Selective Inhibitors of the ErbB-Family of Receptor Tyrosine Kinase

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ARRAY BIOPHARMA

Disclosure Information

2011 AACR Annual Meeting
Eli Wallace

I have the following financial relationships to disclose:

I am stockholder in and employee of Array BioPharma Inc

- and -

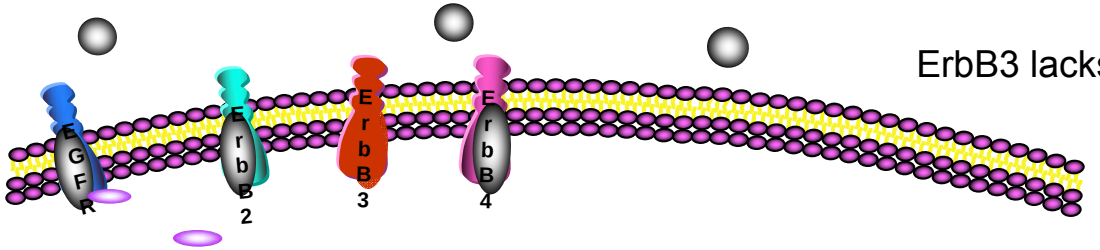
I will discuss Phase 1 investigational use in my presentation.

Rationale for pan-ErbB Inhibition in Cancer

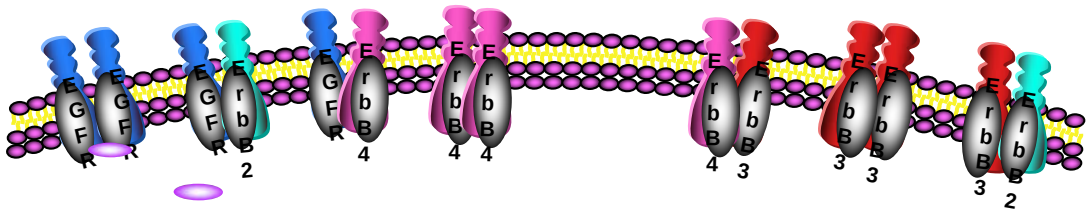
- ErbB receptors undergo various alterations in human tumors
  - EGFR
    - Gene amplification/overexpression and mutations found in many cancers (lung, gastric, HNSCC, biliary, pancreatic)
  - ErbB2
    - Gene amplification/overexpression found in multiple cancers (breast, gastric, endometrial, salivary gland, ovarian)
  - ErbB3
    - Frequently coexpressed with ErbB2
  - Aberrant ErbB signaling is generally associated with aggressive disease and poor clinical outcome

ErbB Receptor Tyrosine Kinases

- The ErbB family consists of four closely related receptors



ErbB2 has no known ligand
Preferred heterodimer partner

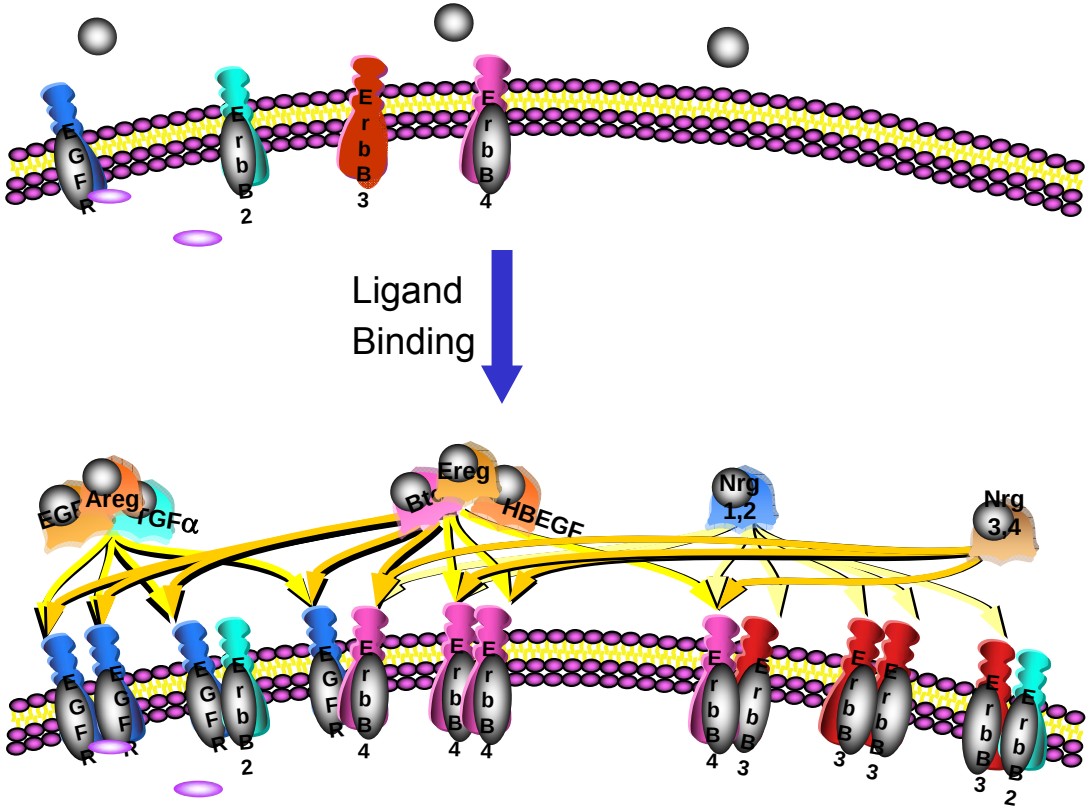


- Ligand binding induces dimerization and kinase activation
- Trans-phosphorylation recruits proteins and activates signaling pathways

Figure Adapted from SABiosciences

ErbB Receptor Tyrosine Kinases

- Growth Factor Signaling is Complex



- Many tumor types co-express multiple ErbB receptors and ligands
- Redundant homo- and heterodimers can mediate signaling

Figure Adapted from SABiosciences

Target pan-ErbB Inhibitor

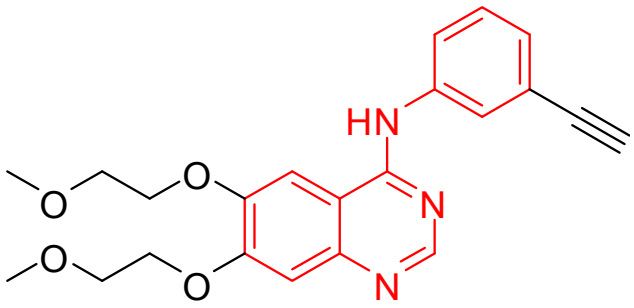
- Aberrant ErbB signaling is generally associated with aggressive disease and poor clinical outcome
- Growth factor signaling is complex with many tumor types co-expressing multiple receptors and ligands
- Tumors that activate redundant ErbB dimers are refractory to selective ErbB inhibitors
- **Hypothesis** - pan-ErbB inhibitor will have broader activity than selective ErbB inhibitors in tumors that signal through multiple ErbB family members
- Potential Indications – Gastric, Head & Neck, Biliary

Project Goals

- Potent, Selective, Reversible, Oral pan-ErbB Inhibitor
- Drug-like Inhibitor
  - Clinical Development Unobstructed by Pharmacokinetics
- Activity in Dual Expressing Tumors
- Simultaneously Explore ErbB2 Selective Inhibitor
  - “ARRY-380: A selective, oral HER2 inhibitor for the treatment of solid tumors” Dr. Kevin Koch - New Drugs on the Horizon 1– Sunday April 3

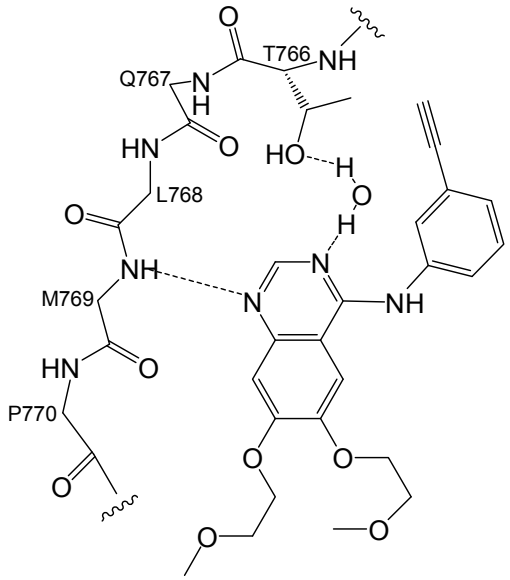
Pan ErbB Inhibitor – Initial Approach

- Investigate Successful Drug Moieties
  - Quinazoline - Balance of potency, selectivity, pharmacokinetics



