Clinical experience with kinase inhibitors for the treatment of cancer

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AstraZeneca

6th RSC / SCI Symposium on kinase inhibitor design

AstraZeneca

Overview

- **Kinase inhibitors approved by FDA (1998-2013)**
  - Targets
  - Inhibitor types

- **Kinase inhibitors in the real world**
  - Do more selective compounds make better drugs?
  - Dose selection
  - Combinations
  - Exploiting oncogene addiction for patient selection

- **Resistance and ‘mutant kinases’**
  - Bcr-Abl
  - EGFR
  - EML4-ALK

- **Future directions**

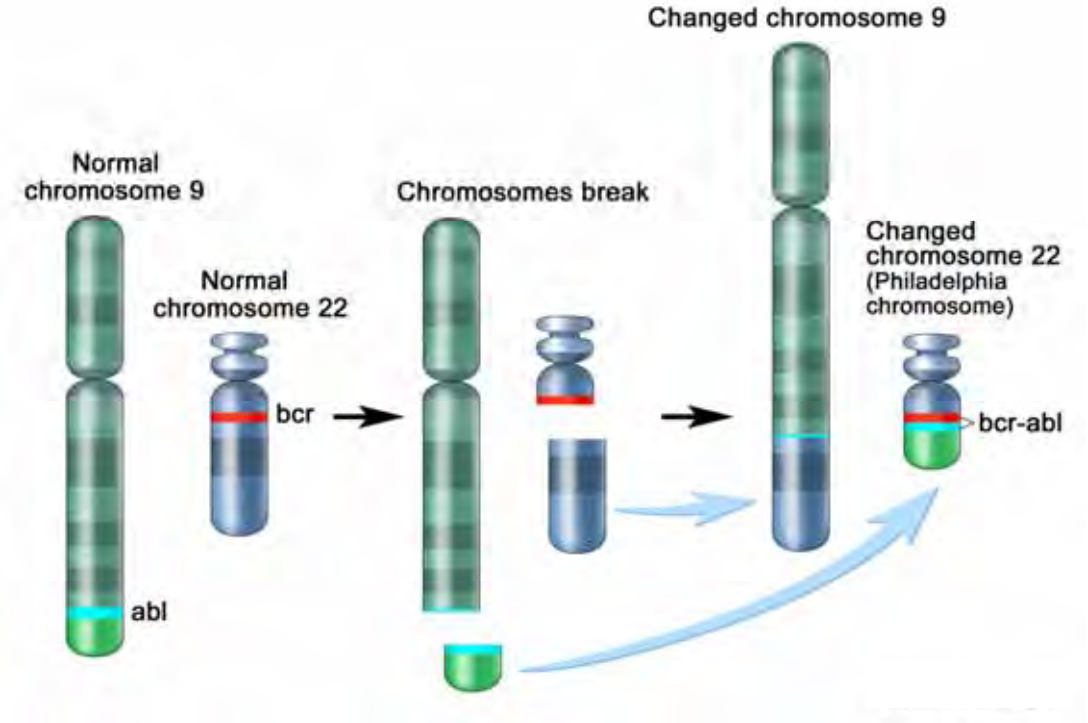
The Kinase Revolution

- More than 50% of current oncology clinical trials

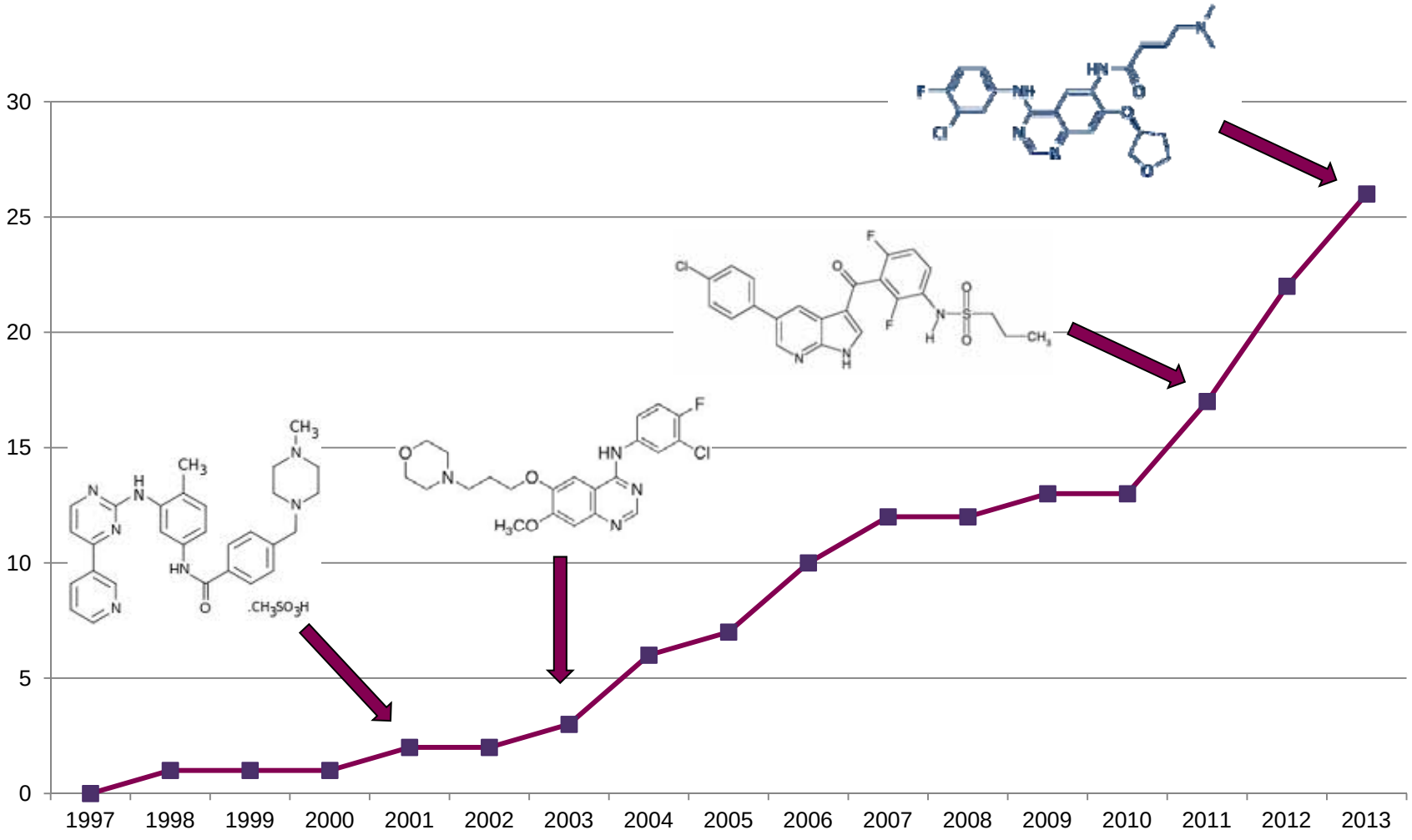
- Kinases are still the most ‘drugable oncogenes’

- Kinase inhibitors have been at the forefront of personalised medicine and diagnostic development

- Launch of Imatinib was truly revolutionary



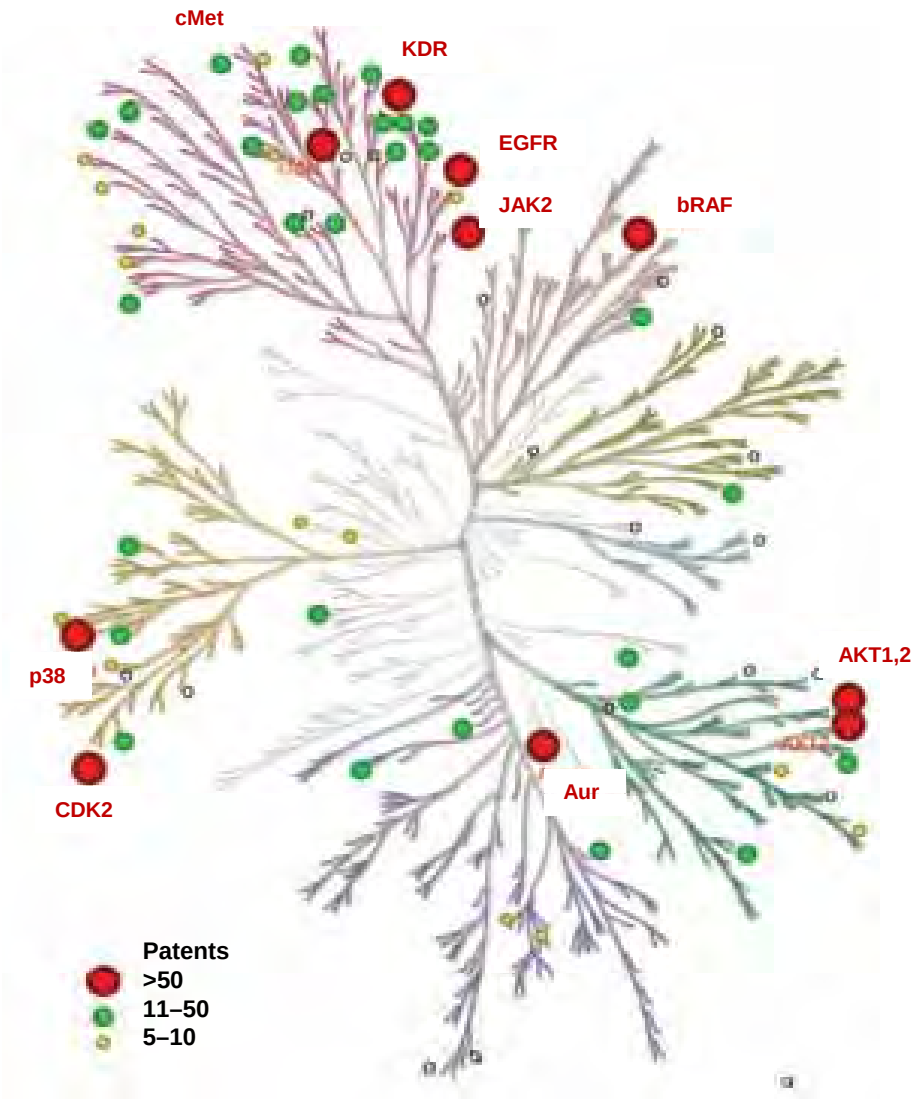
FDA Approved kinase inhibitors for cancer
- Approvals have doubled since 2010



Kinase inhibitor families

- Approved drugs and research in narrow focus

1	**Bcr-Abl**	Imatinib, Dasatinib Nilotinib Bosutinib Ponatinib	CML (GIST)
2	**EGFR**	Gefitinib Erlotinib Afatinib *Panitumumab*	NSCLC (CRC)
3	***ErbB2***	*Trastuzumab* *Lapatinib*	Breast Cancer
4	**VEGFR**	*Bevacizumab* Pegaptinib Sorafenib Sunitinib Axitinib Regorafenib Pazopanib	RCC, CRC, NSCLC, HCC
5	**VEGFR / Ret**	Vandetinib Cabozantib	Thyroid cancer
6	**Ros1 / ALK**	Crizotinib	NSCLC
7	**Braf / MEK**	Vemurafenib Trametinib Debrafenib	Melanoma
8	**JAK**	Ruxolitinib	Myelofibrosis
9	**BTK**	Ibrutinib	MCL, CLL

