Targeted therapy in oncology: mechanisms and toxicity

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A phase I dose escalation study of telatinib (BAY 57-9352), a tyrosine kinase inhibitor of VEGFR-2, VEGFR-3, PDGFR-β and c-Kit, in patients with advanced or metastatic solid tumors

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Abstract

Purpose

Telatinib (BAY 57-9352) is an orally available tyrosine kinase inhibitor of VEGFR-2, VEGFR-3, PDGFR-β, and c-Kit. This phase I dose escalation study was conducted to evaluate the safety and tolerability of telatinib, with additional pharmacokinetic, pharmacodynamic and efficacy assessments.

Patients and methods

Patients with solid tumors refractory to standard therapies or with no standard therapy available were enrolled. Doses of continuously administered telatinib were escalated from 20 mg od to 1500 mg bid.

Results

Fifty-three patients were enrolled. Most frequently observed drug-related adverse events were nausea (26.4%, grade ≥3: 0%) and hypertension (20.8%, grade 3: 11.3%, grade 4: 0%). Two DLTs were observed: one poorly controlled hypertension (600 mg bid), and one grade 2 weight loss, anorexia, and fatigue (1500 mg bid). A formal MTD was not reached. Telatinib was rapidly absorbed, with median t_{max} <3 hours post-dose. Nearly dose proportional increase in exposure was observed with substantial variability. Telatinib half-life averaged 5.5 hours. Biomarker analyses showed dose-dependent increase in VEGF levels and decrease in sVEGFR-2 levels, with a plateau at 900 mg bid. A decrease in tumor blood flow (K_{trans} and $IAUC_{60}$) was observed with DCE-MRI. Best tumor response was stable disease, observed in 50.9% of patients.

Conclusions

Telatinib was safe and well tolerated up to 1500 mg bid. Based upon pharmacodynamic and pharmacokinetic endpoints, telatinib 900 mg bid is the recommended dose for subsequent phase II studies.

Introduction

The vascular endothelial growth factor (VEGF) and its receptors (VEGFRs) play a pivotal role in tumor-related angiogenesis, and the VEGF/VEGFR pathway is an important target for anti-angiogenic drug development and tumor therapy.[1-8]

Telatinib (BAY 57-9352) is an orally available, potent inhibitor of VEGFR-2, VEGFR-3, platelet-derived growth factor receptor (PDGFR-β), and c-Kit tyrosine kinases. Telatinib inhibits VEGFR-2 autophosphorylation in a whole-cell assay of receptor autophosphorylation with an IC_{50} of 19 nM. Telatinib also inhibits VEGF-dependent proliferation of human umbilical vein endothelial cells (HUVECs) with an IC_{50} of 26 nM and PDGF-stimulated growth of human aortic smooth muscle cells with an IC_{50} of 249 nM. Telatinib demonstrates anti-tumor activity in various cancer models. Formation of the N-glucuronides of telatinib is identified as the major biotransformation pathway in man. Telatinib is metabolized by various CYP isoforms and UGT1A4.[9,10]

We performed a phase I, pharmacological, and biomarker study of telatinib. Objectives were to (1) determine maximum tolerated dose (MTD) and define dose-limiting toxicities (DLT), (2) characterize safety, (3) pharmacokinetics, and (4) biomarkers of biological activity, including serum markers and dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) results, and (5) evaluate anti tumor activity.

Patients and Methods

Eligibility criteria

Patients with histologically or cytologically confirmed advanced or metastatic solid tumors for whom no standard therapy was available, with an Eastern Cooperative Oncology Group (ECOG) performance status ≤2 were eligible. Other inclusion criteria were: evaluable or measurable disease by RECIST; age ≥18 years; life expectancy ≥12 weeks; adequate bone marrow, liver, and renal function (hemoglobin ≥9.0 g/dl; absolute neutrophil count ≥1,500/mm^3; platelet count ≥100,000/mm^3; total bilirubin ≤1.5x the upper limit of normal (ULN); alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5x ULN, (liver metastases AST/ALT <5x ULN); alkaline phosphatase ≤ 4x ULN; PT-INR and PTT <1.5x ULN; serum creatinine ≤1.5x ULN). Exclusion criteria were: history of cardiac disease; HIV, hepatitis B or C infection; active infection; serious non-healing wound, ulcer, or bone fracture; symptomatic metastatic brain or meningeal tumors unless >6 months from definitive therapy without evidence of tumor growth, and clinically stable; seizure disorder requiring anticonvulsant medication; history of organ allograft; pregnancy or breast-feeding; history of any condition that could endanger the safety of

the patient; anticancer treatment <4 weeks before the first dose; previous anti-angiogenic therapies/VEGFR-2 inhibitors.