Erlotinib
EGFR inhibitor

- Crystal Structure of EGFR kinase domain and erlotinib



Stamos et al JBC 2002, 277 (48), 46265

Pan ErbB Inhibitor – Initial Approach

- Investigate Successful Drug Moieties
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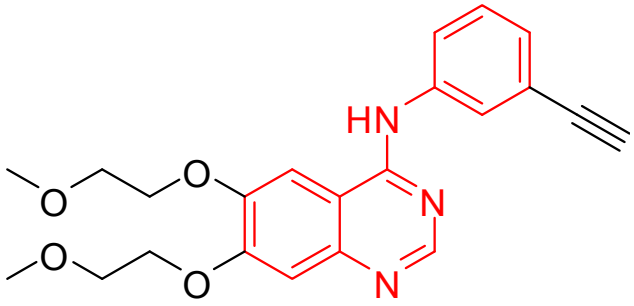
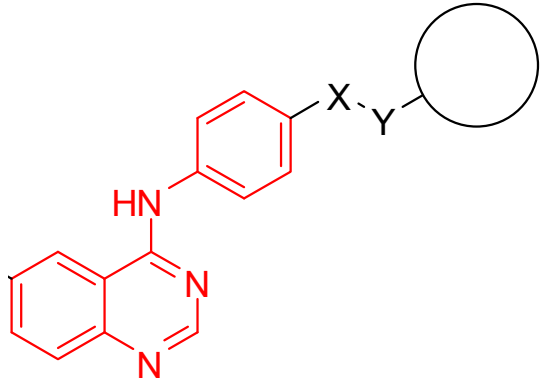
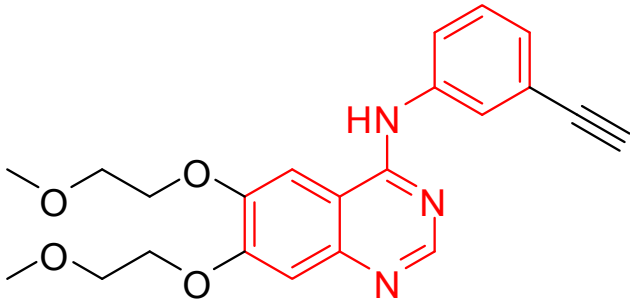


Erlotinib
EGFR inhibitor

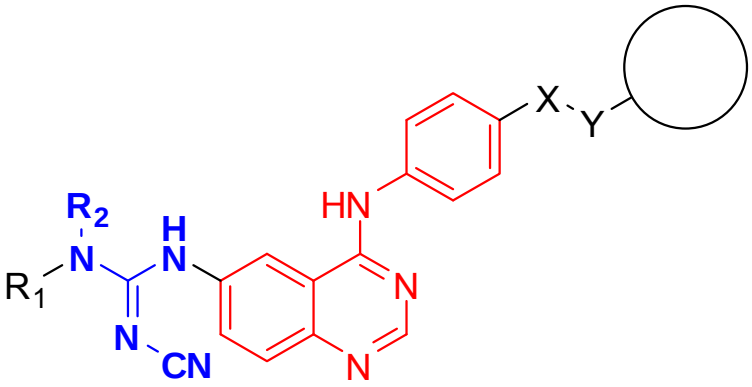


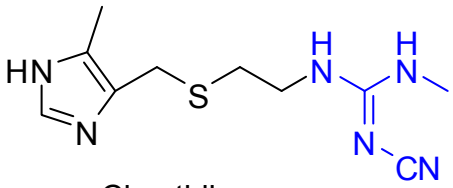
Pan ErbB Inhibitor – Initial Approach

- Investigate Successful Drug Moieties
  - Quinazoline - Balance of potency, selectivity, pharmacokinetics
  - Cyano-Guanidines – Balance of polarity and permeability

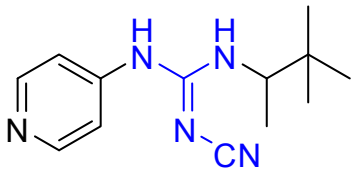


Erlotinib
EGFR inhibitor



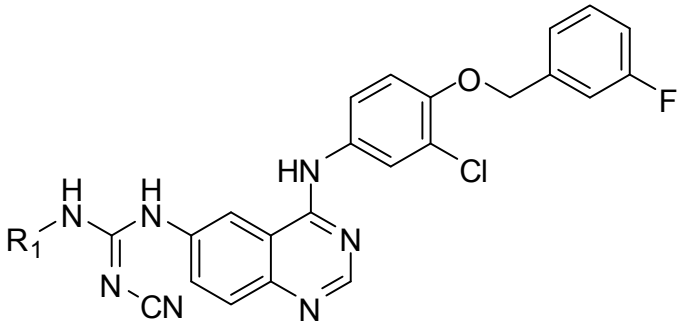


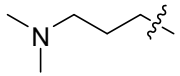
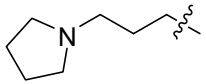
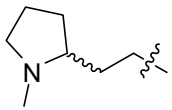
Cimetidine
H2 Antagonist



Pinacidil
KATP opener

Cyano Guanidines - Potent Dual Inhibitors



Compound	R1	EGFR Cell	ErbB2 Cell
1		153	78
2		33	111
3		184	127

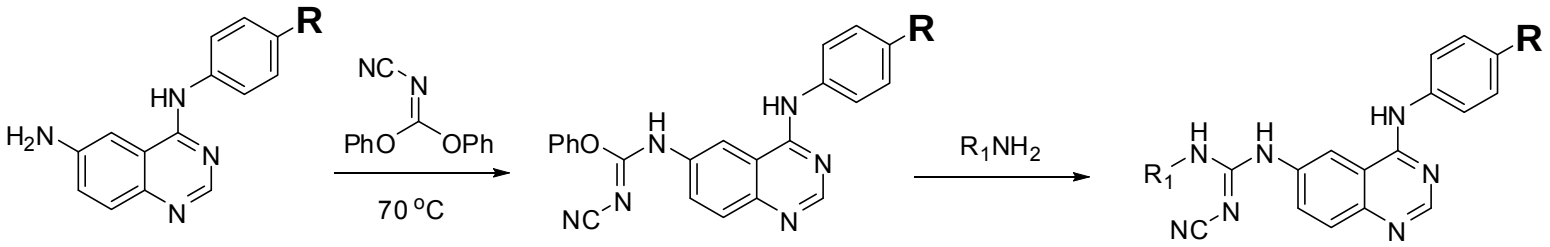
IC_{50} in nanomolar

…Poor in vitro ADME properties and no oral exposure in mice

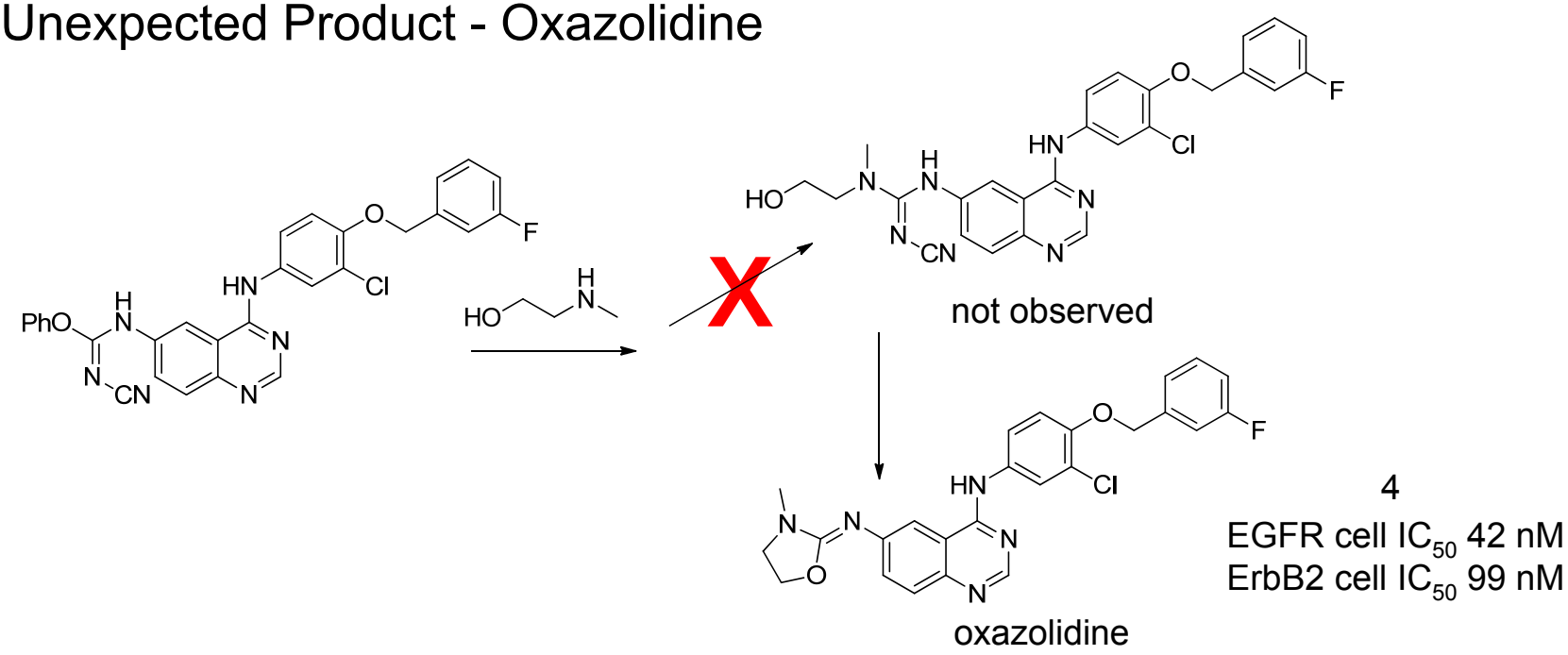
Joe Lyssikatos, Qian Zhao, George Topalov

