Phase I Study of Volasertib Combined with Afatinib in Advanced Solid Tumors #2521

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INTRODUCTION

- Polo-like kinase 1 (Plk1) is a key enzyme that controls several critical steps during mitosis: mitotic entry, centrosome maturation and separation, formation of the bipolar spindle, metaphase to anaphase transition, and initiation of cytokinesis[1,2]
- Overexpression of Plk1 has been observed in several human cancers,[3,4] and its functional relevance has been demonstrated *in vitro* by 'knock-down' experiments where Plk1 inhibition induced cell cycle arrest and apoptosis in cancer cell lines[5,6]
- Volasertib (BI 6727; an investigational compound) is a potent and selective cell cycle kinase inhibitor that induces mitotic arrest and apoptosis by targeting Plk, without inhibitory effects on other kinases (>50 assayed including Flt3 and c-KIT at volasertib concentrations up to 10 μM)[7]
- The epidermal growth factor receptor (EGFR, also called ErbB or HER) family consists of four receptor tyrosine kinases, EGFR (ErbB1), HER2 (ErbB2), ErbB3, and ErbB4,[8,9] and is involved in cell proliferation and differentiation.[8,10] Overexpression has been linked to numerous types of cancer[11] and EGFR is a rational target for antitumor strategies
- Afatinib (BIBW 2992) is an irreversible ErbB family blocker that inhibits signal transduction of kinase receptors from the ErbB family of EGFRs: 1 (ErbB1/HER1), 2 (ErbB2/HER2) and 4 (ErbB4/HER4)[12,13]
- The combination of a Plk1 inhibitor with an agent that has a different mode of action, such as afatinib, may offer improved benefit versus either therapy alone
- Early clinical data indicate that volasertib is well tolerated and has antitumor activity.[14,15] The recommended single-agent dose of volasertib (from a Phase I trial) is 300 mg on Day 1 every 21 days[16]
- Afatinib has demonstrated superior antitumor activity versus best-in-class chemotherapy with a manageable safety profile in the Phase III LUX-LUNG 3 study of patients with EGFR (ErbB1) mutation-positive, non-small cell lung cancer (NSCLC),[17] and afatinib has been granted priority review by the FDA for this indication. In addition, afatinib is in Phase III development for head and neck cancer
- This poster presents final data from a Phase I trial of volasertib in combination with afatinib in patients with advanced solid tumors

METHODS

Endpoints

Primary endpoint

- Determination of the maximum tolerated dose (MTD) of two combination schedules of volasertib and afatinib in patients with advanced or metastatic solid tumors

Secondary endpoints

- Dose-limiting toxicities (DLTs)
- Incidence and intensity of drug-related adverse events (AEs) according to common terminology criteria for AEs (Common Terminology Criteria for Adverse Events, CTCAE v3.0)
- Tumor assessment (objective response rate), performed according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- Individual progression free survival (PFS, defined as the time from start of treatment until progression or death)
- Exploration of pharmacokinetics (PK)

Other endpoints

- Biomarker analyses (including EGFR mutation analysis)

Study design

- This was an open-label, Phase I, dose-escalation trial, conducted at three sites in Belgium
- Volasertib was administered as a single dose by intravenous (iv) infusion over 2 hours, starting at 150 mg in the first dose cohort treatment cycle (then up to 300 mg), on Day 1 every 21 days, and combined with
  - oral afatinib 30–40 mg on Days 2–21 of a 3-week cycle (Schedule A), or
  - oral afatinib 50–90 mg on Days 2–6 of a 3-week cycle (Schedule B)
- Dose escalation of volasertib followed a standard '3 + 3' design, whereby cohorts of three to six patients were entered sequentially into escalating dosage tiers
  - for safety reasons, the first three patients of Cohort 1 (Schedule A) were not entered simultaneously
  - in Schedule B, the starting dose of volasertib and afatinib was dependent on the outcome of the MTD determination in Schedule A
- The MTD of each combination was determined sequentially (Schedule A, then Schedule B) and up to 12 additional patients were enrolled at the MTD of a treatment schedule
- A dose-reduction scheme allowed for individual treatment modification in case of a prespecified AE or DLT