Written informed consent from all patients and approval from the institutional review boards was obtained.

Drug Administration and Dose Escalation Procedure

Telatinib was administered orally, once daily (od) or twice daily (bid), on a continuous basis. Based upon toxicological data, pharmacokinetic data, and a parallel phase I study with telatinib administered in a "14 days on / 7 days off" schedule, the starting dose was 20 mg od. The formulations used in this study were: solution formulation (20 mg od cohort), 25 mg telatinib mesylate tablet formulation (75 mg od cohort), and 150 mg telatinib mesylate tablet formulation (bid dosing cohorts). For the purpose of analysis, one cycle was defined as 21 days of administration.

Doses were doubled for subsequent cohorts if no drug-related toxicity in cycle 1 was observed. When DLT had been observed or following toxicity ≥grade 2 in ≥2 patients, subsequent dose increments were 33-66%.

DLT was defined as grade 4 neutropenia ≥7 days, febrile neutropenia, grade 4 thrombocytopenia, grade 3 thrombocytopenic bleeding, and any drug-related grade 3 or 4 non-hematological toxicity excluding alopecia, nausea and vomiting not refractory to anti-emetics, and hypertension not refractory to anti-hypertensive medication during the first cycle.

If DLT was observed in one patient, three additional patients were recruited at that dose level, with dose escalation proceeding if <2 of 6 patients exhibited DLT. Because pharmacokinetic results of the initial 2 cohorts showed significant inter patient variability, all subsequent cohorts were expanded to a minimum of six patients. If DLT was observed in ≥2 of 3 or ≥2 of 6 patients, the maximum-tolerated dose (MTD) had been exceeded, and additional patients were recruited at the next lower dose level. The MTD was defined as the highest dose level that could be given to 6 patients with <1 patient experiencing DLT. If a patient experienced a drug related DLT, telatinib was withheld for up to 3 weeks. If toxicity resolved to .grade 1, the dose of telatinib was reduced to the next lower dose level. Otherwise, the patient was withdrawn from the study. Administration of telatinib was continued until disease progression or unacceptable toxicity.

One additional cohort of 4 patients was enrolled (as part of a larger group in a companion study) to evaluate the bioavailability of a new 300 mg mesylate tablet formulation in comparison to the 150 mg mesylate tablet formulation. Patients received a single dose of 900 mg using the 300 mg tablet and continued with 150 mg tablets.

Pre-treatment Evaluation and Safety Assessment

Pre-treatment evaluation consisted of a complete medical history, physical examination, ECOG performance status assessment, vital signs, baseline 12 lead ECG, blood sample for complete blood count (CBC), coagulation analysis, biochemistry analysis, sample for urinalysis, serum pregnancy test, plasma and urine sampling for biomarkers, baseline tumor measurements, and DCE-MRI.

On days 1 and 14 of each cycle evaluation consisted of a brief history and physical examination, vital signs, blood samples for CBC, biochemistry, and coagulation analysis, urinalysis, 12-lead ECG. Response evaluation was performed every 2 cycles and was assessed according to RECIST.[11] Patients were evaluated weekly in the first cycle and every 1 or 2 weeks in additional cycles for adverse events and toxicity according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 3.0.

Pharmacokinetic Evaluation

Pharmacokinetic (PK) evaluation was performed by collecting blood samples on days 1 and 14 of cycle 1, and day 14 of cycles 2 and 4 via an indwelling intravenous catheter. In cycle 1, a 5 mL sample was collected pre-dose and at 0.5, 1, 2, 3, 4, 6, 8, 12 hours post-dose. An additional sample was collected at 24 hours post-dose for once daily regimen. In cycles 2 and 4, an abbreviated sampling schedule was used. Pharmacokinetic parameters C_{max}, t_{max}, $AUC_{0\text{-}tn}$, $AUC_{0\text{-}24}$ (for od regimen), $AUC_{0\text{-}12}$ (for bid regimen) and half-life for telatinib and its metabolite (BAY 60-8246) were calculated by non-compartmental analysis using WinNonlin (version 4.1.a).

