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Introduction

Tasisulam sodium (hereafter referred to as tasisulam) is a novel anticancer compound that induces apoptosis and exhibits antiangiogenesis activity in a broad range of cancer models, including non–small-cell lung cancer (NSCLC).

Methods

Tasisulam was administered as a 2-hour infusion every 21 days as third-line treatment in patients with advanced (stage IIIB/IV) NSCLC.

Results

Thirty-two patients received a C_{max} target dose of 420 µg/ml. Median time to progression was 3.12 months, median progression-free survival was 2.69 months, and median overall survival was 8.48 months. There were no objective responses; 43.8% of patients achieved stable disease. A high rate of grade-4 hematologic toxicity in the first 30 patients led to exploration of a lower C_{max} target dose of 380 µg/ml. The rate of grade-4 hematologic toxicity (thrombocytopenia and/or neutropenia) at the 380-µg/ml dose (n = 20) was 20% versus 34% at the 420-µg/ml dose.

Conclusions

Tasisulam has only modest activity as a third-line treatment of patients with unresectable/metastatic NSCLC. The high rate of grade-4 hematologic toxicity observed with this highly albumin– bound compound in this patient population provided challenges for fixed C_{max}-based dosing. Alternative dosing methods, including varying the C_{max} target dose by predose albumin, are under investigation in other studies.

Key Words

- Chemotherapy;
- Non–small-cell lung cancer;
- Phase II;
- Tasisulam

Tasisulam sodium (hereafter referred to as tasisulam), a novel antineoplastic agent,[1] has shown broad activity in cancer cell lines, including non–small-cell lung cancer (NSCLC), and has a unique activity profile.[2] Preclinical in vitro data indicate that tasisulam induces apoptosis of tumor cells by the intrinsic cell-death pathway,[3] and causes an accumulation of cells in the gap 2/mitosis phase of the cell cycle. The precise cellular target of tasisulam is under investigation.

In an initial phase-I study, extensive pharmacokinetic analysis of tasisulam revealed significant interpatient variability in peak plasma concentration (C_{max}) and patient tolerability with repeated flat dosing, and an unexpectedly high degree of high-affinity albumin binding (99.7%–99.9%).[4] This

led to the implementation of a lean body-weight–based[5] dosing paradigm that reduced pharmacokinetic variability and led to the determination of the maximum tolerated dose of tasisulam, with a C_{max} target of 420 µg/ml, which was brought forward into the phase-II program. Among the heavily pretreated patients in the phase-I study, two patients with NSCLC received at least 10 cycles of tasisulam (minimum of 7 months) before disease progression, suggesting a possible clinical benefit.

These findings prompted the current phase-II study in patients undergoing third-line treatment for metastatic or unresectable NSCLC. The primary objective of this nonrandomized, open-label, multicenter phase-II study was to estimate time to progression (TTP). Secondary objectives included evaluations of progression-free survival (PFS), duration of stable disease, objective response rate, overall survival (OS), pharmacokinetics, and safety.

PATIENTS AND METHODS

Patient Eligibility

Key eligibility criteria were male or female sex; age 18 years or more; histological or cytological diagnosis of unresectable stage IIIB or metastatic NSCLC; two previous systemic treatments, including one prior platinum-based regimen; measurable disease, as defined by the Response Evaluation Criteria in Solid Tumors[6]; and Eastern Cooperative Oncology Group performance status zero or one. Because tasisulam sodium is highly albumin bound, a serum albumin level of 30 g/l (3.0 g/dl) or more was also required. This study was approved by the local Institutional Review Board of each participating center. Written informed consent was obtained from all patients before they underwent any study procedure or received study treatment.

Treatment and Assessments

Tasisulam sodium (Eli Lilly and Company, Indianapolis, IN) was administered as a 2-hour (±10 minutes) intravenous infusion at a target C_{max} of 420 µg/ml on day 1 of 21-day cycles. A loading dose was administered in cycle 1, followed by a chronic dose in subsequent cycles, which was 65% of the loading dose. A lower target C_{max} dose of 380 µg/ml, with a 75% chronic dose, was also investigated. The investigators used a validated, Compact Disc—read-only-memory-based dosing calculator, and entered the height and weight of the patient and the cycle number of treatment (loading or chronic dose).[4] The dosing calculator provided the dose (in mg) required to reach the specific C_{max} target.

