



Tykerb:
A Dual EGFR/ErbB2 Inhibitor

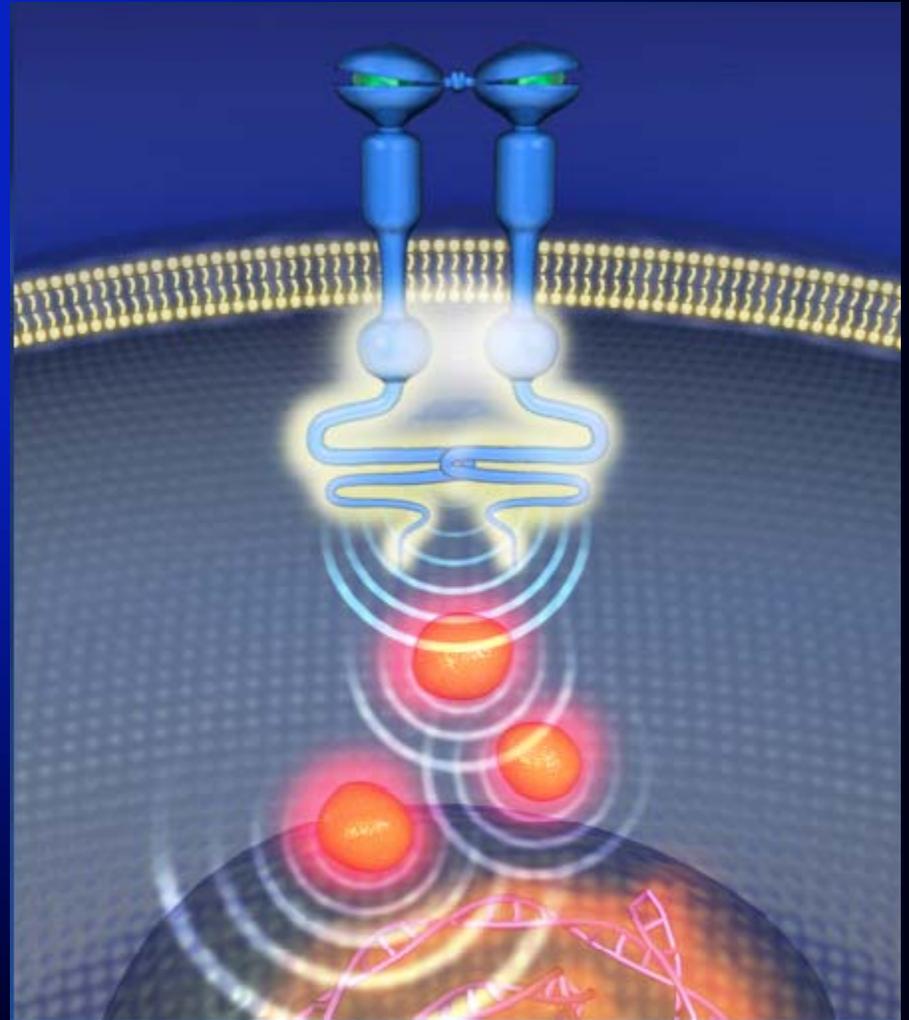
Lisa Shewchuk
GlaxoSmithKline

Outline

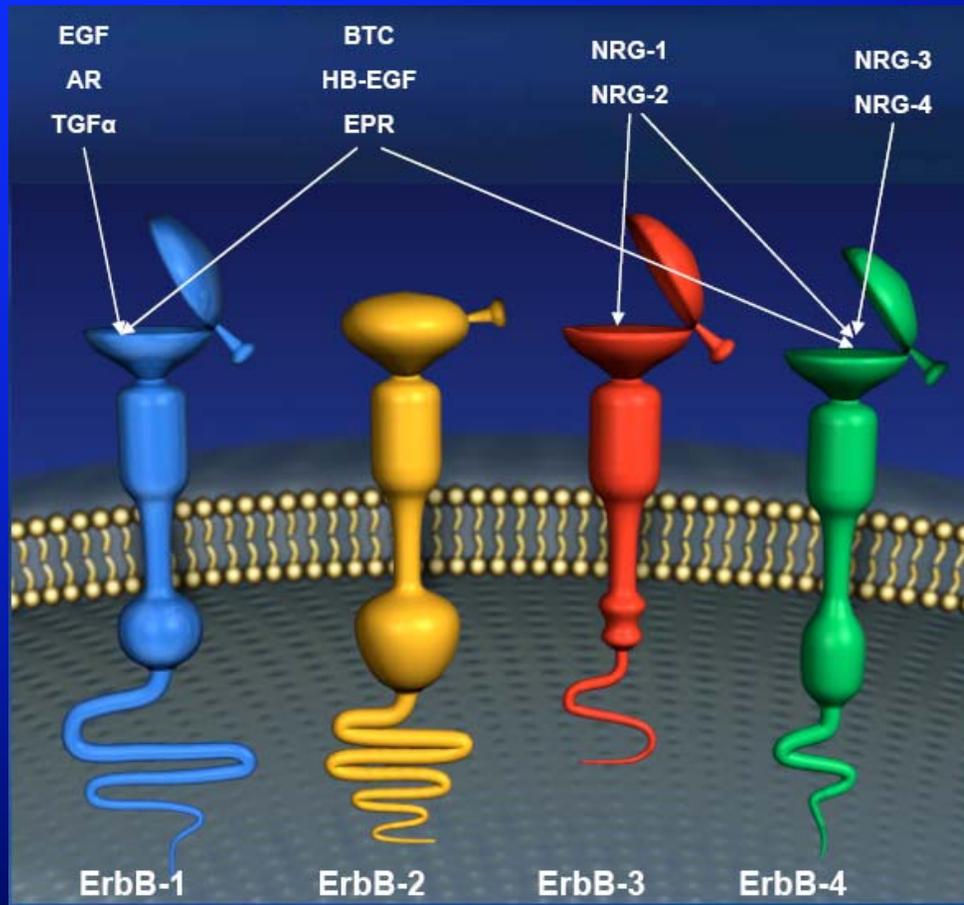
- Background – ErbB RTK Family
- Tykerb
 - Properties
 - Comparison with competitor compounds
- EGFR Structural Studies
- Clinical Highlights

Faulty Signaling Causes Uncontrolled Growth in Cancer

- Most oncogenes encode components of cell signaling pathways
- Abnormal signaling components in cancer include growth factors and their receptors, signaling molecules and transcription factors
- Aberrant cell signaling causes uncontrolled cell proliferation and survival, the hallmarks of cancer



ErbB Receptor Tyrosine Kinase Family



ErbB1 = Her1, EGFR
ErbB2 = Her2, neu
ErbB3 = Her3
ErbB4 = Her4

Four receptors that can homo and hetero-dimerize
Ten growth factor ligands

Normal Role of ErbB Receptors

- Critical in the development of epithelial organs in the embryo, including the brain, heart, lungs, GI tract and skin
- Involved in the growth and differentiation of epithelial organs in the adult
- Important in postnatal development of the mammary gland

