinib[2]

[1]Doebele et al., Clin Can Res 2012 & 7504a ASCO 2012
[2]Mehra et al ASCO 2012

Crizotinib activity in ROS1+ NSCLC (n=14*)

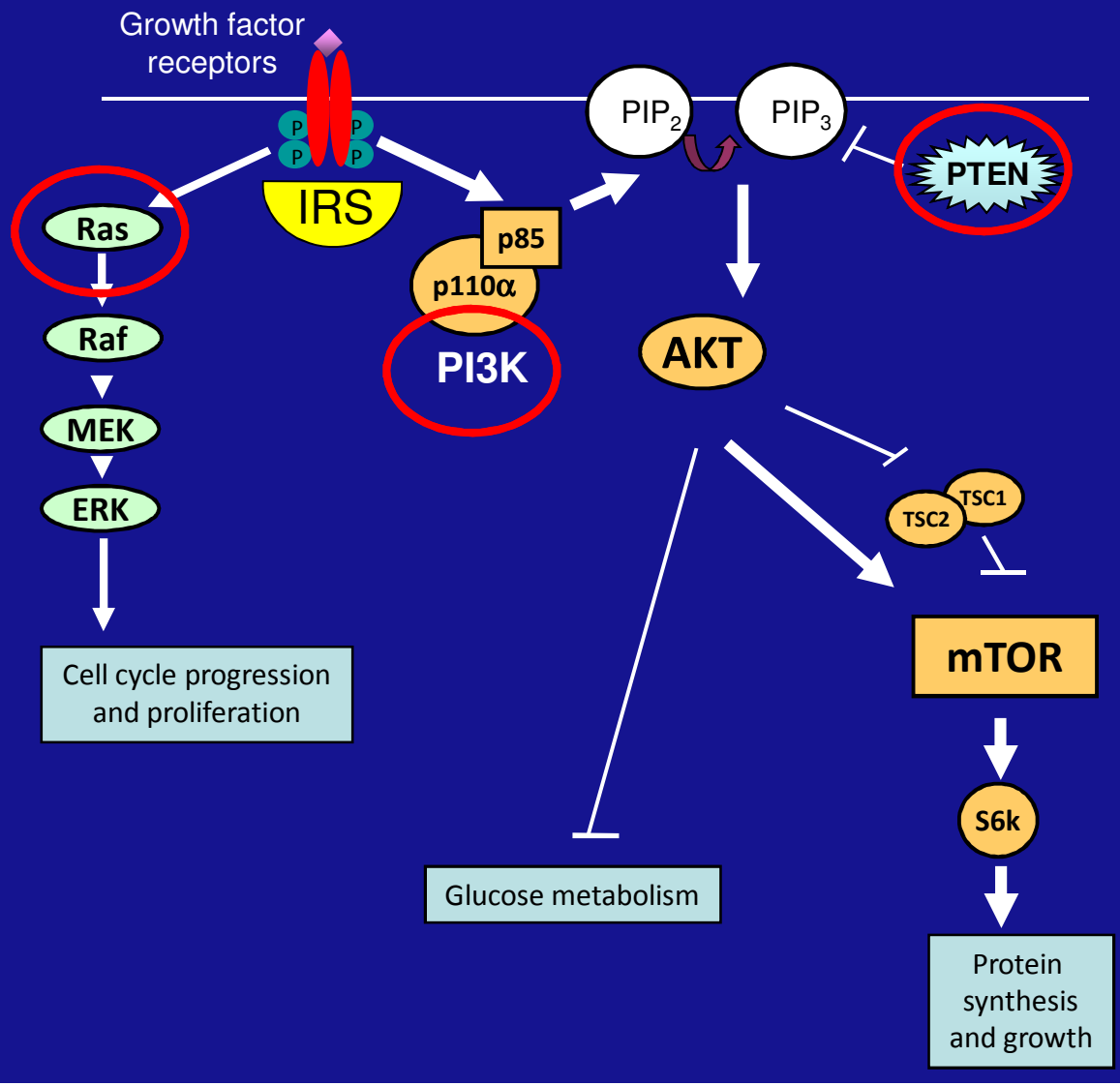


*Response-evaluable population
†Tumour ROS1 FISH-positive, but negative for ROS1 fusion gene expression
‡Crizotinib held for >6 wks prior to first scans which showed PD
+, treatment ongoing

