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RESEARCH

Phase-1 study of vamotinib (PF-114), a 3rd generation *BCR::ABL1* tyrosine kinase-inhibitor, in chronic myeloid leukaemia

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Abstract

Vamotinib (PF-114) is a 3rd -generation, ATP-competitive oral tyrosine kinase inhibitor (TKI) active against wild-type and mutated *BCR::ABL1* isoforms including *BCR::ABL1*^{T315I}. We present final results of a phase-1 vamotinib dose-escalation study to identify maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) followed by expansion cohorts. 51 subjects with chronic myeloid leukaemia (CML) failing≥1 2nd generation TKI or with *BCR::ABL1*^{T315I} were enrolled. Subjects received vamotinib, 50–750 mg/d, continuously. Median exposure was 6 months (range, <1–52 months). Median CML duration pre-study was 10 years (range, <1–23 years). 27 subjects received≥3 prior TKIs and 16 had *BCR::ABL1*^{T315I}. The MTD was 600 mg with the Grade-3 psoriasis-like skin toxicity as the DLT. There were no vascular occlusive events nor deviations of ankle-brachial index. Complete haematologic response (CHR) was achieved in 14 of 30 subjects, major cytogenetic response (MCyR) in 14 of 44 subjects, complete cytogenetic response (CCyR) in 10 of 50 and major molecular response (MMR) in 7 of 51 subjects who did not have a CHR, MCyR, CCyR or MMR at enrollment. The best safety/efficacy dose was 300 mg with MCyR achieved in 6 of 7 subjects, CCyR in 5 of 9 and MMR in 4 of 9 subjects who did not have a MCyR, CCyR or MMR at enrollment. 5 of 16 subjects with *BCR::ABL1*^{T315I} responded including 3 achieving a CHR, 3, a MCyR, and 1,a CCyR. 2 of 5 subjects failing ponatinib achieved a CHR. Vamotinib dose for further phase-3 study is 300 mg/d.

Clinical trial registration

The trial is registered at *clinicaltrials.gov*. The registration number is NCT02885766, August 26, 2016.

Keywords Chronic myeloid leukaemia · Tyrosine kinase inhibitor · PF-114 · Vamotinib

Introduction

Six tyrosine kinase inhibitors (TKIs) are approved to treat *BCR::ABL1* positive chronic myeloid leukemia (*BCR::ABL1*+CML) [1–6]. However, there remains a need for new TKIs because of resistance and intolerance [7–25]. Vamotinib (PF-114) mesylate is a potent, highly specific 3rd generation *BCR::ABL1*-inhibitor for oral use. Vamotinib is rationally designed to avoid inhibition of vascular endothelial growth factor receptor-2 (*VEGFR2*) and other off-target kinases [26–27]. Vamotinib is active against wild-type and mutant *BCR::ABL1* isoforms including *BCR::ABL1*^{T315I}. In pre-clinical studies in animals there were few adverse events including no arterial occlusive events. We present the results of a phase-1 trial of vamotinib in subjects with *BCR::ABL1*-positive CML failing≥2nd generation TKIs (2G-TKIs) or with *BCR::ABL1*^{T315I}.

Extended author information available on the last page of the article

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Methods

Study oversight

The study was designed by Fusion Pharma, LLC, in collaboration with the principal investigators from each clinical centre participating in the study and members of the sponsor's Scientific Advisory Board. Data were collected, analyzed and interpreted by OCT (https://oct-clinicaltrials.com/) a clinical contract research organization (CRO). Principal investigators verified data accuracy and completeness at their site and integrity of the analyses and study conducted consistent with the study protocol.

Subjects

Study subjects ≥ 18 years with *BCR::ABL1* positive CML in chronic (CP) or accelerated phase (AP) using the European LeukemiaNet 2013 guidelines [28]. Subjects, had to have failed ≥ 1 2nd generation TKIs or intolerance to ≥ 2 TKIs or have *BCR::ABL1*^{T315I}. Other eligibility criteria included ECOG performance score 0–2; QTcF interval ≤ 470 milliseconds and resolution of all prior therapy-associated adverse event to ≤ Grade-1 according to NCI CTC AE v4 criteria [29].

Study design

Open-label phase-1 study at 3 clinical centers with dose-escalation using a 3 + 3 scheme with a starting dose of 50 mg/d given continuously. A 28-days of therapy was defined as a cycle. Dose escalation for the subsequent cohort depended on the results of the safety assessment of subjects in the preceding cohort during the 28 days of therapy. Once an MTD was identified expanded cohorts of 10–15 subjects were recruited at doses of interest below the MTD. A modified accelerated dose-escalation regimen was used up to a dose of 400 mg. Dose could be increased for subjects in whom the dose was reduced because of an adverse drug reaction (ADR). Severity of adverse events was assessed using NCI CTC AE v4 [28].

The primary objective was to determine the MTD and DLT of vamotinib during the 1st cycle of therapy. Secondary objectives were to assess the safety and tolerability of vamotinib, determine pharmacokinetics and determine efficacy by response criteria according to 2013 ELN [29].

