2. SYNOPSIS

Name of Sponsor/Company: Taiho Oncology, Inc. (TOI) and Taiho Pharmaceutical Co., Ltd. (TPC)	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: TAS-102		
Name of Active Ingredient: trifluridine (FTD); tipiracil hydrochloride (TPI)		

Title of Study:

An Open-label, Randomized, Phase 2 Study Comparing TAS-102 versus Topotecan or Amrubicin in Patients Requiring Second-Line Chemotherapy for Small Cell Lung Cancer that is Refractory or Sensitive to First-Line Platinum-Based Chemotherapy

Principal Investigators:

- PPD
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Study center(s):

- Japan: 7 sites approved for study participation; 7 sites initiated, and 4 sites enrolled patients.
- Italy: 10 sites approved for study participation; 10 sites initiated, and 4 sites enrolled patients.
- Germany: 6 sites approved for study participation; 0 sites initiated, and 0 patients were enrolled.

Publications (reference):

None

Studied period (years):		**Phase of development:**
First patient enrolled:	05 July 2013	2
Clinical efficacy data cutoff date except for PFS and safety data cutoff date (except for SAEs, death, and AEs leading to discontinuation):	18 December 2013	
PFS data cutoff date and safety data cutoff date for SAEs, death, and AEs leading to discontinuation:	14 February 2014	

Objectives:

To evaluate the following endpoints for TAS-102 (experimental arm) and Investigator's choice of intravenous (IV) topotecan or IV amrubicin (Control arm) in patients requiring second-line chemotherapy for SCLC refractory or sensitive to first-line platinum-based chemotherapy:

Primary:

- Progression-free survival (PFS)

Key Secondary:

- Overall survival (OS)

Other Secondary:

- Disease control rate (DCR)
- Overall response rate (ORR)
- Duration of response (DR)
- Time to treatment failure (TTF)
- Safety and tolerability

Methodology:

This study was conducted under the sponsorship of Taiho Pharmaceutical Co., Ltd. (TPC) for sites in Japan and Taiho Oncology, Inc. (TOI) for sites in Europe.

This was a multicenter, open-label, 2-arm, randomized Phase 2 study of TAS-102 versus Investigator's choice of therapy (IV topotecan or amrubicin) in patients requiring second-line chemotherapy for SCLC refractory or sensitive to first-line platinum-based chemotherapy. Patients were randomly assigned (1:1) to TAS-102 (experimental arm) or Investigator's choice (Control arm), defined as second-line chemotherapy with IV topotecan (Europe/Japan) or IV amrubicin (Japan). In Japan, the treatment for patients randomized to the Control arm was predetermined by the Investigator prior to randomization.

Randomization took place once the consented patient had completed all the necessary Baseline procedures and was deemed eligible for study entry. Patients were randomly assigned (1:1) to TAS-102 (experimental arm) or Investigator's choice of therapy (Control arm) using a centralized fixed and stratified randomization scheme. Patients were stratified by:

- Sensitivity to first-line platinum-based chemotherapy (sensitive versus refractory) defined as follows:
  - Sensitive: Patients who did not progress within 90 days following the last dose of first-line platinum-based chemotherapy
  - Refractory: Patients unresponsive to first-line platinum-based chemotherapy or who were responsive but had radiologic progression <90 days after the last dose of first-line chemotherapy
- Geographic region (Europe versus Japan)

Study medication was to be started within 3 days after the date of randomization and continued until a study treatment discontinuation criterion was met.

For patients randomized to the TAS-102 arm, study medication was to be administered orally twice daily (BID) on Days 1 through 5, with the first dose administered in the morning of Day 1 of each cycle and the last dose administered in the evening of Day 5, followed by a recovery period from Day 6 through Day 7. TAS-102 was to be administered orally BID on Days 8 through 12, with the first dose administered in the morning of Day 8 of each cycle and the last dose administered in the evening of Day 12, followed by a recovery period from Day 13 through Day 28. Each cycle was to last 28 days.

For patients randomized to the Control arm, treatment was administered according to the country-specific approved prescribing information for IV topotecan (Europe/Japan) or IV amrubicin (Japan).

