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A Phase 1/1b Study of IAM1363, a selective and brain penetrant HER2 inhibitor in participants (pts) with advanced cancers harboring HER2 alterations

Clinical Trial information:
NCT06253871

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Background

Current HER2-directed Therapies

- While HER2-directed therapies have significantly improved outcomes for patients with metastatic HER2-altered tumors, these diseases remain largely incurable
- Control of CNS disease is also a pressing need, driving the development of novel CNS penetrant HER2-directed agents
- Approved HER2-directed TKIs are limited by significant off-target toxicity, minimal penetration across the blood brain barrier, and demonstrated benefit confined to either wild type or mutated HER2 disease

IAM1363: Selective & Brain Penetrant TKI with Broad Activity Against HER2

- IAM1363 potently and irreversibly inhibits wild type and TKD mutant HER2
- Active in the CNS, and 10 times more brain penetrant than tucatinib
- >5000-fold selectivity for HER2 over EGFR
- Exhibits tumor enrichment: high tumor/plasma ratio & longer half life in the tumor
- Selectivity and tumor enrichment profile maximize target engagement in tumor, potentially mitigating toxicity

Methods

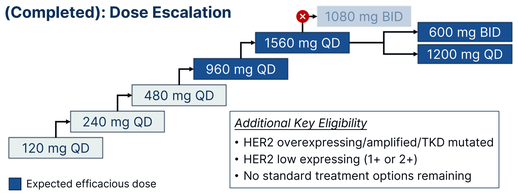
IAM1363-01 Study Design (Four Parts)

Key Eligibility Criteria (all parts)

- HER2-altered advanced cancers*
- Radiographically measurable disease by either/both of the following:
  - CNS disease: RANO-BM
  - Non-CNS disease: RECIST v1.1
- CNS metastases allowed†
- Measurable disease per modified RANO-BM: target lesions ≥5 mm
- Leptomeningeal and other non-measurable disease allowed

*Definition of HER2 alteration varies by study part
†Provided local therapy not indicated

Part 1 (Completed): Dose Escalation



Additional Key Eligibility
- HER2 overexpressing/amplified/TKD mutated
- HER2 low expressing (1+ or 2+)
- No standard treatment options remaining

Enrolling

Part 2: IAM1363 Monotherapy Dose Optimization

1:1 Ratio → 960 mg QD / 1200 mg QD

Additional Key Eligibility
- HER2+ per ASCO/CAP
- HER2 amplified per NGS
- HER2 TKD mutant
- Prior T-DXd allowed; no prior TKI in the metastatic setting*

*Participants with BC are allowed to have received prior tucatinib

Part 4: Combination Therapy Breast Cancer Cohorts

Cohort 4A
IAM1363 + Trastuzumab + Capecitabine

Cohort 4B
IAM1363 + Zanidatamab + Capecitabine

Additional Key Eligibility
- HER2+ per ASCO/CAP
- Prior T-DXd required; prior TKI in metastatic setting, including tucatinib, prohibited

Recommended Dose (Monotherapy)

Part 3 (Pending Recommended Dose): Monotherapy Expansion Basket Cohorts

Cohort A:
HER2 TKD mutant cancers; no prior TKI

Cohort B:
HER2+/amplified cancers, no prior TKI

Cohort C:
HER2 TKD mutant & HER2+/amplified cancers; prior TKI required

For more information about this poster please contact sreenivasa.chandana@startresearch.com

Disclosures
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Results

Disposition/Demographics

- As of the DCO date of 12Sep25, 39 participants were enrolled, 30 in Part 1 and 9 in Part 2
- Median age 62 years (range, 29-79), 54% female
- 77% White, 10% Black, 10% Asian, 3% "Other"
- Overall, 72% (28/39) have discontinued treatment, the majority (75%; 21/28) due to disease progression

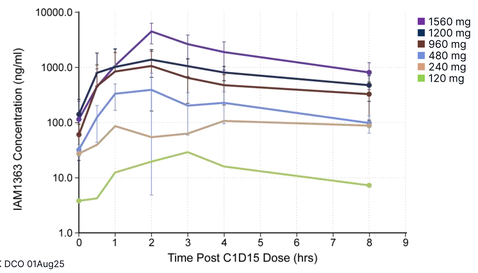
Baseline Disease Characteristics & Prior Therapies

