A phase I study of two dosing schedules of volasertib (BI 6727), an intravenous polo-like kinase inhibitor, in patients with advanced solid malignancies

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Background: Polo-like kinase 1 (Plk1) has an important role in mitosis. Volasertib (BI 6727), a potent and selective cell cycle kinase inhibitor, induces mitotic arrest and apoptosis by targeting Plk; this phase I study sought to determine its maximum tolerated dose (MTD) in Asian patients with advanced solid tumours.

Methods: Patients were enrolled simultaneously into two 3-week schedules of volasertib: a 2-h infusion on day 1 (schedule A) or days 1 and 8 (schedule B). Dose escalation followed a 3+2 design. The MTD was determined based on dose-limiting toxicities (DLT) in the first treatment course.

Results: Among 59 treated patients, the most common first course DLTs were reversible thrombocytopenia, neutropenia and febrile neutropenia; MTDs were 300 mg for schedule A and 150 mg for schedule B. Volasertib exhibited multi-exponential pharmacokinetics (PK), a long terminal half-life of ~135 h, a large volume of distribution (>3000 l), and a moderate clearance. Partial responses were observed in two pre-treated patients (ureteral cancer; melanoma). Volasertib was generally well tolerated, with an adverse event profile consistent with its antimitotic mode of action and a favourable PK profile.

Conclusions: These data support further development of volasertib and a harmonised dosing for Asian and Caucasian patients.

The polo-like kinase (Plk) family of proteins is comprised of five highly conserved serine/threonine protein kinases that have a key role in such cellular processes as cell division and checkpoint regulation of mitosis (Medema et al, 2011). Of the five Plks identified in humans to date, polo-like kinase 1 (Plk1) is the most extensively characterised. Plk1 is involved in regulating multiple essential steps of mitosis including mitotic entry, centrosome maturation and separation, formation of the bipolar spindle, metaphase to anaphase transition, and initiation of cytokinesis (Strebhardt, 2010; Medema et al, 2011). Plk1 was reported to be overexpressed in a range of human cancers, including non-small cell lung, prostate, ovarian, breast, colorectal cancer, and acute myeloid leukaemia (Takahashi et al, 2003; Rudolph et al, 2009; Medema et al, 2011), and high levels of Plk1 expression were...
REPORTED TO BE CORRELATED WITH POOR PROGNOSIS IN VARIOUS CANCERS (STREBHARDT, 2010). PRECLINICAL STUDIES HAVE DEMONSTRATED THE FUNCTIONAL RELEVANCE OF PLK1 AS A POTENTIAL THERAPEUTIC TARGET IN CANCER. PLK1 INHIBITION LEADS TO A DISRUPTION IN SPINDLE ASSEMBLY CAUSING A DISTINCT MITOTIC ARREST PHENOTYPE (‘POLO-ARREST’) AND SUBSEQUENT APOPTOSIS (SPANKUCH-SCHMITT ET AL, 2002; LIU AND ERIKSON, 2003; RUDOLPH ET AL, 2009). AS A RESULT, PLK1 IS EMERGING AS A PROMISING NOVEL TARGET FOR ANTI-CANCER THERAPY.

VOLASERTIB (BOEHRINGER INGELHEIM (BI) 6727; AN INVESTIGATIONAL AGENT CURRENTLY IN CLINICAL DEVELOPMENT) IS A POTENT AND SELECTIVE PLK1 INHIBITOR THAT INDUCES MITOTIC ARREST AND APOPTOSIS (RUDOLPH ET AL, 2009). THE CHEMICAL STRUCTURE OF VOLASERTIB HAS BEEN PREVIOUSLY PUBLISHED (RUDOLPH ET AL, 2009). IN PRECLINICAL STUDIES, VOLASERTIB DEMONSTRATED BROAD ANTITUMOUR ACTIVITY IN MULTIPLE CANCER MODELS AND A PROMISING PHARMACOKINETIC (PK) PROFILE INDICATIVE OF HIGH AND SUSTAINED EXPOSURE IN TUMOUR TISSUE (RUDOLPH ET AL, 2009). IN A PHASE I TRIAL OF CAUCASIAN PATIENTS WITH SOLID TUMOURS, VOLASERTIB ADMINISTERED ON DAY 1 OF A 3-WEEK TREATMENT COURSE DEMONSTRATED ANTITUMOUR ACTIVITY WITH A GENERALLY MANAGEABLE SAFETY PROFILE (SCHÖFSKI ET AL, 2012).