Pharmacodynamic Analysis

Urine samples and 20 ml blood samples for pharmacodynamic (PD) analysis were collected at baseline, pre-dose and 8 hours post-dose on days 1 and 14 of cycles 1 and 2 and on day 1 of cycle 3, and pre-dose on day 1 of each subsequent cycle. The following parameters were measured: plasma soluble VEGFR-2 (sVEGFR-2), plasma VEGF, plasma basic fibroblast growth factor (bFGF), plasma IL-8, urinary VEGF. Samples were analyzed using the relevant quantitative enzyme linked immunosorbent assay (ELISA; R&D Systems Europe, Oxford, UK) according to the manufacturer's instructions.

DCE-MRI scans were performed at baseline, on day 2 of cycle 1, and on day 14 of cycles 2 and 3. We used a 1.5-T MR imaging system (Philips Medical Systems, Best, The Netherlands) using a body coil in retroperitoneal and abdominal lesions. . The tumors were localized using standard T1- and T2- fat-saturated fast spin echo sequences. Subsequently, dynamic MR imaging was performed using T1-weighted turbo field-

echo sequence with TR 5.4/TE 1.4, flip angle of 20°, nonselective inversion preparatory pulse, with delay time of 165 msec, and section thickness of 5–8 mm, with a temporal resolution, of 3 seconds during at least the first 84 seconds. Total acquisition time lasted 5 min. A power injector (Spectris; Medrad, Indianola, Pa) with injection flow rate of 2 mL/sec was used to start intravenous administration of gadopentetate dimeglumine (Magnevist, Bayer-Schering, Berlin, Germany), which was followed by a 20-mL saline flush. Bolus injection was initiated 5 seconds after the start of data acquisition.[12]

Assessed parameter was Ktrans, describing the volume transfer coefficient of contrast between blood plasma and the tumor. Empirical quantitative methods were used to quantify the signal-intensity time curve using the initial area under the contrast-agent concentration-time curve after 60 seconds ($iAUC_{60}$) and time to peak enhancement (TTPE; time period between arterial enhancement and the enhancement of the index lesions).[13,14] The second pre-contrast dynamic images were automatically subtracted from all dynamic contrast-enhanced MR images using software of the MR system.

Statistical analysis

Continuous variables are presented as mean values ± standard deviation and categorical variables as frequencies (percentages), unless otherwise stated. Comparison between variables at baseline and post-dose was performed with paired samples t-test or Wilcoxon signed rank test as appropriate. Correlations with drug exposure were assessed by Spearmans Rank correlation coefficient. All analyses were performed using SPSS version 12.01 (SPSS, Chicago, Ill, USA) and were two-sided, with a level of significance of $\alpha=0.05$.

Results

Between July 2004 and October 2006, 53 patients were enrolled. Patient characteristics are summarized in Table 1.

Safety and Tolerability

All treatment-related adverse events are summarized in Table 2. Most frequently reported treatment-related adverse events were nausea (26.4%) and hypertension (20.8%). Six episodes of grade three drug-related hypertension were observed. There was no apparent dose relationship. Grade 4 drug-related hypertension was not observed. Hypertension was easily manageable with anti-hypertensive medication in most cases.

Table 1. Baseline demographics and patient characteristics

Baseline characteristics	Patients (n (%))
Gender	
Male	29 (55)
Female	24 (45)
Age, years	
Median (range)	55 (17-76)
ECOG performance status	
0	15 (28)
1	32 (60)
2	3 (6)
Not reported	3 (6)
Prior anticancer therapies	
Surgery	51 (96)
Systemic anticancer therapy	45 (85)
Number of previous treatments (range)	2.5 (0-13)
0-1	20 (38)
2-5	29 (55)
>5	4 (8)
Radiation therapy	19 (36)
Tumor type	
Soft tissue sarcoma	11 (21)
Colorectal cancer	10 (19)
Renal cell cancer	5 (9)
Esophageal cancer	5 (9)
Other	22 (42)
Ovarian cancer	3 (6)
Osteosarcoma	3 (6)
Adrenal cancer	3 (6)
Cholangiocarcinoma	3 (6)
Melanoma	3 (6)
Pancreatic cancer	2 (4)
Bladder cancer	1 (2)
Chordoma	1 (2)
Anal cancer	1 (2)
Neuroendocrine carcinoma	1 (2)
Prostate cancer	1 (2)

