Debio0932, a second-generation oral heat shock protein (HSP) inhibitor, in patients with advanced cancer—results of a first-in-man dose-escalation study with a fixed-dose extension phase


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Background: Objective was to determine maximum tolerated dose (MTD), recommended dose (RD) and schedule, safety, pharmacokinetic (PK) profile, pharmacodynamic (PD) effects, and antitumor activity of Debio0932, a new second-generation oral heat shock protein (HSP) inhibitor.

Patients and methods: This was a multicenter, uncontrolled, open-label, nonrandomized, dose-escalation study in adults with treatment-resistant advanced cancer. Groups of three patients received oral Debio0932 either daily or every other day. The starting dose of 50 mg was escalated until the MTD was reached, i.e. dose-limiting toxicity (DLT) occurred in ≥2 patients. Further 9 patients and an extension cohort of 30 patients were treated at the next lower dose (=RD). Adverse events (AEs), tumor response, PK, and HSP70 levels in peripheral blood mononuclear cells were recorded over 30 days.

Results: Fifty patients were treated with doses up to 1600 mg, at which level three DLT occurred (febrile neutropenia, diarrhea, asthenia). In total, 39 patients were then treated at the RD of 1000 mg daily. Most common drug-related AEs were asthenia and gastrointestinal events. No ocular toxicities were observed. Debio0932 was rapidly absorbed and metabolized. Plasma steady state was reached within 9 days. Volume of distribution was high and elimination half-life was retrieve and 1999 EORTC recommendations. European Organization for Research and Treatment of Cancer (EORTC) PET Study Group. Eur J Cancer 1999; 35: 1773–1782.


Introduction

Heat shock protein (HSP90) is a promising cancer drug target, as it acts as chaperone for many proteins involved in cell signaling, proliferation, and survival [1, 2]. Inhibition of HSP90 function was shown to trigger proteosomal degradation of multiple oncoproteins, thereby diminishing cancer cell proliferation and tumor angiogenesis and promoting apoptosis [3–6]. HSP90 inhibitors compete with ATP at the amino-terminal nucleotide-binding site to neutralize the intrinsic ATPase activity of HSP90 which is essential for its chaperone function. Several HSP90 inhibitors have entered clinical development; one is Debio0932 (formerly CUDC-305, CUR-0374441), an oral synthetic imidazopyridine.

In preclinical models, Debio0932 exhibited potent antitumor activity along with high oral bioavailability, selectivity, blood–brain barrier penetration, and extended tumor retention. Debio0932 resulted in stabilization and regression of lung, breast, gastric, glioblastoma, and leukemia tumor xenografts in mice and was tested in 40 different human cancer cell lines. It displayed anti-proliferative activity in cancer cells bearing multiple genetic alterations, with IC_{50} ranging from 100 to 900 nM [7]. Its toxicity profile proved similar to other HSP90 inhibitors affecting the intestine, heart, and hematology parameters. Debio0932 had long-lasting inhibitory pharmacodynamic (PD) effects in vitro and in vivo. It induced the expression of HSP70 in tumor xenografts and affected multiple signaling pathways in tumor cells by inducing the degradation of several key oncogenic drivers, including EGFR, FLT3, and HER2. In vivo, Debio0932 was also shown to accumulate in tumors over time (T_{1/2} ~20 h in tumors versus ~2–7 h in normal tissues) [7].

Consequently, a first-in-man study was undertaken in patients with advanced cancer resistant to standard therapy to determine the maximum tolerated dose (MTD) of Debio0932. Secondary objectives were to establish a dose for further development; to assess safety and PK profiles, antitumor activity and PD effects; and to explore PK/PD relationships.

