SBP-101, a Polyamine Metabolic Inhibitor, Administered in Combination with Gemcitabine and Nab-paclitaxel, Shows Signals of Efficacy as First-Line Treatment for Subjects with Metastatic Pancreatic Ductal Adenocarcinoma

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Abstract

Background: SBP-101, a polyamine metabolic inhibitor, inhibited growth in 6 human pancreatic ductal adenocarcinoma (PDA) cell lines and 3 murine xenograft tumor models of human PDA. SBP-101 monotherapy in heavily pre-treated PDA patients (most had ≥ 2 prior regimens) showed a median survival of 5.9 months at the optimal dose level.
Purpose: To assess the PK, safety, and efficacy of SBP-101 in combination with gemcitabine (G) and nab-paclitaxel (A) in patients with previously untreated metastatic PDA.
Methods: In a modified 3+3 dose escalation scheme, subcutaneous injections of SBP-101 were dosed at 0.2, 0.4 or 0.6 mg/kg days 1-5 of each 28-day cycle. G (1000 mg/m^2) and A (125 mg/m^2) were administered intravenously on Days 1, 8, and 15 of each cycle. PK was evaluated on day 1 of cycle 1 in cohorts 1-3. Safety was evaluated by clinical and laboratory assessments. Efficacy was assessed by CA19-9 levels, objective response using RECIST criteria, progression-free survival (PFS) and overall survival (OS). A 4th cohort using a modified dosing schedule of 0.4 mg/kg SBP-101 days 1-5 for cycles 1-2 and days 1, 8, and 15 every cycle thereafter was added to mitigate hepatic toxicity, and that dose and schedule were recommended for Phase 1b expansion.
Results: Fifty patients were enrolled (N=25, Phase 1a and N=25, Phase 1b) and have received up to 13 treatment cycles. SBP-101 plasma C_{max} and AUC_{0-t} increased in a slightly more than dose proportional manner and were unchanged by the addition of G and A. PK parameters of G and A were unaltered by increasing doses of SBP-101. The most common non-serious adverse events related to SBP-101 (>10%) are fatigue (N=14), LFT/transaminase abnormalities (N=15), vision abnormalities (N=10), injection site pain (N=13), dehydration (N=7), diarrhea (N=7) and nausea (N=7). Serious adverse events related to SBP-101 observed in some subjects include hepatic toxicity (N= 6) and retinal toxicity (N=8) both occurring after prolonged treatment and requiring SBP-101 dose reduction or discontinuation. There is no evidence of SBP-101-related bone marrow suppression or peripheral neuropathy. At the Phase 1b dose and schedule (N=30), CA19-9 levels decreased 60-99% in 19 of 29 evaluable patients, with 1/29 (3%) achieving a complete remission, 13/29 evaluable patients achieving partial responses (45%) and 10/29 achieving stable disease at 8 weeks (34%). PFS was confounded by SBP-101 dosing holds implemented to investigate potential toxicity. Sixteen subjects are in survival follow up. Median OS is 12.0 months and is not final.
Conclusions: Interim results suggest SBP-101 may enhance first-line treatment with G and A in patients with metastatic PDA. Hepatic toxicity can be mitigated with dose reduction or discontinuation. A vision screening program will be used in future studies to mitigate retinal toxicity.

ClinicalTrials.gov Identifier: NCT03412799

Introduction

Polyamines (PAs) are aliphatic cations found in nearly all living cells, and they are critical for cell growth, protein synthesis and apoptosis. Although their concentrations are tightly controlled in normal cells, many tumors, including PDA, have elevated PA levels making them a promising therapeutic target. SBP-101, an analogue of the naturally occurring PA, spermine, is a polyamine metabolic inhibitor (PMI) that reduces native PA pools by inhibiting key synthetic enzymes and induction of catabolic enzymes. Non-clinical studies showed SBP-101 to have efficacy against PDA *in vitro* and *in vivo,* and a first-in-human monotherapy study in heavily pretreated patients (most had ≥2 prior chemotherapy regimens) with metastatic PDA demonstrated an acceptable safety profile below the MTD. In that study there was no significant bone marrow suppression or peripheral neuropathy as is commonly seen with gemcitabine (G) and nab-paclitaxel (A), suggesting the feasibility of SBP-101 as an addition to combination first-line treatment.