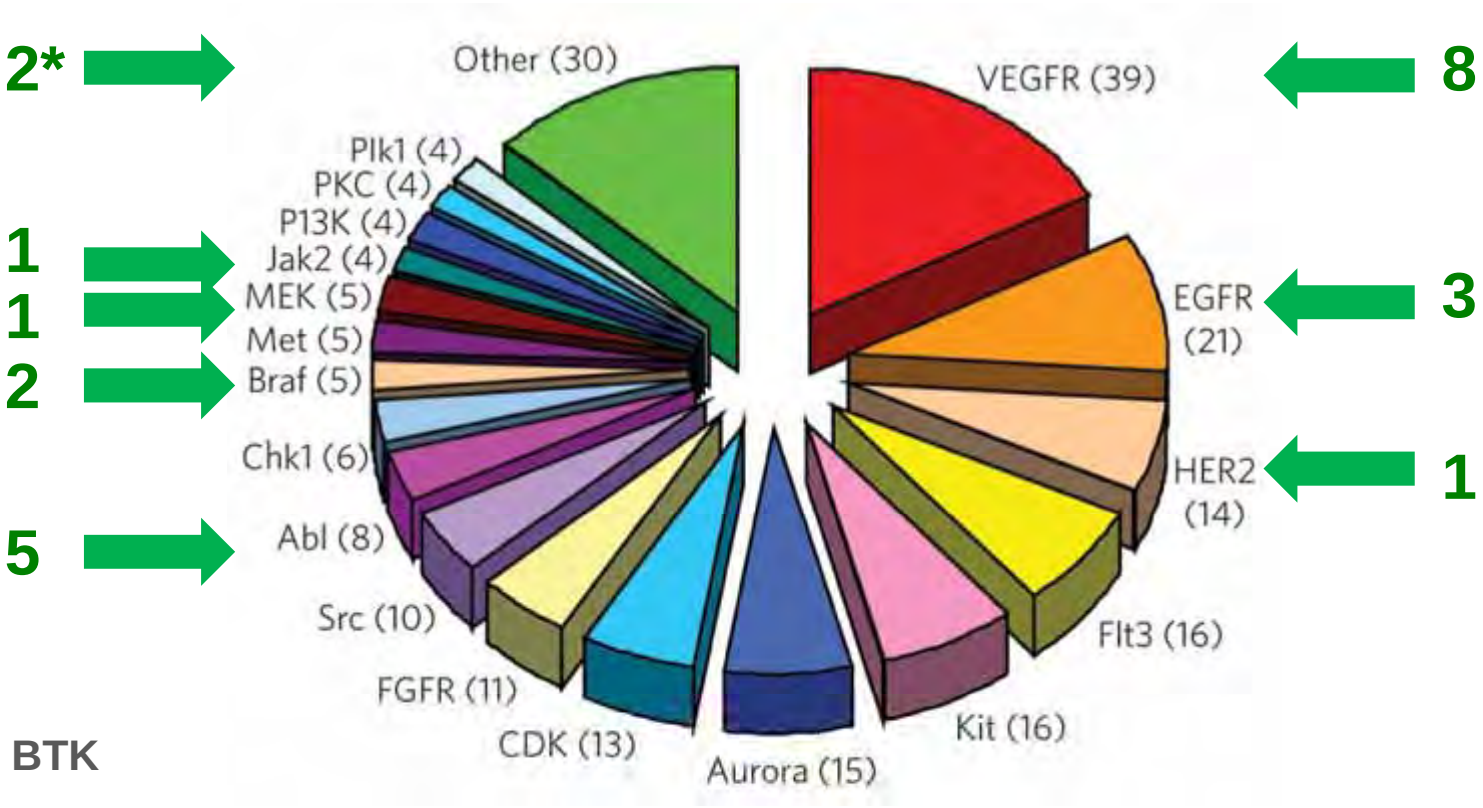


Nature Chemical Biology, 2010, 6, 166169

Most of kinome has yet to be drugged

- Tyrosine kinase inhibitors dominate approved drugs

- Literature review highlighted the total clinical pipeline in 2010.
- Of 23 FDA-aproved small molecule inhibitors, 16 are in just 3 classes (VEGFR, EGFR, Abl)
- This analysis suggests that Flt3, c-kit, Aurora, CDK, FGFR, Src are over-invested



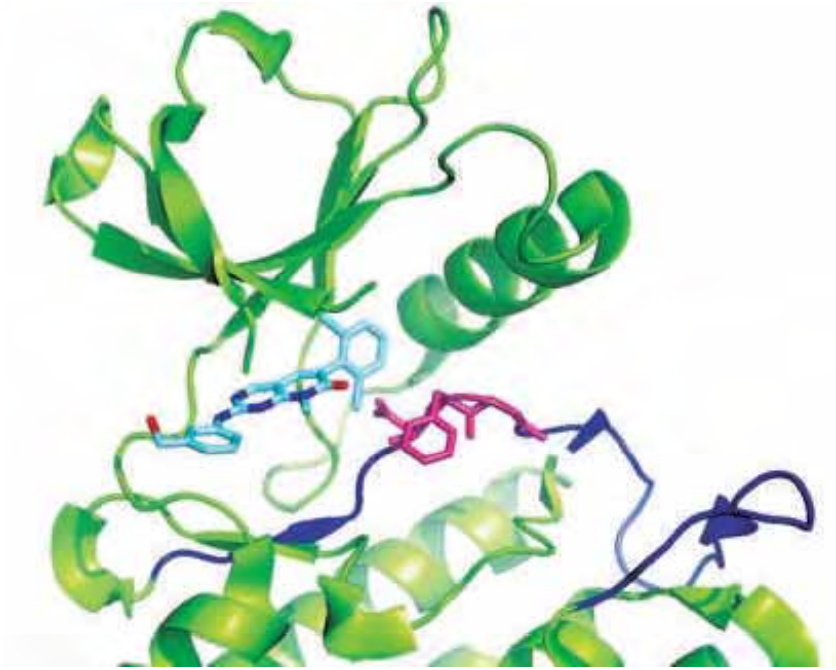
*ALK, BTK

Nature Chemical Biology, 2010, 6, 166169

ATP-competitive inhibitors

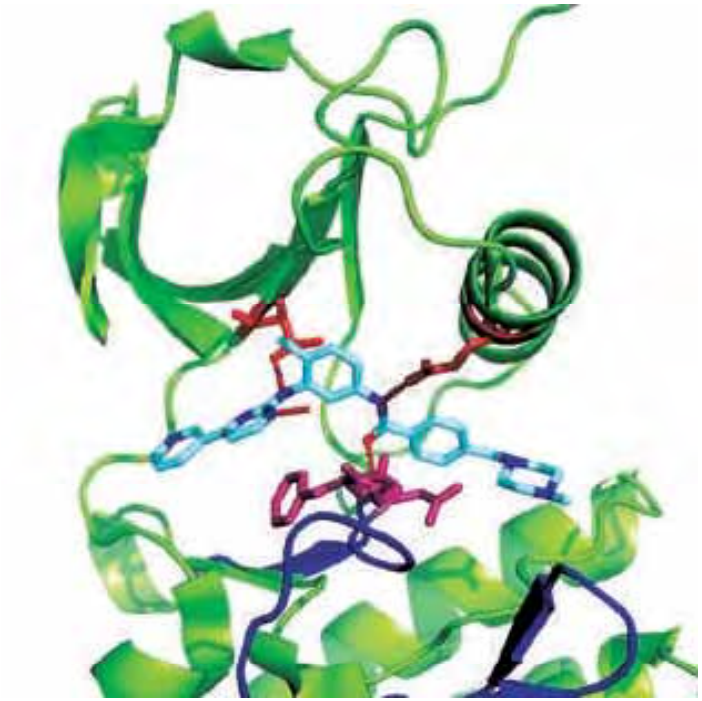
- 18 of 20 Tyrosine Kinase Inhibitors are type I / II

- Type I (DFG - in)



- Gefitinib, Erlotinib, Vandetinib
- Lapatinib, Ruxolitinib, Sunitinib
- Dasatinib, Axitinib,

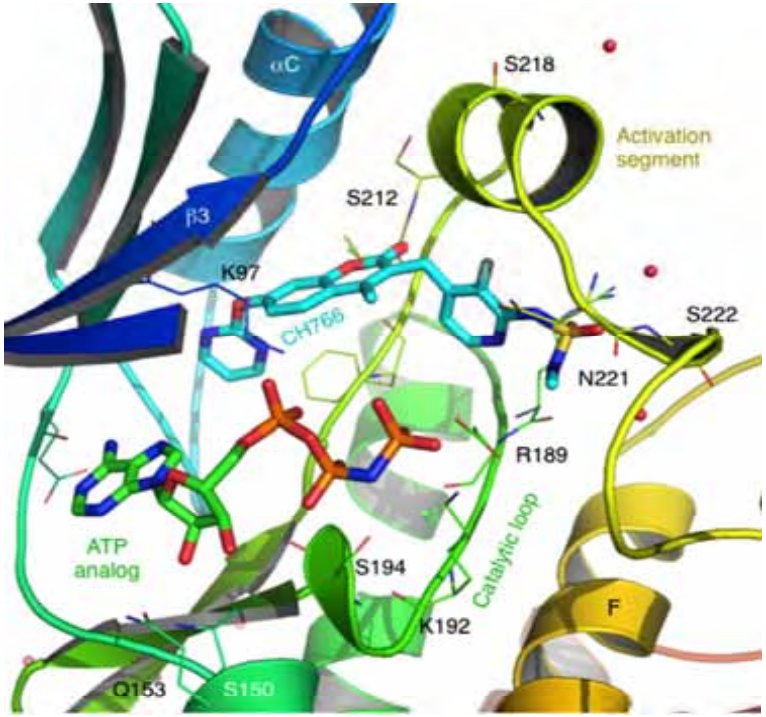
- Type II (DFG – out)



- Sorafenib, Imatinib, Nilotinib

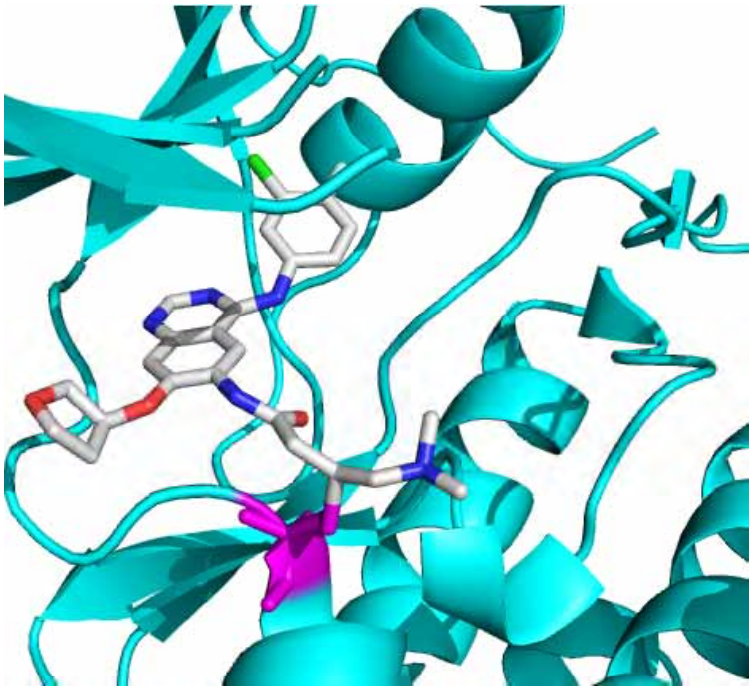
Other Mechanisms of Action
- Novel Modes of Inhibition

- ‘Allosteric inhibitors’



