

Mechanisms of drug resistance and how to overcome first generation EGFR TKI failure

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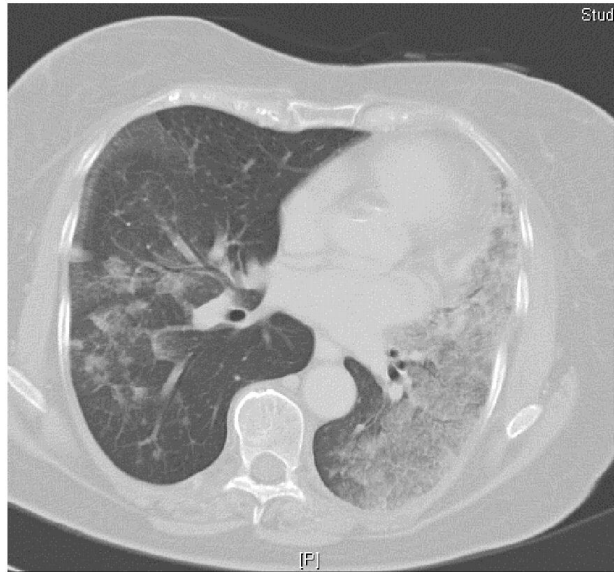
Dana Farber Cancer Institute

EGFR TKI Therapy in 2010

- Efficacy (RR and PFS) greatest in EGFR mutant patients
- Single agent activity in EGFR mutants^{1,2}
 - 1st line response rate: 60%-80%
 - 1st line progression free survival 10 - 14 months
- Gefitinib superior to 1st line chemotherapy¹
 - Higher RR and longer PFS
 - Better toxicity profile

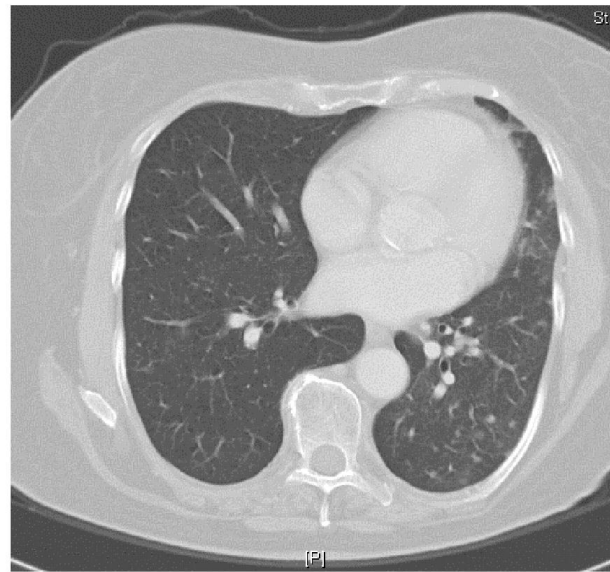
Emergence of acquired resistance to EGFR TKIs

Baseline



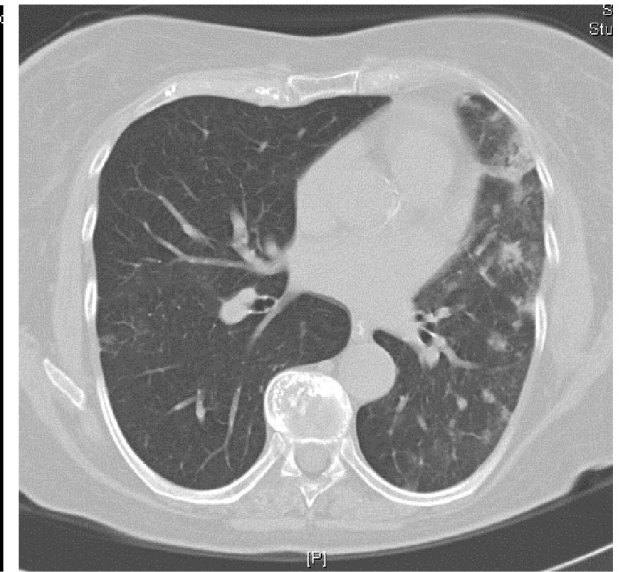
January 2002

Gefitinib Sensitive



October 2004

Gefitinib Resistant



July 2005

How to Improve treatment with EGFR Targeted Therapies ?

- Alternative initial therapies
 - Improve the efficacy of single agent EGFR TKI treatment
- Identify mechanisms of resistance and develop therapeutic strategies
 - Use at the time of drug resistance
 - Use before the development of resistance

How to Improve treatment with EGFR Targeted Therapies ?

- Alternative initial therapies
 - Improve the efficacy of single agent EGFR TKI treatment
 - Add chemotherapy to EGFR TKI -
 - CALGB 30406
 - Use an alternative EGFR inhibitor
 - BIBW 2992

CALGB 30406 Randomized Phase II Study: Trial Design

Chemotherapy-naive patients with stage IIIB/IV adenocarcinoma or BAC who are never or "light" former smokers*
ECOG PS 0-1

Daily oral erlotinib

Daily oral erlotinib +
6 cycles carboplatin/paclitaxel

Daily oral erlotinib

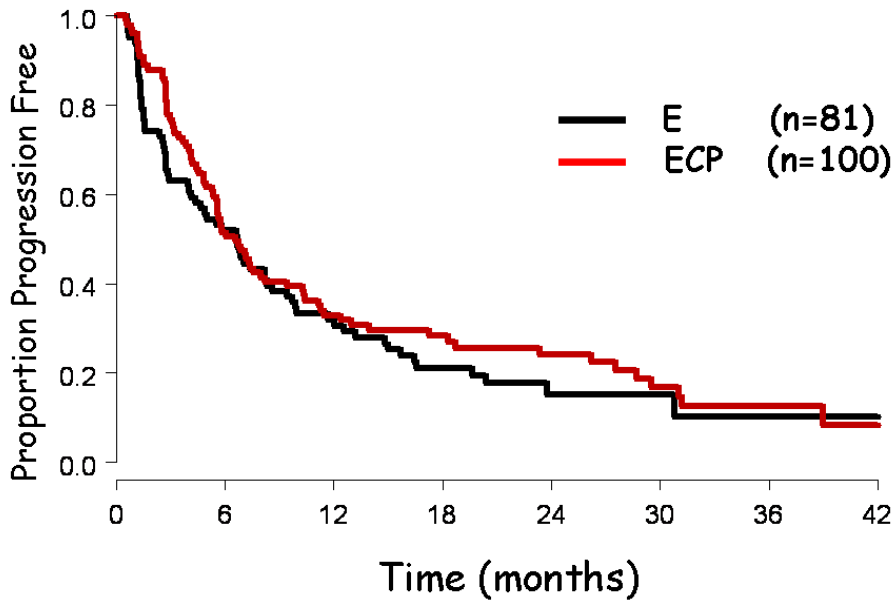
Daily oral erlotinib

Response evaluation every 2 cycles (6 weeks). Therapy could continue until disease progression or toxicity

