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ORIGINAL ARTICLE

Phase 1 first-in-human clinical study of *S-trans*, *trans*-farnesylthiosalicylic acid (salirasib) in patients with solid tumors

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Abstract
Purpose This phase I first-in-human trial evaluated salirasib, an *S*-prenyl derivative of thiosalicylic acid that competitively blocks RAS signaling.
Methods Patients with advanced cancers received salirasib twice daily for 21 days every 4 weeks. Doses were escalated from 100 to 200, 400, 600, and 800 mg.
Results The most common toxicity was dose-related diarrhea (Grade 1–2, 79% of 24 patients). Other toxicities included abdominal pain, nausea, and vomiting. No Grade 3–4 toxicity was noted. Nineteen (79%) patients had no drug-related toxicity >Grade 1. Dose-limiting toxicity (DLT) was not reached, but all three patients treated with 800 mg experienced Grade 1–2 diarrhea, abrogating dose escalation. Six patients were treated at a dose of 600 mg with no DLTs. Seven (29%) patients had stable disease on salirasib for ≥4 months (range 4–23+). The salirasib pharmacokinetic profile was characterized by slow absorption and a rapid elimination phase following oral administration. Salirasib exposure (C_{max}; day 1 AUC_{inf} vs. day 15 $AUC_{0-12\,h}$) was similar between days 1 and 15 ($P > 0.05$). The $T_{1/2}$ (mean ± SD) was 3.6 ± 2.2 h on day 1.
Conclusions Salirasib therapy was well tolerated. The recommended dose for phase II studies is 600 mg twice daily.

Keywords FTS · Solid tumors · Phase I · Toxicity · Pharmacokinetics

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Introduction

Salirasib (*S-trans*, *trans*-farnesylthiosalicylic acid, FTS, Concordia Pharmaceuticals, Ft. Lauderdale, FL), an orally available *S*-prenyl derivative of thiosalicylic acid resembling the carboxyl-terminal farnesylcysteine common to oncogenic Ras proteins, competitively blocks intracellular signaling through the RAS cascade [1]. Three members of the RAS family, the H-RAS, K-RAS, and N-RAS isoforms, are activated by mutation in human cancers [2]. Activated RAS proteins are involved in regulating many malignant cell functions, including proliferation, differentiation, survival, and induction of angiogenesis [3, 4]. RAS mutations are found in approximately one-third of human cancers, with mutations in the *K-Ras* gene found in 90% of pancreatic and 50% of colorectal carcinomas [5].

RAS requires attachment to the membrane binding site for biologic activity and, therefore, the Ras cascade can be interrupted by interfering with the binding of RAS to its plasma membrane anchor protein [6]. Salirasib acts by dislodging all the isoforms of Ras from membrane binding sites and inhibits the growth of Ras-driven cancer cells in vitro [7, 8]. The competitive dislodgement of all RAS isoforms from membrane-binding sites differentiates salirasib from farnesyltransferase inhibitors (FTIs) currently in

development. Unlike salirasib, FTIs such as tipifarnib, lonafarnib, and BMS-214662 do not block the oncogenic activity of the oncoproteins K-Ras and N-Ras because an alternative prenylation process is utilized by these isoforms [9, 10]. This alternative escape pathway limits the activity of FTIs when farnesyltransferase is blocked by these drugs [11, 12].

Preclinically, salirasib bioavailability was shown to be 69.5% for oral carboxymethyl-cellulose (CMC) and 55% for oral corn oil suspensions [13]. The metabolism of salirasib is primarily mediated by the human cytochrome P450 (CYP450) 2C subfamily, particularly the CYP2C19, 2C9, and 2C8 isozymes. Salirasib has shown little or no inhibition of any CYP450 isoenzyme.

