Cancer Therapy: Clinical

Safety, Tolerability, and Preliminary Activity of LB-100, an Inhibitor of Protein Phosphatase 2A, in Patients with Relapsed Solid Tumors: An Open-Label, Dose Escalation, First-in-Human, Phase I Trial

Vincent Chung[1], Aaron S. Mansfield[2], Fadi Braiteh[3,4], Donald Richards[4,5], Henry Durivage[6], Richard S. Ungerleider[6], Francis Johnson[7], and John S. Kovach[8]

Abstract

Purpose: To determine the MTD and to assess the safety, tolerability, and potential activity of LB-100, a first-in-class small-molecule inhibitor of protein phosphatase 2A (PP2A) in adult patients with progressive solid tumors.

Experimental Design: LB-100 was administered intravenously daily for 3 days in 21-day cycles in a 3 + 3 dose escalation design.

Results: There were 29 patient entries over 7 dose escalations. One patient stopped treatment after one dose because of an acute infection and was reenrolled after recovery; each course was analyzed as a separate patient entry. Two patients had dose-limiting toxicity (reversible increases in serum creatinine or calculated serum creatinine clearance) at the 3.1 mg/m^2 level. Probable or possible study drug-related grade 3 adverse events occurred in 6 (20.7%) patients [anemia ($n = 2$), decreased creatinine clearance, dyspnea, hyponatremia, and lymphopenia]. Ten (50%) of 20 response-evaluable patients had stable disease for four or more cycles. One patient with pancreatic adenocarcinoma had a partial response noted after 10 cycles, which was maintained for five additional cycles. The other patients achieving stable disease had one of the following: fibrosarcoma, chondrosarcoma, thymoma, atypical carcinoid of lung, or ovarian, testicular, breast ($n = 2$), and prostate cancer. The recommended phase II dose of LB-100 is 2.33 mg/m^2 daily for 3 days every 3 weeks.

Conclusions: The safety, tolerability, preliminary evidence of antitumor activity, and novel mechanism of action of LB-100 support its continued development alone and in combination with other therapies. *Clin Cancer Res; 1–8. ©2016 AACR.*

Introduction

Phosphorylation of proteins by kinases and their dephosphorylation by phosphatases are critical components of cellular signaling pathways regulating a multiplicity of processes, including cell proliferation and cell death (1). Although phosphatases have long been considered potentially important targets for cancer treatment, there has been little effort to develop phosphatase inhibitors due to concern over toxicity (2). Cantharidin, a naturally occurring toxin from the Chinese blister beetle, and its demethylated analogue, norcantharidin, both potent inhibitors of PP2A (3), were reported to have anticancer activity in patients in China with gastrointestinal cancers (4), although little clinical detail is available.

Fostriecin, another selective inhibitor of PP2A, was evaluated in several NCI (Bethesda, MD)-sponsored phase I trials over 20 years ago. In the largest trial, fostriecin was associated with disease stability in 16 (34.8%) of 46 solid tumor patients without dose-limiting toxicity (DLT; ref. 5). No trials were completed because of insufficient drug supply. The mechanism by which the inhibition of PP2A results in the inhibition of transformed cells of a variety of cell types was puzzling, as PP2A has been considered a tumor suppressor. Chemical inhibitors of PP2A, most notably okadaic acid, and transforming viral antigens Simian virus 40 small T antigen and murine polyoma virus middle T antigen were shown to inhibit PP2A activity as part of the transformation process (2, 6–8).

To study the potential value of PP2A inhibition as an anticancer strategy, we synthesized a series of stable novel inhibitors of PP2A (9). As with fostriecin, the lead compound, LB-100, and its lipid-soluble homolog, LB-102, inhibited proliferation of cell lines from a variety of human solid tumors at low micromolar concentrations (9). More strikingly, both compounds potentiated the activity, without significantly increasing the toxicity, of cisplatin, doxorubicin, and temozolomide against xenografts of pancreatic (10) and hepatocellular carcinoma (11), fibrosarcoma (12), pheochromocytoma (13), neuroblastoma (14), and glioblastoma (14) and of focal X-ray against pancreatic (15), nasopharyngeal (16), and glioblastoma xenografts (17). In addition, LB-100 reversed

[1]City of Hope, Duarte, California. [2]Mayo Clinic, Rochester, Minnesota. [3]Comprehensive Cancer Centers of Nevada, Las Vegas, Nevada. [4]US Oncology Research, The Woodlands, Texas. [5]Texas Oncology, Tyler, Texas. [6]Theradex Systems Inc., Princeton, New Jersey. [7]Chem-Master International, Inc. Stony Brook, New York. [8]Lixte Biotechnology Holdings, Inc., East Setauket, New York.

