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A phase 2 randomized study of TAS-102 versus topotecan or amrubicin in patients requiring second-line chemotherapy for small cell lung cancer refractory or sensitive to frontline platinum-based chemotherapy☆

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ABSTRACT

Objectives: TAS-102 is an oral combination treatment comprised of an antimetabolite, trifluridine, a thymidine-based nucleoside analog, and tipiracil hydrochloride, at a molar ratio of 1:0.5. This antimetabolite has demonstrated efficacy in clinical trials, including a global phase 3 trial in metastatic colorectal cancer. As this agent has shown activity greater than cisplatin in small cell lung cancer xenograft mouse models, the objective of this study was to evaluate TAS-102 in the second-line treatment of small cell lung cancer.
Methods: This was a multicenter, open-label, two-arm, randomized phase 2 study designed to compare oral TAS-102 (35 mg/m^2/dose twice daily) versus control (topotecan or amrubicin). Patients requiring second-line chemotherapy for treatment of small cell lung cancer, either refractory or sensitive to frontline platinum-based chemotherapy, were enrolled.
Results: Eighteen patients were enrolled. Eight of nine patients receiving TAS-102 discontinued treatment due to progressive disease and one patient died due to clinical progression during the safety follow-up. Unplanned interim futility considerations were made, and the study was terminated early because it was unlikely that superiority of TAS-102 versus comparator could be demonstrated. Six control patients discontinued therapy due to progressive disease and one due to an adverse event. Median progression-free survival was 1.4 months (range 0.9–1.8) versus 2.7 months (range 1.0–6.8) for TAS-102 and control, respectively, with a hazard ratio of 3.76 (80% CI, 1.68–8.40) favoring control. The most common adverse events with TAS-102 were neutropenia, diarrhea, anemia, anorexia, and fatigue, each in three patients.
Conclusion: TAS-102 showed no evidence of activity in second-line small cell lung cancer.
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1. Introduction

TAS-102 is an oral combination treatment consisting of trifluridine, a thymidine-based nucleoside analog, and tipiracil, at a molar ratio of 1:0.5. The drug has been approved in Japan and the

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United States, and, at the time of journal submission, is awaiting approval in Europe. Although trifluridine inhibits thymidylate synthase, similar to 5-fluorouracil, the primary cytotoxic mechanism associated with oral dosing is incorporation into DNA via phosphorylation, leading to DNA strand breaks [1,2]. This may explain the activity of TAS-102 in human cancer xenografts resistant to 5-fluorouracil [1,3]. Tipiracil hydrochloride improves bioavailability of trifluridine by inhibiting its catabolism by thymidine phosphorylase [4,5]. TAS-102 has shown promise in a number of phase 1 and 2 trials, with a number of patients demonstrating stable disease, primarily in colorectal cancer [6–9]. In a phase 3 trial in patients with metastatic colorectal cancer, TAS-102 demonstrated significant improvements in progression-free survival (PFS) and overall survival (OS) versus placebo, with hazard ratios (HRs) of 0.48 (95% confidence interval [CI], 0.41–0.57) and 0.68 (95% CI, 0.58–0.81), respectively [10].

Small cell lung cancer (SCLC) is an aggressive tumor with a median 5-year survival of only 1% [11]. Frontline treatment with platinum-based chemotherapy is effective, with an objective response rate of 73% [12]. However, treatment options for relapsed SCLC are limited, especially in patients demonstrating chemoresistance. In the SCLC Lu-24 mouse xenograft model, oral administration of 150 or 300 mg/kg/day for 14 days produced a more prolonged suppression of tumor growth than that seen with intravenous cisplatin (7 mg/kg) given on days 1 and 8, suggesting possible activity in SCLC (unpublished data). Therefore, the objective of this randomized phase 2 study was to evaluate TAS-102 in second-line treatment of SCLC.

2. Materials and methods

2.1. Study design and participants

This was a multicenter, open-label, randomized phase 2 study designed to compare TAS-102 versus investigators' choice of topotecan (Europe and Japan) or amrubicin (Japan). The study (Clinicaltrials.gov number NCT01904253) enrolled patients at eight sites in Italy and Japan. All patients provided written informed consent, and the study was conducted according to the Declaration of Helsinki.

