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IAM1363-01: A Phase 1/1b Study of a Selective and Brain-Penetrant HER2 Inhibitor for HER2-Driven Solid Tumors

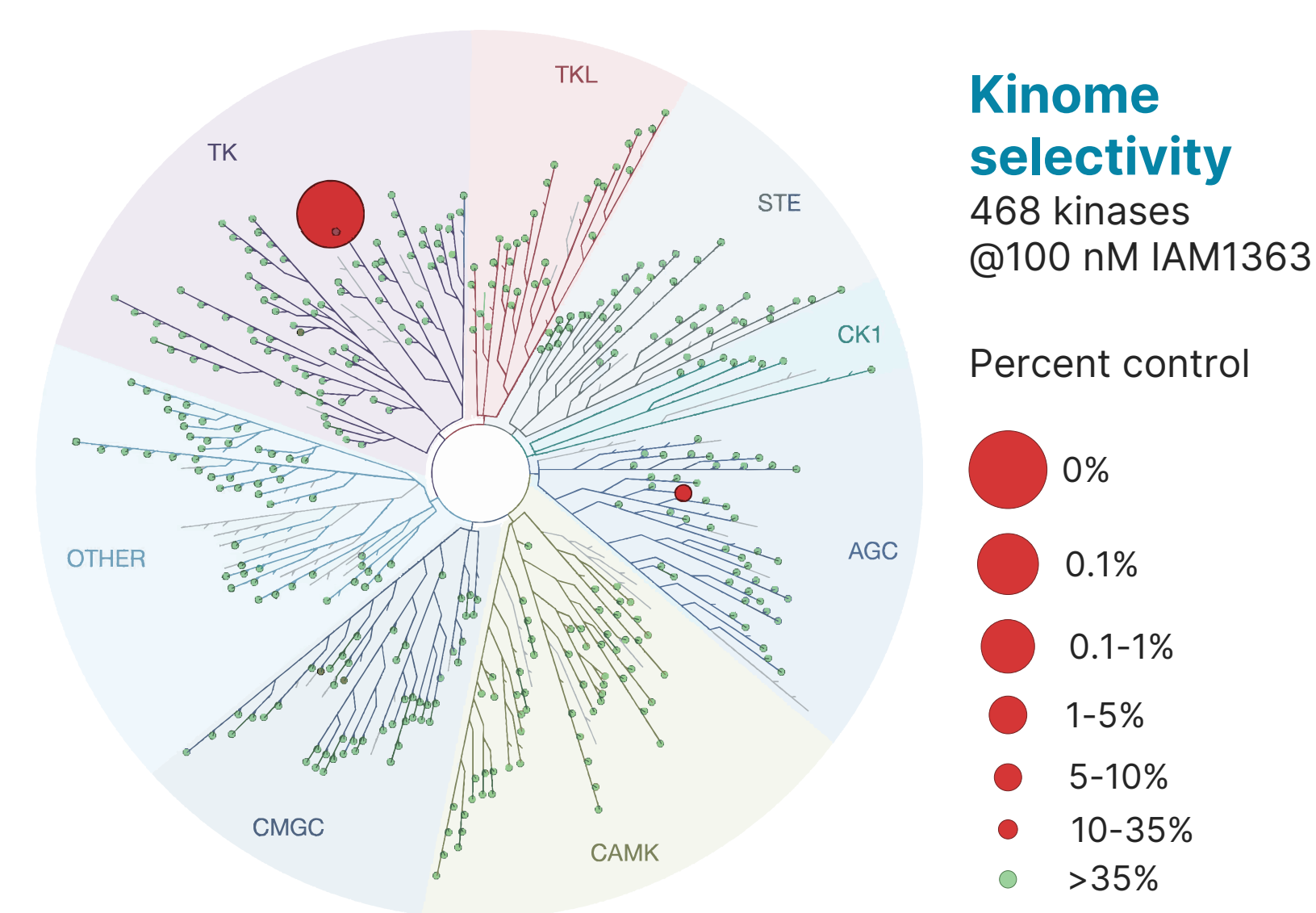
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Background