Corresponding Author: John S. Kovach, Lixte Biotechnology Holdings, Inc., 248 Route 25A, No. 2, East Setauket, NY 11733. Phone: 631-880-2907; Fax: 631-982-5050; E-mail: jkovach@lixte.com

> ## Translational Relevance
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> PP2A has long been recognized as a potentially important target for cancer therapy because of its regulatory role in cell division, DNA damage response, homologous recombination repair, and mitotic exit. However, inhibition of this enzyme has been considered likely too toxic for clinical use. This study shows the safety, tolerability, and potential anticancer activity of an inhibitor of PP2A, LB-100, in patients with refractory solid tumors. PP2A activity is altered by mutation directly or indirectly in many solid tumors and hematologic malignancies. The availability of a clinically safe inhibitor of PP2A opens a promising new avenue for cancer therapy, namely pharmacologic inhibition of PP2A in cancers with mutationally acquired abnormalities in PP2A function and/or DNA damage repair. The results of this study support further development of LB-100 alone and in combination with cytotoxic regimens for refractory cancers.

resistance to cisplatin in ovarian carcinoma (18) and medulloblastoma (19) xenografts. Wei and colleagues (15) demonstrated that inhibition of PP2A by LB-100 sensitized human pancreatic cell lines in culture and as xenografts to radiation by interfering with DNA repair. Moreover, Gordon and colleagues (17) showed that LB-100 enhanced radiation inhibition of glioblastoma xenografts by interfering with mitotic exit, leading to increase mitotic catastrophe. Additional support for the potential value of PP2A inhibition for enhancing cytotoxic therapy was provided by Chang and colleagues (18), who demonstrated that LB-100 sensitized human ovarian cancer xenografts to cisplatin, at least in part by altering cell-cycle checkpoint regulation.

Given the many preclinical *in vivo* studies indicating that inhibition of PP2A by LB-100 enhances the antiproliferative activity of a variety of standard anticancer agents by apparently several mechanisms without significantly enhancing their toxicity (20), we sought to determine the MTD of LB-100 given daily for 3 consecutive days in patients with refractory solid tumors as a first step in developing combination regimens of this PP2A inhibitor with a cytotoxic drug and/or radiation.

Materials and Methods

Eligible patients were aged 18 years or older with proven progressive solid tumors who had failed standard treatments. Patients had to have a life expectancy of at least 12 weeks, an ECOG performance status of 0 or 1, and be able to give informed consent. Before participation, patients must have recovered to baseline or less than grade 1 toxicity from prior treatments, have adequate bone marrow (an absolute neutrophil count $>1.5 \times 10^9/$L and platelet count $>100 \times 10^9/$L), kidney [serum creatinine <1.2 mg/dL and if >1.2 mg/dL, creatinine clearance (Cockcroft–Gault method) >60 mL/minute/1.73 m^2], and hepatic (plasma total bilirubin <1.5 mg/dL, alanine transaminase and aspartate transaminase <2.5× upper limit of normal) function. They must not have any other uncontrolled systemic disease. Women of childbearing potential had to have a negative serum or urine pregnancy test result.

Study design and treatment

We performed an open-label, dose escalation, phase I study to assess the safety, tolerability, and activity of LB-100 administered for 3 consecutive days every 3 weeks. Pharmacokinetic studies were planned at the MTD. The starting dose, 0.25 mg/m², was 1/15th of the highest nonseverely toxic dose in dogs. The dose escalation plan was specified by the FDA. The study was approved by the human investigations committee at each study center and is registered at ClinicalTrials.gov: NCT01837667.