Patients were to be evaluated for efficacy, including PFS, OS, DCR, ORR, DR, and TTF. Tumor assessments were performed throughout the study based on Response Evaluation Criteria in Solid Tumors (RECIST) as described in Section 9.0 of the study protocol. Computed tomography (CT) scans of the chest/liver/adrenal glands (and magnetic resonance imaging [MRI] of the head in the case of cerebral metastases detected via MRI at Baseline) were performed at Baseline and every 6 weeks from the start of study treatment (Day 1, Cycle 1).

Safety was assessed by monitoring of adverse events (AEs), laboratory evaluations, and electrocardiogram (ECG), assessments.

The Sponsors decided to temporarily suspend enrollment into the study on 13 December 2013, following the provisional assessment of the data from the first 18 treated patients (out of a planned 100), as an apparent imbalance in PFS was observed between the two treatment arms in the study at that point of time.

Following further detailed review of the PFS data from the first 18 treated patients, the Sponsors assessed that the study, although premature in accrual, would be extremely unlikely to support the pre-specified superiority hypothesis for the primary endpoint, PFS. The Sponsors decided to prematurely terminate the study on 19 February 2014 and notified all sites of this termination on 24 February 2014.

At the time the study was prematurely terminated (Appendix 16.1.3 and Appendix 16.1.4):

- There was no evidence of a specific safety concern.
- There were no patients with SCLC being treated with TAS-102.
- Patients in the Control arm who remained on study treatment, would continue to be treated and followed according to the amended study protocol.
- Sites were to continue to work with the clinical CRO, PPD , to ensure successful closure of the study.
- Interactive voice/web response system (IXRS) would be closed as of 28 February 2014. Data entry into IXRS in cases of starting subsequent cycle and treatment discontinuation was not required. Medication for patients on study treatment would be dispensed manually, per Quintiles' instructions to sites.
- Regulatory authorities and ethics committees were notified according to applicable regulations and guidelines.

Number of patients (planned and analyzed):

Planned: 100 patients were planned with a minimum target number of at least 40 evaluable patients in each of the sensitivity subgroups (Sensitive and Refractory). However, only 18 patients were enrolled as enrollment was temporarily suspended by the Sponsor on 13 Dec 2013, with a subsequent decision by the Sponsor to prematurely terminate the study made on 19 February 2014. The Sponsors notified all sites of this termination on 24 February 2014, at which point 18 patients had been treated in the study.

Analyzed: 18 patients analyzed for efficacy and summarized for safety in this synoptic report: 9 patients in TAS-102 arm (3 sensitive, 6 refractory, 5 in Japan, 4 in Italy) and 9 patients in Control arm (5 sensitive, 4 refractory, 4 in Japan, 5 in Italy).

Diagnosis and main criteria for inclusion:

Enrolled patients were to be age 18 years or older (20 years or older for patients enrolled in Japan), who had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2, with histologically confirmed SCLC (limited or extensive disease), sensitive or refractory to platinum-based first-line chemotherapy.

Patients were to have progressed or have had recurrence after first-line chemotherapy and were to have had at least one measurable lesion (as defined by RECIST version 1.1).

Patients with cerebral metastases were to be excluded unless all of the following applied:

- Cerebral metastases had been appropriately treated and controlled, e.g., via surgery and/or radiotherapy.
- Cerebral metastases had been stable for ≥2 months post-intervention.
- The patient was not currently receiving corticosteroids as part of treatment of metastases.

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

TAS-102 was provided as an immediate-release film-coated tablet and supplied in 2 strengths (expressed as FTD content):

- The 15-mg white, round tablet contained 15 mg FTD and 7.065 mg TPI (as hydrochloride) as active ingredients.
- The 20-mg pale, red, round tablet contained 20 mg FTD and 9.420 mg TPI (as hydrochloride) as active ingredients.
- Both tablet strengths contained lactose monohydrate, starch pregelatinized, stearic acid, hypromellose, macrogols, titanium dioxide, and magnesium stearate. The 20-mg tablet also contained iron oxide red.

TAS-102 (35 mg/m^2/dose) was administered orally BID on Days 1 through 5 and Days 8 through 12 of each cycle even if doses were missed or held for any reason during Days 1 through 12.

All patients randomized to the Control arm received IV topotecan (Europe/Japan) or IV amrubicin (Japan). For patients enrolled at study sites in Japan, the Investigator's choice of Control treatment (IV topotecan or IV amrubicin) was predetermined prior to randomization. All Control arm medication (IV topotecan or IV amrubicin) used in this study was the commercially available product and was supplied by the study sites.

