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IAM1363 is a Potent, Selective, and Irreversible HER2 and Pan-HER2 Mutant Small Molecule Inhibitor for the Treatment of HER2-Driven NSCLC

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Abstract 1322

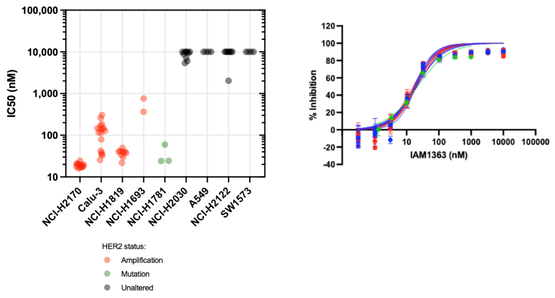
Introduction

HER2 alterations, including gene amplification and activating mutations, occur in approximately 3-5% of non-small cell lung cancer (NSCLC) cases. Currently approved HER2-targeted therapies, such as trastuzumab deruxtecan (T-DXd), demonstrate clinical activity but show limited response durability and are associated with significant treatment-related toxicities, including interstitial lung disease. Moreover, existing HER2 kinase inhibitors often exhibit dose-limiting toxicities driven by collateral EGFR inhibition due to structural homology between EGFR and HER2, emphasizing the urgent unmet need for more selective and effective therapies.

IAM1363 is a novel, potent, irreversible, and highly selective Type II small molecule inhibitor specifically targeting HER2 and pan-HER2 mutants. IAM1363 achieves superior selectivity (>5,000-fold) for HER2 over EGFR, minimizing the potential for EGFR-related toxicities. IAM1363 is brain-penetrant and demonstrates activity in the central nervous system (CNS). It also exhibits a preferential tumor-enrichment property, providing long-lasting, tumor-specific exposure with sustained HER2 target coverage and extended pharmacological activity.

Figure 1: *In Vitro* Response to IAM1363 in NSCLC Cell Lines

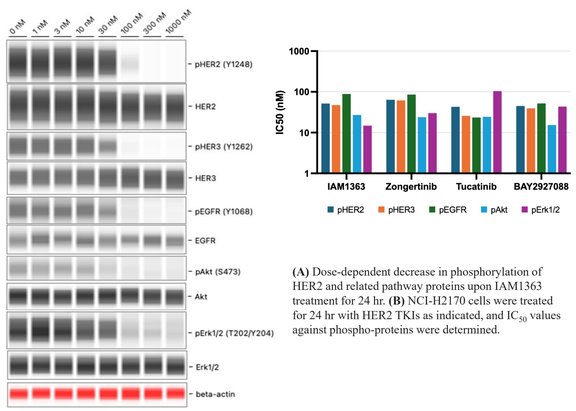
(A) CGI in NSCLC cell panel **(B) Dose response in NCI-H2170 cell**



IAM1363 shows selective activity in HER2-altered NSCLC cell lines. **(A)** IC_{50} on CGI (cell growth inhibition) reveals potent inhibition in HER2-amplified or HER2-mutant lines, while minimal response is observed in HER2-unaltered cell lines. **(B)** Dose-response analysis on CGI in NCI-H2170 cell (triplicate tests).

Figure 2: *In Vitro* PD Effects of IAM1363 in NCI-H2170 Cell

(A) Phospho-protein analysis **(B) PD modulation by HER2 TKIs**

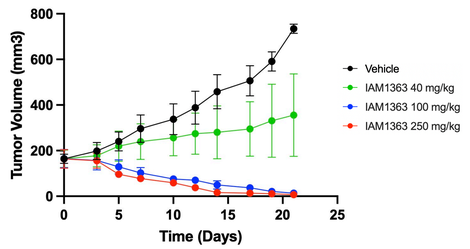


(A) Dose-dependent decrease in phosphorylation of HER2 and related pathway proteins upon IAM1363 treatment for 24 hr. **(B)** NCI-H2170 cells were treated for 24 hr with HER2 TKIs as indicated, and IC_{50} values against phospho-proteins were determined.

Results

Figure 3: IAM1363 Induced Tumor Regression in HER2-amplified NSCLC Xenograft Models

