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Abstract
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Validation of a Novel Type II HER2 Inhibitor Through Preclinical Studies Across Various Cancer Models

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Introduction

- HER2 gene mutations and amplifications are common in breast, ovarian, stomach, and lung cancers
- Despite the development of multiple HER2 targeted therapies there remain significant unmet needs for patients with HER2-altered malignancies
- Residual EGFR inhibition constrains the therapeutic efficacy of existing pan-ERBB and HER2 inhibitors due to dose-limiting adverse effects
- Additionally, intrinsic compensatory pathways in HER2-driven malignancies may substantially increase the required exposure level for sustained pharmacological suppression of HER2 signaling in vivo
- Improved selectivity for HER2 over EGFR can mitigate dose-related toxicities linked to EGFR suppression, thereby enhancing the therapeutic window for HER2-targeted agents

Table 1: Higher selectivity threshold is needed for durable inactivation of HER2

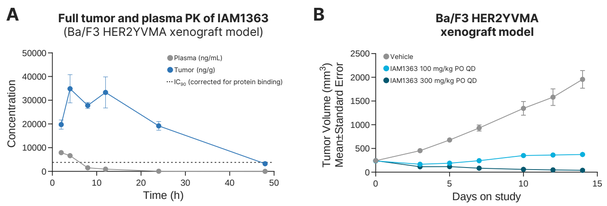
	Intracranial activity	Exon20 mutant activity	In vivo selectivity[1]	
			Cell pHER2 vs. pEGFR[7]	Biochemical HER2 vs. EGFR[8]
Tucatinib (Pfizer)	Marginal[2]	No[3]	**>1200**	-
Zongertinib (BI)	No[4]	**Yes**	-	20
ZN-1041 (Zion/Roche)[5]	**Yes**	No[6]	-	-
ELVN-002[5]	Moderate	**Yes**	180[9]	47[9]
NVL-330[5]	**Yes**	**Yes**	96[9,10]	-
IAM1363	**Yes**	**Yes**	**2800**	**5200**

1. Includes relative tumor exposure as measured by tumor/plasma $AUC_{0\text{-}12h}$ ratio (data reported in Iambic/Entos AACR 2023 poster).
2. Preclinical comparative analysis, see Figure 5C.
3. IC_{50} > 200nM in Ba/F3 HER2YVMA.
4. <0.01 brain-Kp, internal data.
5. Public data.
6. Presumed, based on non-covalent MOA and development plan.
7. Based on internal or public cell PD assay data in BT-474 (pHER2) and A431 (pEGFR), unless specified otherwise.
8. Based on internal or public data for kinact/Ki, see Figure 2D.
9. Tumor/plasma $AUC_{0\text{-}12h}$ ratio is unknown, assumed 1.
10. NCI-N87 (pHER2) from public data.

- In cancers driven by HER2, feedback loops sustain HER2 hyperactivation, potentially elevating the dose or exposure threshold required for clinical efficacy up to 1000-fold
- Tucatinib, the only approved HER2-selective TKI, has limited monotherapy efficacy in HER2+ tumors and potency against key HER2 mutants
- IAM1363 potently inhibits both the wild type and mutant forms of HER2, showing over 1000-fold selectivity against EGFR due to a unique binding mode not seen with other HER2 inhibitors. This leads to exceptional in vivo efficacy and tolerability in various HER2-driven cancer models, including those resistant to existing HER2-targeted agents.

Results

Figure 1: IAM1363 exhibits enriched tumor distribution in HER2-driven models



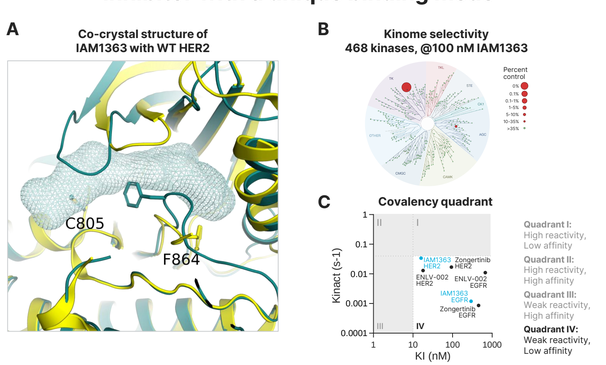
C

IAM1363: High tumor-Kp across HER2-driven tumor models

TGI model	Ba/F3 HER2YVMA		HCC1954	
	IAM1363	Poziotinib	IAM1363	Zongertinib
4 h	3.1	0.36	16.4	0.3
12 h	68	NA	119	0.7