LB-100 was supplied as a single-use solution. Initially, LB-100 was administered in 50 mL of saline over 15 minutes. Because of a nonlimiting reversible increase in serum creatinine at the 2.33 mg/m² level, LB-100 was subsequently administered in 500 mL of normal saline over 2 hours. Dose escalation was prohibited within any cohort. Patients were eligible to receive up to 6 cycles of study therapy, unless unacceptable toxicity, disease progression, or intercurrent illness required discontinuation. More than six cycles were allowed in the absence of progression and toxicity. Because of cardiac and renal toxicity at high doses in animal toxicology studies, patients had extensive monitoring, including ECG, MUGA or echocardiogram, cardiac troponins, and BNP prior to every cycle. Blood chemistries, urinalysis, hematologic profile, and vital signs were monitored prior to and on days 1, 3, 8, 15, and 22 of each cycle. Laboratory parameters were tabulated by maximum NCI-CTCAE (Version 4.0) severity grade. A safety review committee assessed all clinical data every 2 weeks and approved dose escalation between cohorts.

Evaluation of toxicity and clinical activity

Doses of LB-100 were escalated in groups of 3 patients. The first patient at a new dose level was observed for 3 weeks before treating the next 2 patients at that dose. When a potential DLT occurred, 3 new patients were entered at that dose. If another DLT occurred, 3 additional patients were treated at the previous non-DLT dose to determine the safety of that level for phase II trials.

Response to treatment was assessed using RECIST version 1.1. All patients with measurable disease, who completed two cycles of LB-100 and had at least one postbaseline tumor assessment, were evaluable for efficacy. Patients receiving any LB-100 were evaluable for safety. The severity of adverse events and laboratory abnormalities is reported according to NCI-CTCAE version 4.0 and coded using Medical Dictionary for Regulatory Activities.

Outcomes

The main objective was to determine the safety, tolerability, and MTD of LB-100 given intravenously daily for 3 consecutive days every 3 weeks. The secondary objectives were to document any evidence of potential antitumor activity and obtain pharmacokinetic data on LB-100 and a metabolite, endothall, in patients receiving LB-100 at the MTD.

Results

Patient characteristics

Twenty-eight patients with advanced solid tumors were enrolled at four clinical sites. Their demographic features are listed in Table 1. Four patients were not evaluable for toxicity. Three of these patients had disease-associated complications prior

Table 1. Patient baseline clinical and demographic characteristics

Study population ($N = 28$)	
Sex	
Male	14 (50.0%)
Female	14 (50.0%)
Ethnic origin	
White	23 (82.1%)
Asian	3 (10.7%)
Not reported	1 (3.6%)
Other	1 (3.6%)
Age (years)	
N	28
Mean	62.3
SD	10.66
Median	64.0
Minimum	35
Maximum	79
18–64	15 (55.6%)
65+	13 (46.4%)
Primary site	
Lung & bronchus	5 (17.9%)
Large intestine (excl. appendix)	5 (17.9%)
Breast	2 (7.1%)
Connective & soft tissue	2 (7.1%)
Ovary	2 (7.1%)
Testis	2 (7.1%)
Appendix	1 (3.6%)
Bones & joints	1 (3.6%)
Corpus uteri	1 (3.6%)
Pancreas	1 (3.6%)
Prostate gland	1 (3.6%)
Rectum	1 (3.6%)
Small intestine	1 (3.6%)
Thymus	1 (3.6%)
Uterus, NOS	1 (3.6%)
Vulva, NOS	1 (3.6%)

Abbreviation: NOS, not otherwise specified.

to completing cycle 1. A fourth patient with atypical carcinoid of the lung was removed from study after one dose of LB-100 because of an acute infection; he was reentered on study 7 weeks later and achieved stable disease for five cycles, and both courses were included in the analyses. None of these adverse events was considered related to drug administration.