Several in vitro and in vivo studies have reported on salirasib. Gene expression profiling studies suggest that salirasib specifically reregulates defective Ras pathways in human cancer [14]. Salirasib was also shown to induce apoptosis in glioblastoma multiforme by release of the apoptosis "brake" (survivin) and activation of the mitochondrial apoptotic pathway, including dephosphorylation of Bad, activation of Bax, release of cytochrome *C*, and caspase activation [15]. Significant growth delays and tumor stasis have been shown in in vitro cell lines [7, 16] and human xenografts [17] derived from breast, lung, colon, pancreatic, ovarian, brain, and epidermoid cancers. Orally administered salirasib inhibits human pancreatic tumor growth in nude mice [13], and salirasib has also demonstrated synergistic activity with gemcitabine in inhibiting human pancreatic tumor growth in nude mice, which resulted in improved survival [13].

The novel mechanism of action of salirasib as a RAS antagonist, and its preclinical antitumor activity, served as the impetus for its clinical development. To assess the safety and activity of salirasib in humans, we conducted the first phase I clinical trial of salirasib in patients with solid tumors and lymphoma, excluding multiple myeloma. The primary objectives of this study were to determine a safe dose of salirasib for phase II studies, to assess adverse events and pharmacokinetics, and to describe any response or clinical benefit.

Materials and methods

Patients

Eligibility criteria included a histologically confirmed solid tumor, lymphoma, or multiple myeloma that failed therapy of proven efficacy or for which no conventional therapy was available; age $\geq$18 years; body weight >50 kg; and Zubrod performance status 0–2. Other criteria were a serum creatinine level $\leq$2.0 mg/dL; total bilirubin $\leq$2.0 mg/dL; ALT and AST $\leq 3 \times$ the upper limit of normal (ULN); alkaline phosphatase $\leq 3 \times$ ULN (or if the alkaline phosphatase is determined to be of non-hepatic origin, no more than $5 \times$ ULN); leukocyte count $>3 \times 10^9$/L; absolute neutrophil count $>1.5 \times 10^9$/L; platelet count $>100 \times 10^9$/L; and hemoglobin level >10 g/dL. Signed informed consent was obtained from all participants in accordance with institutional policy. The study was approved by the Institutional Review Board. All patients were recruited at The University of Texas M. D. Anderson Cancer Center.

Treatment plan and endpoints

Salirasib was administered orally as a gelatin capsule containing microcrystalline cellulose and 50, 100, or 200 mg of salirasib for 21 days every 28 days as a flat, non-body-surface-area-adjusted dose. Doses were escalated from 100 mg twice daily to 200, 400, 600, and 800 mg twice daily. The trial allowed enrollment of 3–6 patients at each dose level as needed to obtain additional safety information. A one-time intrapatient dose escalation was permitted for the first three dose levels. The National Cancer Institute Common Toxicity Criteria version 3.0 was used to grade toxicity.

Dose-limiting toxicity (DLT) was defined as an adverse event that met any of the following criteria: Grade 4 hematologic toxicity; Grade 3 non-hematologic toxicity; or inability to begin a subsequent treatment course within 7 days of the scheduled start date because of treatment-related toxicity. Treatment was continued until unacceptable toxicity, disease progression (by RECIST criteria) [18], non-compliance, or withdrawal of consent occurred.

Assessment of antitumor activity

Responses were assessed, using the response evaluation criteria in solid tumors (RECIST) [18], after every two cycles and after withdrawal from the study. Baseline positron emission tomography with radiolabeled [^{18}F]-2-fluoro-deoxy-D-glucose (PET-FDG) was performed within 2 weeks before initiation of salirasib therapy. PET-FDG was repeated between days 22 and 28 of the first chemotherapy cycle and then between days 22 and 28 of the second treatment cycle. Patients treated at the third dose level (400 mg twice daily) and the fourth dose level (600 mg twice daily) were screened and monitored for response by PET/computed tomography (CT) imaging (performed at baseline, day 22 and 28 of the first chemotherapy cycle and then between days 22 and 28 of the second treatment cycle).