Study Design

This is a multicenter, open label, Phase 1a/1b study to evaluate to evaluate the safety, tolerability, pharmacokinetics and efficacy of SBP-101 when administered in combination with G and A as first-line therapy in pancreatic cancer patients previously untreated for metastatic disease. The objective was to determine a recommended Phase 2 dose. Using a modified 3+3 dose escalation scheme, cohorts of subjects were dosed with subcutaneous injections of SBP-101 at 0.2, 0.4 or 0.6 mg/kg days 1-5 of each 28-day cycle. G (1000 mg/m^2) and A (125 mg/m^2) were administered intravenously on Days 1, 8, and 15 of each cycle. PK was evaluated on day 1 of cycle 1 in cohorts 1-3. Subjects were to be treated until disease progression or the development of dose-limiting toxicity. Safety was evaluated by clinical and laboratory assessments. Efficacy was assessed by objective response using RECIST criteria and CA19-9 level. The protocol was amended to evaluate progression-free survival (PFS) and overall survival (OS) beginning with patients in Cohort 2. A 4th cohort using a modified dosing schedule of 0.4 mg/kg SBP-101 days 1-5 for cycles 1-2 and days 1, 8, and 15 every cycle thereafter was also added to mitigate hepatic toxicity, and that dose and schedule were evaluated in Phase 1b expansion. Enrolment was completed after 25 subjects were enrolled in Phase 1b. Safety and efficacy results of Cohort 2 vs Cohort 4 + Phase 1b subjects were compared for presentation.

Demographics

	Cohort 1 (0.2 mg/kg) (N=4)	Cohort 2 (0.4 mg/kg) (N=7)	Cohort 3 (0.6 mg/kg) (N=9)	Cohort 4 + Phase 1 b (N=30)	All Cohorts (N=50)
Age (years)					
Mean (SD)	66.8 (9.9)	62.1 (9.5)	65.8 (7.7)	62.6 (9.7)	63.5 (9.2)
Median (Range)	71.0 (52-73)	65.0 (42-72)	68.0 (47-74)	62.5 (37-80)	65.0 (37-80)
Gender n (%)					
Male	2 (50.0%)	4 (57.1%)	5 (55.6%)	22 (73.3%)	33 (66.0%)
Female	2 (50.0%)	3 (42.9%)	4 (44.4%)	8 (26.7%)	17 (34.0%)
Race n (%)					
White	3 (75.0%)	7 (100.0%)	8 (88.9%)	28 (93.3%)	46 (92.0%)
Asian	1 (25.0%)	0	1 (11.1%)	2(6.7%)	4 (8.0%)

Table 1. Demographics of the study population. There were no significant differences in gender or age between cohorts. Most of the subjects were White.

Pharmacokinetics

	Cohort 1 (0.2 mg/kg) (N=4)	Cohort 2 (0.4 mg/kg) (N=7)	Cohort 3 (0.6 mg/kg) (N=5*)
C_{max} (µg/mL)			
Mean	0.0266	0.1147	0.1467
Range	0.0132-0.0416	0.0771-0.167	0.0919-0.195
T_{max} (hr)			
Mean	0.5	0.5	0.5

*PK samples were collected for 5 of the 9 patients in Cohort 3.

Table 2. Pharmacokinetics. Pharmacokinetic parameters (PK) for SBP-101 in cohort 1 were below the limits of detection at most time points, but plasma C_{max} and T_{max} were measurable. C_{max} values were similar to the previous Phase 1 monotherapy study (data on file) and T_{max} was the same in both studies. SBP-101 plasma C_{max} and AUC_{0-t} increased in a slightly more than dose proportional manner and were unchanged by the addition of G and A. PK parameters of G and A were unaltered by increasing doses of SBP-101 (data on file).