Pharmaco-kinetics and -dynamics

Blood samples were obtained to evaluate pharmacokinetics and pharmacodynamics (Tables S1, S1.1, S1.2). Data on phosphorylated CrkL protein (pCrkL) concentration were evaluated in samples from 4 subjects.

Efficacy

Haematological response evaluations were done on the first day of each cycle of therapy; molecular response on the first day of cycles 1, 2, 4, 7, 10, 13 and then every three months; cytogenetic response – at screening and on the first days of cycles 4, 7, 13 and every three months thereafter, provided that there was no major molecular response.

Cytogenetic response was assessed by differential staining of chromosomes and if uninformative, by fluorescent in situ hybridization (FISH). Mutations in *BCR::ABL1* were assessed by Sanger and next generation sequencing (NGS). Sanger sequencing was done at each center; NGS analyses were done in the laboratory of Prof. Susan Branford, University of Adelaide. Discordances were resolved as described in Table S2. Molecular response was assessed using the ratio of *BCR::ABL1* to *ABL1* measured according to the IS [9].

Results

Subjects and baseline co-variates

54 subjects were screened between July, 2016 and January, 2019, 51 of whom were enrolled. The starting dose of vamotinib was 50 mg/d ($n = 3$). Subsequent subjects were sequentially recruited into cohorts at doses of 100 mg ($n = 3$), 200 mg ($n = 11$), 400 mg ($n = 12$), 500 mg ($n = 3$), 600 mg ($n = 6$), 750 mg ($n = 4$), and 300 mg ($n = 9$). All subjects treated at 300 mg daily and 6 subjects at 400 mg were enrolled after the MTD was determined. The cut-off date of the analysis was July 30, 2019.

Baseline co-variates and therapy state of subjects as are displayed in Table 1. Mean follow-up is 27 w (range 0.1–31 w, IQR 65 w). 36 subjects previously received ≥ 3TKIs. 35 subjects had ≥ 1 *BCR::ABL1* kinase domain mutation the most common of which was *BCR::ABL1*^{T315I} in 16 (Table S2.1). All subjects discontinued from the study 1 of whom died later from blast transformation. 7 patients were remaining on the treatment when the study was terminated by the Sponsor's decision (Table 1).

Safety

There was no DLT in cohorts at doses < 400 mg/d. At a dose of 400 mg/d 1 subject developed a Grade-3 psoriasiform dermatitis (Table 2). There were no DLTs at doses of 500 mg/d and 600 mg/d. At a dose of 750 mg/d all 3 subjects treated

Table 1 Baseline co-variates and therapy state

	Cohort 1 50 mg (*N*=3)	Cohort 2 100 mg (*N*=3)	Cohort 3 200 mg (*N*=11)	Cohort 4 400 mg (*N*=12)	Cohort 5 500 mg (*N*=3)	Cohort 6 600 mg (*N*=6)	Cohort 7 750 mg (*N*=4)	Cohort 8 300 mg (*N*=9)	All (*N*=51)
Time on therapy, median (range)–days	308 (28–707)	394 (280–1592)	261 (45-1549)	162 (14–539)	54 (23–79)	102 (31-1002)	35 (13–364)	805 (77-1093)	199 (13-1592)
Therapy state									
Discontinued	3	3	11	12	3	6	4	9	51
Disease progression or need to change therapy in the opinion of the investigator	2	0	2	7	2	3	1	3	20
Adverse event	0	1	1	2	0	1	0	1	6
Intolerable adverse drug reaction in the opinion of the investigator	0	1	0	1	0	0	0	0	2
Withdrawal of informed consent	0	0	0	1	1	1	2	0	5
Participation in another clinical study or additional therapy	1	0	1	1	0	0	0	0	3
Lost to follow-up	0	0	1	0	0	0	0	1	2
Sponsor's decision to terminate the study	0	1	2	0	0	1	0	3	7
Other	0	0	4	0	0	0	1	1	6
ECOG performance-status score									
0	3	2	8	9	2	5	2	9	40
1	0	1	3	3	0	1	2	0	10
2	0	0	0	0	1	0	0	0	1
No. of previous TKIs									
1	0	0	1	4	0	0	0	0	5
2	1	2	5	1	2	2	1	5	19
≥3	2	1	6	8	1	6	6	6	36
Previous TKI									
Imatinib	3	3	11	12	3	5	3	9	49
Nilotinib	2	2	4	7	2	5	4	6	32
Dasatinib	2	2	7	6	2	5	4	5	33
Bosutinib	1	0	4	1	0	2	3	3	14
Ponatinib	0	0	1	2	0	1	0	1	5
***BCR::ABL1*transcript**									
p 210	3	3	11	11	3	6	4	9	50
p 190 (e1a2)	0	0	0	1	0	0si	0	0	1

