ARRY-380, a Selective HER2 Inhibitor: From Drug Design to Clinical Evaluation

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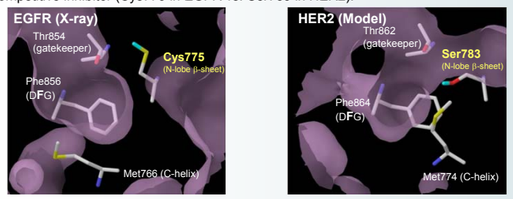
We Thank the Patients and Their Families

Introduction

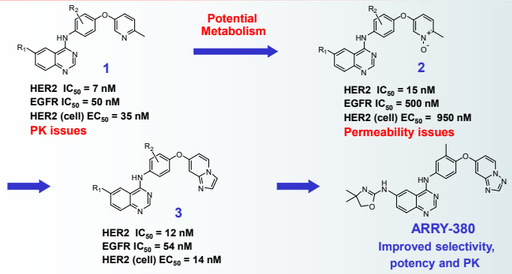
- EGFR and HER2 are closely related cell surface receptor tyrosine kinases that transduce growth signals and are involved in the carcinogenesis of many malignancies.
- HER2 is a validated and high-value target. Approximately 30% of breast cancers have an amplification of the *HER2/neu* gene or overexpression of its protein product, HER2.
- Overexpression of HER2 also occurs in gastric, colorectal, NSCLC and ovarian cancers.
- The goal of developing a selective drug that inhibits HER2 without EGFR-related side effects, such as rash and GI issues, is desirable, especially since it appears that inhibition of EGFR does not improve the efficacy of HER2-targeted therapy in patients with HER2+ metastatic breast cancer (MBC) (Arteaga, et al. Clin Cancer Res. 2008; 14(19):6277-83).

Designing a Selective HER2 Inhibitor

- Designing a selective, small-molecule HER2 inhibitor is challenging, as the ATP-binding pockets of EGFR and HER2 differ by only 2 amino acids and only 1 of these is involved with binding an ATP-competitive inhibitor (Cys775 in EGFR vs. Ser783 in HER2).



Small-Molecule Inhibitors: Optimization of HER2 Activity



- Compound **1**, with good HER2 potency in enzyme and cellular assays, had PK liabilities.
- Compound **1** also had the potential to be metabolized to form the N-oxide **2**, which, in turn, had poor permeability. However, **2** was discovered to have excellent HER2 selectivity.
- Incorporation of a bicyclic ring in order to block metabolism, as in compound **3**, provides good HER2 potency, but sub-optimal selectivity and PK properties.
- Combining all of the preferred structural elements provides ARRY-380, with improved HER2 selectivity, potency and PK properties.

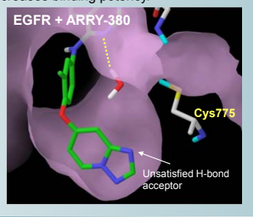
ARRY-380: a Potent and Selective HER2 Inhibitor

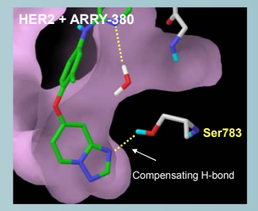
- ARRY-380 is an orally bioavailable, potent, selective, small-molecule tyrosine kinase inhibitor of HER2.
- ARRY-380 is a reversible, ATP-competitive inhibitor with nanomolar activity against HER2 enzyme. In cell-based assays, ARRY-380 is ~500-fold selective for HER2 vs. EGFR and is equipotent against truncated p95-HER2.
- In vivo, ARRY-380 significantly inhibits tumor growth in multiple HER2-dependent tumor xenograft models and showed additive activity in combination with standard-of-care agents.

Compound	Cellular Selectivity Data			
	HER2 IC_{50} (nM)	EGFR IC_{50} (nM)	p95 HER2 IC_{50} (nM)	HER2 IC_{50} (nM) 50% Human Serum
ARRY-380	**8**	**4000**	**7**	**67**
Neratinib	7	8	NT	39
Lapatinib	49	31	25	810

Proposed Binding Mode of ARRY-380

- The proposed binding mode of ARRY-380 to HER2 involves an interaction with a structural H_2O and a hydrogen bond with Ser783.
  - Ser783 in HER2 prefers a rotamer that allows interaction with ARRY-380.
  - Cys775 in EGFR prefers a rotamer that cannot interact with ARRY-380. A desolvation penalty decreases binding potency.