ECOG: Eastern Cooperative Oncology Group

Table 2. Number of patients with treatment-related adverse events

Adverse Event	Cohort 1 20 mg od n=4		Cohort 2 75 mg od n=6		Cohort 3 150 mg od n=6		Cohort 4 300 mg od n=6		Cohort 5 600 mg od n=6		Cohort 6 900 mg once, bid later n=4		Cohort 7 900 mg od n=15		Cohort 8 1500 mg od n=6		Total incidence n=53
	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4	Any grade n (%)
Any event	3	–	1	1	2	1	3	1	2	2	2	–	8	3	5	–	34 (64.0)
Hypertension	–	–	–	1	1	1	1	1	–	1	–	–	3	2	–	–	11 (20.8)
Hematologic toxicity																	
Anemia	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0 (0.0)
Leukopenia	–	–	–	–	–	–	1	–	–	–	–	–	–	–	–	–	1 (1.9)
Thrombopenia	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	0 (0.0)
GI toxicity																	
Anorexia	–	–	–	–	1	–	–	–	1	–	–	–	2	–	1	–	5 (9.4)
Constipation	–	–	–	–	–	–	–	–	–	–	–	–	1	–	1	–	2 (3.8)
Diarrhea	–	–	–	–	–	–	1	–	1	–	1	–	2	–	3	–	8 (15.1)
Nausea	1	–	–	–	2	–	1	–	3	–	2	–	4	–	1	–	14 (26.4)
Vomiting	1	–	–	–	1	–	1	–	1	–	–	–	2	–	1	–	7 (13.2)
Metabolic toxicity																	
AST/ALT	–	–	–	–	–	–	–	–	–	1	–	–	–	–	1	–	2 (3.8)
Constitutional toxicity																	
Fatigue	–	–	–	–	–	–	1	–	–	–	–	–	3	–	3	–	7 (13.2)
Dermatological toxicity																	
Dry skin	1	–	1	–	–	–	–	–	–	–	–	–	–	–	–	–	2 (3.8)
HFS	–	–	–	–	–	–	–	–	1	–	–	–	–	–	–	–	1 (1.9)
Miscellaneous																	
Hemorrhage	–	–	–	–	–	–	–	–	1	–	–	–	–	–	–	–	1 (1.9)
Headache	–	–	–	–	–	–	–	–	3	–	1	–	1	1	–	–	6 (11.3)
Hoarseness	–	–	–	–	–	–	1	–	–	–	–	–	6	–	3	–	10 (18.9)

GI: gastro-intestinal, AST: aspartate aminotransferase, ALT: alanine aminotransferase, HFS: hand-foot syndrome

Two DLTs were observed. At 600 mg bid one episode of poorly controlled hypertension in a patient with metastatic renal cell carcinoma, prior nephrectomy and pre-existing hypertension was observed. Despite addition of a third antihypertensive agent and two dose reductions, grade 3 hypertension persisted and telatinib was permanently discontinued. At 1500 mg bid one episode of the combination of persistent grade 2 weight loss, grade 2 anorexia, and grade 2 fatigue was felt to be intolerable by the patient and therefore was considered DLT. Despite two dose reductions, this patient did not tolerate telatinib. Four additional patients experienced possible drug-related adverse events requiring dose reduction, interruption or discontinuation. One patient at 300 mg bid reported grade 2 diarrhea requiring permanent discontinuation of telatinib. One patient at 600 mg bid experienced grade 3 AST and ALT elevation, normalizing after dose reduction. One patient at 900 mg bid with well-controlled pre-existing hypertension reported grade 3 headache requiring two dose reductions of telatinib. One patient at 1500 mg bid discontinued telatinib following an episode of otherwise uncomplicated grade 3 esophageal varices bleeding. Due to the low incidence of treatment-related DLT, a formal MTD could not be defined.

Pharmacokinetics

Telatinib pharmacokinetic parameters are summarized in Table 3. Telatinib was rapidly absorbed, with t_{max} values observed less than 3 hours post-dose.

Although an overall dose proportional increase in exposure was observed in the 150-1500 mg bid dose range, high interpatient variability was observed, similar to that observed with other VEGF-R or EGF-R tyrosine kinase inhibitors.[15-20] In the intermediate dose levels (e.g. 300 mg BID and 600 mg BID) deviation from dose proportionality was observed likely due to pharmacokinetic variability. Plasma half-life of telatinib averaged 5.5 hours and is consistent with the observation that steady-state is achieved within the first 14 days of telatinib administration. A limited number of patients provided cycle 4 pharmacokinetic samples, yielding comparable results at cycle 2 day 14 and cycle 4 day 14.