Serendipity

- General Route



- Unexpected Product - Oxazolidine



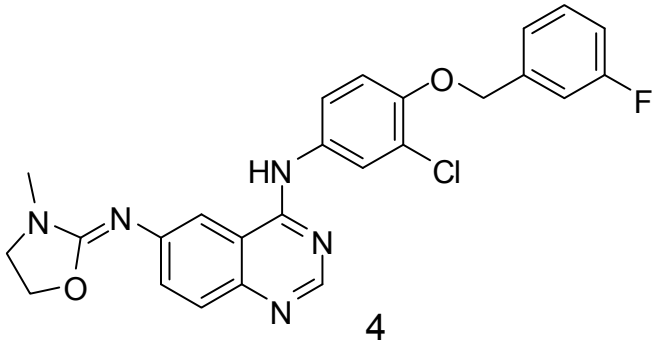
4

EGFR cell IC_{50} 42 nM

ErbB2 cell IC_{50} 99 nM

Oxazolidine Lead

- Potent, Orally Bioavailable Lead – Opportunity for Optimization



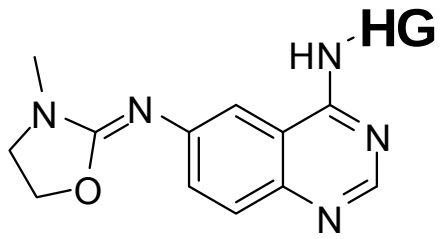
4

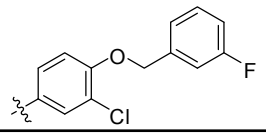
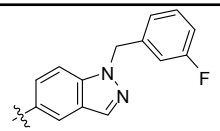
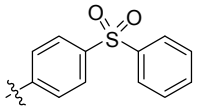
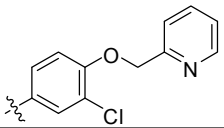
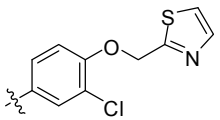
EGFR Cell	42
ErbB2 Cell	99
Mouse Pharmacokinetics	AUC 2.0 μg.hr/ml @ 10 mg/kg
Kinase selectivity (17 kinases)	No inhibition at 10 μM
Properties	MW 478 / Clog P > 6.5

IC_{50} in nanomolar

Head Group SAR

- Potency Obtainable with More Polar Analogs



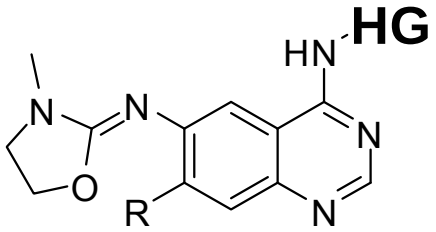
Compound	HG	EGFR Cell	ErbB2 Cell	Clog P
4		42	99	>6.5
5		11	17	5.8
6		80	112	4.7
7		183	65	5.1
8		214	84	5.0

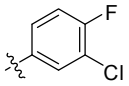
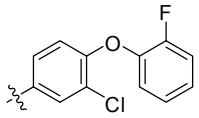
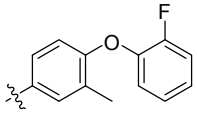
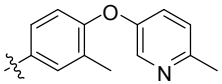
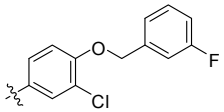
IC_{50} in nanomolar

George Topalov, Andy Ren, Alex Buckmelter, Jeremy Hans, Gene Tarlton, Josh Tullis, Greg Miknis

Head Group SAR

- Selectivity



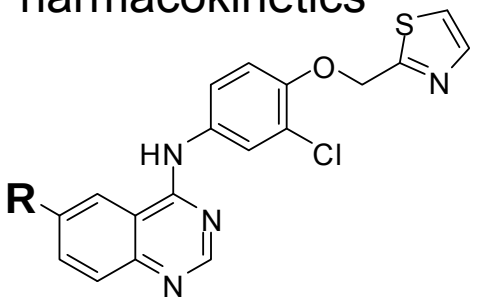
Compound	HG	R	EGFR Cell	ErbB2 Cell	Selectivity EGFR / ErbB2
9		H	12	2117	0.006
10			44	25	1.8
11			249	20	12
12			Enzyme 460	218	> 50
13		OMe	218	2017	0.1

IC_{50} in nanomolar

George Topalov, Andy Ren, Alex Buckmelter, Jeremy Hans, Gene Tarlton, Josh Tullis, Greg Miknis

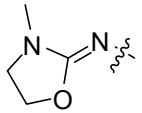
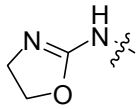
Oxazolidine versus Dihydro-oxazole

- Dihydro-oxazole – Improved Pharmacokinetics



SAR -

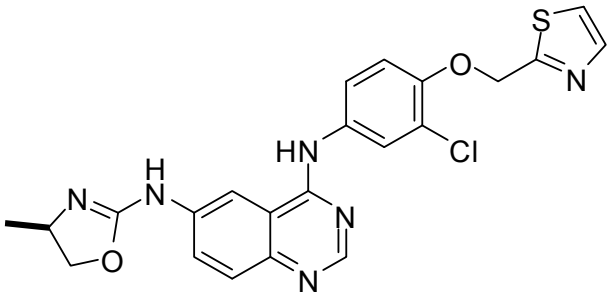
potency / selectivity
ADME
safety / efficacy

Compound	R	EGFR Cell[1]	ErbB2 Cell[1]	Rat Pharmacokinetics 2 mg/kg IV 20 mg/kg PO		
				CL[2]	Oral AUC[3]	%F
8	**oxazolidine** 	214	84	22 31% ER	1.8	11
14	**dihydro-oxazole** 	93	67	1.5 2% ER	55	24

[1] IC_{50} in nanomolar
[2] ml/min/kg
[3] μg.hr/ml

Joe Lyssikatos, Andy Ren, Qian Zhao, George Topalov

ARRY-543: A Potent, Selective ErbB Inhibitor



ARRY-543
Varlitinib

	EGFR	ErbB2	ErbB4
Enzyme IC_{50}	7 nM	0.5 nM	4 nM
Cellular IC_{50} (phospho-receptor)	43 nM	36 nM	130 nM
Mutant Cell IC_{50}	100 nM (Exon 19 Del)	47 nM (p95 Del)	---

- Balanced inhibition of ErbB kinases
- Selective for the ErbB family members
  - No inhibition of > 150 other kinases
- Potent in cell based assays
  - Activity on clinically important mutants
- Reversible inhibitor – opportunity for good safety profile

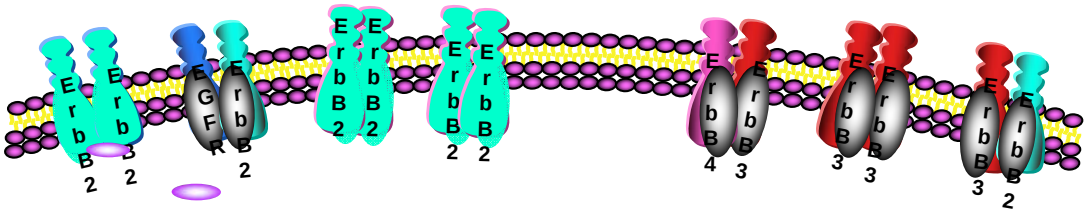
ARRY-543 Displays Favorable PK in Preclinical Species

- Good oral exposure – 50 to 100% F in rat and monkey
- Low-to-moderate CL
  - Human Predicted Liver Extraction Ratio – 33 to 48%
- V_{ss} indicative of tissue penetration
- Good Permeability – no efflux in Caco-2
- Exposure not limited by solubility

