2. SYNOPSIS

Name of Sponsor/Company: Taiho Oncology, Inc. (TOI)	
Name of Finished Product: TAS0728	
Name of Active Ingredient: TAS0728	
Title of Study: A Phase 1/2, Open-label, Multicenter Study to Investigate the Safety, Pharmacokinetics, and Efficacy of TAS0728, an Oral Covalent Binding Inhibitor of HER2, in Subjects with Advanced Solid Tumors with HER2 or HER3 Abnormalities	
Principal Investigators: PPD	
Study Center(s): Patients were enrolled at a total of 10 study centers: United States (6); London, France, Spain, and South Korea (1 each).	
Publications (reference): There were no publications based on this study.	
Studied Period (years): Date first patient enrolled: 22 March 2018 Date of early termination: 27 June 2019	**Phase of Development**: Phase 1/2
Objectives: <u>Primary</u>: • To determine the MTD and/or the recommended Phase 2 dose of TAS0728 when administered orally BID in 21-day cycles to adult patients with advanced solid tumors harboring HER2 or HER3 overexpression, amplification, or mutation <u>Secondary</u>: • To assess the safety and tolerability of TAS0728 • To investigate the clinical PK of TAS0728 • To evaluate the ORR in patients who received TAS0728	

Methodology:

This open-label, multicenter study was designed to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics, pharmacogenomics (PGx), and efficacy of TAS0728 in patients with advanced solid tumors with HER2 or HER3 overexpression, amplification, or mutation who have progressed despite standard therapy or for which no standard therapy exists.

The original study was to consist of 3 parts: a Phase 1, dose-escalation portion, a Phase 2a portion, and a Phase 2b portion. This study enrolled and treated patients in the Phase 1, dose-escalation portion of the study; however, the study was stopped due to unacceptable toxicity during the dose-escalation portion (Phase 1) of the study and did not progress to Phase 2.

This clinical study report includes methodology and results from the Phase 1 portion of the study only.

Number of patients (planned and analyzed):

In total, 25 patients were enrolled in the study. Of these, 19 were treated with study drug, and 15 were DLT evaluable (Table 1). Of the 19 patients who were treated with TAS0728, 18 (94.7%) discontinued treatment, mostly (73.7%) due to disease progression. Other reasons for treatment discontinuation included adverse events and patient withdrawal (n=2; 10.5% each) (Table 2).

One patient was still receiving treatment with TAS0728 as of the data cut-off; this patient had received TAS0728 50 mg BID for 489 days at the time of study termination.

Table 1: Enrolled Patients and Screened Failures (All Enrolled Population)

Dose Level/Group	Enrolled (N=25)	Treated (N=19)	DLT Evaluable (N=15)
Screen failures	4	0	0
Dose escalation, Dose Level 1: 50 mg BID	3	3	3
Dose escalation, Dose Level 2: 100 mg BID	4	3	3
Dose escalation, Dose Level 3d: 150 mg BID	6	6	3
Dose escalation, Dose Level 3: 200 mg BID	8	7	6

Table 2: Patient Disposition (All Treated Population)

	50 mg BID (N=3) n (%)	100 mg BID (N=3) n (%)	150 mg BID (N=6) n (%)	200 mg BID (N=7) n (%)	Total (N=19) n (%)
All treated patients					
Ongoing	1 (33.3)	0	0	0	1 (5.3)
Discontinued treatment	2 (66.7)	3 (100)	6 (100)	7 (100)	18 (94.7)
Primary reason for treatment discontinuation					
Adverse event/SAE	0	0	1 (16.7)	1 (14.3)	2 (10.5)
Disease progression	2 (66.7)	3 (100)	4 (66.7)	5 (71.4)	14 (73.7)
Patient withdrew from treatment	0	0	1 (16.7)	1 (14.3)	2 (10.5)
Death	0	0	0	0	0

Key Inclusion/Exclusion Criteria:

The main criteria for inclusion included the following:

