Phase I Study of TAS0728 in Patients with Advanced Solid Tumors with HER2 Aberration (TAIBRAKHER Study)

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Background

- TAS0728 is a novel oral small-molecule inhibitor targeting HER2's tyrosine kinase domain via covalent binding, showing significant antitumor activity in preclinical models[1].
- *HER2* gene aberrations, including mutations, amplifications, and overexpression, drive various solid tumors. Despite advances in HER2-targeted therapies, unmet needs remain, particularly in advanced-stage disease and post-standard-therapy settings.
- In the first-in-human phase I study of TAS0728 at escalating doses from 50 to 200 mg BID for 21-day cycles, dose-limiting toxicity of Grade 3 diarrhea was observed at 150 mg and 200 mg BID. And partial responses were observed in 2 of 14 evaluable patients. However, the maximum tolerated dose was not determined due to the occurrence of unacceptable toxicity at 150 mg BID.[2]
- This study aims to assess the safety, tolerability, and pharmacokinetics, and to determine the recommended phase II dose (RP2D) of TAS0728 at escalating doses of 50, 75, and 100 mg BID for 21-day cycles in Japanese patients.

METHODS & STUDY DESIGN

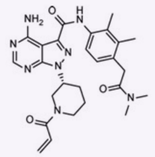
Drug Characteristics

TAS0728 Key Features:

- Covalent binding inhibitor with highly selective HER2 targeting
- More selective than Pan-HER inhibitors
- Strong and effective signal blockade
- High efficacy against HER2 antibody/ADC resistance
- Specific targeting of HER2 mutations (ex20ins)
- Potentially active in patients with prior HER2-targeted therapy

Binding Mechanism:

- Covalent: TAS0728 (HER2 selective)



MW = 504.58
HER2 IC_{50} = 36 ±3 nmol/L

Chemical structure of TAS0728[1]

Study design

Screening

HER2 aberration confirmation
Eligibility assessment

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Dose Escalation Part (3+3 Design)

Cohort 1	Cohort 2	Cohort 3
50 mg BID	75 mg BID	100 mg BID

DLT assessment during Cycle 1 (21 days)

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Expansion Part at RP2D

Safety assessment
Preliminary efficacy

Methods

- Multicenter phase I study with dose escalation and expansion parts
- 3+3 design for dose escalation
- Dose levels: 50 mg, 75 mg, and 100 mg BID (21-day cycles)
- Target enrollment: Total 30 patients

Inclusion Criteria

- ☐ Male or female patients
- ☐ Aged ≥18 years at the time of informed consent.
- ☐ Histologically or cytologically confirmed unresectable or metastatic solid tumors
- ☐ Presence of HER2 aberration confirmed by one of the following:
  - For non-lung cancer: HER2 overexpression or gene alteration defined as:
  - IHC 3+, or
  - IHC 2+ and ISH positive, or
  - HER2 gene mutation or amplification confirmed by a validated method.
  - For lung cancer: HER2 mutation (including amplification).
- ☐ ECOG performance status of 0–1.
- ☐ Adequate organ and bone marrow function within 7 days prior to treatment initiation-
- ☐ QTcF <450 ms (male) or <470 ms (female) on ECG.
- ☐ Left ventricular ejection fraction (LVEF) ≥50% by echocardiogram or MUGA scan.

Exclusion Criteria

- ☐ Clinically significant cardiovascular disease or abnormal cardiac function.
- ☐ Chronic respiratory failure requiring supplemental oxygen.
- ☐ Known hypersensitivity to TAS0728 or any of its excipients.
- ☐ Patients with a history of hypersensitivity to components of the investigational drug
- ☐ Patients who require continuation of strong CYP3A inhibitors or inducers

ADITIONAL ANALYSIS

ABCG2 genotyping:

- TAS0728 is a substrate for breast cancer resistance protein (BCRP)
- ABCG2 genotypes as candidate factors for pharmacokinetic variability

HER2 gene status analysis:

- From circulating tumor DNA (ctDNA) in blood
- Collected at baseline and disease progression
- Correlation with treatment response

ENDPOINTS

Primary: Determine the RP2D in the dose escalation part
Evaluate safety at the RP2D in the expansion part

Secondary: Safety and tolerability
Pharmacokinetic profile

Preliminary efficacy assessment: Disease control rate (DCR)

STUDY INFORMATION

- The TAIBRAKHER study is currently active with enrollment ongoing at multiple centers across Japan.
- This study is funded by Taiho Pharmaceutical Co., Ltd.,
- For more information: kazuki.nozawa7@gmail.com
- Trial Registration: jRCT2031240235

REFFERENCES

1) Irie H, et al. Mol Cancer Ther. 2019 Apr;18(4):733-742.
2) Piha-Paul SA, et al. Invest New Drugs. 2021 Oct;39(5):1324-1334.