- Trametinib

- Covalent binders



- Afatinib, Ibrutinib

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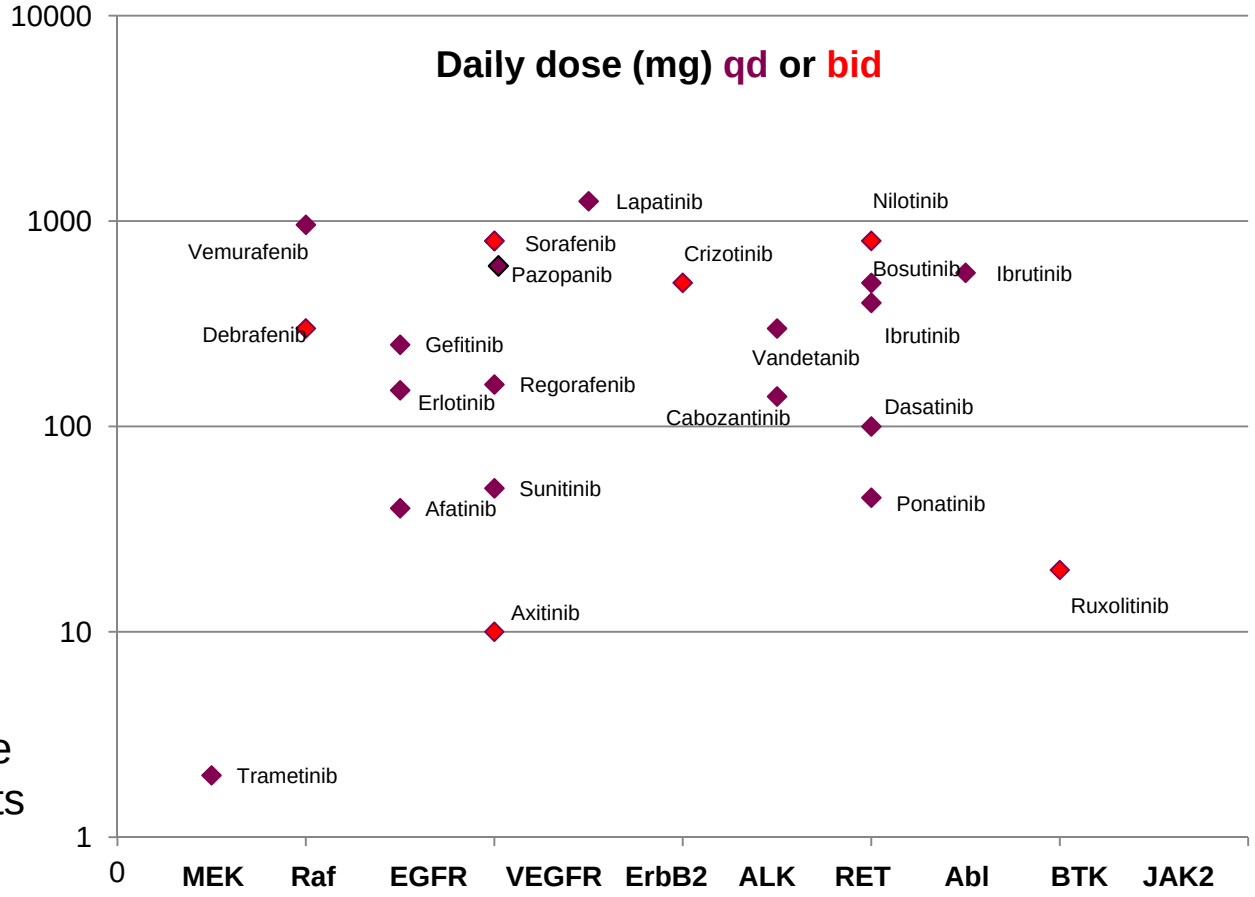
  - EGFR
  - EML4-ALK
- Future directions

Dose and Schedule
- Monotherapy still dominates

- With exception of Lapatinib, kinase inhibitors typically dosed as continuous monotherapy
- Three quarters of compounds given once daily (qd)
- Median daily dose is 275 mg/day although this is lower for recently approved compounds

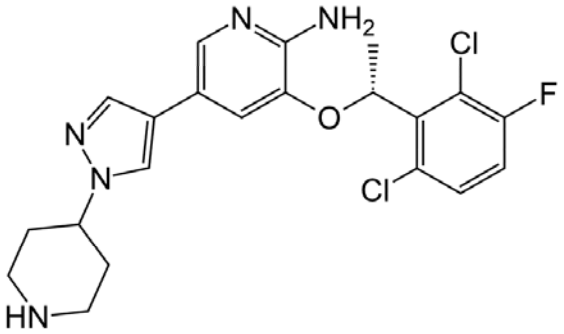
Lapatanib – 1250mg qd dose delivered as 5 x 250mg tablets



When lack of selectivity pays off...
- Crizotinib and Vandetinib

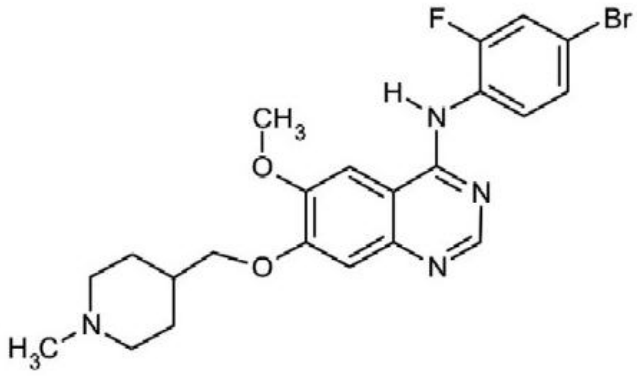
- Crizotinib, originally selected as a c-Met inhibitor, first dosed to patients in 2006
- ALK activity established pre-clinically in 2005 (20 fold more potent) ...also ROS1
- First reports on EML4-ALK fusion published July 2007
- First ALK-fusion patient dosed with Crizotinib in December 2007

- FDA approval in EML4-ALK NSCLC cancer granted in 2011



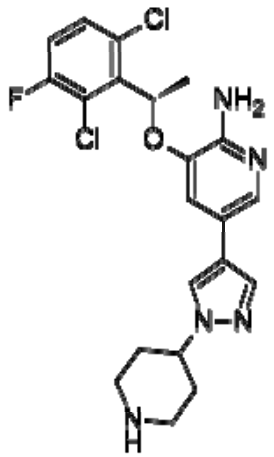
- Vandetanib originally developed as VEGFR inhibitor with some EGFR activity
- Completed a Phase III study in NSCLC in combination with docetaxel (2009)
- Ret activity demonstrated after start of Phase I by collaborator (2002)
- Clinical studies in thyroid cancer started in 2004

- FDA approval in medullary thyorid cancer granted in 2011



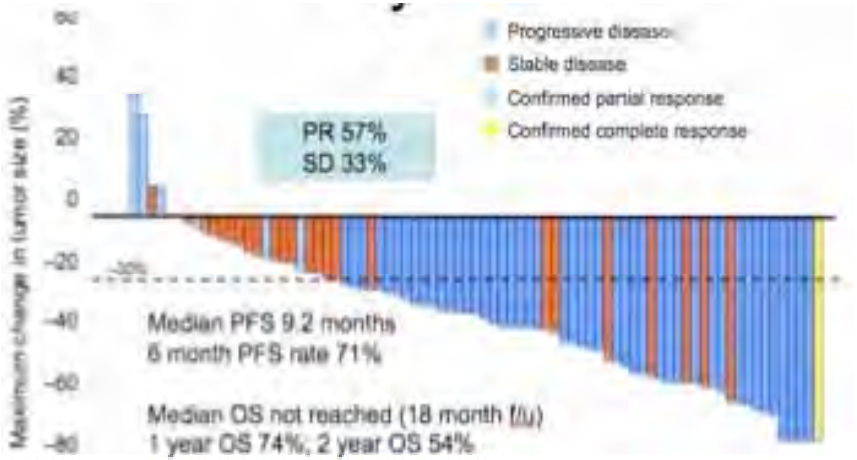
Drug Design, Development and Therapy 2011:5

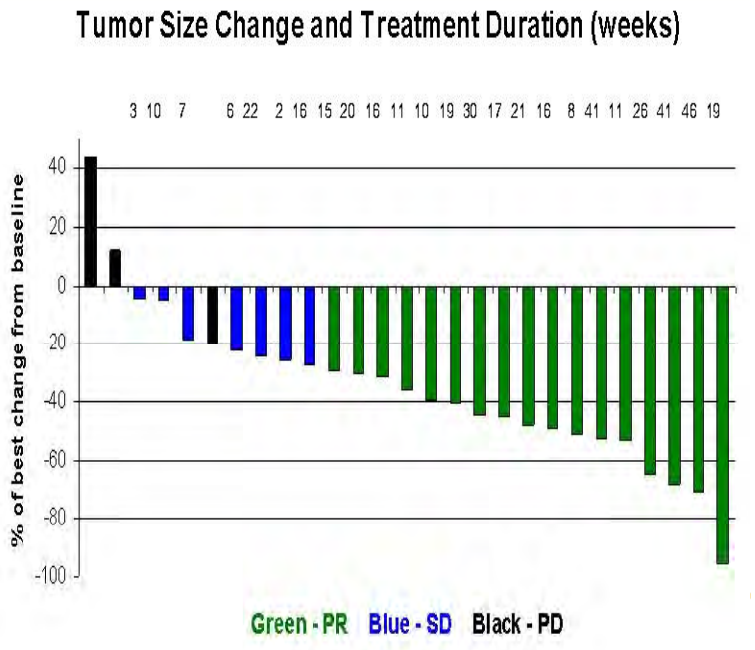
But, ultimately, selectivity is important
- Crizotinib v PF-06463922



Issues with Crizotinib

- **Weak activity against other mutant forms of ALK**
- **Limited brain penetration**
- **Response rate 'only' 57%**
- **Limited duration of response (~7 months)**
- **>60% patients suffer visual impairment**
- **~0.4% incidence of fatal liver failure**





Tolerability of kinase inhibitors

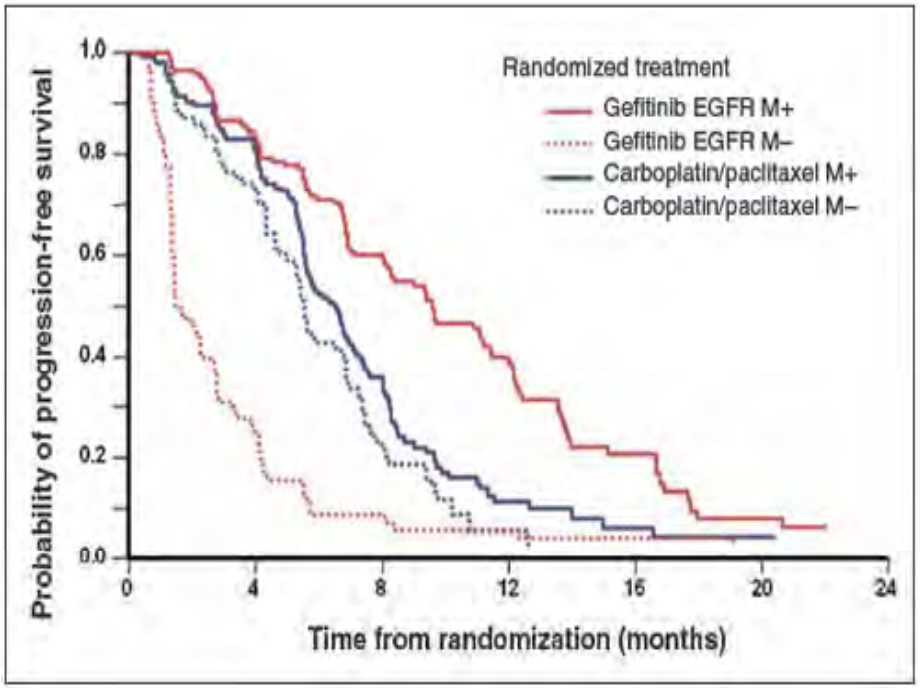
- Better than cytotoxics but not clean...