Table 2 Subjects' treatment and dose-limiting toxicities

Cohorts	Cohort 1 50 mg (*N*=3)	Cohort 2 100 mg (*N*=3)	Cohort 3 200 mg (*N*=11)	Cohort 4 400 mg (*N*=12)	Cohort 5 500 mg (*N*=3)	Cohort 6 600 mg (*N*=6)	Cohort 7 750 mg (*N*=4)	Cohort 8 300 mg (*N*=9)	All subjects, (*N*=51)
Time on treatment, median (range)–days	308 (28–707)	394 (280–1592)	261 (45-1549)	162 (14–539)	54 (23–79)	102 (31-1002)	35 (13–364)	805 (77-1093)	199 (13-1592)
DLTs	0	0	0	1	0	0	3	0	4
Subjects with dose delay, n	1	2	6	6	1	4	3	4	27
Subjects with dose reduction, n	1	1	3	4	1	2	3	0	15

developed skin DLTs, therefore 600 mg/d was defined as the MTD. Additional subjects were enrolled in the 200 mg/d, 300 mg/d, and 400 mg/d cohorts. Therapy duration was briefer at a dose of 400 md/d. Rates of dose-reductions and therapy-interruptions were higher for 400 mg/d compared with lower doses (Table 2).

The most common non-hematological adverse event was psoriasiform dermatitis in 19 subjects 4 of which were Grade-3/-4 (Table 3). There was diarrhea in 14 subjects, all

Table 3 Most common adverse events

Adverse Events	All subjects ($N=51$)		Advanced phase ($N=5$)
	All grades	Grade 3–4*	Grade 3–4*
	Number of subjects (percent)		
Skin and subcutaneous tissue disorders	**32 (63)**	**11 (22)**	**1 (20)**
Dermatitis psoriasiform	19 (37)	4 (8)	
Toxic skin eruption	9 (18)	7 (14)	1 (20)
Dry skin	9 (18)		
Pruritus	5 (10)	1 (2)	
Erythema	4 (8)		
Rash papular	2 (4)		
Gastrointestinal disorders	**17 (33)**		
Diarrhoea	14 (28)		
Nausea	6 (12)		
Abdominal pain upper	4 (8)		
Abdominal pain	2 (4)		
Anal fissure	2 (4)		
Dyspepsia	2 (4)		
Blood and lymphatic system disorders	**12 (24)**	**7 (14)**	**2 (40)**
Thrombocytopenia	8 (16)	4 (8)	1 (20)
Neutropenia	5 (10)	3 (6)	2 (40)
Anaemia	2 (4)	1 (2)	
Leukopenia	1 (2)	1 (2)	
Investigations	**7 (14)**	**1 (2)**	
Blood cholesterol increased	3 (6)		
Cardiac disorders	3 (6)		
Eye disorders	3 (6)		
Alanine aminotransferase increased	2 (4)		
Low density lipoprotein increased	2 (4)		
Transaminases increased	1 (2)	1 (2)	
Hepato-biliary disorders	**1 (2)**	**1 (2)**	
Hepatitis toxic	1 (2)	1 (2)	

*Dermatitis psoriasiform – 2 subjects on 400 mg; 2 subjects on 600 mg; Toxic skin eruption – 1 subject on 300 mg; 1 subject on 400 mg; 2 subjects on 500 mg; 1 subject on 600 mg; 2 subjects on 750 mg; Pruritus – 1 subject on 600 mg; Hepatitis toxic – 1 subject on 400 mg; Thrombocytopenia – 1 subject on 200 mg; 1 subject on 500 mg; 1 subject on 600 mg; 1 subject on 750 mg; Neutropenia – 2 subjects on 400 mg; 1 subject on 500 mg; Anaemia – 1 subject on 200 mg; Leukopenia – 1 subject on 400 mg

<Grade-3. Dry skin and rash occurred in 8 subjects 6 subjects had a Grade-3/-4 toxic skin rash. 6 subjects had serious adverse events (Table S3).

Haematological adverse events were common but usually Grade-1/-2 (Table 3). No cardio-vascular or arterial occlusive adverse events were reported at any dose, including no cases of occlusion of large peripheral blood vessels and no clinically significant deviations of the ankle-brachial index from its normal range 1.00-1.29 [30]. The 3 observed cases of drug-related cardiac disorders were Grade-2 atrial fibrillation (400 mg), Grade-1 extrasystoles (600 mg) and Grade-1 pericarditis (400 mg).

Rash

Rash was the most common non-haematological adverse event and were seen in 32 subjects (Table 4). Grade-3 rash occurred in 10 subjects at doses≥400 mg/d. Rash was the reason for dose-reduction ($n=9$) and study withdrawal ($n=6$). No rash was coded as a serious adverse events. The most common rash was psoriasiform with erythema, lymphoplasmacytic infiltration of derma and desquamation of well-defined foci. Rashes were often in sites of friction and stretching and painless but occasionally associated with paresthesia. Other types of rashes included dryness and redness mainly in the setting of development or regression of psoriasiform rashes. Toxicity resolved within 1–2 weeks after discontinuation of the drug. Lipoic acid (tablets), vitamin E, and topical drugs including tacrolimus 0.1, betamethasone 0.05, calcipotriol, hydrocortisone 0.5 eye ointment, urea 10, thermal water were given for skin lesions. Skin lesions were resolved after 4–6 months.