Dose escalation and toxicity

Twenty-four patients completed at least one 3-day cycle of LB-100. The tested dose levels were 0.25, 0.50, 0.83, 1.25, 1.75, 2.33, and 3.1 mg/m^2. There was no DLT during the first six dose levels. At the 3.1 mg/m^2 dose level, a patient with prostate cancer and one with chondrosarcoma had no DLT during 4 and 9 cycles of treatment, respectively. A third patient with ovarian cancer had a grade 3 increase in calculated creatinine clearance after cycle 1, with a return to normal by day 8 and received three more cycles at a reduced dose of 2.33 mg/m^2 before tumor progression. A fourth patient with fibrosarcoma had a grade 3 increase in calculated creatinine clearance after the first course. The creatinine returned to pretreatment value by day 21, and a second course at 2.33 mg/m^2 resulted in a grade 2 increase in creatinine clearance without other toxicity. The dose was decreased to 1.75 mg/m^2, and 10 more cycles were administered without toxicity until progression after 36 weeks. Because 2 of 4 patients at 3.1 mg/m^2 had grade 3 increases in creatinine clearance during cycle 1, 3 additional patients were evaluated at the preceding dose level of 2.33 mg/m^2. They had no limiting

toxicity, thereby establishing the MTD at that level. There was no symptomatic toxicity other than reversible mild to moderate fatigue. Adverse events possibly related to drug administration are listed in Table 2.

Pharmacokinetics

The plasma concentrations of LB-100 and endothall were measured (21) prior to and over 4 hours after completion of the 2-hour infusion at the MTD of 2.33 mg/m^2 of LB-100 on day 1 in one patient and on days 1 and 3 in 2 patients. The pharmacokinetics of LB-100 were similar on day 1 and 3 and were characterized by a low clearance, low volume of distribution, and a short half-life. Plasma concentrations of endothall were low throughout the infusion, being below the lower limit of detection (5 ng/mL) in one patient. In the other 2 patients, the maximal concentration of endothall (34.7 ng/mL) was observed at the last sampling time point (4 hours), which precluded determination of its elimination half-life (Table 3).

Evaluation of clinical activity

Of 20 patients with measurable disease, one patient with pancreatic cancer had a partial response (Fig. 1) noted after 10 cycles and lasting for five more cycles, and 16 patients had no progression of their indicator lesion(s). Patients were removed from study for either the appearance of a new lesion or symptoms judged to represent clinical progression. Only 3 patients, 1 with duodenal and 2 with colonic adenocarcinomas, had significant increases in the size of their indicator lesion(s) by RECIST criteria (Fig. 2).

Achievement of partial response or stability of disease was not clearly dose dependent, occurring at 0.83 mg/m^2 in pancreatic cancer (15 cycles) and atypical carcinoid of the lung (five cycles), at 1.25 mg/m^2 in breast cancer (four cycles) and testicular cancer (five cycles), and at 1.75 mg/m^2 in malignant thymoma (eight cycles) and ovarian cancer (six cycles). At 3.1 mg/m^2, a patient with chondrosarcoma was stable for eight cycles of LB-100 without any alteration in normal renal function, whereas a patient with fibrosarcoma started at 3.1 mg/m^2 was stable for 12 cycles after two dose reductions (Fig. 3).

Discussion

We determined the MTD of LB-100, a potent inhibitor of PP2A, in patients with solid tumors. The recommended phase II starting dose is 2.33 mg/m^2 daily for 3 days every 3 weeks with escalation to 3.1 mg/m^2 in the absence of renal toxicity and deescalation to 1.75 mg/m^2 or lower for renal toxicity in the event of stable or regressing disease. In animal toxicity studies of LB-100 (22), the lowest doses tested, approximately 4.5 and 6.0 mg/m^2 i.v. daily for 5 days, were associated with some microscopic hematuria and microscopic histologic changes in the renal tubules in the male rat and male and female dog, respectively. These changes were minimal in the 3-week recovery postmortem examination. At higher doses, in both species, microscopic changes in the renal tubules were more pronounced, suggesting that impairment of renal tubular function was a likely toxicity. In this study, DLT was asymptomatic transient reversible increases in serum creatinine. This toxicity was identical to that encountered in the phase I trials of fostriecin, another selective inhibitor of PP2A (5). De Jong and colleagues (23) showed that increases in