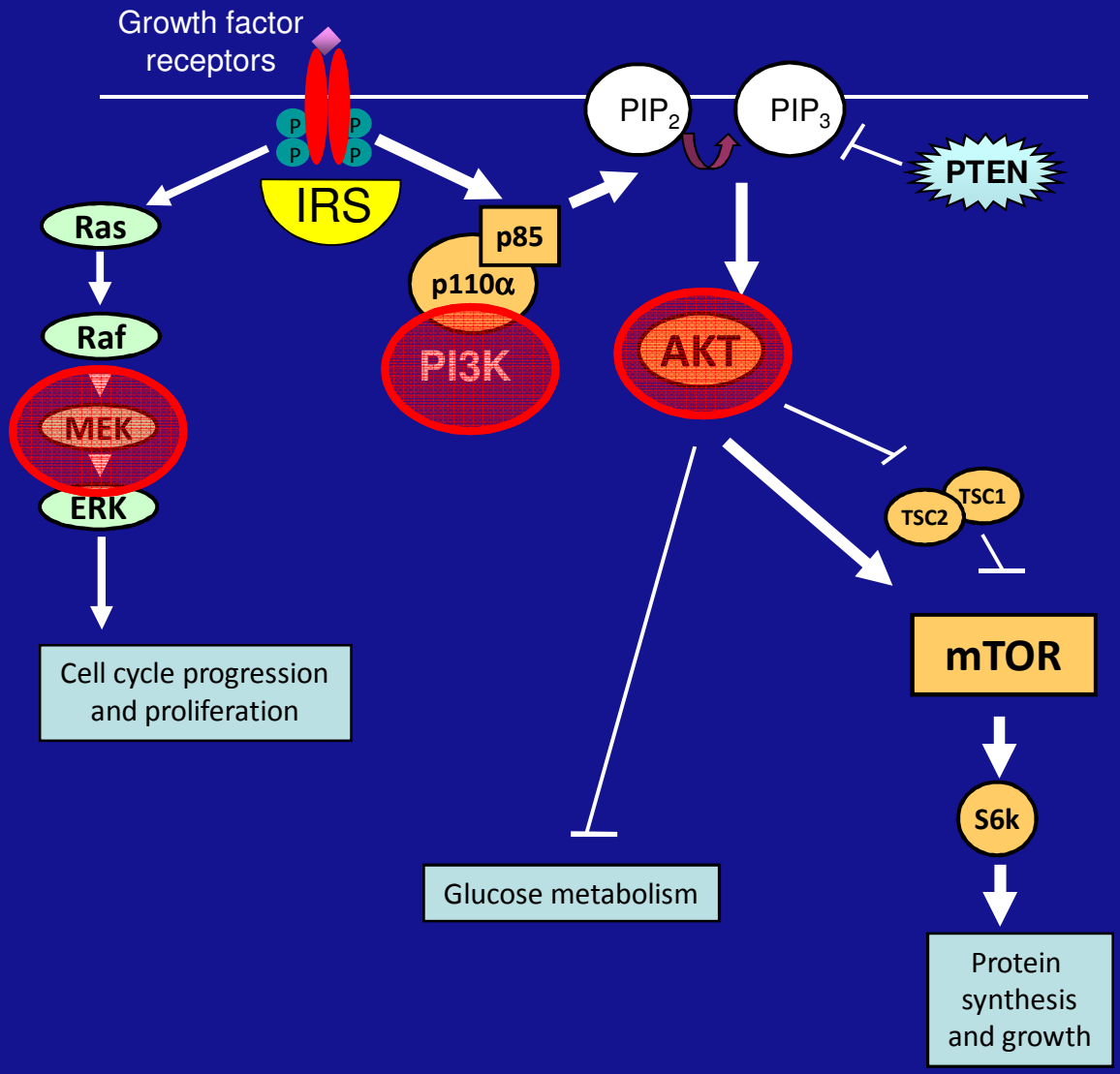
Tsang, Shaw et al. J Clin Oncol 30, 2012 (suppl; abstr 7508)

