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A phase I, dose-escalation study of volasertib combined with nintedanib in advanced solid tumors

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Background: Volasertib is a potent and selective cell-cycle kinase inhibitor that induces mitotic arrest and apoptosis by targeting Polo-like kinases. This study determined the maximum tolerated dose (MTD) and pharmacokinetics of volasertib combined with nintedanib, a potent and orally bioavailable triple angiokinase inhibitor, in patients with advanced solid tumors.

Patients and methods: This open-label, dose-escalation trial recruited patients with advanced metastatic solid tumors following failure of conventional treatment (NCT01022853; Study 1230.7). Volasertib was administered by intravenous infusion over 2 h, starting at 100 mg in the first dose cohort. Nintedanib was administered orally at a dose of 200 mg twice daily. The first treatment cycle comprised 28 days (days 1–7 and days 9–28: nintedanib; day 8: volasertib). From cycle 2 onwards, volasertib was administered on day 1 of a 21-day cycle and nintedanib was administered days 2–21. The primary objective was the MTD of volasertib in combination with nintedanib.

Results: Thirty patients were treated. The MTD of volasertib plus fixed-dose nintedanib was 300 mg once every 3 weeks, the same as the recommended single-agent dose of volasertib in solid tumors. Two of 12 assessable patients treated with the MTD experienced dose-limiting toxicities [grade 3 increased alanine aminotransferase (ALT); grade 3 ALT increase and grade 3 increased aspartate aminotransferase]. Disease control [stable disease (SD)/partial response (PR)/complete response (CR)] was achieved in 18 patients (60%): 1 CR (breast cancer), 1 PR (nonsmall-cell lung cancer), and 16 patients with SD. Volasertib showed that multiexponential pharmacokinetic behavior and co-administration of nintedanib had no significant effects on its exposure.

Conclusions: Volasertib could be combined with fixed-dose nintedanib at the recommended single-agent dose. At this dose, the combination had a manageable safety profile without unexpected or overlapping adverse events, and showed antitumor activity.

Key words: advanced cancer, volasertib, nintedanib, Plk1, angiogenesis, phase I trial

introduction

Members of the Polo-like kinase (Plk) family are key regulators of cell mitosis [1]. Plk1, the best characterized family member, is known to regulate various mitotic processes [2]. Various human tumors overexpress Plk1 [3] and its functional relevance in cancer was shown in experiments in which Plk1 depletion reduced cell proliferation and induced cell-cycle arrest and apoptosis in cancer cell lines [4, 5]. Volasertib is a highly potent and selective inhibitor of Plk that inhibits proliferation and induces mitotic arrest and apoptosis [6]. The efficacy of volasertib has been demonstrated in various tumor models [6], and phase I trials in solid tumors have shown favorable pharmacokinetics and manageable toxicity [7, 8]. Disease control rates of 45% [including three partial responses (PR) in 65 assessable patients] [8] and 47% (including two PRs in 59 assessable patients) [7] were observed.

Proangiogenic factors such as platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and basic fibroblast growth factor (bFGF) have been implicated in tumor angiogenesis [9], a process essential for invasive growth and metastasis [10]. Nintedanib is a potent and orally bioavailable triple angiokinase inhibitor of PDGF, VEGF, and bFGF receptors [11].

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In addition, nintedanib inhibits FLT3, RET, and members of the Src family. Clinical trials of nintedanib have demonstrated antitumor activity and a generally manageable safety profile as a monotherapy in patients with various solid tumors and in combination with cytotoxic chemotherapy in two phase III studies in advanced nonsmall-cell lung cancer (NSCLC) [12, 13] and a phase III study in advanced ovarian cancer [14]. One complete response (CR) and two PRs were observed with nintedanib monotherapy in a phase I trial [15].