Table 2. Adverse events in the safety population

MedDRA preferred term[a,b]	Grade 1–2	Grade 3	Grade 4	Grade 5
Total patients with related treatment-emergent adverse events[c]	22 (75.9%)	6 (20.7%)	0	0
Fatigue	8 (27.6%)	0	0	0
Blood creatinine increased	5 (17.2%)	0	0	0
Aspartate aminotransferase increased	4 (13.8%)	0	0	0
Headache	3 (10.3%)	0	0	0
Hypernatremia	3 (10.3%)	0	0	0
Hypoalbuminemia	3 (10.3%)	0	0	0
Nausea	3 (10.3%)	0	0	0
Proteinuria	3 (10.3%)	0	0	0
Pyrexia	3 (10.3%)	0	0	0
Alanine aminotransferase increased	2 (6.9%)	0	0	0
Constipation	2 (6.9%)	0	0	0
Neuropathy peripheral	2 (6.9%)	0	0	0
Edema peripheral	2 (6.9%)	0	0	0
Sinus tachycardia	2 (6.9%)	0	0	0
Abdominal discomfort	1 (3.4%)	0	0	0
Abdominal distension	1 (3.4%)	0	0	0
Accelerated hypertension	1 (3.4%)	0	0	0
Anemia	1 (3.4%)	2 (6.9%)	0	0
Arthralgia	1 (3.4%)	0	0	0
Blood alkaline phosphatase increased	1 (3.4%)	0	0	0
Blood urea increased	1 (3.4%)	0	0	0
Candidiasis	1 (3.4%)	0	0	0
Chest pain	1 (3.4%)	0	0	0
Chills	1 (3.4%)	0	0	0
Decreased appetite	1 (3.4%)	0	0	0
Dermatitis acneiform	1 (3.4%)	0	0	0
Diarrhea	1 (3.4%)	0	0	0
Dizziness	1 (3.4%)	0	0	0
Ejection fraction decreased	1 (3.4%)	0	0	0
Electrocardiogram QT prolonged	1 (3.4%)	0	0	0
Gait disturbance	1 (3.4%)	0	0	0
Gastrointestinal disorder	1 (3.4%)	0	0	0
Generalized edema	1 (3.4%)	0	0	0
Gingival pain	1 (3.4%)	0	0	0
Hypercalcemia	1 (3.4%)	0	0	0
Hyperkalemia	1 (3.4%)	0	0	0
Hypertension	1 (3.4%)	0	0	0
Hypoesthesia	1 (3.4%)	0	0	0
Hypokinesia	1 (3.4%)	0	0	0
Hypotension	1 (3.4%)	0	0	0
Hypoxia	1 (3.4%)	0	0	0
Insomnia	1 (3.4%)	0	0	0
Mucosal inflammation	1 (3.4%)	0	0	0
Muscle twitching	1 (3.4%)	0	0	0
Muscular weakness	1 (3.4%)	0	0	0
Neutropenia	1 (3.4%)	0	0	0
Edema	1 (3.4%)	0	0	0
Pain of skin	1 (3.4%)	0	0	0
Peripheral coldness	1 (3.4%)	0	0	0
Peripheral sensory neuropathy	1 (3.4%)	0	0	0
Platelet count decreased	1 (3.4%)	0	0	0
Pleural effusion	1 (3.4%)	0	0	0
Tachypnea	1 (3.4%)	0	0	0
Tremor	1 (3.4%)	0	0	0
Vomiting	1 (3.4%)	0	0	0
Weight decreased	1 (3.4%)	0	0	0
Creatinine renal clearance	0	1 (3.4%)	0	0
Dyspnea	0	1 (3.4%)	0	0
Hyponatremia	0	1 (3.4%)	0	0
Lymphocyte count decreased	0	1 (3.4%)	0	0

[a]Number of patients used as denominator to calculate percentages.
[b]Patients with multiple treatment-emergent adverse events are counted once within a preferred term.
[c]Treatment-emergent adverse events are defined as all adverse events that occurred after the first dose of study medication or within 30 days posttreatment period.