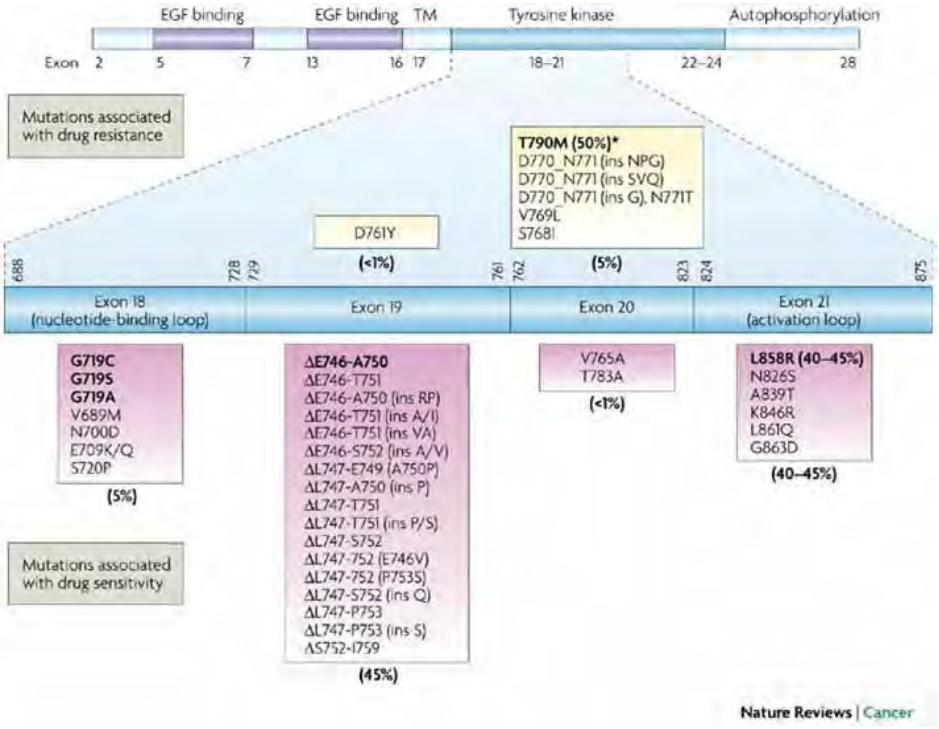
- In a study of 34 patients on Sorafenib and Sunitinib :
  - 10 patients (34%) had stabilization of disease, 8 patients (28%) had a partial response, and 11 patients (38%) had progression of disease
  - Grade 3 or 4 adverse event occurred in 19 patients (56%)
  - 8 patients (24%) required drug discontinuation and 11 patients (32%) required dose reductions, but were able to resume the targeted dose
- Toxicity due to both lack of selectivity and role of kinases in normal physiology
- 11 of 26 FDA-approved kinase inhibitors carry black box warnings :

Drug	Sponsor	Target	Black box warning(s)	FDA AD
Trastuzumab	Genentech	HER2	Pulmonary toxicity, cardiomyopathy and a confusion warning	25/09/1998
Bevacizumab	Genentech	VEGF	GI perforation, haemorrhage and wound healing complications	26/02/2004
Sunitinib	Pfizer	VEGFR, PDGFR	Hepatotoxicity	26/01/2006
Panitumumab	Amgen	EGFR	Dermatologic reactions and infusion reactions	10/10/2006
Lapatinib	GlaxoSmithKline	ErbB2	Hepatotoxicity	13/03/2007
Nilotinib	Novartis	Bcr-Abl	QT interval prolongation and electrolyte anomalies	29/10/2007
Pazopanib	GlaxoSmithKline	VEGFR, PDGFR, c-KIT	Hepatotoxicity	19/10/2009
Vandetanib	AstraZeneca	VEGFR, EGFR, RET, BRK	QT interval prolongation	21/04/2011
Regorafenib	Bayer	RET, VEGFR, PDGFR	Hepatotoxicity	27/09/2012
Cabozantinib	Exelixis	RET, c-Met, VEGFR	GI haemorrhage, perforation and fistula	29/11/2012
Ponatinib	ARIAD	Bcr-Abl, PDGFR, FGFR, ...	Liver failure, blood clots and hepatotoxicity	14/12/2012

Activating Mutations - 1
- EGFR and lung adenocarcinoma

- Gefitinib trial in unselected patients shows marginal PFS benefit
- Being female, of Asian origin and a non-smoker increased benefit
- iPass trial (below) showed dramatic differences in wt and mutant patients

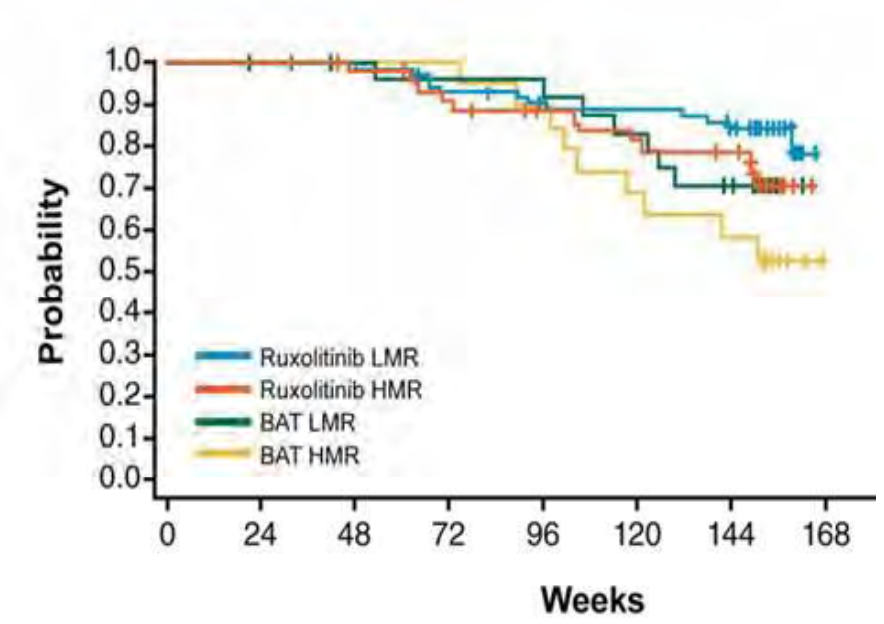


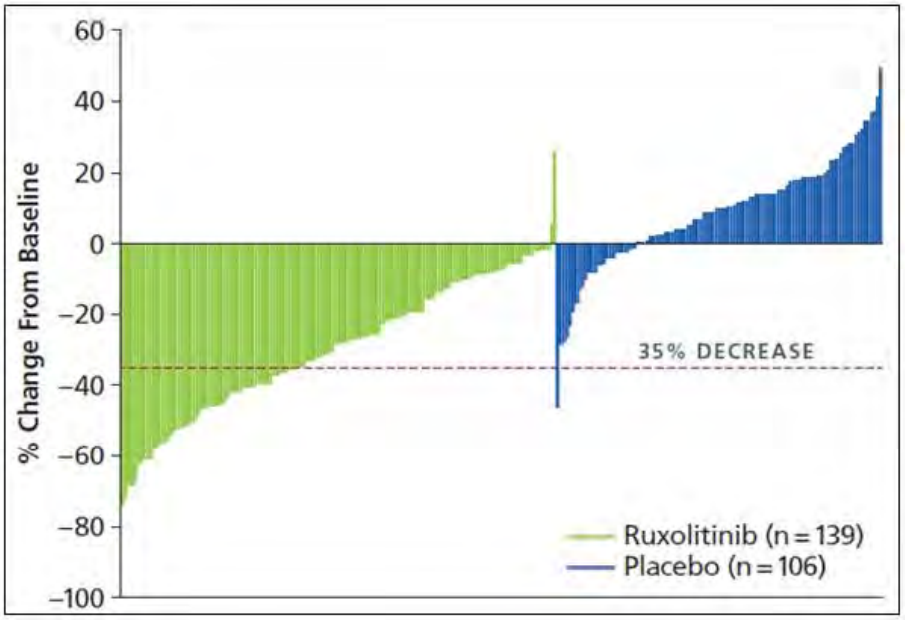


- Gefitinib used with diagnostic test in 18-35% patients who have EGFR mutations
- Most common genetic events are exon 19 deletion and L858R mutation (exon 21)

Activating Mutations - 2 - JAK2 and Myelofibrosis

- 60% patients with myelofibrosis (IMF) have V617F mutation in JAK2
- Ruxolitinib trials recruited roughly equal numbers of V617F JAK2 +/- patients
- Level of reduction of splenomegaly considerably better than with placebo
- Impact on overall survival less clear



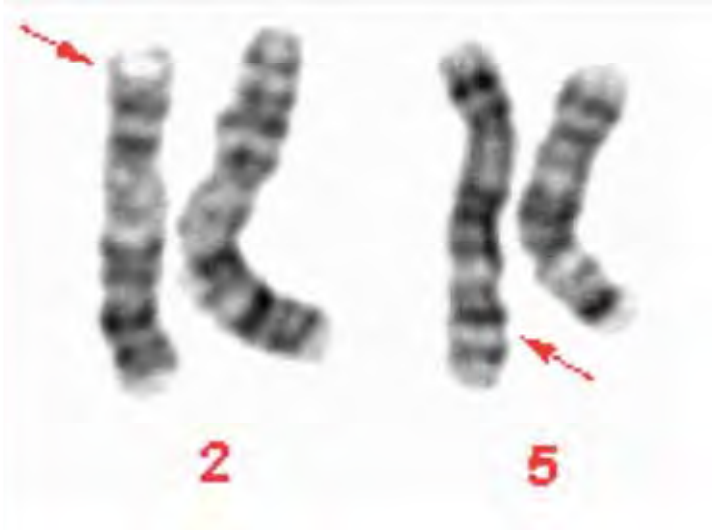


- Level of reduction of splenomegaly (above) has no significant link with JAK2 mutation status (‘low molecular risk’ v ‘high molecular risk’)

- Ruxolitinib used without diagnostic test in all patients with IMF

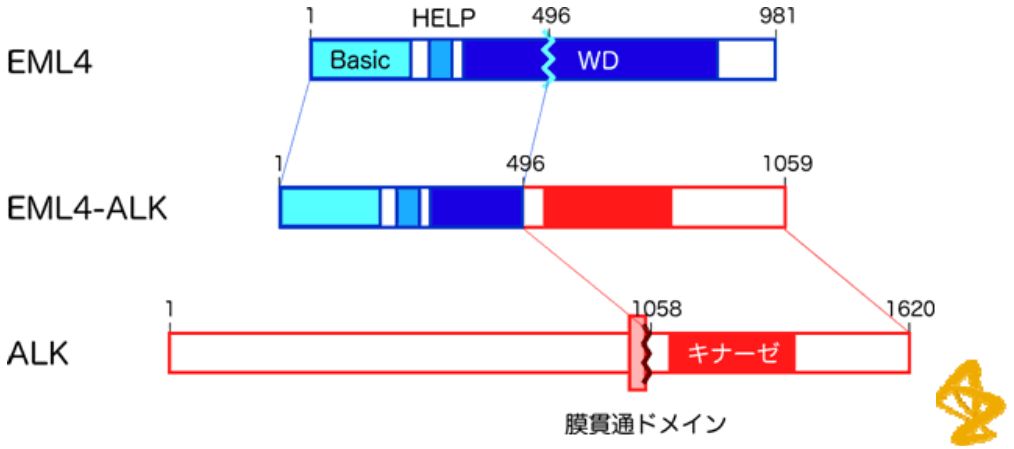
Kinase Translocation and Fusion Proteins
- Highly oncogenic but often rare genetic events