The first postbaseline radiographic assessment by computed tomography was performed at the end of cycle 2, with subsequent scans performed at the end of every other cycle. Radiologic confirmation of response was performed at least 28 days from response detection, using the same method as at baseline. Tumors were evaluated according to Response Evaluation Criteria in Solid Tumors Version 1.0.[6] Adverse events (AEs) were rated using the Common Terminology Criteria for Adverse Events, version 3.0. Treatment-related AEs were considered by the investigator to be possibly related to the study drug.

Blood samples for cycle 1 were collected at the following time points: predose; 2 hours (end of infusion), at one time point from 12 to 36 hours, and at one time point from 72 to 168 hours. The population pharmacokinetic dataset was analyzed using the nonlinear mixed-effects modeling program NONMEM (Version 6) with PREDPP (Version V) (ICON plc; Dublin, Ireland).[7] The final two-compartment total drug model that was developed from the previous phase-I trial[4] was applied to the current pharmacokinetic analysis.

Statistical Considerations

A sample size sufficient to exclude 2.2 months from a 90% confidence interval (CI) would be desired if the true median TTP for tasisulam was 4 months. On the basis of results from 500 simulated trials under these assumptions, a recruitment rate of five patients per month, and a 12-month follow-up period for each patient, a sample size of 50 patients would provide an 80% probability that the lower limit of the 90% CI of the median would exclude 2.2 months.[8,9]

The objective response rate, the clinical benefit rate, and the 90% CIs were estimated using unadjusted normal approximation for binomial proportions (z approximation). Kaplan-Meier analyses, including estimations of 90% CIs, were performed on the observed survival distributions of TTP and OS.

RESULTS

Between September 2006 and February 2008, 52 patients were enrolled in the study at seven study sites in Germany and Italy. Thirty-two patients received the original planned target C_{max} dose of 420 µg/ml (with a chronic dose that was 65% of the cycle-1 loading dose). Preliminary review of the ongoing safety data showed that 10 of the first 30 treated patients experienced grade-3/4 hematologic toxicity (mainly grade 4) during cycle 1, which prompted exploration of a lower target C_{max} dose of 380 µg/ml, with a chronic dose of 75% (*n* = 20). In addition, the cycle-1 loading dose was capped at an absolute maximum dose of 2500 mg at the 380-µg/ml dose level. Patient characteristics are summarized in Table 1.

TABLE 1.

Baseline Demographics and Disease Characteristics

Characteristic	**Target C_{max} 420 µg/ml (N = 32)**	**Target C_{max} 380 µ/ml (N = 20)**	**Total (N = 52)**
Age, median (range), yrs	61.5 (38.0–73.0)	61.0 (45.0–73.0)	61.0 (38.0–73.0)
Sex, *n* (%)			
Female	7 (21.9)	6 (30.0)	13 (25.0)
Male	25 (78.1)	14 (70.0)	39 (75.0)
Race, n (%)			
Caucasian	32 (100.0)	20 (100.0)	52 (100.0)
Pathological diagnosis, n (%)			
Squamous-cell carcinoma	11 (34.4)	7 (35.0)	18 (34.6)
Nonsquamous-cell carcinoma	21 (65.6)	13 (65.0)	34 (65.4)
Adenocarcinoma	12 (37.5)	12 (60.0)	24 (46.2)

Characteristic	Target C_{max} 420 µg/ml (N = 32)	Target C_{max} 380 µ/ml (N = 20)	Total (N = 52)
Poorly differentiated NSCLC	6 (18.8)	1 (5.0)	7 (13.5)
Large-cell carcinoma	2 (6.3)	0 (0.0)	2 (3.8)
Bronchoalveolar carcinoma	1 (3.1)	0 (0.0)	1 (1.9)
Disease stage, n (%)			
Stage IIIB	5 (15.6)	4 (20.0)	9 (17.3)
Stage IV	27 (84.4)	16 (80.0)	43 (82.7)
ECOG performance status, n (%)			
0	19 (59.4)	10 (50.0)	29 (55.8)
1	13 (40.6)	10 (50.0)	23 (44.2)
Smoking status, n (%)			
Yes	6 (18.8)	5 (25.0)	11 (21.2)
No	18 (56.3)	12 (60.0)	30 (57.7)
Missing/not assessed	8 (25.0)	3 (15.0)	11 (21.2)

Some percentages do not add up to 100 because of rounding.

ECOG, Eastern Cooperative Oncology Group; N, number of patients; NSCLC, non–small-cell lung cancer.