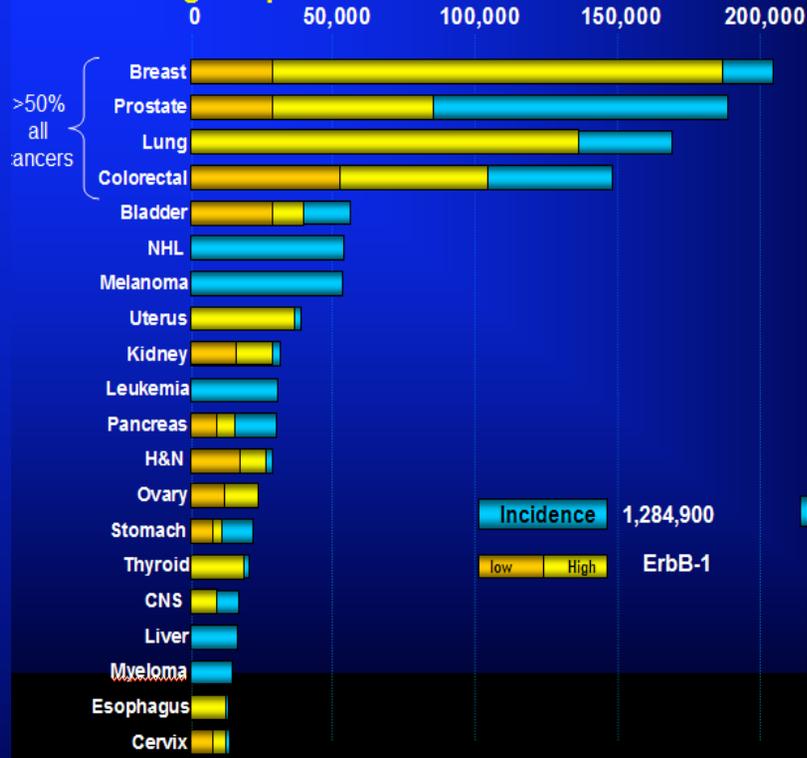


Inactive in quiescent cells
Very active in proliferating cells

Expression in Tumor Cells

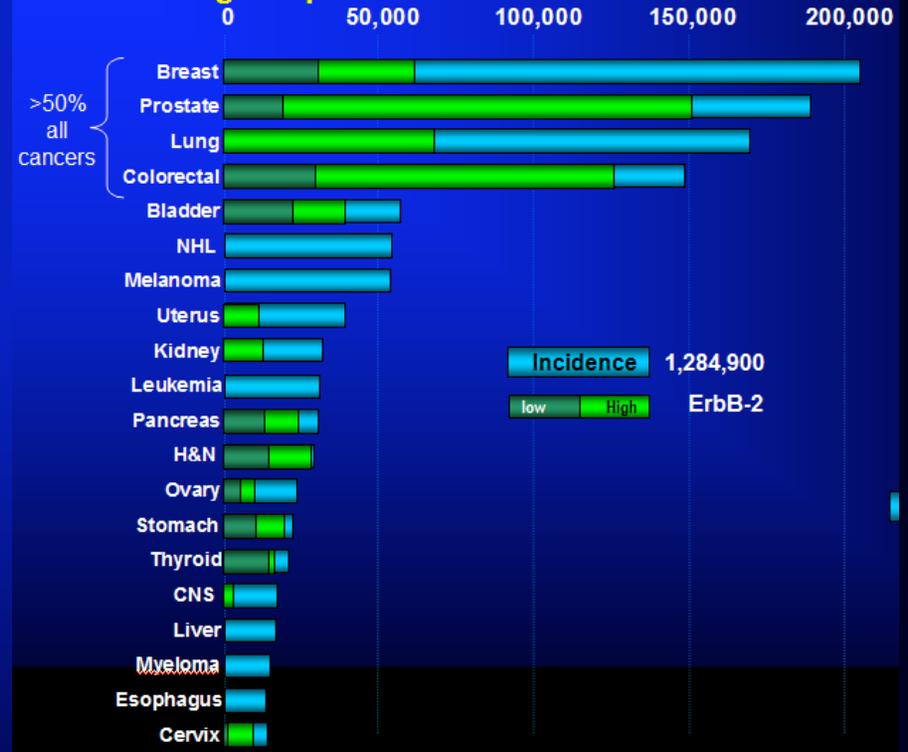
EGFR Expression

Low and High Reports in Literature



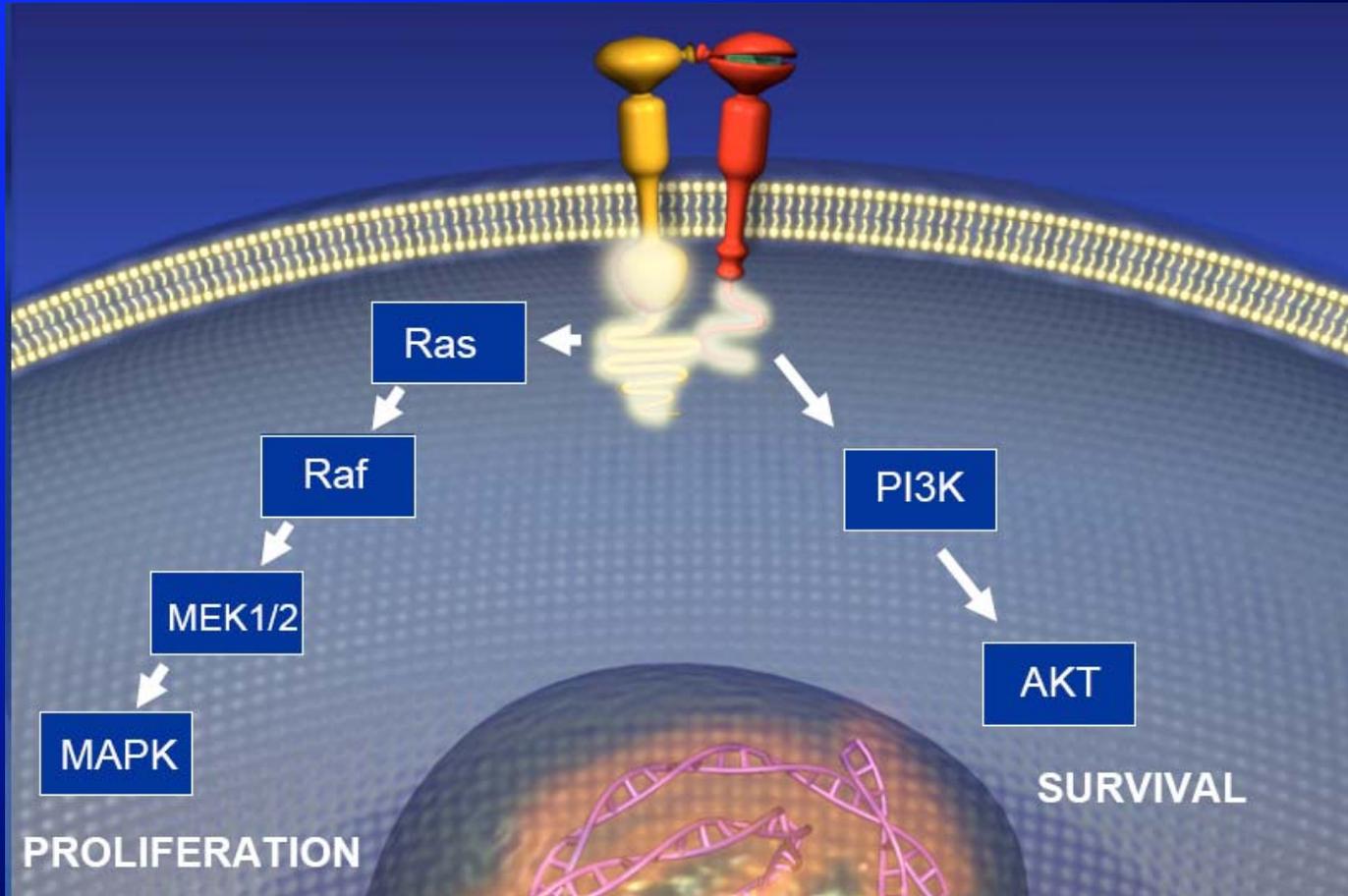
ErbB-2 (Her2) Expression

Low and High Reports in Literature



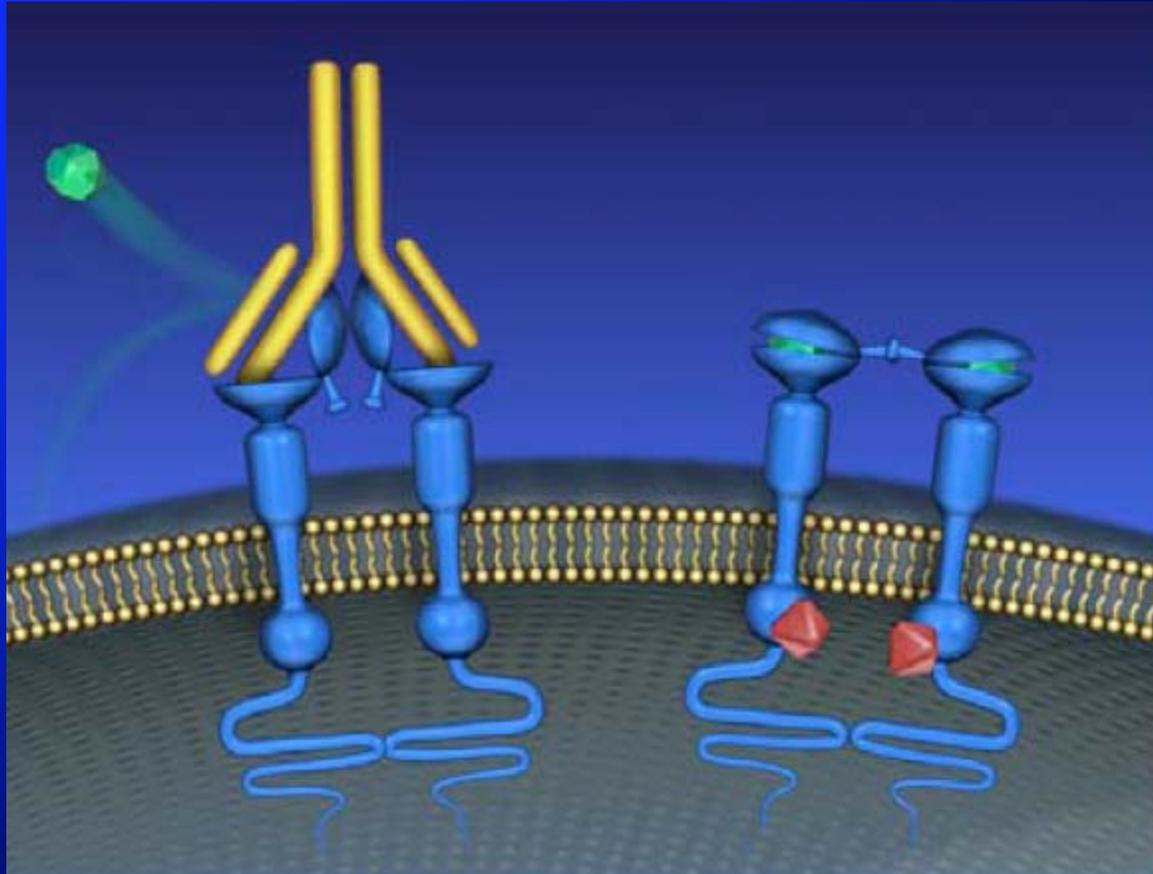
EGFR and ErbB2 are expressed in a large percentage of the 4 major tumor types

Important ErbB Signaling Pathways



- ErbB receptors are overexpressed in many tumor types
- ErbB2 overexpression correlates with poor prognosis in breast cancer
- ErbB family signals through major proliferation and survival pathways

Strategies for ErbB Receptor Inhibition



- 1) Target the extracellular ligand-binding domain – eg. Herceptin
- 2) Target the intracellular kinase domain
- 3) Target multiple family members

Tykerb Properties

- Dual ErbB2 (13nM) and ErbB1 (3nM) inhibitor
- Highly selective for ErbB2 and ErbB1 versus other kinases
