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Phase I study of the safety, tolerability and pharmacokinetics of PHA-848125AC, a dual tropomyosin receptor kinase A and cyclin-dependent kinase inhibitor, in patients with advanced solid malignancies

Glen J. Weiss,

Virginia G. Piper Cancer Center at Scottsdale Healthcare (VGPPC), 10510 N 92nd St, Ste 200, Scottsdale, AZ 85258, USA

Manuel Hidalgo,

Johns Hopkins, Baltimore, MD, USA

Mitesh J. Borad,

Virginia G. Piper Cancer Center at Scottsdale Healthcare (VGPPC), 10510 N 92nd St, Ste 200, Scottsdale, AZ 85258, USA

Daniel Laheru,

Johns Hopkins, Baltimore, MD, USA

Raoul Tibes,

Virginia G. Piper Cancer Center at Scottsdale Healthcare (VGPPC), 10510 N 92nd St, Ste 200, Scottsdale, AZ 85258, USA

Ramesh K. Ramanathan,

Virginia G. Piper Cancer Center at Scottsdale Healthcare (VGPPC), 10510 N 92nd St, Ste 200, Scottsdale, AZ 85258, USA

Lisa Blaydorn,

Virginia G. Piper Cancer Center at Scottsdale Healthcare (VGPPC), 10510 N 92nd St, Ste 200, Scottsdale, AZ 85258, USA

Gayle Jameson,

Virginia G. Piper Cancer Center at Scottsdale Healthcare (VGPPC), 10510 N 92nd St, Ste 200, Scottsdale, AZ 85258, USA

Antonio Jimeno,

Johns Hopkins, Baltimore, MD, USA

Jeffrey D. Isaacs,

Virginia G. Piper Cancer Center at Scottsdale Healthcare (VGPPC), 10510 N 92nd St, Ste 200, Scottsdale, AZ 85258, USA

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Correspondence to: Glen J. Weiss, gweiss@tgen.org.

Present Address: M. J. Borad, R. Tibes, Mayo Clinic Cancer Center-Arizona, Scottsdale, AZ, USA

Present Address: A. Jimeno, University of Colorado Cancer Center, Aurora, CO, USA

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Angela Scaburri,

Milano International Oncology (MIO), Nerviano Medical Sciences S.r.l., Nerviano, Milan, Italy

Maria Adele Pacciarini,

Milano International Oncology (MIO), Nerviano Medical Sciences S.r.l., Nerviano, Milan, Italy

Francesco Fiorentini,

Accelera S.r.l., Nerviano, Milan, Italy

Marina Ciomei, and

Oncology, Nerviano Medical Sciences S.r.l., Nerviano, Milan, Italy

Daniel D. Von Hoff

Virginia G. Piper Cancer Center at Scottsdale Healthcare (VGPC), 10510 N 92nd St, Ste 200, Scottsdale, AZ 85258, USA

Glen J. Weiss: gweiss@tgen.org

Summary

Purpose—This phase I trial assessed the safety, maximally tolerated dose (MTD) and pharmacokinetics of TRKA/CDK inhibitor PHA-848125AC in adult patients with advanced/metastatic solid tumors.

Patients and methods—Patients with relapsed or refractory solid tumors, for which no standard therapy existed, were eligible. PHA-848125AC was administered orally in two schedules: daily for 7 consecutive days in 2-week cycles (i.e. 7 days on/7 days off q2wks; S1) or daily for 4 consecutive days a week for 3 weeks in 4-week cycles (i.e. 4 days on/3 days off × 3wks q4wks; S2).

Result—Thirty-seven patients were treated in this study, 22 in S1 and 15 in S2. The recommended phase II dose (RP2D) was 150 mg/day for either schedule. The dose-limiting toxicities (DLTs) in S1 included ataxia (Grade 2–4) and tremors (Grade 2–3). In S2, DLTs included tremors (Grade 2–3), elevated lipase (Grade 3), increased creatinine (Grade 2), and nausea and vomiting (Grade 3). These events were all reversible. In S2, out of 14 patients evaluable for efficacy, 2 patients with thymic carcinoma, showed partial response and stable disease was observed in 3 patients. Stable disease was observed in 6 out 14 patients evaluable for efficacy on S1. Drug pharmacokinetics demonstrated a half-life of approximately 33 h, and dose-proportionality with accumulation by a factor of 3 after repeated administrations.

Conclusion—The RP2D of PHA-848125AC was 150 mg/day on both schedules. Based on the responses noted in thymic carcinoma, a phase II study for patients with that disease is currently enrolling.