There was no correlation between telatinib exposure and toxicity or time to progression. This is partly due to the low incidence of some of the toxicities and the relatively small number of patients per cohort.

Comparison of geometric mean AUC of telatinib and its metabolite BAY 60-8246 indicate that exposure to the metabolite is less than 20% of exposure to parent compound.

In a cohort of four patients in whom bioavailability of the 300 mg mesylate tablet was compared to that of the 150 mg mesylate tablet, high interpatient variability in the pharmacokinetic parameters precluded a definitive conclusion.

Table 3. Geometric mean (% coefficient of variation) of telatinib pharmacokinetic parameters, cycle 1 day, cycle 1 day 14 and cycle 2 day 14.

	Cohort						
	20 mg od (n = 4)	**75 mg od** (n = 6)	**150 mg bid** (n = 6)	**300 mg bid** (n = 6)	**600 mg bid** (n = 6)	**900 mg bid** (n = 15)	**1500 mg bid** (n = 6)
				Cycle 1 Day 1			
C_{max}, mg/L	0.106 (65%)	0.166 (85%)	0.113 (51%)	0.455 (129%)	0.597 (143%)	0.629 (81%)	1.767 (94%)
t_{max}, h [a]	2 [0.5 – 2]	2.5 [1 – 4]	3 [0.5 – 4]	3.5 [0.5 – 6]	3 [0.5 – 6.3]	2 [0.5 – 4]	1.5 [0.5 – 3]
$AUC_{(0-12)}$, [b] mg×h/L	0.596 (55%)	0.921 (102%)	0.590 (52%)	2.286 (145%)	4.592 (112%) [c]	3.735 (58%)	7.659 (79%)
Half-life, h	3.80 (12%)	4.05 (38%)	3.19 (32%)	3.96 (22%)	3.62 (23%) [c]	6.02 (87%)	3.58 (24%)
				Cycle 1 Day 14			
C_{max}, mg/L	0.135 (29%)	0.185 (58%)	0.188 (55%)	0.795 (71%)	0.822 (91%)	1.135 (60%)	1.608 (55%)
t_{max}, h [a]	2 [1 – 4]	3.5 [1 – 24]	2.5 [0.5 – 4]	2 [0.5 – 3.1]	2 [1 – 3]	1.5 [0.5 – 4]	4.5 [2 – 8]
$AUC_{(0-12)}$, [b] mg×h/L	1.082 (43%)	1.554 (30%)	1.187 (55%)	4.887 (62%)	5.060 (97%)	6.521 (49%)	12.227 (67%)
Half-life, h	5.06 (42%)	5.58 (59%)	6.91 (196%)	5.22 (66%)	5.26 (78%)	5.66 (67%)	5.42 (26%) [d]
				Cycle 2 Day 14			
C_{max}, mg/L	0.162 (25%)	0.163 (102%)	0.179 (34%)	0.482 (108%)	0.965 (86%)	0.880 (42%)	0.990 (131%)
t_{max}, h [a]	2 [0.5 – 3]	2 [1 – 10]	4.1 [1 – 8.2]	3.4 [0.5 – 5]	3 [0.6 – 3]	2 [0.5 – 4]	0.6 [0.5 – 8]
$AUC_{(0-12)}$, [b] mg×h/L	1.056 (34%)	1.117 (132%) [c]	1.101 (44%) [c]	3.203 (104%)	4.393 (115%)	5.647 (35%)	8.40 (70%) [c]
Half-life, h	4.73 (8%)	5.89 (156%) [c]	8.73 (211%) [c]	6.13 (94%)	5.45 (87%)	8.36 (72%)	4.59 (92%) [c]

a: Median [range], b: For once daily cohorts $AUC_{(0-24)}$, mg×h/L is reported, c: Sample size reduced by 1, d: Sample size reduced by 2

Pharmacodynamics

SVEGFR-2 and VEGF plasma levels

Changes in plasma levels of VEGF and sVEGFR-2 in relation to telatinib dose are summarized in figure 1A and 1B. Over the dose range studied, increasing exposure to telatinib resulted in lower plasma sVEGFR-2 levels (both pre-dose and post-dose) after 14 con-