- The first protein kinase translocation was the Philadelphia chromosome t(9;22) in CML



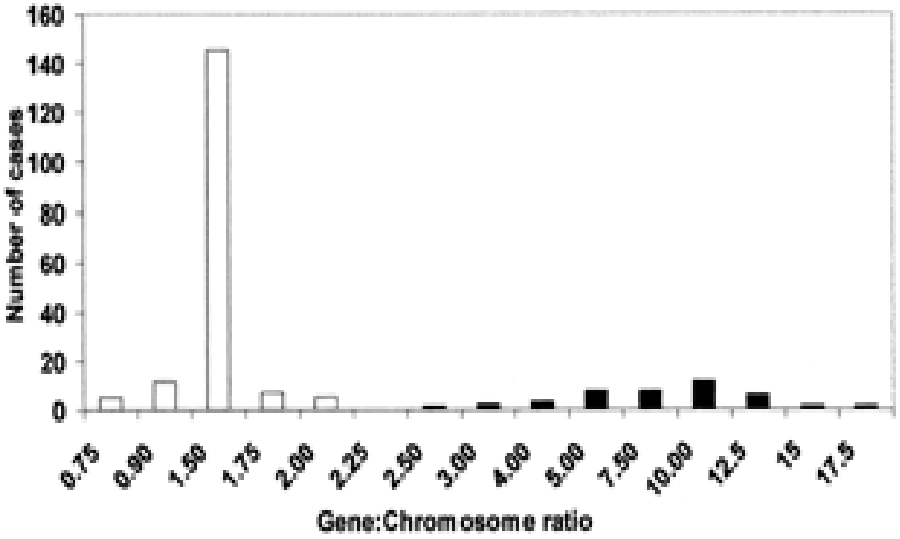
- Other fusion proteins have been found with cytosolic tyrosine kinases
  - *TEL - JAK2*
  - *TEL – SYK*
  - *ITK - SYK*

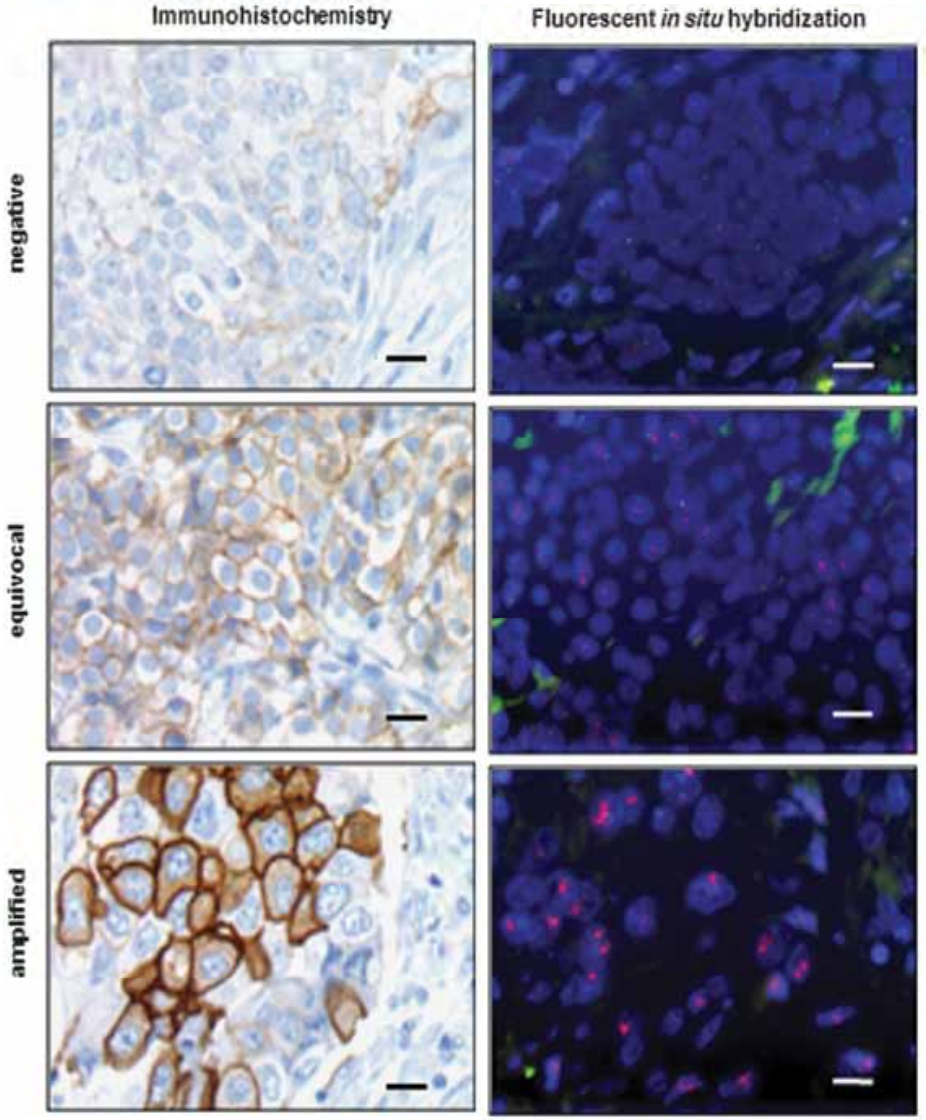
- Other fusion proteins have been found with receptor tyrosine kinases
  - *FIP1L1 - PDGFRA*
  - *EML4 - ALK*
  - *TACC3 – FGFR3*
  - *TACC1 – FGFR1*
  - *RET – PTC*



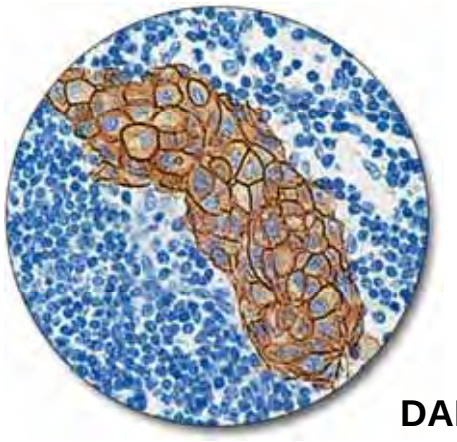
Amplification and Overexpression - ErbB2 and Breast Cancer

- Approximately 20% of invasive breast cancers overexpress Her2, and are associated with poor prognosis
- Overexpression of the Her2 protein is primarily due to amplification of the HER2 oncogene on chromosome 17
- However, increased HER2 copies may also result from chromosome 17 polysomy





Patient selection strategies
- Diagnostic Development



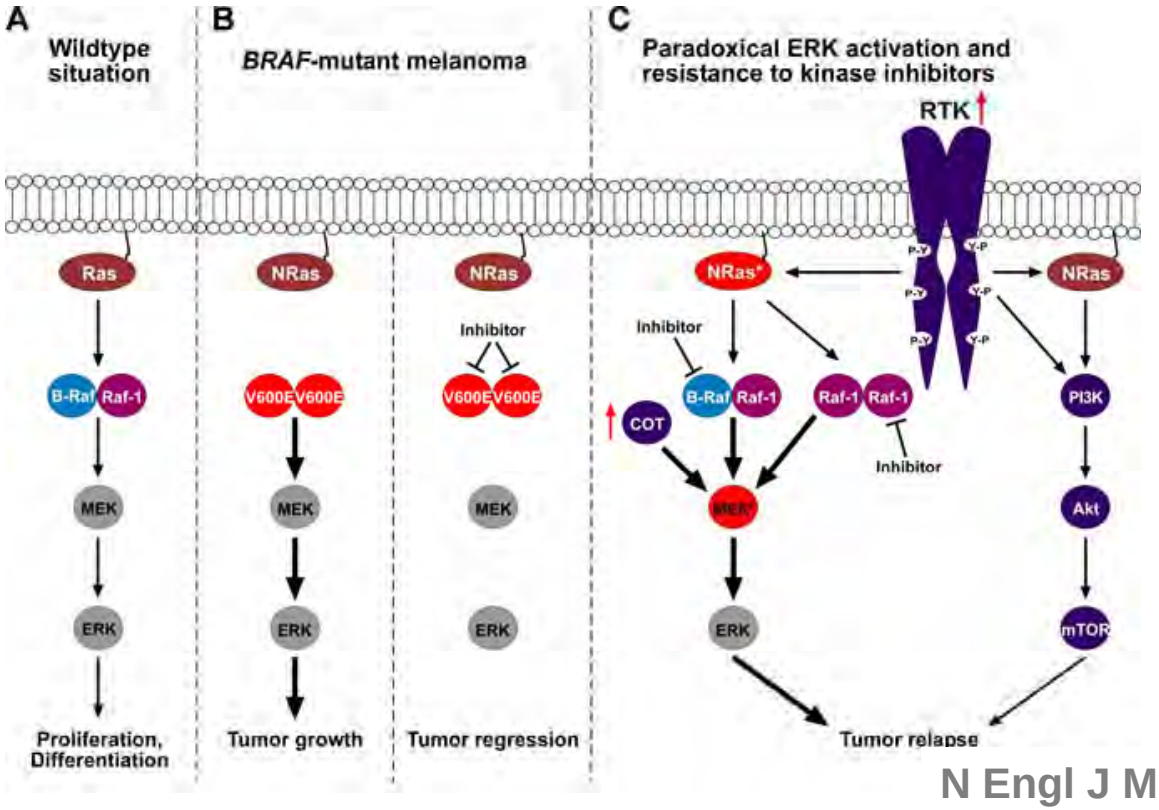
DAKO Herceptest

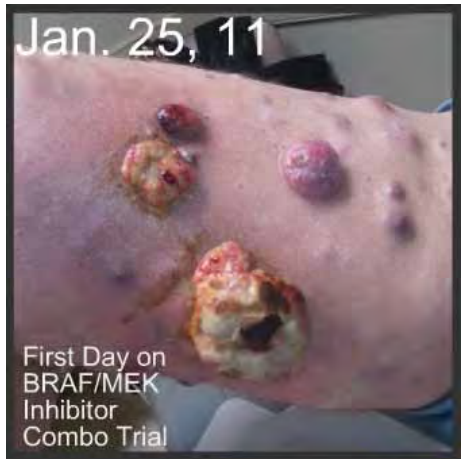
- 18 (of19) FDA-approved companion diagnostics for oncology are for kinase targets, of which 10 are for Her2
- Imatinib uses Philadelphia chromosome status (Ph+)
- Numbers of diagnostics set to increase rapidly