Keywords

Tropomyosin receptor kinase A; Cyclin-dependent kinase; PHA-848125AC; Phase I clinical trial; Investigational agent

Introduction

Tropomyosin receptor kinases, comprising TRKA, TRKB and TRKC, are high-affinity receptors for neurotrophin family of protein ligands, which include nerve growth factor (NGF). Physiologically, the TRK/neurotrophin axis plays a role in neuronal maintenance and survival during development, whereas its role in the adult organism is still controversial [1]. TRKA expression has been demonstrated in a wide range of cancer types with autocrine or paracrine activation reported in neuroblastoma, mesothelioma, pancreas, prostate, ovarian

and breast carcinoma [2-8] and genetic re-arrangement in colon and papillary thyroid cancers [9]. Thus, inhibition of TRKA is an attractive modality for cancer therapeutics.

Cyclin-dependent kinases (CDKs) are serine/threonine kinases that, in concert with their positive and negative regulators, play a crucial role in cell cycle progression [10]. Deregulation of CDKs activity, alterations of expression and/or genetic mutations of CDK inhibitors (CDKis) and other components of the retinoblastoma protein (pRb) pathway, have been reported in more than 90% of human neoplasms [11]. The pRb pathway plays a critical role in regulating progression through the mammalian cell cycle. The high frequency with which alterations have been found in the core members of this pathway in human tumors has led to the suggestion that its disruption is an obligatory event for the development of all human cancers. The most studied and best understood targets for pRb are members of the E2F transcription factor family. The E2Fs are essential for the transcriptional regulation of a number of genes whose products control cell cycle progression. These include genes essential for the entry into the S phase of the cell cycle, such as CCNE1 (Cyclin E1) and CCNA2 (Cyclin A2), and genes that are involved in the regulation of DNA replication. Alterations in the Rb pathway lead to increased activity of CDK2/Cyclin complexes.

Altered regulation of CDK2 activators, such as Cyclin E and A (overexpressed in 50% of breast and lung cancer) and of their natural inhibitors such as p27KIP1 (decreased levels of p27 predict a poor prognosis in breast, prostate, colon, gastric, lung and esophageal cancer) strongly support a pharmacological inhibition of CDKs as an attractive strategy in the treatment of human cancers [12-16]. Experimental results on the role of CDKs in controlling cell cycle progression indicate that a broad spectrum of activity versus different CDKs could be advantageous to bypass potential compensatory and/or resistance-based mechanisms of cancer cells [17-20].

PHA-848125AC as a potent inhibitor of the kinase activity of TRKA ($IC_{50}=53$ nM) supports the rationale for testing the agent in selected cancer types where the neurotrophin/TRK receptor axis plays a relevant role in terms of cancer cell survival and dissemination, such as pancreatic and prostate cancers [2, 3]. In addition, PHA-848125AC has inhibitory activity on CDK2/Cyclin A complex ($IC_{50}=45$ nM), and inhibitory activity towards CDK1, CDK2, CDK4, CDK5, and CDK7 [21]. This profile versus different CDKs might have the potential for synergistic inhibition. This is the first investigational agent reported to dually target TRKA and CDKs. Here we present the final results of the first-in-human study of single agent PHA-848125AC in patients with advanced/metastatic solid tumors.

Patients and methods

Eligibility criteria

The study was approved by the institutional review board of the two participating institutions and was conducted in accordance with the 1996 Declaration of Helsinki. This was a Phase I, open-label, two-center, non-randomized, dose-escalation study in sequential cohorts of 3 to 6 adult patients with advanced/metastatic solid tumors. Patients of age ≥ 18 that provided signed informed consent, with relapsed or refractory solid tumors, for which no standard therapy existed, were eligible for the study. Other eligibility criteria included: Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–1, life expectancy ≥ 3 months, baseline laboratory data indicating acceptable bone marrow reserve, liver, and renal function, Grade ≤ 1 retinopathy, and the capability to swallow capsules intact. Except for prior exposure to experimental CDK2 inhibitors, prior systemic therapy was allowed if completed 4–6 weeks prior to study entry.

Main exclusion criteria included: history of cardiovascular diseases in the past 6 months, brain metastases, known active infections, pregnant or breast feeding women, uncontrolled diabetes mellitus or diabetic retinopathy, severe peripheral vascular disease, previous or current presence of neurological disorders, stroke and cerebellar injury, gastrointestinal diseases that would impact drug absorption.

Safety and efficacy assessments

Safety assessments were completed at baseline and during treatment at different time points, and at the end of treatment. They included the standard panel of laboratory tests, coagulation tests and electrocardiogram (ECG), ophthalmic examination, electroretinography (ERG), and evaluation of potential CNS toxicity. Monitoring of neurological effects and visual function (through ERG, fundoscopy and visual acuity examination) was introduced based on toxicity observed in animals. Neurotoxicity was evident in all species, whereas ocular toxicity was observed only in rats and only after prolonged schedules of administration.