Efficacy

Efficacy parameters are summarized in Table 2 and FIGURE 1 and FIGURE 2. Median TTP was 3.12 months at the original target C_{max} dose of 420 µg/ml (censoring rate of 12.5%) and 1.64 months (censoring rate 25.0%) at C_{max} 380 µg/ml. Median PFS and OS at C_{max} 420 µg/ml were 2.69 and 8.48 months, respectively. There were no objective responses; 14 patients (43.8%) achieved stable disease (SD) at C_{max} 420 µg/ml as did 7 patients (35.0%) at C_{max} 380 µg/ml; median SD durations were 4.21 and 4.93 months, respectively. In the post hoc analysis of TTP by histology, median TTP (for both dose groups combined) was longer for patients with squamous-cell carcinoma (n = 12, 4.21 months, 90% CI: 2.69, 5.72) versus patients with nonsquamous-cell histology (n = 31, 2.04 months, 90% CI: 1.38, 3.52; defined as large-cell carcinoma, adenocarcinoma, poorly differentiated carcinoma, and bronchoalveolar carcinoma; however, this difference was not significant (p = 0.3297).

TABLE 2.

Efficacy Parameters

Parameters	**Target C_{max} 420 µg/ml (N = 32)**	**Target C_{max} 380 µg/ml (N = 20)**
Time-to-Event Parameters, 90% CI, months		
Median time to progression[a]	3.12 (2.04–4.21)	1.64 (1.35–5.19)
Median progression-free survival[b]	2.69 (1.38–4.17)	1.43 (1.31–3.22)
Median overall survival[c]	8.48 (5.06–10.15)	7.97 (4.07–12.06)
Response		
Objective response (CR or PR), *n* (%)	0 (0.0)	0 (0.0)
Stable disease, *n* (%)	14 (43.8)	7 (35.0)
Progressive disease, *n* (%)	7 (21.9)	7 (35.0)
Unknown, *n* (%)	11 (34.4)	6 (30.0)
Median duration of stable disease[d](90% CI), months	4.21 (3.58–5.72)	4.93 (3.22–10.35)

CI, confidence interval; CR, complete response, PR, partial response.

a

Time from the date of the first dose to the first date of progressive disease or death from study disease.

b

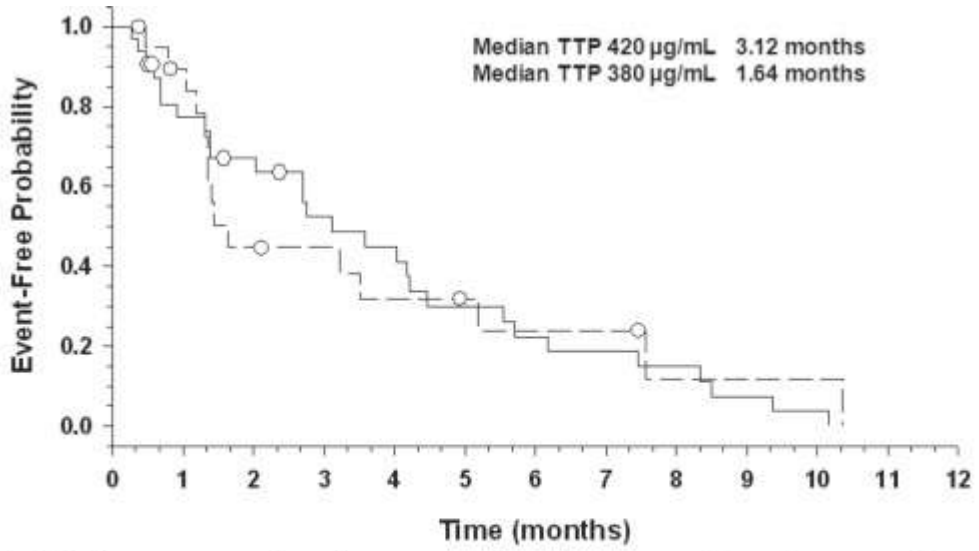
Time from the date of the first dose to the first date of progressive disease or death from any cause.

c

Time from the date of the first dose to the date of death from any cause.

d

Time from the date of the first dose until documented progressive disease. The minimal time interval required between two measurements for determination of stable disease was 6 weeks (±72 hours).