* never smoker: ≤ 100 cigarettes/lifetime; "light" former smoker: quit ≥ 1 year ago and ≤ 10 pack years

Progression Free and Overall Survivals

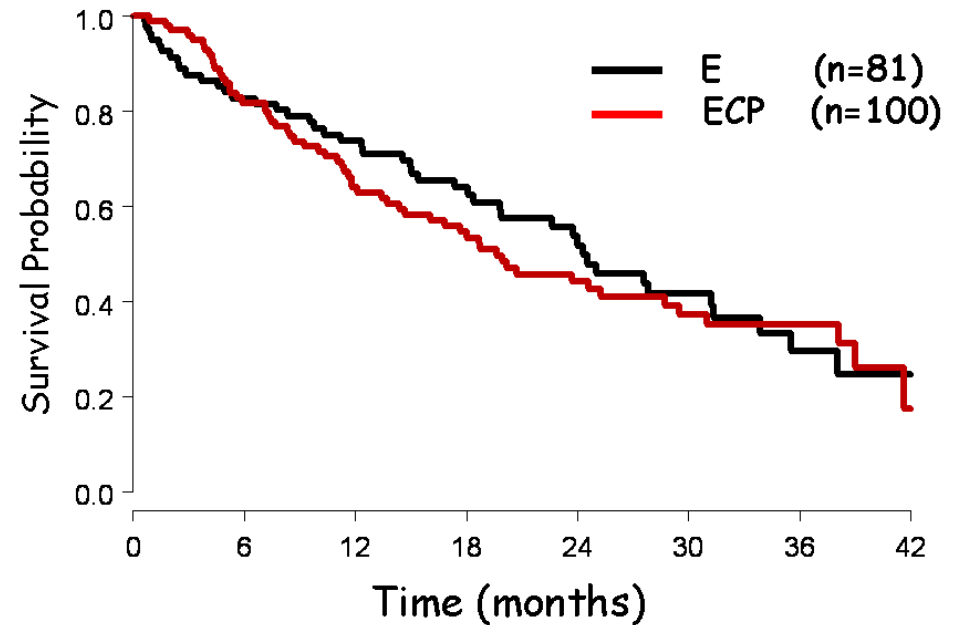
Progression Free Survival



Erlotinib : 6.7 (4.0-8.3)

Erlotinib/CP: 6.6 (5.4-8.2)

Overall Survival



Erlotinib : 24.3 (18.4 -31.3)

Erlotinib/CP: 19.6 (14.4 - 28.7)

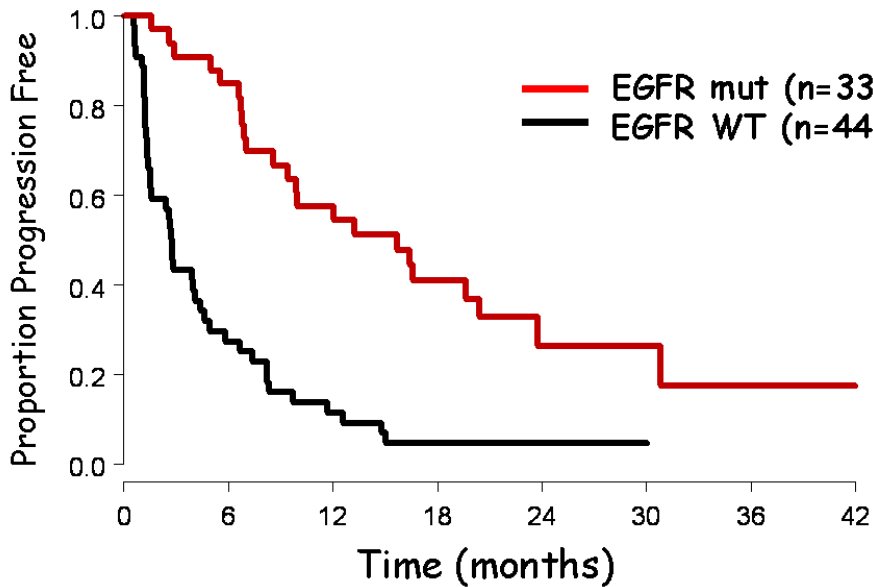
Response Rate

Erlotinib: 35%

Erlotinib/CP: 48%

Erlotinib

Erlotinib/CP

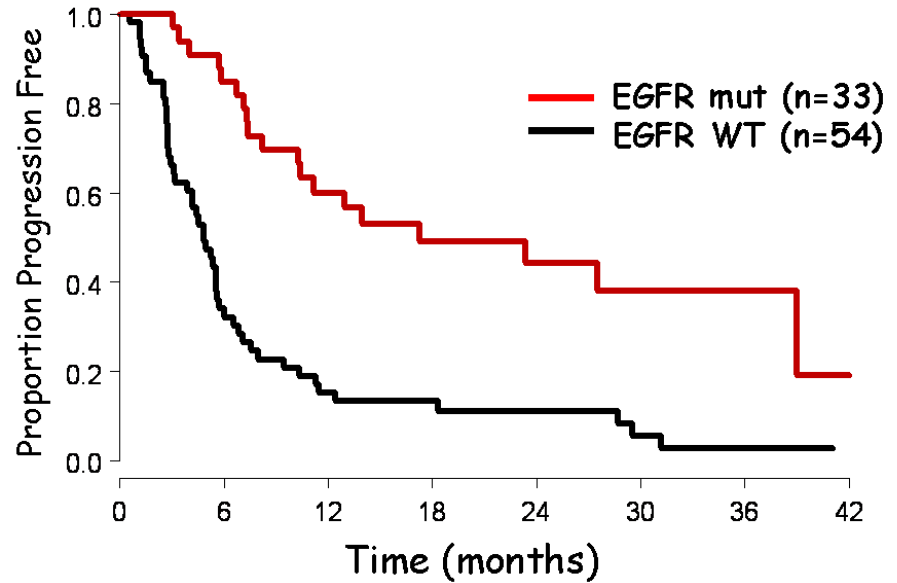


EGFR mutant : 15.7 (8.6 - 20.4)