Table 3. Pharmacokinetic parameters for LB-100 and endothall

| | | | | | **LB-100** | | |
Subject group	Day nominal	Subject	Gender	Dose (mg/m2)	Apparent CL (ng·h/mL)	Apparent V_{ss} (ng·h/mL)	$t_{1/2}$ (h)
1	1	001-0030	Male	2.33	2.5	0.52	1.10
	3			2.33	5.7	1.10	0.95
1	1	002-0028	Female	2.33	2.7	0.65	1.35
	3			2.33	2.0	0.47	1.56
1	1	003-0029	Female	2.33	4.7	1.06	1.58

| | | | | | **Endothall** | | | |
Subject group	Day nominal	Subject	Gender	Dose (mg/m²)	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)	AUC (ng·h/mL)
1	1	001-0030	Male	2.33	ND[a]	ND[a]	ND[b]	ND[c]
	3			2.33	ND[a]	ND[a]	ND[b]	ND[c]
1	1	002-0028	Female	2.33	11.5	4	ND[b]	22
	3			2.33	34.3	4	ND[b]	143
1	1	003-0029	Female	2.33	14.8	4	ND[b]	28

NOTE: Clearance value and volume of distribution at steady state represents a close approximation because the plasma concentration–time profile was only characterized through 4 hours after completion of the infusion.
[a]Plasma concentrations of endothall were below the lower limit of quantification (5 ng/mL).
[b]Terminal elimination half-life could not be defined.
[c]AUC values could not be defined.

serum creatinine following fostriecin given by intravenous infusion daily for 5 days were maximal after one or two doses, did not increase with continued administration, and were not greater at doses five times larger than those producing an initial grade 3 increase in creatinine. They concluded that fostriecin produced reversible hemodynamic changes in the kidney compatible with renal tubular damage. Whether further dose escalation of LB-100 in the face of initial impairment of renal tubular function is tolerable and not associated with cumulative renal dysfunction remains to be determined. However, as the MTD and lower doses of LB-100 used in this study were associated with apparent clinical activity, we did not pursue dose escalation in the face of grade 3, albeit transient, renal toxicity.

We were encouraged that 10 (50%) of 20 patients receiving at least 2 cycles of LB-100 had stable disease for up to 15 cycles of therapy without limiting or cumulative toxicity.

It is of note that stabilization of disease occurred over a range of doses (0.83–2.33 mg/m² daily for 3 days). The pharmacokinetic data indicate that plasma concentrations of LB-100 were uniformly low, with a half-life between 1 and 2 hours. Pharmacodynamic preclinical studies showed that despite the short plasma half-life of LB-100, maximum PP2A inhibition in xenografts occurs 2 to 4 hours after a single intraperitoneal injection and that full recovery of PP2A activity requires at least 24 hours (13, 14), suggesting accumulation or at least persistence of LB-100 at concentrations and durations longer than in the plasma. This possibility is supported by Martiniova and colleagues (12), who