Patients were followed for adverse events (AE) from the first dose until all drug-related toxicities had resolved or an alternative anticancer therapy was started. AEs were graded according to the National Cancer Institute Common Toxicity Criteria (NCI CTCAE), version 3.0. Disease status was assessed after every 8 weeks and at study discontinuation using the Response Evaluation Criteria in Solid Tumors (RECIST) [22]. Patients remained on study until disease progression, patient refusal, or unacceptable toxicity.

Study treatments and dose-escalation

Initially, patients received PHA-848125AC administered once daily for 7 consecutive days in 2-week cycles (Schedule 1, S1). The 7-day schedule was chosen as it allowed safe dose-escalation and attainment of potentially active exposures based on half-life in animals [23]. At a later time, based on the observation on the first 22 patients treated in S1, where tremors start appearing after 3–4 days of treatment, a pause in drug administration after 4 days was thought to prevent, or better control, tremors and ataxia, while avoiding underexposure to the PHA-848125AC. A protocol amendment was introduced, adding a second treatment schedule, Schedule 2 (S2): 15 patients were treated with PHA-848125AC once daily for 4 consecutive days a week for 3 weeks in 4-week cycles. A starting dose of 150 mg/day was selected for S2, since this dose was well tolerated in S1.

S1 was an accelerated dose escalation design, in which cohorts of 3 patients were treated at a dose twice the dose of the previous cohort until 2 patients experienced grade 2 toxicity attributable to the study drug or 1 patient experienced a dose-limiting toxicity (DLT) during any treatment cycle; then dose escalation proceeded by dose increments of 50%. In S2, the dose of each cohort was decided based on the tolerability of the previous cohort. The recommended phase II dose (RP2D) is defined as the dose with 0 or 1 DLT observed among 6 patients. Dose reduction and/or treatment delay were allowed to manage drug-related toxicity. DLT was defined as any of the following attributable to the study drug: Grade 4 neutropenia lasting 7 days, febrile neutropenia, Grade 3 neutropenic infection, Grade 3 thrombocytopenia lasting 5 days, any other Grade 4 hematologic toxicity lasting 7 days, Grade 3 non-hematologic toxicity 5 days (Grade 3 nausea, vomiting or diarrhea despite supportive therapy), Grade 2 seizures or other CNS toxicity at any time during the study, increase of 1 Grade retinopathy or any sign of worsening of ERG compared to baseline, failure to recover to Grade 1 toxicity (except alopecia) after delaying the initiation of next treatment by a maximum of 2 weeks; for S2, also the failure to complete the cycle with at least 80% of the planned dose because of a drug-related toxicity.

Pharmacokinetic assessments

Plasma samples for evaluation of the PHA-848125 pharmacokinetic (PK) and of its metabolite were collected for patients in S1: during Cycle 1 on Days 1, 2, 4, 7, 8, 9 and Cycle 2 on Days 1, 4, 7. For patients in S2: during Cycle 1 on Days 1, 4, 15, 18, and on Cycle 2 Day 1. Detailed pharmacokinetic sampling was done in Cycle 1 on Day 1 (from 30 min up to 24 h after dosing) and Day 7 (from 30 min up to 96 h after dosing) in S1 and on Day 1 (from 30 min up to 24 h after dosing) and Day 18 (from 30 min up to 96 h after dosing) in S2, to coincide with the first and the last day of treatment cycle in each schedule. Plasma and urine concentrations of PHA-848125 and of its metabolite were measured by validated LC-MS-MS methods. The calibration ranges of the assay for plasma samples were 0.00109–1.09 and 0.00105–1.05 μM for PHA-848125 and the metabolite, respectively. The calibration ranges of the assay for urine samples were 0.217–109 and 0.210–105 μM for PHA-848125 and metabolite, respectively. Urine was collected only in patients treated at the RP2D in S1. Analytical determinations and pharmacokinetic analysis were performed at Accelera S.r.l., Nerviano, Milan, Italy.

Results

Patient characteristics

Table 1 summarizes the patient characteristics. Overall, between April 2006 and December 2009 thirty-eight patients were enrolled: 22 in S1 and 16 in S2. All patients received study medication except for one patient in S2 never treated due to clinical deterioration. Most patients were male (68.2% and 73.3%), white (100% and 80%), ECOG performance status was predominantly 0 (72.7%) in S1 and 1 (60%) in S2 and the median age was 62.8 years and 56.8 for S1 and S2; respectively. All patients had metastatic cancer except for one patient who had refractory locally-advanced prostate cancer. Prostate cancer (27.3%), colorectal cancer (18.2%), and NSCLC (13.6%) were the most frequent cancer type in S1 and colorectal (40%), thymic (20%), and prostate (13.3%) cancers in S2. Most patients had received prior systemic therapies for the advanced disease (S1: median 3, range 0–6; S2: median 2, range 0–6), and the majority received prior surgery and radiotherapy. In S1, 22 patients received a total of 111 two-week cycles (median 3, range 1–27) and in S2, 15 patients received a total of 67 four-week cycles (median 2, range 1–24). Treatment was discontinued due to AEs in 13.6% and 13.3% of patients in S1 and S2; respectively.