Main eligibility criteria

Inclusion

- Patients with confirmed diagnosis of advanced, non-resectable and/or metastatic solid tumors following failure of conventional treatment, or patients who are not amenable to established forms of treatment, or patients for whom no therapy of proven efficacy exists
- Age ≥18 years
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤2
- Recovery from clinically significant toxicities from previous systemic anticancer therapies or radiotherapies (except alopecia grade 2)

Exclusion

- Serious illness or concomitant non-oncological disease, active infectious disease or known HIV infection, or mental problem considered by the investigator to be incompatible with the trial
- Treatment with other investigational drugs or participation in another clinical interventional trial within 4 weeks prior to the first administration of the trial drugs or concomitantly with this trial
- Major surgery, systemic anticancer therapy or radiotherapy within the past 4 weeks or concomitantly with this trial, with the exception of steroids, hormone therapy and bisphosphonates
- History or presence of cardiovascular abnormalities deemed clinically relevant by the investigator, or known history of relevant QT-prolongation (e.g. long QT syndrome)
- Serious illness or organ system dysfunction, including creatinine >1.5 x upper level of normal
- Absolute neutrophil count (ANC) <1,500/μL or platelet count <100,000/μL

Assessments

Maximum tolerated dose

- MTD of the combination was defined as
  - the highest dose at which no more than one of six MTD evaluable patients experienced a DLT during the first cycle

Dose-limiting toxicities

- DLTs were defined as drug-related (CTCAE for all)
  - grade 4 neutropenia (ANC, including bands, <500/mm³) for more than 7 days
  - grade 3 or 4 neutropenia associated with fever >38.5°C (febrile neutropenia) or neutropenic infection grade ≥3
  - grade 4 thrombocytopenia or grade 3 thrombocytopenia associated with bleeding requiring whole blood transfusion
  - non-hematologic grade ≥3 toxicity excluding: untreated grade 3 diarrhea, nausea, vomiting and/or rash
  - grade 2 increase in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) in conjunction with a grade ≥2 elevated bilirubin level
  - grade 2 nausea/vomiting despite optimal supportive/antiemetic treatment for ≥7 days
  - grade 2 diarrhea for 2 or more consecutive days despite antidiarrheal medication
  - grade ≥2 decrease in left ventricular function

Safety

- All treated patients were included in the safety analyses
- Key safety measures included
  - incidence and intensity of AEs graded according to highest CTCAE grade
  - incidence and intensity of laboratory parameters

Anti-tumor activity

- CT or MRI scans were performed at baseline, after every 3 cycles (i.e. every 9 weeks) and at the end of treatment

Pharmacokinetics

- Plasma concentrations for both agents were assessed on Day 1 of the first 2 cycles at predose and at up to nine timepoints after a 2-hour iv infusion of volasertib and after repeated dosing of afatinib. Samples were analyzed by validated high-performance liquid chromatography, tandem mass spectrometry (HPLC–MS/MS) assay in the laboratory of Boehringer Ingelheim. Geometric mean plasma concentrations were plotted against time
- Standard non-compartmental PK evaluation was performed using WinNonlin™ Professional (Pharsight® Co., version 5.2) software

RESULTS

Patient demographics

- A total of 57 patients were treated: 29 in Schedule A and 28 in Schedule B. The overall median age was 58 years and most patients (60%) had an ECOG PS of 1 (Table 1)
- Patients received between 0 and 18 cycles of treatment. The median (range) of number of cycles was 3 (0–18) in Schedule A, and 3 (0–10) in Schedule B.
- Most patients discontinued volasertib due to progressive disease (22 [75.9%] and 22 [78.6%] in Schedules A and B, respectively) or an AE (four [13.8%] and five [17.9%], respectively). Patients discontinued afatinib mostly also due to progressive disease (20 [69.0%] and 23 [82.1%] in Schedules A and B, respectively) or an AE (three [10.3%] and five [17.9%], respectively)