- Male or female ≥18 years of age
- Patients with histologically confirmed, advanced cancer, who had progressed on (or not been able to tolerate) standard therapy or for whom no standard anticancer therapy exists. Patients may have received 2 different forms of specific anti-HER2 therapy for their cancer, except for breast cancer, where receipt of up to 4 lines of anti-HER2 therapy was allowed prior to enrollment
- For Phase 1, only patients with measurable or evaluable disease and one of the following molecular/genetic alterations were enrolled:
  - HER2+ determined by local laboratory, for example: immunohistochemistry (IHC) 3+ and/or fluorescence in situ hybridization (FISH)+ by an accurate and validated assay
  - Potentially actionable HER2 or HER3 mutation or amplification by next-generation sequencing
- ECOG performance status of 0 or 1
- Patients needed to have the following laboratory values:
  - ANC ≥1.5×109/L
  - Hemoglobin ≥8.0 g/dL
  - Platelet count ≥75×109/L
  - Albumin ≥3 g/dL
  - Serum potassium, magnesium, phosphorus, sodium, total calcium (corrected for serum albumin) or ionized calcium within institutional normal limits
  - AST/serum glutamic-oxaloacetic transaminase and ALT/serum glutamic-pyruvic transaminase ≤3× ULN or ≤5.0× ULN if liver metastases were present
  - Total serum ≤1.5× ULN
  - Serum creatinine ≤1.4× ULN or 24-hour or calculated creatinine clearance (Ccr) ≥50 mL/min.
- Women of childbearing potential must have had a negative pregnancy test (urine or serum) within 7 days prior to starting study drug. Both males and females agreed to use effective birth control during the study (prior to the first dose and for 6 months after the last dose) if conception was possible during this interval. Female patients were considered to not be of childbearing potential if they had a hysterectomy or were postmenopausal (no menses for 12 months without an alternative medical cause).
- Patients needed to be able to swallow and retain orally administered medication and not have any clinically significant GI abnormalities that could alter absorption, such as malabsorption syndrome or major resection of the stomach or bowels.
- Able to agree to and sign informed consent and to comply with the protocol.

The main criteria for exclusion included the following:

- Patients with a history of brain metastases or who had signs/symptoms attributable to brain metastases and were not assessed with radiologic imaging to rule out the presence of brain metastases. Patients with treated brain metastases that were asymptomatic and had been clinically stable for at least 4 weeks were eligible.

- Patients who have a history of another primary malignancy, other than:
  - carcinomas in situ, eg, breast, cervix, and prostate (patients with early-stage prostate
  - cancer not requiring therapy were eligible)
  - locally excised nonmelanoma skin cancer
  - A patient who had no evidence of disease from another primary cancer for ≥2 years
- Any other clinically significant acute or chronic medical or psychiatric condition or any laboratory abnormality that could increase the risk associated with study drug administration, or could interfere with the interpretation of study results such as, but not limited to:
  - Uncontrolled diabetes mellitus
  - Liver disease such as decompensated liver disease
  - Life-threatening autoimmune disease
  - Diseases that significantly affect GI absorption of the compound
- Patients who have impaired cardiac function or clinically significant cardiac disease, including any of the following:
  - Baseline corrected QT level using Fridericia formula (QTcF) >480 ms or congenital QT syndrome
  - History or presence of serious uncontrolled ventricular arrhythmias
  - Any New York Heart Association Classification of Heart Failure ≥ Class II
  - Echocardiogram or multiple grated acquisition (MUGA) scan under 50% ejection fraction
- Chemotherapy, biologic therapy, targeted therapy, immunotherapy, extended-field radiotherapy, or investigational agents within 5 half-lives or within 4 weeks whichever is shorter) prior to administration of first dose of study drug on Day 1 or unresolved clinically significant toxicities (as assessed by the investigator) attributed to any prior therapy.
- Major surgery/surgical therapy for any cause within 4 weeks of first dose

Test product, dose, and mode of administration:

TAS0728 (25-mg and 100-mg tablets) was to be taken orally BID (each morning and evening) at one of six dose levels. At the time of study termination, patients had only been treated at the first three dose levels.