Pharmacokinetic studies

Pharmacokinetic studies were performed on days 1, 8, and 15 of the first treatment cycle. Blood samples were

collected in lithium heparin-containing tubes before salirasib administration and at 0.5, 1, 1.5, 2, 4, 6, 8, and 24 h after administration of salirasib on days 1 and 15. On day 8, blood samples were collected before and 1 h after administration of salirasib. Samples were processed within 30 min of collection by centrifugation for 10 min at 1,500*g* under refrigeration (~2 to 8°C). The plasma supernatant was stored at −80°C until subsequent analysis using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) method developed by Ricerca Biosciences (Cleveland, OH) [19]. Briefly, salirasib was extracted from plasma using acetonitrile precipitation. Separation of salirasib and the internal standard, *S-trans, trans*-5-fluoro-farnesylthiosalicylic acid, was achieved on a Phenomenex Aqua C18 (3 µm, 50 × 2 mm ID) analytical column using a mobile phase consisting of acetonitrile/ammonium acetate (5 mM containing formic acid [0.05%, v/v] [85:15, v/v]) and an isocratic flow of 0.30 mL/min. Salirasib and the internal standard were monitored by tandem-mass spectrometry with electrospray negative ionization. Detection was performed by monitoring the ion transitions from *m/z* 357.2 → 153.2 for salirasib and *m/z* 375.1 → 171.2 for the internal standard. The linear calibration curves were generated over the range of 1–500 ng/mL. Plasma samples that were diluted 1:10 (v/v) or 1:100 (v/v) with pooled plasma were accurately quantified. The accuracy and within- and between-day precision met the acceptance criteria for bioanalytical assays [20].

Analysis of pharmacokinetic studies

Pharmacokinetic parameters were calculated from salirasib concentration-time data using standard non-compartmental methods, as implemented in WinNonlin version 5.2 (Pharsight Corp., Mountain View, CA) [21]. If the pretreatment sample was obtained after salirasib administration or if the 24-h sample was obtained after a second dose of salirasib, the concentration was excluded from the analysis. The following pharmacokinetic parameters were calculated: maximum plasma concentration (C_{max}), the time to C_{max} (T_{max}), the terminal half-life ($T_{1/2}$) on day 1, area under the concentration–time curve (AUC) to infinity (AUC_{inf}) on day 1 and to 12 h on day 15, and apparent systemic clearance (Cl/F).

Statistical methods

Pharmacokinetic parameters were summarized using descriptive statistics for each dose level and pharmacokinetic period. Differences between the pharmacokinetic parameters of salirasib on days 1 and 15 were evaluated statistically by use of a Wilcoxon matched pairs signed-rank test. Kruskal–Wallis analysis of variance by ranks was used to compare the differences in Cl_s/F and dose-normalized C_{max} and AUC as a function of dose level. All statistical tests were performed using JMP Statistical Discovery software (version 7; SAS Institute, Cary, NC). The a priori level of significance was set at $P < 0.05$.

Results

Patient demographics

From May 2006 to March 2007, 25 patients with advanced solid tumors and lymphoma (excluding multiple myeloma) were enrolled in this phase I clinical trial, and 24 were evaluable (one patient's insurance company denied payment prior to initiation of therapy). Performance status was 1 in 22 (92%) patients and 0 in 2 (8%) patients. Three patients [1 with medullary thyroid carcinoma and 2 with neurofibromatosis type 2 [NF2]-associated tumors (ependymomas, $n = 1$ and ependymomas, schwannomas, and meningiomas, $n = 1$)] had no prior systemic therapy (only resection of their tumors). The remaining patients had a median of three prior therapies (range 1–7) (Table 1). Fourteen patients had received prior radiation therapy.

Toxicity

To date, a total of 103 cycles of salirasib therapy have been administered. The median number of cycles per patient was 2 (range 1–13 cycles). All patients were treated at their initial dose level, except for one patient whose dose was escalated from 100 to 200 mg in the second cycle (total cycles, 2). The drug-related adverse events by dose are listed in Table 2. Only Grade 1–2 drug-related toxicities occurred. The most common toxic effect was diarrhea, which occurred in 79% of the patients (Grade 1 in 75% and Grade 2 in 4%). The duration of diarrhea increased with the salirasib dose. The frequency of diarrhea also was higher in patients treated with higher salirasib doses: 67% (2 of 3 patients), 67% (4 of 6), 100% (6 of 6), 67% (4 of 6), and 100% (3 of 3) in patients treated with 100, 200, 400, 600, and 800 mg of salirasib twice daily, respectively. Diarrhea did not result in abnormalities in clinical chemistry parameters, and it was usually reversible with oral antidiarrheal agents such as loperamide or diphenoxylate hydrochloride. Patients were instructed to use these medications if diarrhea occurred. Nineteen (79%) patients had no toxicities greater that Grade 1. Other toxicities included abdominal pain in 21% of patients and nausea, vomiting, and fatigue in 17% each. No classic DLT was reached at 800 mg twice daily, the highest dose tested. However, all three patients treated at this dose developed Grade 1–2 prolonged diarrhea, and it was decided that further dose escalation would not be tolerable. At 600 mg p.o. twice daily, no patients experienced a