Newer targets to be validated clinically

PI-3-kinase (PI3K) & MAPK pathways:



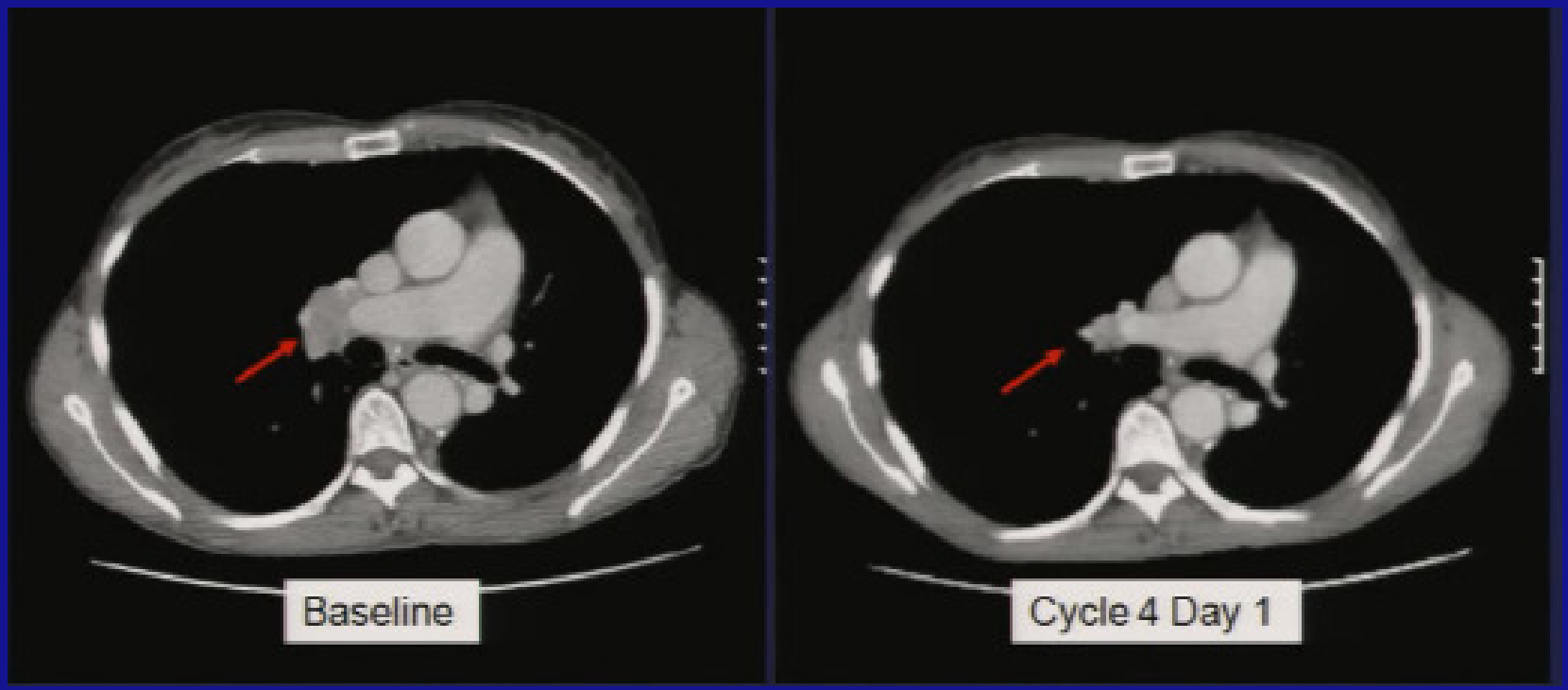
kinase targets downstream from RTKIs:



Combination of PI3K and MEK inhibition

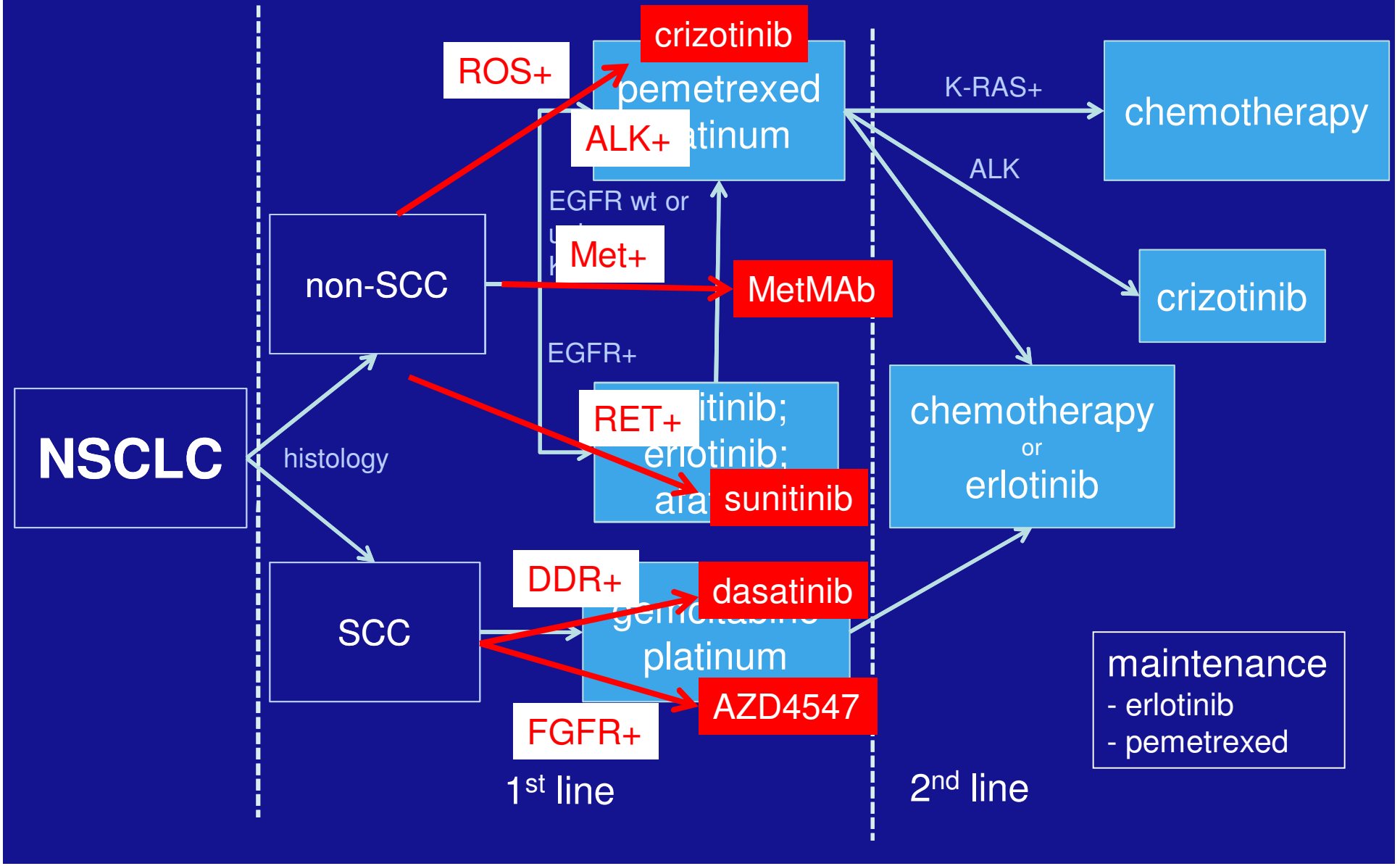
Phase 1 combination study

- MK2206 **AKTi**+ AZD6244 **MEKi**
- response in *KRAS* mutant NSCLC



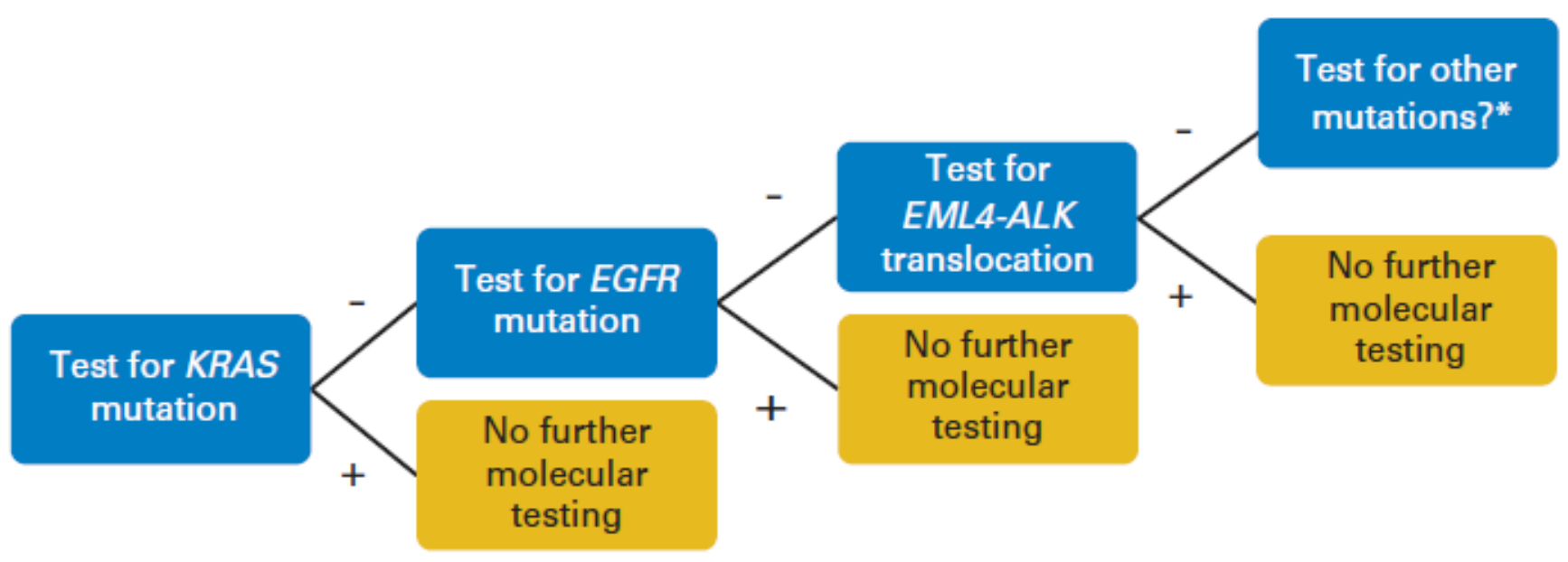
Tolcher et al ASCO 2011

Advanced NSCLC standard of care: soon



Molecular testing in NSCLC

Potential algorithm for patients with adenocarcinoma[1]



* 'Other mutations' includes BRAF[2], MEK1, AKT1, PI3KCA, as well as others

Selected and sequential analysis may be cost effective, but slow and will miss mutations[3]