Phase 1 Clinical Evaluation of ARRY-380

- The objectives of this first-in-human Phase 1 dose-escalation and expansion study were to determine the maximum tolerated dose (MTD) and assess the safety, pharmacokinetics (PK), and preliminary efficacy of ARRY-380 in patients with advanced solid tumors that express the HER2 target.
- All data presented is as of September 1, 2011.

Dose-escalation Phase (3 + 3 design)

Schedule and Doses of ARRY-380*
In 28-day cycles:
25 mg to 800 mg BID
(starting on Cycle 1 D3)
*single QD dose on C1D1 only

Safety
DLTs and MTD
AEs, clinical laboratory tests, physical exams, vital signs, ECGs, ECHO/MUGA scans

Pharmacokinetics
Plasma samples
(Cycle 1: D1, D3, D15)

Efficacy
Tumor response via modified RECIST
(every 2 cycles)

Expansion Phase (HER2+ MBC patients)

Schedule and Dose of ARRY-380
In 28-day cycles:
600 mg BID
(MTD determined in dose escalation)

Safety
AEs, clinical laboratory tests, physical exams, vital signs, ECGs, ECHO/MUGA scans

Pharmacokinetics
Plasma samples
(Cycle 1: D15; Cycle 2: D1)

Efficacy
Tumor response via RECIST v1.1
(every 2 cycles)

Patient Demographics

	N = 50*
Gender (male/female), n	5/45
Median age (range), years	58 (31-77)
ECOG (0/1/2), n	16/31/3
Race (Asian/Black/Caucasian), n	4/4/42
Tumor type, n Breast (HER2+) Other (colorectal, salivary gland)	 43 7
HER2+ Breast Cancer, n Median age (range), years Median prior HER2 therapies for advanced disease (range), n Prior trastuzumab Prior lapatinib	43 56 (31-69) 4 (1-13) 100% 84%

* 33 patients in completed Dose-escalation Phase and 17 patients in ongoing Expansion Phase (enrollment is complete).

Safety Summary

- 50 patients overall have been evaluated for safety at doses of 25 to 800 mg BID ARRY-380.
- Two reversible Grade 3 DLTs (1 elevated AST and 1 elevated AST/ALT) at 800 mg BID, thus ***600 mg BID was declared the MTD.***
- All DLTs resolved with interruption of dosing and upon rechallenge at a lower dose, patients tolerated continued treatment with ARRY-380.
- Other non-DLT Grade 3 events: rash (n = 1), night sweats (n = 1), edema (n = 1), hypokalemia (n = 2), anemia (n = 1) .
- No Grade 4 treatment-related events have been reported.
- No cardiac AEs have been reported.
- Majority of treatment-related AEs have been Grade 1-2.
  - Only 1 patient had Grade 2 diarrhea (2%). No Grade 3 or 4 diarrhea reported.

Treatment-related AEs at Doses ≥ 200 mg BID (≥ 10% Pts)

	ARRY-380 Dose (BID)											
	200 mg n = 3		300 mg n = 3		500 mg n = 4		600/650 mg n = 27			800 mg n = 4		
Grade	1	2	1	2	1	2	1	2	3	1	2	3
Nausea	2	0	2	0	0	1	7	2	0	1	0	0
Diarrhea	1	0	2	0	0	0	6	1	0	1	0	0
Fatigue	0	2	0	0	1	0	2	3	0	0	0	0
Elevated AST/ALT	0	0	0	0	1	0	1	2	0	0	0	2
Rash	1	0	2	0	0	0	2	0	1	1	0	0
Vomiting	1	0	1	0	0	0	2	1	0	0	0	0

