A Phase II Study of the Histone Deacetylase Inhibitor Panobinostat (LBH589) in Pretreated Patients with Small-Cell Lung Cancer

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Background: In vitro data suggest that panobinostat (LBH589), a pan-deacetylase inhibitor, may add therapeutic benefit in the treatment of small-cell lung cancer (SCLC) with regression of tumors.

Methods: This multicenter, nonrandomized phase 2 trial was designed to evaluate antitumor activity of LBH589 in patients with previously treated SCLC. Patients received LBH589 administered intravenously at a dose of 20 mg/mq (days 1–8) every 21 days.

Results: A total of 21 patients with extensive- or limited-stage SCLC were enrolled. Patients received a median of two cycles (range, 1–6). LBH589 was well tolerated, and the most common toxicities were grade 1 to 2 gastrointestinal disorders (nausea 38%, diarrhea 24%, vomiting 19%), grade 1 to 2 thrombocytopenia (14.3%). Of 19 patients evaluable for efficacy, two cases showed shrinkages more than 30% at first assessment, with time to progression of 14 and 21 weeks, respectively, and there were three long disease stabilizations of 12, 10, and 13 weeks. The study was prematurely closed because of a lack of activity.

Conclusion: This is the first report of a pan-deacetylase inhibitor inducing tumor shrinkage and sustained stable disease in SCLC. We believe that although the trial was prematurely discontinued, modest clinical activity of LBH589 combined with a favorable safety profile in pretreated SCLC patients was observed, which warrants further exploration of the potential contribution of LBH589 in other trials.

Key Words: Panobinostat, LBH58, Small-cell lung cancer, Phase II trial, Deacetylase inhibitor.

(*J Thorac Oncol.* 2013;8: 1091-1094)

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Disclosure: The authors declare no conflict of interest.

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ISSN: 1556-0864/13/0808-1091

Small-cell lung cancer (SCLC) is the most aggressive and lethal form of lung cancer, and is associated with a high incidence of tumor relapse and very poor life expectancy.[1] Current management usually consists of combination chemotherapy regimens based on cisplatin or carboplatin and etoposide,[2] with a median overall survival of approximately 10.2 months.[3] Despite the high response rate (RR), approximately 80% of patients with limited disease and nearly all patients with extended disease develop disease progression. Topotecan is at present the only agent approved for second-line treatment of SCLC patients. However, activity particularly in refractory patients is very modest, with a time to progression of 13 weeks, and a median overall survival of 25 weeks.[4,5] The research of a new therapeutic agent that is able to improve the natural history of SCLC would be an important goal to achieve. Deacetylases (DACs) are enzymes that remove the acetyl groups from histones, the core proteins in chromatin around which DNA is wrapped. For this reason, these enzymes are often referred to as histone deacetylases (HDACs).[6] Histone proteins are implicated in epigenetic modifications, which could cause decrease of tumor suppressor gene activity (p21, p27)[7] with a progression of cell growth that is associated with down-regulation of the cyclin-dependent kinase inhibitors. This shows a crucial, nonredundant role for HDACs in regulating cell proliferation. The second major target for DACs are nonhistone proteins, like tumor-suppressor protein p53, α-tubulin, hypoxia inducible factor-1α, and heat-shock protein,[8,9] which have been shown to modulate cancer cell growth and survival pathways. A pan-DAC inhibitor can target all classes of DACs, thereby modulating histone and nonhistone proteins implicated in oncogenesis and ultimately interfering with multiple hallmarks of cancer.[7] Panobinostat (LBH589) is a novel hydroxamate analog pan-DAC inhibitor available for intravenous and oral administration. LBH589 has been shown to inhibit purified HDAC enzyme in vitro and in vivo, causing an increase of histone H3 and H4 acetylation levels, and to produce p21 activation as a consequence of the inhibition of nonhistone protein.[10] Preclinical data showed high sensitivity of SCLC cells lines to LBH589,[11] and in transgenic mice experiments induced almost complete regression of the tumors at tolerable dosages.[10] Two studies analyzed combinations of LBH589 and cytotoxic agents in SCLC cell lines and xenograft

models. Concentrations of the DNA methyltransferase inhibitor decitabine (5-AZA-dC) and the HDAC inhibitors (LBH589) synergistically reduced the proliferation of five of nine SCLC cell lines.[12] LBH589 was, however, particularly effective in SCLC xenografts, and the addition of the chemotherapy agent etoposide augmented antitumor effects.[13] The high activity of LBH589 in SCLC cell lines together with preliminary clinical data give the rationale to test this drug in this disease.