Table 1 Patient demographics

Characteristics	Number of patients by salirasib dose, mg BID					
	100 ($N = 3$)	200 ($N = 6$)	400 ($N = 6$)	600 ($N = 6$)	800 ($N = 3$)	All doses ($N = 24$)
Age (years)						
Median	66	51	61	51	61	55
Range	39–76	36–74	28–69	37–66	26–64	26–76
Sex						
Male	2	3	2	2	2	11
Female	1	3	4	4	1	13
Race						
Caucasian	2	6	5	6	3	22
Asian	1	0	1	0	0	2
Type/site of tumor						
Colon	2	2	–	–	1	5
Appendix	–	–	1	2	–	3
Neurofibromatosis type 2	–	–	–	1	1	2
Pancreas	–	1	–	–	1	2
Other	1[a]	3[b]	5[c]	3[d]	–	12

[a] Parotid gland

[b] Lacrimal gland, thyroid, and unknown cancer

[c] Uterus, buccal mucosa, osteosarcoma, carcinoid, and breast cancer

[d] Ocular melanoma, carcinoid, and renal cancer

Table 2 Toxicities by salirasib dose in patients with advanced solid tumors [all Grade 1–2 (G1, G2)]

Toxicities (%)	Number of patients by salirasib dose, mg BID											
	100 mg ($N = 3$)		200 mg ($N = 6$)		400 mg ($N = 6$)		600 mg ($N = 6$)		800 mg ($N = 3$)		All mg ($N = 24$)	
	G1	G2	G1	G2	G1	G2	G1	G2	G1	G2	G1	G2
Diarrhea	2 (67)	–	4 (67)	–	6 (100)	–	4 (67)	–	2 (67)	1 (33)	18 (75)	1 (4)
Abdominal pain	–	–	1 (17)	3 (50)	–	–	–	1 (17)	–	–	1 (4)	4 (17)
Nausea	–	–	–	–	1 (17)	–	2 (33)	1 (17)	–	–	3 (13)	1 (4)
Fatigue	–	–	3 (50)	–	1 (17)	–	–	–	–	–	4 (17)	–
Vomiting	–	–	–	1 (17)	1 (17)	–	1 (17)	1 (17)	–	–	2 (8)	2 (8)

DLT or prolonged diarrhea, and therefore, it was felt that this dose would be optimal for the phase II study.

Antitumor effects

Although this was primarily a safety and pharmacokinetic study, all patients who completed at least one cycle of treatment were evaluable for tumor response. Seven (29%) of the 24 patients had stable disease on salirasib therapy for 4 months or longer (range 4–13+ months) (diagnoses: metastatic carcinoid tumor, $n = 2$; NF2-associated tumors, $n = 2$; myoepithelial cancer of lacrimal gland, $n = 1$; thyroid medullary carcinoma, $n = 1$; and breast cancer, $n = 1$). If the three patients who had only surgical resection of their tumors were excluded, the rate of disease stabilization was 17% (4 of 24 patients). Characteristics of patients whose disease remained stable for at least 4 months during salirasib therapy are listed in Table 3. Disease stabilization was noted with a salirasib dose of $\geq$200 mg twice daily. Two patients with NF2-associated tumors remained stable on salirasib therapy for 16 and 22+ months, respectively (1 cycle $\approx$ 1 month).