- There is a critical need for novel agents to treat HER2-driven cancers, as current inhibitors display significant off-target toxicity and lack efficacy against certain mutations
- IAM1363** is an irreversible and brain-penetrant small molecule inhibitor targeting both wildtype HER2 and oncogenic HER2 mutants, including the recalcitrant exon 20 mutations
- IAM1363**, discovered through Iambic Therapeutics' AI-driven discovery platform, represents the only example of a Type II HER2 inhibitor
- The promising target specificity and pharmacokinetic profile of **IAM1363** offers the potential to bridge gaps left by current standard of care HER2 targeted treatments

Key Features of IAM1363*



>1000-fold selectivity vs. EGFR
Highly potent against wild-type HER2 and tyrosine kinase domain mutants

~10-fold preferential tumor distribution
Maximizing target engagement in tumors, further minimizing potential side effects

Highly brain-penetrant
10x more distribution into the CNS than tucatinib

*Kulyk L et al. In Proceedings of the 115th Annual Meeting of AACR; 2024. Abstract 1980.

IAM1363-01: Study Design

Key Inclusion/Exclusion Criteria

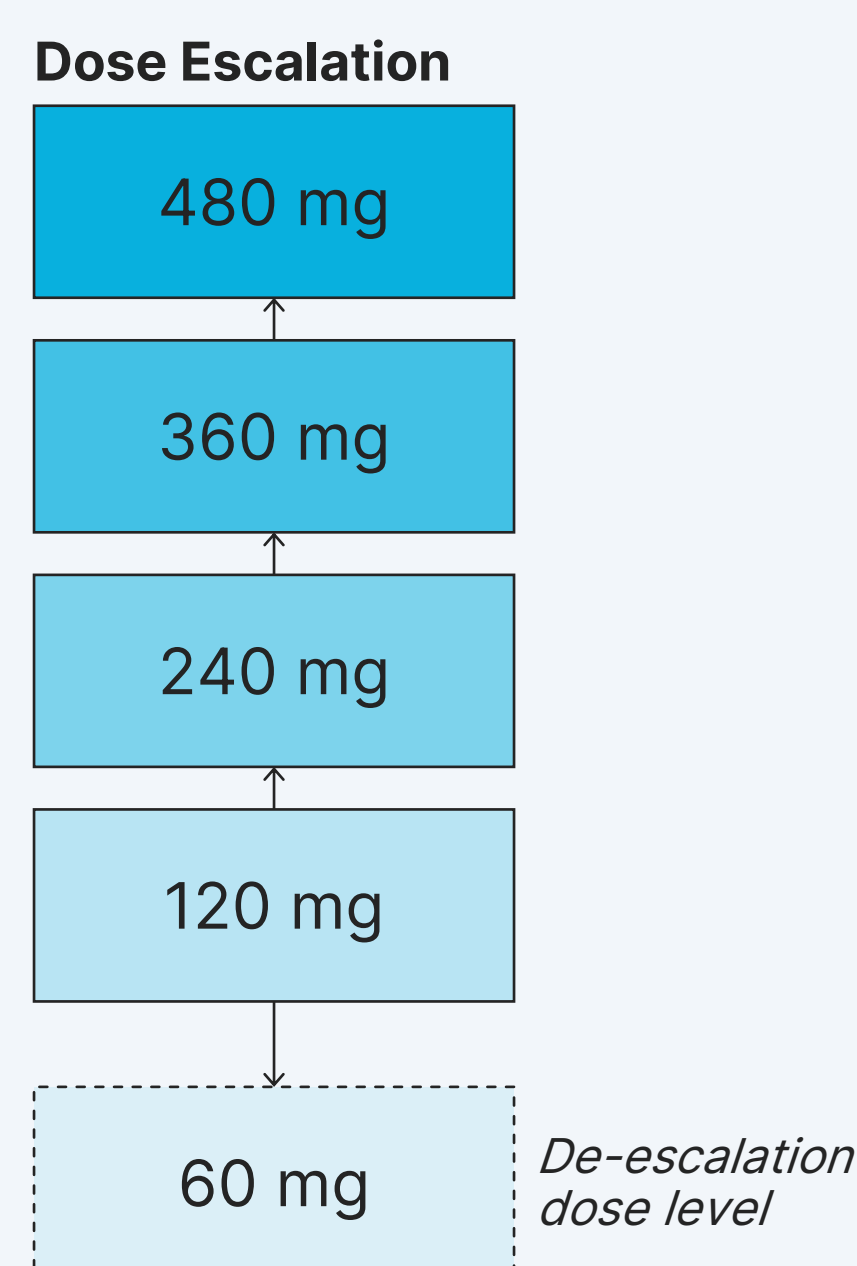
- HER2-altered malignancy (e.g., HER2 tyrosine kinase domain mutations, gene amplification, or protein overexpression)
- R/R disease with no existing standard therapy likely to provide clinical benefit
- RECIST v1.1 measurable disease
- ECOG performance score 0-1
- Adequate baseline hematologic parameters, renal, liver, and cardiac function
- Not require immediate local therapy for brain metastases (mets), if present

