EUROPEAN JOURNAL OF CANCER 48 (2012) 179–186

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A phase I, dose-escalation study of the novel Polo-like kinase inhibitor volasertib (BI 6727) in patients with advanced solid tumours ☆

Patrick Schöffski [a,*], *Ahmad Awada* [b], *Herlinde Dumez* [a], *Thierry Gil* [b], *Sylvie Bartholomeus* [b], *Pascal Wolter* [a], *Martine Taton* [c], *Holger Fritsch* [d], *Patricia Glomb* [d], *Gerd Munzert* [d]

[a] *Department of General Medical Oncology and Laboratory of Experimental Oncology, University Hospitals, Leuven Cancer Institute, Leuven, Belgium*

[b] *Medical Oncology Clinic, Institut Jules Bordet, Université Libre de Bruxelles, Brussels, Belgium*

[c] *Boehringer Ingelheim Belgium, Brussels, Belgium*

[d] *Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany*

ARTICLE INFO

Article history:
Available online 24 November 2011

Keywords:
Polo-like kinase (Plk) inhibitor
Phase I
Solid tumours
Volasertib (BI 6727)
Dose escalation

ABSTRACT

Background: Volasertib (BI 6727) is a potent and selective cell-cycle kinase inhibitor that induces mitotic arrest and apoptosis by targeting Polo-like kinase (Plk). This phase I dose-escalation study evaluated the maximum tolerated dose (MTD) of volasertib, safety and efficacy, and pharmacokinetic (PK) parameters.

Methods: This trial followed an open-label, toxicity-guided dose-titration design. Patients with progressive advanced or metastatic solid tumours received a single 1-h infusion of volasertib every 3 weeks. A total of 65 patients were treated at doses of 12–450 mg.

Results: Reversible haematological toxicity was the main side-effect; thrombocytopenia, neutropenia, and febrile neutropenia constituting the main dose-limiting events. Anaemia (all grades 22%; grade 3: 8%), neutropenia (15%; grade 3/4: 14%), fatigue (15%; grade 3: 2%), and thrombocytopenia (14%; grade 3/4: 14%) were the most frequent drug-related adverse events. The MTD was 400 mg; however, 300 mg was the recommended dose for further development based on overall tolerability. Three patients achieved confirmed partial response. Stable disease as best response was reported in 40% of patients. Two patients remained progression free for >1 year. PK analysis showed no indication of deviation from 'dose-linear PK' behaviour, a large volume of distribution (>4000 l), moderate clearance and a long half-life (~111 h).

Conclusion: This first-in-man trial demonstrated a favourable PK profile of volasertib, with manageable toxicities. As expected, the most common events were haematological. Encouraging preliminary antitumour activity has been observed, supporting Plk inhibition as a therapeutic approach. Clinical development of volasertib in phase II monotherapy and combination trials is ongoing.

☆ *Previous publication:* Oral presentation at the 20th European Organisation for Research and Treatment of Cancer, National Cancer Institute and American Association for Cancer Research (EORTC–NCI–AACR) Symposium on 'Molecular Targets and Cancer Therapeutics', Geneva, Switzerland, 2008, and at the American Society of Clinical Oncology (ASCO) Annual Meeting, Chicago, IL, 2010.

* *Corresponding author:* Address: Department of General Medical Oncology and Laboratory of Experimental Oncology, Leuven Cancer Institute, University Hospital Gasthuisberg, Catholic University Leuven, Herestraat 49, 3000 Leuven, Belgium. Tel.: +32 16 34 69 00; fax: +32 16 34 69 01.

E-mail address: patrick.schoffski@med.kuleuven.be (P. Schöffski).