Pharmacokinetics

Pharmacokinetic measurements were done on days 1 and 29–30 of treatment. The time to reach C_{max} was about 4 h, the half-life of 13.5 h, which confirmed the validity of the once a day regimen. Steady-state was reached after 8 days of dosing, Fig. 1. The concentration-time profiles suggest linear or near-linear pharmacokinetics of vamotinib over the entire dose range studied (50–750 mg). Dose proportionality assessment showed a less than dose-dependent increase in AUC and C_{max} of vamotinib (Table S4). Starting from a dose of 200 mg, the concentration of vamotinib in the blood during the day exceeds 75 nM, corresponding to the IC50 of cytotoxicity for BaF3 cells expressing *BCR::ABL1*^{T315I} [26].

Analysis of changes in blood pCrkL done for subjects with leukocytosis on days 1, 8 and 29 of therapy but was uninformative because of poor quality of samples.

Efficacy

Efficacy and best responses to treatment are summarized in Table 5 and Table S5 correspondingly. 30 subjects did not have a complete hematological response (CHR) at baseline 14 of whom achieved a CHR (Table 5). Median time to achieving a CHR was 3.8 months, (range, 1–4 months). Of the 44 and 50 subjects who did not have a major cytogenetic response (MCyR) and a complete cytogenetic response

Table 4 Skin toxicity

	Severity	Cohort 1 50 mg	Cohort 2 100 mg	Cohort 3 200 mg	Cohort 4 400 mg	Cohort 5 500 mg	Cohort 6 600 mg	Cohort 7 750 mg	Cohort 8 300 mg	Overall
		N=3	*N*=3	*N*=11	*N*=12	*N*=3	*N*=6	*N*=4	*N*=9	*N*=51
Psoriasiform dermatitis, n	Grade 3	0	0	1	2	0	1	0	0	4
	Total	1	3	4	8	0	1	0	2	19
Dry skin, n	Grade 3	0	0	0	0	0	0	0	0	0
	Total	0	1	1	4	1	1	0	1	9
Erythema, n	Grade 3	0	0	0	0	0	0	0	0	0
	Total	0	0	0	2	1	1	0	0	4
Pruritus, n	Grade 3	0	0	0	0	0	1	0	0	1
	Total	0	0	0	3	0	2	0	0	5
Toxic skin eruption, n	Grade 3	0	0	1	1	1	1	3	0	7
	Total	0	0	1	1	1	3	3	0	9
Rash papular, n	Grade 3	0	0	0	0	0	0	0	0	0
	Total	1	0	0	1	0	0	0	0	2

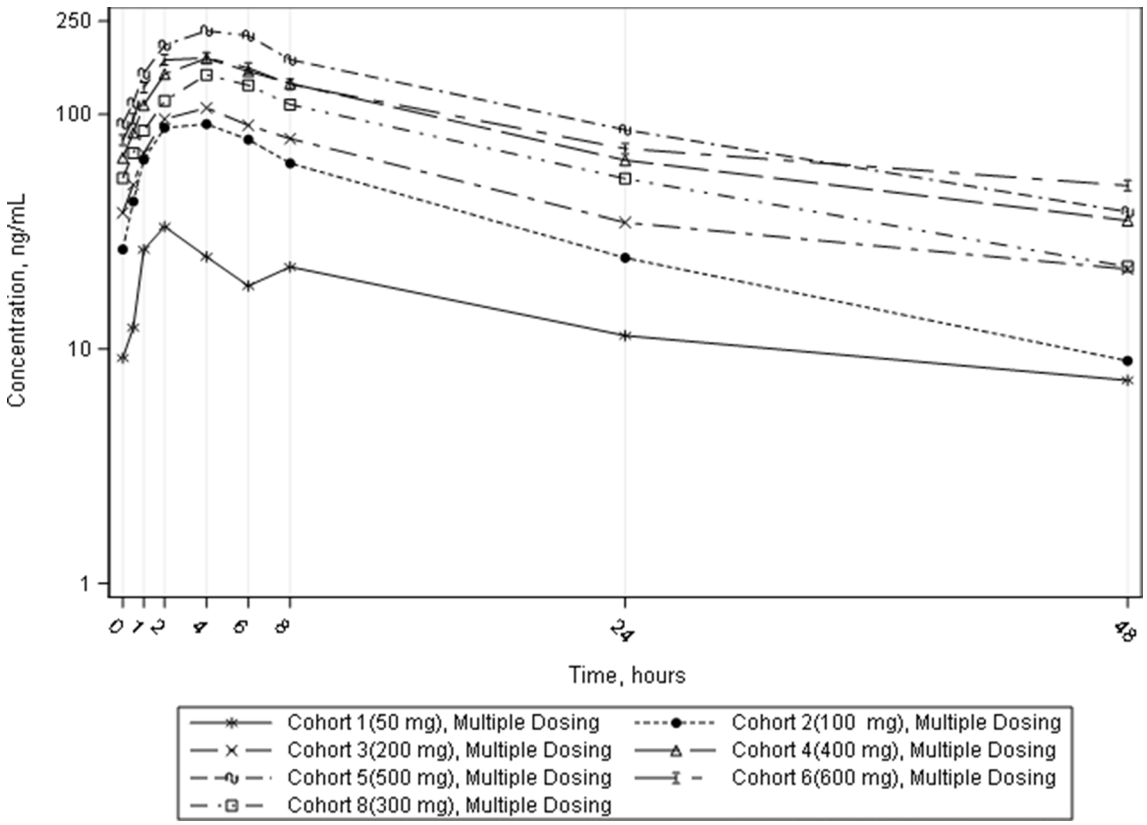

Fig. 1 Vamotinib concentrations after multiple-dose administration (Days 1–2 of the cycle 2 of therapy) of vamotinib mesylate for all subjects by dosage cohorts (population for PK evaluation)