EGFR WT: 2.7 (1.4 - 4.4)

$P < 0.0001$

Response Rate: 67%



EGFR mutant : 17.2 (10.3 - NA)

EGFR WT: 4.8 (3.1 - 5.6)

$P < 0.0001$

Response Rate: 73%

BIBW 2992

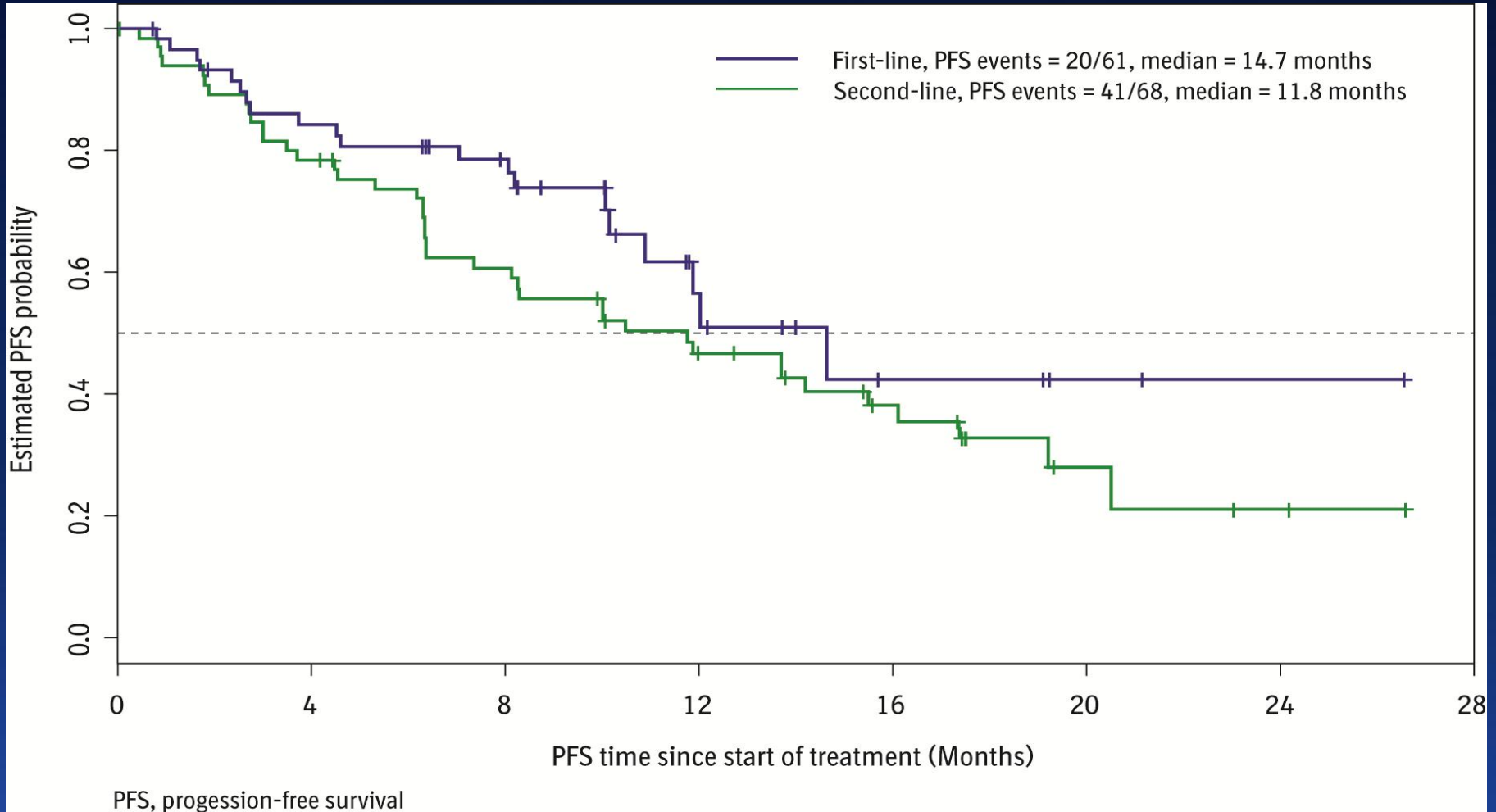
- Novel representative of a new generation of EGFR/HER1 and HER2 TKIs
- Potent, orally bioavailable, irreversible inhibitor of EGFR (IC₅₀: 0.5 nM) and HER2 (IC₅₀: 14 nM) tyrosine kinases¹

Mutation:	WT	Activated	Resistance	Target	Binding mode
	wild type	L858R	L858R+T790M		
	H1666	H3255	NCI1975		
BIBW 2992	60	0.7	99	EGFR/HER2	Irreversible
Gefitinib	157	5	>4000	EGFR	Reversible
Erlotinib	110	40	>4000	EGFR	Reversible
Lapatinib	534	63	>4000	EGFR/HER2	Reversible

EC₅₀ values for the inhibitory activities of different compounds on the proliferation of NSCLC cells with EGFR mutations