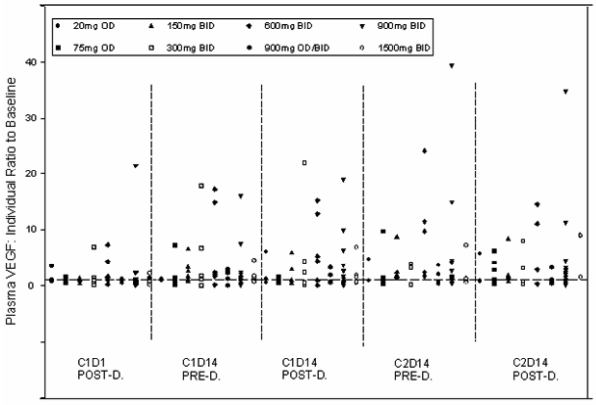
Table 4. Combined pharmacodynamic results (DCE-MRI and plasmalevels of VEGF and sVEGFR-2) : baseline and post-dose median Ktrans, $IAUC_{60}$ and TTPE values per cohort as well as plasma levels of VEGF, sVEGFR-2

		Cohort								Correlations	
		20 mg od	75 mg od	150 mg bid	300 mg bid	600 mg bid	900 mg bid	1500 mg bid	All cohorts	Telatinib $AUC_{(0\text{-}tn)}$ C1D14	Telatinib Cmax C1D14
Ktrans	N	0	0	0	0	1	13	2	16		
(min^{-1})	Pre					3.27	2.99	5.99	3.31	R = -0.285	R = -0.132
	Post					6.25	1.60	0.63	1.62	p = 0.284	p = 0.625
	% Change					+91.1	-46.7	-89.5	-51.2		
$IAUC_{60}$	N	0	0	0	0	1	13	2	16		
(mmol/ l*s)	Pre					14.14	19.26	4.10	17.07	R = -0.135	R =-0.085
	Post					14.12	17.35	2.51	14.47	p = 0.617	p = 0.753
	% Change					-0.1	-9-.9	-38.7	-15.2		
TTPE	N	1	4	3	4	4	15	1	32		
(sec)	Pre	3.00	4.55	6.00	4.95	9.80	3.20	5.80	5.25	R = 0.374	R = 0.228
	Post	3.00	4.55	6.00	5.65	9.85	5.60	11.20	5.60	p = 0.035*	p = 0.209
	% Change	0.0	0.0	0.0	+14.1	+0.6	+75.0	+93.1	+6.67		
VEGF	N	3	6	6	5	6	20	6	52		
(pg/ml,	Baseline	92.2	121.6	78.2	68.0	38.6	112.8	237.8	114.3	R = -0.222	
median)	C1D14	103.9	116.1	139.6	105.4	211.6	261.2	372.1	237.2	p = 0.140	
	Ratio mean	1.05	0.84	2.09	1.90	2.62	1.75	1.68	1.57		
SVEGFR-2	N	3	6	7	5	6	20	6	53		
(pg/ml,	Baseline	7276.1	6772.2	6500.3	7106.7	7736.9	7461.7	8000.9	7167.4	R = -0.035	
median)	C1D14	5932.1	6119.7	5866.1	5840.2	5507.3	5689.4	4919.6	5820.7	p = 0.810	
	Ratio mean	0.95	0.95	0.90	0.88	0.75	0.73	0.64	0.80		

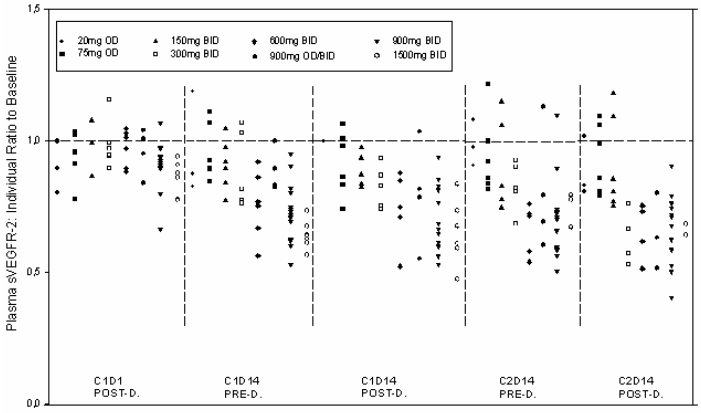
N: number of patients, TTPE: time to peak enhancement, Ratio is mean value to baseline at cycle 1 day 14
* correlation is significant at the 0.05 level

Fig 1. Biomarker results: plasma VEGF (fig 1A) and sVEGFR-2 (fig 1B) levels; individual patient's ratios over baseline value for cycle 1 day 1 through cycle 2 day 14, pre-dose (PRE-D) and post-dose (POST-D). Plasma sVEGFR-2 ratio over baseline value versus telatinib AUC_{0-24} on cycle 1 day 14 (fig 1C) and versus telatinib C_{max} on cycle 1 day 14 (fig 1D)