- Excellent cell potency <0.2 μ M
- Efficacious in xenograft models
- Inhibits ErbB1 and ErbB2 p-Tyr, p-ERK1/2, p-AKT, cyclin D in tumor cell lines and xenografts

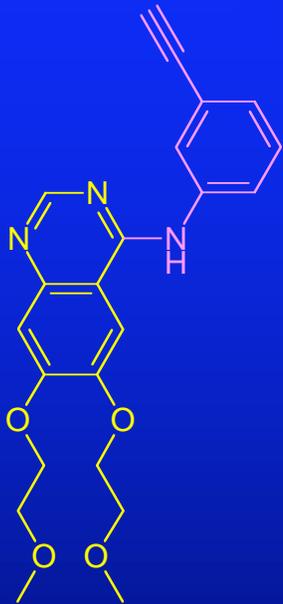


N-{3-Chloro-4-[(3-fluorobenzyl)oxy]phenyl}-6-[5-({[2-(methylsulfonyl)ethyl] amino}methyl)-2-furyl]-4-quinazolinamine

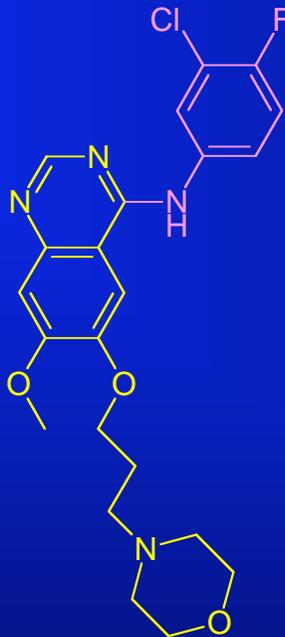
Tykerb was selected for progression to clinical trials based on **22** selection criteria which included:

- Efficacy parameters (cellular and in vivo)
- Biometabolism parameters (time of drug exposure, %F, p450 enzymes)
- Toxicity (cellular, cardiovascular, 7 day rat studies, Ames, etc)
- Chemical issues (cost of goods and scaleability)

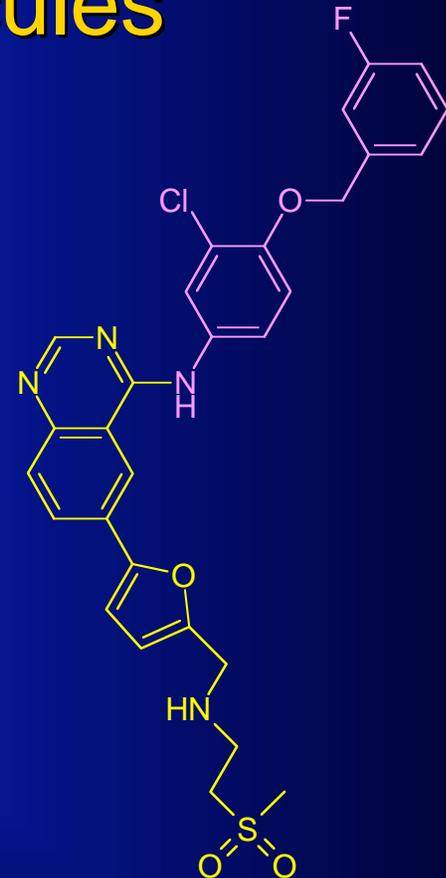
Structure of Tykerb and Competitor Molecules



Erlotinib
Tarceva



Gefitinib
Iressa



GW572016/Lapatinib
Tykerb

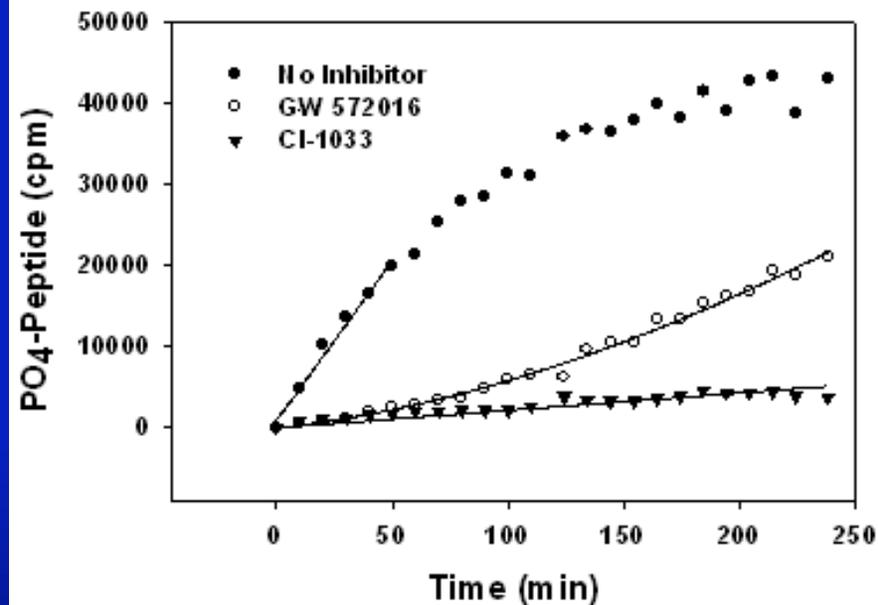
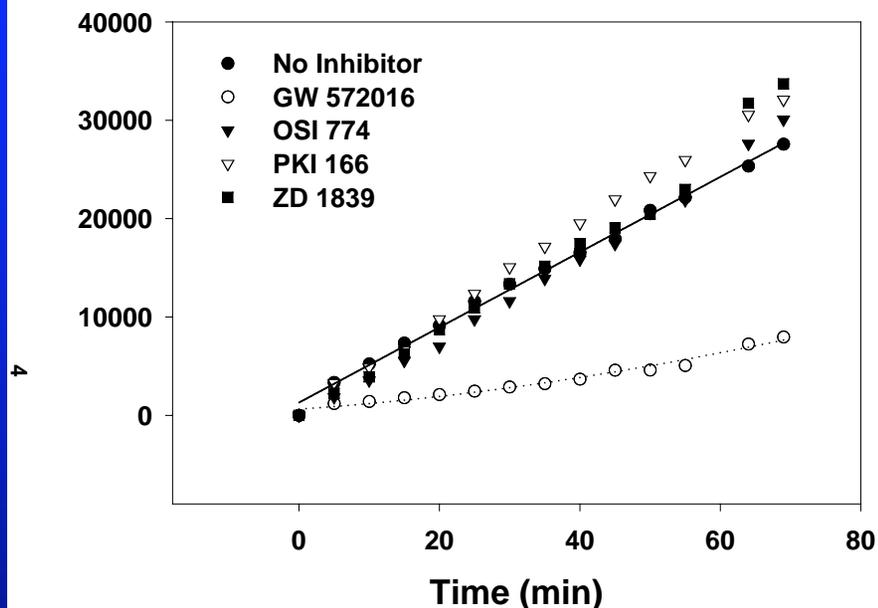
Small head group quinazolines