PATIENTS AND METHODS

Study Population

The eligibility criteria for patients included were: histological or cytological diagnosis of SCLC; age less than 75 years; two or lesser prior chemotherapy lines; progression after and not during last chemotherapy treatment (platinum-refractory patients were excluded); measurable disease as defined by Response Evaluation Criteria in Solid Tumor, (RECIST) version 1.0;[14] Eastern Cooperative Oncology Group performance status of 0 to 1; life expectancy of at least 3 months; adequate hematological (hemoglobin ≥ 9 g/dl; platelet count ≥ 100,000/mm^3; neutrophils count ≥ 1500/mm^3), liver (serum bilirubin ≤ 1.5 × aspartate aminotransferase and alanine aminotransferase ≤ 2.5 × upper normal limit (UNL) or ≤ 5.0 × UNL if the transaminase elevation is because of hepatic involvement, albumin ≥ 2.5 g/dl, alkaline phosphatase ≤ 2.5 × UNL), and renal functions (total UNL; serum creatinine ≤ 1.5 × UNL or 24-hour creatinine clearance ≥ 50 ml/minutes).

The protocol was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study was approved by the ethics committee of each participating institution, and written informed consent was obtained from each patient before inclusion.

Study Design and Treatment

This was a multicenter, international, open-label, nonrandomized phase 2 trial, designed to evaluate antitumor activity of LBH589 in patients with SCLC. The ClinicalTrials. Government Identifier: NCT01222936. LBH589 was administered as a 30-minute intravenous infusion at a dosage of 20 mg/m^2, on days 1 and 8, every 21 days.

Clinical examination was performed before every cycle. Complete blood cell count was performed weekly. Twelve-lead electrocardiograph (ECG) assessments were performed at screening preinfusion, 4 and 24 hours after infusion, and on day 8. Evaluation of the disease was organized every 6 weeks (2 cycles) by computed tomography sca,n according to RECIST (version 1.0). Toxicity was determined according to the National Cancer Institute Common Toxicity Criteria (version 3.0).[15] Prophylactic antiemetic measures before administration of infusion, loperamide as initial therapy of diarrhea, and recombinant hematopoietic growth factors were allowed during treatment at the discretion of investigators.

Patients were taken off study in case treatment recycling was delayed by more than 2 weeks, occurrence of unacceptable adverse events (AE), protocol violation, or noncompliance with study protocol. Dosage was modified at next cycle to 15 and 10 mg/m^2 after recovery to grade 1 toxicity in case of: grade 4 hematological toxicity, febrile neutropenia, cardiac toxicity defined as multiple QTcF higher than 480 but less than 500 msec (determined by more ECGs), or any QTc higher than or equal to 500 but less than 515 msec; grade 3 or 4 nonhematological toxicity. Treatment was administered till patient's progression. LBH589 was given by Novartis in accordance with the ethical principles, which have their origin in the Declaration of Helsinki and are consistent with Good Clinical Practice, and the applicable regulatory requirements.

Statistics

The primary endpoint was the RR. Secondary endpoints included characterization of toxicities, duration of response, and time to progression.

A Simon's two-step optimal design was used to assess the primary endpoint, assuming an unacceptable RR of 7%, and an acceptable rate of 20% on a sample of 48 evaluable patients, with a type I error of 1.0 and a power of 0.85.[16]

Accrual was terminated if less than two objective responses were achieved on the first 17 evaluable patients. If at the end of the trial less than five responses were achieved, no further investigation was warranted.

RESULTS

Between May 2008 and April 2009, a total of 21 patients with progressed SCLC were enrolled in the study.