0959-8049/$ - see front matter
doi:10.1016/j.ejca.2011.11.001

1. Introduction

The dihydropteridinone volasertib (BI 6727) is a potent and selective cell-cycle kinase inhibitor that induces mitotic arrest and apoptosis by targeting the Polo-like kinase (Plk) family of proteins. Volasertib inhibits Plk1 in an ATP-competitive manner, with a half maximal inhibitory concentration (IC_{50}) of 0.87 nM,[1] and has been shown to disrupt spindle assembly causing a distinct mitotic arrest phenotype ('Polo-arrest') and subsequent apoptosis in cancer cell lines.[1] Plk1 has been established as a valid target for anti-cancer treatment in preclinical studies; Plk1 is overexpressed in a number of human tumours[2,3] and high levels of Plk1 overexpression are associated with poor prognosis in various cancers.[2] As such, volasertib is one of several agents targeting the Plk pathway to enter clinical development.[4–7]

Preclinical studies have shown that volasertib has marked antitumour activity in multiple cancer models and has a pharmacokinetic (PK) profile indicative of high and sustained exposure in tumour tissue.[1] Here, we report the findings of the first-in-man phase I dose-escalation study of volasertib. The primary objective was to determine the maximum tolerated dose (MTD) of volasertib, when administered as a 1-h infusion in patients with advanced solid tumours.

2. Patients and methods

2.1. Study design

This was a phase I, open-label, dose-escalation study conducted at two centres in Belgium between January 2006 and August 2009. The trial was carried out in accordance with the Declaration of Helsinki (1996 Version), the ICH Harmonised Tripartite Guideline for Good Clinical Practice, and local regulatory requirements. All patients provided written informed consent.

Dose escalation was based on an accelerated titration design; volasertib was started at 12 mg (1-h infusion) in the first patient cohort. A dose of 12 mg was derived as a safe clinical starting dose according to Food and Drug Administration guidance after determination of the highest non-severely toxic dose in animals.[8] Dose levels were then doubled until the first reports of Common Terminology Criteria for Adverse Events (CTCAE v 3.0) grade 2 toxicity. Subsequent dose levels were escalated by $\leqslant$50% of the preceding dose level. If a first dose-limiting toxicity (DLT) was observed in 1 of a maximum of six patients in a treatment cohort, dose escalation proceeded with a maximum 35% increase. DLT was defined as any drug-related CTCAE grade 3 or 4 non-haematological toxicity (except emesis or diarrhoea responding to supportive treatment), drug-related CTCAE grade 4 neutropenia persisting for $\geqslant$7 d, and/or complicated by infection, febrile neutropenia, or CTCAE grade 4 thrombocytopenia. Since QT prolongation was detected at high doses in preclinical models in two animal species, [Boehringer Ingelheim, data on file] mandatory QT analysis was implemented in the trial.

Each cohort consisted of at least three eligible and evaluable patients per dose level. If one patient experienced a DLT, up to three additional patients were enrolled at that dose level. If no patients experienced a DLT during course 1, dose was escalated. If two or more out of a maximum of six patients experienced a DLT, further enrolment into this cohort ceased. In order to define the MTD, three additional patients were treated at one dose tier below the DLT level, unless six patients had already been treated at that dose tier. The MTD was defined as the highest dose at which not more than one out of six patients experienced a DLT in the first treatment course.

Determination of the recommended phase II dose was based on safety data from all treatment courses. An additional 14 patients, the extension cohort, were then treated at that dose to better characterise safety and investigate potential QT interval changes. Patients in the extension cohort received volasertib 300 mg as a 1-h infusion in course 1 and a 2-h infusion in course 2 (300 mg; 1h2 h) or volasertib 300 mg as a 2-h infusion in course 1 and a 1-h infusion in course 2 (300 mg; 2h1 h), to assess schedule-dependent electrocardiogram (ECG) changes.

Each treatment course comprised 21 d; patients with clinical benefit were eligible to receive additional courses. Patients experiencing DLTs could be retreated at a lower dose if they experienced benefit from therapy and had recovered from adverse events (AEs).

2.2. Study population

This study included adult patients (aged $\geqslant$18 years) with a confirmed diagnosis of advanced, non-resectable and/or metastatic solid tumours who had failed established treatments and had an Eastern Cooperative Oncology Group (ECOG) performance score of 0–2. Patients included in the extension cohort were required to have measurable tumours (using the Response Evaluation Criteria in Solid Tumours [RECIST version 1.0][9]).