Ten patients were assessed for response by PET imaging studies, 5 in the 400 mg and 5 in the 600 mg twice-daily dose groups. A 47-year-old woman with a history of metastatic uterine leiomyosarcoma had a mixed response to treatment. Her baseline PET scan showed multiple sites of bone and soft tissue metastases in the chest bilaterally and in the pelvis and multiple bones. A second PET scan after two cycles of salirasib (400 mg twice daily) demonstrated the disappearance of metabolic activity in a soft tissue lesion (posterior to the left side of T1), which decreased in

Table 3 Characteristics of patients whose disease remained stable with salirasib therapy

Pt. no.	Age	Sex	PS	Diagnosis	No. of prior Rx[a]	Prior therapies	Salirasib dose, mg BID	No. of cycles	Comments
104	39	F	1	Myoepithelial cancer of lacrimal gland	5	Paclitaxel + ifosfamide + carboplatin; capecitabine; exherin; gefitinib; paclitaxel hepatic arterial infusion	200	4	
106	36	M	1	Thyroid medullary carcinoma	0	Multiple surgical resections	200	4	
109	55	M	1	Metastatic carcinoid tumor	4	Bevacizumab; pegylated interferon + bevacizumab; NS-9; Atiprimod	200	4	
116	61	F	1	Breast cancer	4	FAC; paclitaxel; gemcitabine + taxotere; IGF-R antibody	400	4	
120	38	F	1	Metastatic carcinoid tumor	2	Octreotide; liposomal daunorubicin, bortezomib, gemcitabine	600	13	
122	37	F	1	Type 2 neurofibromatosis	0	Multiple surgical resections	600	16	
124	26	M	0	Type 2 neurofibromatosis	0	Surgical resection	800	22+	11% decrease by RECIST at 20 months

FAC 5-fluorouracil, adriamycin, cyclophosphamide; *PS* performance status; *Rx* therapies

[a] Surgical resection excluded

size, but no changes in another lesion (in the right lower back) and an increase in size without significant change in metabolic activity in other lesions (right mediastinal mass, right anterior chest wall mass, and several lung nodules).

A 76-year-old male patient developed gastrointestinal obstructive symptoms and died of progressive colorectal carcinoma with malignant pleural effusion 8 days after he was taken off the study. Another patient, a 39-year-old male, died from progressive high-grade myoepithelial carcinoma of the right parotid gland 2 weeks after he was taken off-study for progressive disease. He had developed malignant pleural effusion in the right lung, and at the time of death was undergoing palliative radiotherapy for spinal metastases in the region of T8, T9, and T10. No other patient died on study or within a month after being taken off-study.

Table 4 Pharmacokinetic parameters for salirasib in plasma after single and multiple doses

Dose (mg)	Treatment day	Pharmacokinetic parameters[a]					
		T_{max} (h)	C_{max} (ng/mL)	V/F(L)	Cl_s/F (L/h)	$T_{1/2}$ (h)	AUC[b] (ng × h/mL)
100	1	4.0, 6.0 (2)	736.0, 828.0 (2)	NR	NR	NR	NR
100	15	8.0 (6.0–8.0) (3)	812.0 ± 309.0 (3)	NR	NR	NR	NR
200	1	1.3 (0.5–6.0) (6)	1032.8 ± 818.6 (6)	594.1 ± 498.4 (3)	149.3 ± 146.2 (3)	4.0 ± 4.4 (3)	2428 ± 1827 (3)
200	15	5.0 (4.0, 8.0) (6)	922.8 ± 381.3 (6)	120.5 ± 46.0 (3)	56.1 ± 13.9 (3)	NR	3744 ± 1082 (3)
400	1	5.0 (4.0, 8.0) (6)	1725.5 ± 778.0 (6)	195.4 ± 92.2 (4)	36.0 ± 10.1 (4)	3.6 ± 0.9 (4)	11855 ± 3654 (4)
400	15	4.0 (1.0, 8.0) (6)	2365.7 ± 1669.4 (6)	193.8 ± 132.1 (3)	87.2 ± 44.1 (3)	NR	5653 ± 3293 (3)
600	1	6.0 (2.0–8.0) (6)	2017.8 ± 1797.0 (6)	672.1 ± 694.2 (3)	146.0 ± 143.1 (3)	3.0 ± 0.3 (3)	7517 ± 5757 (3)
600	15	4.0 (0.0–4.0) (5)	1966.4 ± 1050.7 (5)	384.5 ± 221.9 (5)	73.3 ± 48.7 (5)	NR	12260 ± 9589 (5)
800	1	4.0 (4.0–6.5) (3)	2225.7 ± 735.0 (3)	NR	NR	NR	NR
800	15	1.5, 2.0 (2)	2148.0, 4107.0 (2)	203.4 (1)	82.8 (1)	NR	9667 (1)
All dose levels	1	4.0 (0.5–8.0) (23)		458.0 ± 466.1 (10)	103.0 ± 112.5 (10)	3.6 ± 2.2 (10)	
	15	4.0 (0.0–8.0) (22)		255.7 ± 187.8 (12)	73.3 ± 37.3 (12)	NR	