AS POPULATION-SPECIFIC DATA ARE CRUCIALLY NEEDED TO OPTIMISE DOSING FROM A SAFETY PERSPECTIVE OWING TO POTENTIAL ETHNIC DIFFERENCES, THIS PHASE I STUDY OF ESCALATING DOSES OF VOLASERTIB ADMINISTERED TO ASIAN PATIENTS WITH ADVANCED SOLID MALIGNANCIES WAS CONDUCTED. THE PURPOSE OF THIS STUDY WAS TO CONFIRM IN ASIAN CANCER PATIENTS THE MAXIMUM TOLERATED DOSE (MTD) PREVIOUSLY ESTABLISHED IN CAUCASIANS, AND TO ESTABLISH THE MTD OF AN ALTERNATIVE ADMINISTRATION SCHEDULE. THE SAFETY, TOLERABILITY, PK, AND EFFICACY OF VOLASERTIB WERE ASSESSED USING TWO DIFFERENT SCHEDULES WITH IDENTICAL CYCLE LENGTHS (21 DAYS): VOLASERTIB WAS ADMINISTERED ONCE ON DAY 1 (SCHEDULE A) AND VOLASERTIB WAS ADMINISTERED ONCE A WEEK ON DAYS 1 AND 8 (SCHEDULE B).

MATERIALS AND METHODS

TRIAL DESIGN. THIS WAS AN OPEN-LABEL PHASE I DOSE-ESCALATION STUDY OF VOLASERTIB IN PATIENTS WITH ADVANCED CANCER CONDUCTED AT TWO SITES IN TAIWAN (NCT00969553). THE PRIMARY END POINT WAS THE DETERMINATION OF THE MTD, DEFINED AS THE HIGHEST DOSE OF VOLASERTIB STUDIED FOR WHICH THE INCIDENCE OF DOSE-LIMITING TOXICITY (DLT) WAS LESS THAN TWO OF SIX PATIENTS IN THE FIRST TREATMENT COURSE, FOR THE TWO DOSING SCHEDULES. SECONDARY END POINTS INCLUDED THE INCIDENCE AND INTENSITY OF ADVERSE EVENTS (AEs), OBJECTIVE TUMOUR RESPONSES, PROGRESSION-FREE SURVIVAL (PFS), RESPONSE DURATION, AND PK. THE STUDY WAS CONDUCTED IN ACCORDANCE WITH THE PRINCIPLES LAID DOWN BY THE DECLARATION OF HELSINKI AND APPROVED BY THE INDEPENDENT ETHICS COMMITTEES AND/ OR INSTITUTIONAL REVIEW BOARDS OF THE PARTICIPATING CENTRES.

PATIENT SELECTION. PATIENTS AGED ≥18 YEARS OF AGE WITH HISTOLOGICALLY OR CYTOLOGICALLY CONFIRMED DIAGNOSIS OF ADVANCED, NON-RESECTABLE, AND/OR METASTATIC SOLID CANCER, WHO HAD FAILED CONVENTIONAL TREATMENT, OR FOR WHOM NO THERAPY OF PROVEN EFFICACY EXISTS, OR WHO ARE NOT AMENABLE TO ESTABLISHED FORMS OF TREATMENT, WERE ELIGIBLE FOR INCLUSION. OTHER ELIGIBILITY CRITERIA INCLUDED THE EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS ≤2, RECOVERY FROM TOXICITIES FROM PREVIOUS TREATMENTS, ADEQUATE BONE MARROW, LIVER, AND Renal FUNCTION (ABNORMAL NEUTROPHEL COUNT >1500 mm⁻³, PLATELET COUNT >100 000 mm⁻³, TOTAL BILIRUBIN ≤1.5 mg dl⁻¹ (≤26 µmol l⁻¹, SI UNITEquivalent), ASPARTATE AMINOTRANSFERASE AND OR ALANINE AMINOTRANSFERASE ≤2.5 TIMES THE UPPER LIMIT OF NORMAL (ULN, IF RELATED TO LIVER METASTASES <5 × ULN), AND SERUM CREATININE ≤1.5 × ULN), A LIFE EXPECTANCY ≥12 WEEKS, NO CHENO-, RADIO-, IMMUNO-, MOLECULAR-TARGETED, OR INVESTIGATIONAL THERAPY ≤4 WEEKS BEFORE TREATMENT WITH THE STUDY DRUG (EXCEPT STEROIDS AND BISPHOSPHONATES), AND NO KNOWN HISTORY OF RELEVANT QT-PROLONGATION. ALL PATIENTS WERE REQUIRED TO PROVIDE WRITTEN INFORMED CONSENT CONSISTENT WITH INTERNATIONAL CONFERENCE ON HARMONISATION-GOOD CLINICAL PRACTICE AND LOCAL LEGISLATION.