Treatment exposure and dose-limiting toxicities

In S1, 22 patients were treated with PHA-848125AC at 5 dose levels (DLs): 50, 100, 150, 200, and 300 mg/day. In S2, three DLs (150, 180, or 200 mg/day) were evaluated in 15 patients. All 37 treated patients were evaluable for safety. In S1 the median treatment duration was 7.1 weeks (range 3.0–58.0) and in S2 8.0 weeks (range 2.1–104.0).

In S1, DLTs Grade 3 were noted at doses 200 mg/day. At 200 mg/day, DLTs occurred in 3 out of 6 patients and were Grade 3 ataxia and Grade 2–3 tremors, leading to dose reduction in one patient (with no recurrence of the events) and to treatment cessation in the other two patients (recovery of both events occurred in 4–14 days after treatment withdrawal). At 300 mg/day Grade 4 ataxia occurred in the only patient treated, resolving completely in the rest week. Dose-escalation proceeded to 300 mg/day since in the first 3 patients treated at 200 mg/day no DLTs had yet been observed. At 150 mg/day (RP2D) one DLT consisting in Grade 2 tremors and Grade 2 ataxia (at Cycle 7) leading to dose reduction to 100 mg/day was reported in one out of 6 patients; this patient continued treatment until Cycle 27 (with complete recovery of ataxia in 9 days and tremors resolving at end of treatment).

In S2, DLTs occurred at all the 3 DLs: at 180 mg/day in 3 out of 6 patients and were Grade 2 tremors in one patient (then continuing treatment at 150 mg/day until Cycle 7 without showing tremors), Grade 3 nausea and vomiting in another patient, and Grade 2 creatinine elevation in a third patient (who presented Grade 1 at baseline); at 200 mg/day, DLTs occurred in 2 out of 4 patients: Grade 2 tremors in one patient (then continuing at 150 mg/day with Grade 1 tremors) and Grade 3 tremors (lasting 3 days) in the second patient; at 150 mg/day (RP2D) one DLT occurred in one out of 5 patients and consisted in Grade 3 lipase elevation (asymptomatic).

Safety

The most frequently reported drug-related events were similar in both schedules and included nausea, diarrhea, vomiting, fatigue, and neurologic effects. The most frequent (20%) and all the Grade 3–4 drug-related adverse events by dose level and maximum CTC Grade reported during the study are listed in Table 2.

In S1 drug-related events of Grade 3 were reported by eight patients (36.4%) starting from 100 mg/day with a trend towards a dose-relationship and consisted mainly of neurological toxicities, ataxia ($N=3$) and tremors ($N=2$), and diarrhea ($N=2$). A drug-related Grade 4 ataxia was reported in the only patient treated at 300 mg/day. In S2, drug-related events of Grade 3 were reported by 9 patients (60%) and consisted mainly of gastrointestinal symptoms including vomiting ($N=3$) and diarrhea ($N=2$). Nausea and vomiting were manageable with conventional anti-emetic treatment. There were no Grade 4 events.

Neurological toxicities were observed across both schedules, being more severe and frequent in S1 during the dose escalation phase (ataxia was not observed in S2). All of these effects were rapidly reversible upon drug discontinuation and did not require any treatment other than hydration. It was observed that Grade 3 ataxia started from the dose of 200 mg/day in S1, where a mean Day 7 AUC_{0–24} was $29 \pm 5 \mu\text{M}\cdot\text{h}$ (Grade 4 ataxia occurred in the only patient treated at 300 mg/day, with a Day 7 AUC_{0–24} of $84 \mu\text{M}\cdot\text{h}$; this patient was treated before the occurrence of Grade 3 ataxia at 200 mg/day). At the RP2D of 150 mg/day in both schedules (mean Day 7 AUC_{0–24} $25 \pm 8.6 \mu\text{M}\cdot\text{h}$ in S1 and Day 18 AUC_{0–24} $23 \pm 9.5 \mu\text{M}\cdot\text{h}$ in S2, respectively), neurological effects were only mild/moderate in severity.