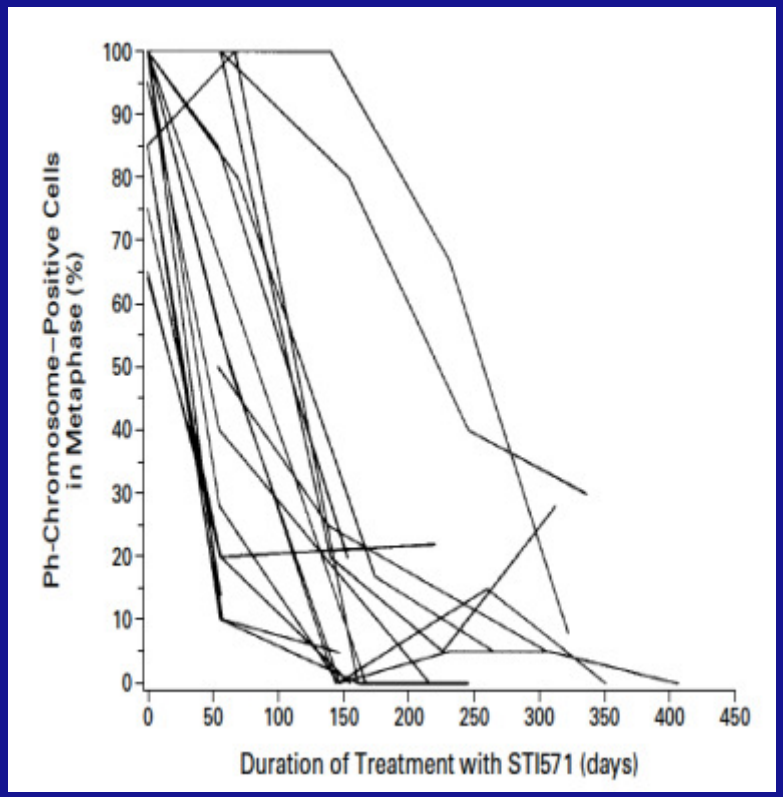
Multiplex analysis may be the way forward:

- Illumia; IonTorrent; Sequenom; NanoString; SNaPshot

1. Horn L and Pao W. J Clin Oncol 2009;27:4232–5; 2. Paik P, et al. J Clin Oncol 2011;29:2046; 3. Bunn P and Doebele R. J Clin Oncol 2011;29:1943–5.

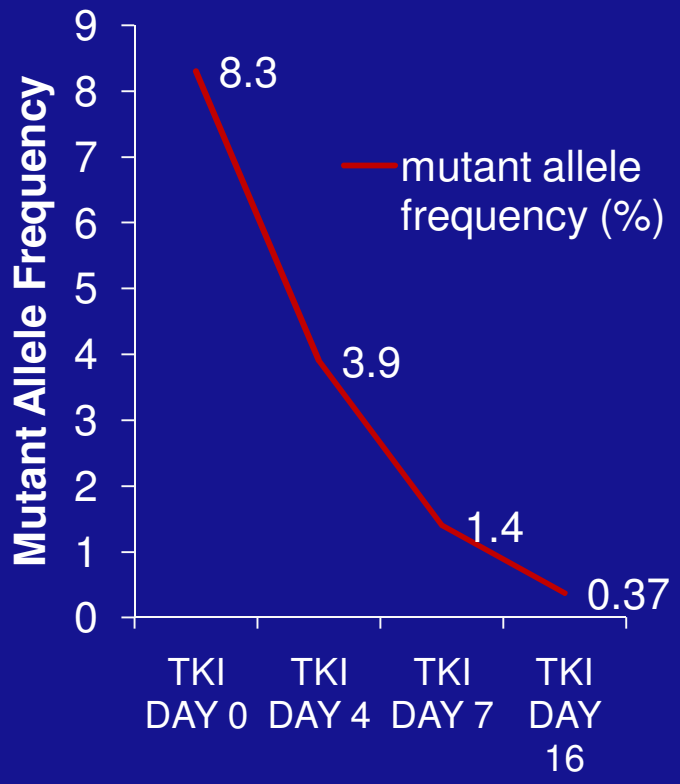
Serial assays in liquid and solid tumours

bcr-abl fusion kinase



Druker et al. NEJM 2001

EFGR deletion exon 19 allele frequency



Conclusions

- Many cancers fragmenting into many molecularly-defined diagnoses
- A growing proportion of these molecular drivers can be targeted, and most are kinases
- Resistance mechanisms are being defined even for newer therapies
- Extended molecular profiling, and sequential analysis, will soon become key components of diagnosis and treatment selection