TREATMENT AND DOSE-ESCALATION. PATIENTS WERE SEQUENTIALLY ASSIGNED TO ONE OF THE TWO VOLASERTIB DOSE ESCALATING SCHEDULES AND A 3 + 3-DOSE ESCALATION DESIGN (KANG AND AHN, 2002) WAS USED TO EVALUATE THE MTD IN EACH TREATMENT ARM. VOLASERTIB WAS ADMINISTERED BY INTRAVENOUS INFUSION FOR OVER 2h USING TWO SCHEDULES: DAY 1 EVERY 3 WEEKS (SCHEDULE A) OR DAY 1 AND DAY 8 EVERY 3 WEEKS (SCHEDULE B). THE PREPLANNED DOSE LEVELS WERE 100, 200, 250, AND 300 mg (IN CASE OF GOOD TOLERABILITY, THE DOSE COULD BE FURTHER ESCALATED UP TO 400 mg) FOR SCHEDULE A AND 50, 100, 150, AND 200 mg (WITH ESCALATION TO 250 mg IN CASE OF GOOD TOLERABILITY) FOR SCHEDULE B.

COHORTS OF THREE TO SIX PATIENTS WERE ENROLLED SEQUENTIALLY INTO ESCALATING DOSE TIERs OF VOLASERTIB. DOSE ESCALATION WAS CONDUCTED FOR EACH TREATMENT GROUP FOLLOWING A 3 + 3-DESIGN, WHERE COHORTS OF THREE PATIENTS WERE TREATED PER Dose UNTIL THE HIGHEST Dose (MTD) WAS FOUND AT WHICH NO MORE THAN ONE OUT OF SIX PATIENTS EXPERIENCED A DLT IN THE FIRST TREATMENT COURSE. IF ONE OF THE THREE PATIENTS EXPERIENCED A DLT IN THE FIRST Course, THREE ADDITIONAL PATIENTS WERE ENROLLED TO THE COHORT. A DLT WAS DEFINED AS THE FOLLOWING EVENTS: DRUG-RELATED NEUTROPENIA (COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE) GRADE 4 FOR ≥7 DAYS OR ANY GRADE DRUG-RELATED FEbrILE NEUTROPENIA OR NEUTROPenic INFECTION; DRUG-RELATED GRADE 4 THROMBOCYTOPENIA; OR DRUG-RELATED GRADE ≥3 NON-HEMALOGENIC TOXICITY (EXCEPT UNTREATED NAUSEA, VOMITING, OR DIARRHOEA). THE FOLLOWING EVENTS ALSO CONSTITUTED A DLT FOR SCHEDULE B ONLY, IF CONSIDERED TO BE DRUG-RELATED AND PRESENT ON DAY 8: GRADE ≥3 NEUTROPENIA, GRADE ≥3 THROMBOCYTOPENIA, OR GRADE ≥2 NON-HEMALOGENIC TOXICITY (EXCEPT ALOPECIA, UNTREATED NAUSEA, VOMITING, OR DIARRHOEA). DURING COURSE 1, THE USE OF GROWTH FACTORS FOR THE TREATMENT OF HAE MATOTOXICITY WAS NOT ENCOURAGED EXCEPT FOR LIFE-THREATENING CIRCUMSTANCES.