1. Li et al. Oncogene 2008;27:4702–4711
EGFR, epidermal growth factor inhibitor; TKIs, tyrosine kinase inhibitors

PFS in EGFR mutant NSCLC patients broken down by prior therapy



Outcome of Chemotherapy naïve EGFR mutant NSCLC patients

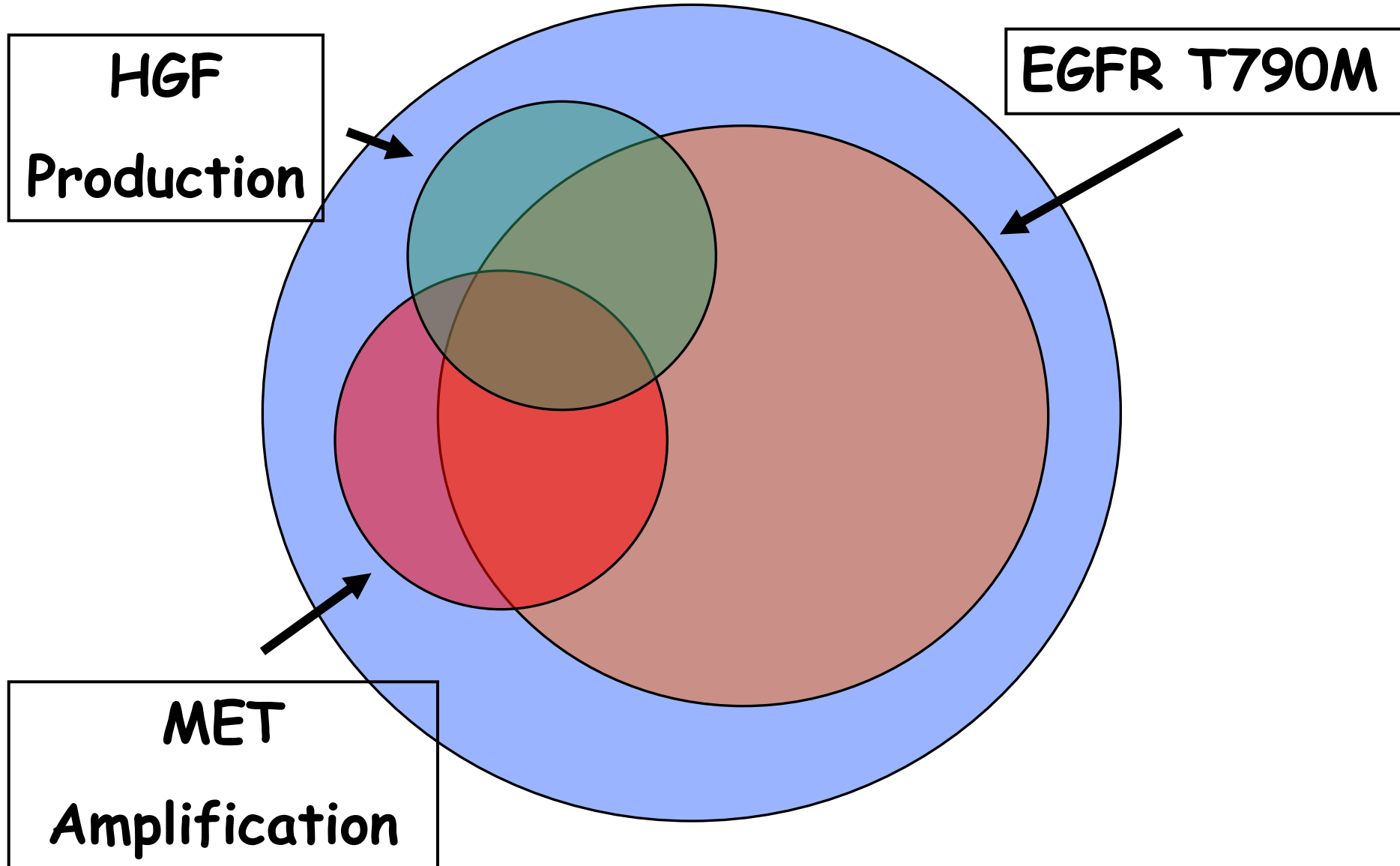
Study	Drug	Pts	RR	PFS
Rossell ¹	Erlotinib	197	71%	14.0 mos
CALGB ²	Erlotinib	33	67%	15.7 mos
CALGB ²	CP/Erlotinib	33	73%	17.2 mos
Yang ³	BIBW2992	61	64%	14.7 mos

¹Rossell et al. NEJM 2009; ²Jänne et al. ASCO 2010; ³Yang et al. ASCO 2010

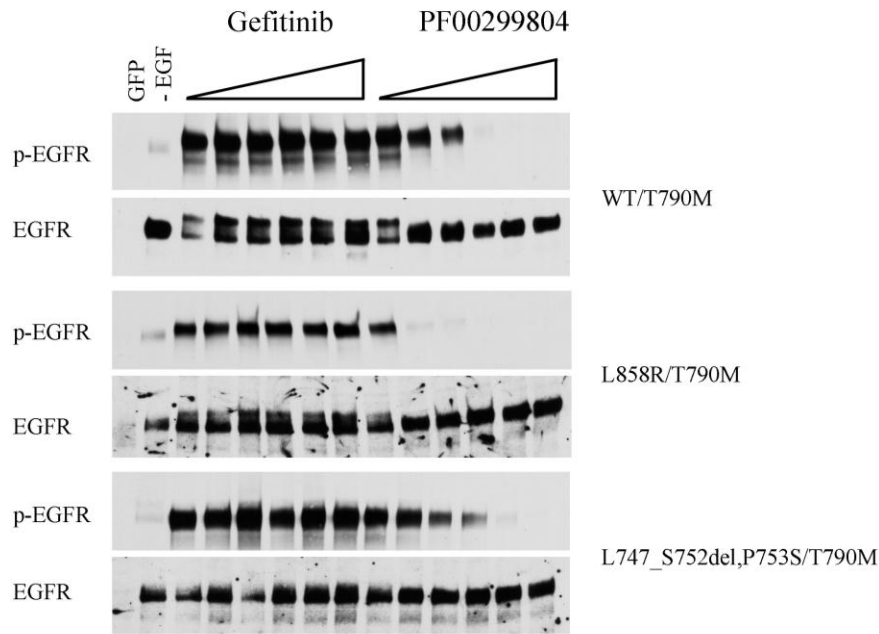
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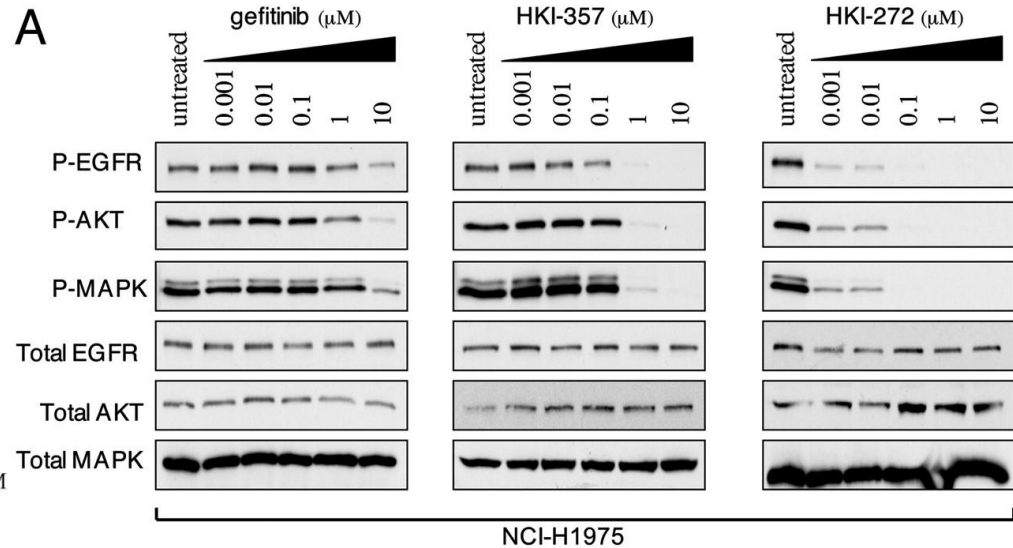
Resistance Mechanisms in EGFR mutant NSCLC