(CCyR) at the start of therapy, respectively, 14 (32%) achieved MCyR and 10 (20%) achieved CCyR during therapy. The median time to achievement of MCyR and CCyR were 4.5 months (range 1.9–19.4) and 5.6 months (range 2.8–15), respectively. None of the 51 subjects had a major molecular response (MMR) at study entry, and 7 (13.7%) subjects achieved MMR during therapy. One subject on a dose of 300 mg achieved a deep molecular response of MR4.5. It is worth mentioning that 4 of 7 subjects achieving MMR had intolerance to prior TKI therapy before enrollment to the study (Table S5). The median time to MMR was 5,6 months (range 2.8–22.2), and no subject has lost after 24 months. One subject, treated at a dose of 300 mg, achieved a MR4.5. In general, the higher the level of response to therapy was achieved the more sustainable it was: 8 of 14 CHRs were subsequently lost, whereas none of 7 MMRs were lost. Most molecular and cytogenetic responses were observed at doses of 300 and 200 mg. The lower number of responses

Table 5 Efficacy

	Cohort 1 50 mg	Cohort 2 100 mg	Cohort 3 200 mg	Cohort 4 400 mg	Cohort 5 500 mg	Cohort 6 600 mg	Cohort 7 750 mg	Cohort 8 300 mg	Total
	N=3	*N*=3	*N*=11	*N*=12	*N*=3	*N*=6	*N*=4	*N*=9	*N*=51
Absence of CHR at baseline – no. (%)	2 (67)	0	5 (46)	7 (58)	2 (67)	6 (100)	4 (100)	4 (44)	30 (59)
CHR achieved at treatment – no. (%)	1 (50)	0	2 (40)	4 (57)	0	2 (33)	1 (25)	4 (100)	14 (47)
CHR by the 3 months – no. (%)	0	0	2 (40)	2 (29)	0	2 (33)	1 (25)	4 (100)	11 (37)
CHR by the 6th months – no. (%)	0	0	2 (40)	2 (29)	0	2 (33)	1 (25)	4 (100)	11 (37)
CHR by the 12th months – no. (%)	1 (50)	0	2 (40)	4 (57)	0	2 (33)	1 (25)	4 (100)	14 (47)
Subjects with loss of CHR – no. (%)	0	0	2 (100)	4 (100)	0	0	0	2 (50)	8 (57)
Absence of MCyR at baseline – no. (%)	3 (100)	2 (67)	8 (73)	11 (92)	3 (100)	6 (100)	4 (100)	7 (78)	44 (86)
MCyR achieved at treatment – no. (%)	0	2 (67)	4 (50)	2 (19)	0	0	0	6 (86)	14 (32)
MCyR by 6 months – no. (%)	0	1 (33)	3 (38)	2 (19)	0	0	0	4 (57)	10 (23)
MCyR by 12 months – no. (%)	0	1 (33)	3 (38)	2 (19)	0	0	0	5 (83)	11 (25)
Subjects with loss of MCyR – no. (%)	0	0	1 (25)	0	0	0	0	1 (17)	2 (14)
Absence of CCyR at baseline – no. (%)	3 (100)	3 (100)	10 (91)	12 (100)	3 (100)	6 (100)	4 (100)	9 (100)	50 (98)
CCyR achieved at treatment – no. (%)	0	1 (33)	3 (30)	1 (8)	0	0	0	5 (56)	10 (20)
CCyR by 6 months – no. (%)	0	0	2 (20)	1 (8)	0	0	0	3 (33)	6 (12)
CCyR by 12 months – no. (%)	0	0	2 (20)	1 (8)	0	0	0	4 (44)	7 (14)
Subjects with loss of CCyR – no. (%)	0	0	1 (33)	0	0	0	0	1 (20)	2 (20)
Absence of MMR at baseline – no. (%)	3 (100)	3 (100)	11 (100)	12 (100)	3 (100)	6 (100)	4 (100)	9 (100)	51 (100)
MMR achieved at treatment – no. (%)	0	1 (33)	2 (18)	0	0	0	0	4 (44)	7 (14)
MMR by 6 months – no. (%)	0	0	1 (9)	0	0	0	0	3 (33)	4 (8)
MMR by 12 months – no. (%)	0	0	1 (9)	0	0	0	0	3 (33)	4 (8)
MMR by 24 months – no. (%)	0	1 (33)	2 (18)	0	0	0	0	4 (44)	7 (14)
Subjects with loss of MMR – no. (%)	0	0	0	0	0	0	0	0	0

