2. SYNOPSIS

Name of Sponsor/Company: Taiho Oncology, Inc.	**Study TO-TAS-114-201** Abbreviated Clinical Study Report Synopsis
Name of Finished Product: TAS-114	
Name of Active Ingredient: TAS-114	

Title of Study:

A Randomized, Open-Label, Multicenter, International Phase 2 Study of TAS-114 in Combination with S-1 in Patients with Advanced or Metastatic Non-Small Cell Lung Cancer

Principal Investigator:

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Study centers:

Patients were randomized at a total of 26 sites in 5 countries: Italy (4 sites), Spain (4 sites), France (5 sites), the United States (6 sites), and Japan (7 sites).

Publications: None

Studied period:		**Phase of development:**
Date first patient randomized:	29 August 2016	Phase 2
Data cut-off dates:	30 November 2017 (survival data) 30 September 2017 (other data)	

Objectives:

Primary:

- To compare progression-free survival (PFS) of patients with advanced or metastatic non-small cell lung cancer (NSCLC), when treated with TAS-114/S-1 combination versus S-1.

Secondary:

- To investigate the overall survival (OS), overall response rate (ORR), disease control rate (DCR), and duration of response (DR)
- To investigate the safety and tolerability.

Exploratory:

- (Optional) To explore the relationship between the expression levels of biomarkers in tumor and the efficacy of TAS-114/S-1.

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Methodology:

Protocol TO-TAS-114-201 was a randomized, open-label, Phase 2 study of TAS-114 administered in combination with S-1 to investigate the efficacy, safety, and tolerability of the TAS-114/S-1 regimen in patients, aged 18 years or older (≥ 20 years old in Japan), with advanced or metastatic NSCLC who received at least 2 prior therapies for advanced or metastatic disease condition, including platinum doublet and pemetrexed, docetaxel, or immunotherapy and who were refractory to or unable to tolerate their last prior therapy.

Randomization was stratified by geographical region (Asian vs. Western) and histological subtypes (squamous vs. nonsquamous/mixed). Patients were randomized (1:1) to receive either:

- TAS-114 (400 mg) plus S-1 (30 mg/m^2) twice per day (BID); or
- S-1 (30 mg/m^2 BID)

In both arms, treatment followed a 21-day cycle in which treatment was administered for 14 consecutive days followed by a 7-day rest period. Patients continued to receive study therapy until documentation of progressive disease (PD), intolerable toxicity, withdrawal of consent, or other discontinuation criteria were met.

Central tumor imaging assessments were performed throughout study treatment per Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST 1.1). Computed tomography (CT) scans were performed every 6 weeks (± 1 week) until PD was documented or the patient initiated a new anticancer therapy. Following Cycle 6, CT assessments were performed every 9 weeks instead of every 6 weeks.

Adverse events (AEs) were recorded from the time a patient started receiving study treatment until 30 days after the last dose of study drug or until the start of new antitumor therapy, whichever was earlier. Events were graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. Safety assessments also included evaluation of laboratory test results, vital signs measurements, physical examination findings, and changes in ECOG performance status (ECOG PS).

Number of patients (planned and analyzed): The study was planned to enroll approximately 124 patients with advanced or metastatic NSCLC.

- A total of 128 patients were randomized (64 to each study arm) and made up the intent-to-treat (ITT) population.
- In the S-1 Arm, 1 patient was randomized but not treated; the as-treated population thus comprised 127 patients (N=64 in the TAS-114/S-1 arm and 63 in the S-1 arm).
- The Tumor Response (TR)-Evaluable population (Independent Review), consisting of all patients evaluable for response, comprised 119 patients (N=61 in the TAS-114/S-1 arm and 58 in the S-1 arm).

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Diagnosis and main criteria for inclusion:

Key entry criteria are listed in this section; the complete list of criteria is provided in the study protocol (Appendix 16.1.1 to this report).

Key Inclusion Criteria

- Provision of written informed consent.
- Age ≥18 years old (≥20 years old in Japan).
- Advanced or metastatic NSCLC (Stage IIIB/Stage IV disease or recurrent disease following radiation therapy or surgical resection).
- At least 2 prior therapies for advanced or metastatic disease condition, including platinum doublet and pemetrexed, docetaxel, or immunotherapy, and were refractory to or unable to tolerate their last prior therapy. For patients with known epidermal growth factor receptor (EGFR) activating mutations or anaplastic lymphoma kinase translocations, and/or ROS1 rearrangements, appropriate targeted treatment should have been used.
- Tumor is not suitable for surgery and radiotherapy is not indicated.
- Measurable disease as defined by RECIST 1.1.
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
- Predicted life expectancy of at least 3 months.
- Able to take medications orally.
- Adequate bone marrow, liver, and renal function.
- Women of childbearing potential (WOCBP) had a negative pregnancy test (urine or serum) within 7 days prior to starting the study drug. Both males and females must agree to use effective birth control during the study (prior to the first dose and for 6 months after the last dose) if conception is possible during this interval.