EGFR T790M and Irreversible EGFR TKIs

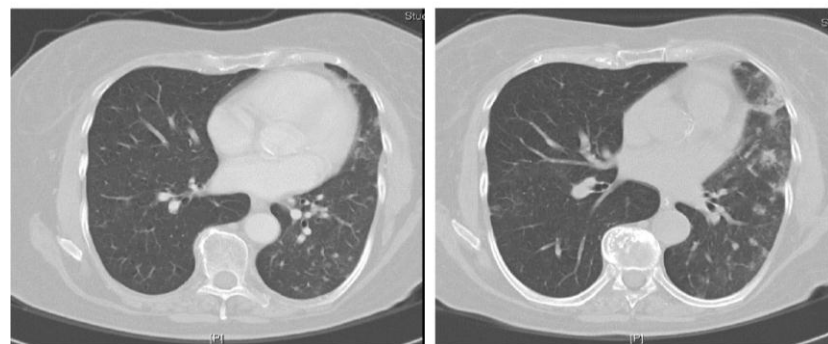
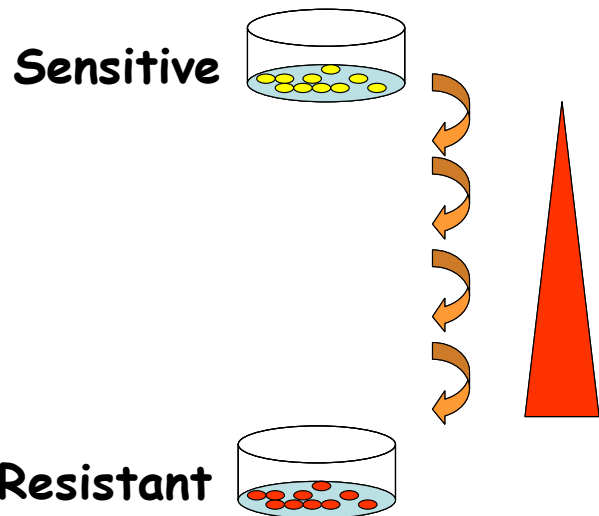


PF00299804



HKI-272

Irreversible EGFR Inhibitors: Lab to Clinic



Drug Resistant Patients

HKI-272, BIBW2992 & PF002994804
in clinical development

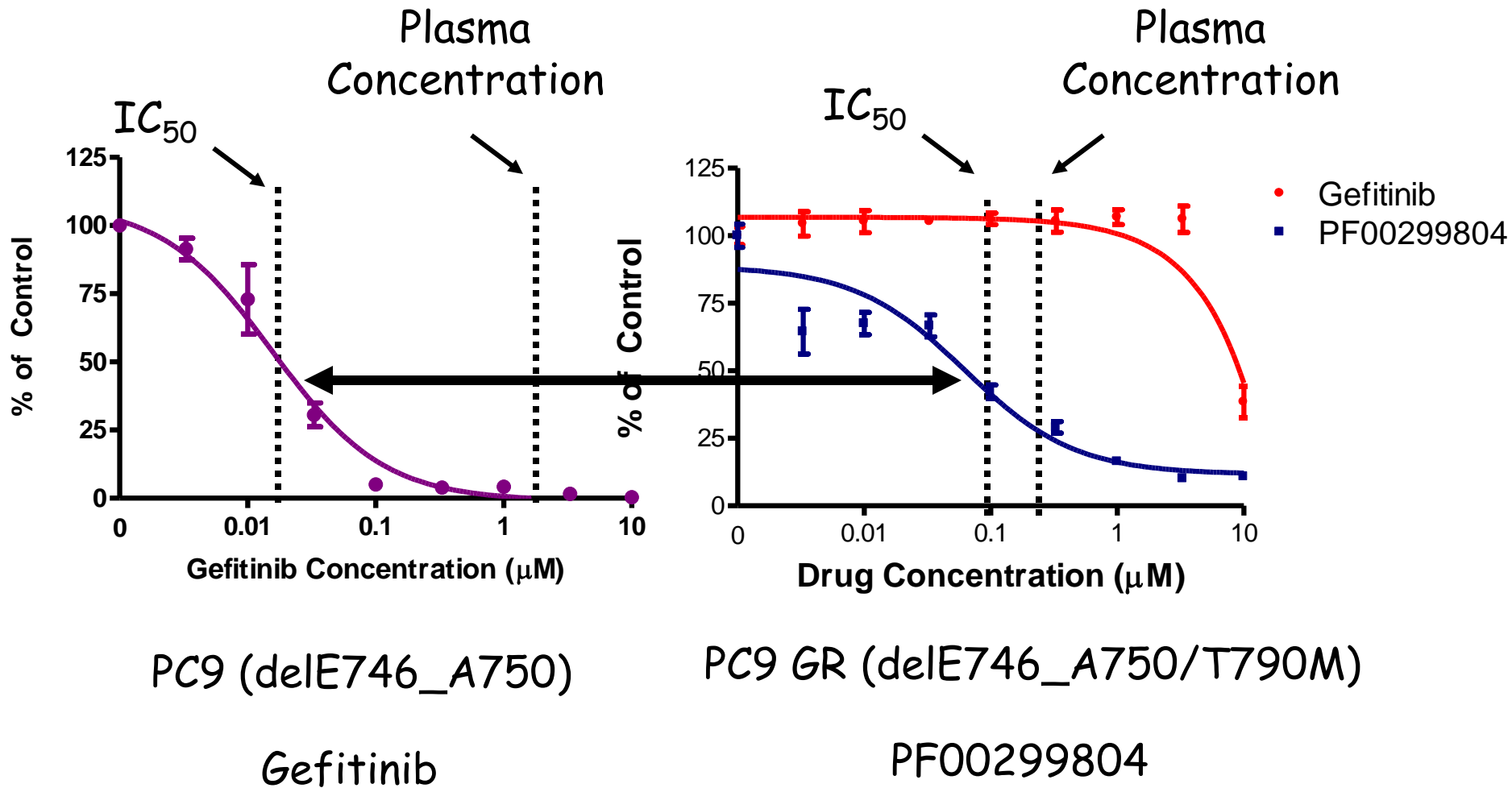
Preclinical Efficacy
against EGFR T790M
containing models

Clinical activity has been very limited
Tumor response rates < 5%

Why ?