Large head group quinazoline

In Vitro Potency of Tykerb vs Competitor Molecules

Compound	EGFR K_i^{app} (nM)	ErbB2 K_i^{app} (nM)	ErbB4 K_i^{app} (nM)
Tykerb	3.0 +/- 0.2	13 +/- 1	347 +/- 16
Gefitinib	0.4 +/- 0.1	870 +/- 90	1130 +/- 370
Erlotinib	0.7 +/- 0.1	1000 +/- 100	1530 +/- 270

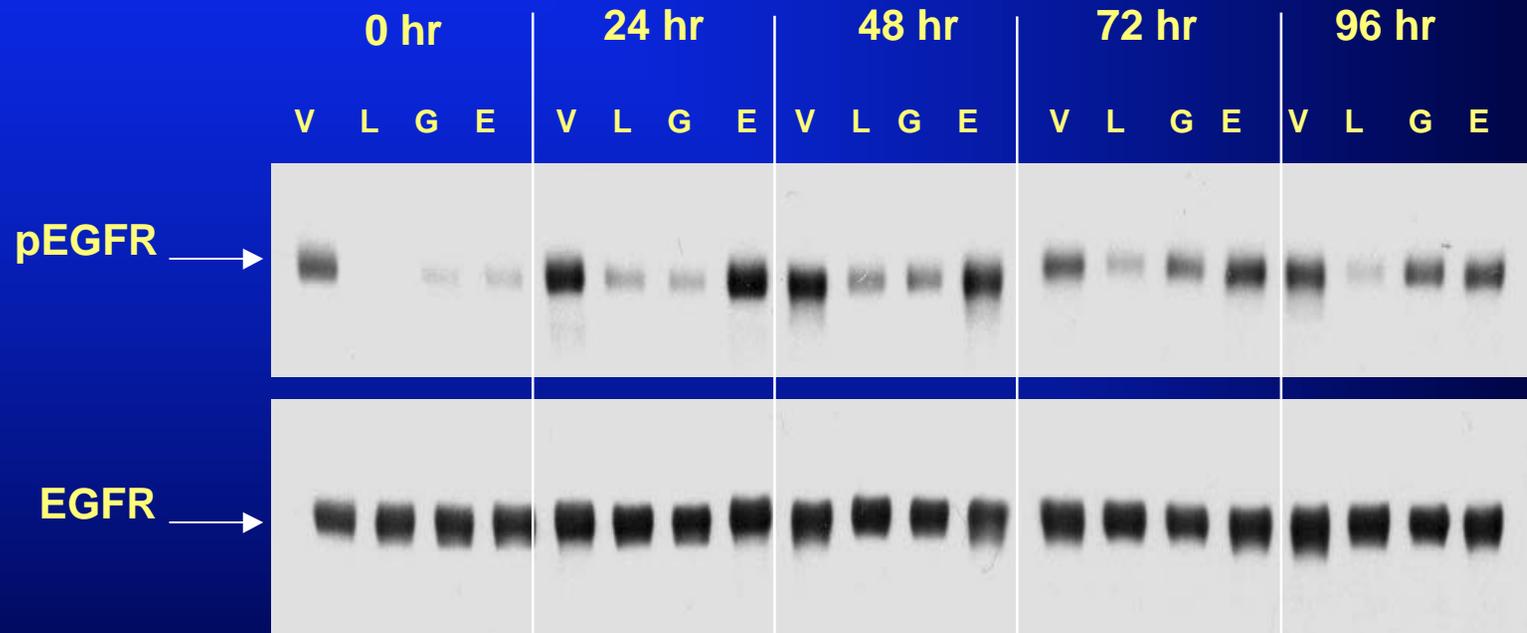
Unusual Kinetic Behavior of Tykerb



Compound	erbB-2 K_i (nM)	EGFR K_i (nM)	dissociation rates	EGFR activity post compound washout
Tykerb	13 +/- 1	3.0 +/- 0.2	$T_{1/2} = 300$ min	15% @ 72h
Tarceva	870 +/- 90	0.4 +/- 0.1	$T_{1/2} < 10$ min	100% @ 24h

In Vivo Effects Correlate with *In Vitro* Half Life

Recovery of EGFR phosphorylation in HN5 cells treated with ErbB inhibitors for 4hr



Key:
V = Treated with DMSO
L = Treated with Lapatinib
G = Treated with Gefitinib
E = Treated with Erlotinib

Wood et al Cancer Res 2004: [64](#), 6652

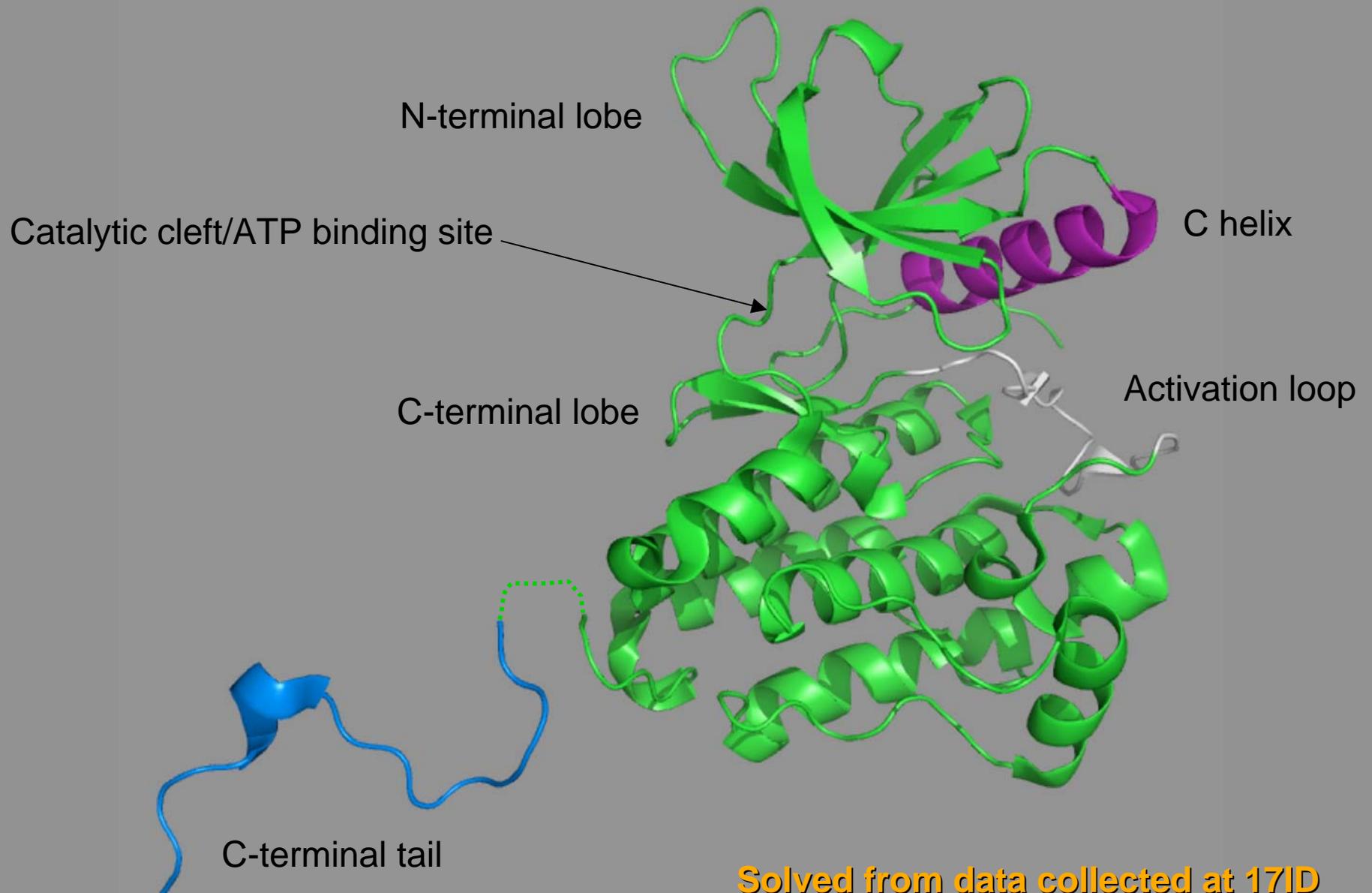
Long half life *in vitro* and *in vivo*
Slow binding kinetics

Is it a property of the compound or what
the compound is doing to its target?



