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 (> 2 prior regimens, N=4) showed a median survival of 5.9 months at the optimal dose level.
Purpose: To assess the safety, tolerability, PK, 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/m2) and A (125 mg/m2) were administered intravenously on Days 1, 8, and 15 of each cycle. Safety and tolerability were evaluated by clinical and laboratory assessments. PK was evaluated on day 1 of cycle 1. Efficacy was assessed by CA19-9 levels, objective response as assessed by RECIST criteria, progression-free survival (PFS) and overall survival (OS).
Interim Results: Fifteen patients have been enrolled in 3 cohorts (1: N=4, 2: N=7, 3: N=4) and received up to 6 cycles of treatment (7 subjects are ongoing in cohorts 2 and 3). The most common adverse events related to SBP-101 are fatigue (N=4), nausea (N=2) and injection site pain (N=2). There is no evidence of SBP-101-related bone marrow suppression or peripheral neuropathy. One patient in cohort 2 developed grade 3-4 reversible liver enzyme elevation. PK parameters in cohort 1 were below the limits of detection at most time points, but plasma C_{max} and AUC_{0-t} were measurable in cohorts 2 and 3. In those cohorts, CA19-9 levels decreased 76-95% in 7 of 8 evaluable subjects (1 additional subject TBD), with 5 patients achieving partial responses (4 ongoing) and 1 achieving stable disease. Median PFS and OS have not yet been reached.
Conclusions: Preliminary results suggest SBP-101 is well tolerated when administered with G and A. Signals of efficacy support continued development of SBP-101 in combination first-line treatment for PDA.
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 PA pools by inhibiting key synthetic 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 with metastatic PDA (most had ≥2 prior chemotherapy regimens) 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. Safety and tolerability were evaluated by clinical and laboratory assessments. PK was evaluated on day 1 of cycle 1. Efficacy was assessed by objective response rate (ORR) using RECIST criteria and by changes in CA19-9 levels. Subjects were treated until disease progression or the development of dose-limiting toxicity. Based upon initial safety findings and preliminary signals of efficacy, the protocol was amended to evaluate progression-free survival (PFS) and overall survival (OS) and expand the study to up to 36 subjects at the recommended Phase 2 dose. As of January 4, 2020, 20 subjects were enrolled in cohorts 1-3 and were evaluated for dose limiting toxicity and early signals of efficacy.

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)	All Cohorts (N=20)
Age (years)				
Mean (SD)	66.8 (9.88)	62.1 (9.55)	65.8 (7.66)	64.7 (8.53)
Median (Range)	71 (52-73)	65 (42-72)	68 (47-74)	66 (42-74)
Gender n (%)				
Male	2 (50.0%)	4 (57.1%)	4 (44.4%)	10 (50.0%)
Female	2 (50.0%)	3 (42.9%)	5 (55.6%)	10 (50.0%)
Race n (%)				
White	3 (75.0%)	7 (100.0%)	8 (88.9%)	18 (90.0%)
Asian	1 (25.0%)	0	1 (11.1%)	2 (10.0%)

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	0.147
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 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 increased linearly with dose. T_{max} was the same in both studies.

Safety

The Safety Population includes all subjects who received at least one dose of SBP-101 (N=20). 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					Total N (%)
	1	2	3	4	5	
Fatigue	4	3	1	0	0	8 (40%)
Elevated LFTs	0	0	3	1	0	4 (20%)
Injection site pain	4	0	0	0	0	4 (20%)
Diarrhea	1	1	0	0	0	2 (10%)
Nausea	1	1	0	0	0	2 (10%)

Table 3A. SBP-101-related adverse events occurring in ≥2 subjects (10%), N=20. LFTs-Liver Function Tests

Grade ≥3 AEs of Special Interest	N	%	G+A%*
Hematologic Events			
Neutropenia	6	30%	38%
Leukopenia	3	15%	31%
Anemia	3	15%	13%
Thrombocytopenia	1	5%	17%
Non-hematologic Events			
Peripheral Neuropathy	0	0%	17%
Fatigue	1	5%	17%
Diarrhea	0	0%	6%