Not a single patient with a documented
EGFR T790M has had a tumor response

Comparison of IC_{50} and achievable plasma concentrations



Dose escalation is limited by development of toxicity (rash and diarrhea)

Identification of EGFR kinase inhibitors

Wild Type EGFR enzyme



Screen Drug Libraries

Inhibitors of Wild Type
EGFR enzyme

Quinazoline based inhibitors

Cellular Screen with EGFR T790M

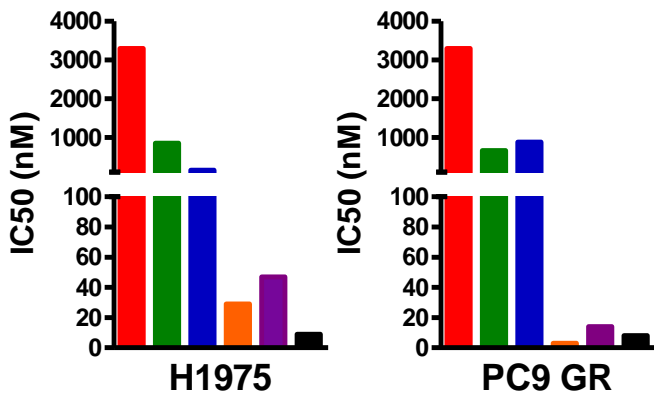
PC9 GR (Exon 19 del/T790M)



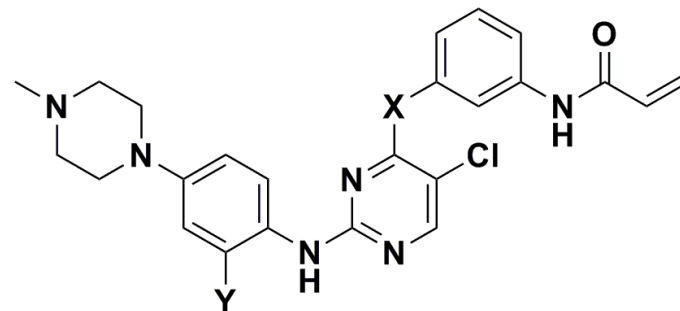
Screen Focused Library of
Irreversible Inhibitors

Can we identify novel
EGFR kinase inhibitors ?

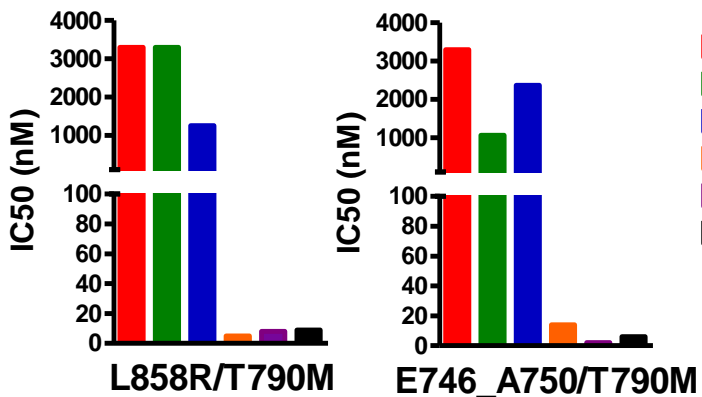
All current clinical EGFR inhibitors were identified before EGFR mutations or the EGFR T790M resistance mutation



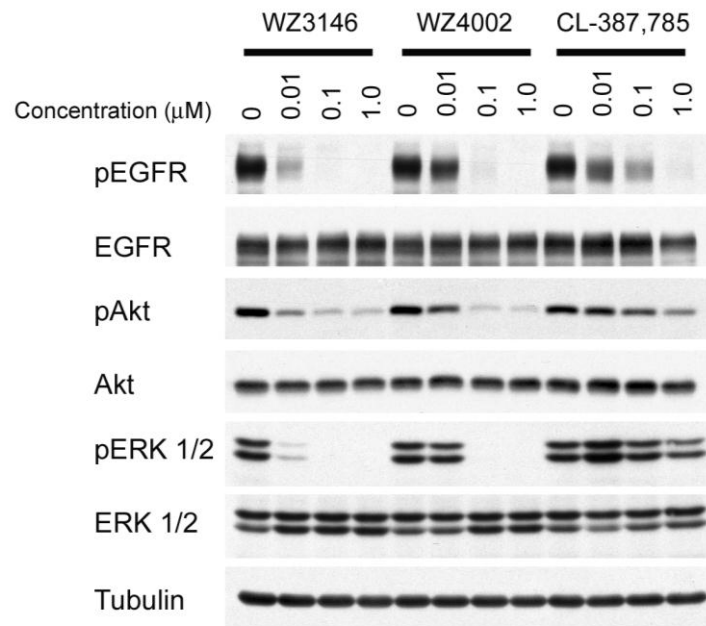
NSCLC cell lines



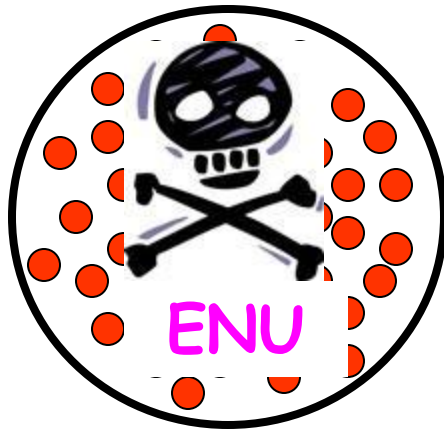
WZ3146 X=O, Y=H
 WZ4002 X=O, Y=OMe
 WZ8040 X=S, Y=H



Ba/F3 cells



Can WZ4002 prevent the emergence of EGFR T790M ?