Figure 1. IAM1363 demonstrates a preferential tumor tissue distribution profile. (A) IAM1363 exhibits sustained enriched tumor exposure after a single PO dose at 300 mg/kg in BaF3 HER2YVMA xenograft model. (B) IAM1363 treatment led to significant tumor regression at 300 mg/kg dose level in the Ba/F3 HER2YVMA tumor model. (C) The improved tumor exposure resulted in high tumor-Kp in multiple HER2-driven models (selected data shown). The high tumor-Kp is a differentiated property of IAM1363 and not observed with other HER2 inhibitors such as Zongertinib or Poziotinib. Enriched tumor targeting yields >1000x HER2/EGFR selectivity window. All three are covalent inhibitors.

Figure 2: IAM1363 is a potent and selective inhibitor with a unique binding mode



D

Enzyme inactivation kinetic parameters

	HER2			EGFR			Kinetic EGFR/HER2 selectivity
	Kinact (s^{-1})	Ki (nM)	kinact/Ki (M^{-1} s^{-1})	Kinact (s^{-1})	Ki (nM)	kinact/Ki (M^{-1} s^{-1})	
IAM1363	3.4E-02	16	2.2E+06	1.2E-03	293	4.2E+03	515
Zongertinib	1.7E-02	94	1.8E+05	8.6E-04	455	1.9E+03	93
ELVN-002*	1.3E-02	18	7.3E+05	1.1E-02	676	1.6E+04	47

Data from COVALfinder® (TR_FRET based binding assay) performed at Enzymlogic.
*From AACR 2023 poster #4019.

Figure 2. IAM1363 is a highly selective type II kinase inhibitor. (A) IAM1363 is a covalent HER2 inhibitor binding to the inactive DFG-out conformation of HER2 WT. A co-crystal structure (3.4Å) of IAM1363 (teal) is overlaid with PDB structure 7PCD (yellow). (B) IAM1363 is selective in KINOMEscan scanMAX (Eurofins). (C) IAM1363 and reference molecules compared in covalency quadrant. (D) IAM1363 demonstrates enhanced HER2/EGFR kinetic selectivity vs. reference molecules.

Figure 3: IAM1363 overcomes resistance to HER2 ADC demonstrated in Ba/F3 p95HER2 xenograft

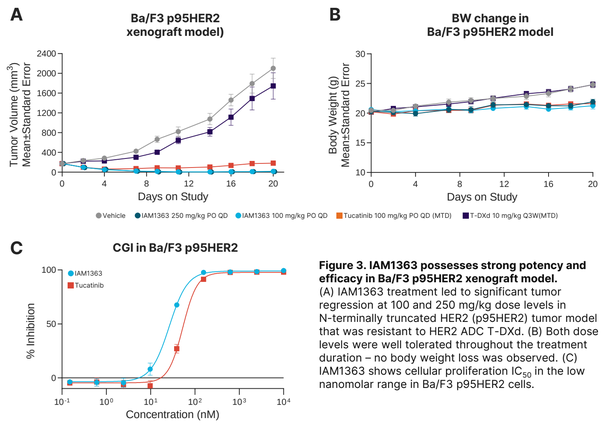
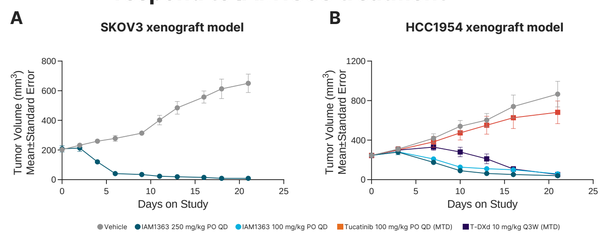


Figure 3. IAM1363 possesses strong potency and efficacy in Ba/F3 p95HER2 xenograft model. (A) IAM1363 treatment led to significant tumor regression at 100 and 250 mg/kg dose levels in N-terminally truncated HER2 (p95HER2) tumor model that was resistant to HER2 ADC T-DXd. (B) Both dose levels were well tolerated throughout the treatment duration – no body weight loss was observed. (C) IAM1363 shows cellular proliferation IC_{50} in the low nanomolar range in Ba/F3 p95HER2 cells.