Figure 1.
Comparable coronal CT views of pancreatic cancer (X) at entry onto study (left) and after 10 cycles of LB-100 (right).
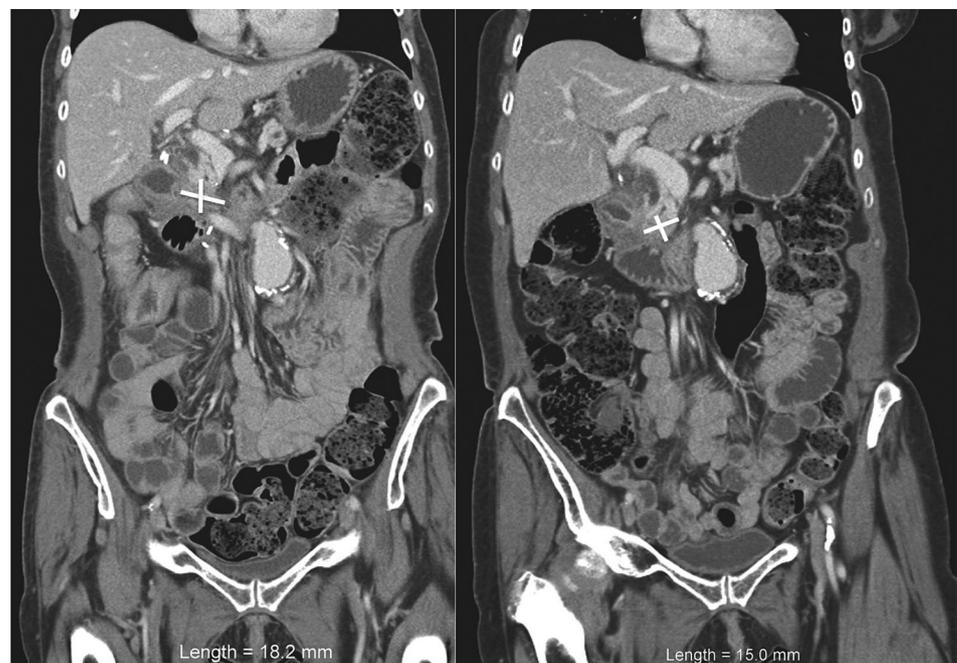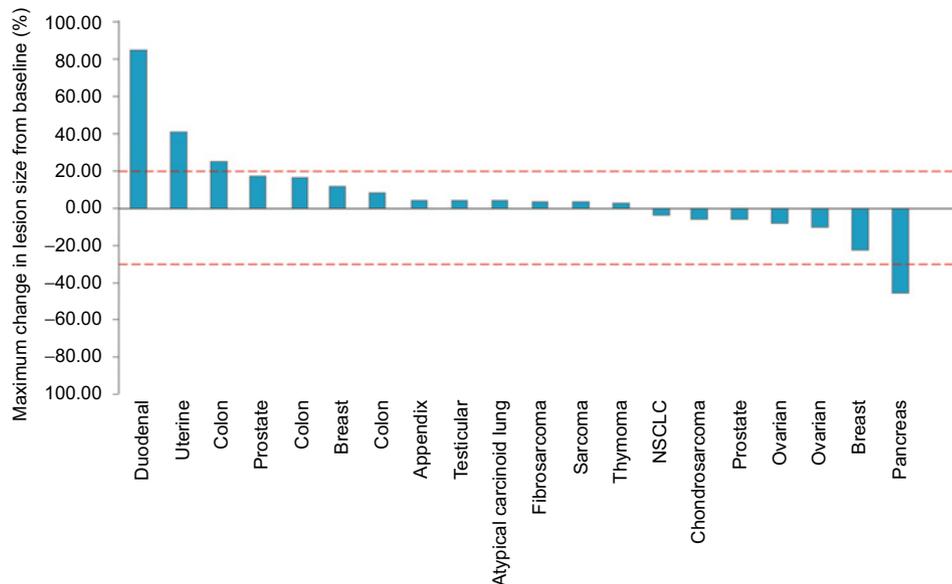
Figure 2.

Greatest change in size of indicator lesion in patients with measurable disease at entry. NSCLC, non–small cell lung cancer.

showed that LB-100 given by continuous infusion via an intra-peritoneally implanted Alzet pump at 1.5 mg/m^2 ($\sim$4.5 mg/m^2) over 24 hours for 7 days markedly enhanced the effectiveness of temozolomide against mouse pheochromocytoma (PC12) xeno-grafts in the liver of immunosuppressed mice, whereas LB-100 alone had no and temozolomide alone had little antitumor effect.

Given the multiplicity of signaling pathways important to cell proliferation that are regulated by PP2A, it is not clear why essentially nontoxic doses of a PP2A inhibitor should result in antitumor activity. Our hypothesis is that tumors sensitive to PPA inhibition have acquired defects in PP2A activity or regulation that make them more vulnerable to pharmacologic inhibition of PP2A than normal cells. There is a large and growing body of evidence that endogenous inhibitors of PP2A, especially the SET/I2PP2A and CIP2A oncoproteins, are overexpressed in and responsible for reduced PP2A activity in many types of solid tumors and acute and chronic myeloid leukemias (8, 24–26). Several groups are pursuing pharmacologic means to either inhibit SET or increase PP2A as treatment for such cancers (27–32). We believe that just the opposite approach, further pharma-cologic reduction of PP2A activity, is likely to be selectively cytotoxic to PP2A-deficient cells. Thus, LB-100 may be active as a single agent and effective at potentiating cytotoxic regimens in cells deficient in PP2A activity as has been shown clinically in the del(5q) myelodysplastic syndrome (33). In these neoplastic cells, an allele for a catalytic subunit of PP2A is deleted, and lenalido-mide, a standard agent for the treatment of myelodysplastic syndrome, has been shown to be selectively cytotoxic to these PP2A haplo-insufficient cells by virtue of its moderate PP2A-inhibitory activity (33).