Patients with known brain metastases, active infectious disease or a serious illness thought to interfere with the protocol were excluded, as were patients with a known secondary malignancy requiring therapy, abnormal haematological values or impaired renal or liver function at baseline.

2.3. Concomitant medications

Concomitant medications were given as clinically necessary. Symptomatic treatment of AEs or tumour-associated symptoms was permitted, although additional chemo-, immuno-, hormone- or radiotherapy was not permitted (with the exception of steroids and bisphosphonates). Concomitant palliative radiotherapy was permitted after discussion and agreement with the study sponsor and as clinically indicated. Haematopoietic growth factors were not routinely given.

2.4. Safety and tolerability assessments

Safety was evaluated by reporting of AEs according to CTCAE version 3.0, laboratory evaluations, ECOG performance status, physical examination and assessment of vital signs. All patients were subject to centralised ECG analysis before administration and directly after completion of infusion on the day

of treatment in every treatment course. AEs with an onset between the first administration of volasertib and 21 d after the last infusion of volasertib were considered as treatment-emergent.

2.5. *Efficacy assessments*

Objective response was assessed by tumour measurements and evaluated according to RECIST version 1.0.[9] Patients were assessed at screening and at the end of every other treatment course.

2.6. *PK sampling and data analysis*

Blood samples for the evaluation of PK parameters were collected before drug administration, at 15, 30 and 45 min and 1, 1.5, 2, 4, 8, 24, 48, 96, 168 and 336 h after start of the infusion. Volasertib plasma concentrations were determined by validated high-performance liquid chromatography coupled to tandem mass spectrometry (HPLC–MS/MS) at Boehringer Ingelheim Pharma GmbH & Co. KG, Germany. Non-compartmental PK parameters were determined using WinNonlin™ Version 5.2 or another validated programme.

2.7. *Statistical analyses*

All patients who received at least one dose of volasertib (treated set) were included in the efficacy, safety and PK analyses. The dataset was analysed in an exploratory and descriptive manner; no statistical testing was undertaken.

3. Results

3.1. *Patient population*

A total of 67 patients were enrolled in this study, of whom 65 received treatment with volasertib; one patient withdrew consent and one had not recovered from previous therapy-related toxicity at study entry. Fourteen patients were included as part of the extension cohort (300 mg, 1h2h, $n = 8$; 300 mg, 2h1h, $n = 6$). Patient demographics and clinical characteristics are summarised in Table 1. The majority of patients discontinued treatment due to disease progression ($n = 61$; 94%). Three patients (5%) discontinued due to AEs (300 mg, $n = 1$; 300 mg; 1h2h, $n = 2$), and one patient is still receiving volasertib with clinical benefit after 55 3-week courses.

3.2. *Safety and tolerability*

Overall, 35% of patients received and completed two courses of treatment, six patients (9%) received $\geqslant 10$ courses (125 mg [$n = 1$], 450 mg [$n = 1$], and 300 mg [$n = 4$]), and one patient has received 55 courses (450 mg dose group; reduced to 300 mg from course 2 due to AEs); treatment is ongoing. The median period of volasertib exposure was 65 d (range 16–1452).

Table 2 lists the DLTs reported during all treatment courses; the majority of DLTs were haematological. During dose escalation, the MTD was determined to be volasertib 400 mg per administration; after MTD definition per protocol and consecutive expansion of the 400 mg cohort, three out of 10 patients experienced DLTs during the first course. After de-escalation to 350 mg, another three out of five patients had DLTs in the first course. Expansion of the 300 mg cohort resulted in a recommended phase II dose of 300 mg (Table 2).

One further patient in the extension cohort experienced a DLT in the first course and six patients reported DLTs during subsequent treatment courses (see Table 2).

