Lung Cancer (2008) **60**, 374—380

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/lungcan

Phase II study of plitidepsin in pretreated patients with locally advanced or metastatic non-small cell lung cancer

Christian Peschel[a,*], Joerg T. Hartmann[b], Alexander Schmittel[c], Carsten Bokemeyer[b,d], Folker Schneller[a], Ulrich Keilholz[c], Dieter Buchheidt[e], Susana Millan[f], Miguel Ángel Izquierdo[f], Ralf-Dieter Hofheinz[e]

[a] *Technische Universität, III. Medizinische Klinik, München, Germany*
[b] *Universitätsklinik Tübingen, Medizinische Klinik, Abteilung II, Otfried-Müller-Str. 10, 72076 Tübingen, Germany*
[c] *Charité Campus Benjamin Franklin, Medizinische Klinik III Hämatologie, Onkologie und Transfusionsmedizin Hindenburgdamm 30, 12200 Berlin, Germany*
[d] *Universitätsklinikum Hamburg-Eppendorf, Medizinische Klinik II, Onkologie und Hämatologie, Martinistr. 52, 20246 Hamburg, Germany*
[e] *Onkologisches Zentrum, III. Medizinische Klinik, Universitätsklinikum Mannheim, Theodor-Kutzer-Ufer, 68267 Mannheim, Germany*
[f] *Pharma Mar S.A., Avenida de los Reyes, 1 Polígono Industrial La Mina-Norte, 28770 Colmenar Viejo, Madrid, Spain*

Received 27 June 2007; received in revised form 10 October 2007; accepted 22 October 2007

KEYWORDS
Plitidepsin;
Cancer;
Lung;
NSCLC;
Chemotherapy;
Second-line

Summary
Objective: To evaluate the progression-free rate (PFR) at 3 months (13 ± 1 weeks), antitumor response, time-to-event efficacy endpoints, and toxicity profile of plitidepsin administered as a 3-h continuous i.v. infusion at a dose of 5 mg/m^2, every 2 weeks, to patients with chemotherapy pretreated advanced non-small cell lung cancer (NSCLC).
Patients and methods: This was a multicenter, non-randomized, exploratory, phase II study. Treatment lasted until disease progression, unacceptable toxicity, patient refusal or treatment delay for >2 weeks. PFR (primary efficacy endpoint) and objective response rate (secondary efficacy endpoint) were evaluated according to RECIST, while the toxic profile of plitidepsin was assessed using the NCI-CTC, version 2.0.
Results: A total of 21 patients with a median age of 61 years and with locally advanced or metastatic non-resectable NSCLC, who had previously received only one line of chemotherapy in an advanced setting, received a total of 54 cycles of treatment (median of two cycles per

* Corresponding author at: Technische Universität München, III. Medizinische Klinik, Klinikum Rechts der Isar, Ismanninger Str. 22, 81675 München, Germany. Tel.: +49 894140 4111; fax: +49 894140 4879.
E-mail address: christian.peschel@lrz.tu-muenchen.de (C. Peschel).

0169-5002/$ — see front matter
doi:10.1016/j.lungcan.2007.10.019

patient; range: 1—8). Antitumor activity was seen in 3 (1 PR, 2 SD) out of 17 evaluable patients according to RECIST. One patient was responder for the primary (PFR at 13 ± 1 weeks) and secondary efficacy endpoint (stable disease according to RECIST). Other two patients were non-responders for the primary efficacy endpoint, but had stable disease (not confirmed at weeks 13 ± 1 due to previous withdrawal due to adverse events). With a median follow-up of 12.3 months, the median time to progression (TTP) and the median overall survival (OS) were 1.2 months and 4.3 months, respectively. The incidence of plitidepsin-related toxicities was low and most of them were mild-to-moderate in severity. The most common side effects were anemia, and asymptomatic and non-cumulative increases of gamma-glutamyltransferase (GGT) and liver transaminase levels.

Conclusion: This study shows that plitidepsin 3-h continuous i.v. infusion (5 mg/m^2) every 2 weeks, was feasible and well tolerated in patients with pretreated NSCLC. The lack of evidence of antitumor activity precludes further studies with this plitidepsin schedule in this tumor setting.