Combined administration of multiple drugs, an approach long adopted with traditional anticancer agents, is now under evaluation with targeted therapies [16]. This strategy is based on the hypothesis that combination therapy using agents with different mechanisms of action, such as an antimitotic (volasertib) and an angiokinase inhibitor (nintedanib), would be more effective than single-agent therapy. Here we report the first clinical trial designed to determine the maximum tolerated dose (MTD), safety, and pharmacokinetics of volasertib combined with fixed-dose nintedanib in patients with advanced solid tumors resistant or refractory to standard therapy.

patients and methods

patients

Eligible patients had a confirmed diagnosis of advanced, metastatic solid tumors following failure of conventional treatment, for whom no therapy of proven efficacy existed or who were not amenable to established forms of treatment. Full eligibility criteria are provided in supplementary Patients and Methods, available at *Annals of Oncology* online. All patients provided written informed consent.

study design

This was an open-label, phase I, dose-escalation trial, conducted at two sites in Italy between January 2010 and February 2013 (EudraCT number: 2008-008304-41; ClinicalTrials.gov identifier: NCT01022853; Study 1230.7). Cohorts of patients were sequentially allocated to different volasertib doses. Volasertib was administered once every 3 weeks (q3w) by intravenous infusion over 2 h, starting at 100 mg in the first cohort and escalated in four dose steps (200, 300, 350, and 400 mg). Nintedanib was administered orally at a dose of 200 mg twice daily (b.i.d.) on non-volasertib infusion days. This nintedanib dose is currently being evaluated in phase III trials and was selected based on the findings of phase I/II studies [15, 17, 18]. Nintedanib treatment was started 7 days before treatment with volasertib to induce nintedanib steady-state levels at the time of first volasertib administration. Administration of nintedanib was skipped on the days that volasertib was administered based on the schedule of nintedanib combined with other agents in phase III trials [12, 13]. The first cycle comprised 28 days: days 1–7 and 9–28, nintedanib b.i.d.; day 8, volasertib. From cycle 2 onwards, volasertib was administered on day 1 of a 21-day cycle and nintedanib was administered b.i.d. days 2–21. Dose escalation of volasertib followed a traditional '3 + 3' design. An expansion cohort of additional patients treated at the MTD was planned to provide additional safety data. A dose-reduction scheme allowed for treatment modification in case of a prespecified adverse event (AE) or dose-limiting toxicity (DLT). If the treatment was tolerable, patients received additional therapy cycles until clinical progression.

study objectives

The primary objective was the MTD of volasertib q3w combined with continuous nintedanib 200 mg b.i.d. Secondary objectives were: incidence and intensity of drug-related AEs; incidence of DLTs; pharmacokinetics of volasertib and nintedanib; tumor response, and progression-free survival (PFS).

assessments

MTD and DLTs. MTD was defined as the highest dose at which no more than one of six patients experienced a DLT during or after volasertib administration between days 8 and 21 of the first cycle. The replacement criteria for patients non-assessable for the MTD analysis are listed in supplementary Patients and Methods, available at *Annals of Oncology* online. DLTs were defined as: drug-related Common Terminology Criteria for Adverse Events (CTCAE) grade 3/4 nonhematologic AEs (except untreated vomiting, nausea, or diarrhea); drug-related CTCAE grade 4 neutropenia for ≥7 days and/or complicated by infection; and CTCAE grade 4 thrombocytopenia. All DLTs during all treatment cycles were considered when selecting a volasertib dose to be used for further development in combination with nintedanib.

safety. All AEs that occurred during treatment or within 28 days after last administration of study medication were recorded. AE incidence and intensity were graded according to National Cancer Institute (NCI) CTCAE v3.0 [19]. AEs were classified according to relationship to study medication; however, no systematic attribution of AEs to either volasertib or nintedanib was carried out. Other safety measures are listed in supplementary Patients and Methods, available at *Annals of Oncology* online.

pharmacokinetics. Plasma concentrations of volasertib and its major metabolite CD 10899 were obtained on days 8 (before and after volasertib infusion), 9, 10, 15, and 22 of the first treatment cycle (11 time points), and on day 1 of the second cycle. Plasma concentrations of nintedanib were obtained on days 8, 9, and 10 of the first treatment cycle and on day 1 of the second cycle. Samples were analyzed by validated high-performance liquid chromatography, tandem mass spectrometry assay in the laboratory of Boehringer Ingelheim Pharma GmbH & Co. KG (Biberach, Germany).