Table 1. Patient demographics

	Volasertib + afatinib (30–50 mg) Days 2–21 (Schedule A; N=29)	Volasertib + afatinib (50–90 mg) Days 2–6 (Schedule B; N=28)
Age, years Median (min, max)	54.0 (38, 77)	63.5 (47, 81)
Male/female, %	48.3/51.7	53.6/46.4
ECOG, n (%) 0 1 2	12 (41.4) 16 (55.2) 1 (3.4)	8 (28.6) 18 (64.3) 2 (7.1)
Median number of metastatic sites at screening (min, max)	2 (0–6)	3 (1–5)
Tumor type (≥3 patients in either arm), n (%) Colorectal cancer Head and neck cancer Pancreas Breast Other	7 (24.1) 8 (27.6) 1 (3.4) 3 (10.3) 3 (10.3)	16 (57.1) 1 (3.6) 4 (14.3) 2 (7.1) 1 (3.6)
Previous anticancer therapy, n (%) Systemic cancer therapy Radiotherapy Surgery	26 (89.7) 17 (58.6) 28 (96.6)	28 (100.0) 10 (35.7) 25 (89.3)

ECOG, Eastern Cooperative Oncology Group

Determination of MTD

- The MTDs of the combination schedules were determined to be 300 mg for volasertib combined with afatinib 30 mg Days 2–21 (Schedule A) or afatinib 70 mg Days 2–6 (Schedule B)
- CTCAE DLTs were experienced by a low number of patients in Cycle 1: two patients in Schedule A and three patients in Schedule B (Table 2)

Table 2. Dose cohorts and occurrence of DLTs in Cycle 1 (MTD evaluable patients)

Dose cohorts	Dose level/dose	Number of patients with DLT (%)	DLTs in Cycle 1 (n of patients)
Volasertib + afatinib on Days 2–21 (Schedule A; N=15)	A1: 150 + 30 (n=3)	0	–
	A2: 225 + 30 (n=3)	0	–
	A3: 300 + 30 (n=6)	0	–
	A4: 300 + 40 (n=3)	2 (66.7)*	Diarrhea (2), infection (1), decreased ejection fraction (1)
Volasertib + afatinib on Days 2–6 (Schedule B; N=15)	B1: 300 + 50 (n=3)	0	–
	B2: 300 + 70 (n=6)	1 (16.7)	Diarrhea (1)
	B3: 300 + 90 (n=6)	2 (33.3)*	Neutropenia (2), thrombocytopenia (2), diarrhea (1), nausea (1), neutropenic infection (1)

*Some patients had more than one DLT
DLT, dose-limiting toxicity

Overall Safety

- For all patients treated and across all treatment cycles, the most common DLTs in Schedule A were: diarrhea (5 patients), neutropenia (3 patients), fatigue (2 patients) and decreased ejection fraction (2 patients), and in Schedule B were: thrombocytopenia (6 patients), neutropenia (5 patients), diarrhea (4 patients) and febrile neutropenia (3 patients)
- Grade 3/4 AEs that occurred in ≥2 patients (7%) of patients in either Schedule A or B during all cycles are listed in Table 3
  - across all treatment cycles, there was a similar number of grade 3/4 AEs in Schedules A and B
  - most common grade 3/4 AEs were neutropenia, thrombocytopenia, diarrhea and hypokalemia
- Serious AEs occurred in 13 patients (44.8%) in Schedule A and in 16 patients (57.1%) in Schedule B
- Five deaths (grade 5 AEs) during treatment were reported: two in Schedule A (volasertib 300 mg + afatinib 30 mg) and three in Schedule B (two [volasertib 300 mg + afatinib 70 mg] and one [volasertib 300 mg + afatinib 90 mg]); these were attributable to progressive disease (PD) and were not considered to be related to drug treatment as judged by the investigator