1. Introduction

For patients with advanced stages (stage III with malignant pleural effusion and/or IV) of non-small cell lung cancer (NSCLC), no curative chemotherapy, alone or in combination with radiation therapy, is currently available [1,2]. Although current available chemotherapy may result in a modest improvement in patient survival, overall prognosis of these patients remains poor [3,4]. Therefore, development of more effective systemic therapies is urgently needed for patients with unresectable NSCLC.

Plitidepsin is a naturally occurring cyclic depsipeptide first isolated from the Mediterranean tunicate *Aplidium albicans* and currently produced by chemical synthesis. The primary mode of action of plitidepsin has not been fully elucidated; however, several mechanisms have been proposed, including oxidative stress resulting in cellular apoptosis [5], induction of apoptosis via activation of the Rac1-JNK pathway [6,7], EGFR (epidermal growth factor receptor) phosphorylation *in vitro* [8], and increased level of cell membrane phospholipids oxidation and DNA oxidation *in vitro* [9]. In addition, plitidepsin reduced growth and induced apoptosis in anaplastic thyroid cancer xenografts and human leukemia MOLT-4 cells through the inhibition of expression of several angiogenic genes and the inhibition of VEGF (vascular endothelial growth factor) secretion [10,11]. Six phase I studies that comprised dosage intervals of daily $\times$ 5, weekly and every-2-week infusions, infusion times over 1 h, 3 h and 24 h and dose levels ranging from 0.08 mg/m^2 to 8 mg/m^2 were conducted [12—17]. Evidences of objective remissions and tumor control were found in patients with several advanced tumors, including NSCLC. The dose-limiting toxicities (DLTs) observed with most of the schedules included muscular toxicity, transient transaminitis, fatigue and diarrhea. Cutaneous rash was also observed with the daily $\times$ 5 schedule. Plitidepsin showed a remarkable absence of severe bone marrow toxicity.

Based on the pharmacokinetic and toxicity profiles of plitidepsin, the dose intensity delivered and the antitumor activity seen with all schedules tested during the phase I program, the current multicenter, exploratory, open-label, single-arm, phase II clinical trial assessed the antitumor activity and safety profile of plitidepsin given as a 3-h infusion every 2 weeks (at the proposed recommended dose of 5 mg/m^2) to patients with unresectable and pretreated NSCLC.

2. Patients and methods

This phase II clinical trial was conducted at four German centers. The protocol was approved by the institutional review boards of each participating center, and a signed written informed consent was obtained from each patient before registration.

2.1. Study design and endpoints

This multicenter, two-stage, open-label, single-arm, exploratory phase II study in adult patients with refractory advanced and unresectable NSCLC was designed to determine the efficacy and tolerability of plitidepsin 5 mg/m^2, administered as a 3-h i.v. infusion every 2 weeks.

The primary endpoint was to assess the progression-free rate (PFR) at 3 months, defined as the proportion of evaluable patients without progressive disease at 3 months (13 ± 1 weeks) after the start of therapy. Secondary endpoints were to evaluate the objective tumor response rate and the time-to-event efficacy endpoints (tumor response duration, time to progression (TTP), progression-free survival (PFS) and overall survival (OS)), and to further study the toxic profile of plitidepsin.

2.2. Patient population

Patients were required to have unresectable locally advanced or metastatic histologically proven NSCLC with progressive disease (PD) documented within 4 months prior to registration. All patients had to have received no more than one previous line of systemic chemotherapy for advanced disease at least 3 weeks prior to the first administration of plitidepsin. Neoadjuvant chemotherapy was to be considered a first-line therapy when it was completed within 6 months after the administration of last cycle. Patients had to have age $\geq$18 years, Karnofsky performance status (PS) >50, and adequate organ function (creatinine clearance $\geq$40 ml/min, serum bilirubin $\leq$1.5 mg/dl, alkaline phosphatase (AP) $\leq 2.5 \times$ the institutional upper limit of normal (ULN) and up to $\leq 5 \times$ ULN in case of extensive bone