TABLE 1. Patients Characteristics

Patients Characteristics	(N = 21)
Demographics	
Age (yr) median (range)	62 (47–75)
Men/women	12/9 (57%–43%)
ECOG PS	
0	9 (42.9%)
1	12 (57.1%)
Stage at study entry	
Extensive	12 (57.1%)
Limited	7 (33.3%)
Not evaluable	2 (9.5%)
Progression disease status	
Sensible[a]	14 (66.6%)
Resistant[b]	7 (33.3%)
Prior therapy	
Radiotherapy	18 (85.7%)
Surgery	3 (14.3%)
Prior systemic therapy (Metastatic/recurrent disease)	21 (100%)
Prior chemotherapy for metastatic disease[c]	20 (95.2%)
First-line	13 (61.9 %)
Second-line	7 (33.3 %)

[a]Progression of disease >90 days from previous treatment.
[b]Progression of disease <90 days from previous treatment.
[c]Each prior systemic chemotherapy for metastatic disease after which patient progressed is counted as first-line. Prior systemic chemotherapy for metastatic disease administered in absence of PD are not counted as new-line. One patient received prior chemotherapies and started study treatment without PD.

ECOG, Eastern Coopeartive Oncology Group; PS, performance status; PD, progressive disease.

TABLE 2. Most Significant Drug-Related Adverse Events

Toxicity	Grade 1–2 N (%)	Grade 3 N (%)
Hematological		
Thrombocytopenia	3 (14.3)	—
Anemia	3 (14.3)	—
Blood alkaline phosphatase increased	1 (4.8)	—
Nonhematological		
Asthenia	2 (9.5)	1(4.7)
Fatigue	3 (14.3)	—
Diarrhea	5 (23.8)	—
Nausea	8 (38.1)	—
Vomiting	4 (19)	—
Constipation	2 (9.5)	—

Patients characteristics are shown in Table 1. The percentage of patients who had extensive disease was 57.1%, and 33.3% were resistant to previous treatment. All patients entered in the study were treated with LBH589 and received total number of 49 cycles, with a median number of two cycles (range, 1–6). Overall compliance was good, and reduction of dosage was done in 12 of 49 cycles because of AEs. Mean relative dosage intensity was 87.6% of the planned dosage. Even though the trial was prematurely closed at the end of step 1 in the absence of RECIST-defined partial responses (PRs), this is the first study that showed some signal activity of DAC in SCLC.

Toxicity

LBH589 was generally well tolerated; the most common toxicities were grade 1 to 2 gastrointestinal disorders (nausea 38%; diarrhea 24%; vomiting 19%) and grade 1 to 2 thrombocytopenia (14.3%). One patient experienced grade 3 hypertension, which was not drug related. Among the 15 patients experiencing treatment-related AE, six had a grade 3 or higher treatment-related AEs; no treatment-related serious adverse events occurred. Among the 122 ECGs analyzed, there was no QTc greater than 480 msec increased from baseline (with exception of a slight increase in one patient). There was no neccesity for dosage reduction or discontinuation because of cardiac toxicity. The most significant drug-related AEs are shown in Table 2.

Response

In the 19 patients evaluable for efficacy, we observed shrinkages of more than 30% in two cases at first assessment (week 6), which did not qualify for PR at week 12 because of the appearance of a new lesion in first case, and reduced shrinkage (19% stable disease [SD]) in the second case (time to progression 14 and 21 weeks) and also obtained three long-lasting disease stabilizations of 12, 10, 13 weeks (time on study and response are shown in Fig. 1). Accrual was terminated if less than two objective responses were achieved on the first 17 evaluable patients.