Table 3. Frequency of patients with highest CTCAE grade 3/4 AEs occurring in ≥2 patients (7%) of all patients who received volasertib and afatinib in Schedules A and B

	Volasertib + afatinib (30–50 mg) Days 2–21 (Schedule A; N=29)		Volasertib + afatinib (50–90 mg) Days 2–6 (Schedule B; N=28)	
	Grade 3/4 AEs	All AEs	Grade 3/4 AEs	All AEs
Total number of AEs, n (%)	16 (55)	29 (100)	16 (57)	28 (100)
AE by preferred term, n (%)*				
Neutropenia	9 (31)	10 (35)	11 (39)	13 (46)
Thrombocytopenia	3 (10)	8 (28)	10 (36)	14 (50)
Hypokalemia	1 (3)	1 (3)	4 (14)	5 (18)
Nausea	0	13 (45)	3 (11)	13 (46)
Febrile neutropenia	0	0	3 (11)	3 (11)
Anemia	2 (7)	10 (35)	2 (7)	14 (50)
Dyspnea	1 (3)	4 (14)	2 (7)	6 (21)
Mucosal inflammation	0	7 (24)	2 (7)	4 (14)
Metastases to central nervous system	0	1 (3)	2 (7)	2 (7)
Diarrhea	4 (14)	22 (76)	1 (4)	24 (86)
Fatigue	2 (7)	19 (66)	1 (4)	18 (64)
Cholangitis	0	0	2 (7)	2 (7)
Leukopenia	0	0	2 (7)	2 (7)
Sepsis	0	0	2 (7)	2 (7)

*Ordered by greatest frequency of grade 3/4 AEs in schedule where greater number of AEs occurred (Schedule B)
AE, adverse event

Anti-tumor activity

- Two patients treated in schedule A achieved a PR as best overall response (BOR), one with NSCLC (volasertib 150 mg/afatinib 30 mg) and one with cancer of the tongue (volasertib 300 mg/afatinib 30 mg)
  - Patient 3200201 (NSCLC) received 18 cycles of study treatment after progression following adjuvant cisplatin/paclitaxel/docetaxel/vinorelbine, palliative carboplatin/pemetrexed (BOR = stable disease [SD]) and erlotinib (BOR = PD) and failure of docetaxel due to toxicity. PR on study was observed after cycle 6 (dose escalated to volasertib 300 mg/afatinib 30 mg)
  - Patient 3200106 (cancer of the tongue) received 10 cycles of study treatment after progression following adjuvant chemoradiation and palliative cisplatin/cetuximab plus cetuximab maintenance (BOR= SD). PR on study was observed after cycle 2 (300 mg/afatinib 30 mg)

Table 4. Response assessment

	Volasertib + afatinib (30–50 mg) Days 2–21 (Schedule A; N=29)	Volasertib + afatinib (50–90 mg) Days 2–6 (Schedule B; N=28)
Best overall response		
PR	2 (6.9)	0
SD	8 (27.6)	8 (28.6)
PD	16 (55.2)	16 (57.1)
Not evaluable/unknown	3 (10.3)	4 (14.3)
Median duration of PR, days (min, max)	224.0 (189, 259)	N/A
Median duration of disease control (PR or SD), days (min, max)	143.0 (85, 387)	150.5 (65, 246)

Efficacy data reported here are based on best overall response
PR, partial response; SD, stable disease; PD, progressive disease; N/A, not available