During the study, 64 (98%) patients experienced at least one AE and 32 (49%) experienced a drug-related AE. The most frequently reported drug-related AEs were anaemia (22%), fatigue (15%) and neutropenia (15%) (Table 3). All cases of neutropenia, febrile neutropenia, and thrombocytopenia were considered drug-related. Table 4 lists grade 3 and 4 drug-related AEs. No fatal drug-related AEs or grade 4 non-haematological events were reported. The majority of grade 3 and 4 AEs were related to haematological toxicity.

AEs leading to treatment discontinuation were reported in 10 (15%) patients. The most common AE leading to withdrawal was general physical health deterioration ($n = 4$); all four events were considered unrelated to study medication. Two patients discontinued due to treatment-related AEs. One patient treated with volasertib 400 mg experienced neutropenia and one patient treated with volasertib 300 mg, 1h2h, experienced fatigue and weight loss. The four remaining AEs leading to withdrawal were unrelated to treatment.

Thirty-three patients (51%) had at least one serious AE (SAE). Eleven patients experienced SAEs that led to death; all were unrelated to volasertib treatment. Nine patients experienced a total of 17 SAEs that were considered to be drug-related (leukopaenia [$n = 1$], neutropenia [$n = 3$], thrombocytopenia [$n = 5$], anaemia [$n = 3$], febrile neutropenia [$n = 4$] and blurred vision [$n = 1$]).

No dose-related laboratory changes were observed other than haematological toxicities, and no consistent changes in vital signs were seen.

Two out of 14 extension cohort patients withdrew during the QT_c evaluation phase due to disease progression and one patient was excluded due to the presence of a cardiac pacemaker. No clinically relevant ECG abnormalities were observed in these patients. Adjusted mean QT_{cF} interval changes from baseline 5 min before the end of the infusion and 24 h after infusion, respectively, ranged from 15.09 to 1.64 ms in the 1-h infusion and from 13.24 to –4.32 ms in the 2-h infusion. Larger QT_{cF} prolongations were observed during the 1-h infusion than during the 2-h infusion (comparison versus 1-h infusion –4.56 ms at the time of maximum QT_{cF} prolongation, 5 min before infusion ends). No new onset of QT_{cF} intervals >470 ms or absolute QT intervals >500 ms were observed. In analysis using individual baseline, no patients had a QT_{cF} interval prolongation >60 ms, although one patient had an uncorrected QT change from baseline >60 ms (65 ms at 4 h after start of the 2-h infusion course) with an uncorrected QT interval of 396 ms.

In the analysis of QT_{cF} change from baseline in all patients, all dose groups receiving $\geqslant 300$ mg of volasertib displayed mean increases of at least 16.2 ms with respect to baseline. One patient (300 mg group) experienced grade 3 QT prolongation (QT_{cF} interval 453 ms). QT changes observed were not associated with specific cardiac AEs or clinical symptoms.

Table 1 – Patient demographics and characteristics – treated set.

Number of patients	65
Gender, *n* (%)	
Male	38 (58)
Female	27 (42)
Age (years)	
Median	58
Range	19–79
ECOG performance score, *n* (%)	
0	17 (26)
1	41 (63)
2	7 (11)
Type of cancer, *n* (%)	
Melanoma	12 (18)
Non-small cell lung cancer	10 (15)
Colorectal carcinoma	8 (12)
Soft-tissue sarcoma	7 (11)
Urothelial carcinoma	6 (9)
Prostate cancer	4 (6)
Other	18 (28)
Prior anti-cancer therapy, *n* (%)	
Surgery	48 (74)
Radiotherapy	31 (48)
Immunotherapy	7 (11)
Hormone therapy	4 (6)
Chemotherapy	65 (100)
⩾3 chemotherapies	58 (89)

ECOG = Eastern Cooperative Oncology Group.

3.3. *Efficacy*

All 65 patients were assessed for response. Three patients showed an objective response to treatment; all three patients had a confirmed partial response (PR).