…combined with potency led to efficacy in dual and ErbB2 driven models of cancer

N87 Human Gastric Carcinoma – ErbB2 or Dual Driven

Absence of Growth Factors – ErbB2 Expression and Signaling

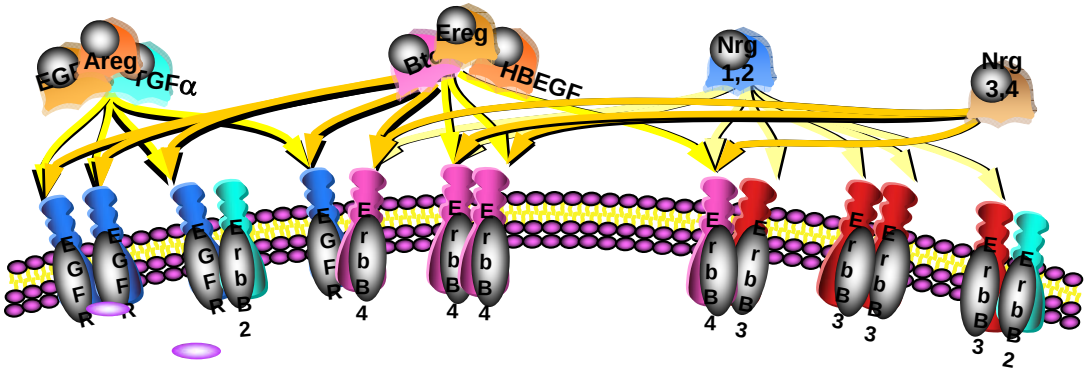


Growth Inhibition (IC_{50} (nM) / fold shift)

	No Stimulation
	IC_{50}(nM)
ARRY-543	87
Selective ErbB2	6
Erlotinib	1500

N87 Human Gastric Carcinoma – ErbB2 or Dual Driven

Presence of Growth Factors – Dual Expression and Signaling



Growth Inhibition (IC_{50} (nM) / fold shift)

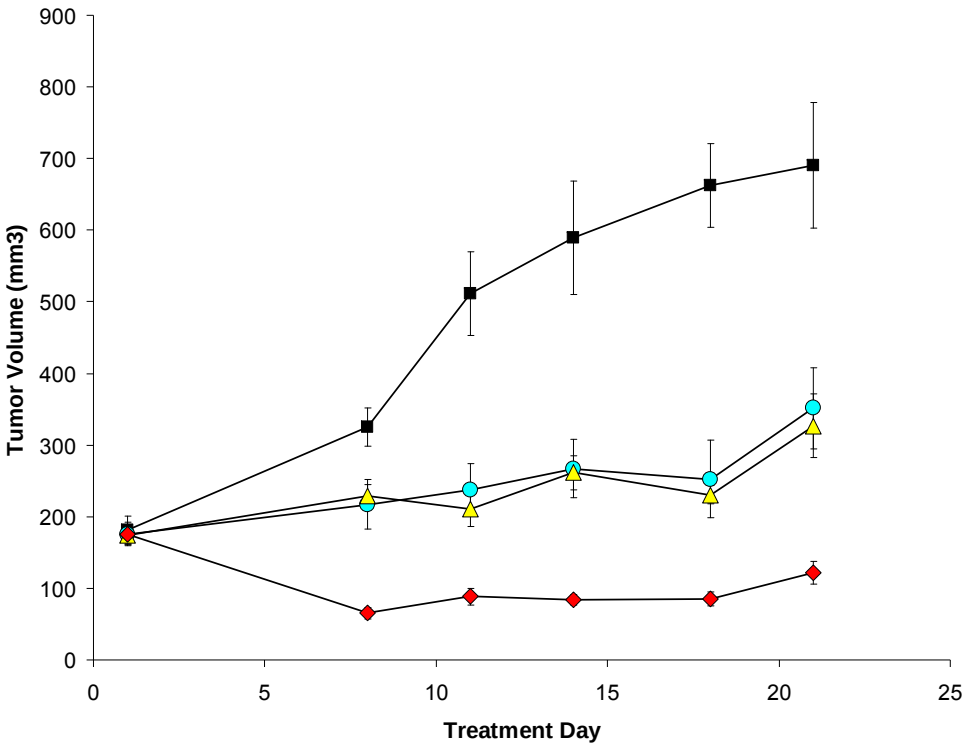
	No Stimulation	Epiregulin	
	IC_{50}(nM)	IC_{50}(nM)	shift
ARRY-543	87	312	4
Selective ErbB2	6	132	22
Erlotinib	1500	892	0.5

- Similar results with EGF, heregulin β1, betacellulin, amphiregulin, HB-EGF, TGFα
- In the presence of EGF, an increase in EGFR homodimers and EGFR:ErbB2 heterodimers was observed (Monogram Bioscience)

Ryan Blackwell, Jenn Garrus

Pan ErbB2 Inhibition more Efficacious Than Selective Targeting

- NCI-N87 Human Gastric Carcinoma Xenograft



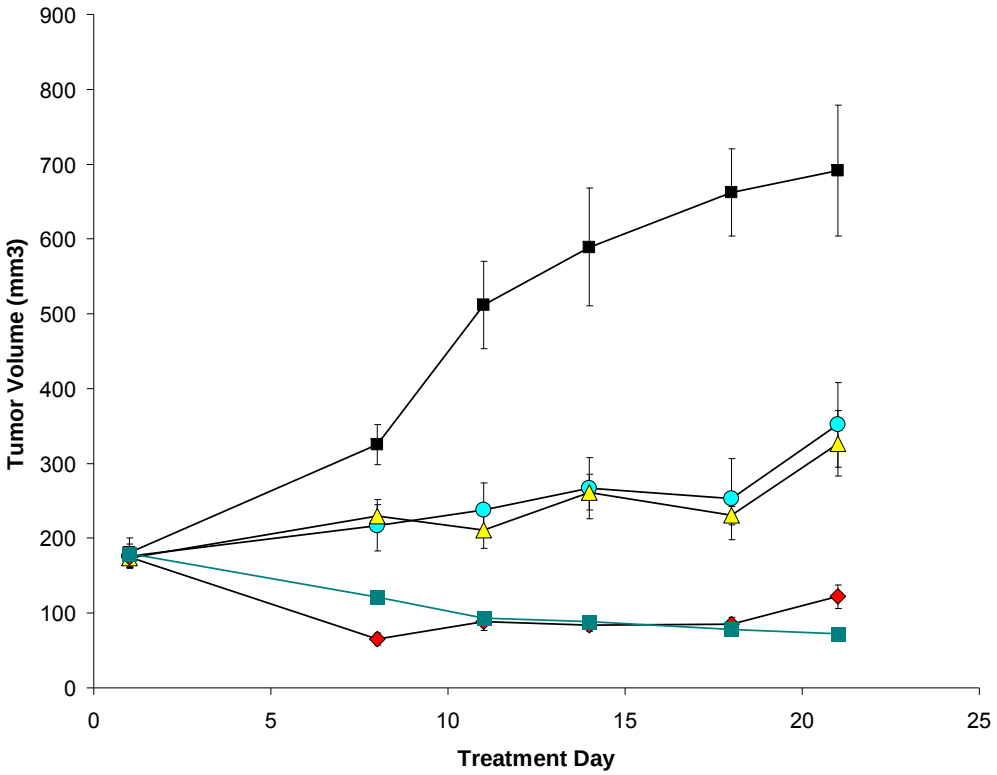
Treatment Group	% TGI	PR
Control	---	---
Erlotinib 100 mg/kg / QD	53	0/8
ARRY-380 50 mg/kg / QD	49	1/8
Erlotinib 50 mg/kg / QD + ARRY-380 50 mg/kg / QD*	82	8/8

TGI –tumor growth inhibition
PR - Partial response, ≥ 50% regression of an individual tumor
*Dose of Erlotinb was dropped from 100 to 50 mg/kg on day 8 due to tolerability