EGFR complexed with Tykerb

Crystal Structure of EGFR

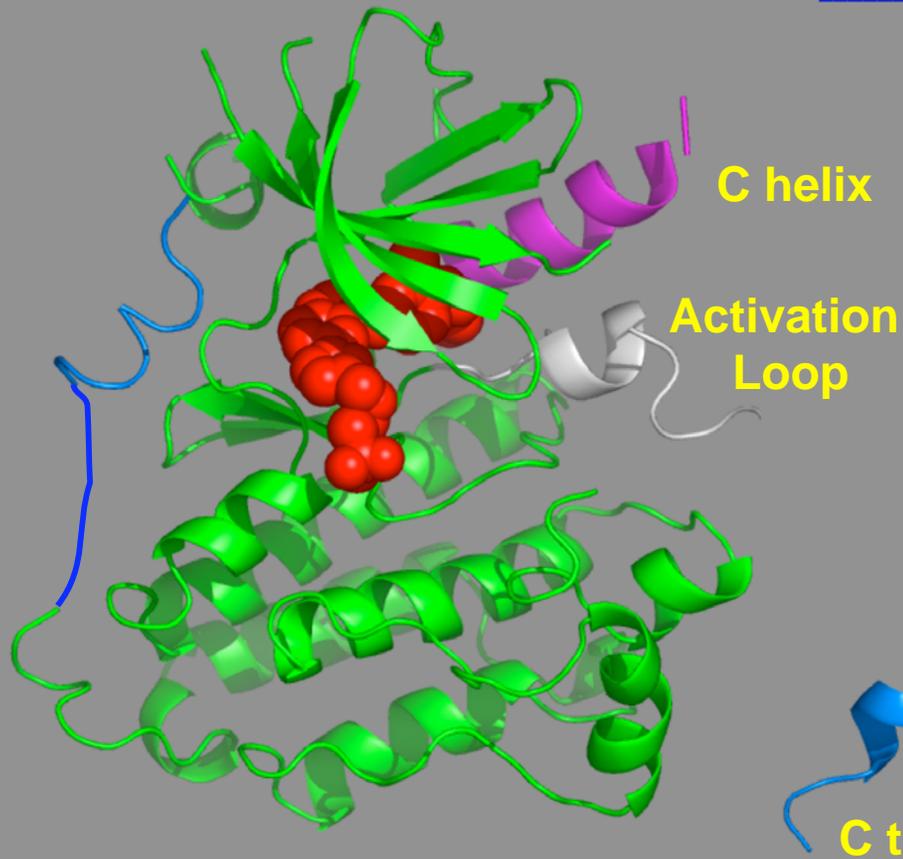


Solved from data collected at 171D

Structure Summary

Tykerb

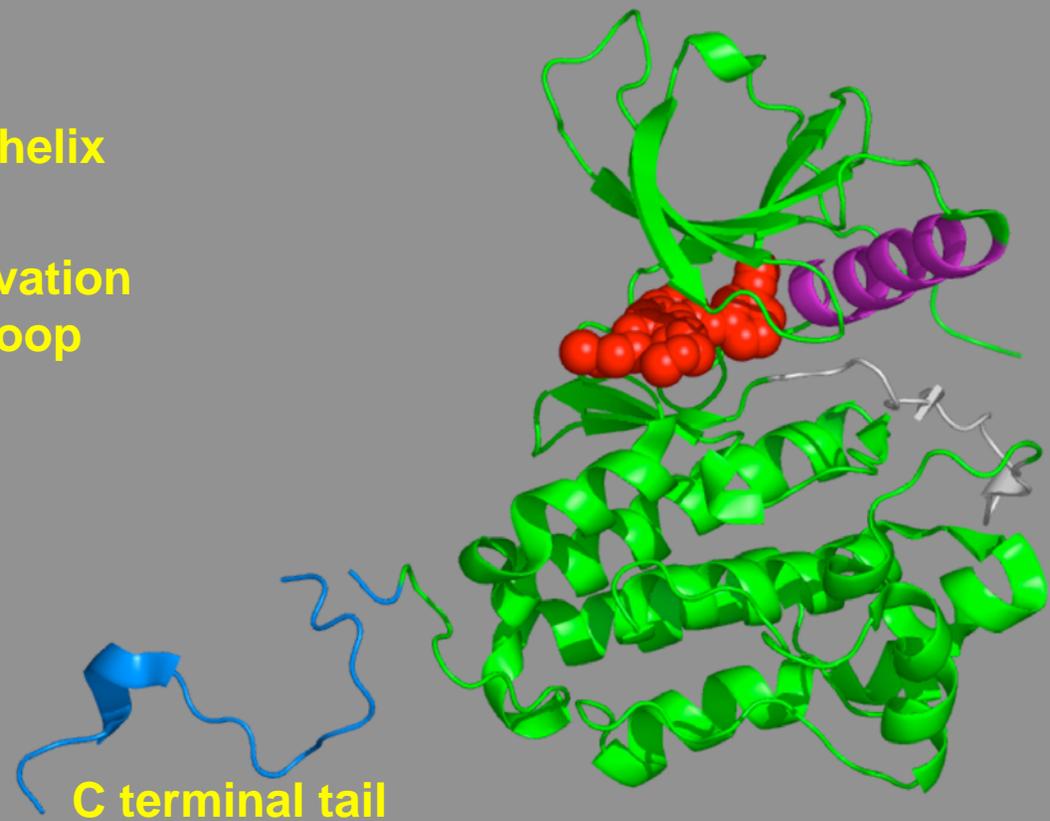
Inactive-like conformation



closed down ATP cleft
activation loop - inactive conformation
incorrect arrangement of catalytic residues
C-terminal tail not accessible