One patient with melanoma (300 mg group) had PR from course 2 until the end of course 9 (207 d progression-free survival [PFS; censored]) when this patient discontinued due to progressive decrease in bodyweight, whilst still being in PR. This patient previously received cisplatin and dacarbazine chemotherapy, followed by radiotherapy after progression and subsequent ipilimumab when progression occurred again.

A 58-year-old female patient with ovarian cancer (400 mg dose group; decreased to 300 mg from course 2 due to AEs) had a PR up to the end of course 4 (148 d PFS). During volasertib treatment a decrease in CA 125 was observed from course 2 until course 5 when further progression was noted. This patient had initially been treated with surgery, cisplatin/topotecan (four cycles) and paclitaxel/carboplatin (four cycles), resulting in no evidence of disease (NED). Treatments received before volasertib included six cycles of paclitaxel/carboplatin (best response = complete response), four cycles of intraperitoneal cisplatin, six cycles of liposomal doxorubicin, letrozole and topotecan.

A 61-year-old male patient with urothelial cancer (450 mg dose group; dose reduced to 300 mg from course 2 due to AEs) had a confirmed PR at all assessments until treatment course 16; after resection of a residual target tumour lesion, treatment was restarted and an additional 39 courses have been given with further tumour shrinkage being observed (403 d PFS, censored at date of last assessment in course 16). The average course duration in this patient was 25 d. Previous treatments (best response) included surgery of curative intent with adjuvant gemcitabine/cisplatin (NED), paclitaxel (PR) and capecitabine plus investigational agents (PR).

One additional patient with non-small cell lung cancer (300 mg dose group) had stable disease (SD) as best overall response and 550 d PFS. This patient did not respond to earlier platinum-based, first-line chemotherapy or docetaxel as

Table 2 – Patients with dose-limiting toxicities.

Dose level (mg)	Treatment course	Dose-limiting toxicity[a]
Dose escalation		
300	1	Neutropenia (grade 4), QT prolongation (grade 3)
450	1	Neutropenia (grade 4), thrombocytopenia (grade 4)
450	1	Neutropenia (grade 4), thrombocytopenia (grade 4)
Dose expansion		
300	12	Thrombocytopenia (grade 4)
300	3	Febrile neutropenia (grade 3)
350	1	Febrile neutropenia (grade 4)
350	1	Bleeding in the corpus vitreum (grade 3), thrombocytopenia (grade 3)
350	1	Febrile neutropenia (grade 3)
400	1	Febrile neutropenia (grade 4), thrombocytopenia (grade 4)
400	1	Febrile neutropenia (grade 4), neutropenia (grade 4)
400	1	Neutropenia (grade 3), thrombocytopenia (grade 4)
400	2	Neutropenia (grade 4)
400	2	Neutropenia (grade 4)
Extension cohort[b]		
300 (2h1h)	1	Neutropenia (grade 4), thrombocytopenia (grade 4)
300 (1h2h)	3	Neutropenia (grade 3)
300 (1h2h)	2	Fatigue (grade 3), weight decreased (grade 3)

a Neutropenia ⩾7 d.
b Extension cohort looking to QT changes.

Table 3 – Number of patients with treatment-related AEs occurring at a rate >5% total population – treated set, all courses.

AE, *n* (%)	Volasertib										
	12 (*n* = 4)	24 (*n* = 3)	48 (*n* = 3)	75 (*n* = 2)	125 (*n* = 4)	200 (*n* = 3)	300 (*n* = 29)	350 (*n* = 5)	400 (*n* = 10)	450 (*n* = 2)	Total (*n* = 65)
Any drug-related AEs	1 (25)	–	–	–	1 (25)	2 (67)	14 (48)	3 (60)	9 (90)	2 (100)	32 (49)
Anaemia	–	–	–	–	–	1 (33)	4 (14)	2 (40)	7 (70)	–	14 (22)
Fatigue	–	–	–	–	1 (25)	–	5 (17)	–	2 (20)	2 (100)	10 (15)
Neutropenia	–	–	–	–	–	–	3 (10)	–	5 (50)	2 (100)	10 (15)
Thrombocytopenia	–	–	–	–	–	–	2 (7)	2 (40)	3 (30)	2 (100)	9 (14)
Nausea	1 (25)	–	–	–	–	–	5 (17)	–	–	–	6 (9)
Alopecia	–	–	–	–	–	–	3 (10)	1 (20)	2 (20)	–	6 (9)
Febrile neutropenia	–	–	–	–	–	–	1 (3)	2 (40)	2 (20)	–	5 (8)

AE = adverse event.

second-line therapy; best response was progressive disease for both treatments.