Drug-related SAEs were reported in five patients, all treated in S1: Grade 4 and Grade 3 ataxia occurred in one and three patients respectively, at doses higher than the RP2D, while Grade 3 dehydration occurred in a patient treated at the RP2D. No on study deaths were reported. Three patients (13.6%) in S1 and 3 patients (20%) in S2 discontinued study treatment due to AEs. All AEs leading to treatment discontinuation in S1 were assessed as related to study medication (Grade 3 increased ALT/Grade 3 neutropenia; Grade 3 tremor/Grade 3 ataxia; Grade 3 ataxia) while only one drug-related event caused treatment withdrawal in S2 (Grade 2 renal failure).

No significant blood chemistry and hematology abnormalities were reported in any schedule (except for lymphocytopenia, occurring in half of cases in both schedules).

Treatment with PHA-848125AC did not cause significant effects on coagulation, alterations of blood pressure, or ECGs. In S1, an ocular clinically relevant abnormality during treatment was reported in one hypertensive patient (4.5%), in presence of a normal ERG; the abnormality (acuity changes) was judged secondary to ERG procedure (corneal abrasion). No abnormal ERG findings emerged during treatment; drug-related eye disorders were reported in a single patient (4.5%, Grade 1 increased lacrimation). In S2 neither clinically relevant abnormality at fundoscopy nor ERG abnormalities emerged during treatment in any

patient. Drug-related Grade 1 blurred vision, dry eye, photopsia, vitreous floaters and vitreous hemorrhage were reported in 3 patients (20%).

Antitumor activity (RECIST)

No objective response was reported in patients treated in S1 while partial response was achieved in S2 in 2 patients (14.3%) with thymic carcinoma at 150 mg/day. These patients achieved a confirmed PR at Cycle 11 and Cycle 7, respectively. The former, had baseline neuropathic pain (7 out of 10) [24] in the left anterior chest likely from brachial plexus involvement, resolving with cessation of pain medication during Cycle 2. Disease stabilizations were observed in 6 out of 14 (42.9%) evaluable patients treated in S1 and in 3 out of 14 (21.4%) evaluable patients in S2. Long lasting stabilizations were achieved in 4 patients, 2 in each schedule: one lasting 55.6 weeks in a CRC patient at 150 mg/day in S1, one lasting 24.6 weeks in a NSCLC patient at 200 mg/day in S1, one lasting 39.3 weeks in a pancreatic adenocarcinoma patient and one lasting 29.1 weeks in a patient with carcinoid, both at 180 mg/day in S2. Duration of treatment and responses are summarized in Fig. 1. Radiological images (baseline and Cycle 11) for the first thymic carcinoma responding patient treated at the RP2D of 150 mg/day are reported in Fig. 2.

Pharmacokinetics

PHA-848125 pharmacokinetic parameters are summarized in Table 3. Overall, no differences in the pharmacokinetics were observed between the two treatment schedules at similar doses, with no relevant deviations from dose-proportionality up to 200 mg/day and limited inter-patient variability (approximately 40%). PHA-848125 was absorbed with median $t_{\max}$ of 2–4 h post dosing. In both schedules, after repeated administrations, PHA-848125 levels accumulated by a factor of 3, as expected based on the half-life of the compound (approximately 33 h). At the RP2D (150 mg/day), in S1 mean ($\pm$ SD) Day 7 $C_{\max}$ and AUC_{0-24} were respectively $1.5 \pm 0.5 \mu\text{M}$ and $25 \pm 8.6 \mu\text{M}\cdot\text{h}$ and in S2 mean ($\pm$ SD) Day 18 $C_{\max}$ and AUC_{0-24} were respectively $1.2 \pm 0.3 \mu\text{M}$ and $23 \pm 9.5 \mu\text{M}\cdot\text{h}$. Across doses, $C_{\max}$ and AUC_{0-24} values of the metabolite were approximately 30% those of the parent compound. The amounts of PHA-848125 and metabolite excreted in urine accounted for 29 and 13% of dose, respectively.

Pharmacodynamic studies

The effects of PHA-848125 on cell-cycle related markers by immunohistochemistry (IHC) and on a compound specific gene signature by qRT-PCR was extensively studied on skin biopsies of patients enrolled in a parallel Phase I study using a daily $\times$ 14 every 3 week schedule. The results of this study [25] indicate that cell-cycle related markers (Cyclin A, Cyclin B, phospho Rb and Ki67 investigated by IHC and/or qRT-PCR) were affected in a dose-dependent manner, with a strong modulation in all patients at the recommended Phase II dose of 54 mg/m²/day.