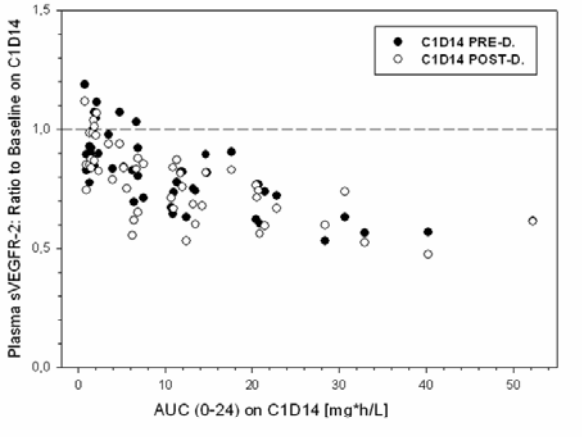
1A



1B



1C



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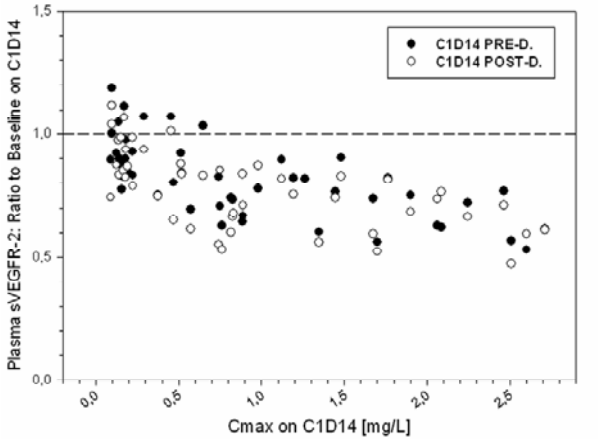

Table 5. Best Tumor Response

Cohort	N	Best Tumor Response		
		Stable disease	Progressive disease	Unknown
20 mg od	4	2	2	–
75 mg od	6	2	4	–
150 mg bid	6	2	4	–
300 mg bid	6	3	3	–
600 mg bid	6	4	1	1
900 mg once, bid later	4	2	2	–
900 mg bid	15	8	7	–
1500 mg bid	6	4	2	–

tinuous days of dosing (Figures 1C and 1D, table 4) There was no statistical correlation between dose of telatinib and plasma levels of VEGF and sVEGFR-2. Changes in plasma levels of VEGF and sVEGFR-2 plateaued at 900 mg bid, suggesting a saturable effect. There were no consistent changes in plasma levels of bFGF, and IL-8 and urinary levels of VEGF.

DCE-MRI

Reproducible DCE-MRI results for screening and at least for one post screening assessment were available from 16 subjects for evaluation of Ktrans and $iAUC_{60}$, and from 32 patients for evaluation of TTPE. DCE-MRI data for evaluation of Ktrans and $iAUC_{60}$

were missing from 37 patients for several reasons: no DCE-MRI performed (n=17), analysis unreliable due to poor quality, i.e. low signal-to-noise ratio, interference artifacts (n=14), only one scan performed (n=4), no contrast agent given (n=1), unknown (n=1). DCE-MRI data for evaluation of TTPE were missing from 21 patients for the following reasons: no DCE-MRI performed (n=17), only one scan performed (n=1), no contrast agent given (n=1), unknown (n=2).

DCE-MRI results are summarized in Table 4. For TTPE, a clear dose-response relationship was seen. TTPE changes from baseline were positively correlated to telatinib AUC.

Anti tumor activity

A disease control rate (DCR) of 50.9% was observed with 27 of 53 patients having stable disease as best tumor response (Table 5). Disease control for 6-12 months was seen in 3 patients, 12-18 months in 2, and >18 months in 4 patients. There were no complete or partial responses, however, some degree of tumor shrinkage was observed in 16 patients (30.2%).

Discussion

In this phase I dose escalation study we explored tolerability, safety and biological activity of the selective VEGFR tyrosine kinase inhibitor telatinib (BAY 57-9352).