Safety

The Safety Population includes all subjects who received at least one dose of SBP-101 (N=50). Related adverse events (AEs) were defined as definitely, probably or possibly related and not related events as unlikely or not related. In the total N, subjects are counted only once at the highest grade for each event.

Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total N (%)
Elevated Liver Function Tests	1	0	12	1	1*	15 (30%)
Fatigue	7	5	2	0	0	14 (28%)
Injection site pain	12	2	0	0	0	13 (26%)
Vision events**	0	4	6	0	0	10 (20%)
Dehydration	1	4	2	0	0	7 (14%)
Nausea	4	2	1	0	0	7 (14%)
Diarrhea	2	3	1	0	0	6 (12%)

*Subject exceeded the maximum tolerated dose and schedule
**includes blurred vision, visual impairment, visual acuity reduced, blindness, and retinopathy

Table 3A. SBP-101-related adverse events occurring in ≥5 subjects (10%), N=50.

Grade ≥3 AEs of Special Interest	N	%		G+A %*
Hematologic Events				
Neutropenia	20	40%		38%
Leukopenia	0	-		31%
Anemia	9	18%		13%
Thrombocytopenia	1	2%		17%
Febrile Neutropenia	1	2%		3%
Non-hematologic Events				
Peripheral Neuropathy	3	6%		17%
Fatigue	6	12%		17%
Diarrhea	6	12%		6%

*Historical control data, MPACT study G+A arm, N=431 Von Hoff NEJM 2013

Table 3B. Grade ≥3 adverse events of special interest compared to historical data on G+A.

Event	SBP-101	G+A	All 3	Total N (%)
Neutropenia	0	19 (1G, 18 G+A)	1	20 (40%)
Elevated LFTs	5	0	9	14 (28%)
Anemia	0	7 (G+A)	0	9 (18%)
Diarrhea	0	6 (4A, 2G+A)	1	7 (14%)
Fatigue	0	4 (G+A)	2	6 (12%)
Vision events	4	1 (G)	2	7(14%)
Dehydration	2	2 (1A, 1 G+A)	0	4 (8%)
Peripheral neuropathy	0	3 (A)	0	3 (6%)

Table 3C. Grade ≥3 adverse events attributable to any study medication, N=50. The most common Grade ≥3 AEs related to any study medication were neutropenia in 20 subjects (19 attributed to G+A and 1 attributed to all 3) and elevated liver function tests in 14 subjects (5 attributed to SBP-101 and 9 attributed to all 3). SBP-101-related increases in LFTs were asymptomatic in all but 2 subjects and reversed in all but one subject when SBP-101 administration was interrupted and dose-reduced or discontinued. Six subjects experienced vision adverse events (4 possibly related to SBP-101, 1 related to gemcitabine and 2 related to all 3 based on PI assessment. All are considered by the sponsor to be possibly related to SBP-101) 6 had findings consistent with retinopathy. A statistical correlation analysis suggested an association with high cumulative doses of corticosteroids, total cumulative dose of SBP-101 and duration of treatment, prior history of eye disorders and prior treatment for a different malignancy.

The addition of SBP-101 to the treatment regimen did not result in any substantial changes in the frequency of Grade ≥3 hematologic events, peripheral neuropathy, or fatigue when compared with historical control data on G+A combination therapy. Liver toxicity seen early in the study was successfully mitigated by dose reduction. Retinopathy ≥ Grade 3 occurred in 14% of patients, all but one of whom exceeded a total cumulative dose (TCD) threshold. Limiting the TCD of SBP-101 and vision screening with eye examinations and vision-specific questionnaires will be conducted at baseline and regular intervals in future studies to mitigate potential retinal toxicity, including the ongoing randomized phase 2 clinical trial (CL-SBP-101-04).

Efficacy Results

Efficacy results are presented for subjects in Cohort 2, N=7, and Cohort 4 + Phase 1b, N=30. In 11 subjects SBP-101 was suspended to investigate vision AEs; those subjects continued treatment with G and A.