PP2A inhibition also results in synthetic lethality of cancer cells overexpressing Mad2 (mitotic arrest deficiency protein 2; ref. 34).
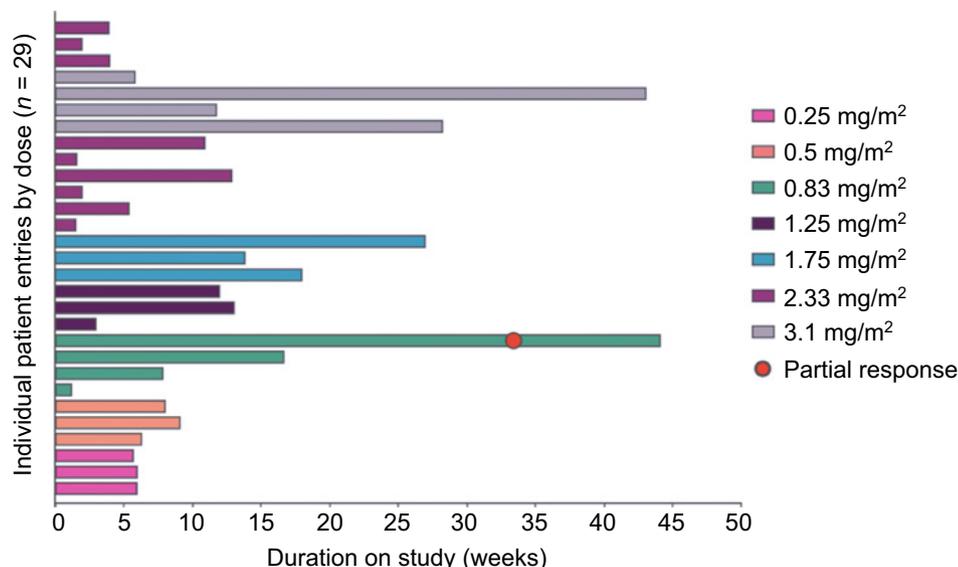

Figure 3.

Duration of stability or partial response (red circle) of disease (number of cycles) for each patient in ascending order of entry onto study.

Overexpression of Mad2 accompanies mutations in the Rb and/or p53 pathways and is thought to be a key feature of chromosome instability in cancer cells (35). Mad2 is frequently overexpressed in human cancers, including breast, gastric, NSCLC, colon, endometrial, ovarian (mucinous), soft tissue and osteosarcomas, hepatocellular cancer, and seminomas. In this study, the pancreatic cancer of the patient having a partial response markedly overexpressed Mad2. We were not able to obtain tumor tissue from the other patients on this trial for Mad2 assessment. Molecular identification of overexpression of endogenous inhibitors of PP2A and of Mad2 in future studies offers the possibility of selection of patients with a variety of common solid tumors and hematologic cancers for therapy with LB-100.

The availability of a clinically safe inhibitor of PP2A provides an opportunity to exploit a long-appreciated but neglected therapeutic target for cancer therapy. The current trial suggests that LB-100 alone may have anticancer activity. A large number of preclinical studies, however, suggest that pharmacologic inhibition of PP2A is likely to be most effective for cancer therapy when combined with cytotoxic drugs, particularly for tumors with acquired abnormalities in PP2A function and/or in the DNA damage repair pathway (18, 36). The next step in LB-100 development is to determine whether the apparent selectivity of this therapeutic strategy in animal models holds true in the clinic.

Disclosure of Potential Conflicts of Interest

J.S. Kovach has ownership interest in Lixte Biotechnology Holdings, Inc. A.S. Mansfield is a consultant/advisory board member for Genentech and Rockpointe. F. Braiteh reports receiving speakers bureau honoraria from Amgen, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Genentech, Incyte, INSYS, IPSEN, Merck, and Pfizer and is a consultant/advisory board member for Amgen, AstraZeneca, Eli Lilly, and Genentech. No potential conflicts of interest were disclosed by the other authors.

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Clinical Cancer Research

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Vincent Chung, Aaron S. Mansfield, Fadi Braiteh, et al.

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