IN THE DOSE ESCALATION PART OF THIS STUDY, AN IN-PATIENT Dose ESCALATION FROM LOWER Dose LEVELs OF VOLASERTIB TO HIGHER Dose LEVELs (WITHOUT EXCEEDING THE MTD OR DEFINED MAXIMAL Dose) WAs ALLOWED, IF SUPPORTED BY SAFETY OBSERVATIONS, TO INCREASE THE PROBABILITY OF CLINICAL BENEFIT (GOOD TOLERABILITY RESULTING IN A PERMISSIBLE Dose ESCALATION WAs DEFINED AS NON-HEMALOGENIC DRUG-RELATED AEs GRADE <2 AND HEMALOGENIC DRUG-RELATED AEs GRADE <3). ALL DECISIONS REGARDING IN-PATIENT Dose ESCALATION WERE MADE ONLY IN AGREEMENT BETWEEN THE INVESTIGATOR AND SPONSOR. PATIENTS EXPERIENCING DLTs WERE ELIGIBLE FOR FURTHER TREATMENT AT ONE Dose TIER BELOW. TREATMENT WAS DISCONTINUED IF THE DLT WAs NOT REVERSIBLE. AFTER DETERMINATION OF THE MTD, OR ON REACHING THE HIGHEST PRE-SPECIFIED Dose LEVEL, A TOTAL OF UP TO 18 PATIENTS WERE ENTERED AT THE MTD IN ORDER TO GAIN ADDITIONAL SAFETY DATA. PATIENTS WERE TREATED AS LONG AS CLINICALLY BENEFITTING OR UNTIL OCCURRENCE OF AN INTOLERABLE AE OR CONSENT WITHDRAWAL.

ASSESSMENTS. SAFETY MEASUREMENTS INCLUDED MONITORING OF AEs, VITAL SIGNS, ELECTROCARDIOGRAMS (ECGs), LABORATORY EVALUATIONS, AND PATIENT PERFORMANCE STATUS. THE INCIDENCE AND INTENSITY OF AEs DURING THE COURSE OF THE STUDY WERE RECORDED AND CLASSIFIED ACCORDING TO CTCAE VERSION 3.0. AEs WERE CODED CENTRALLY USING THE MEDICAL DICTIONARY FOR REGULATORY ACTIVITIES. THE DURATIONS OF CYTOPENIAS REPORTED AS DLTs WERE CALCULATED BASED ON CORRESPONDING LAB VALUES. TRIPlicate DIGITAL 12-LEAD RESTING ECGs WERE PERFORMED AT BASELINE (DEFINED AS THE MEAN OF THE TRIPlicate AT THE TIME POINT CLOSEST TO, BUT BEFORE, THE START OF THE INFUSION), BEFORE INFUSION, AND AFTER (1, 2, 3, 8, AND 24 h) VOLASERTIB INFUSION.

BLOOD SAMPLES FOR THE DETECTION OF VOLASERTIB IN PLASMA WERE OBTAINED PREDOSE AND AT UP TO SEVEN TIME POINTs (1, 2, 2.5, 3, 4, 8, AND 24 h) AFTER A 2h INFUSION OF VOLASERTIB. Samples WERE ANALYSed BY A VALIDATED HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY, TANDEM MASS SPECTROMETRY assay. STANDARD NON-COMPARTMENTAL PK
Patient demographics and disposition. A total of 59 patients (32 in schedule A, 27 in schedule B) were enrolled between 28 August 2009 and 10 March 2011. All patients received previous anticancer therapies; many patients were heavily pre-treated with 46.9% (schedule A) and 40.7% (schedule B) previously treated with at least three chemotherapy regimens (Table 1). As of 27 October 2011, 31 patients in schedule A (96.9%) and 25 patients in schedule B (92.6%) had discontinued treatment, the majority owing to progressive disease (65.6% and 77.8%, respectively). Three patients (one patient in schedule A and two in schedule B) were still receiving treatment as of 27 October 2011.