Table 6 Subjects with the *BCR::ABL1*^{T315I}, resistance/intolerance to ponatinib or in accelerated phase

Variable	Subjects with BCR::ABL1^{T315I} (*N*=16)	Subjects after ponatinib (*N*=5)	Advanced phase CML (*N*=5)
Median follow-up (range), days	78 (17–987)	53 (8-266)	150 (15–539)
CHR no./total no.	3/12*	2/5	2/5
MCyR no./total no.	3/15**	0/5	0/5
CCyR no./total no.	1/16	0/5*	0/5
MMR no./total no.	0/16	0/5*	0/5

* 4 subjects had a CHR at enrollment

** 1subject had a MCyR at enrollment

at doses of 400 mg and above may be explained by the fact that the resulting (skin) toxicity prevented long-term treatment of subjects at these doses.

Of the 16 subjects with *BCR::ABL1*^{T315I}, 12 did not have CHR at study entry; 3 of them achieved CHR during vamotinib therapy. Of the 15 subjects without MCyR and 16 without CCyR, 3 and 1 subjects achieved responses, respectively (Table 6). Responses to vamotinib in subjects with *BCR::ABL1*^{T315I} were transient, lasting 2.8 months (MCyR) and 2.8 months (CCyR). Most subjects with *BCR::ABL1*^{T315I} were treated at doses of 400 mg and above, which were characterized by premature withdrawal from the study due to toxicity. No subject with *BCR::ABL1*^{T315I} was included in the 300 mg dose cohort, which performed optimally in terms of efficacy and safety. Five subjects had received prior therapy ponatinib. None had CHR at study entry and 2 achieved CHR; however, none achieved MCyR or CCyR (Table 6). Five subjects with advanced phase CML (4 in AP and 1 in blast phase, BP) were treated. 2 achieved a CHR but none achieved MCyR or CCyR. 1 subject continued on therapy (Table 6).

A subject with myeloid variant M0 blast crisis was treated with vamotinib due to the lack of other available at that time therapies [31–32]. BP was identified on enrollment and accompanied by i(17) and *BCR::ABL1*^{T315I}. A CHR was achieved after 5 weeks of vamotinib lasting for 18 months with no cytogenetic response. At 1 year there was extramedullary relapse and the CHR was lost and vamotinib discontinued.

Discussion

Vamotinib is safe and reasonably effective in people with CML resistant and/or intolerance to 1st and 2nd generation TKIs, ponatinib and in those with *BCR::ABL1*^{T315I}. The MTD is 600 mg with rash the dose-limiting and most common DLT and adverse event. Rash was seen in pre-clinical toxicology studies in rats and dogs [26]. PDGFRa seems the most likely off-target kinase causing skin toxicity of

vamotinib, as follows from the kinase inhibition profiles of vamotinib, ponatinib and dasatinib [26]. Ponatinib and vamotinib, known to cause skin toxicity, potently inhibited PDGFRa, unlike dasatinib, for which skin toxicity is not characteristic. PDGFRa was also spotted among the off-target kinases of another *BCR::ABL1* kinase inhibitor olverembatinib [33], which is currently under intensive clinical evaluation [34–35] and for which skin pigmentation was the most common non-hematologic adverse reaction [34]. Interestingly, vamotinib showed no arterial-occlusive events despite the close structural similarity with ponatinib [23–24]. Comparison of kinase inhibition profiles of ponatinib and vamotinib [26] may suggest that inhibition of EPHA6, EPHA7, TAK1, TIE2, VEGFR2, ZAK kinases by ponatinib but not vamotinib may contribute to cardiovascular toxicity of the former. No cardio-vascular findings were observed in pre-clinical toxicology studies of vamotinib as well [26]. Recent clinical studies of olverembatinib, also a structural homologue of ponatinib, revealed some drug related cardiovascular adverse events, including vascular occlusions, however potentially less common compared to ponatinib [34]. Olverembatinib is a potent inhibitor of discussed above kinases TAK1, TIE2 and ZAK, but not EPHA6, EPHA7 and VEGFR2 [33], which puts it somewhere between ponatinib and vamotinib.

The study has its limitations due to the relatively small sample size, heterogeneous pretreatment status of the enrolled patients, and the lack of reliable pharmacodynamic readouts. Despite the small statistics, promising efficacy of vamotinib was observed in the 300 mg cohort where 4 of 9 patients achieved MMR, Some patients with *BCR::ABL1*^{T315I} achieved MCyR and CCyR. However no patients with *BCR::ABL1*^{T315I} were enrolled in 300 mg cohort in this study, so more data are needed to characterize the efficacy of vamotinib 300 mg in subjects with *BCR::ABL1*^{T315I}. Previous data on ponatinib [21], asciminib [6] and olverembatinib [34–35] suggest comparable efficacy of these drugs in subjects with or without *BCR::ABL1*^{T315I}.

In conclusion, vamotinib is safe and effective in some subjects failing≥2 TKIs, ponatinib and with *BCR::ABL1*^{T315I}. The dose selected for further study is 300 mg/d. Vamotinib is currently being evaluated in a phase-3 study versus high-dose imatinib in subjects resistance to standard-dose imatinib without *BCR::ABL1* mutations known to confer resistance to imatinib [36].