In the present study, only patients receiving a dose level above the one with toxicity > CTC Grade 2 were invited to participate in the optional biomarker study. Skin biopsies were not mandatory and patients not consenting to have their tissue specimens analyzed were not denied study participation. Fourteen patients consented to skin sampling; however paired pre- and post- treatment skin biopsies suitable for analyses were too scant to allow sound considerations from the results obtained. The available results were in line with those previously reported, indicating a down modulation of CDK related biomarkers Cyclin A2, Cyclin B1 and Ki67. Expression modulation of the corresponding genes by qRT-PCR on skin biopsies of one patient treated at the RP2D of 150 mg/day (Schedule 2) is reported in Fig. 3.

Discussion

PHA-848125AC is an oral, potent dual TRKA inhibitor and multi-CDK inhibitor [21, 25]. The safety and efficacy profile of PHA-848125AC differentiates it from other TRKA inhibitors and CDKi tested in the clinic. CEP-701 was the first oral TRK inhibitor evaluated in human clinical trials [26]. Seven of 30 patients had stable disease for more than three months, and three had stable disease for at least six months, including one patient each with SCLC, prostate cancer, and liposarcoma. The most frequently reported side effects were predominantly GI-related (nausea, diarrhea, anorexia, constipation, and vomiting), and asthenia [26].

Avlocidib (flavopiridol) was the first CDKi evaluated in humans and demonstrated inhibition of CDK1, CDK2, CDK4, and CDK7 [27, 28]. Administered intravenously, flavopiridol showed activity in some patients with non-Hodgkin's lymphoma, renal, prostate, colon, and gastric carcinomas [27]. The main side effects of this agent include: secretory diarrhea, a proinflammatory syndrome associated with hypotension, and hyperglycemia [27, 28]. To date, this agent has advanced to several phase II studies with promising activity in chronic lymphocytic leukemia [29]. Other CDK inhibitors such as seliciclib, dinaciclib and AZD438 [30-32] show myelotoxicity, GI toxicity, fatigue, skin rash and electrolytes imbalance, with no neurological toxicity. Mechanisms for the ataxia/tremor observed with PHA-848125 in humans are not well defined. These neurological effects were reported also in animals (mainly tremors and increased reactivity to external stimuli) after administration of high single or repeated doses of the compound. In addition, PHA-848125 was shown to cross the blood brain barrier and to attain a brain/plasma ratio >1 in both rodent and non-rodent species. Neurological effects were always reversible and no morphological changes were seen. The inhibition of the neurotrophin/TRKA axis in brain may play a role in the induction of the neurological effects. Indeed there are indications that adding NGF to the brain, a significant reduction of basic symptoms of parkinsonism was observed [33].

In our phase I study, the safety profile of PHA-848125AC was consistent with that expected based on preclinical experience. DLTs were primarily neurological in both schedules, consisting mainly in rapidly reversible tremors and ataxia that were dose-dependent in frequency and severity, and dose-limiting at doses >150 mg/day. The RP2D was identified as 150 mg/day for both schedules. Overall, non-hematologic and hematologic toxicities of Grade >2 in severity were uncommon and PHA-848125AC was generally well-tolerated. No significant alterations in visual function were reported.

Disease stabilizations were observed in 42.9% of evaluable patients in S1 and in 21.4% in S2. While no objective response was reported in patients in S1, there were two patients with confirmed partial response in S2, both with thymic carcinoma. The loss of control of cell cycle checkpoints seems a common occurrence in thymic epithelial tumors (TETs); negative expressions of p21 and p27 significantly correlates with poor prognosis for disease-free survival [34]. The effects of a pan-CDK inhibitor such as flavopiridol on thymus was also shown in preclinical models as thymic atrophy [35]. Moreover, members of TRK family seem to play a significant role in this disease [36].

PHA-848125AC may have some analgesic effect for neuropathic pain as observed in one thymic carcinoma patient on study. The concomitant overexpression of NGF and TRKA mRNA is in close relationship to pain generation, suggesting that targeting of NGF/TRKA might influence pain generation and control [37].

PHA-848125AC has a favorable PK profile, with good oral absorption and dose-proportionality in systemic exposure up to 200 mg/day, limited inter-patients variability,

terminal half-life of approximately 33 h and an accumulation factor of 3 after repeated administrations.

In conclusion, the RP2D of PHA-848125AC was 150 mg/day on both schedules, with manageable and reversible side effects. Based on responses in patients with thymic carcinoma, an international phase II study in this disease is currently enrolling, with administrations of 150 mg/day 7 days on/7 days off. This schedule was chosen in consideration of the higher dose intensity offered to patients and in view of the substantially similar safety profile compared to the 4 days on/3 days off schedule.

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Fig. 1.

Depiction of duration of treatment in months for each patient with type of cancer listed to the right of bar. KEY: PR-partial response, SD-stable disease, PD-progressive disease, NE-not evaluable for response. Black dot in green bar depicts time point when partial response was achieved

Fig. 2.
Partial Response in a patient with thymic carcinoma after 11 cycles of treatment: left pleural mass along diaphragm (*top*) and left pleural node (*bottom*)

Fig. 3.