Control treatment (regimen/dose) was based on country-specific prescribing information (Appendix C of the protocol) for IV topotecan (Europe/Japan) and IV amrubicin (Japan) as well as following local dosing recommendations at the Investigator's discretion.

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Duration of treatment:

Patients were to receive study treatment until a discontinuation criterion was met.

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

None

Criteria for evaluation:

Efficacy:

Tumor assessments were to be performed every 6 weeks during study treatment and analyzed using RECIST criteria (version 1.1, 2009). Sites of disease manifestation at Baseline were to be followed-up via CT scans of chest/liver/adrenal glands (and MRI of the head in case of cerebral metastases detected via MRI at Baseline).

Safety:

Standard safety monitoring was performed and adverse events (AEs) were graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

Statistical Methods:

Study Populations:

Due to the premature termination of the study and the limited study size, only the Primary Efficacy Population was used for the study analyses, which includes all treated patients according to the treatment randomized.

Study Endpoint – Progression-Free Survival

PFS was defined as the time (in months) from the date of randomization until the date of the investigator-assessed radiological disease progression or death due to any cause. Patients who were alive with no disease progression as of the analysis cutoff date were to be censored at the date of the last tumor assessment. Patients who received non-study cancer treatment before disease progression, or patients with clinical but not radiologic evidence of progression were to be censored at the date of the last evaluable tumor assessment before the non-study cancer treatment was initiated.

Analytical Methods:

Considering the premature termination of the study, the statistical methodology was modified to provide a comprehensive assessment of futility and investigate any adverse safety trends in the limited study population.

Simple descriptive statistics are provided for the overall demographic/Baseline characteristics and by region.

For the primary efficacy endpoint, PFS, the comparison between the two treatment arms for the Primary Efficacy Population is based on the unstratified log-rank test, considering the limited overall study size at the time of the futility analysis and the distribution among the prespecified strata:

a) sensitivity to first-line platinum-based chemotherapy (refractory versus sensitive), and
b) geographic region (Japan versus Europe).

The estimate of the hazard ratio (HR) and 2-sided 80% confidence interval (CI), consistent with the hypothesis tested, as well as the corresponding 2-sided 95% CI is provided using a Cox proportional hazards model. PFS for each arm is summarized using Kaplan Meier curves and further characterized in terms of the median and the corresponding 2-sided 80% and 95% CIs.

The conditional power for the study is derived assuming the hypothesized target PFS HR of 0.6, as well as a retrospectively chosen HR of 0.75. The latter was chosen to reflect a minimum HR of clinical importance in this particular population and indication.

Considering that no a priori futility criteria were specified in the protocol, additional futility considerations are based on within group assessments. Specifically, the futility criteria based on the 2-stage Simon optimal design were derived based on the same study operating characteristics, that is, 1-sided 10% alpha and 80% power. The Progression-free (PF) rate was evaluated at 10 weeks. The target PF rates were based on the hypothesized medians for the Control arm, 3 months, and the targeted rate for the TAS-102 arm, 5 months based on a HR of 0.6. The target PF rates at 10 weeks were derived based on an exponential distribution assumption, as 59% (‘poor’ performance) versus 73% (‘good’ performance).

The study was to be considered futile, for this comparison alone, if 9 or more patients progressed/died by Week 10 out of a possible 23 patients (for a PF rate <61%).

The 2-sided 80% and 95% exact confidence intervals for the PF rates at 10 weeks were also to be derived.

A listing of all patient deaths, on-treatment and during follow-up, was to be presented. Further OS analyses were not warranted considering the very limited number of events.

Considering the very limited exposure in this patient population, safety was to be summarized by treatment group based on AEs reported and coded based on the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Specifically, all AEs were to be summarized using the preferred term, as well as all Grade 3 and higher AEs. Serious adverse events (SAEs) and AEs resulting in treatment discontinuation were to be listed.