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethical approval The protocol was approved by the ethics committee of the Ministry of Health of Russian Federation and by the participating clinical sites' ethics committees. The study was conducted in accordance with the 1964 Declaration of Helsinki and the Good Clinical Practice Guidelines of the International Conference on Harmonization. All patients provided written informed consent.

Consent for publication Not applicable.

Competing interests AT – speaker: Novartis, Pfizer, R-Pharm, consultancy/advisory board: Novartis; OV: no competing interests to declare; EL has received fees for lecturing and expert opinion from Novartis, Pfizer, Sotex, Pharmstandard and Fusion Pharma; ES: no competing interests to declare; OS: no competing interests to declare; EC – speaker: Novartis, Pfizer, R-Pharm, consultancy: Ascentage Pharma; DS: no competing interests to declare; IN: no competing interests to declare; AP: speaker: Novartis, Alexpharm; AB: no competing interests to declare; NS: no competing interests to declare; Vasily Shuvaev received fees for lecturing and expert opinion from Novartis, Pfizer, Amgen, and AbbVie; IM: no competing interests to declare; FN was employed by Fusion Pharma; Veronika Shulgina: was employed by Fusion Pharma; AH: Honoraria and research funding (Novartis, Incyte); research funding (Bristol Myers Squibb, Pfizer, MSD); OO: Amgen, Incyte, Celgene, Roche, Fusion Pharma, Novartis: honoraria. Amgen, Incyte, and Celgene: research funding; JC: Consultancy (Pfizer, Takeda, Nerviano, Sun Pharma, Novartis, Biopath Holdings, Tigel); research funding (Ascentage, Novartis, Sun Pharma, Tern Pharma, Abbvie); membership on an entity's board of directors or advisory committees (BioPath Holdings); RPG is a consultant to Antengene Biotech LLC, Ascentage Pharma Group and NexImmune Inc.; Medical Director, FFF Enterprises Inc.; A speaker for Janssen Pharma and Hengrui Pharma; Board of Directors: Russian Foundation for Cancer Research Support; and Scientific Advisory Boards, Nanexa AB and StemRad Ltd.; GC is employed by Fusion Pharma.