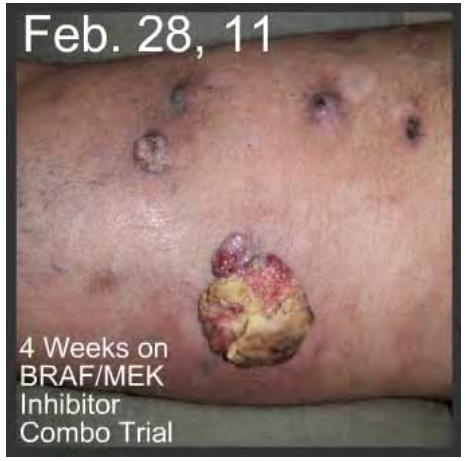
FDA	Device Trade Name	Product	Target	Device Manufacturer
1	*therascreen* KRAS RGQ PCR Kit	Cetuximab	Kras (EGFR-wt)	Qiagen Manchester, Ltd.
2	DAKO EGFR PharmDx Kit	Cetuximab, Panitumumab	EGFR	Dako North America, Inc.
4	therascreen EGFR RGQ PCR Kit	Afatinib	EGFR	Qiagen Manchester, Ltd.
5	DAKO C-KIT PharmDx	Imatinib	c-Kit	Dako North America, Inc.
6	INFORM HER-2/NEU	Trastuzumab	Her2	Ventana Medical Systems, Inc.
7	PATHVYSION HER-2 DNA Probe Kit	Trastuzumab	Her2	Abbott Molecular Inc.
8	PATHWAY ANTI-HER-2/NEU (4B5) Rabbit Monoclonal Primary Antibody	Trastuzumab	Her2	Ventana Medical Systems, Inc.
9	INSITE HER-2/NEU KIT	Trastuzumab	Her2	Biogenex Laboratories, Inc.
10	SPOT-LIGHT HER2 CISH Kit	Trastuzumab	Her2	Life Technologies, Inc.
11	Bond Oracle Her2 IHC System	Trastuzumab	Her2	Leica Biosystems
12	HER2 CISH PharmDx Kit	Trastuzumab	Her2	Dako Denmark A/S
13	INFORM HER2 DUAL ISH DNA Probe Cocktail	Trastuzumab	Her2	Ventana Medical Systems, Inc.
14	HERCEPTEST	Trastuzumab, Pertuzumab	Her2	Dako Denmark A/S
15	HER2 FISH PharmDx Kit	Trastuzumab, Pertuzumab	Her2	Dako Denmark A/S
16	THxID™ BRAF Kit	Trametinib, Debrafenib	Braf	bioMérieux Inc.
17	cobas EGFR Mutation Test	Erlotinib	EGFR	Roche Molecular Systems, Inc.
18	VYSIS ALK Break Apart FISH Probe Kit	Crizotinib	EML4-ALK	Abbott Molecular Inc.
19	COBAS 4800 BRAF V600 Mutation Test	Vemurafenib	Braf	Roche Molecular Systems, Inc.

Rational combinations have huge promise - Braf-MEK combination

- Comparison of Trametiinib + Debrafenib v Debrafenib
- Median PFS for the combination was 9.4 months, as compared with 5.8 months for Debrafenib (HR = 0.39)
- 0.25 to 0.62; P<0.001).
- The rate of CR/PR was 76%, (54% for monotherapy)







N Engl J Med 2012; 367:1694-1703

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  - EGFR
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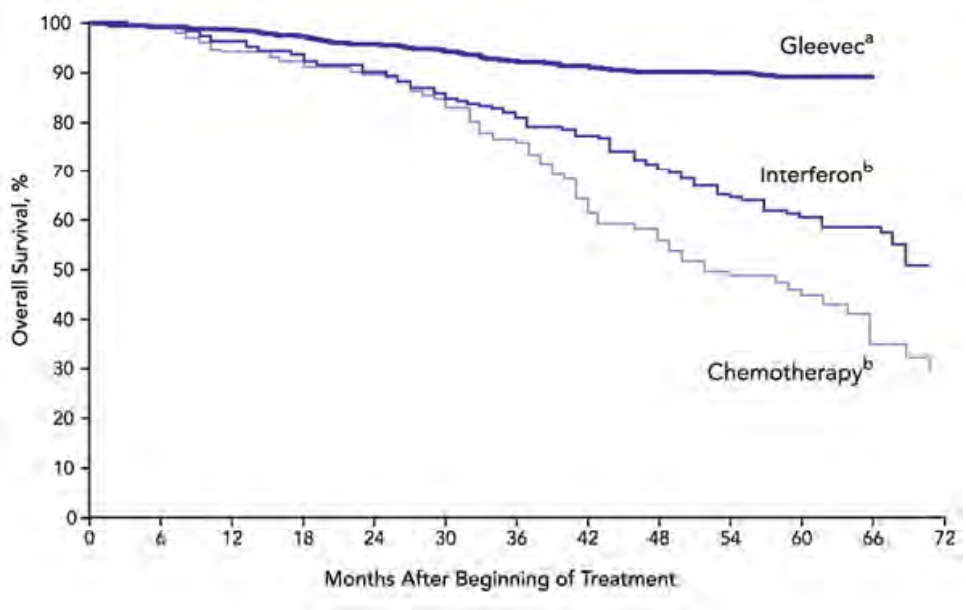
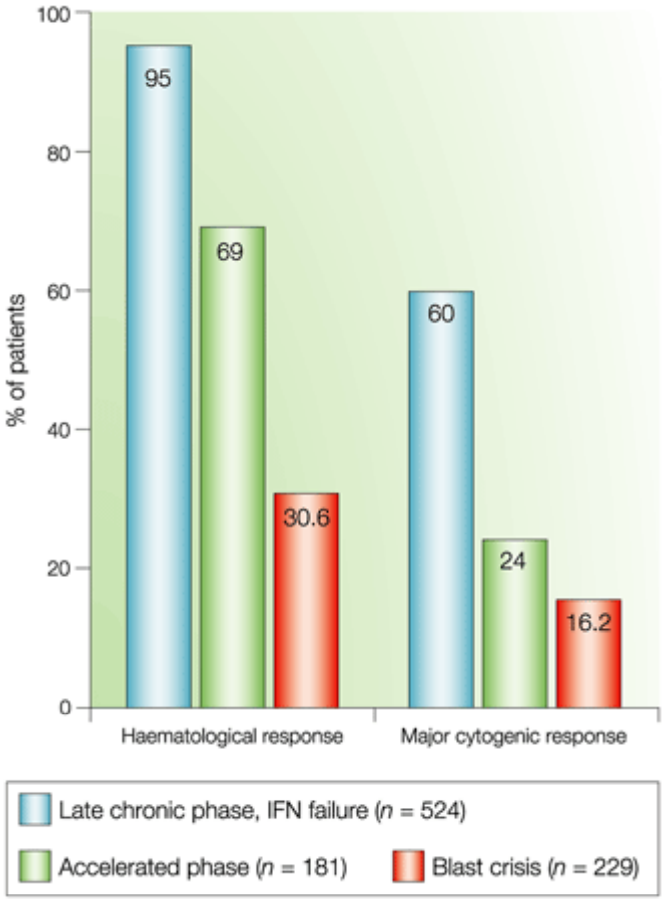
- **Future directions**

Mutant kinases

- Bcr-Abl : Imatinib's real world performance

- Imatinib has revolutionised treatment of CML
- Patients typically stay on drug > 3years
- However, the benefit of Imatinib is greatest in early stages of disease (lower clonal burden)
- Resistance to Imatinib through both Bcr-Abl mutations and overexpression