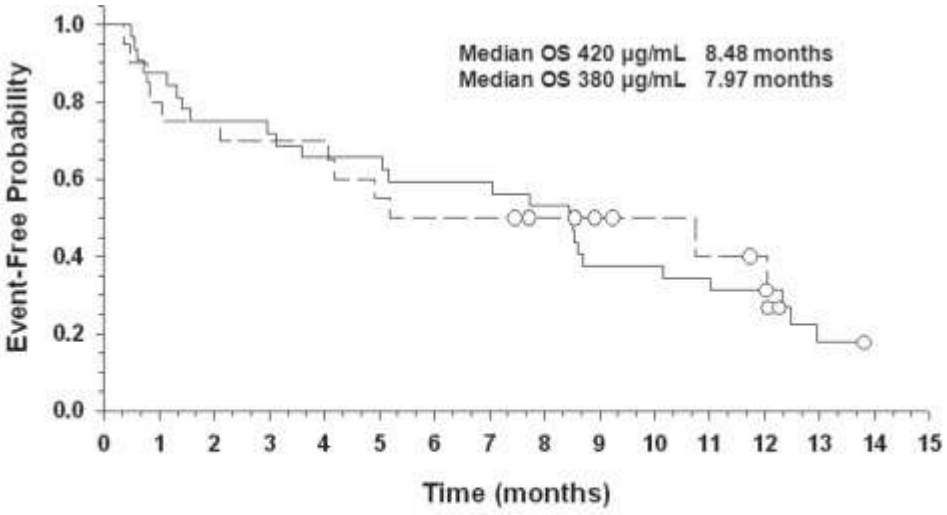


Probability (90% CI):	3 months	6 months	9 months	12 months
420 µg/mL	0.52 (0.36, 0.66)	0.22 (0.11, 0.36)	0.07 (0.02, 0.19)	0.00
380 µg/mL	0.45 (0.25, 0.62)	0.24 (0.09, 0.43)	0.12 (0.02, 0.33)	0.00

FIGURE 1.

Kaplan-Meier curve for time to progression (TTP). Circles represent censored observations. The probabilities of not progressing at 3, 6, 9, and 12 months are shown below the graph. CI, confidence interval; 380 µg/ml, target C_{max} of 380 µg/ml (*n* = 20; censoring rate = 25.0%); 420 µg/ml, target C_{max} of 420 µg/ml (*n* = 32; censoring rate = 12.5%).

Figure options



Probability (90% CI):	3 months	6 months	9 months	12 months	15 months
420 µg/mL	0.72 (0.56, 0.83)	0.59 (0.44, 0.72)	0.38 (0.24, 0.51)	0.31 (0.19, 0.45)	0.18 (0.08, 0.32)
380 µg/mL	0.70 (0.50, 0.83)	0.50 (0.31, 0.67)	0.50 (0.31, 0.67)	0.40 (0.20, 0.59)	0.27 (0.08, 0.50)

FIGURE 2.

Kaplan-Meier curve for overall survival (OS). Circles represent censored observations. The probabilities being alive at 3, 6, 9, 12, and 15 months are shown below the graph. CI, confidence interval; 380 µg/ml, target C_{max} of 380 µg/ml (*n* = 20; censoring rate = 40.0%); 420 µg/ml, target C_{max} of 420 µg/ml (*n* = 32; censoring rate = 21.9%).

Safety

The most common grade-3/4 AEs considered possibly related to the study drug (both dose groups) were thrombocytopenia (37%) and neutropenia (29%) (Table 3). Grade-4 hematologic toxicity (thrombocytopenia and/or neutropenia) occurred in 11 patients (34%) at the target C_{max} dose of 420 µg/ml, most often during cycle 1 (seven patients). At the 380-µg/ml dose level, grade-4 hematologic toxicity occurred in 4 patients (20%).

TABLE 3.

Incidence of Drug-Related Treatment-Emergent Adverse Events,[an (%)]

	Target C_{max} 420 µg/ml (N = 32)		**Target C_{max} 380 µ/ml (N = 20)**	
Adverse Events	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Hematologic				
Thrombocytopenia	3 (9.4)	11 (34.4)	2 (10.0)	3 (15.0)
Neutropenia	4 (12.5)	5 (15.6)	4 (20.0)	2 (10.0)
Anemia	4 (12.5)	1 (3.1)	1 (5.0)	0 (0.0)
Leukopenia	2 (6.3)	1 (3.1)	0 (0.0)	1 (5.0)
Blood/bone-marrow/other	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
Nonhematologic				
Febrile neutropenia	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspnea	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
Fatigue	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
Fever	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperglycemia	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
Nausea	1 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
Pneumonitis/pulmonary infiltrates	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)

	Target C_{max} 420 µg/ml (N = 32)		Target C_{max} 380 µ/ml (N = 20)	
Adverse Events	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Rash: acne/acneform	0 (0.0)	0 (0.0)	1 (5.0)	0 (0.0)
Sinus tachycardia	0 (0.0)	1 (3.1)	0 (0.0)	0 (0.0)

CTCAE, Common Terminology Criteria for Adverse Events, version 3; MedDRA, Medical Dictionary for Regulatory Activities.