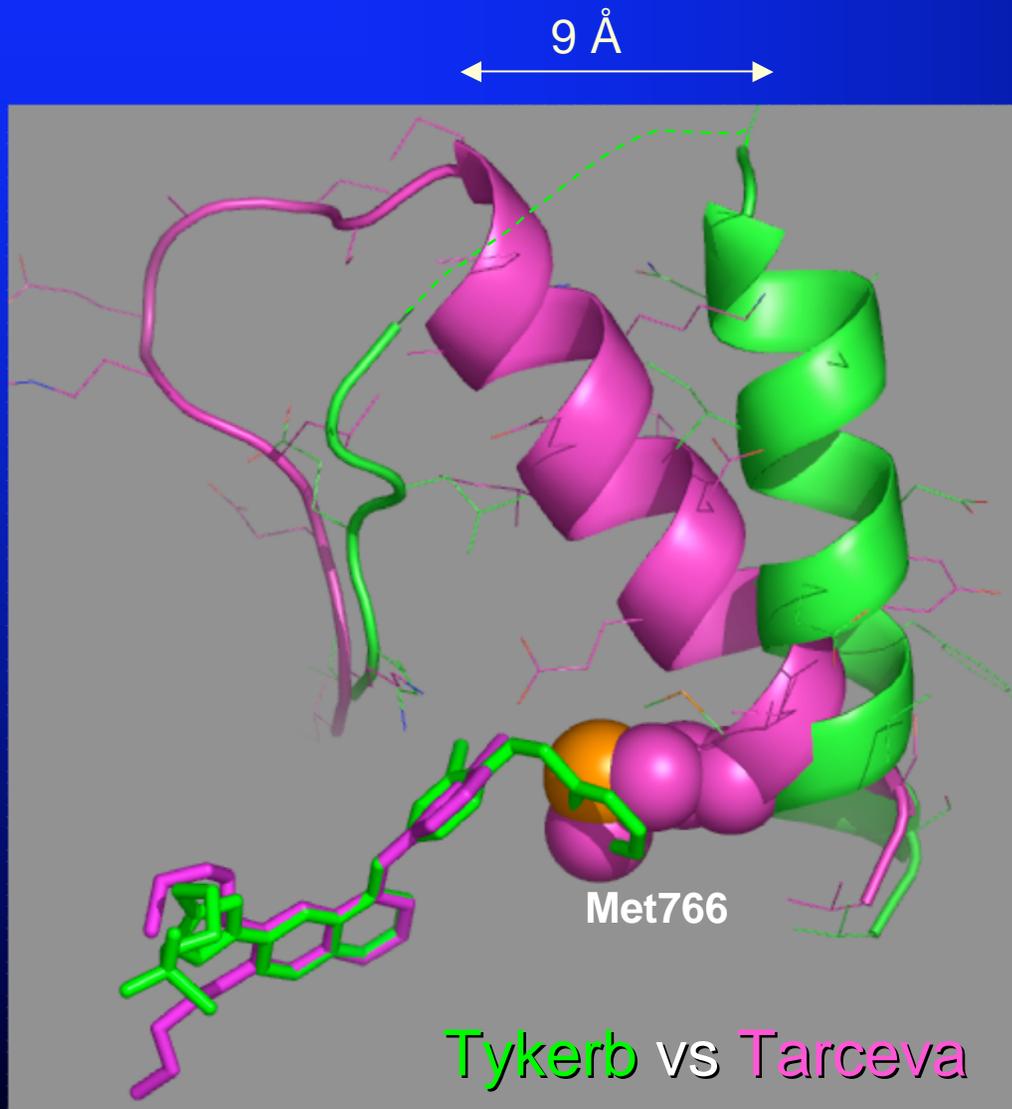
Tarceva

Active-like conformation



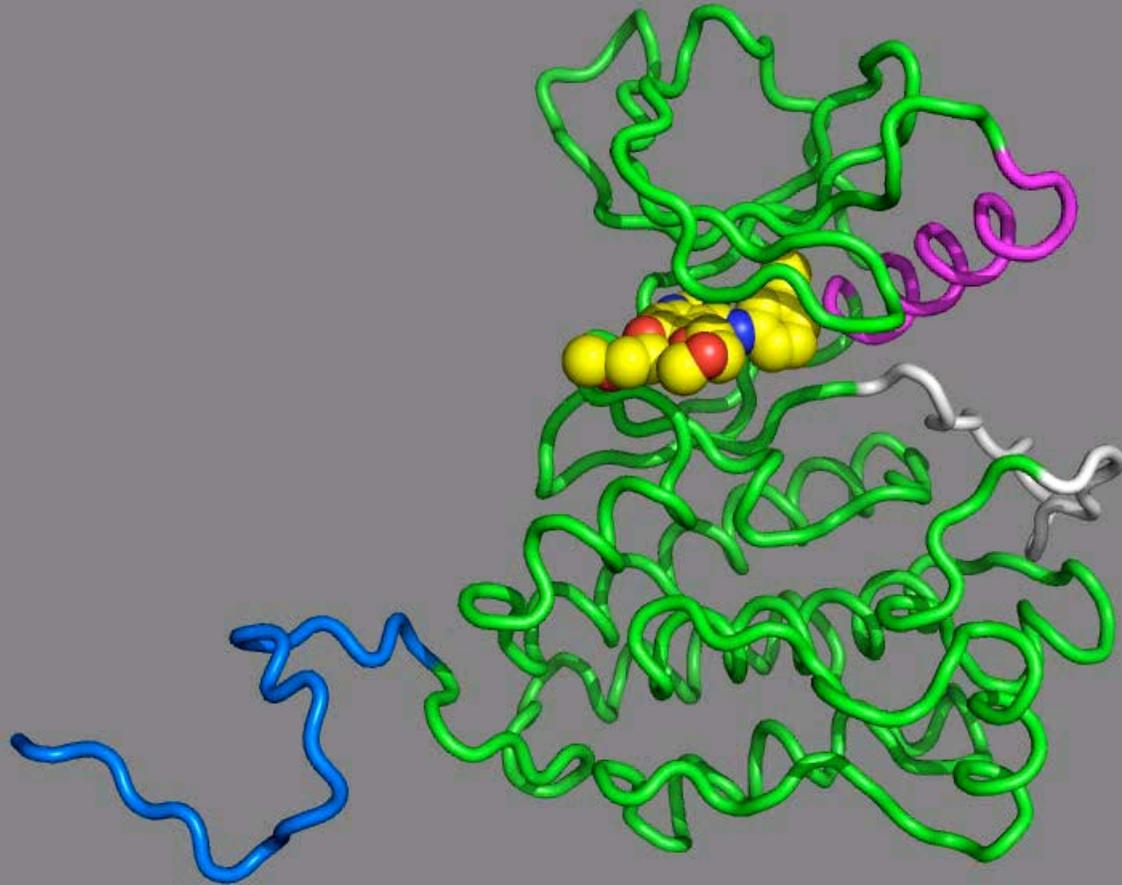
open ATP cleft
activation loop - active conformation
correct arrangement of catalytic residues
C-terminal tail extended