Karyn Bouhana, Shannon Winski, Patrice Lee

Pan ErbB2 Inhibition more Efficacious Than Selective Targeting

- NCI-N87 Human Gastric Carcinoma Xenograft



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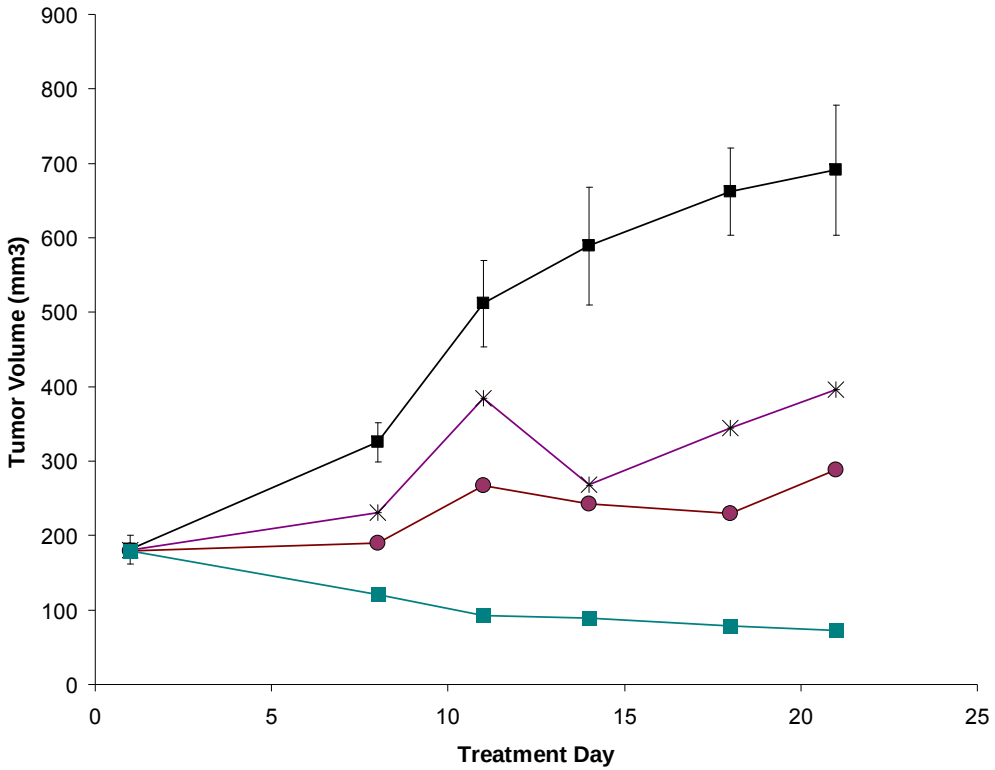
Control	---	---
Erlotinib 100 mg/kg / QD	53	0/8
ARRY-380 50 mg/kg / QD	49	1/8
Erlotinib 50 mg/kg / QD + ARRY-380 50 mg/kg / QD *	82	8/8
ARRY-543 100 mg/kg / BID	90	7/8

TGI –tumor growth inhibition
PR - Partial response, ≥ 50% regression of an individual tumor
*Dose of Erlotinb was dropped from 100 to 50 mg/kg on day 8 due to tolerability

Karyn Bouhana, Shannon Winski, Patrice Lee

Pan ErbB2 Inhibition more Efficacious Than Selective Targeting

- NCI-N87 Human Gastric Carcinoma Xenograft



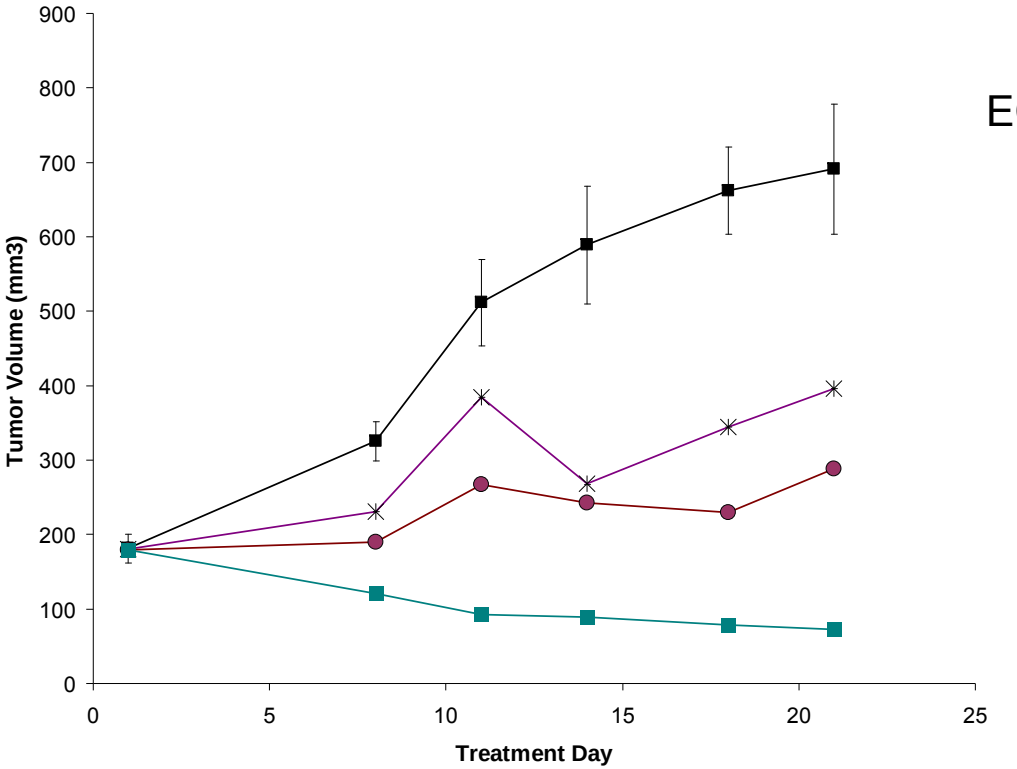
Treatment Group	% TGI	PR
Control	---	---
Erlotinib 100 mg/kg / QD	53	0/8
ARRY-380 50 mg/kg / QD	49	1/8
Erlotinib 50 mg/kg / QD + ARRY-380 50 mg/kg / QD*	82	8/8
ARRY-543 25 mg/kg / BID	43	0/8
ARRY-543 50 mg/kg / BID	58	1/8
ARRY-543 100 mg/kg / BID	90	7/8

TGI –tumor growth inhibition
PR - Partial response, ≥ 50% regression of an individual tumor
*Dose of Erlotinb was dropped from 100 to 50 mg/kg on day 8 due to tolerability

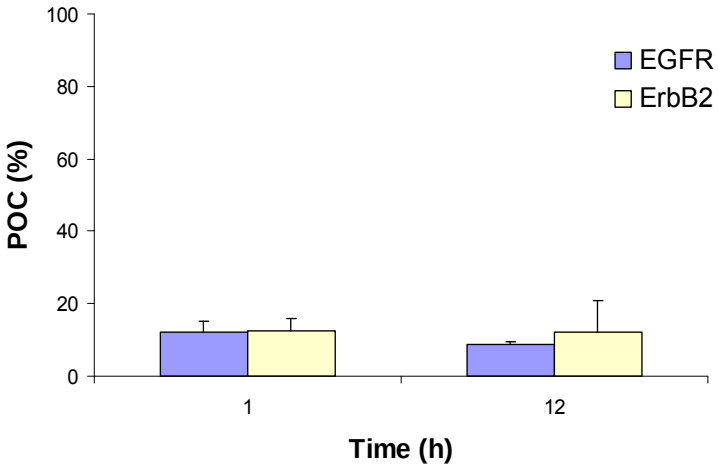
Karyn Bouhana, Shannon Winski, Patrice Lee

Pan ErbB2 Inhibition more Efficacious Than Selective Targeting

- NCI-N87 Human Gastric Carcinoma Xenograft
- Efficacy correlates with inhibition of both receptors