	IAM1363 Dose Level							
	120 mg QD (N=1)	240 mg QD (N=1)	480 mg QD (N=4)	960 mg QD (N=17)	1200 mg QD (N=10)	600 mg BID (N=3)	1560 mg QD (N=3)	Total (N=39)
Primary Tumor Type, n (%)								
Breast	0	1 (100%)	1 (25%)	5 (29%)	3 (30%)	0	2 (67%)	12 (31%)
Colorectal	1 (100%)	0	1 (25%)	2 (12%)	1 (10%)	0	0	5 (13%)
NSCLC	0	0	0	3 (18%)	0	2 (67%)	0	5 (13%)
Gynecologic*	0	0	0	0	3 (30%)	1 (33%)	0	4 (10%)
GEA	0	0	1 (25%)	1 (6%)	0	0	1 (33%)	3 (8%)
Pancreatic	0	0	1 (25%)	1 (6%)	1 (10%)	0	0	3 (8%)
Other†	0	0	0	5 (29%)	2 (20%)	0	0	7 (18%)
CNS Metastases, n (%)	0	1 (100%)	0	5 (29%)	3 (30%)	1 (33%)	2 (67%)	12 (31%)
HER2 Alteration‡								
Overexpressing/Amplified	1 (100%)	0	4 (100%)	7 (41%)	6 (60%)	1 (33%)	2 (67%)	21 (54%)
IHC3+	1/1	0	3/4	6/7	4/6	0	1/2	15/21
Amplified	0	0	1/4	1/7	2/6	1/1	1/2	6/21
Mutated	0	0	0	4 (24%)	3 (30%)	2 (67%)	1 (33%)	10 (26%)
Other	0	1 (100%)	0	6 (35%)	1 (10%)	0	0	8 (21%)
Prior regimens§, median (range)	3 (NA)	4 (NA)	4.5 (2-8)	3 (1-6)	3 (1-6)	3 (1-3)	5 (2-7)	3 (1-8)
Prior HER2-directed regimens§, median (range)	1 (NA)	1 (NA)	2.5 (1-4)	2 (1-6)	2 (1-5)	1.5 (1-2)	4 (2-4)	2 (1-6)
Specific prior HER2-directed agents, n (%)								
T-DXd	0	1 (100%)	4 (100%)	8 (47%)	4 (40%)	2 (67%)	2 (67%)	21 (54%)
Trastuzumab	1 (100%)	0	3 (75%)	5 (29%)	4 (40%)	0	3 (100%)	16 (41%)
Tucatinib	0	0	1 (25%)	5 (29%)	3 (30%)	0	2 (67%)	11 (28%)
Pertuzumab	1 (100%)	0	2 (50%)	3 (18%)	2 (20%)	0	1 (33%)	9 (23%)
T-DM1	0	0	0	2 (12%)	0	0	2 (67%)	4 (10%)
Afatinib	0	0	0	0	0	1 (33%)	0	1 (3%)
Lapatinib	0	0	0	1 (6%)	0	0	0	1 (3%)
Zanidatamab	0	0	0	1 (6%)	0	0	0	1 (3%)
Investigational¶	0	0	1 (25%)	1 (6%)	1 (10%)	0	0	3 (8%)

*Includes cervical, endometrial, and ovarian cancers. †One participant each with bladder, intestinal-type adenocarcinoma, kidney, liver, prostate, salivary gland, and small bowel cancer. ‡By local testing. §All in the metastatic setting. ¶Three participants received experimental HER2-directed therapies—BDC-01001, HF158K1 and TAS2940.

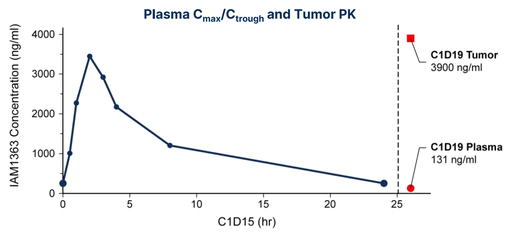
Pharmacokinetics

PK Exposures at Steady State by Dose Level



PK DCO 01Aug25

Tumor Enrichment PK Profile



- Paired tumor biopsy and PK draw performed in participants treated at 120 mg QD and 1560 mg QD IAM1363
- ≥20-fold enrichment in tumor vs plasma demonstrated in both participants
- Data shown from participant treated at 1560 mg QD

Safety

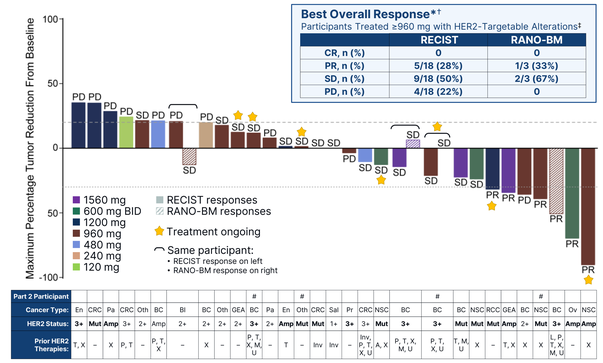
TEAEs Reported in ≥10% of Participants by Preferred Term