Dose Escalation Levels		**Dose De-escalation Levels**	
Dose Level	Daily Dose	Dose Level	Daily Dose
Dose level 1	50 mg BID	Dose level 1d	25 mg BID
Dose level 2	100 mg BID	Dose level 2d	75 mg BID
Dose level 3	200 mg BID	Dose level 3d	150 mg BID
Dose level 4	400 mg BID	Dose level 4d	300 mg BID
Dose level 5	600 mg BID	Dose level 5d	500 mg BID
Dose level 6	800 mg BID	Dose level 6d	700 mg BID

Duration of treatment:

TAS0728 was to be taken on Day 1 to Day 21 for each cycle and repeated every 21 days until the patient met any of the administration discontinuation criteria. Two dose modifications are permitted during the study.

Reference therapy, dose and mode of administration, batch number:

Not applicable

Criteria for evaluation:

Efficacy:

Efficacy was assessed according to RECIST guidelines (Version 1.1, 2009) for each tumor type.

Safety:

Primary: Phase 1

Incidence of DLTs (first cycle only) at each dose level

Secondary: Phase 1 Dose Escalation

Type, frequency, and severity of adverse drug reactions according to NCI CTCAE, Version 5.0

Pharmacokinetics:

Secondary: Phase 1 Dose Escalation

Dose escalation only: TAS0728 plasma concentrations, urinary concentrations and basic PK parameters, including but not limited to: AUC_{last}, $AUC_{0\text{-}inf}$, AUC0-12, C_{max}, T_{max}, CL/F, Vz/F, R, $T_{1/2}$, MRT, fe (%), renal clearance, and other PK parameters if deemed appropriate (Phase 1)

Statistical Methods:

All the analyses of safety data for this study were performed using CCI [redacted]. All safety analyses will be performed considering all treated patients, summarized by As Treated group. The PK data were analyzed using PPD [redacted].

Results:

Demographic and Baseline Characteristics:

Demographic and key baseline characteristics are summarized in Table 3.

.

Table 3: Demographics and Key Baseline Characteristics (All Treated Population)

	50 mg BID (N=3)	**100 mg BID (N=3)**	**150 mg BID (N=6)**	**200 mg BID (N=7)**	**Total (N=19)**
Age (years)					
n	3	3	6	7	19
Mean (SD)	67.3 (13.32)	62.0 (7.0)	52.2 (14.20)	56.6 (13.43)	57.7 (13.06)
Range	52, 76	57, 70	29, 66	38, 79	29, 79
Age groups					
<65 years	1 (33.3)	2 (66.7)	5 (83.3)	6 (85.7)	14 (73.7)
≥65 years	2 (66.7)	1 (33.3)	1 (16.7)	1 (14.3)	5 (26.3)
Sex, n (%)					
Male	1 (33.3)	2 (66.7)	4 (66.7)	3 (42.9)	10 (52.6)
Female	2 (66.7)	1 (33.3)	2 (33.3)	4 (57.1)	9 (47.4)
Race, n (%)					
Caucasian/White	3 (100)	2 (66.7)	5 (83.3)	3 (42.9)	13 (68.4)
Asian/Oriental	0	0	1 (16.7)	1 (14.3)	2 (10.5)
Other	0	0	0	1 (14.3)	1 (5.3)
Missing	0	1 (33.3)	0	2 (28.6)	3 (15.8)
ECOG Performance Status, n (%)					
0	1 (33.3)	1 (33.3)	1 (16.7)	4 (57.1)	7 (36.8)
1	2 (66.7)	2 (66.7)	5 (83.3)	3 (42.9)	12 (63.2)

Cancer diagnoses and genotype are summarized in Table 4.