With regard to safety, the most frequently reported treatment-related adverse events were nausea (26.4%) and hypertension (20.8%). Nausea occurred throughout all dose levels and was mild. Hypertension was easily managed with a maximum of two anti-hypertensive agents in all but one patient. Based upon previous experience and considering the potential underlying mechanisms of the observed hypertension, angiotensine converting enzyme inhibitors and calcium antagonists were most frequently prescribed. It is conceivable that hypertension should be considered an indication of biological activity of VEGF inhibitors rather than as side-effect.[1,3,15,21-25]

As only one out of 6 patients at 1500 mg bid experienced DLT (combination of grade 2 weight loss, anorexia, and fatigue), we formally could not define the MTD of telatinib based upon clinical toxicity. Eventhough grade 2 toxicity formally did not define DLT in this study, on ongoing (combination of) grade 2 toxicity induced by continuous drug administration must be considered to be cumbersome and therefore can define as intolerable.

In our study, pharmacokinetics of telatinib were dose proportional in the overall dose range studied, albeit with substantial interpatient variability and deviation from dose proportionality in the intermediate dose levels. This observation may be attributed to in-

herent variability in absorption and/or metabolism of telatinib, as well as various patient and tumor characteristics. In a parallel study with telatinib, a markedly less than dose proportional increase in exposure was observed at dose levels exceeding 900 mg bid.[26]

Telatinib induced changes in plasma levels of VEGF and sVEGFR-2 that are consistent with findings in trials with telatinib and other VEGFR inhibitors.[15,16,19,26,27] These changes plateaued at 900 mg bid suggesting a saturable effect.

Based upon the combined analysis of pharmacokinetic and pharmacodynamic results observed in the two dose escalation studies with telatinib, and based upon practical issues such as number of tablets to be taken, we defined 900 mg bid as the dose recommended for phase II studies. Based upon the mechanism of action of VEGFR-2 tyrosine kinase inhibitors, a continuous dosing schedule may prove to have optimal activity, and therefore studies exploring continuous administration of telatinib in combination with various anticancer therapies have been initiated.[28]

DCE-MRI analysis revealed changes in TTPE that are correlated to telatinib exposure. Similar studies with other angiogenesis inhibitors support our results.[29-31] A trend to a dose-effect relationship was seen, but no significant correlation could be assessed. We could not determine a statistical correlation between DCE-MRI results and clinical outcome such as disease control rate (data not shown separately). Eventhough DCE-MRI analyses should be considered a non-validated technique, results obtained in our study indicate an antiangiogenic effect of telatinib and seem to support the results of additional analyses of changes in flow mediated dilatation (FMD), nitroglycerin-mediated dilatation (NMD), and capillary density that were done in this study and are reported separately.[32]

Determining antitumor activity of telatinib was a secondary endpoint of this study. Complete or partial responses were not observed in this study, but some minor tumor regressions and prolonged periods of disease stabilization are indicative of anti-tumor activity and merit confirmation in a phase II study program. Among cases of prolonged disease stabilization is a young patient with an epitheloid hemangio-endothelioma of the scalp who is now on medication for more than three years.

Two VEGF tyrosine kinase inhibitors (sunitinib and sorafenib) have gained regulatory approval. Telatinib may have some theoretical advantages over sunitinib and sorafenib. Theoretically, side effects like thyroid dysfunction, cardiac function impairment, and reversible posterior leukoencephalopathy syndrome observed with sunitinib or sorafenib may be caused by blocking pathways not described in the pre-clinical or clinical studies or by the redirection of signals through other pathways.[33-38] These side effects can therefore by agent-specific and to date, albeit in a relatively small number of patients, telatinib has not induced any of these side effects.

Compared to telatinib, vatalanib (PTK787/ZK222584) seems to have some similarities. In our opinion, telatinib has potential benefit over vatalanib. The IC_{50} of vatalanib for VEGFR-3, c-Kit, and PDGFRβ are respectively 18, 20, and 16 times higher than the IC_{50} for VEGFR-2. For telatinib these IC_{50}'s are 0.66, 0.17 and 2.5 times higher, respectively. Activation of VEGFR-3 in lymphatic endothelial cells can facilitate lymphangiogenesis and lymphatic spread of tumor cells.[39] Therefore, theoretically, the superior potency of telatinib compared to vatalanib with regard to VEGFR-3 inhibition will hopefully translate into increased clinical efficacy. Future studies will have to prove this optimism.

In conclusion, telatinib (BAY 57-9352) administered as continuous treatment is safe and well tolerated. Based upon the combined analysis of clinical, pharmacodynamic, and pharmacokinetic endpoints, 900 mg bid is the dose recommended for future phase II studies.

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