Key Exclusion Criteria:

- Serious illness or medical condition(s) as detailed in the study protocol.
- Major surgery within the prior 4 weeks, minor surgery within the prior 7 days, radiotherapy for extended field within the prior 4 weeks, radiotherapy for limited field within the prior 2 weeks, or any anticancer or investigational therapy within the prior 3 weeks.
- Previous use of TAS-114, S-1, or 5-fluororacil, or known hypersensitivity to S-1 or its metabolites.
- Rare hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose/galactose malabsorption.

Test product, dose and mode of administration, batch number:

TAS-114, supplied as 100 mg tablets packaged in kits containing 20 tablets for Europe and the US and 120 tablets for Japan. Batch numbers of TAS-114 used in this study will be provided upon request.

TAS-114 (400 mg per dose) was administered to patients in the TAS-114/S-1 arm orally BID, with a glass of water within 1 hour after completion of morning and evening meals, for 14 days, followed by a 7-day rest period.

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

S-1 is an immediate release dosage form contained in hard gelatin capsules in which tegafur (FT), gimeracil (CDHP), and oteracil as monopotassium salt (Oxo) are combined at a molar ratio of 1:0.4:1. Study drug was packaged in kits containing 28 capsules (15-mg or 20-mg capsules) for all regions.

Patients in both arms received S-1 at a dose of 30 mg/m^2 BID, with a glass of water within 1 hour after completion of morning and evening meals, for 14 days, followed by a 7-day rest period.

Duration of treatment:

There was no pre-defined treatment duration; patients were permitted to receive the assigned treatment until one or more discontinuation criteria were met.

Statistical methods:

Sample size determination

The study was designed to differentiate a median PFS of 4.2 months with TAS-114/S-1 from a median of 2.2 months with S-1 alone (hazard ratio [HR] of 0.524), with 80% statistical power and a 1-sided type 1 error of 0.05. Using a treatment allocation of 1:1 (TAS-114/S-1: S-1), a target of 60 events (PD or deaths) was required for the primary analysis, which corresponded to 71 events based on investigator review under the assumption that the discrepancy in PD events between the independent central review and investigator review was 15%. Assuming an accrual period of 10 months, a percentage of PFS events of 65%, and 10% of patients lost to follow-up, a total of 124 patients were planned.

Primary endpoint

PFS was defined as the time from the day of randomization to the start of disease progression or death (any cause), whichever occurs first, based on the blinded radiological review assessment of response. PFS was compared between the 2 treatment groups using the stratified log-rank test with significance level of 1-sided 5%. The estimate of the hazard ratio and corresponding 90% and 95% confidence interval (CI) were provided using a Cox proportional hazards (CPH) model including treatment and the 2 stratification factors in the model; survival curves were estimated using the Kaplan-Meier method.

Other efficacy endpoints

OS was defined as the time from the day of randomization to the date of death by any cause. The estimate of the HR and corresponding 95% CI was provided using a univariate CPH model. Survival curves were estimated using the Kaplan-Meier method, and treatment arms were compared using an unstratified log-rank test. ORR and DCR were compared using Fisher's exact test; duration of response was analyzed in the same manner as OS.

Safety endpoints

Comprehensive safety analyses were based on the As-Treated population. Simple descriptive statistics were provided for safety endpoints and demographic/baseline characteristics.

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Disposition of patients and demographic characteristics:

Disposition

A total of 128 patients were randomized (64 to each study arm) at 26 study sites located in 5 countries. In the S-1 Arm, 1 patient was randomized but not treated; the as-treated population thus comprised 127 patients (64 patients receiving TAS-114 plus S-1 and 63 patients receiving S-1 only).

Of 127 treated patients, 107 (84.3%) had discontinued as of 30 September 2017. The primary reason for discontinuation was disease progression (radiographic or clinical) for 66.1% of treated patients (n=84). A total of 11 patients in the TAS-114/S-1 Arm (17.2%) and 7 patients in the S-1 Arm (11.1%) discontinued due to an adverse event (AE).

Demographics

The baseline properties of the safety population, including demographics, medical history, prior therapies, and disease characteristics, were generally consistent with a population of patients with advanced or metastatic NSCLC. Further, arms were generally well balanced with respect to nearly all parameters, with the exception of a higher incidence of male patients in the S-1 arm (75.0%) than in the TAS-114/S-1 arm (64.1%). There is no evidence that any imbalance between arms in terms of baseline characteristics affected the efficacy or safety results observed in this study.