Treatment exposure. Patients received between 1 and 23 courses of treatment with volasertib, with a median (range) of 4 (1, 16) courses initiated in schedule A and 3 (1, 23) courses initiated in schedule B. The median total exposure time in both treatment schedules was 85 days, which is consistent with a median of four courses based on a course length of 21 days. The median total dose in both treatment schedules was 900 mg. Overall, 12 patients had a dose escalation, 10 (31.3%) in schedule A and two (7.4%) in schedule B. Ten patients that continued treatment following evaluation was assessed using WinNonlin (v5.2, Pharsight Co., St Louis, MO, USA).

Objective tumour response was assessed by tumour measurements using computed tomography or magnetic resonance-imaging scans, performed at baseline and at the end of every other treatment course, and evaluated according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.0 (Therasse et al., 2000). PFS was analysed using the Kaplan–Meier method (Kaplan and Meier, 1958).

RESULTS

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Table 1. Patient demographics

| Schedule A (n = 32)                  | Schedule B (n = 27)                  |
|-------------------------------------|-------------------------------------|
| **Median age, years (range)**       | 53.3 (37–78)                        |
| Male/female, (%)                    | 62.5/37.5                           |
| **Baseline ECOG, n (%)**            |                                      |
| 0                                  | 12 (37.5)                           |
| 1                                  | 19 (59.4)                           |
| 2                                  | 1 (3.1)                             |
| **Type of cancer, n (%)**           |                                      |
| Colorectal                          | 6 (18.8)                            |
| Urothelial                          | 5 (15.6)                            |
| Oesophagus                          | 2 (6.3)                             |
| Melanoma                            | 4 (12.5)                            |
| Liver and biliary tree              | 1 (3.1)                             |
| Lung                                | 2 (6.3)                             |
| Soft tissue sarcoma                 | 2 (6.3)                             |
| Head and neck                       | 3 (9.4)                             |
| Other                               | 7 (21.9)                            |
| Any prior anticancer therapy, n (%) | 32 (100.0)                          |
| Chemotherapy                        | 29 (90.6)                           |
| ≥ 3 chemotherapies                  | 15 (46.9)                           |
| Surgery                             | 26 (81.3)                           |
| Radiotherapy                        | 15 (46.9)                           |
| Other                               | 10 (31.3)                           |

Abbreviation: ECOG = Eastern Cooperative Oncology Group.
Asian patients with solid cancer at the determined doses. In addition, among patients who had intra-individual dose escalation, three patients in schedule A and one patient in schedule B, respectively, had been treated at the MTD and were escalated from the MTD to a higher dose (up to 350 mg and 200 mg, respectively). No DLTs were observed in this cohort.

**Table 2. Patients with DLTs (any treatment course)**

| Schedule | Dose (mg) | Course | DLT |
|----------|-----------|--------|-----|
| A        | 250       | 1      | Neutropenia (grade 4 for ≥7 days) |
|          | 300       | 5      | Febrile neutropenia (grade 3) |
|          | 300       | 1\(^b\) | Febrile neutropenia (grade 4) |
|          |           |        | Neutropenia (grade 4 for ≥7 days) |
|          | 300       | 1\(^b\) | Neutropenia (grade 4 for ≥7 days) |
|          | 300       | 1\(^b\) | Neutropenia (grade 4 for ≥7 days) |
|          | 350       | 1      | Febrile neutropenia (grade 3) |
|          |           |        | Neutropenia (grade 4 for ≥7 days) |
|          | 350       | 1      | Thrombocytopenia (grade 4) |
|          | 350       | 1      | Neutropenia (grade 4 for ≥7 days) |
| B        | 150       | 2      | Neutropenia (grade 3 on day 8 before second administration) |
|          | 150       | 5      | Tinnitus (grade 2 on day 8 of the course) |
|          | 150       | 14     | Alanine aminotransferase increased (grade 3 on day 8 of the course) |
|          | 200       | 1      | Febrile neutropenia (grade 3) |
|          | 200       | 1      | Neutropenia (grade 4 for ≥7 days) |

Abbreviation: DLT = dose-limiting toxicity.

\(^a\)At first occurrence.

\(^b\)Patients who were enrolled after maximum tolerated dose (MTD) had been determined.