Abbreviations: CRC, colorectal cancer; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; mets, metastases; NSCLC, non-small cell lung cancer; R/R, relapsed/refractory; RECIST, Response Evaluation Criteria In Solid Tumors.

Part 1: Monotherapy dose escalation

Clinical Trial Design (mTPI-2)

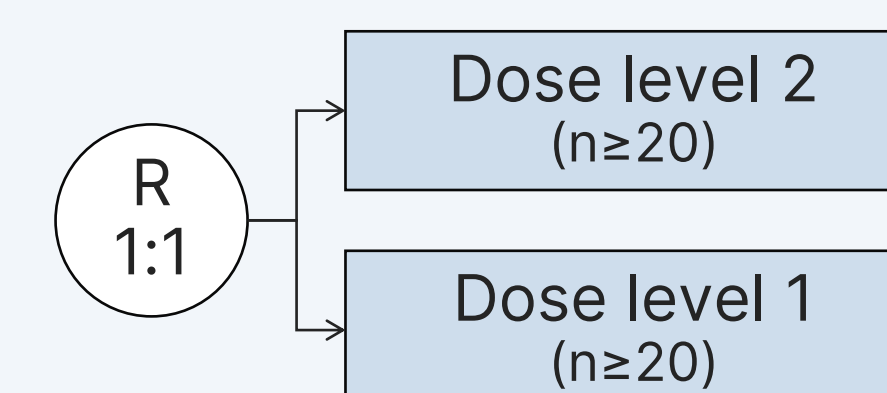
- R/R malignancy with documented diagnosis of HER2 alterations
- Daily dosing (21-day cycles)
- Four planned dose levels
- De-escalation dose level: 60 mg