Similar Binding Mode for Quinazoline Core Very Different Protein Conformation

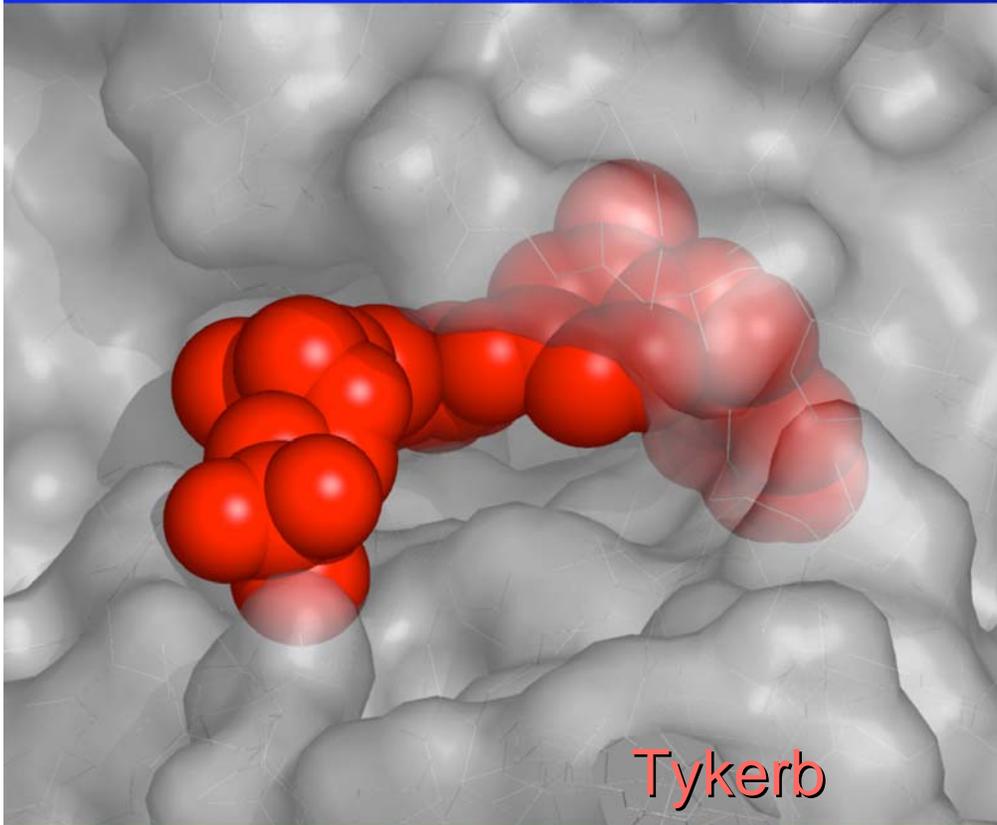


The C helix needs to shift to accommodate the large head group of Tykerb

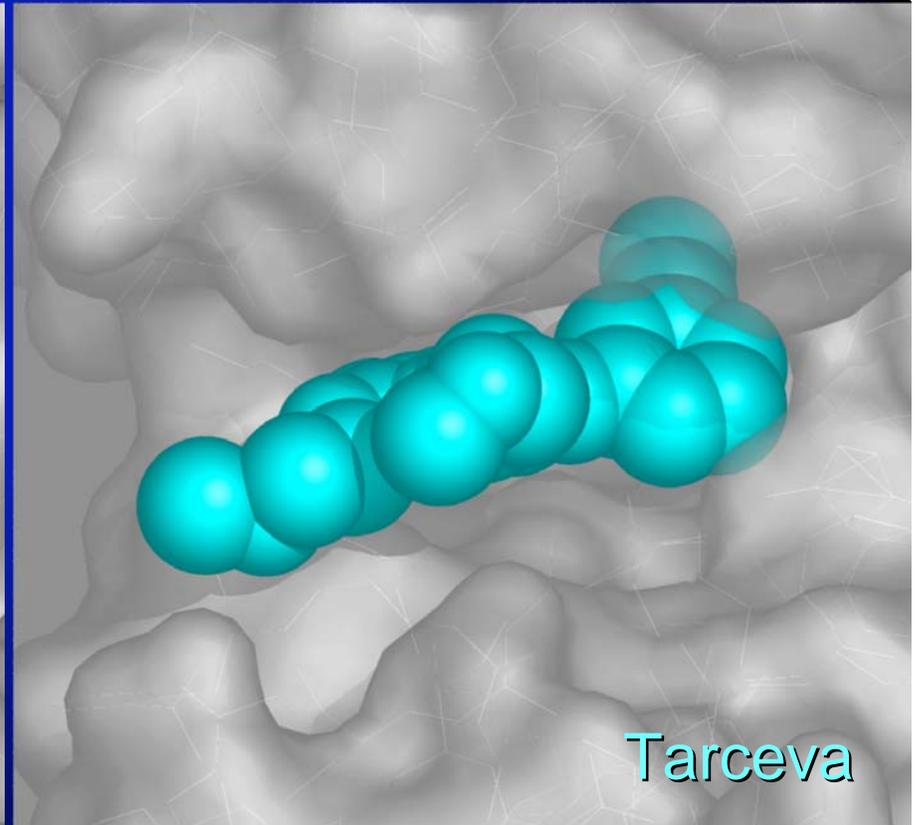
Conformational Differences Extend Beyond ATP Site



Conformational Differences Lead to Different Shaped Binding Sites



- inhibitor is buried deep within a closed down binding cleft
- very slow off rate