EGFR / ErbB2 PD – 100 mg/kg ARRY-543

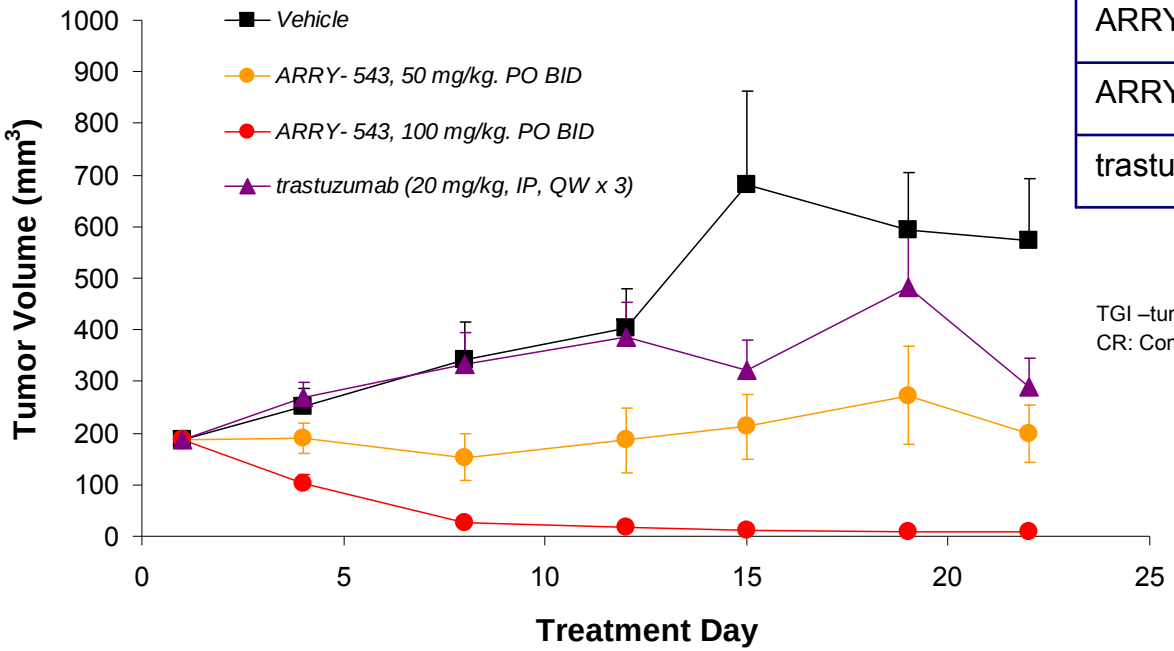


EGFR / ErbB2 dimers detected

Karyn Bouhana, Shannon Winski, Patrice Lee, Monogram Bioscience

BT474 Human Breast Carcinoma: ARRY-543 +/- trastuzumab

- Significant inhibition of tumor growth at 50 and 100 mg/kg
  - At 100 mg/kg complete response observed in 8 of 10 animals
- Trastuzumab also had significant TGI (53%) as a single agent



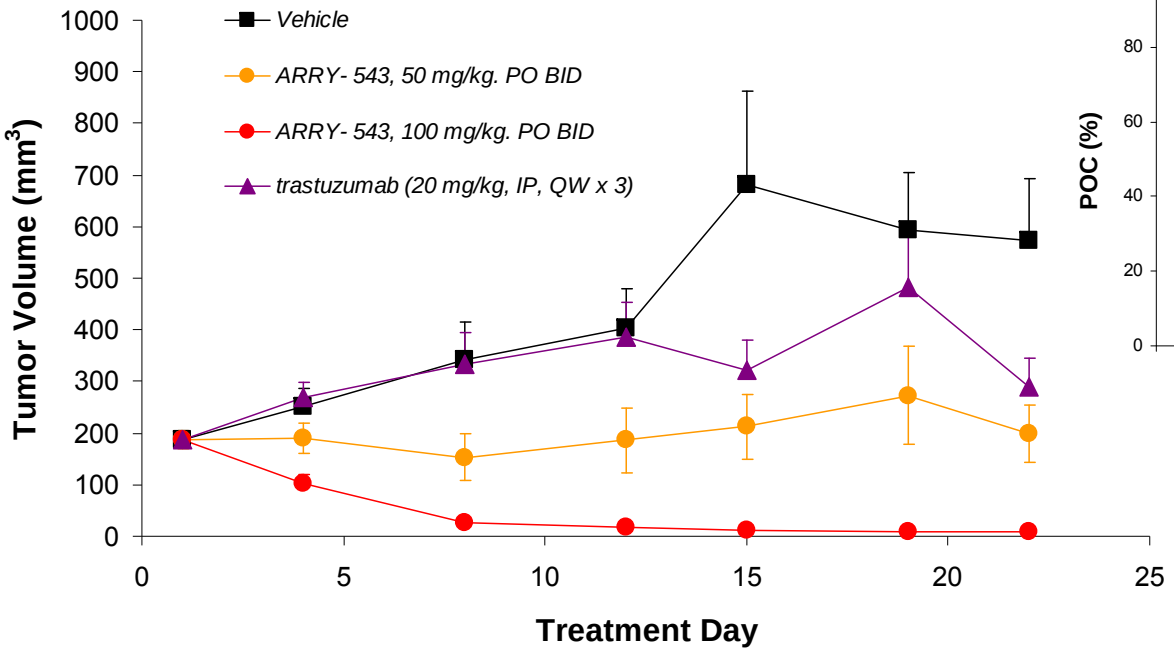
Treatment Group	% TGI	CR
ARRY-543 50 mg/kg	69	0/11
ARRY-543 100 mg/kg	98	8/10
trastuzumab 20 mg/kg	53	0/10

TGI –tumor growth inhibition
CR: Complete response, 100% regression of an individual tumor

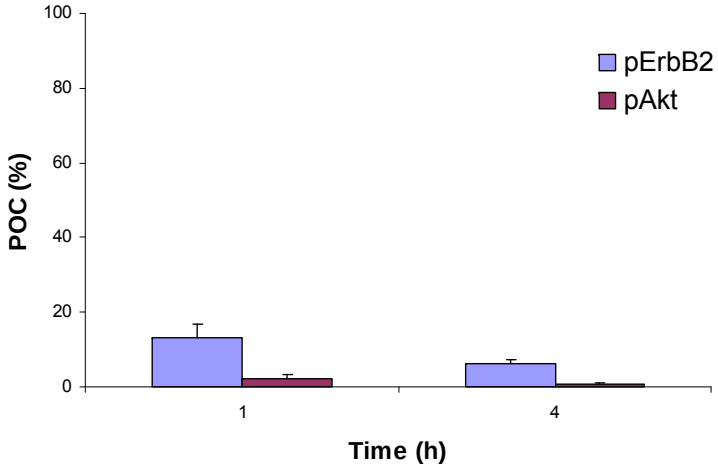
Tracy Pheneger, Shannon Winski, Patrice Lee and Piedmont Research Center

BT474 Human Breast Carcinoma: ARRY-543 +/- trastuzumab

- Efficacy correlates with inhibition of ErbB2 and Akt



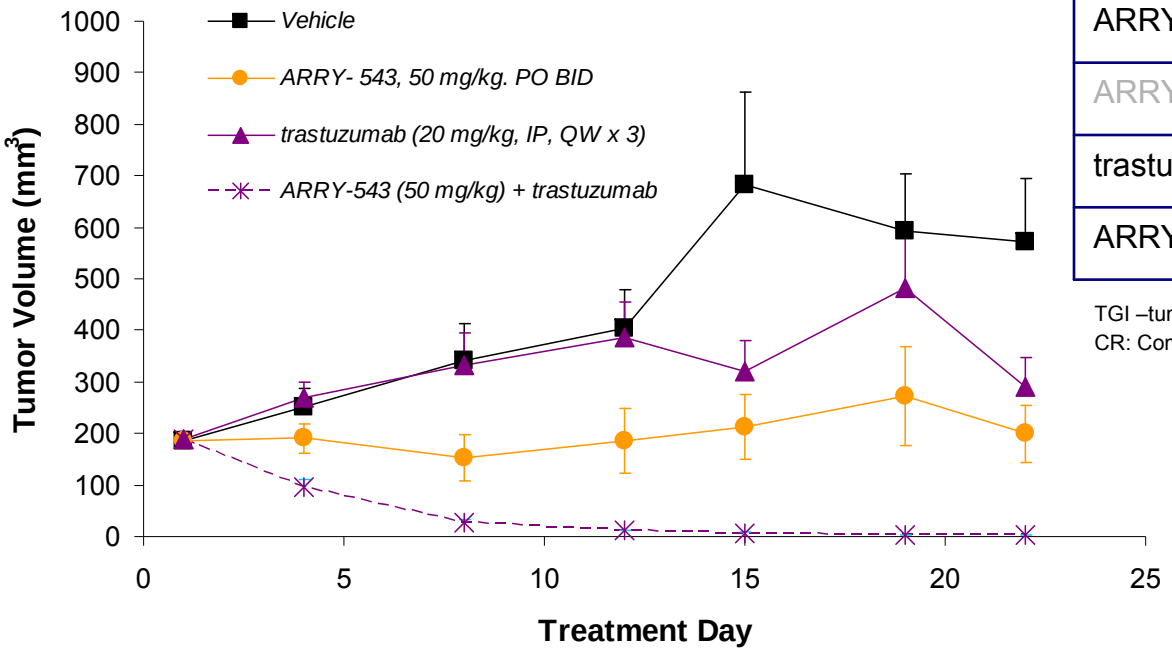
PD Assay– 100 mg/kg ARRY-543



Tracy Pheneger, Shannon Winski, Patrice Lee and Piedmont Research Center

BT474 Human Breast Carcinoma: ARRY-543 +/- trastuzumab

- ARRY-543 + trastuzumab - additive activity with complete response in all mice



Treatment Group	% TGI	CR
ARRY-543 50 mg/kg	69	0/11
ARRY-543 100 mg/kg	98	8/10
trastuzumab 20 mg/kg	53	0/10
ARRY-543 (50 mg/kg) + t-mab	99	11/11

TGI –tumor growth inhibition
CR: Complete response, 100% regression of an individual tumor

Tracy Pheneger, Shannon Winski, Patrice Lee and Piedmont Research Center

Summary – Nonclinical Studies

- ARRY-543 is a potent, well-tolerated, reversible, orally bioavailable ErbB family inhibitor