Patients requiring second-line chemotherapy for treatment of SCLC were enrolled. Key inclusion criteria included histologically or cytologically confirmed SCLC that had progressed or recurred within 30 days of randomization, ≥18 years of age (≥20 years in Japan), at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST) criteria (version 1.1, 2009), Eastern Cooperative Oncology Group performance status 0–2, ability to receive oral medications, and adequate organ function. Women must have a negative pregnancy test and be willing to use highly effective birth control during the study and up to 6 months after study discontinuation. Key exclusion criteria included serious concurrent illness, brain metastases (unless clinically managed and stable for at least 2 months, and the patient was not receiving corticosteroids), major surgery, anticancer therapy, any investigational agent, or extended-field radiation within 4 weeks, limited-field radiation within 2 weeks prior to study drug administration, and any unresolved toxicity attributed to prior therapy.

2.2. Randomization and treatment

Patients were centrally randomized 1:1 to TAS-102 or investigator's choice (determined prior to randomization) using an interactive voice/web response system. Patients were stratified by sensitivity to frontline platinum (sensitive versus refractory) and by geographic region (Europe versus Japan). TAS-102, available as 15-mg or 20-mg tablets, was given orally with a glass of water at a dose of 35 mg/m^2/dose twice daily (within 1 h of morning and evening meals) on days 1–5 and 8–12 of a 28-day cycle. Up to three dose reductions, in 5-mg/m^2/dose increments, to 20 mg/m^2/dose were permitted. In the event of a Grade 3 adverse event (AE), treatment was suspended until it had resolved to Grade 0 or 1, and treatment restarted at one dose level lower. Amrubicin and topotecan were administered according to local labeling. Treatment was continued until RECIST-defined disease progression, clinical progression, treatment-related Grade 4 nonhematologic event, unacceptable toxicity, physician decision, withdrawal of consent, or pregnancy.

2.3. Assessments

Baseline signs and symptoms, including performance status, were evaluated within 28 days prior to the start of treatment on day 1 of cycle 1, and a complete physical exam was conducted within 5 days prior to randomization. These assessments were repeated within 24 h of each subsequent cycle and at the 30-day follow-up visit. In addition, 12-lead electrocardiogram was performed within 28 days prior to randomization; 2 h after the first dose of TAS-102; on day 12 of cycle 1, 2 h after the am dose; and at the 30-day follow-up visit for the TAS-102 arm. Blood samples for hematology and serum chemistry were collected within 5 days prior to randomization, on days 8, 15, and 21 of cycle 1, and on days 1, 8, 15, and 21 of each cycle thereafter for the TAS-102 arm.

2.4. Outcomes

The primary endpoint was PFS, defined as time from randomization until date of investigator-assessed radiological disease progression or death from any cause. OS (time from randomization to death) was a key secondary endpoint. Patients included in the safety analysis set (all patients who received study drug) were evaluated for AEs and hematologic and chemistry abnormalities. AEs were assessed using Common Terminology Criteria for Adverse Events (version 4.03).

2.5. Statistics

Sixty-nine disease progression or death events were required to detect a 40% risk reduction in the TAS-102 arm compared with control; HR for PFS of 0.6 and two-sided 80% CI was derived using a Cox proportional hazards model. It was estimated that 100 randomized patients were required to meet this endpoint. Similarly, 69 deaths were required for analysis of OS. Efficacy analyses were based on the primary efficacy population consisting of all randomized patients.

Differences in PFS and OS between the two groups were compared using an unstratified log-rank test. Based on an unplanned preliminary assessment of futility, a decision was made to suspend enrollment after 18 patients were randomized until futility results were confirmed. Considering the premature termination of the study, the statistical methodology was modified to provide a comprehensive assessment of futility and to investigate any adverse safety trends. The study was to be considered futile if ≥9 patients out of a possible 23 in the TAS-102 arm progressed or died by week 10 (progression-free rate [PF] <61%), based on a two-stage Simon design (one-sided 10% alpha and 80% power to detect 59% PF versus 73% PF).

3. Results

Eighteen patients were enrolled and randomized (Fig. 1). Baseline characteristics are shown in Table 1. Due to the small numbers enrolled, there was some imbalance between arms, with more

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