Methods

Design

This was a multicenter, uncontrolled, open-label, nonrandomized, sequential dose-escalation study with two parallel groups of patients receiving the same oral dose either every day (continuous dosing) or every other day (intermittent dosing). Enrollment started in groups of three patients for each dosing schedule. Dose escalation followed a 3+3 design [8] based on the severity of treatment-related adverse events (AEs) according to NCI-CTC v3.0 during the first 30 days of treatment. Dose-limiting toxicity (DLT) was defined as (a) non-hematological toxicity of grade ≥3 (excluding alopecia, nausea, rash, vomiting, diarrhea, and electrolyte imbalances unless persisting despite optimal supportive therapy); (b) thrombocytopenia <25 000/µl lasting ≥5 days or <50 000/µl with bleeding or requiring platelet transfusion; (c) neutropenia of grade 4 for >5 days, or of grade ≥3 along with fever >38.5°C or grade ≥3 with infection; (d) any treatment delay >2 weeks due to drug-induced toxicity; or (e) any other life-threatening toxicity.

Doses were escalated if none of the three patients experienced DLT; if one patient experienced DLT, another three patients were enrolled and treated at the same dose level. The dose increment was 100% if maximum toxicity at a given dose level was grade <2, 50% if =2, and 33% if >2 or a DLT occurred. Dose escalation was stopped if ≥2 patients experienced DLT at the same dose and schedule (=MTD). For continuous and intermittent dosing groups, the next lower dose was determined by a safety committee to be the recommended dose (RD) at which six additional patients were treated. Based on PK and safety, a dosing schedule was selected and an extension cohort of 30 patients treated to collect further safety and PK data.

The study was compliant with all applicable legal obligations, the requirements of the Declaration of Helsinki and Good Clinical Practice. It was approved by the Institutional Review Boards of all sites and registered under Clinicaltrials.gov (identifier: NCT01168752).

Patients

Eligible were adult patients with histologically confirmed advanced or metastatic cancer for which no suitable therapy was available. Patients had to have an ECOG performance status ≤1; life expectancy ≥3 months; absolute neutrophil count ≥1500/µl; platelets ≥100 000/µl; calculated creatinine clearance ≥60 ml/min; total bilirubin ≤1.5x upper limit of normal (ULN); aminotransferases ≤2.5x ULN (in case of liver metastases ≤3.5x ULN); prothrombin time ≤1.5x ULN; and potassium, magnesium, and phosphate below normal.

Treatment

Debio0932 was available as 25 and 100 mg capsules. The starting dose for both regimens was 50 mg, representing one-sixth of the NOAEL in dogs. Dose escalation depended on the grade and frequency of the toxicity observed. If not discontinued by patient or investigator for any reason, treatment lasted until disease progression.

Clinical end points

The primary safety end point was the occurrence of DLTs; secondary end points were the incidence of AEs, severe adverse events (SAEs), and of treatment discontinuations due to AEs, laboratory abnormalities, changes in ECG [RR, partial response (PR), QRS, QT, and QTcF intervals], and left ventricular ejection fraction. Efficacy end points were the rate of complete response (CR) or PR according to RECIST 1.1 [9] and International Workshop Criteria [10] and the duration of response and disease control (i.e. no disease progression). In the extension phase, tumor metabolic response was assessed in NSCLC patients by 18F-FDG-PET scan; the relative change in standardized uptake from baseline to Days 21 and 57 and the rate of complete or partial tumor metabolic response was measured according to EORTC criteria [11].
PD effects of treatment were assessed by determining the change in plasma concentrations of soluble epidermal growth factor receptor 2 (HER-2), a HSP90 client protein, and the HSP70 expression in peripheral blood mononuclear cells (PBMCs). PK was determined based on Debio0932 and Debio0932-MET1 levels in plasma and urine of fasted patients after single dose and at steady state. In addition, PKs were compared in a subset of patients of the extension cohort in fasted and fed condition.