A MedDRA terms with CTCAE, version 3.0, grading.

Seven deaths were attributed to AEs, of which two occurred in the setting of AEs considered possibly related to the study drug; these AEs were hypovolemic shock (C_{max} 420 µg/ml) with unknown etiology, and respiratory failure (C_{max} 380 µg/ml) in the course of radiation pneumonitis, radiation pneumonitis/pleuritis, and bronchopneumonia.

Pharmacokinetics

For the target C_{max} doses of 420 and 380 µg/ml, cycle-1 geometric means were 380 µg/ml (range, 250–496) and 338 µg/ml (range, 260–440), respectively. Observed C_{max} values were within 20% of the target dose for 92% (C_{max} 420 µg/ml) and 75% (C_{max} 380 µg/ml) of the patients. Given the sparse sampling in this phase-II study, estimation of pharmacokinetic parameters required incorporating the pharmacokinetic data from the first human phase-1 study.[4] Consistent with previous observations,[4] tasisulam demonstrated a bi-exponential disposition pattern with a predicted distribution half-life ranging from 0.2 hour to 1.2 hours, and a median terminal elimination half-life of 12 days, likely reflecting the high-affinity binding of tasisulam to albumin.

DISCUSSION

Second-line therapy with pemetrexed or docetaxel,[10] or second-/third-line therapy with the epidermal growth factor receptor-tyrosine kinase inhibitor erlotinib[8] demonstrated response rates of approximately 9%, median TTP of approximately 3.5 months, and PFS of 2 to 3 months. Our study of third-line tasisulam administration in NSCLC suggests modest activity, with a median TTP of 3.12 months, no complete or partial responses, and a PFS of 2.69 months at C_{max} 420 µg/ml. Although there were no responses in the current study, the SD rate of 43.8% is comparable with such rates in second- to fourth-line treatments for NSCLC (37%–43%).[8],[10],[11] The observed PFS (2.69 months at C_{max} 420 µg/ml) is consistent with that in other studies of heavily pretreated patients with NSCLC. [8], [10] and [11]

The predominant toxicity of tasisulam was bone-marrow suppression, particularly grade-4 thrombocytopenia and/or neutropenia. This toxicity proved particularly challenging in this heavily pretreated patient population, as these events occurred in 11 of 32 patients (34%) at the target C_{max} 420-µg/ml dose level, and were associated with four of the six discontinuations. Of note, four of the seven patients with grade-4 thrombocytopenia and/or neutropenia in cycle 1 had clinical signs of disease progression, suggesting that tumor-related cachexia and declining albumin (to which tasisulam is highly bound) may also have contributed to the development of this toxicity.

The exploratory, lower dose of tasisulam (target C_{max} of 380 μg/ml) was associated with a lower rate of grade-4 thrombocytopenia and/or neutropenia (four of 20 patients; 20%); median TTP and PFS were 1.64 months and 1.43 months, respectively. Although the small sample sizes precluded formal statistical efficacy/safety comparison of the C_{max} dosing groups, these results suggest that a fixed reduction in target C_{max} dose for all patients may not have provided the optimal balance of efficacy and safety.

In summary, tasisulam administered as a 2-hour infusion in 21-day cycles only had modest activity as a third-line treatment of patients with metastatic or unresectable NSCLC. Although the nonhematologic toxicity profile of tasisulam was relatively favorable relative to standard chemotherapeutic agents like taxanes and cisplatin, bone-marrow suppression proved dose limiting in this heavily pretreated patient population. Lowering the target C_{max} dose of tasisulam was associated with a lower risk of grade-4 hematologic toxicity, but further studies will be required to identify pharmacokinetic and patient factors that might further optimize dosing. Alternative dosing methods, including varying the target C_{max} dose by predose albumin, are under investigation in other studies.

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