Table 4: Cancer Diagnosis (All Treated Population)

	50 mg BID (N=3)	100 mg BID (N=3)	150 mg BID (N=6)	200 mg BID (N=7)	Total (N=19)
Time since initial diagnosis (mos)					
n	3	3	6	7	19
Mean (SD)	18.4 (11.23)	87.6 (88.65)	18.3 (3.53)	24.3 (11.42)	31.5 (39.57
Range	11, 31	24, 189	13, 23	10, 46	10, 189
Metastasis status					
Yes	3 (100)	3 (100)	6 (100)	7 (100)	19 (100)
No	0	0	0	0	0
Cancer type, n (%)					
Biliary tract	0	0	0	2 (28.6)	2 (10.5)
Breast	1 (33.3)	1 (33.3)	0	1 (14.3)	3 (15.8)
Esophagus	0	1 (33.3)	0	1 (14.3)	2 (10.5)
Gastroesophageal junction	0	0	2 (33.3)	0	2 (10.5)
iCCA	0	0	1 (16.7)	0	1 (5.3)
Malignant neoplasm of vulva	1 (33.3)	0	0	0	1 (5.3)
NSCLC	1 (33.3)	0	1 (16.7)	1 (14.3)	3 (15.8)
Pancreas	0	1 (33.3)	0	0	1 (5.3)
Rectum	0	0	1 (16.7)	1 (14.3)	2 (10.5)
Urothelial	0	0	1 (16.7)	1 (14.3)	2 (10.5)
HER2 amplification	1 (33.3)	1 (33.3)	2 (33.3)	3 (42.9)	7 (36.8)
Genotype, n (%)					
HER2 overexpression	1 (33.3)	1 (33.3)	3 (50.0)	1 (14.3)	6 (31.6)
Immunohistochemistry (IHC X)	1 (33.3)	1 (33.3)	3 (50.0)	1 (14.3)	6 (31.6)
0	0	0	0	0	0
1+	0	0	0	0	0
2+	0	0	0	0	0
3+	1 (33.3)	1 (33.3)	3 (50.0)	1 (14.3)	6 (31.6)

Safety:

An overview of adverse events is presented in Table 5.

Dose-limiting toxicities occurred in a total of 3 patients (2 patients at the 200-mg BID dose level, followed by 1 patient at the reduced dose of 150 mg BID). Due to excessive toxicity and the early termination of this study, the MTD was not determined. Seven (36.8%) patients received study drug at the highest dose administered in this study (200 mg BID) before a dose reduction to 150 mg BID was conducted in 6 patients.

Table 5: Overview of Treatment-emergent Adverse Events (All Treated Population)

	50 mg BID (N=3) n (%)	100 mg BID (N=3) n (%)	150 mg BID (N=6) n (%)	200 mg BID (N=7) n (%)	Total (N=19) n (%)
Patients with AEs	3 (100)	3 (100)	6 (100)	7 (100)	19 (100)
Patients with SAEs	1 (33.3)	0	4 (66.7)	3 (42.9)	8 (42.1)
Patients with DLT AEs	0	0	1 (16.7)	2 (28.6)	3 (15.8)
Patients with Grade ≥3 AEs	2 (66.7)	0	3 (50.0)	4 (57.1)	9 (47.4)
Patients with treatment-related AEs	3 (100)	3 (100)	5 (83.3)	6 (85.7)	17 (89.5)
Patients with treatment-related and Grade ≥3 AEs	0	0	2 (33.3)	4 (57.1)	6 (31.6)
Patients with AEs that led to study treatment discontinuation	0	1 (33.3)	1 (16.7)	1 (14.3)	3 (15.8)
Patients with AEs that had an outcome of death	0	0	1 (16.7)	0	1 (5.3)

AE=adverse event; BID=twice daily; DLT=dose-limiting toxicity; SAE=serious adverse event

Dose-limiting toxicities occurred in a total of 3 patients (2 patients at the 200-mg BID dose level, followed by 1 patient at the reduced dose of 150 mg BID). The 2 patients at the 200-mg BID dose level experienced a DLT of diarrhea ≥Grade 3 that lasted >48 hours and was unresponsive to intensive antidiarrheal medication. Subsequently, the dose of TAS0728 was reduced to 150 mg BID. At this dose, 1 patient experienced a DLT of diarrhea ≥Grade 3 that lasted >48 hours and was unresponsive to intensive antidiarrheal medication.