Skin biopsies were obtained with 3 mm punch procedure at baseline (before treatment) and after the last compound administration in the first cycle. Data are presented as the relative gene expression values normalized to an average of internal reference controls ("housekeeping" genes) and relative to a calibrator sample

Table 1

Patient characteristics (treated patients)

Demographic variable	Schedule 1 (7 days on/7 days off q2wks) N=22		Schedule 2 (4 days on/3 days off × 3 wks q4wks) N=15	
	N	%	N	%
Age (yrs)				
Mean (range)	62.8 (31.0–83.0)		56.8 (24.0–84.0)	
18–65 yrs	14	63.6	11	73.3
65 yrs	8	36.4	4	26.7
Gender				
Female	7	31.8	4	26.7
Male	15	68.2	11	73.3
Race				
White	22	100	12	80
Not listed	–	–	3	20
Weight (Kg)				
Mean (range)	84.4 (55.3–123.9)		82.1 (44.5–114.3)	
Height (cm)				
Mean (range)	173.0 (154.5–190.0)		172.2 (149.5–183.5)	
BSA (m ²)				
Mean (range)	2.0 (1.6–2.5)		1.9 (1.4–2.4)	
Performance status (ECOG)				
0	16	72.7	6	40
1	6	27.3	9	60
Primary Reason for Discontinuation				
Adverse event	3	13.6	2 ^a	13.3 ^a
Consent withdrawn	1	4.5	–	–
Lack of efficacy	18	81.8	13	86.7
Cancer Type				
Colorectal	4	18.2	6	40.0
Liposarcoma	2	9.1	–	–
Non-small cell lung cancer	3	13.6	–	–

Demographic variable	Schedule 1 (7 days on/7 days off q2wks) <i>N</i> =22		Schedule 2 (4 days on/3 days off × 3 wks q4wks) <i>N</i> =15	
	<i>N</i>	%	<i>N</i>	%
Other	7 ^b	31.8	4 ^c	26.7
Prostate	6	27.3	2	13.3
Thymic carcinoma	–	–	3	20.0
Sites of Metastases				
Bone	14	63.6	5	33.3
Liver	7	31.8	8	53.3
Lung	8	36.4	12	80.0
Lymph nodes	14	63.6	10	66.7
Other	8	36.4	8	53.3
No. of Recurrences/Progressions				
1	1	4.5	2	13.3
2	10	45.5	4	26.7
>2	11	50.0	9	60.0
No. of Prior Systemic Therapies ^d				
Median (range)	3 (0–6)	2 (0–6)		

^aOne patient treated at 150 mg/day, had treatment permanently withdrawn due to adverse event: brain metastases, unrelated to study drug

^bAnal (*n*=1); Angiosarcoma (*n*=1); Bladder (*n*=1); Breast (*n*=1); Mesothelioma (*n*=1); Renal cell (*n*=1); Small cell lung cancer (*n*=1)

^cCarcinoid (*n*=1); Leiomyosarcoma (*n*=1); Pancreas (*n*=1); Unknown primary (*n*=1)

^dFor the advanced disease

Table 2

Most frequent (> 20%) and all grade 3–4 drug-related adverse events by dose level and maximum CTC Grade (all cycles)

Adverse event	Schedule 1 (7 days on/7 days off q2wks) (mg/day)						Schedule 2 (4 days on/3 days off × 3 wks q4wks) (mg/day)					
	CTC Grade		50 N=3		100 N=6		150 N=6		200 N=6		300 N=1	
	N	%	N	%	N	%	N	%	N	%	N	%
Any	1–4	3	6	100.0	1	22	100.0	5	6	4	15	100.0
	3–4	–	1	2	5	9	40.9	4	3	2	9	60.0
Nausea	1–4	1	3	4	4	13	59.1	3	3	1	7	46.7
	3–4	–	–	–	–	–	–	–	1	–	1	6.7
Diarrhea	1–4	–	1	4	5	11	50.0	3	3	3	9	60.0
	3–4	–	–	1	1	2	9.1	–	1	1	2	13.3
Tremor	1–4	–	2	4	4	11	50.0	3	3	2	8	53.3
	3–4	–	–	–	2	2	9.1	–	–	1	1	6.7
Vomiting	1–4	–	3	2	4	10	45.5	2	3	1	6	40.0
	3–4	–	–	–	–	–	–	1	2	–	3	20.0
Fatigue	1–4	–	2	5	2	10	45.5	–	2	3	5	33.3
	3–4	–	1	–	–	1	4.5	–	–	–	–	–
Ataxia	1–4	–	–	1	3	1	5	22.7	–	–	–	–
	3–4	–	–	–	3	1	4	18.2	–	–	–	–
Dehydration	1–4	–	–	2	–	1	3	13.6	–	3	1	4
	3–4	–	–	1	–	–	1	4.5	–	–	–	–
Anemia	1–4	–	–	1	–	–	1	4.5	2	–	4	26.7
	3–4	–	–	–	–	–	–	–	–	–	–	–
Dizziness	1–4	–	–	1	1	3	13.6	–	2	2	4	26.7
	3–4	–	–	–	–	–	–	–	–	–	–	–
Syncope	1–4	–	–	–	1	–	1	4.5	–	–	–	–
	3–4	–	–	–	1	–	1	4.5	–	–	–	–
Neutropenia	1–4	–	–	–	1	–	1	4.5	1	1	3	20.0
	3–4	–	–	–	1	–	1	4.5	–	–	–	–
Decreased Hb	1–4	–	1	–	–	–	1	4.5	–	–	–	–
	3–4	–	1	–	–	–	1	4.5	–	–	–	–