AUC area under the concentration–time curve, C_{max} maximal plasma concentration, Cl_s/F apparent systemic clearance, *NR* not reportable, T_{max} time of the maximal plasma concentration, *V/F* apparent volume of distribution

[a] Values are reported as the arithmetic mean ± standard deviation (n). The T_{max} is reported as the median (range). When $n \leq 2$, individual values are reported

[b] AUC_{inf} is reported for all dose levels for day 1; $AUC_{0-12\,h}$ is reported for all dose levels for day 15

The remaining patients had progressive or stable disease. Fifteen patients received subsequent therapy, and six of those died from progressive disease.

Salirasib plasma pharmacokinetics

Pharmacokinetic data were obtained and evaluable from 24 patients, involving 41 pharmacokinetic study periods (Table 4). The salirasib pharmacokinetic profile was characterized by slow absorption and a rapid elimination phase following oral administration (Fig. 1). Accumulation did not occur, as salirasib exposure (C_{max}; day 1 AUC_{inf} vs. day 15 $AUC_{0-12\,h}$) was similar between days 1 and 15 ($P > 0.05$). The $T_{1/2}$ (mean ± SD) was 3.6 ± 2.2 h on day 1. Salirasib had a Cl_S/F (mean ± SD) of 103.0 ± 112.5 and 73.3 ± 37.3 L/h on days 1 and 15, respectively, and showed extensive distribution in excess of blood volume with a V/F of 458.0 ± 466.1 and 255.7 ± 187.8 L on days 1 and 15, respectively (Table 4).

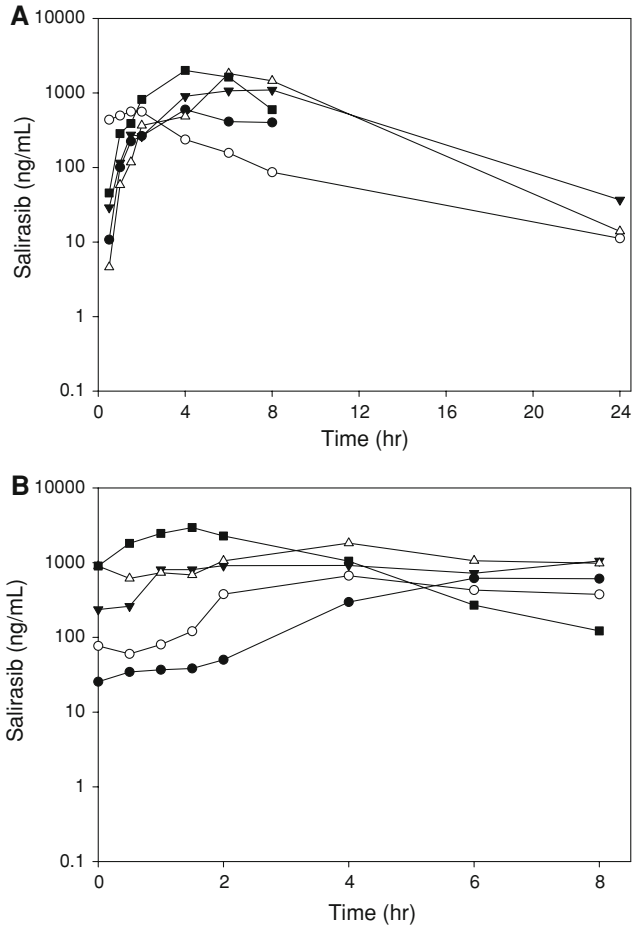

Fig. 1 Average plasma concentration time for all patients with advanced solid tumors after a single (day 1; **a**) or multiple doses (day 15; **b**) of salirasib. The *solid circle*, *open circle*, *solid triangle*, *open triangle*, and *solid square* represent 100, 200, 400, 600, and 800 mg, respectively