In total, 26 (40%) patients showed SD as their best overall response to volasertib. An additional two patients had non-evaluable, but clinically non-progressive disease, as best response, thus 31 (48%) patients experienced clinical benefit. Over all doses, 20 patients had a clinical response or disease stabilisation >3 months (>3, but <6 months, $n = 12$ [1 PR, 11 SD]; >6 months, $n = 8$ [2 PR, 6 SD]).

3.4. *Pharmacokinetics*

The PK parameters for volasertib given as a 1-h infusion are shown in Table 5. Volasertib exhibited a multi-compartmental PK behaviour. Individual geometric mean dose-normalised drug plasma concentration–time profiles are shown in Fig. 1. Unbound volasertib plasma concentrations higher than the IC_{50} value of 0.87 nM were achieved up to 96 h following a 300 mg dose of volasertib. The mean volume of distribution of volasertib was 5340 l/min, suggesting extensive distribution into tissues. The apparent average terminal elimination half-life was 111 h (33.7–256 h) and was dose independent. Volasertib was detected up to 21 d after drug administration in plasma, and total plasma clearance was moderate 792 ml/min (range 237–1640 ml/min) following administration of 12–450 mg. Higher clearance was observed in the lower dose range when compared with the clearance estimated for doses >125 mg.

The area under the curve $(AUC)_{0-24\,h}$ obtained after a 2-h infusion in the extension cohort was similar to that obtained after a 1-h infusion. As expected, half of the maximum concentrations (C_{max}) were observed following a 2-h infusion compared with the 1-h infusion.

4. Discussion

This phase I, open-label, dose-escalation study was designed to determine the MTD and QT changes (1-h and 2-h infusion schedules), pharmacokinetics and safety of volasertib in patients with advanced solid tumours and represents the first-in-man study to investigate antitumour effects of volasertib. The MTD was determined to be 400 mg per administration; however, 300 mg was subsequently chosen as the recommended dose for further phase II development. This decision was based on an assessment of overall safety and tolerability, the incidence of dose reductions in subsequent courses, and considering AEs and DLTs in all treatment courses, as well as PK data.

Volasertib was easily administered and, compared to other agents routinely used in patients with advanced solid tumours, the clinical impact of the associated haematological toxicities observed in this study was limited. The most frequently reported treatment-related AEs were generally haematological, and included anaemia, neutropenia, and thrombocytopenia; no neurotoxicity was observed. The most relevant AE associated with volasertib was dose-dependent neutropenia, both with and without infection. Importantly, neutropenia was not cumulative and was managed with appropriate care in this study. The incidence and

Table 4 – Number of patients with drug-related CTCAE grade 3 or 4 AEs – treated set, all courses.

AE, *n*	Volasertib									
	300 (*n* = 29)		350 (*n* = 5)		400 (*n* = 10)		450 (*n* = 2)		Total (*n* = 65)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3 (%)	Grade 4 (%)
Drug related AE ⩾ grade 3	–	–	–	–	–	–	–	–	4 (6)	12 (18)
Neutropenia	–	3	–	–	1	3	–	2	1 (2)	8 (12)
Thrombocytopenia	–	2	2	–	1	2	–	2	3 (5)	6 (9)
Anaemia	1	–	1	–	3	–	–	–	5 (8)	–
Febrile neutropenia	–	–	1	1	–	2	–	–	1 (2)	3 (5)
Leukopaenia	–	1	–	–	–	–	–	–	–	1 (2)
Fatigue	1	–	–	–	–	–	–	–	1 (2)	–
Weight decreased	1	–	–	–	–	–	–	–	1 (2)	–
Vision blurred	–	–	1	–	–	–	–	–	1 (2)	–
QT prolongation	1	–	–	–	–	–	–	–	1 (2)	–