efficacy. Clinical tumor assessment was carried out at baseline and after every other treatment cycle using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 [20]. Time from start of treatment to time of progression or death (PFS) was determined for each patient.

statistics

Patients who were replaced during the first treatment course were not considered for determination of the MTD. All treated patients were included in the safety and efficacy analysis. All evaluable subjects who received at least one dose of volasertib and nintedanib and provided at least one valid plasma concentration value were included in the pharmacokinetic (PK) analysis. SAS® v9.2 (SAS Institute, Inc., Cary, NC, USA) was used for all statistical analyses. Details of statistical analyses, including sample size calculation and reasons for replacement of patients, are provided in supplementary Patients and Methods, available at *Annals of Oncology* online.

results

patients

Forty-three patients were enrolled and 30 patients were treated (see supplementary Results for Patient Disposition, available at *Annals of Oncology* online). Median age was 56.5 years (Table 1). Most patients (60%) had Eastern Cooperative Oncology Group performance status (ECOG PS) 1; 87% had received ≥3 prior chemotherapies. The most common tumor type was colorectal cancer (33%). All patients presented with metastases. Median (range)

Table 1. Patient demographics and disease characteristics

	Nintedanib 200 mg + volasertib					All patients ($N = 30$)
	100 mg ($N = 3$)	200 mg ($N = 4$)	300 mg ($N = 13$)	350 mg ($N = 8$)	400 mg ($N = 2$)	
Median age, years (min, max)	51.0 (45, 63)	57.5 (55, 70)	57.0 (40, 74)	52.5 (33, 69)	59.0 (55, 63)	56.5 (33, 74)
Male/female, *n* (%)	2/1 (67/33)	3/1 (75/25)	6/7 (46/54)	6/2 (75/25)	1/1 (50/50)	18/12 (60/40)
ECOG performance status, *n* (%)						
0	0	2 (50)	5 (39)	2 (25)	1 (50)	10 (33)
1	3 (100)	2 (50)	7 (54)	5 (63)	1 (50)	18 (60)
2	0	0	1 (8)	1 (13)	0	2 (7)
Metastases at screening, *n* (%)	3 (100)	4 (100)	13 (100)	8 (100)	2 (100)	30 (100)
Tumor type, *n* (%)						
Head/neck	0	0	2 (15)	0	0	2 (7)
NSCLC	0	1 (25)	3 (23)	1 (13)	0	5 (17)
Mediastinum	0	0	2 (15)	2 (25)	0	4 (13)
Colorectal	1 (33)	2 (50)	3 (23)	2 (25)	2 (100)	10 (33)
Kidney	0	1 (25)	0	1 (13)	0	2 (7)
Breast	0	0	2 (15)	0	0	2 (7)
Other[a]	2 (67)	0	1 (8)	2 (25)	0	5 (17)
Previous anticancer therapy, *n* (%)						
Surgery	3 (100)	4 (100)	12 (92)	6 (75)	2 (100)	27 (90)
Chemotherapy	3 (100)	4 (100)	13 (100)	8 (100)	2 (100)	30 (100)
2 lines	2 (67)	1 (25)	0	1 (13)	0	4 (13)
≥3 lines	1 (33)	3 (75)	13 (100)	7 (88)	2 (100)	26 (87)
Radiotherapy	3 (100)	2 (50)	4 (31)	6 (75)	0	15 (50)

Some groups may add up to more or less than 100% due to rounding of percentages.
[a]Includes soft tissue sarcoma, pancreas, bladder, urethra/penis, and pleura ($n = 1$ for each tumor type).
ECOG, Eastern Cooperative Oncology Group; NSCLC, nonsmall-cell lung cancer.

duration on treatment was four (1–18) cycles. Treatment was discontinued due to progressive disease (80%), DLTs (3%), or other reasons (17%).