	IAM1363 Dose Level							
	120 mg QD (N=1)	240 mg QD (N=1)	480 mg QD (N=4)	960 mg QD (N=17)	1200 mg QD (N=10)	600 mg BID (N=3)	1560 mg QD (N=3)	Total (N=39)
Nausea, n (%)								
Any Grade	0	1 (100%)	2 (50%)	6 (35%)	6 (60%)	2 (67%)	2 (67%)	19 (49%)
≥ Grade 3*	0	0	0	0	0	0	0	0
Diarrhea, n (%)								
Any Grade	0	0	0	6 (35%)	5 (50%)	3 (100%)	2 (67%)	16 (41%)
≥ Grade 3*	0	0	0	0	0	0	2 (67%)	2 (5%)†
Vomiting, n (%)								
Any Grade	0	0	1 (25%)	5 (29%)	1 (10%)	3 (100%)	2 (67%)	12 (31%)
≥ Grade 3*	0	0	0	0	0	0	0	0
Fatigue, n (%)								
Any Grade	0	0	1 (25%)	4 (24%)	1 (10%)	0	1 (33%)	7 (18%)
≥ Grade 3*	0	0	0	0	0	0	0	0
Hypokalemia, n (%)								
Any Grade	0	1 (100%)	0	2 (12%)	1 (10%)	0	1 (33%)	5 (13%)
≥ Grade 3*	0	1 (100%)	0	0	0	0	0	1 (3%)
Anemia, n (%)								
Any Grade	0	0	0	2 (12%)	2 (20%)	0	0	4 (10%)
≥ Grade 3*	0	0	0	0	2 (20%)	0	0	2 (5%)‡
Decreased appetite, n (%)								
Any Grade	0	0	1 (25%)	1 (6%)	1 (10%)	0	1 (33%)	4 (10%)
≥ Grade 3*	0	0	0	0	0	0	0	0
Dehydration, n (%)								
Any Grade	0	1 (100%)	0	1 (6%)	1 (10%)	0	1 (33%)	4 (10%)
≥ Grade 3*	0	0	0	0	1 (10%)	0	0	1 (3%)

*All AEs Grade 3 only (no Grade 4 or 5 AEs). †Both events of Grade 3 diarrhea in the 1560 mg dose level resolved after dose hold and initiation of anti-diarrheal medication. ‡Neither event of Grade 3 anemia was assessed as related to IAM1363 by the Investigator.

Efficacy: Best Reduction in Target Lesion by Dose Level

RECIST and RANO-BM Evaluable Participants*



Best Overall Response*†
Participants Treated ≥960 mg with HER2-Targetable Alterations‡

	RECIST	RANO-BM
CR, n (%)	0	0
PR, n (%)	5/18 (28%)	1/3 (33%)
SD, n (%)	9/18 (50%)	2/3 (67%)
PD, n (%)	4/18 (22%)	0

Part 2 Participant																														
Cancer Type:	En	CRC	Pa	CRC	Oth	BC	BI	BC	Oth	GEA	BC	Pa	En	Oth	CRC	Sal	Pr	CRC	NSC	BC	BC	BC	NSC	RCC	GEA	BC	NSC	BC	Ov	NSC
HER2 Status:	3+	Mut	Amp	3+	2+	Amp	2+	2+	2+	2+	3+	2+	Amp	Mut	Mut	1+	3+	3+	Mut	3+	3+	Mut	Mut	Mut	Mut	Amp	2+	Mut	3+	Amp	Amp
Prior HER2 Therapies:	T, X	–	X	P, T	–	P, T, X	–	X	–	–	P, T, X, M, U	–	T	–	Inv	Inv	–	Inv, P, T, X, U	A, X	P, T, X, M, U	P, T, X, U	T, M, U	X	–	T, X	X	X	L, P, T, X, M, U	–	X

*Includes participants with measurable disease and at least 1 post-baseline scan
†Includes confirmed and unconfirmed responses.
‡HER2-targetable alterations defined as IHC 3+, amplified or mutated and bolded in table above.

Cancer Type legend: BC, breast cancer; BI, bladder cancer; CRC, colorectal cancer; En, endometrial cancer; GEA, gastric and gastroesophageal cancers; NSC, non-small lung cancer (NSCLC); Oth, other (includes small bowel, cholangiocarcinoma, intestinal-type adenocarcinoma, and cervical cancer); Ov, ovarian cancer; Pa, pancreatic cancer; Pr, prostate cancer; RCC, renal cell carcinoma; Sal, salivary gland cancer.

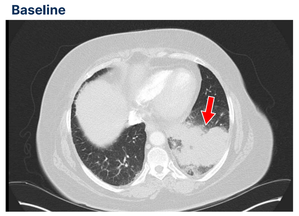
HER2 Status legend: 1+ 2+ 3+, immunohistochemistry (IHC); Amp, HER2 amplified; Mut, HER2 mutated; Oth, other HER2 status.