Adverse event	Schedule 1 (7 days on/7 days off q2wks) (mg/day)										Schedule 2 (4 days on/3 days off x 3 wks q4wks) (mg/day)					
	CTC Grade					Any Dose					150			200		
	N	50	100	150	200	N	300	N	200	150	N	N	N	N	N	Any Dose N=15
Increased ALT	1-4	-	-	-	-	1	-	1	1	4.5	1	-	-	-	1	6.7
	3-4	-	-	-	-	1	-	1	1	4.5	1	-	-	-	1	6.7
Increased Lipase	1-4	-	-	-	-	-	-	-	-	-	1	-	-	-	1	6.7
	3-4	-	-	-	-	-	-	-	-	-	1	-	-	-	1	6.7
Hypokalemia	1-4	-	-	-	-	-	-	-	-	-	1	-	-	-	1	6.7
	3-4	-	-	-	-	-	-	-	-	-	1	-	-	-	1	6.7

Abbreviations: ALT=alanine aminotransferase

The table lists the most frequent adverse events (AE), i.e. the events occurring in at least 20% of patients at any dose level and all reported drug-related CTC Grade 3 or 4 events

Table 3

Plasma Pharmacokinetic Parameters (Mean±SD) of PHA-848125 on Day 1 and Day 7 (S1) and on Day 1 and Day 18 (S2)

S1: 7 Days on/7 Days off in a 14-day cycle									
Dose (mg/day)	C _{max} (μM)	Day 1	Day 7	AUC ₀₋₂₄ (μM·h)	Day 7	AUC ₀₋₂₄ (μM·h)	t _{1/2,z} (h)	CL/F (L/h)	V _z /F (L)
50	0.2±0.1	0.4±0.2	2.5±0.6	6.8±2.2	11.7±5.4	25.3±4.18*	19.7±4.35*	707±39.8*	
100	0.4±0.1	1.2±0.5	6.0±2.2	20±11	43.4±26.8	42.9±15.9	13.7±6.49	840±550	
150	0.7±0.2	1.5±0.5	8.8±2.6	25±8.6	46.5±19.4	33.1±9.53	14.3±5.07	686±318	
200	0.7±0.3	1.7±0.2	9.6±3.6	29±4.5	63.5±9.04	32.4±4.79	15.2±2.44	721±207	
300	1.2	5.1	23	84	168	31	7.78	348	
S2: 4 days on/3 days off x 3 wks q4wks									
Dose (mg/day)	C _{max} (μM)	Day 1	Day 18	AUC ₀₋₂₄ (μM·h)	Day 1	Day 18	AUC ₀₋₂₄ (μM·h)	t _{1/2,z} (h)	V _z /F (L)
150	0.4±0.1	1.2±0.3	7.2±2.8	23±9.5	54.6±25.1	43.1±10.7	16.4±6.16	1010±456	
180	0.5±0.2	1.1±0.5	7.0±2.1	17±8.8	35.1±26.3	23.5±8.42	27.7±12.3	882±353	
200	1.0±0.4	2.5±0.5	12±6.3	35±4.6	63.6±17.5	25.8±1.46	12.7±1.60	473±68.4	

AUC: Area under the plasma concentration vs. time curve from time 0 up to the last detectable concentration; CL/F: Oral Clearance; t_{1/2,z}: Apparent terminal half-life; V_z/F: Volume of distribution of the terminal phase

50 mg/day: n=3, 100 mg/day: n=6, 150 mg/day: n=6, 200 mg/day: n=6, 300 mg/day: n=1;

* n=2

150 mg/day: n=4; 180 mg/day: n=4; 200 mg/day: n=3