RESULTS

DISPOSITION:

Out of a total of 18 patients enrolled in the study, 9 each were randomized to the Control arm and TAS-102 arm. In the Control arm 5 patients in Italy and 1 patient in Japan received IV topotecan, and 3 patients in Japan received IV amrubicin, as study treatment. Eight patients in the TAS-102 arm discontinued treatment due to PD and 1 patient died due to clinical PD during the Safety Follow-up Period. Six patients in the Control arm (5 who received topotecan and 1 who received amrubicin) discontinued due to PD, 1 patient discontinued treatment due to an adverse event, and 2 were ongoing treatment at the date of analysis cutoff. Two patients in the TAS-102 arm and 1 patient who received topotecan in the Control arm died during the survival follow-up period.

EFFICACY RESULTS:

In the limited number of patients followed prior to premature termination of the study (18% of the target accrual), the HR (Cox proportional hazards model) was 3.76 in favor of the Control arm (80% CI: 1.68 - 8.40). The median PFS in the TAS-102 arm was 1.4 months versus 2.7 months in the Control arm. PFS in the Control arm appears within the hypothesized range, based on historical data. A total of 4 patients (3 in the TAS-102 arm and 1 in the Control arm) died following progressive disease (PD). Of these, 1 patient died due to clinical PD.

Based on these observed results at the time of the futility assessment, the conditional power under the hypothesized HR of 0.60 is 16%. Considering the unlikely scenario of the true HR being 0.60, the conditional power was also derived under the assumption of the HR being 0.75, which would reflect a minimal, but still meaningful clinical benefit in this study population. The conditional power under this assumption is 5%.

Finally, considering that no a priori futility criteria were specified in the protocol, additional futility considerations were based on within group (TAS-102) assessments using a 2-stage Simon design. Futility would be reached if 9 or more patients progressed or died by Week 10 out of the first 23 patients randomized in the TAS-102 arm, for a PF rate estimate of less than 61%. All 9 patients in the TAS-102 arm versus 4 patients in the Control arm, experienced PD by Week 10. As a result, the futility criteria based on a 2-stage design were met.

SAFETY RESULTS:

A total of 39 CTCAE Grade 3 or 4 AEs were reported among 12 patients: 6 patients each in the TAS-102 and Control arms. Most of the CTCAE Grade 3 or 4 AEs were hematologic (28/39 events overall, 7/18 events in the TAS-102 arm, and all 21 events in the Control arm) and were considered related (28/39 events overall, 7/18 events in the TAS-102 arm, and all 21 events in the Control arm) to the treatment received.

One patient in the TAS-102 arm died due to clinical PD during the 30-day Safety Follow-up Period.

There were 5 SAEs that occurred in 3 TAS-102-treated patients only. SAEs that were considered unrelated to study drug by the Investigator were Grade 3 asthenia and pyrexia, and Grade 5 hepatic

function abnormal. SAEs of Grade 3 pneumonia and pleurisy were considered related to study drug by the Investigator. No subjects were discontinued from the study due to an SAE.

One patient in the Control Arm was discontinued from study medication (Topotecan) due to due to nonserious adverse events of Grade 4 neutrophil count decreased and platelet count decreased as well as Grade 3 leukopenia and anemia, which were all considered related to study drug by the Investigator.

CONCLUSIONS:

This study was an open-label, randomized, Phase 2 study comparing TAS-102 versus topotecan or amrubicin in patients requiring second-line chemotherapy for small cell lung cancer that was refractory or sensitive to first-line platinum-based chemotherapy. Male and female patients age 18 years or older (20 years or older for patients enrolled in Japan) who had an ECOG performance status of 0, 1 or 2, with histologically confirmed SCLC (limited or extensive disease), sensitive or refractory to platinum-based first-line chemotherapy were enrolled in this study. Patients must have progressed or had recurrence after first-line chemotherapy and must have had at least one measurable lesion (as defined by RECIST version 1.1).

The study was prematurely terminated with limited accrual and PFS events. There were very few deaths to make any quantitative assessments. There was some imbalance between arms with respect to Baseline characteristics, with a few more refractory and extensive disease subjects in the TAS-102 arm. PFS in the Control arm appeared within the range of historical estimates. Within and between treatment group assessments appeared consistent in futility evidence for TAS-102. Based on these results, the study would be extremely unlikely to support the prespecified superiority hypothesis and as such premature termination was warranted. The most frequently reported adverse events across all grades and for Grades 3 and 4 were hematologic. Upon review of available data, the events observed (including hematologic and GI events) were consistent with the established safety profile of TAS-102 in other clinical trials.

Date of the report: 01 July 2014