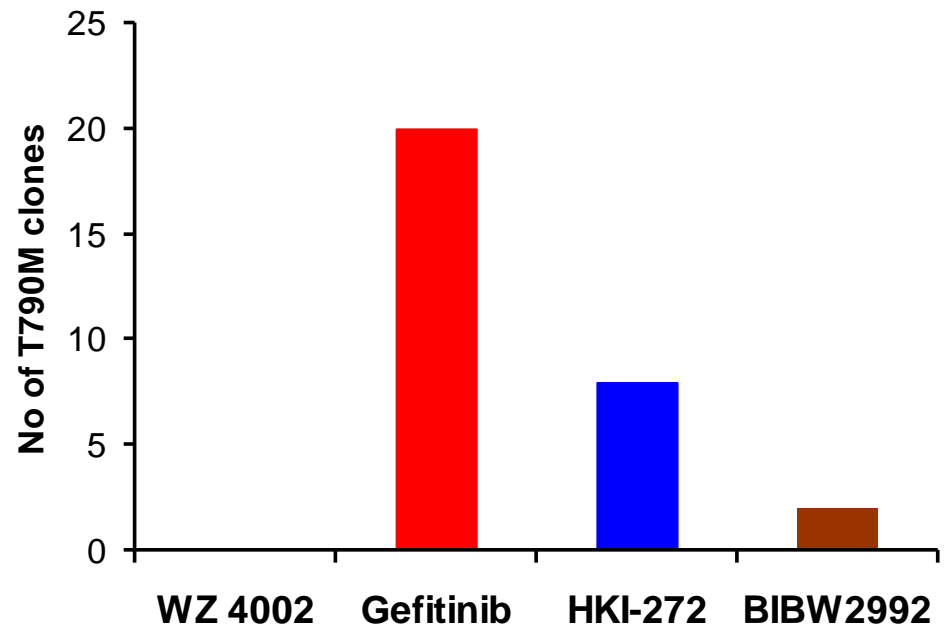
Ba/F3 cells

L858R or
DelE746_A750

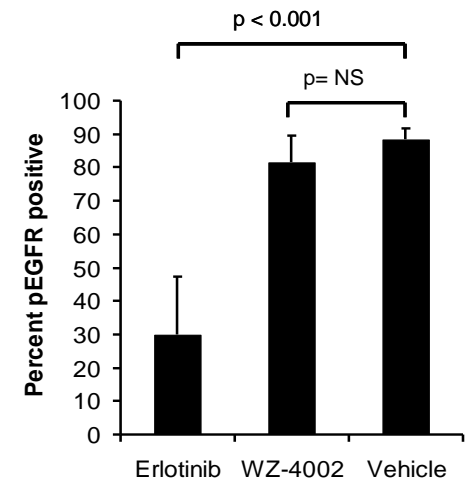
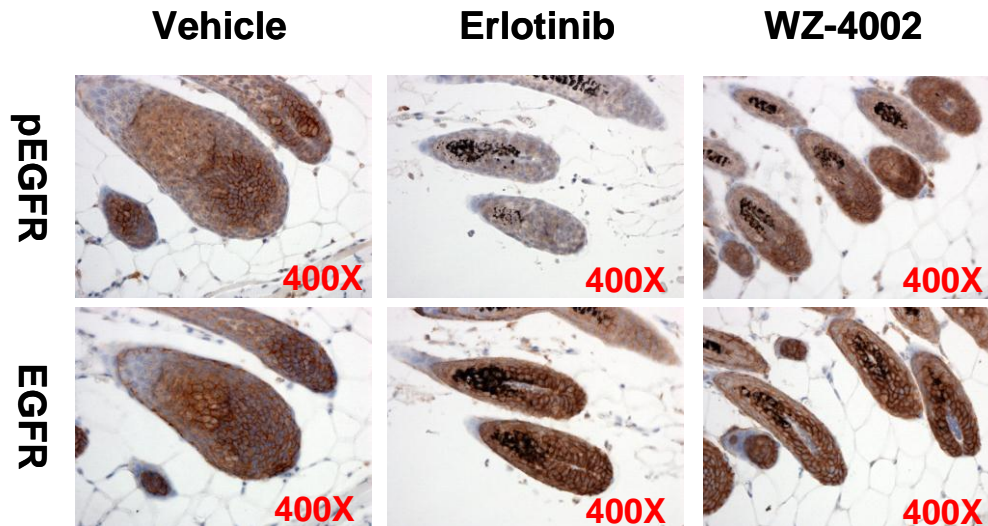
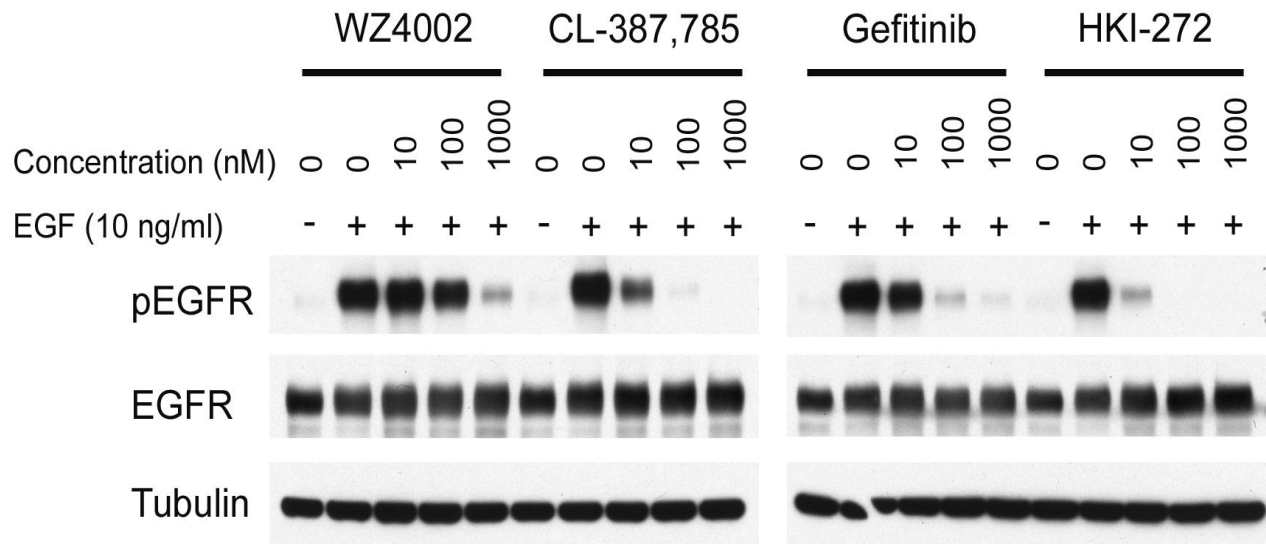
Select
resistant
cells