To summarize, five patients (26.3%) achieved SD, 14 patients (73.6%) progressive disease (PD), and two patients

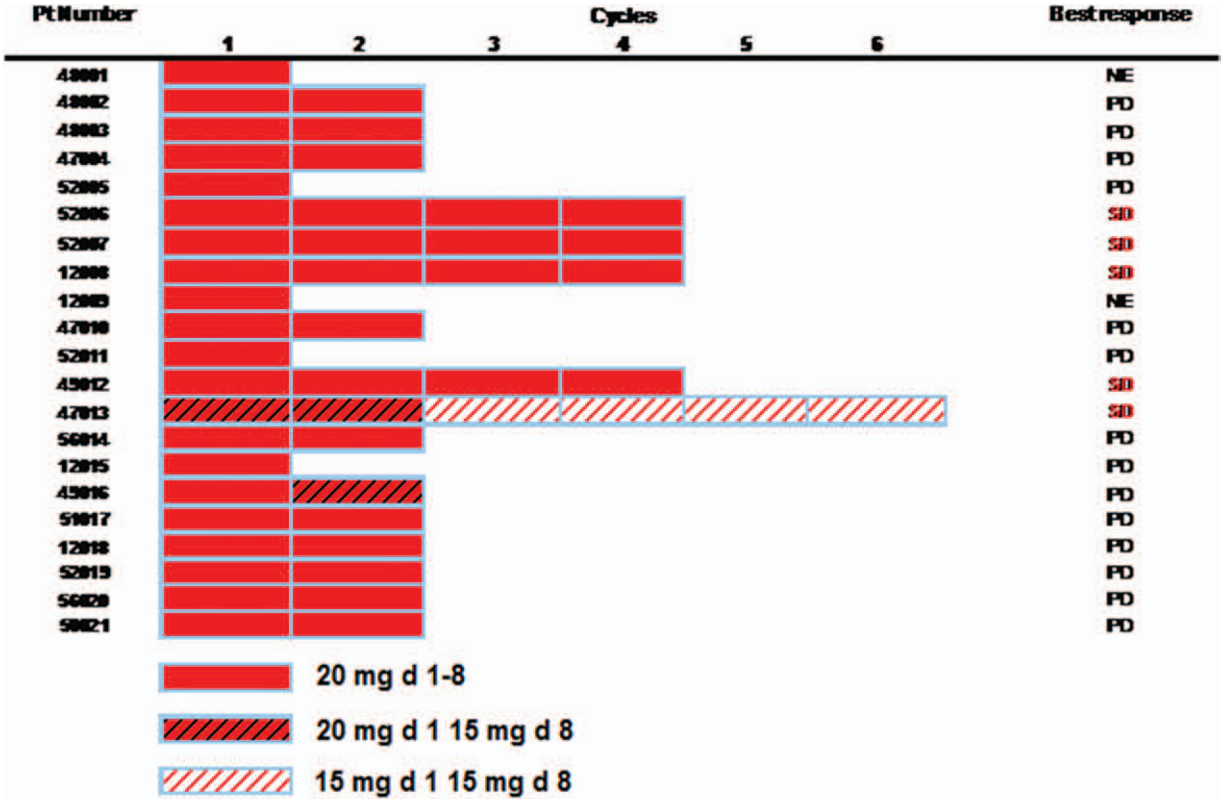

FIGURE 1. Time on study and response. SD, standard deviation.

(10, 5%) were not evaluable for response because of early withdrawal from the study because of disease-related events (cardiac and respiratory insufficiency leading to death 19 days after the enrollment and to asthenia G3). Two patients with a PR at 6 weeks were resistant (PD < 90 days) to previous treatment.

Median time to progression was only 1.41 months (95% confidence interval: 1.3–2.2). Median duration of SD was 3 months (95% confidence interval: 2.3–4.9).

DISCUSSION AND CONCLUSION

Several drugs have been evaluated in SCLC second-line treatment, but without success. Recent progress in the understanding of the biology of SCLC has led to the identification of crucial signaling pathways and the subsequent development of targeted therapies. Several novel molecules are presently undergoing evaluation; in this trial, a pan-HDAC inhibitor LBH589 showed modest activity in SCLC. LBH589 is a pan-HDAC inhibitor that has demonstrated preclinical anticancer effects in non–small-cell lung cancer and SCLC models; this agent was also tested in non–small-cell lung cancer patients in a phase I trial in combination with erlotinib.[17]Disease stabilization could be considered a clinically relevant result in patients affected by SCLC in second-line setting.[18] In this patient population, SD and PR were associated with a survival benefit versus PD; interestingly, the survival benefit was similar between the two groups (PR and SD). These results suggest that at least in these populations, SD may represent a potential benefit of chemotherapy, and therefore, the distinction between SD and PR may not be useful. LBH589 monotherapy is well tolerated in patients and has modest single-agent activity, even if there were no complete or partial responses. The potential contribution of LBH589, in combination with standard cytotoxic regimens, should be investigated, given the results obtained in preclinal studies.