determination of maximum tolerated dose

No DLTs were observed in the 100 mg ($n = 3$), 200 mg ($n = 4$; one patient was non-assessable due to an incorrect nintedanib dose in week 1 of cycle 1), 300 mg ($n = 3$), and 350 mg cohorts ($n = 4$; one patient was non-assessable as laboratory examinations were not carried out per protocol). Two patients were treated with 400 mg volasertib and both experienced DLTs [grade 4 thrombocytopenia (duration: 11 days), $n = 1$; grade 4 thrombocytopenia (21 days) and grade 4 febrile neutropenia (3 days), $n = 1$]. Four additional patients then enrolled to the de-escalated dose of 350 mg volasertib (one patient did not receive volasertib and was non-assessable). Of the three assessable patients, two experienced DLTs [grade 4 neutropenia (15 days) and grade 4 thrombocytopenia (17 days), $n = 1$; grade 4 neutropenia (9 days) and grade 3 alanine aminotransferase (ALT) increase (15 days), $n = 1$]. As the number of acceptable DLTs was exceeded again at 350 mg (2/6), three additional patients were treated with de-escalated 300 mg volasertib without experiencing DLTs. As no DLTs occurred in the six patients treated with 300 mg during the dose-escalation period, the MTD of volasertib combined with nintedanib was established as 300 mg. Another seven patients were treated with 300 mg volasertib in an extension cohort, of which six were assessable (one was excluded as a result of a protocol violation due to receiving granulocyte-colony stimulating factor for nonlife-threatening grade 4 neutropenia); two experienced DLTs during the first course [grade 3 ALT increase (11 days), $n = 1$; grade 3 ALT increase and grade 3 aspartate aminotransferase (AST) increase (7 days each), $n = 1$]. Therefore, the overall incidence of DLTs in the 300 mg cohort occurring during the first treatment course was 2 of 12 patients and the MTD was confirmed as 300 mg.

safety

Over all cycles, drug-related AEs were reported in 90% of patients (Table 2) and serious AEs occurred in 27%. Overall, 47% of patients experienced AEs that led to a reduction in either the volasertib and/or nintedanib dose, and 17% experienced AEs that led to discontinuation [due to progression of cancer, hematological abnormalities (neutropenia, thrombocytopenia), and hypertension in the volasertib 300 mg group ($n = 2$); progression of cancer in the 350 mg group ($n = 1$); and hematologic abnormalities (febrile neutropenia, leukopenia, neutropenia, thrombocytopenia) and dyspnea in the 400 mg group ($n = 1$)]. Drug-related AEs reported in ≥6 patients (20%) are listed in supplementary Table S1, available at *Annals of Oncology* online. Of 13 patients treated with the MTD (300 mg; includes 1 patient non-assessable for MTD determination), the most common all grade, drug-related AEs were neutropenia (69%), diarrhea and thrombocytopenia (62% each), and increased ALT and AST (54% each). The most common grade 3/4 drug-related AEs were neutropenia (50%), thrombocytopenia (30%), increased ALT (23%), and increased AST (17%). Two patients died during treatment (one each in the 300 and 350 mg cohorts); both

Table 2. Summary of adverse events

	Nintedanib 200 mg + volasertib					All patients ($N = 30$)
	100 mg ($N = 3$)	200 mg ($N = 4$)	300 mg ($N = 13$)	350 mg ($N = 8$)	400 mg ($N = 2$)	
Any AE, *n* (%)	3 (100)	4 (100)	13 (100)	8 (100)	2 (100)	30 (100)
Maximum CTCAE grade						
1	0	0	1 (8)	0	0	1 (3)
2	3 (100)	1 (25)	0	1 (13)	0	5 (17)
3	0	3 (75)	9 (69)	4 (50)	0	16 (53)
4	0	0	2 (15)	2 (25)	2 (100)	6 (20)
5	0	0	1 (8)	1 (13)	0	2 (7)
Any drug-related AE, *n* (%)	3 (100)	3 (75)	12 (92)	7 (88)	2 (100)	27 (90)
Any AE leading to discontinuation of study medication, *n* (%)	0	0	2 (15)	1 (13)	2 (100)	5 (17)
Any AE leading to reduction of study medication dose, *n* (%)	0	1 (25)	8 (62)	4 (50)	1 (50)	14 (47)
Any SAE, *n* (%)	0	0	5 (39)	2 (25)	1 (50)	8 (27)

Some groups may add up to more or <100% due to rounding of percentages.
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events (v3.0); SAE, serious adverse event.