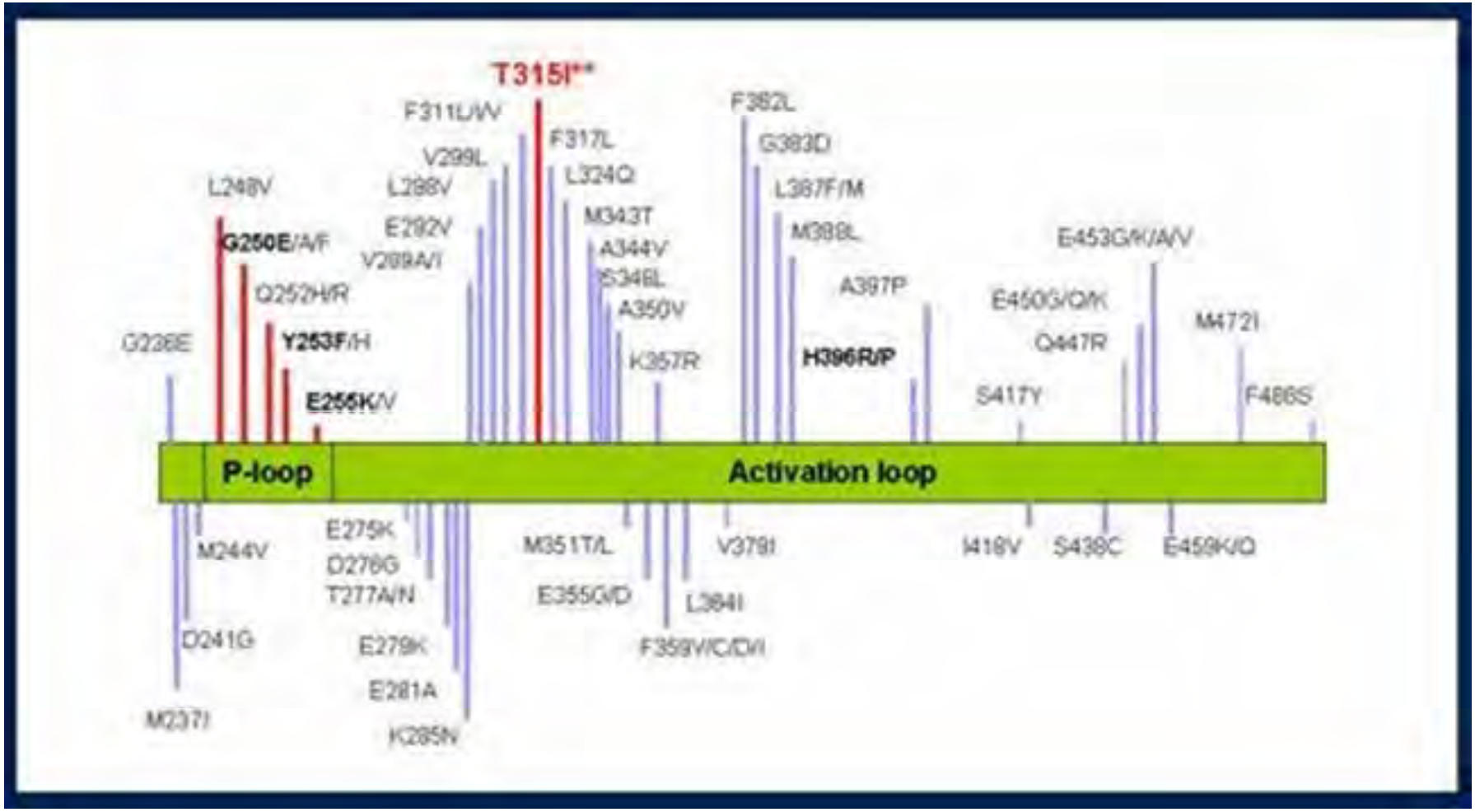




Mutant kinases

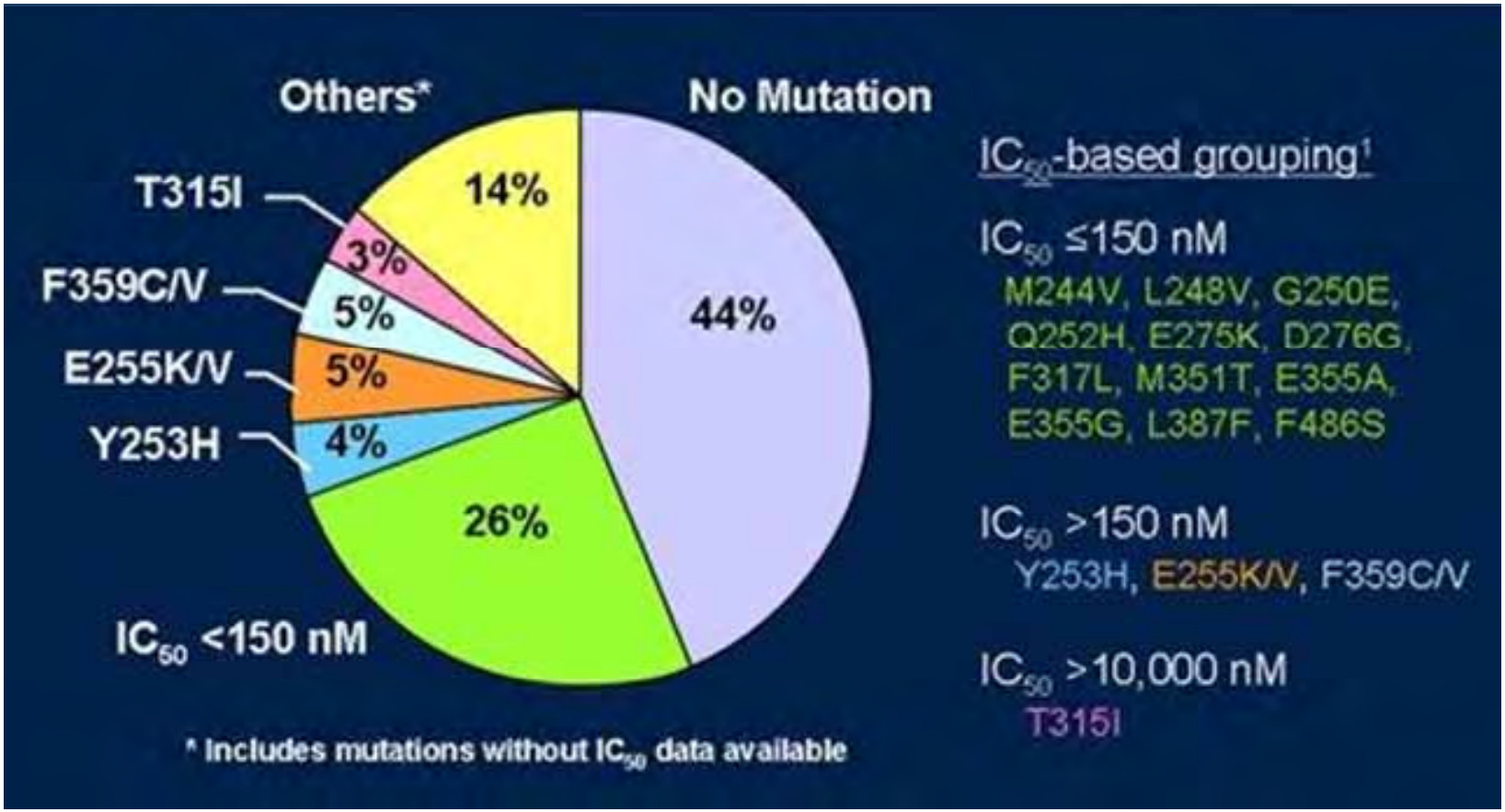
- Bcr-Abl : Imatinib resistance mutations

- Initially 33 mutations were found, now over 90, although many are very rare



Mutant kinases
- Bcr-Abl : clonal evolution

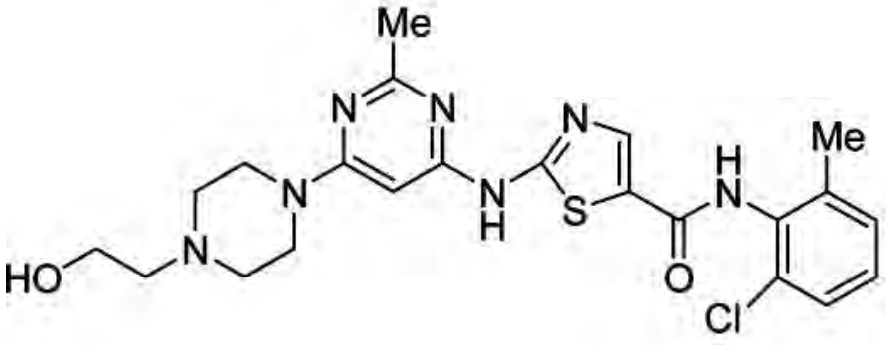
- Baseline mutational status established for patients who are resistant to Imatinib
- Over half patients harbour mutations
- Thus there is high clonal heterogeneity before Imatinib treatment

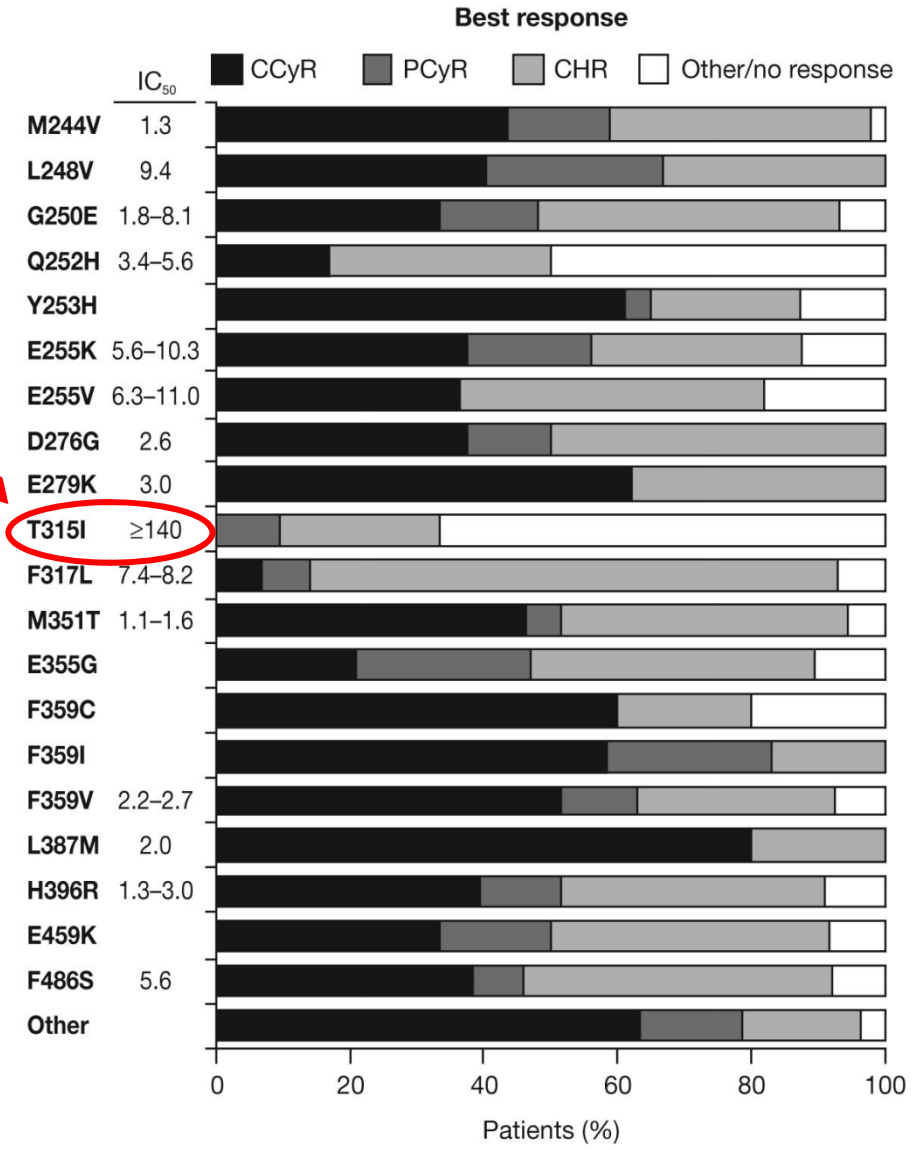


Mutant kinases
- Bcr-Abl : enter Dasatinib

- In contrast to Imatinib, Dasatinib is a type I (DFG-in) RTK inhibitor
  - Much more potent against Abl
  - Effective against all mutant forms except T315I (gatekeeper)
  - Also active against Src family
  - Broader RTK activity

- Pattern of resistant mutants different from Imatinib (Sawyers, 2004)

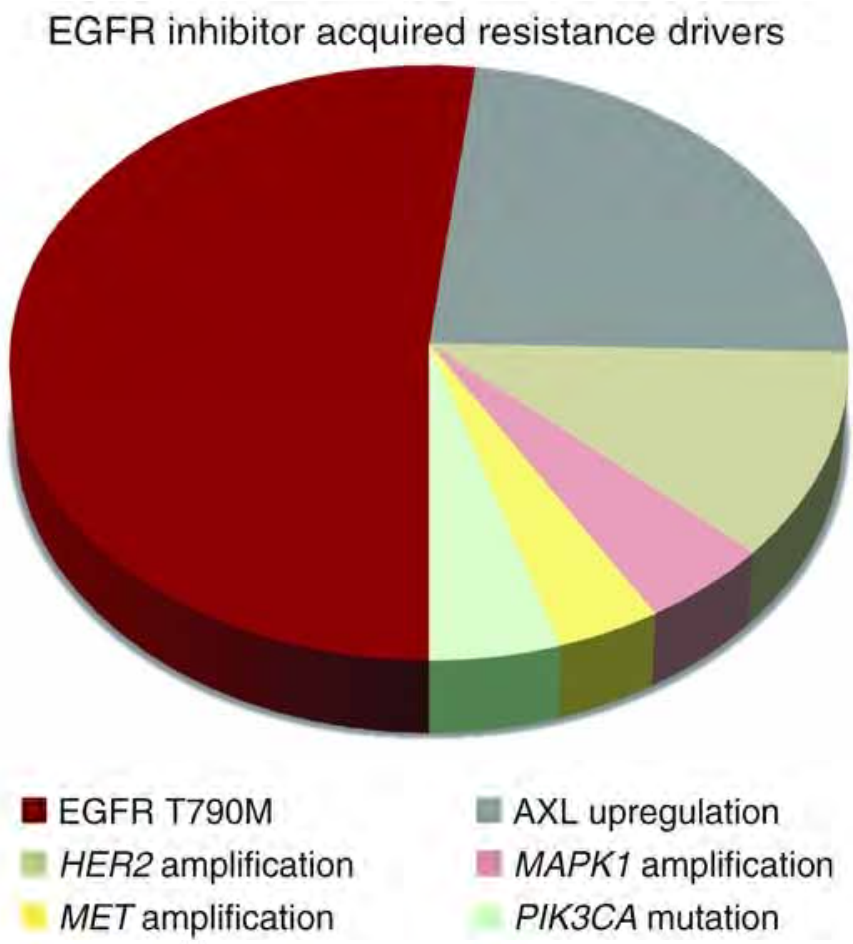




Mutant kinases
- EGFR : post Gefitinib or Erlotinib

- Median time on Erlotinib or Gefitinib is around 10 months
- Afatinib (irreversible) claims to increase this by 2 months but toxicity is greater
- In contrast to Imatinib, T790M is the dominant resistant clone
- Activation of other RTKS (cMet, her2) also important resistance mechanisms
- Transformation to Small Cell Lung Cancer (or squamous histology)is reported, but incompletely understood