(A) NCI-H2170

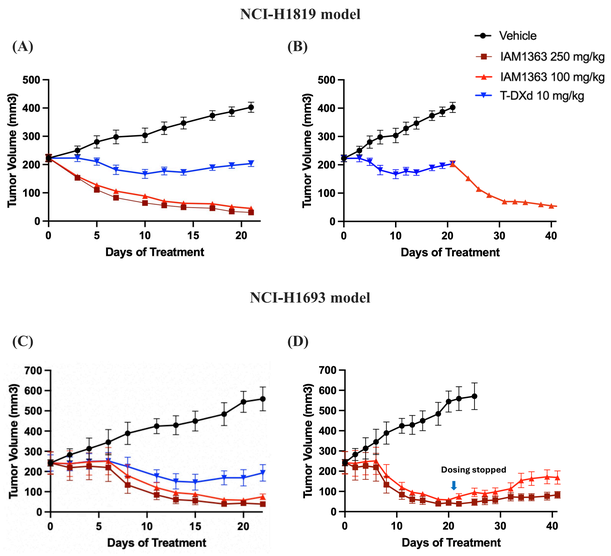


(B) HER2-amplified NSCLC models

	NCI-H2170	Calu-3	NCI-H1819	NCI-H1693
HER2 gene CN	5.5	5.1	3	2.07
HER2 mRNA	11.2	10.3	9.8	5.9
Tumor regression	-96%	-75%	-92%	-82%

(A) Tumor response in the HER2-amplified NSCLC NCI-H2170 xenograft model treated with IAM1363 at doses of 40, 100, or 250 mg/kg PO QD, demonstrating dose-dependent tumor regression. **(B)** Table summarizing HER2 gene copy number (log2(relative to ploidy+1)), HER2 mRNA expression levels (CCLE), and percent tumor regression across four HER2-amplified NSCLC xenograft models (copy number and expression data from CCLE). Tumor regression was observed in all models.

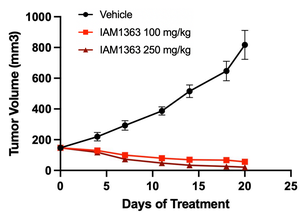
Figure 4: IAM1363 Demonstrates Superior Anti-tumor Activity Over T-DXd in HER2-amplified NSCLC Xenograft Models



(A) Mice bearing NCI-H1819 xenografts were treated with IAM1363 (PO QD) or T-DXd (IV Q3W). IAM1363 treatment induced marked tumor regression, whereas T-DXd caused tumor stasis. **(B)** Sequential administration of T-DXd followed by IAM1363 (starting Day 21) resulted in tumor regression, suggesting superior activity of IAM1363. **(C)** Mice bearing NCI-H1693 xenografts were treated with IAM1363 (PO QD) or T-DXd (IV Q3W). Both IAM1363 doses induced deep and sustained tumor regression, superior to modest efficacy by T-DXd. **(D)** After cessation of treatment on Day 21, the IAM1363 treated groups exhibited prolonged post-treatment tumor suppression.

Figure 5: IAM1363 Demonstrates Potent Anti-tumor Activity in HER2-mutant NSCLC Xenograft Models

(A) NSCLC PDX model (HER2 YVMA) **(B) Two HER2-mut NSCLC models**

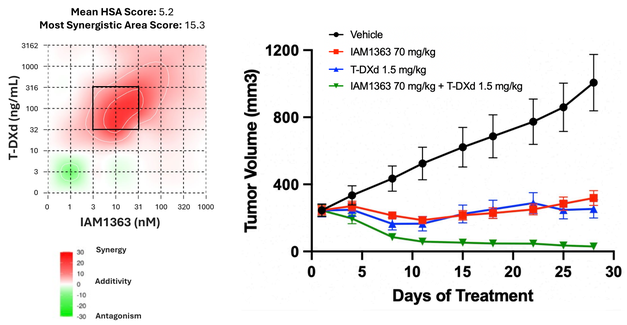


	LU11717	NCI-H1781
Type	PDX	CDX
HER2 mutation	Exon 20 YVMA	Exon 20 VC
Tumor regression	-85%	-90%

In vivo efficacy of IAM1363 was evaluated in HER2 exon 20 insertion mutant NSCLC models. **(A)** Tumor growth inhibition in a HER2 A775_G776insYVMA mutant PDX model (LU11717) treated with IAM1363 (PO QD). **(B)** Summary of tumor regression (%) in two HER2 exon 20 insertion models.

Figure 6: Synergy of IAM1363 + T-DXd Combination in HER2-mut NSCLC NCI-H1781 *In Vitro* and *In Vivo*

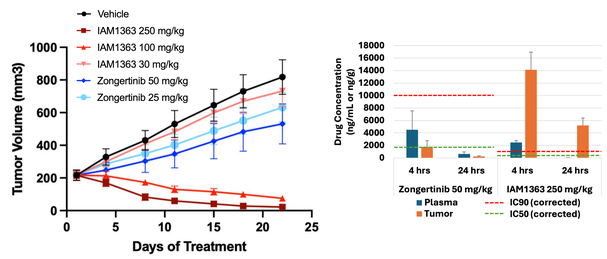
(A) *In vitro* **(B) *In vivo***



(A) Combination of IAM1363 with T-DXd in NCI-H1781 cell is synergistic. The highest single agent (HSA) score was calculated using SynergyFinder+ software and the most synergistic area is outlined in the middle of the synergy map. **(B)** Mice with NCI-H1781 NSCLC xenografts were treated with IAM1363 (PO QD) , T-DXd (IV Q3W) , or their combination for 28 days. Tumor volumes were shown. The combination regimen was well tolerated. Combination of IAM1363 with T-DXd in NCI-H1781 showed synergistic effect ($p < 0.05$).