**statistical methods**

A sample size up to 80 was planned, depending on the number of dose escalations required to define MTD and of another 30 patients to be treated with the RD regimen in the extension cohort. Due to the exploratory nature of the study, sample sizes were not based on presumed effect sizes and statistical analysis was mainly descriptive. Patients treated with the RD were pooled study, sample sizes were not based on presumed effect sizes and statistical methods

**results**

Between April 2010 and October 2011, overall 50 patients were enrolled in the dose-escalation study, 22 receiving doses intermittently and 28 daily, altogether forming the safety population (Figure 1). MTD and preliminary efficacy evaluations were based on data of 45 patients (21/24 and 20/25 in intermittent/ continuous dosing groups for safety and efficacy, respectively). In total, 44 patients (88%) discontinued treatment due to disease progression, 31 of whom died during the study or follow-up; 14 were still alive at study end; for 5 status was unknown; 39 patients were treated at the RD of 1000 mg daily, 9 in the dose-escalation part and 30 in the extension study, from February 2012 until April 2013 (Figure 1).

Patients had similar baseline characteristics in groups receiving continuous and intermittent dosing except for a higher percentage of women in the latter (Table 1). The frequency of cancer types was balanced (Table 1). Before enrollment, over 70% of patients had received ≥3 lines of treatment. The extension cohort had comparable baseline demographics, however beyond NSCLC, patients were most commonly suffering from colorectal cancer (Table 1).

**tolerability and safety**

In general, Debio0932 was well tolerated with an average of 37 (range: 7–110) dose administrations per patient in the intermittent dosing group, 71 (9–270) in the continuous dosing group, and 55 (8–238) in the 39 patients exposed to the RD of 1000 mg/day. DLTs occurred at doses of 1600 mg only, one (febrile neutropenia) when given intermittently and two (diarrhea and asthenia) when given daily. For daily dosing, MTD was determined at 1600 mg; for the intermittent schedule dose escalation was stopped due to the excessive number of capsules to be taken.

In the dose-escalation part, 21 (95.5%) patients dosed intermittently reported 224 AEs of which 64 in 14 cases (63.6%) were considered related to Debio0932 (Table 2). Corresponding numbers in the 28 patients (100%) receiving daily doses were 375 and 136 AEs in 22 cases (78.6%), respectively. Most AEs were mild (CTC grade 1 or 2) and affecting the gastrointestinal system. Asthenia (42%), diarrhea (40%), nausea (32%), decreased appetite (24%), and vomiting (22%) were the most common related AEs (Table 2).

Eight patients (36.4%) receiving intermittent doses and 11 patients (39.3%) with daily doses experienced 10 and 13 SAEs, respectively. Apart from one case of Henoch–Schönlein purpura after 5 months of treatment with 200 mg daily, all SAEs considered related to Debio0932 occurred at doses ≥1000 mg. Four patients discontinued the study due to SAE (asthenia, diarrhea, febrile neutropenia). Neither grade 5 toxicities nor any relevant eye or cardiac toxicity were observed. There were no substantial changes in laboratory parameters or vital signs either.

This safety profile was confirmed in the 39 patients receiving the RD of 1000 mg/day who experienced 487 AEs, mainly asthenia, decreased appetite, diarrhea, nausea, and vomiting. Of these 256 in 37 patients (94.9%) were considered drug-related; 21 patients (53.8%) experienced 43 SAEs, of which 15 in 9 patients (23.1%) were considered drug-related. Fifteen patients (38.5%) died because of disease progression, three within 30 days after last drug administration (after 17, 28, and 30 days).

**efficacy**

In the dose-escalation part, disease control was reported in 6 (30%) and in 8 (32%) patients receiving intermittent and daily doses, respectively. Mean duration of disease control was >37 (maximum 273) days regardless of dosing frequency. The best overall response in the intermittent dosing group was PR in

![Figure 1. Patient flow chart.](Image)
2 (10%) and SD in 4 (20%) patients whereas in all 8 (32%) patients receiving daily doses the best response was SD (Figure 2).

SD was most common for NSCLC with 5 of 8 (62.5%) patients. One confirmed PR for 16 weeks was seen in a 63-year-old man with stage IV Kras-mutated adenocarcinoma of the lung, intermittently treated with 100 mg Debio0932. The other PR lasting for 11 weeks was observed in a 66-year-old woman with stage II breast cancer treated intermittently with 800 mg Debio0932. No con-
**pharmacodynamic**

Large interpatient variability in HSP70 induction and HER-2 plasma levels, but no dose response was observed (supplementary Table S2, available at Annals of Oncology online).