ACKNOWLEDGMENTS

The study was sponsored by Southern Europe New Drugs Organization and supported by Novartis.

REFERENCES

1. Sandler AB. Chemotherapy for small cell lung cancer. *Semin Oncol* 2003;30:9–25.
2. Murray N, Turrisi III AT. A review of first-line treatment for small cell lung cancer. *J Thorac Oncol* 2006;1:270–8.
3. Sundstrøm S, Bremnes RM, Kaasa S, et al.; Norwegian Lung Cancer Study Group. Cisplatin and etoposide regimen is superior to cyclophosphamide, epirubicin, and vincristine regimen in small-cell lung cancer: results from a randomized phase III trial with 5 years' follow-up. *J Clin Oncol* 2002;20:4665–4672.
4. Riemsma R, Simons JP, Bashir Z, Gooch CL, Kleijnen J. Systematic Review of topotecan (Hycamtin) in relapsed small cell lung cancer. *BMC Cancer* 2010;10:436.
5. von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. *J Clin Oncol* 1999;17:658–667.
6. Minucci S, Pelicci PG. Histone deacetylase inhibitors and the promise of epigenetic (and more) treatments for cancer. *Nat Rev Cancer* 2006;6:38–51.
7. Bolden JE, Peart MJ, Johnstone RW. Anticancer activities of histone deacetylase inhibitors. *Nat Rev Drug Discov* 2006;5:769–784.
8. Mehnert JM, Kelly WK. Histone deacetylase inhibitors: biology and mechanism of action. *Cancer J* 2007;13:23–29.
9. Garber K. HDAC inhibitors overcome first hurdle. *Nat Biotechnol* 2007;25:17–19.
10. Crisanti MC, Wallace AF, Kapoor V, et al. The HDAC inhibitor panobinostat (LBH589) inhibits mesothelioma and lung cancer cells in vitro and in vivo with particular efficacy for small cell lung cancer. *Mol Cancer Ther* 2009;8:2221–2231.
11. Edwards A, Li J, Atadja P, Bhalla K, Haura EB. Effect of the histone deacetylase inhibitor LBH589 against epidermal growth factor receptor-dependent human lung cancer cells. *Mol Cancer Ther* 2007;6:2515–2524.
12. Luszczek W, Cheriyath V, Mekhail TM, Borden EC. Combinations of DNA methyltransferase and histone deacetylase inhibitors induce DNA damage in small cell lung cancer cells: correlation of resistance with IFN-stimulated gene expression. *Mol Cancer Ther* 2010;9:2309–2321.
13. Crisanti MC, Wallace AF, Kapoor V, et al. The HDAC inhibitor panobinostat (LBH589) inhibits mesothelioma and lung cancer cells in vitro and in vivo with particular efficacy for small cell lung cancer. *Mol Cancer Ther* 2009;8:2221–2231.
14. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–216.
15. Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0. Available at: http://ctep.cancer.gov. Accessed August 9, 2006.
16. Simon R, Wittes RE, Ellenberg SS. Randomized phase II clinical trials. *Cancer Treat Rep* 1985;69:1375–1381.
17. Ramalingam SS. Histone deacetylase inhibitors. *J Thorac Oncol* 2011;6(11 Suppl 4):S1808–S1809.
18. Cesano A, Lane SR, Poulin R, et al. Stabilization of disease as a useful predictor of survival following second- line chemotherapy in small cell lung cancer and ovarian cancer patients. *Int J Oncol* 1999;15:1233–8.