As of September 1, 2011

Best Response in All HER2+ MBC Patients at Doses ≥ 200 mg BID

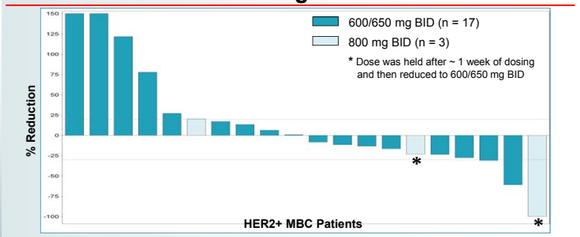
Investigator Assessment	ARRAY-380 Dose (BID), HER2+ MBC Pts (n)					
	200 mg n = 2	300 mg n = 1	500 mg n = 4	600/650 mg n = 27	800 mg n = 4	Total n = 38
PR	0	0	0	1	1*	2
PR + SD ≥ 6 months	0	0	1	3	1	5
Stable Disease						
< 6 months	1	1**	2	14**	1*	19
≥ 6 months	0	0	1	2	0	3
PD	1	0	1	9	1	12
Not Evaluable	0	0	0	1	1	2

* Dose was held after ~ 1 week of dosing and then reduced to 600/650 mg BID.
** Two patients had an unconfirmed PR (300 mg BID [1] and 600/650mg BID [1]).

Responses in HER2+ MBC Patients with Measurable Disease at Doses ≥ 600 mg BID

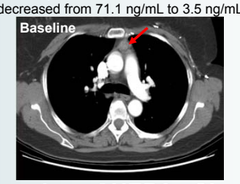
- Of the 29 HER2+ MBC patients evaluable for response at doses ≥ 600 mg BID, 20 had measurable disease. Of these 20 patients:
  - Partial Response (PR):
    - 2 patients (10%) had a confirmed PR.
    - 1 patient (5%) had an unconfirmed PR.
  - Stable Disease (SD):
    - 1 patient (5%) demonstrated SD ≥ 6 months.
    - 4 patients with SD continue on therapy.
  - Of patients with follow-up > 6 months (n = 17):
    - 17% of patients had either SD ≥ 6 months, PR or CR.

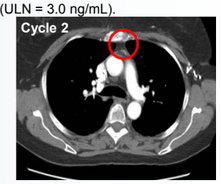
Waterfall Plot of Target Lesions in HER2+ MBC Patients at Doses ≥ 600 mg BID



Confirmed Partial Response in a HER2+ MBC Patient

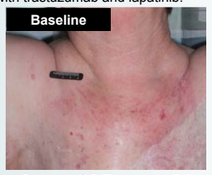
- Complete response in tumor lesions.
- CEA decreased from 71.1 ng/mL to 3.5 ng/mL (ULN = 3.0 ng/mL).

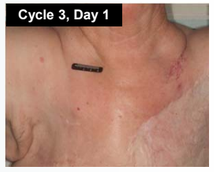




Regression of HER2+ Chest Wall Lesions

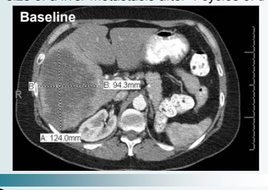
- Confirmed HER2+ chest wall lesions regressed in patient (650 mg BID) previously treated with trastuzumab and lapatinib.

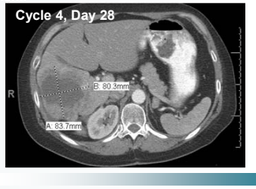




Regression of Visceral Lesions

- HER2+ breast cancer patient (200 mg BID), with prior trastuzumab, had reduction in size of a liver metastasis after 4 cycles of treatment.





Summary

- ARRY-380 is an oral, potent, selective, reversible, small-molecule inhibitor of HER2.
- The MTD of ARRY-380 was determined to be 600 mg BID.
- ARRY-380 has an acceptable safety profile with low incidence and severity of EGFR-related side effects (diarrhea, rash, fatigue).
- Preliminary signs of efficacy at doses ≥ 200 mg BID in heavily pre-treated HER2+ MBC pts.
- Future studies may include combinations with trastuzumab and/or chemotherapy.
- ARRY-380 has met the original design goal of HER2 selectivity, leading to an acceptable safety profile and preliminary signs of efficacy.