- In efficacy studies, ARRY-543 demonstrated dose-dependent inhibition of tumor growth, with regressions
  - ARRY-543 inhibits growth in multiple tumor types
    - EGFR-expressing (wild-type and mutant – exon 19 deletion)
    - ErbB2-expressing xenograft tumors
    - Dual-responsive tumors

- In combination studies with capecitabine, docetaxel, trastuzumab and cetuximab
  - ARRY-543 was well-tolerated with combination drugs
  - ARRY-543 had additive or super-additive activity with combination drugs
  - Increased regressions in combination

ARRY-543 Clinical Results

- Five Phase Ia and Ib Studies Completed with 543 Monotherapy and in Combination with Cytotoxic Therapies
  - > 200 patients treated
- Single Agent Safety
  - MTD 500 mg BID
    - DLTs were Grade 3 anorexia and Grade 3 increased AST/ALT
    - Events of rash were mild-to-moderate in severity
    - No treatment-related cardiac events have been reported
- Cytotoxic Combination Safety
  - MTDs determined in capecitabine, docetaxel, and gemcitabine Phase 1b studies

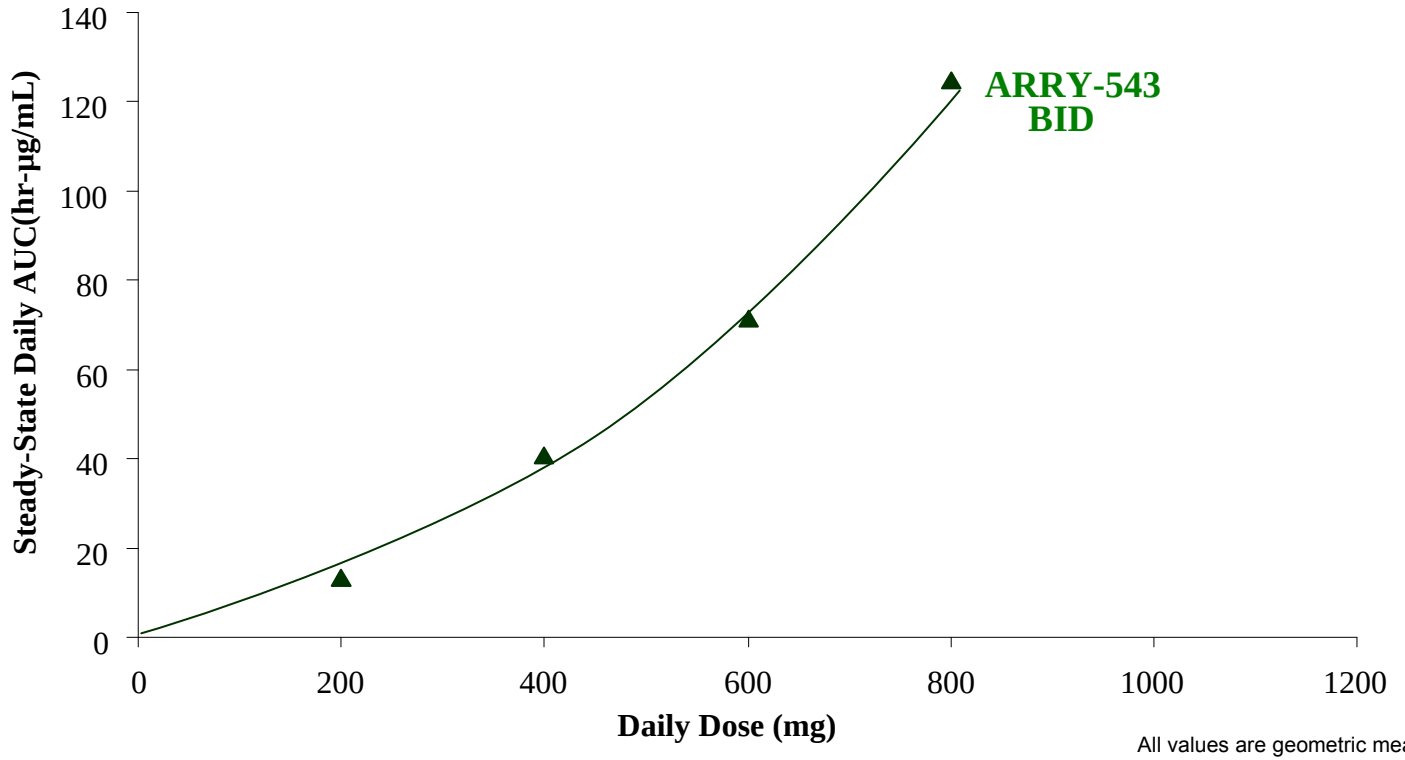
Chemotherapy	ARRY-543 MTD
docetaxel + GCSF	500 mg BID
capecitabine	400 mg BID
gemcitabine	300 mg BID

[1]The single agent MTD of 500 mg BID precluded additional dose escalation so a non-tolerated dose was not achieved with the docetaxel combination

- No Change in Pharmacokinetics of Either Agent in Any of the Combinations

ARRY-543 – Exposure Increases with Dose

- At steady state during BID dosing, ARRY-543 exposure tends to increase with increasing dose
- Clinical Development Unobstructed by Pharmacokinetics