Table 3. Noncompartmental pharmacokinetic parameters of volasertib (100–350 mg) after 2 h intravenous infusion on day 8 of cycle 1

Pharmacokinetic parameter, volasertib gMean (gCV%)	Volasertib + nintedanib 200 mg			
	100 mg ($N = 3$)	200 mg ($N = 4$)	300 mg ($N = 12$)	350 mg ($N = 6$)
$C_{max,norm}$ (ng/ml)	1.64 (77.6)	2.05 (23.3)	1.77 (33.3)	1.52 (25.5)
$AUC_{0-504,norm}$ (ng·h/ml/mg)	21.9 (20.3)	23.0 (3.77)	19.9 (33.5)	20.6 (33.9)
CL (ml/min)	720 (19.3)	685 (4.22)	792 (34.2)	849 (29.3)
V_{ss} (l)	5710 (39.9)	5590 (6.53)	5010 (34.7)	6080 (21.2)
$t_{1/2}$ (h)	143 (10.9)	142 (12.2)	124 (27.3)	127 (26.2)
$RAUC_{0-\infty,CD10899/volasertib}$	21.3 (19.5)	16.4 (39.2)	16.8 (45.9)	17.6 (31.4)

Evaluations were carried out using WinNonlin™ Professional (Pharsight® Co., v5.2) software.
$AUC_{0-504,norm}$, dose-normalized area under the plasma concentration–time curve from time 0 to 504 h; CL, total plasma clearance; $C_{max,norm}$, dose-normalized maximum plasma concentration; gCV, geometric coefficient of variance; gMean, geometric mean; $RAUC_{0-\infty,CD10899/volasertib}$, ratio of the area under the plasma concentration–time curve from time zero to infinity (metabolite/volasertib); $t_{1/2}$, terminal half-life; V_{ss}, volume of distribution at steady state.

deaths were due to progressive disease and were not considered drug-related.

Laboratory examinations reflected the AE profile such that most patients with possibly clinically significant abnormalities had transaminase elevations and/or changes in hematologic parameters. No clinically meaningful changes in vital signs or ECOG PS status were reported. Electrocardiogram analyses showed transient Fridericia corrected QT interval (QTcF), Bazett corrected QT interval, and QT prolongations which peaked at or shortly after the end of the volasertib infusion and returned to baseline levels within 24 h. An outlier analysis identified one patient with a notable finding (QT interval >500 ms at 2-h time point); the patient's QT interval recovered immediately at the next measured time point.

pharmacokinetics

Volasertib exhibited multiexponential PK behavior with fast distribution after the end of infusion, followed by slower elimination phases; the major metabolite CD 10899 showed similar PK behavior (supplementary Figure S3, available at *Annals of Oncology* online). Volasertib had a long half-life (124–143 h), a moderate clearance (685–849 ml/min), and a large volume of distribution (>5000 l); there were no significant deviations from dose proportionality with respect to the maximum plasma concentration or area under the concentration–time curve (Table 3). CD 10899 exposure was ~16%–21% of the volasertib exposure (Table 3).

Maximum plasma concentrations of nintedanib occurred within 2–3 h after oral administration, steady-state plasma concentration was achieved after 7 days of continuous oral administration of 200 mg b.i.d. Per protocol, nintedanib 200 mg b.i.d. was not administered on the day of the volasertib infusion; nintedanib steady state was achieved again 1 day after the restart of its administration and maintained for the rest of the treatment course. The shape of the nintedanib concentration time profiles were similar across cohorts, although exposure to nintedanib increased (see supplementary

Table S2, available at *Annals of Oncology* online, for nintedanib PK parameters).

efficacy

A best overall response of CR was observed in one patient (moderately differentiated ductal infiltrating breast carcinoma) and a PR was observed in one patient with NSCLC (bronchioloalveolar adenocarcinoma with KRAS mutation) [see supplementary Figure S1, available at *Annals of Oncology* online, for computerized tomography (CT) scans]. Both patients received 300 mg volasertib plus nintedanib and had PFS of 447 and 267 days, respectively. Stable disease (SD) was reported in an additional 16 patients. Disease control (SD/PR/CR) was observed in 18 patients (60%) with a median duration of 161.5 days (range, 56–512 days). The duration of disease control is shown in supplementary Figure S2, available at *Annals of Oncology* online.