Primary Efficacy Endpoint – Progression-Free Survival:

Study TAS-114-201 did not meet its primary endpoint, with a HR of 1.16 (95% CI: 0.71, 1.88) and p = 0.2744 (TAS-114/S-1 relative to S-1 alone). The median PFS was 3.65 months in the TAS-114/S-1 arm and 4.17 months in the S-1 arm. In a supportive unstratified analysis, the HR was 1.06 (95% CI: 0.66, 1.70) (p = 0.4092).

A sensitivity analysis was performed evaluating PFS based on investigator assessment of disease progression. Some benefit was noted, but the result was not statistically significant. A number of other sensitivity / supplemental analyses were performed. Although marginal benefit was observed for a minority of subgroups, taken collectively these sensitivity and subgroup analyses confirmed the primary result, further demonstrating the lack of treatment effect of TAS-114 in this study.

Other Efficacy Endpoints:

The addition of TAS-114 to S-1 did not result in an improvement in OS, with stratified and unstratified HRs of 1.31 and 1.27, respectively (median OS was 7.92 months in the TAS-114/S-1 arm and 9.82 months in the S-1 arm). None of the differences between arms were statistically significant.

The ORR was 19.7% for the TAS-114/S-1 Arm and was 10.3% for the S-1 Arm, with a 9.33% difference between the 2 groups (p=0.2030). The DCR was 80.3% for the TAS-114/S-1 Arm and was 75.9% for the S-1 Arm, with a 4.47% difference between the 2 groups (p=0.6586).

A post-hoc analysis of time to treatment failure (TTF) was also performed. The median TTF (per investigator review) was 2.66 months in the TAS 114/S-1 arm and 1.54 months in the S-1 arm. The difference between arms was not statistically significant (stratified HR = 1.04 [95% CI: 0.71, 1.53).

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Safety Summary:

In this study, patients receiving TAS-114 in combination with S-1 experienced an increase in overall toxicity versus patients receiving S-1 alone, with higher proportions of patients in the TAS-114/S-1 arm experiencing severe (Grade 3-5) AEs and serious adverse events (SAEs), as well as events with an outcome of study treatment discontinuation or death. The proportion of patients requiring dose reduction was also higher in the TAS-114/S-1 arm (31.3% vs. 11.1% in the S-1 arm).

Although the absolute percentage of fatal (Grade 5) events was slightly higher in the TAS-114/S-1 arm (12.5%) than in the S-1 arm (7.9%), no treatment-related fatal events were observed. The majority of deaths on study or within 30 days after the last dose of study therapy were attributable to PD.

Incidence of all-grade hematologic toxicity, including anemia, neutropenia, thrombocytopenia, and leukopenia, as well as corresponding laboratory terms, was elevated in the TAS-114/S-1 arm compared to the S-1 arm. For anemia, this imbalance included Grade ≥3 events, which were not observed in the S-1 arm but affected 23.4% of patients in the TAS-114/S-1 arm.

Skin toxicity was more common in the TAS-114/S-1 arm than in the S-1 arm, and was the most common cause of dose reduction and treatment discontinuation among patients receiving TAS-114. Moreover, in the S-1 arm, there were no Grade ≥3 events in the System Organ Class of Skin and Subcutaneous Tissue Disorders. Grade ≥3 events in this class were reported for 20.3% of patients in the TAS-114/S-1 arm. The majority of these events were events of rash or maculo-papular rash (7.8%; n=5 for both terms).

No clinically important differences were observed between arms in terms of vital signs, physical examination results, or any other safety parameters. Analysis of electrocardiogram findings did not indicate any cardiac safety concerns with TAS-114.

Conclusions:

In this trial, the addition of TAS-114 to S-1 did not result in a statistically significant improvement in the primary endpoint of PFS or any other efficacy parameter. Based on the observed lack of efficacy associated with the combination therapy, Study TAS-114-201 was terminated upon completion of the primary analysis and no additional OS follow-up was conducted for the final analysis.

The combination of TAS-114 and S-1 resulted in greater overall toxicity, including elevated incidence of severe AEs (Grade ≥3) and SAEs, versus S-1 alone. In particular, patients receiving TAS-114 had higher rates of a number of hematologic toxicities. This was most prominent in the case of anemia; patients in the TAS-114/S-1 arm had much higher incidences of all-grade anemia (65.6% vs. 27.0%), Grade ≥3 anemia (23.4% vs. 0%), and Grade 3 low hemoglobin (laboratory finding, 25.0% vs. 0%). In addition, skin toxicity, notably maculo-papular and other rashes, was both more common and more severe among patients receiving TAS-114 plus S-1 than among patients receiving S-1 alone.

The Sponsor concludes that the benefit-risk balance of this combination in the treatment of NSCLC is negative based on current data. No further development of this combination in third- or later-line NSCLC is planned.

Date of the initial report: 30 November 2018