Overall, the incidence of AEs reported during the study was higher at doses of 150 mg and 200 mg BID TAS0728 compared with lower doses; however, all 19 (100.0%) patients in the All Treated population experienced an AE during the study at all doses administered, most of which were considered by the Investigator to be treatment related.

The AEs with the highest incidence (≥20% of patients) were diarrhea (78.9%), anemia (31.6%), fatigue (26.3%), pyrexia (26.3%), nausea (21.1%), vomiting (21.1%), dermatitis acneiform (21.1%), and hypokalemia (21.1%). Almost half (47.4%) of the AEs experienced overall were considered ≥Grade 3 in severity with the highest incidence of diarrhea (31.6%).

Four patients died during the study, 3 of which occurred >30 days after the last dose of study treatment, all due to clinical progression. One patient had an SAE with an outcome of death (a patient with cardiac arrest experienced after receiving 1 cycle of TAS0728 at a dose of 150 mg BID).

No clinically meaningful changes from Baseline were noted during the study in clinical laboratory or ECG results.

Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic

Because the study was terminated before any patients were enrolled into the Phase 2 proof-of-concept portion of the study, the PK, pharmacodynamic, and pharmacogenomic analyses that were planned per the protocol for this phase of the study were not performed.

Efficacy:

Out of a total of 19 treated patients, 14 were evaluable for treatment response (that is, had a baseline assessment and at least 1 post-baseline assessment). There were a total of 2 objective responses: a partial response (PR) in a patient with NSCLC treated at 50 mg BID and a PR in a patient with biliary tract cancer treated at a dose of 200 mg BID. In all, disease control (best response of PR or SD) was observed in 10 of 14 response-evaluable patients.

Conclusion:

This Phase 1 Dose Escalation study was intended to assess the safety and tolerability of TAS0728 in a population of adult patients with advanced solid tumors harboring HER2 or HER3 abnormalities. Following escalation of the dose to 200 mg BID per protocol, a total of 2 DLTs were observed, both cases of Grade 3 diarrhea lasting more than 48 hours and not responsive to aggressive antidiarrheal treatment. Following de-escalation of the dose to 150 mg BID, another DLT of Grade 3 diarrhea was observed.

In nonclinical studies, the inhibitory effect of TAS0728 was much greater against HER2 and HER3 than against the EGFR; accordingly, it was hypothesized that treatment with TAS0728 might result in a lower incidence of adverse events characteristically associated with EGFR inhibition, including gastrointestinal and cutaneous toxicity. However, the majority of patients in this study experienced 1 or more toxicities of this type. In some cases, these toxicities were significant.

Moreover, a fatal instance of cardiac arrest occurred in a patient with no history of heart disease; although the etiology of this event was not clear, a causal relationship to TAS0728 could not be ruled out.

Absorbed TAS0728 reached C_{max} at approximately 0.5 to 4 hours after administration, and then declined with $T_{1/2}$ of approximately 2.0 hours on Cycle 1, Day 1. Due to the dose interruptions, reductions, or discontinuations, the ability to evaluate steady-state PK on Cycle 2, Day 1 was limited. No significant accumulation of TAS0728 exposure was observed following the BID multiple-dose administration.

Although evaluation of efficacy was not a primary objective of the dose escalation portion of this study, some evidence of clinical benefit was obtained; this included 2 partial responses among 14 patients evaluable for best overall response. However, considering the toxicity profile discussed above, and taking into account the fatal AE of cardiac arrest considered possibly related to TAS0728, the Sponsor determined that the overall risk-benefit ratio no longer favored continuation of the study.

Date of the report:

11 January 2021