CTCAE = Common Toxicity Criteria for Adverse Events; AE = adverse event.

severity of neutropenia and thrombocytopenia observed were expected based on the preclinical profile of volasertib and its proposed mechanism of action were frequently low grade, always reversible, and may serve as an indirect marker for Plk1 inhibition. Fatigue was the most frequently reported treatment-related, non-haematological AE, although was generally mild-to-moderate in severity.

Volasertib showed encouraging antitumour activity in this heavily pretreated phase I population; three patients experienced confirmed PR and 40% of patients had SD as best response. In addition, two patients (both receiving ⩾300 mg) experienced prolonged treatment benefit, with PFS being greater than 1 year, one of whom is still receiving treatment following 55 courses. These findings further support 300 mg as the recommended dose for phase II development.

Volasertib is not the first dihydropteridinone derivative to enter clinical development; BI 2536, a highly selective and potent small-molecule Plk inhibitor,[10] has been previously evaluated in a range of solid tumour types.[7,11–13] Although limited clinical activity was observed in these studies, BI 2536 demonstrated a favourable safety profile without cumulative toxicity or relevant neurotoxicity. As with volasertib, reversible neutropenia was the main DLT observed. Thus, volasertib represents the second dihydropteridinone derivative to enter clinical trials.

Volasertib displayed a favourable PK profile in this study. PK analyses revealed multi-compartmental PK behaviour and a fast distribution after the end of the infusion. There was no indication of deviation from 'dose-linear PK' behaviour. The apparent terminal elimination half-life was, on average, 111 h (33.7–256 h), which is greater than that of the first-generation dihydropteridinone derivative BI 2536.[14] Volasertib also demonstrated a large volume of distribution (>4000 l). It is likely that the high volume of distribution and long terminal half-life of volasertib favours sustained exposure of tumour tissues, contributing to the improved clinical activity observed with volasertib in this study, compared with previous studies with BI 2536.

The encouraging preliminary antitumour activity of volasertib reported here further supports the rationale for Plk inhibition in cancer treatment and, in particular, the potential role of Plk1 as a therapeutic target. However, there remains a need for validated biomarkers for Plk1 inhibition, to both help define appropriate patients for treatment and monitor Plk1 inhibitory activity. Although preclinical investigations have shown that Ras-mutant cells show increased sensitivity to Plk1 inhibitors compared with their respective wild-type counterparts, suggesting that RAS status could be used as a marker for patient selection,[15] other preclinical studies with BI 2536 showed comparable inhibitory activity in RAS-mutant cells versus wild-type cells.[16] As such, studies to date have not selected patients based on RAS mutational status. Identifying biomarkers for Plk-1 inhibitors remains challenging given that Plk1 interacts with multiple downstream mechanisms in mitosis, and our understanding of these mechanisms remains incomplete.

5. Conclusions

Data from this first-in-man trial demonstrate a favourable PK profile of volasertib with manageable toxicities in patients with advanced solid tumours. Additionally, the encouraging preliminary antitumour activity observed here not only supports Plk1 as a therapeutic target, but also supports the further clinical development of this compound in a range of cancer indications. Phase II monotherapy and combination trials of volasertib are currently ongoing in several tumour types, guided by the PK, safety and efficacy results observed in this trial.

Role of the funding source

Boehringer Ingelheim sponsored this trial and provided financial support for editorial assistance from Ogilvy Healthworld and GeoMed. P.S., H.D., H.F. and G.M. contributed to study design. All authors contributed to data collection, analysis or interpretation. P.S. was responsible for drafting, editing and finalising the manuscript.