Figure 7: IAM1363 Has Superior Activity in HER2-mut NSCLC NCI-H1781 Xenograft Model

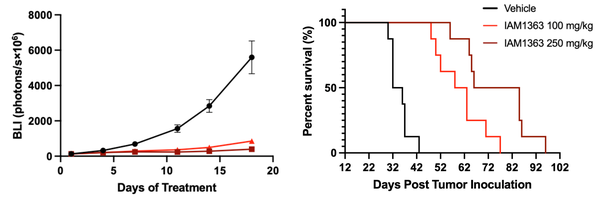
(A) Tumor growth inhibition **(B) Tumor/plasma exposure**



(A) Tumor growth in H1781 xenografts treated with IAM1363 (PO QD) or zongertinib (PO QD). IAM1363 caused dose-dependent tumor regression, compared to tumor growth inhibition only by zongertinib. **(B)** Drug concentrations in plasma and tumor at 4- and 24-hours post-dosing. IAM1363 achieved superior tumor enrichment versus zongertinib, with sustained intratumoral levels exceeding protein-binding-adjusted IC_{90} thresholds.

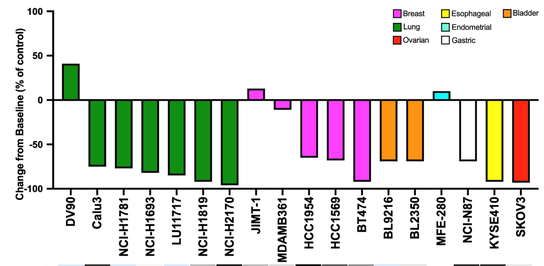
Figure 8: IAM1363 Demonstrates CNS Anti-tumor Activity in Intracranial HER2-amplified NSCLC Calu-3 Model

(A) Tumor growth inhibition **(B) Survival curve**



(A) Calu-3-luc human lung cancer cells (HER2+) were stereotactically injected into the forebrain of female mice. Mice were treated with IAM1363 at 100 or 250 mg/kg for up to 84 days. Tumor burden was assessed using bioluminescence imaging (BLI), and **(B)** survival was monitored.

Figure 9: Anti-tumor Activity of IAM1363 in Human Tumor Xenograft Models with HER2 Amplification or Mutation



ERBB2 Alteration: CN or mutation	a	5.1	b	2.07	c	3	5.5	3	2.5	5.88	4.5	3.64	d	2.3	1.89	5.27	5.26	2.26
PIK3CA mutation	N	N	N	N	N	N	N	Y	Y	Y	N	Y	N	N	Y	N	N	Y
Kras mutation	Y	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	Y	N
Myc-amplification	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N
Cell cycle pathway dysregulation	N	Y	N	N	N	N	Y	N	N	N	Y	N	N	N	N	N	N	Y

Key: ERBB2 Copy Number: log2(relative to ploidy+1), a: HER2 V842I, b: HER2 exon 20 VC, c: HER2 exon 20 YVMA, d: HER2 S310F

IAM1363 was administered at 250 mg/kg PO QD to mice bearing human tumor cell line xenografts or PDX as indicated. Percent change from baseline tumor volume relative to vehicle-treated controls was calculated between Days 19–22 across models. HER2 status was evaluated via ERBB2 copy number and specific HER2 mutations. Additional genomic alterations are annotated for PIK3CA, KRAS, Myc, and cell cycle regulators commonly found in human NSCLC with HER2 overexpression.[1]

Conclusions

- IAM1363 exhibits potent anti-tumor activity in HER2-amplified NSCLC models, demonstrating strong *in vitro* inhibition of cell growth and robust pharmacodynamic target engagement.
- *In vivo* studies show broad efficacy, with significant tumor regression across multiple HER2-amplified NSCLC models and superior brain metastasis control in the intracranial model.
- IAM1363 outperforms current standards including T-DXd and zongertinib in HER2-amplified and mutant NSCLC tumors, with improved tumor penetration despite lower plasma exposure.
- Efficacy is retained across genetically diverse backgrounds, remaining active regardless of common co-mutations (e.g., TP53, EGFR, PIK3CA, CDK, Myc), highlighting its robustness.
- Combination studies support synergistic potential, with IAM1363 and T-DXd showing enhanced anti-tumor effects both *in vitro* and *in vivo* in HER2-mutant NSCLC models.

References:
- Hong, L., et al. (2024). Molecular landscape of ERBB2 alterations in 3000 advanced NSCLC patients. NPJ Precis Oncol. 8(1):217
- Kulyk L, et al. 2024 AACR.
- Zhao C., et al. 2023 AACR