- Only about 4% of patients have <u>detectable</u> T790M at first biopsy



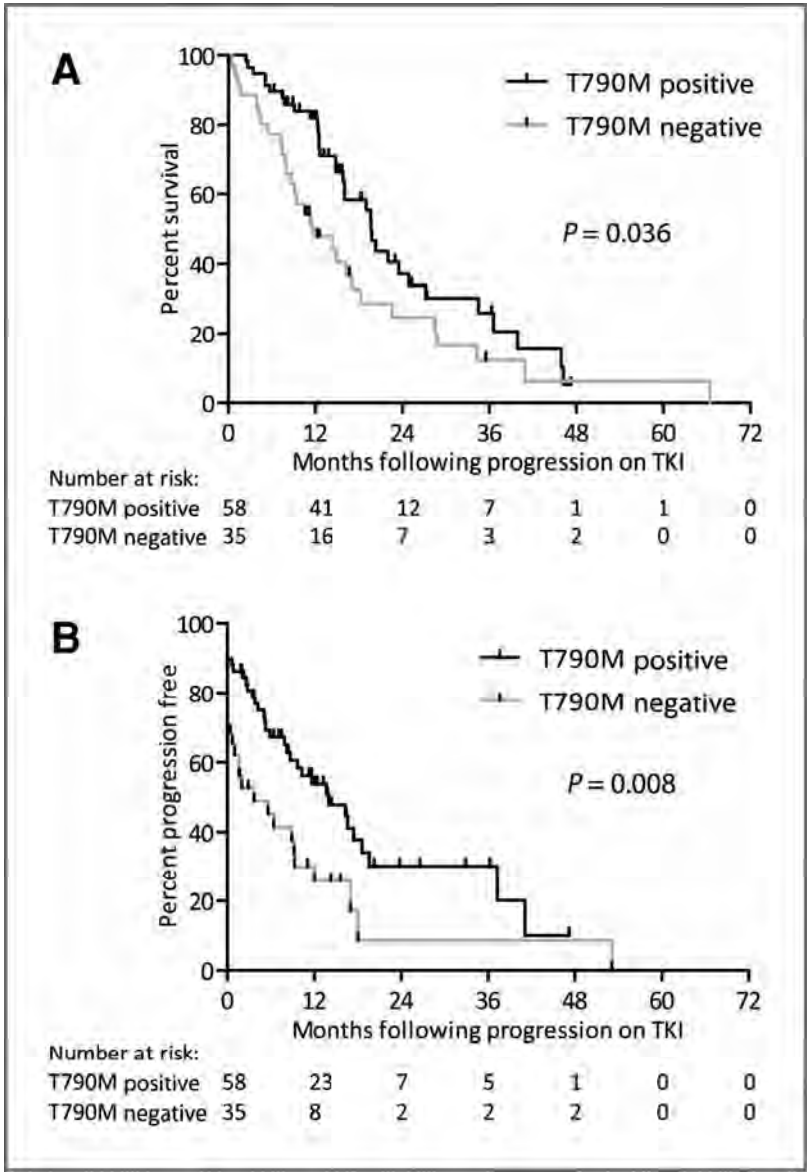
Mutant kinases
- T790M EGFR

- T790M +ve has better prognosis (19 month PFS) v T790M –ve (12 month PFS)
- In 2010 William Pao reported 5 patients with germ-line T790M (ages 50-72)
- 3 of the 5 patients also had the L858 (exon 19 mutation)

- *The T790M mutation merely restores ATP affinity to the level of the WT kinase*.

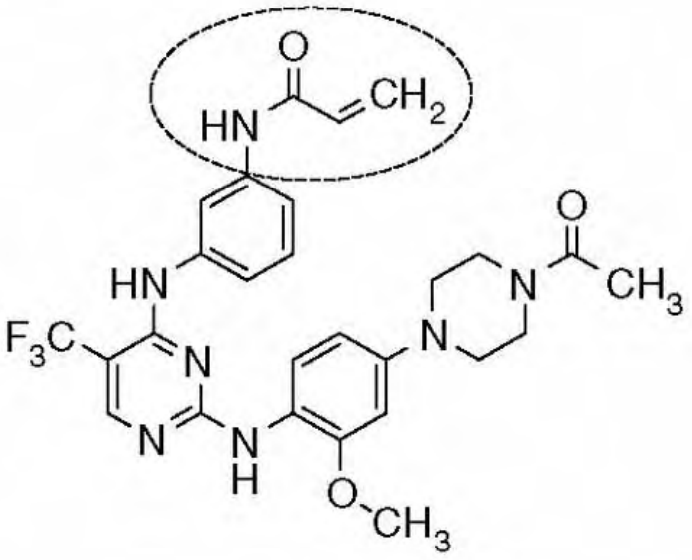
Kinase	$K_{m[ATP]}$, μM	k_{cat}, s^{-1}	$k_{cat}/K_{m[ATP]}$, $\mu M^{-1}.s^{-1}$
WT	5.2 ± 0.2	0.026	5.00E-3
T790M	5.9 ± 0.1	0.137	2.32E-2
L858R	148 ± 4	1.484	1.00E-2
L858R/ T790M	8.4 ± 0.3	0.456	5.43E-2

PNAS, 2007, 2070-75

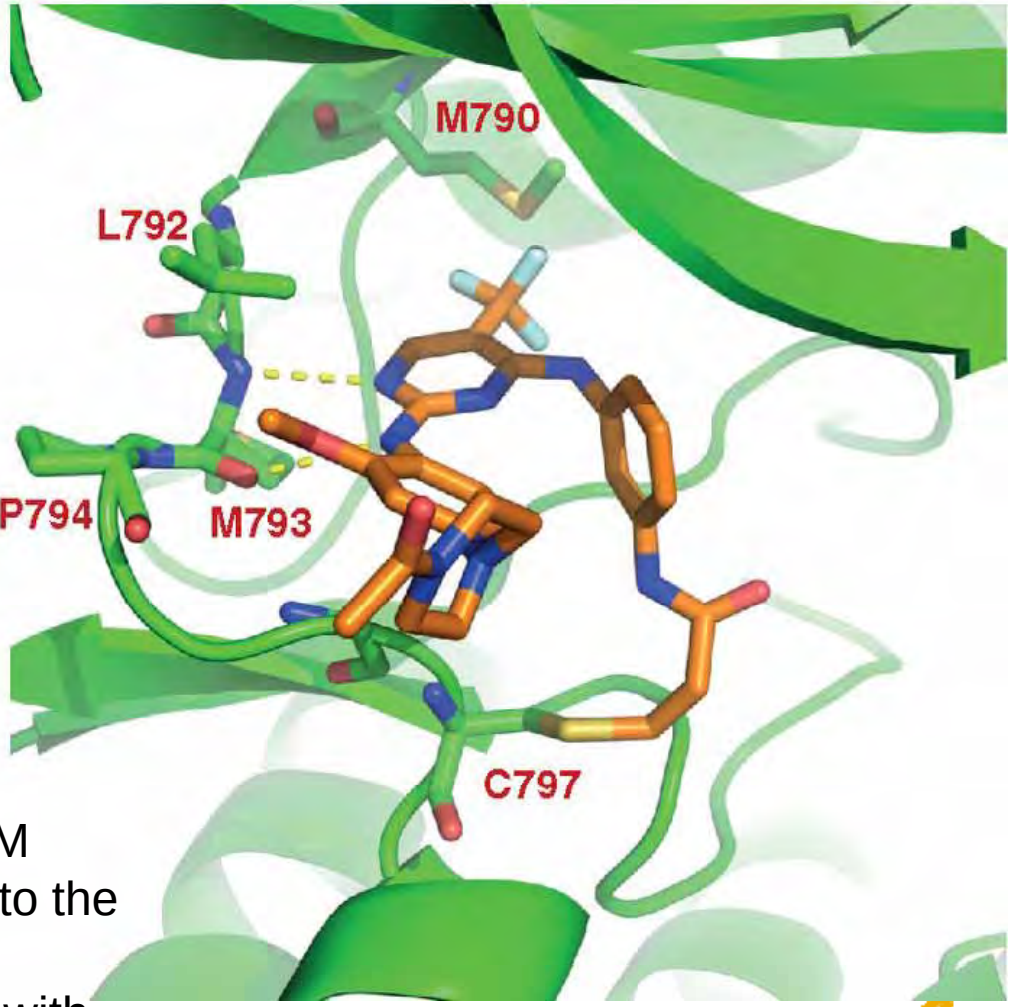


Clin Cancer Res 2011;17:1616-1622

Mutant kinases
- Irreversible inhibitors bind T790M EGFR



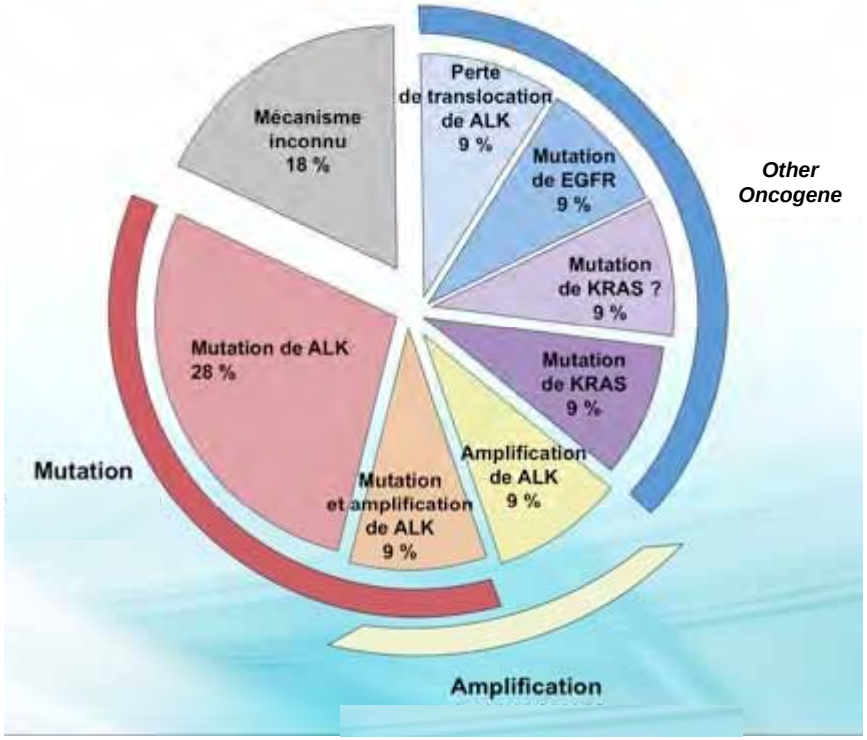
CO-1686



- Irreversible inhibitors overcome the increased Km for ATP shown by T790M
- The Cysteine at residue 797 traps onto the Michael acceptor in the inhibitor
- The inhibitor avoids steric interaction with the bulkier methionine at residue 790

Mutant kinases
EML4-ALK – post Crizotinib

- Median duration of treatment on Crizotinib is ~8 months
- Patient numbers are small but resistance mutations account for lower % of resistance
- No dominant clones
- Many clones seem to be less indolent than the original EML4 fusion



- Vey different situation to both Imatinib and Gefitinib resistance
- But likely to be very drug dependent

- Resistance to second generation compound (LDK378, PF-06463922) will differ

Future Directions
- Predictions for the 2020 talk...

- Rational combinations of kinase inhibitors – Braf / MEK will not be unique
- More effective combinations with non-chemotherapy backbone treatments
- More sophisticated scheduling to maximise pathway inhibition

- Other protein kinases will have approved inhibitors, e.g.
  - CDK4/6, CDK9, PLK1, Aurora A/B,
  - Wee1, Chk1/2, ATR,
  - IRAK4, AKT
- Lipid kinase inhibitors will be approved (e.g. PI3Kα, PI3Kδ...)
- Increasing use of non-ATP competitive inhibition strategies

- Patients will stay on therapy longer due to improved efficacy in resistant clones
- Patient selection will use Next Generation Sequencing (NGS) and will be provide longitudinal data
- Disease monitoring will routinely use blood borne markers (e.g. cfDNA)