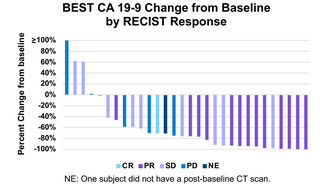
	BEST OVERALL RESPONSE				Objective	Disease
	CR	PR	SD	PD	Response	Control
COHORT 2 n=7	0	5 (71%)	2 (29%)	0	5/7 (71%)	6/7 (86%)
COHORT 4+1B n=29	1 (3%)	13 (45%)	10 (34%)	5 (17%)	14/29 (48%)	22/29 (76%)
G+A* n=431	<1%	23%	27%	20%	23%	48%

Table 4A. Response rates for Cohort 2, Cohort 4+1b, and a historical control administered G+A. The objective response rate (ORR) and disease control rate (DCR) with SBP-101 in combination with G+A were greater than the historical cohort administered only G+A.

	PFS			OS		
Cohort	2	4+1b	G+A*	2	4+1b	G+A*
Median (mo)	5.6	6.0	5.5	10.3	12.0+**	8.5
6 mo (%)	43%	52%	44%	100%	86%	67%
12 mo (%)	0	10%	16%	43%	52%	35%

*Von Hoff NEJM 2013
**Median OS has not been reached

Table 4B. Progression-Free (PFS) and Overall (OS) Survival for Cohort 2, Cohort 4+1B, and a historical control administered G+A. PFS may have been negatively impacted by dosing interruptions to evaluate potential toxicity. Median overall survival in Cohort 4 + Phase 1B has not yet been reached. Two subjects in Cohort 2 are still alive at 29.3+ and 30.7+ months, respectively.



NE: One subject did not have a post-baseline CT scan.

Figure 1. Best CA 19-9 percent change from Baseline by Response – Cohort 4 + Phase 1b, N=30. Twenty-one subjects in Cohort 4 + Phase 1b (70%) had a maximum CA 19-9 decrease greater than 60%.

Cohort 2
- **ORR 71% DCR 86%**
- **Median PFS 5.6 mo, OS 10.3 mo.**
- **Two subjects are alive at 29+ and 30+ months**

Cohort 4 + Phase 1b
- **The dose and schedule recommended for phase 2**
- **29 of 30 subjects were response-evaluable**
- **11 subjects had treatment with SBP-101 interrupted to evaluate retinal toxicity, potentially confounding final efficacy results**
  - **ORR 48%**
  - **DCR 76%**
  - **PFS 6.0 mo.**
  - **6 and12 month PFS and OS rates are promising**
- **Median OS of 12.0 mo. is not yet final**

Conclusions

Conclusions:

- Interim results suggest SBP-101 may enhance first-line treatment with G and A in patients with metastatic PDA
- The dose and schedule used for Cohort 4 and phase 1b is being used for the phase 2 trial
- Treatment-related liver function abnormalities seen early in the study were successfully mitigated with dose and schedule changes in Phase 1b
- There was no evidence that SBP-101 potentiates the Grade ≥3 hematologic events or peripheral neuropathy seen with G+A alone
- Vision SAEs in some subjects, not observed in earlier studies, will require baseline and periodic ophthalmology examinations in future studies
- Objective Response Rate (48%) and DCR (76%) in Cohort 4+1b exceeded the historical rates reported for G+A* (23%, 48%) and FOLFIRINOX** (32%, 70%) in pivotal trials
- Radiologic responses were accompanied by large decreases in CA19-9 levels
- Signals of efficacy support continued development of SBP-101 as an addition to first-line treatment for advanced PDA
- Favorable median PFS and PFS at 6 and 12 months suggest SBP-101 may be suitable for use with G+A as a neo-adjuvant treatment for patients with potentially resectable PDA

- **At 12.0 months, the median OS has not been reached**.

Sources: *Von Hoff NEJM 2013, **Conroy NEJM 2011