Pharmacokinetics

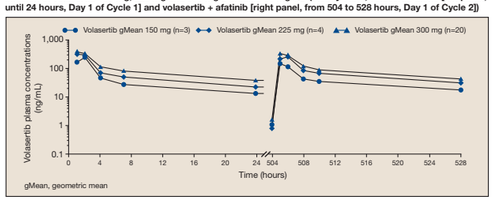
- Volasertib PK characteristics were comparable between patients receiving volasertib + afatinib versus volasertib alone (Figure 1). Geometric mean (gMean) and geometric coefficient of variation (gCV%) PK parameters of volasertib are presented in Table 5
- Volasertib exhibited multi-exponential PK behavior with a long half-life (130 hours), moderate clearance (900 mL/min) and large volume of distribution (Vss >6,000 L)
- Afatinib PK characteristics and parameters were comparable between patients receiving afatinib + volasertib versus afatinib alone. Intra-individual comparison plots of the PK parameter, $AUC_{tau,ss}$ is presented in Figure 2

Table 5. Comparison of non-compartmental PK parameters (gMean and gCV%) of volasertib following administration of a 2-hour iv infusion of volasertib 150 mg, 225 mg and 300 mg ± afatinib 30 mg QD dosed (steady state; dose group pooled)

	Cycle 1 of Schedule A and B Volasertib alone			Cycle 2 of Schedule A Volasertib + afatinib		
Volasertib	N	gMean	gCV%	N	gMean	gCV%
$AUC_{0-24,ND1}$ (ng•h/mL/mg)	41	7.74	31.7	15	6.93	27.7
$C_{max,ND1}$ (ng/mL/mg)	55	1.44	38.3	25	1.17	35.3

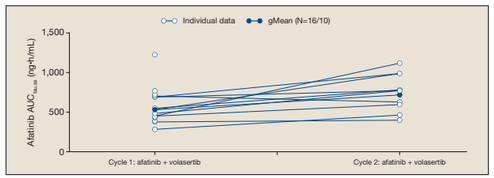
gMean, geometric mean; gCV%, geometric coefficient of variation; $AUC_{0-24h,ND1}$, dose normalized area under the curve from zero to 24 hours; $C_{max,ND1}$, dose normalized maximum plasma concentration

Figure 1. gMean drug plasma concentration-time profiles of volasertib following administration of 2-hour iv infusion of volasertib 150 mg, 225 mg and 300 mg ± afatinib 30 mg QD (steady state; volasertib alone [left panel, until 24 hours, Day 1 of Cycle 1] and volasertib + afatinib [right panel, from 504 to 528 hours, Day 1 of Cycle 2])



gMean, geometric mean

Figure 2. Comparison of intra-individual and gMean $AUC_{tau,ss}$ values of afatinib after oral administration of 30 mg QD afatinib after (Cycle 1) and before (Cycle 2) 2-hour iv infusion of volasertib 300 mg in Schedule A



CONCLUSIONS

- The MTD for the combination was determined as:
  - Schedule A: volasertib 300 mg (Day 1) + afatinib 30 mg (Days 2–21)
  - Schedule B: volasertib 300 mg (Day 1) + afatinib 70 mg (Days 2–6)
- At the MTD, combination treatment with volasertib and afatinib was manageable in both schedules in patients with advanced or metastatic solid tumors
- Overall, there was a similar number of grade 3/4 AEs in Schedules A and B. The most frequently reported grade 3/4 AEs were neutropenia, thrombocytopenia, diarrhea and hypokalemia
- The observed safety profile in this study was comparable to the combination of the specific drug-related AEs of each drug and specific AEs were not aggravated when the two drugs were combined at previously shown active single-agent doses
- Two patients treated in Schedule A for more than 6 months (one with NSCLC, and one with head and neck cancer) achieved a PR after previously progressing following two lines and one line of palliative treatments for metastatic disease, respectively. None of the patients (including the NSCLC patient with the PR) whose tumor was tested in this study had an EGFR mutation (among the 29 mutations tested that included L858R and exon 19 deletion mutations)
- Based on the limited data available and considering the variability observed, volasertib and afatinib coadministration had no significant effect on the PK characteristics of either agent
- Findings from this Phase I study suggest that this combination may be feasible; however, further studies would be required to study the potential effectiveness of this combination. Furthermore, the identification of biomarkers could help select patients who would be most likely to benefit

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DISCLOSURES

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