**discussion**

The first-generation HSP90 inhibitors evaluated in clinical studies were geldanamycin derivatives. Despite encouraging clinical activity, their pharmaceutical properties and toxicities impaired further clinical development [12–14]. To overcome these limitations, second-generation synthetic HSP90 inhibitors were produced and entered clinical development. The most advanced products are ganetespib and NVP-AUY922. Both products are not orally available and administered intermittently. Other compounds include purines (BIIB-021), isoxazoles (VER-52296, NVP-AUY922), and indazole (SNX-5422) derivatives [15–17]. Even though most second-generation products exhibit improved pharmacological properties and safety when compared with 17-AAG inhibitors, development of some was halted due to ophthalmic and cardiac toxicities [18–20].

In this first-in-man study, overall 80 patients were treated with Debio0932 at doses ranging from 50 to 1600 mg, including 39 at the RD of 1000 mg daily. Safety at doses up to 1000 mg appeared acceptable with diarrhea, nausea, asthenia, and fatigue being the most common AEs. Those were mostly of grade 1 or 2.

**Table 2. Number of patients (%) with AEs at least twice considered related to Debio932**

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<th>200</th>
<th>400</th>
<th>800</th>
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<td>7</td>
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Bold values indicate maximum NCI-CTC AE v3.0 severity grade regardless of relatedness.

Bold-italic values represent the exact number of patients and % with AEs by disorders categories (e.g. cardiac disorders, gastrointestinal disorders…).

Italic values represents the exact number of patients (N).

<sup>a</sup>Maximum NCI-CTC AE v3.0 severity grade regardless of relatedness.

<sup>b</sup>Of any class and any term.
and reversible after the drug was discontinued. The three DLTs observed at 1600 mg (febrile neutropenia, diarrhea, and asthenia) were rather unspecific and dose escalation for the intermittent dosing regimen was not ceased for safety, but feasibility. The main reason for treatment discontinuation was disease progression. No relevant eye and cardiac toxicity was detected although retinal toxicity is supposed to be inherent to HSP90 inhibition [18, 19].

PK analysis demonstrated large interindividual variability, but generally rapid absorption and high first-pass metabolism of Debio0932 whereas there was no evidence of any food effect. The high Vz/F indicates accumulation in tissues, compatible

Figure 2. Best target lesion versus overall response in patients with at least one on-treatment assessment in the extension study.
with the previously observed accumulation of Debio0932 in preclinical xenograft tumor models [21, 22]. PK data support a once daily administration and good tolerability allows for a daily dosing schedule.

Induction of HSP70 protein has been widely used as PD marker for HSP90 inhibition in preclinical models. Translation of these observations to clinical settings had mostly to rely on the detection of HSP70 induction in surrogate tissue, notably PBMCs. Overall, maximum HSP70 levels might have increased in our study but without correlation to exposure to Debio0932. For many HSP90 inhibitors, variable levels of HSP70 induction in PBMCs with only limited dose dependency have been noted. It remains therefore unclear if the induction of HSP70 in PBMCs is a valid PD marker of HSP90 inhibition or even of clinical activity. Similarly, there was no such correlation with HER-2 expression, as suggested for some HSP90 inhibitors in breast cancer [23], but not in others [24].

Of the 45 patients for whom antitumor activity was able to be assessed only two showed PR, in line with results of clinical studies with other HSP90 inhibitors. Responses to HSP90 inhibitors generally appear to be rare in patients with advanced solid tumors. However, in the subgroup of 8 patients with NSCLC, 1 had PR, 4 SD, and 3 progressive disease. Given the acceptable safety and pharmacological profile demonstrated in this study, this is pointing at further development of Debio0932 in this indication, at a daily dose of 1000 mg and perhaps in combination with other anticancer agents.

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disclosure

DP, ER, and RB were employed by Debiopharm at the time of the trial; PF has acted as consultant/advisor for pharmaceutical companies including Debiopharm; J-CS has received honoraria by Debiopharm. All remaining authors have declared no conflicts of interest.

references