Authors' contributions

P.S. was the Principle Investigator of the trial and was involved in study initiation, data entry and monitoring. P.S., H.D., H.F. and G.M. contributed to trial design. A.A., H.D., T.G., S.B.,

Table 5 – Geometric mean (gCV [%]) non-compartmental pharmacokinetic parameters of volasertib after 1-h intravenous infusion on day 1 course 1.

Parameter	12 mg (n = 4)	24 mg (n = 3)	48 mg (n = 3)	75 mg (n = 2)	125 mg (n = 3)	200 mg (n = 3)	300 mg (n = 11)	350 mg (n = 5)	400 mg (n = 9)	450 mg (n = 2)
	gMean (gCV [%])									
$AUC_{0-\infty}$ (ng h/mL)	149 (31.6)	380 (38.9)	778 (25.1)	1270 (7.6)	2140 (27.9)	5670 (36.7)	6540 (32.6)	10000 (57.6)	7510 (19.3)	10900 (14.0)
$AUC_{0-\infty,\ norm}$ (ng h/mL/mg)	14·7 (32.2)	19·0 (44.4)	18·0 (20.2)	18·2 (9.17)	17·6 (23.4)	30·5 (28.8)	21·9 (32.6)	28·6 (57.6)	19·4 (20.7)	29·6 (44.6)
C_{max} (ng/mL)	18·8 (14.3)	50·7 (12.4)	91·1 (17.6)	169 (11.7)	234 (30.9)	470 (57.6)	758 (28.8)	724 (23.6)	1020 (20.9)	1450 (8.8)
$C_{max,\ norm}$ (ng h/mL/mg)	1·86 (11.9)	2·54 (19.3)	2·11 (19.2)	2·43 (10.2)	1·92 (26.5)	2·52 (45.9)	2·54 (29.2)	2·07 (23.6)	2·63 (15.3)	3·94 (38.8)
$t_{1/2}$ (h)	9·69 (32.0)	107 (16.9)	156 (40.1)	126 (28.9)	153 (30.7)	149 (49.9)	105 (27.2)	119 (36.7)	88·4 (49.2)	101 (20.4)
Clearance (mL/min)	1140 (32.2)	876 (44.4)	924 (20.2)	918 (9.20)	947 (23.4)	547 (28.8)	762 (32.6)	583 (57.6)	858 (20.7)	562 (44.6)
V_{ss} (L)	7730 (30.8)	6670 (46.0)	9630 (36.7)	7520 (50.9)	9320 (13.3)	4580 (41.2)	4550 (37.1)	4570 (19.8)	4240 (49.0)	2970 (51.6)

AUC = area under the curve; C_{max} = maximum concentration; $t_{1/2}$ = terminal half-life; V_{ss} = volume of distribution; norm, dose normalised.

Fig. 1 – Geometric mean drug plasma concentration–time profiles. Geometric mean drug plasma concentration–time profiles of volasertib after intravenous infusion (1-h) of 12 mg, 24 mg, 48 mg, 75 mg, 125 mg, 200 mg, 300 mg, 350 mg, 400 mg, and 450 mg in course 1.

P.W., M.T. and P.G. were responsible for data collection. P.S., A.A., P.W., M.T., H.F., P.G. and G.M. were responsible for data analysis. A.A., H.D., M.T., H.F., P.G. and G.M. were responsible for data interpretation. Editorial assistance was provided by Ogilvy Healthworld and GeoMed and funded by Boehringer Ingelheim. P.S. was responsible for drafting, editing and finalising the manuscript.

Conflict of interest statement

Patrick Schöffski: Honoraria received from Boehringer Ingelheim for educational activities, Advisory Board member for Boehringer Ingelheim; Martine Taton, Holger Fritsch, Patricia Glomb, Gerd Munzert: Employee of Boehringer Ingelheim Pharma GmbH and Co. KG; and no conflict of interest for other authors.

Acknowledgements

This study was supported by Boehringer Ingelheim. The authors would like to acknowledge the editorial assistance of Ogilvy Healthworld and GeoMed.

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