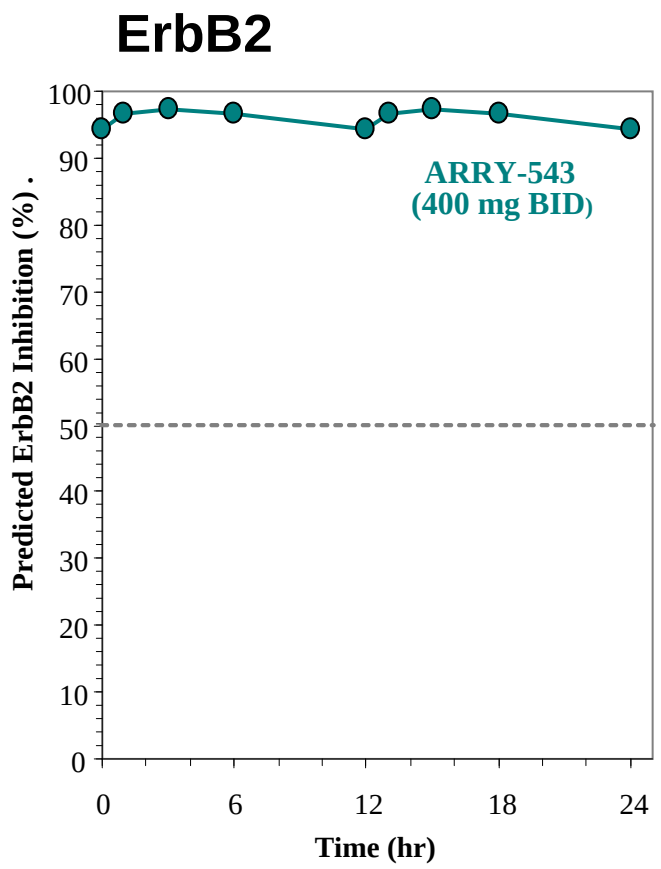
All values are geometric means

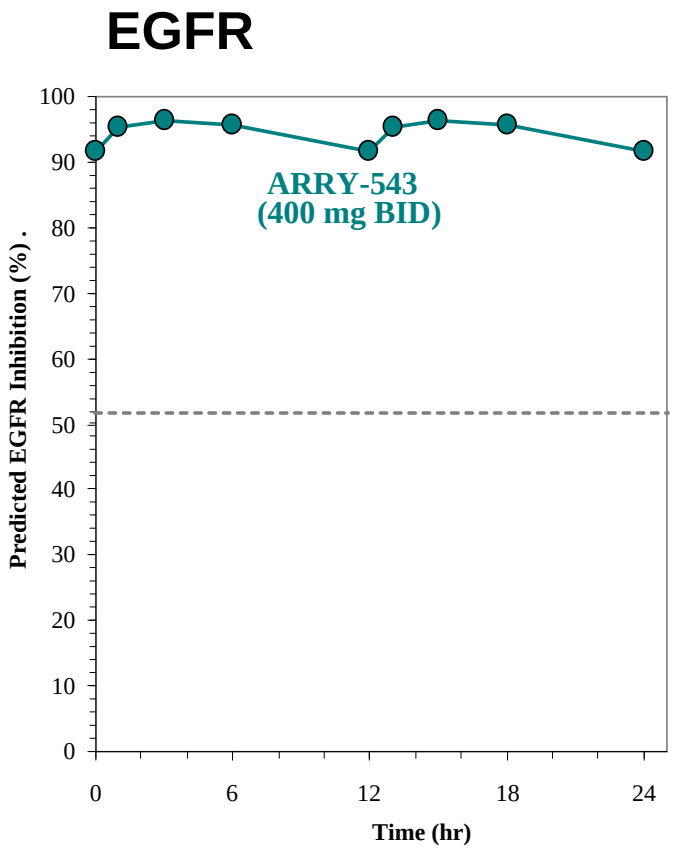
ARRY-543

- $t_{1/2}$ ~7 h
- T_{max} ~ 3 h
- Peak-to-Trough Ratio ~ 2

ARRY-543 - PK/PD Modeling

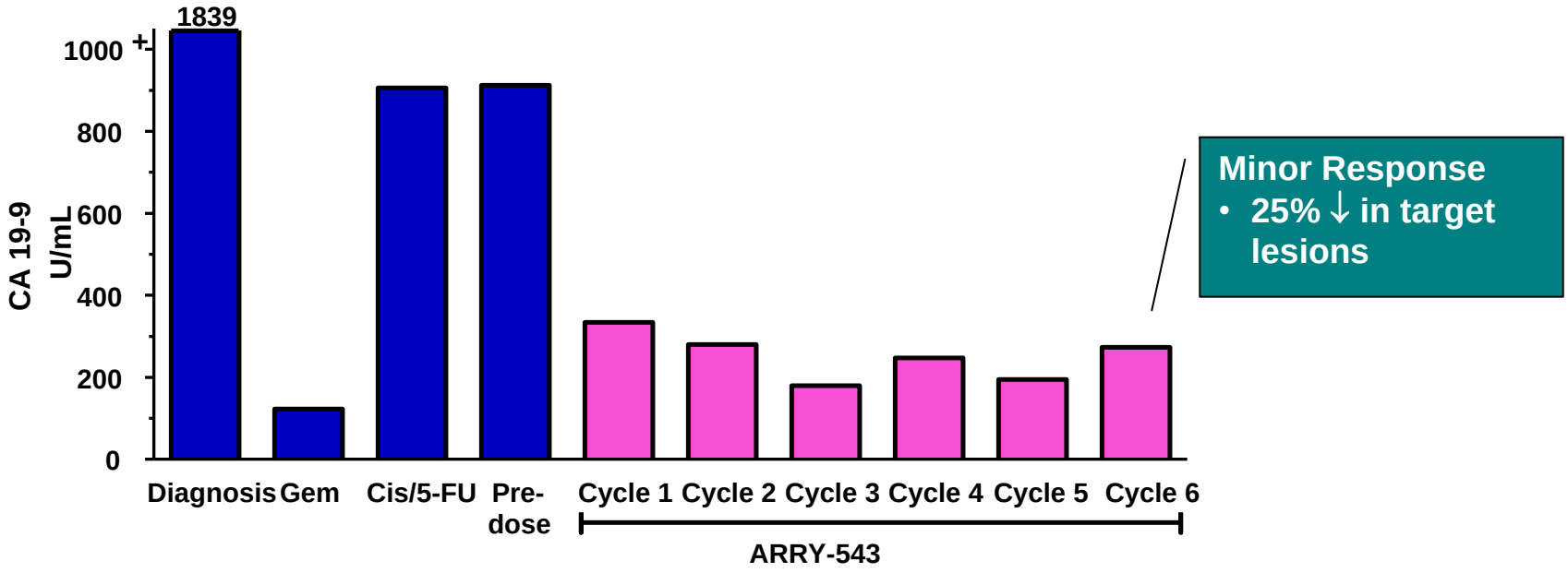
- Mean ARRY-543 exposure at 400 mg BID in patients is predicted to inhibit both ErbB2 and EGFR > 90%





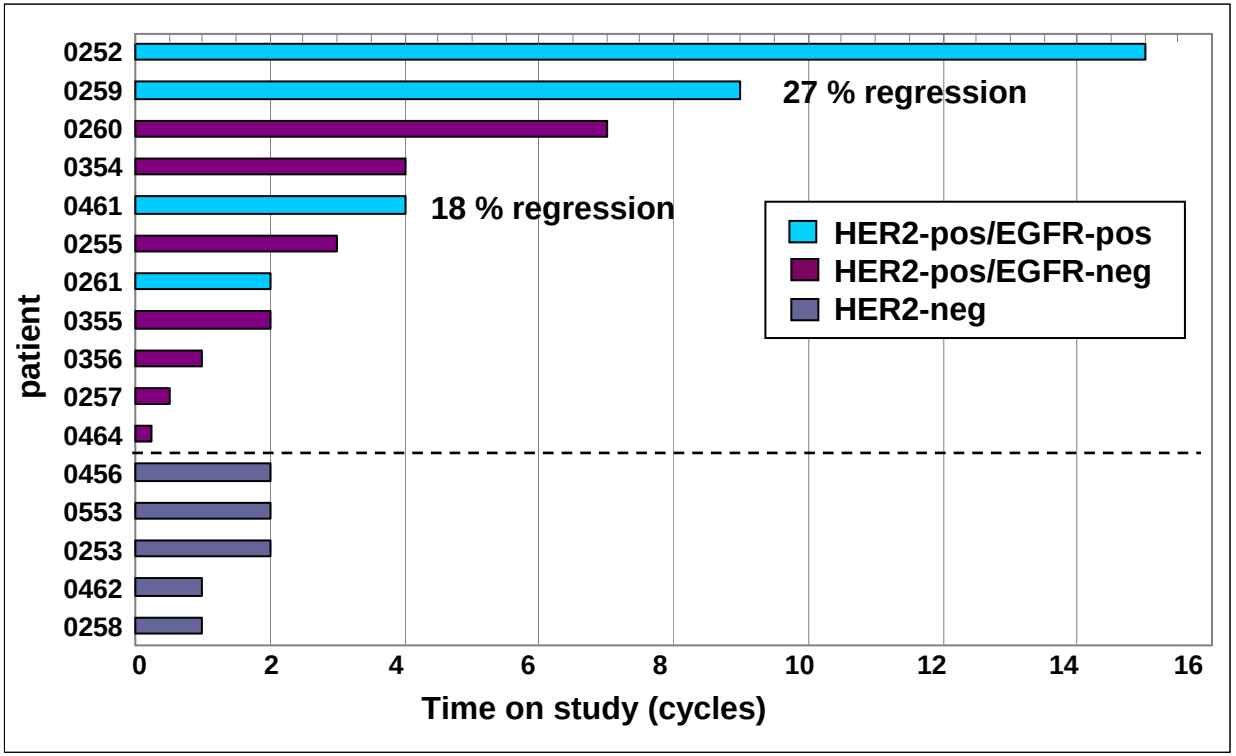
ARRY-543 – Preliminary Clinical Activity

- Biliary Cancer Patient (ARRY-543 Monotherapy, 400 mg BID)
  - 3rd-line, progressed after:
    - 1st-line gemcitabine (Best response = PR)
    - 2nd line cisplatin/5-FU (Best response = PD)
  - EGFR (3+) Status supports activity against EGFR



ARRY-543 – Preliminary Clinical Activity

- Metastatic Breast Cancer (ARRY-543 Monotherapy, 400 mg BID)
  - Significant activity in MBC associated with HER2 expression
  - The patients with the highest percent regression of target lesions were positive for both EGFR & HER2



ARRY-543/ Varlitinib

- Potent, reversible, oral and selective ErbB family inhibitor
- Favorable clinical PK
  - Clinical exposures predict >90% inhibition of EGFR and ErbB2
- Demonstrated acceptable / competitive safety profile when dosed as monotherapy or in combination with chemotherapeutic agents
- Demonstrates evidence of clinical activity in both $ErbB2^{+}$ and $EGFR^{+}$ cancers
- Opportunity to differentiate as first-in-class in “dual-responsive” tumor types

ARRY-543 Contributors
Special thanks to our patients and their families

Clinical Investigators

- Dr. Meyer – Vanderbilt University
- Dr. Gelmon – BCCA – Vancouver
- Dr. Cohen – Fox Chase Cancer Center
- Dr. Ellard – BCCA-Kelowna
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- Dr. Jonker – Ottawa Cancer Centre
- Dr. Hotte – Juravinski Cancer Centre
- Dr. Weekes – University of Colorado
- Dr. Infante – Sarah Cannon Research Institute
- Dr. Wolpin – Dana-Farber Cancer Institute
- Dr. Camidge – University of Colorado
- Dr. Molina – Mayo Clinic
- Dr. Dent – Ottawa Cancer Centre
- Dr. Borges – University of Colorado
- Dr. Dy – Roswell Park
- Dr. Kwak – Mass General Hospital
- Dr. Gordon – Premiere Oncology - Arizona
- Dr. Rosen – Premier Oncology – Santa Monica

Everyone at Array BioPharma

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