**Table 3. Number of patients with adverse events grade 3 or 4 in >5% of patients in schedules A and B combined irrespective of relatedness: schedule A (all doses)**

| Schedule A (mg) n (%) | Grade 3 | Grade 4 | Grade 3 | Grade 4 | Grade 3 | Grade 4 | Grade 3 | Grade 4 | Grade 3 | Grade 4 | Grade 3 | Grade 4 | Grade 3 | Grade 4 | Grade 3 | Grade 4 | Grade 3 | Grade 4 | Grade 3 | Grade 4 |
|----------------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
|                      | Neutropenia |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |        |
|                      | 1        | —       | —       | —       | —       | 2       | 5       | 5       | —       | 3       | 6       | 18.8    | 10      | 31.3    | 10      | 31.3    | 5       | 15.6    | 4       | 12.5    |
|                      | Thrombocytopenia | 1       | —       | —       | —       | 1       | 1       | 7       | 2       | 1       | 2       | 10(31.3) | 5       | 15.6    | 10      | 31.3    | 5       | 15.6    | 4       | 12.5    |
|                      | Anaemia | 1       | —       | —       | —       | 3       | 1       | 2       | 2       | 1       | 8       | 25.0    | 4       | 12.5    | 8       | 25.0    | 4       | 12.5    | 8       | 25.0    |
|                      | Leukopenia | —       | —       | —       | —       | —       | 1       | 7       | —       | 2       | —       | 9       | 28.1    | 1       | 3.1     | 9       | 28.1    | 1       | 3.1     |
|                      | Febrile neutropenia | —       | —       | —       | —       | —       | 1       | 1       | 1       | 1       | —       | 2       | 6.3     | 1       | 3.1     | 2       | 6.3     | 1       | 3.1     |
|                      | Abdominal pain | —       | —       | —       | —       | —       | —       | —       | 2       | —       | —       | 3       | 9.4     | —       | —       | 3       | 9.4     | —       | —       |
|                      | Fatigue | 1       | —       | —       | —       | —       | 1       | —       | —       | —       | 2       | 6.3     | —       | —       | 2       | 6.3     | —       | —       |
|                      | Pain | —       | —       | —       | —       | —       | —       | —       | —       | —       | 1       | 3.1     | —       | —       | 1       | 3.1     | —       | —       |
|                      | Hypokalaemia | —       | —       | —       | —       | 1       | —       | —       | —       | —       | 1       | 3.1     | —       | —       | 1       | 3.1     | —       | —       |
|                      | Infection | —       | —       | —       | —       | —       | 1       | —       | —       | —       | —       | 1       | 3.1     | —       | —       | 1       | 3.1     | —       | —       |
|                      | Ileus | —       | —       | —       | —       | 1       | —       | —       | —       | —       | 1       | 3.1     | —       | —       | 1       | 3.1     | —       | —       |
|                      | Upper GI haemorrhage | 1       | —       | —       | —       | —       | —       | —       | —       | —       | 1       | 3.1     | —       | —       | 1       | 3.1     | —       | —       |

Abbreviation: GI = gastrointestinal.

**PK.** Volasertib exhibited multi-exponential plasma concentration profiles (Figure 1). The volume of distribution at steady state ($V_{ss}$ > 3000 l) was large with a moderate clearance of $>770\text{ ml min}^{-1}$.

An apparent terminal half-life ($t_{1/2}$) of $\sim135\text{ h}$ was observed (Table 5). No accumulation was observed when volasertib was administered on day 1 and day 8 in schedule B.
Antitumour activity. Two partial responses were observed in this study. A patient with ureteral urothelial carcinoma (wild-type \textit{FGFR3}) was treated with volasertib (350 mg in schedule A) started in July 2010 (two courses), and achieved a partial response. This patient had initially been treated with surgery without adjuvant therapy in July 2008 and subsequently with chemotherapy after presentation with bone metastases in July 2009 (gemcitabine and cisplatin from August 2009) resulting in a partial response. The patient was diagnosed with bone and liver metastases in June 2010 before enrolment in this study. The patient discontinued volasertib after a second occurrence of DLT (grade 4 thrombocytopenia) at 300 mg. A second patient with melanoma and lymph node involvement (wild-type \textit{BRAF}, \textit{NRAS}, and \textit{cKIT}) was treated with volasertib (150 mg in schedule B) and achieved a partial response. The patient had previously been treated with surgery in December 2008 and then presented with lung and lymph node metastases in September 2010 before enrolment in this study. The patient received nine courses of volasertib before discontinuing owing to disease progression.