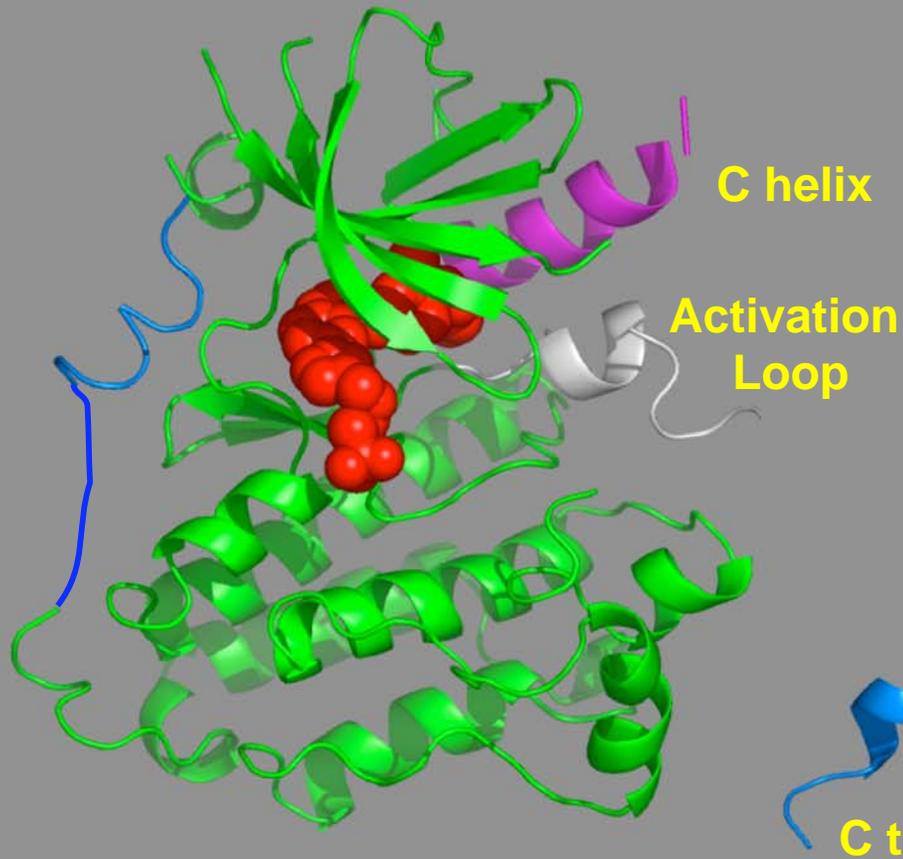


- inhibitor is solvent exposed in an open binding cleft
- rapid on/off rate

Structure Summary

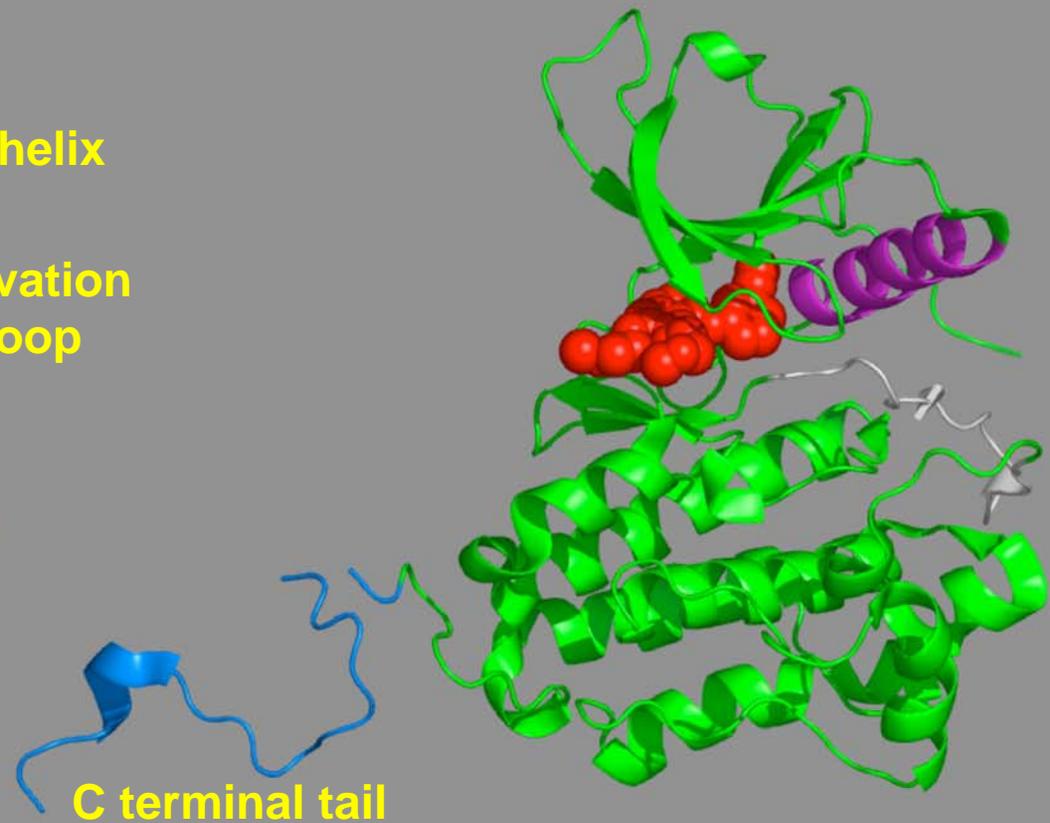
Tykerb

Inactive-like conformation



Tarceva

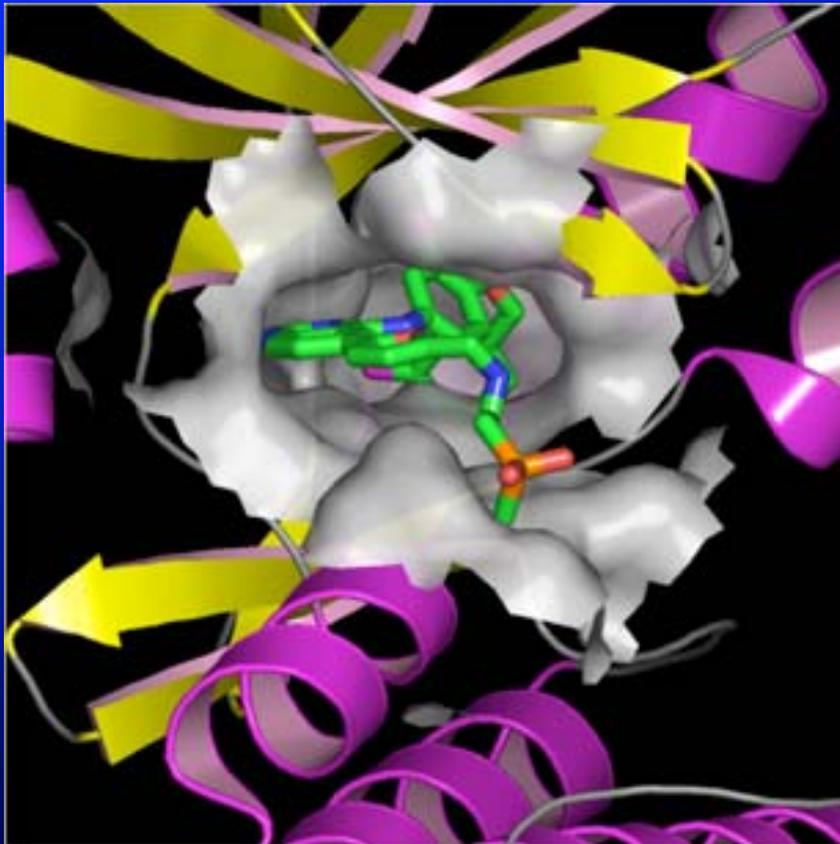
Active-like conformation



closed down ATP cleft
activation loop - inactive conformation
incorrect arrangement of catalytic residues
C-terminal tail not accessible

open ATP cleft
activation loop - active conformation
correct arrangement of catalytic residues
C-terminal tail extended

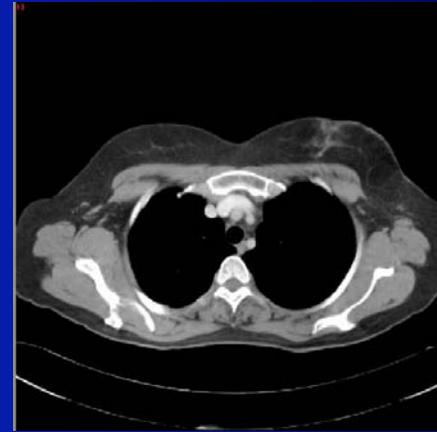
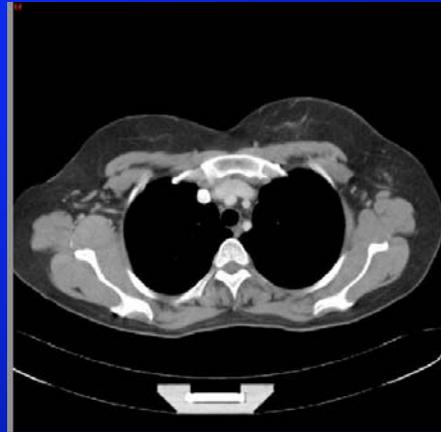
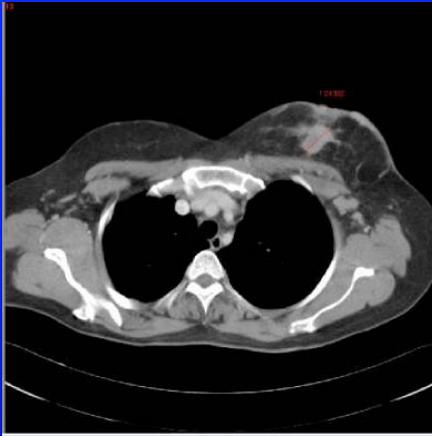
How has *in vitro* and *in vivo* cellular activity translated to the clinic?



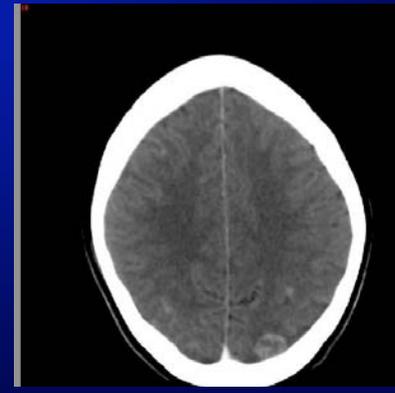
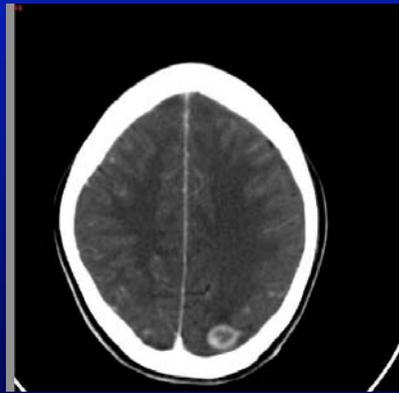
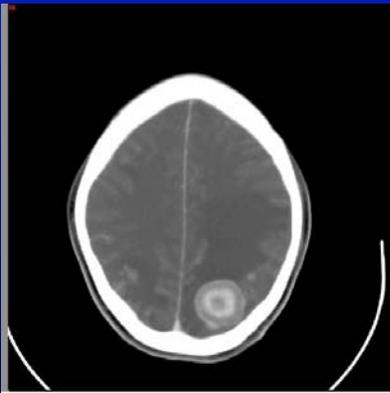
Phase 1 initiated Feb 2001



Promising Results in Several Tumor Types



Patient A
Breast CT Scan



Patient B
Brain lesion

Baseline

8 weeks

12 weeks

Lapatinib + Paclitaxel: PR

63 yo female with metastatic IBC (ErbB1+/ErbB2 3+).

5 prior metastatic regimens; prior docetaxel, trastuzumab.

Treatment duration 9 months: 6 cycles 175 mg/m² paclitaxel (q3 wk) + 1500 mg/day lapatinib; continued treatment with lapatinib alone.



Pretreatment



After Cycle 6

April 2006

**A Phase III Randomized, Open-Label,
International Study Comparing
Lapatinib and Capecitabine vs. Capecitabine
in Women with Refractory Advanced or Metastatic
Breast Cancer (EGF100151)**

Study Enrollment Terminated due to Positive
Interim Analysis

March 2007

Press Release



FDA APPROVES TYKERB® (LAPATINIB) IN COMBINATION WITH XELODA® (CAPECITABINE) FOR THE TREATMENT OF ADVANCED OR METASTATIC BREAST CANCER IN WOMEN WHO HAVE PROGRESSED ON PRIOR THERAPY

GlaxoSmithKline's New Breast Cancer Drug May Give Women More Options

PHILADELPHIA, PA, March 13, 2007 – GlaxoSmithKline plc [NYSE: GSK, LSE: GSK] announced today that the United States Food and Drug Administration (FDA) approved TYKERB® (lapatinib), in combination with Xeloda® (capecitabine), for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab. It is the first targeted, once-daily oral treatment option for this patient population. TYKERB was granted Priority Review by the FDA in November 2006.

"TYKERB is a significant breakthrough for women with advanced HER2 (ErbB2) positive breast cancer. The data clearly show that this small molecule, oral, targeted agent, in combination with capecitabine, is effective for women whose disease has progressed on previous therapies, including anthracyclines, taxanes and trastuzumab," said Paolo Paoletti, MD, Senior Vice President of the Oncology Medicine Development Center at GSK. "The approval of TYKERB demonstrates our R&D organization's strong commitment to the discovery and development of novel cancer treatments. We are dedicated to the further study and development of TYKERB in a variety of settings including adjuvant breast cancer as well as in other solid tumor types."

This approval reflects more than 16 years of research, including over 60 clinical trials and investigator-initiated research studies

Tykerb Summary

- Tykerb is an orally available, reversible, small-molecule inhibitor of EGFR/ErbB2
- Safety and tolerability demonstrated in Phase I studies, with healthy volunteers as well as cancer patients
- Clinical responses were observed at a variety of doses in heavily pre-treated subjects with metastatic disease
- Approved by the FDA in March 2007 for use in metastatic breast cancer in combination with Xeloda for patients that have progressed on prior therapy
- Additional studies under way in a number of tumor types, either as monotherapy or in combination with other therapies

Tykerb Summary

- Studies are ongoing at beam line 17ID to understand the effect of clinically relevant mutations on ErbB activity and protein conformation

Acknowledgements- Collaborators

The patients who participated in these trials

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Project Leaders

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