Part 2: Dose optimization

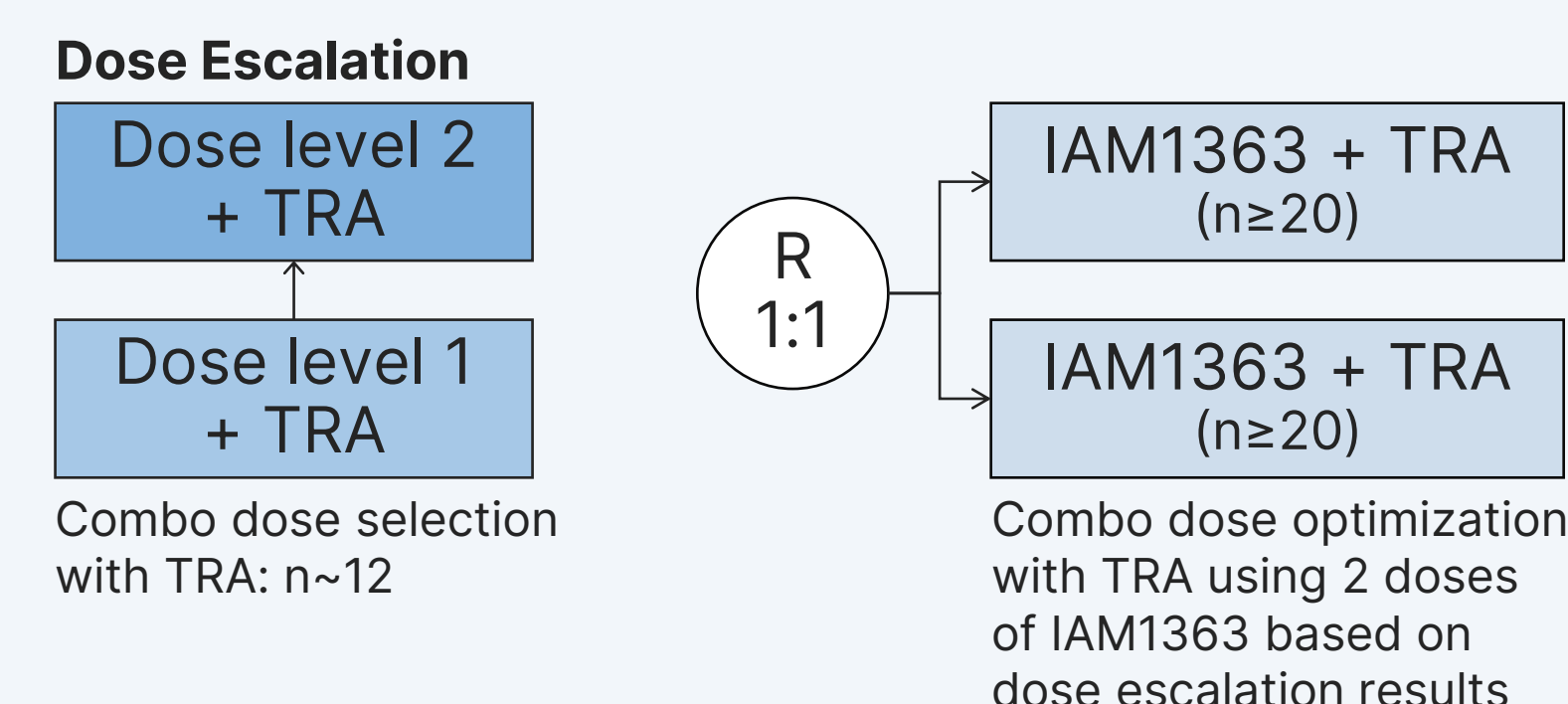
Part 2a: Monotherapy dose optimization

- CRC with or without brain mets
- NSCLC with brain mets



Part 2b: Combo dose selection/optimization

- Breast cancer with brain mets
- CRC with or without brain mets



Part 3: Simon 2-stage

IAM1363 monotherapy

- Bladder cancer*
Stage 1, (n=15)
if ≥ 3 responses →
Stage 2 +13, (n=28)
 - CRC*
Stage 1, (n=18)
if ≥ 5 responses →
Stage 2 +15, (n=33)
 - NSCLC*
Stage 1, (n=22)
if ≥ 3 responses →
Stage 2 +18, (n=40)
- *With or without brain mets

Combo: IAM1363 + TRA

- Breast cancer with brain mets
Stage 1, (n=22)
if ≥ 3 responses →
Stage 2 +18, (n=40)

Methods

- IAM1363-01** is a first-in-human, multicenter, open-label, Phase 1/1b dose escalation and expansion trial evaluating IAM1363 alone and in combination with trastuzumab (TRA)
- The study will enroll patients with relapsed/refractory malignancies that have documented HER2 gene alterations (amplification or tyrosine kinase domain mutations) or protein overexpression
- IAM1363** will be given orally once daily at a starting dose of 120 mg/day

Primary Study Objectives and Endpoints

Parts 1 and 2:

Determine MTD/
RP2D of IAM1363
monotherapy and
in combination

- Incidence and severity of DLTs
- Incidence of TEAEs and SAEs graded according to CTCAE v5.0 and changes from baseline in safety parameters (lab parameters, vital signs and ECGs)

Part 3:

Characterize the
efficacy of IAM1363
as monotherapy and
in combination

- For all groups:* Percentage of subjects who achieve a confirmed objective response per RECIST v1.1
- For the breast cancer and NSCLC subgroups only:* Percentage of subjects who achieve a confirmed intracranial objective response per RANO-BM

Study Size and Status

Clinical trial information:
NCT06253871

~287 evaluable patients

- Part 1 (monotherapy escalation): N~54 patients
- Part 2 (dose optimization):
 - Part 2a (monotherapy): N~40 patients
 - Part 2b (TRA combination): N~52 patients
- Part 3 (Simon 2-stage evaluation): N~141 patients

~30 sites are expected to participate in the study

- 15 sites in the US
- 15 ex-US sites (these sites will not be opened for Part 1)
- Dose escalation is ongoing