Overall, 26 (44.1%) patients showed stable disease as their best overall response (14 (43.8%) patients in schedule A and 12 (44.4%) patients in schedule B). Eleven patients have been treated for 10 courses or more, and one patient with bladder urothelial cancer with lymph node metastasis was treated for 23 courses. This patient was initially treated at 50 mg in schedule B and her disease remained stable for 48 months, before the dose was escalated to 150 mg after disease progression. The median PFS over all dose groups was 49 days (range, 30–274 days) in schedule A and 56 days (range, 8–499 days) in schedule B.

### DISCUSSION

This study was the first to assess the MTD, safety, and efficacy of volasertib in a day 1 and day 8 dosing schedule, and also the first to investigate the MTD of volasertib in Asian patients with cancer.
The MTD of volasertib as a 2-h infusion was determined to be 300 mg when administered on day 1 of a 3-week treatment course (schedule A) and 150 mg when administered on days 1 and 8 of a 3-week treatment course (schedule B). The MTD determined in schedule A of this study is the same as the recommended phase II 3-week treatment course (schedule B). The MTD determined in schedule A gMean when administered on day 1 of a 3-week treatment course (schedule B) was 300 mg.

Volasertib had antitumour activity in this cancer patient population comparable to that observed in other phase I/II trials in Western populations (Schoffski et al, 2012; Stadler et al, 2014). Volasertib demonstrated multi-compartmental PK behaviour with an apparent half-life of 135 h, moderate clearance and a large volume of distribution. It is likely that the high volume of distribution (>3000 l) and long t1/2 (135 h) of volasertib resulted in an increased and more sustainable tumour exposure than in previous studies with BI 2536, a dihydropteridinone derivative similar to volasertib. This is in contrast to studies of BI 2536, which demonstrates an inferior PK profile (lower volume of distribution (1000 l) and shorter t1/2 (15 h)) compared with volasertib and did not demonstrate objective responses in patients with solid tumours (Mross et al, 2008; Hofheinz et al, 2010; Frost et al, 2012; Schoffski et al, 2012). Volasertib is primarily eliminated unchanged with metabolism representing a relatively minor elimination route as indicated by low exposures of the main metabolite (data not shown). Therefore, PK drug–drug interactions are not expected to influence the safety profile of volasertib.

Table 5. Non-compartmental PK parameters of volasertib (gMean and gCV %) after the first 2-h intravenous infusion of volasertib 100–350 mg (schedule A) or 50–200 mg (schedule B)
(Doi et al, 2011). In contrast, no objective responses were reported to date in phase I trials of either GSK461364 (Olmos et al, 2011) or HMN-214 (Garland et al, 2006) in patients with advanced solid malignancies. Phase I trials of NMS-1286937 and TAK-960 in patients with advanced solid tumours are currently ongoing.

In conclusion, this phase I study determined that intravenous volasertib was generally well tolerated up to the identified MTDs of 300 mg (schedule A) and 150 mg (schedule B). Volasertib had a safety profile consistent with its antimitotic mode of action, and a favourable PK profile. These data support Plk as a therapeutic target, warrant further development of volasertib, and support a harmonised dosing for Asian and Caucasian patients.

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CONFLICT OF INTEREST

A-LC: Honoraria from speakers bureau, Bayer Taiwan Co., Ltd, and consultant/advisory board Eisai Inc. and Exelixis Inc. DC-LH, HF, FV, and TT: employment, Boehringer Ingelheim. JC-HY: provided uncompensated expert testimony to afatinib produced by Boehringer Ingelheim in Taiwan FDA. The remaining authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

The authors were fully responsible for all content and editorial decisions, were involved at all stages of manuscript development, and have approved the final version.

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