Figure 4: Tumors harboring PI3K and KRAS mutations respond to IAM1363 treatment



C

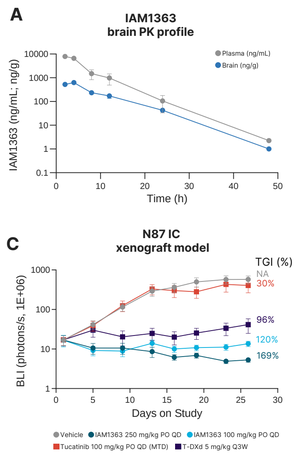
IAM1363 efficacy in TGI models

Model	Indication	ERBB2 copy number[1]	PIK3CA mutation status	KRAS mutation status	TGI
BT474	Breast	3.64	K111N	N	192%
N87	Gastric	5.27	N	N	120%
HCC1954	Breast	5.88	H1047R	N	176%
KYSE410	Esophageal	5.26	N	G12C	192%
SKOV3	Ovarian	2.26	H1047R	N	195%#
Calu3	Lung	5.1	N	N	180%#
HCC827	Lung	1.41	N	N	191%#
MFE-280	Endometrial	1.89	H1047Y	N	88%#
H2122	Lung	1.15	N	G12C	63%
A549	Lung	1.28	N	G12S	71%#
A431	Epidermoid	1.10	N	N	78%#

1. Log_2(relative to ploidy + 1)

Figure 4. IAM1363 is efficacious across a broad range of HER2-driven tumor models. (A) A deep regression achieved in PIK3CA H1047R mutant SKOV3 TGI model. (B) Stronger efficacy demonstrated by IAM1363 compared to reference compounds in PIK3CA H1047R mutant HCC1954 TGI model. (C) IAM1363 (100 mg/kg PO QD or 250 (#) mg/kg PO QD) is efficacious in models with variable levels of HER2 expression and co-occurring mutations.

Figure 5: Regression and favorable brain PK in intracranial tumor treated with IAM1363



B

IAM1363 brain Kp,uu

	mouse	monkey[1]
	IAM1363	IAM1363
2 h	0.29	0.31
6-8 h	0.36	0.40

[1]CSF concentrations were treated as free concentration in the brain

Figure 5. IAM1363 is brain permeable and shows efficacy in IC models. (A) IAM1363 has sustained brain exposures in mouse at 300 mg/kg measured in Ba/F3 HER2YVMA tumor bearing mice, samples collected at the time period from 2 to 48 hours after dosing. (B) IAM1363 is brain penetrant in mouse (CD-1) and monkey (cyno). (C) IAM1363 treatment led to the regression of N87 intracranial tumors at 250 mg/kg (QD, PO), in comparison to the tumor static effect of T-DXd (5 mg/kg, Q3W).

Conclusion

- IAM1363 binds to HER2 through the DFG-out conformation, previously unseen for this target
- The mechanism underlies its unparalleled selectivity, including > 500-Fold kinetic selectivity vs. EGFR
- IAM1363 demonstrates efficacy in a broad spectrum of xenograft models with different levels of HER2 amplification, mutations and coexisting mutations in other genes
- IAM1363 is by far the only disclosed HER2 small molecule inhibitor that demonstrates sustained intra-tumoral exposure, with a PK/tumor-Kp profile that predicts for better target engagement with fewer off-target effects
- IAM1363 is brain penetrant and causes regression of intracranial tumors
- IAM1363 is currently being evaluated in Phase 1/1b clinical trial (NCT06253871)

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