Prior HER2 Therapies legend: A, afatinib; Inv, investigational; L, lapatinib; M, T-DM1; P, pertuzumab; T, trastuzumab; U, tucatinib; X, T-DXd; Z, zanidatamab.

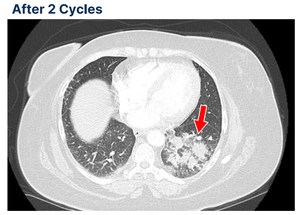
Case Study

- 65yo black female, metastatic HER2-amplified NSCLC
- Prior therapies included carboplatin, pemetrexed, nivolumab, T-DXd
- All TRAES were Grade 1 or 2
- PR after 2 cycles of IAM1363 (960 mg QD), response ongoing at >6 mos

Baseline



After 2 Cycles

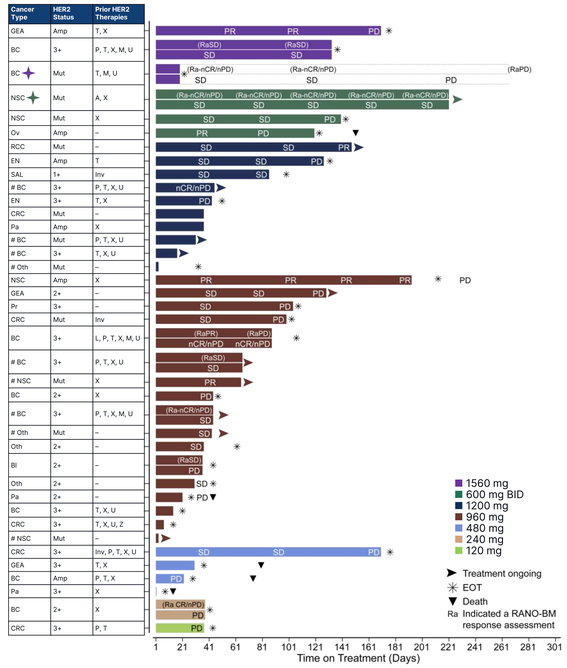


Key Safety Findings

- The majority of TEAEs were low grade
- Only 1 discontinuation of IAM1363 due to a TRAE that occurred in a Part 1 participant who experienced a DLT of Grade 3 diarrhea and was therefore required to stop study treatment
- No TRSAEs and no deaths due to AEs
- In Part 1, no DLTs until 1560 mg. This dose declared the MAD because of 2 events of Grade 3 diarrhea, one of which was a DLT (lasting >72 hours) and the other a near DLT (lasting <72 hours).
- In participants treated at 960 mg and 1200 mg, the most common TRAEs in ≥10% of participants were nausea (41%), diarrhea (41%), vomiting (22%), and fatigue (18%), all Grade 1 or 2; no ≥ Grade 3 TRAEs reported

Efficacy: Treatment Duration by Dose Level

All Treated Participants



Participant required to discontinue IAM1363 after DLT in C1; CNS and systemic disease stability >6 mos with no intervening anti-cancer therapy
Participant with LMD and CNS and systemic disease stability ongoing at >7 mos

Conclusions

- IAM1363 was well-tolerated across dose levels, with low grade TEAEs at therapeutic doses
- At an early interim evaluation, IAM1363 demonstrates promising monotherapy activity in heavily pretreated participants
- IAM1363 was active across both HER2 wild type and mutated cancers, across multiple disease types, including indications without approved HER2-directed therapies (amplified NSCLC and ovarian cancer)
- Majority of responses seen post-treatment with T-DXd; CNS response seen in a participant with BC post T-DXd and tucatinib
- Tumor enrichment profile, with ≥20-fold higher concentration of IAM1363 in tumor vs plasma, a potential contributor to IAM1363's promising safety and efficacy profile

Abbreviations: AE, adverse event; ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BC, breast cancer; BID, twice daily; C_{max}, maximum concentration; C_{trough}, trough concentration; CNS, central nervous system; CRC, colorectal cancer; DCO, data cutoff; DCR, disease control rate; DLT, dose-limiting toxicity; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EOT, end of treatment; GEA, gastric/gastroesophageal adenocarcinoma; IHC, immunohistochemistry; LMD, leptomeningeal disease; MAD, maximum administered dose; nCR/nPD, non-CR/non-PD; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; PK, pharmacokinetic; PR, partial response; QD, daily; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; RCC, renal cell carcinoma; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; T-DM1, ado-trastuzumab emtansine; T-DXd, fam-trastuzumab deruxtecan-nxki; TEAE, treatment-emergent adverse event; TKD, tyrosine kinase domain; TKIs, tyrosine kinase inhibitors; TRAE, treatment-related adverse event; TRSAEs, treatment-related serious adverse events.

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