Despite the variability in the majority of the pharmacokinetic parameters, salirasib drug exposure (C_{max} and AUC) and Cl_S/F were similar on days 1 and 15 ($P > 0.05$) according to matched pairs analysis. The lack of accumulation in C_{max} or AUC is consistent with a dosing interval approximately four times longer (i.e., 12 h) than the $T_{1/2}$ (i.e., 3.6 h). C_{min} concentrations appeared to reach a plateau at 8 days, whereas $C_{1\,h}$ values were consistent on days 1, 8, and 15. The systemic drug exposure (C_{max} and AUC) increased in a manner proportionate with the increase in salirasib dose from 100 to 800 mg, as demonstrated by there being no significant difference between dose-normalized parameters by dose group ($P > 0.05$).

Discussion

Although salirasib has been extensively explored in the preclinical setting [7, 13–17], this is the first phase I clinical trial of salirasib in advanced tumors. Our data demonstrate that salirasib therapy was well tolerated at up to 600 mg twice daily. The most common toxicity was Grade 1–2 diarrhea, which occurred in 79% of the patients. It was not, however, associated with electrolyte abnormalities, and its severity and duration were dose dependent.

Although there were no confirmed objective responses in this study of advanced refractory tumors, antitumor activity was suggested by disease stabilization lasting for at least 4 months (1 month ≈ 1 cycle) in 7 (29%) patients, including two patients with NF2-associated tumors who remained stable for 16 and 23+ months.

Interestingly, neurofibromatosis 2 is caused by loss-of-function mutations of a tumor suppressor gene encoding NF2/merlin [22]. Although the basis of the tumor-suppressing activity of merlin is not completely understood, several investigators have proposed that merlin acts through modulation of Ras-related oncogenic pathways [23–25]. Thus, mutation of the *NF2* gene results in failure to suppress Ras transformation, leading to the NF2 phenotype.

Pharmacokinetic studies demonstrated that, despite the substantial variability in oral absorption, salirasib pharmacokinetics were linear with respect to C_{max} and AUC across the dose levels studied. The half-life of the drug was 3.6 h. Salirasib C_{max} values on both day 1 and day 15 were within or greater than the concentration range of 285–2,000 ng/mL that was determined to be effective in preclinical models [26–28]. The pharmacokinetic parameters did not differ between single-dose (day 1) and multiple-dose (day 15) salirasib administration, suggesting no time-dependent changes in salirasib pharmacokinetics.

Certain limitations are inherent in the design of the present study. The trial was stopped before the classic maximum-tolerated-dose endpoint was reached. This decision

was based on the fact that all three patients at a dose of 800 mg twice daily had persistent Grade 1–2 diarrhea. It was decided that a higher dose would not be tolerable, especially because salirasib was given continuously for 21 days of a 28-day cycle. Further, it was felt that even this dose would be difficult to tolerate for a prolonged period of time. In contrast with the 600 mg dose, there were no DLTs in the six patients treated, and though diarrhea was present, it was mild and less persistent. Our results are consistent with those of Dr Riely (Memorial Sloan Kettering, personal communication), who in a phase II study using salirasib in non-small cell lung cancer found that one-third of patients required dose reductions due to diarrhea at the 800 mg bid dose, but that the 600 mg bid dose was well tolerated. Therefore, our recommended starting phase II salirasib dose is 600 mg twice daily.

Given the tolerability and potential activity of salirasib in advanced solid tumors shown in the current study, together with available in vitro and in vivo data, a phase I clinical trial of salirasib and gemcitabine combination therapy in chemotherapy-naïve patients with advanced biliary tract cancers and ductal adenocarcinoma of the pancreas and a phase II clinical trial of salirasib in untreated and recurrent non-small cell lung cancer are under way.

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