discussion

This first clinical study of volasertib in combination with nintedanib demonstrates that this combination was generally well tolerated by patients with advanced solid malignancies resistant or refractory to standard therapy. The MTD of volasertib combined with 200 mg nintedanib b.i.d. was established as 300 mg volasertib q3w, the same dose recommended for single-agent treatment of solid tumors [8]. The incidence of hematological DLTs at volasertib doses >300 mg was consistent with comparable phase I dose-escalation studies [7, 8]. Transaminase elevations are known AEs with nintedanib; however, phase I/II studies suggested a dose threshold of >200 mg nintedanib b.i.d. for increased incidences of transaminase elevations. In this study, the incidences of transaminase elevations classified as DLTs at 200 mg nintedanib b.i.d. indicated a greater impact by the addition of volasertib.

Observed hematologic AEs are consistent with the actions of volasertib on the cell cycle and with previous studies [7, 8]. Overall reported AEs of the combination were consistent with the known safety profiles of both volasertib and nintedanib. Antitumor activity was observed with two patients achieving an objective response with treatment at the MTD and SD was observed in a total of 16 patients across all dose cohorts. The disease control rate was 60.0% and seven patients maintained disease control ≥6 months. The disease control rate observed in this study is higher than in comparable volasertib phase I dose-escalation studies [7, 8] and consistent with similar phase I trials investigating angiogenetic inhibitors in combination with chemotherapy in patients with solid tumors [21, 22]. These studies contribute to our understanding of oncogenesis and support Plk and angiogenesis as valid therapeutic targets in cancer. Given the phase I design, this study is of limited value in defining the patient population that would benefit from this combination in future clinical studies. However, given the wide antitumor activity (response or significant disease stabilization) observed in this heavily pretreated patient population, further clinical investigation of combination volasertib and nintedanib is warranted.

Systemic exposure and PK characteristics of volasertib and CD 10899 were similar to those observed in earlier studies of volasertib monotherapy in solid tumors [7, 8], suggesting that nintedanib has no influence on the PK characteristics and metabolism of volasertib. The PK concentration–time profile of nintedanib was also similar to that observed in previous studies with nintedanib monotherapy [15, 18]. Given the large variability in exposure, it can be suggested that the exposure to the nintedanib metabolites BIBF 1202 and BIBF 1202-glucuronide was similar across volasertib dose cohorts, and co-administration of volasertib did not appear to affect nintedanib metabolism. However, slight increases in nintedanib exposure were observed as the dose of volasertib was increased. As volasertib is an inhibitor of the efflux transporter P-glycoprotein (P-gp) and nintedanib is a P-gp substrate, this effect may be explained by the inhibitory effect of volasertib on the P-gp-mediated efflux in the gut following oral administration of nintedanib. In general, however, the individual variability of the PK data for nintedanib and its metabolites was high and, therefore, the data regarding the influence of volasertib on nintedanib pharmacokinetics and metabolism should be interpreted with caution.

In conclusion, this study established that, in patients with solid tumors, volasertib can be combined with fixed-dose nintedanib at the recommended single-agent dose of volasertib. At this dose, the safety profile of combination treatment is manageable and in line with the known safety profiles of the individual drugs and the combination may be feasible in patients with solid tumors based on the very good compliance and the long-lasting disease stabilization observed in this study. The identification of biomarkers predictive of response will be critical for the further development of this therapy in patients with advanced solid tumors.

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disclosure

FDB received honoraria from GlaxoSmithKline, MSD, Novartis Oncology, Amgen, and Bristol Myers Squibb. SC was a compensated consultant for Celgene and Lilly, and received honoraria from Roche, Amgen, and Merck. KP was a compensated employee of Boehringer Ingelheim Pharma GmbH & Co. KG at the time of execution and analyses of the study. LC is a compensated employee of Boehringer Ingelheim. DL and PS are compensated employees of Boehringer Ingelheim Pharma and Co. KG. All remaining authors have declared no conflicts of interest.

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