*Historical control data, MPACT study G+A arm, N=431
Source: 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	6	0	6 (30%)
Elevated LFTs	4	1 (+G)	0	4 (20%)
Anemia	0	3	0	3 (15%)
Thrombocytopenia	0	1	0	1 (5%)
Fatigue	0	0	1	1 (5%)
Increased LIpase	1	0	0	1 (5%)
Dyspnea	0	0	1	1 (5%)
Delirium	0	1 (A)	0	1 (5%)
Hiccups (Intractable)	0	1 (A)	0	1 (5%)
Hyponatremia	0	0	1	1 (5%)
Dehydration	0	1	0	1 (5%)

Table 3C. Grade ≥3 adverse events attributable to any study medication. The most common Grade ≥3 AEs related to any study medication were neutropenia in 6 subjects attributed to G+A, and elevated liver function tests in 4 subjects attributed to SBP-101, one of which was also attributed to G. SBP-101-related increases in LFTs occurred after several cycles of treatment, were asymptomatic in all but 1 subject, and reversed in all subjects when SBP-101 administration was interrupted and dose-reduced or discontinued.

The addition of SBP-101 to the treatment regimen did not increase the frequency of Grade ≥3 hematologic events, peripheral neuropathy, fatigue or diarrhea when compared with historical control data on G+A combination therapy.

Results

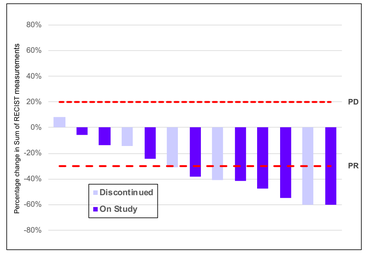

Figure 1A. Best Response per subject – Cohorts 2 and 3, N=13. Best response in evaluable subjects was PR in 8 (62%) and SD in 5 (38%). Three subjects did not have post baseline scans with RECIST tumor assessments.

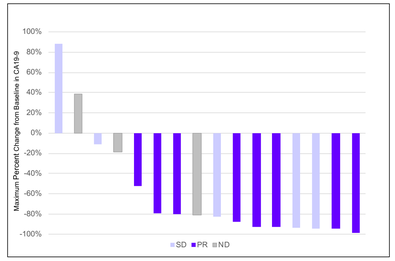

Figure 1B. Maximum CA19-9 percent change from baseline by response - Cohorts 2 and 3, N=16. Eleven subjects in cohorts 2 and 3 (69%) had a CA 19-9 maximum decrease greater than 60%. ND - Not Done

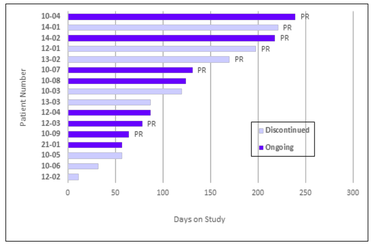

Figure 1C. Days on study – Cohorts 2 and 3. As of January 4, 2020, 8 of 16 subjects in cohorts 2 and 3 remain on study. Reasons for discontinuation include radiologic PD (N=1), adverse events (N=2), clinical progression (N=4), and patient decision (N=1). Four subjects have expired from pancreatic cancer.

As of January 4, 2020 in the response-evaluable subjects in cohorts 2 and 3 (N=13):

- **The objective response rate was 62%; 4 PRs were observed after 2 cycles of therapy and 4 PRs were observed after 4 cycles of therapy.**
- **The disease control rate (DCR) was 85% by RECIST criteria (at least SD for ≧ 16 weeks); 4 subjects have not reached week 16 scans.**
- **Median duration of response, PFS and OS have not been reached.**

Conclusions

Conclusions: SBP-101 was well-tolerated when administered at doses tested in combination with G+A in subjects with previously untreated metastatic pancreatic adenocarcinoma. Treatment-related liver function abnormalities were mostly asymptomatic and reversed when SBP-101 was interrupted and dose-reduced or discontinued. There was no evidence that SBP-101 potentiates the Grade ≥3 hematologic events or peripheral neuropathy typically seen with G+A alone. ORR (62%) and DCR (85%) exceeded the historical rates reported for G+A* (23%, 48%) and FOLFIRINOX** (32%, 70%) in pivotal trials; responses were accompanied by large decreases in CA19-9 levels. Signals of early efficacy support continued development of SBP-101 as an addition to first-line treatment for advanced PDA and as neo-adjuvant treatment for patients with potentially resectable disease.
Sources: *Von Hoff 2013, **Conroy 2011