↓

1 μ M Gefitinib
200 nM HKI-272
200 nM BIBW2992
100 nM WZ4002
1 μ M WZ4002



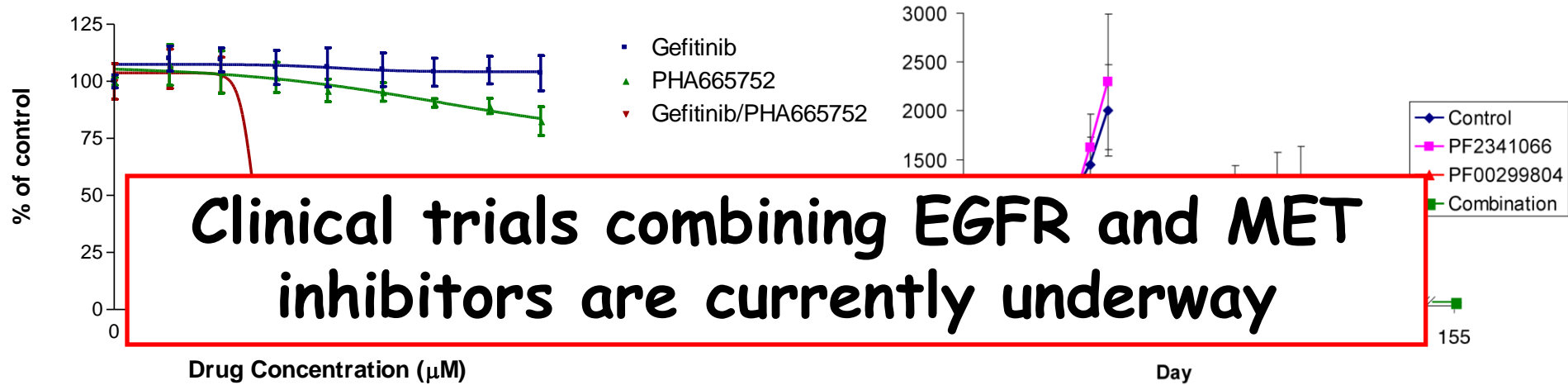
WZ Irreversible EGFR inhibitors are less potent against WT EGFR



Mutant Selective EGFR Kinase Inhibitors

- Overcome some of the limitations of current clinical agents
 - More potent against EGFR T790M
 - Less potent against WT EGFR; ? less toxic clinically -> higher tumor drug concentrations
- May be suitable before or after gefitinib resistance
- Need to undergo clinical development

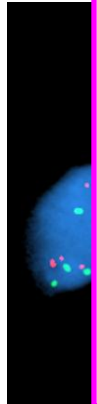
Inhibition of both EGFR and MET is necessary to overcome resistance in MET amplified NSCLC



Clinical trials combining EGFR and MET inhibitors are currently underway

However all studies are combining MET inhibitors with erlotinib

Not inhibiting the most common resistance mechanism: EGFR T790M



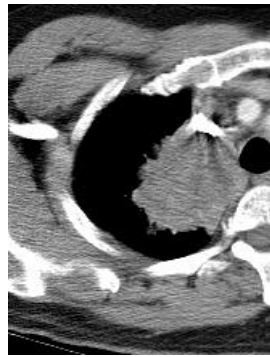
Pre-Gefitinib

Post-Gefitinib

Engelman et al. Science 2007

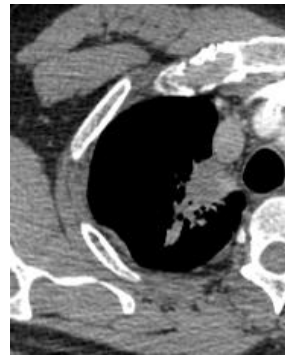
Turke, Zejnullahu et al., Cancer Cell 2010

Example of response in MET amplified erlotinib resistant NSCLC



1/30/08

Rx Tarceva



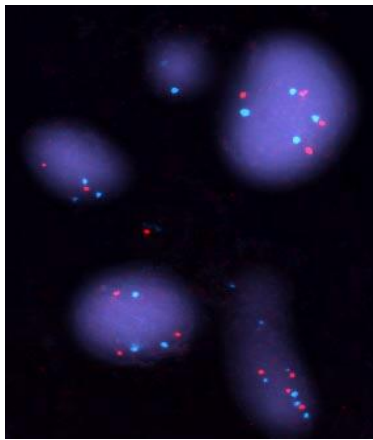
3/31/08



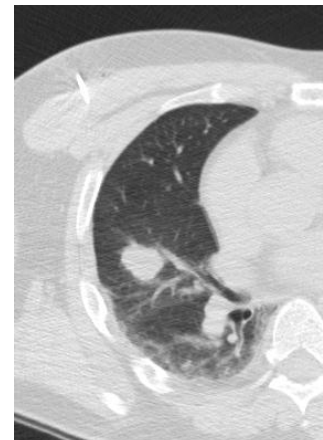
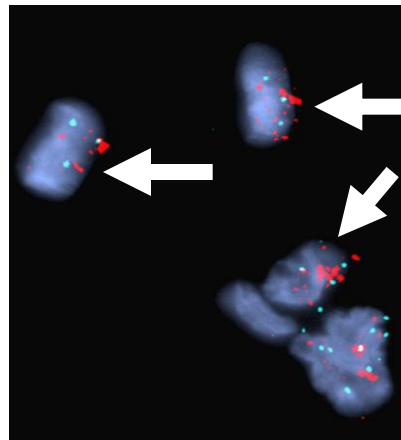
Developed
Resistance
to Tarceva

10/08

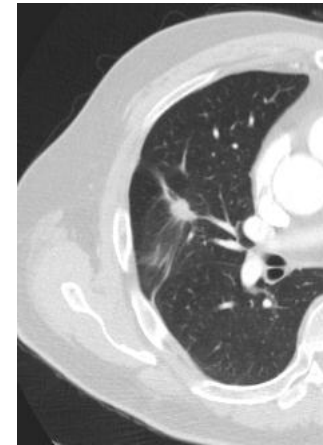
Pre-Rx



Resistant



Rx with
XL184 &
Erlotinib
inhibitor



Treatment of EGFR TKI resistant cancers

- Need to inhibit both EGFR T790M and MET signaling (amplification/HGF)

Treatment of EGFR TKI resistant cancers

- Need to inhibit both EGFR T790M and MET signaling (amplification/HGF)
- Alternative strategy to inhibit critical components of EGFR signaling
 - ERBB3
 - Combination of PI3K/MEK inhibitors
 - HSP90 inhibitors

Mechanisms of drug resistance and how to overcome first generation EGFR TKI failure

- Single agent EGFR TKI remains standard of care for EGFR mutant NSCLC
- Development of drug resistance is the critical next step to understand & treat
- Many therapeutic strategies currently underway to prevent/treat drug resistant cancers