References

1. Druker BJ, Guilhot F, O'Brien SG et al (2006) Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N Engl J Med 355:2408–2417. https://doi.org/10.1056/NEJMoa062867
2. Kantarjian H, Shah NP, Hochhaus A et al (2010) Dasatinib versus Imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 362:2260–2270. https://doi.org/10.1056/nejmoa1002315
3. Saglio G, Kim DW, Issaragrisil S et al (2010) Nilotinib versus Imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med 362:2251–2259. https://doi.org/10.1056/nejmoa0912614
4. Cortes JE, Gambacorti-Passerini C, Deininger MW (2017) Bosutinib Versus Imatinib for newly diagnosed chronic myeloid leukemia: results from the Randomized BFORE Trial. J Clin Oncol 36:231–237. https://doi.org/10.1200/jco.2017.74.7162
5. Cortes JE, Kantarjian H, Shah NP et al (2012) Ponatinib in refractory Philadelphia chromosome–positive leukemias. N Engl J Med 367:2075–2088. https://doi.org/10.1056/nejmoa1205127
6. Hughes TP, Mauro MJ, Cortes JE et al (2019) Asciminib in chronic myeloid leukemia after ABL kinase inhibitor failure. N Engl J Med 381:2315–2326. https://doi.org/10.1056/nejmoa1902328
7. Shah NP, Nicoll JM, Nagar B et al (2002) Multiple BCR-ABL kinase domain mutations confer polyclonal resistance to the tyrosine kinase inhibitor imatinib (STI571) in chronic phase and blast crisis chronic myeloid leukemia. Cancer Cell 2:117–125. https://doi.org/10.1016/s1535-6108(02)00096-x
8. Branford S, Rudzki Z, Walsh S et al (2003) Detection of BCR-ABL mutations in patients with CML treated with imatinib is virtually always accompanied by clinical resistance, and mutations in the ATP phosphate-binding loop (P-loop) are associated with a poor prognosis. Blood 102(1):276–283. https://doi.org/10.1182/blood-2002-09-2896
9. Hughes T, Deininger M, Hochhaus A et al (2006) Monitoring CML patients responding to treatment with tyrosine kinase inhibitors: review and recommendations for harmonizing current methodology for detecting BCR-ABL transcripts and kinase domain mutations and for expressing results. Blood 108(1):28–37. https://doi.org/10.1182/blood-2006-01-0092
10. O'Hare T, Eide CA, Deininger MWN (2007) Bcr-abl kinase domain mutations, drug resistance, and the road to a cure for chronic myeloid leukemia. Blood 110(7):2242–2249. https://doi.org/10.1182/blood-2007-03-066936
11. Cortes J, Jabbour E, Kantarjian H et al (2007) Dynamics of BCR-ABL kinase domain mutations in chronic myeloid leukemia after sequential treatment with multiple tyrosine kinase inhibitors. Blood 110:4005–4011. https://doi.org/10.1182/blood-2007-03-080838
12. Hughes TP, Saglio G, Quintás-Cardama A et al (2015) BCR-ABL1 mutation development during first-line treatment with dasatinib or imatinib for chronic myeloid leukemia in chronic phase. Leukemia 29:1832–1838. https://doi.org/10.1038/leu.2015.168
13. Braun TP, Eide CA, Druker BJ (2020) Response and resistance to BCR-ABL1-Targeted therapies. Cancer Cell 37(4):530–542. https://doi.org/10.1016/j.ccell.2020.03.006
14. Lipton JH, Chuah C, Guerci-Bresler A et al (2016) Ponatinib versus Imatinib for newly diagnosed chronic myeloid leukaemia: an international, randomised, open-label, phase 3 trial. Lancet Oncol 17(5):612–621. https://doi.org/10.1016/s1470-2045(16)00080-2
15. Moslehi JJ, Deininger M (2015) Tyrosine kinase inhibitor-Associated Cardiovascular toxicity in chronic myeloid leukemia. J Clin Oncol 33(35):4210–4218. https://doi.org/10.1200/jco.2015.62.4718
16. Steegmann JL, Baccarani M, Breccia M et al (2016) European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia. Leukemia 30(8):1648–1671. https://doi.org/10.1038/leu.2016.104
17. Saydam G, Ali R, Demir AM et al (2022) The effect of comorbidities on the choice of tyrosine kinase inhibitors in patients with chronic myeloid leukemia. Int J Hematol Oncol 11(1):IJH38. https://doi.org/10.2217/ijh-2021-0010
18. Soverini S, Colarossi S, Gnani A et al (2006) GIMEMA Working Party on Chronic Myeloid Leukemia. Contribution of ABL kinase domain mutations to imatinib resistance in different subsets of Philadelphia-positive patients: by the GIMEMA Working Party on chronic myeloid leukemia. Clin Cancer Res 12(24):7374–7379. https://doi.org/10.1158/1078-0432.ccr-06-1516
19. Etienne G, Dulucq S, Huguet F et al (2019) Incidence and outcome of BCR-ABL mutated chronic myeloid leukemia patients who failed to tyrosine kinase inhibitors. Cancer Med 8(11):5173–5182. https://doi.org/10.1002/cam4.2410
20. Réa D, Mauro MJ, Boquimpani C et al (2021) A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. Blood 138(21):2031–2041. https://doi.org/10.1182/blood.2020009984
21. Cortes JE, Kim D-W, Pinilla-Ibarz J et al (2013) A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. N Engl J Med 369(19):1783–1796. https://doi.org/10.1056/nejmoa1306494
22. Cortes JE, Kim D-W, Pinilla-Ibarz J et al (2018) Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia: final 5-year results of the phase 2 PACE trial. Blood 132(4):393–404. https://doi.org/10.1182/blood-2016-09-739086
23. Valent P, Hadzijusufovic E, Schernthaner G-H et al (2015) Vascular safety issues in CML patients treated with BCR/ABL1 kinase inhibitors. Blood 125(6):901–906. https://doi.org/10.1182/blood-2014-09-594432
24. Januzzi JL, Garasic JM, Kasner SE et al (2022) Retrospective analysis of arterial occlusive events in the PACE trial by an independent adjudication committee. J Hematol Oncol 15(1):1–25. https://doi.org/10.1186/s13045-021-01221-z
25. Pulte ED, Chen H, Price LSL et al (2022) FDA approval Summary: revised indication and dosing regimen for Ponatinib based on the results of the OPTIC Trial. Oncologist 27(2):149–157. https://doi.org/10.1093/oncolo/oyab040
26. Mian AA, Rafiei A, Haberbosch I et al (2015) PF-114, a potent and selective inhibitor of native and mutated BCR/ABL is active against Philadelphia chromosome-positive (Ph+) leukemias harboring the T315I mutation. Leukemia 29(5):1104–1114. https://doi.org/10.1038/leu.2014.326
27. Ivanova ES, Tatarskiy VV, Yastrebova MA et al (2019) PF-114, a novel selective inhibitor of BCRABL tyrosine kinase, is a potent inducer of apoptosis in chronic myelogenous leukemia cells. Int J Oncol 55(1):289–297. https://doi.org/10.3892/ijo.2019.4801
28. National Cancer Institute Common Terminology Criteria for Adverse Events 4.03, 14 (2010) June https://www.eortc.be/services/doc/ctc/ctcae_4.03_2010-06-14_quickreference_5x7.pdf
29. Baccarani M, Deininger MW, Rosti G et al (2013) European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood 122(6):872–884. https://doi.org/10.1182/blood-2013-05-501569
30. McDermott MM, Liu K, Criqui MH et al (2005) Ankle-Brachial Index and Subclinical Cardiac and Carotid Disease the multi-ethnic study of atherosclerosis. Am J Epidemiol 162:33–41. https://doi.org/10.1093/aje/kwi167

31. Copland M (2022) Treatment of blast phase chronic myeloid leukaemia: a rare and challenging entity. Br J Haematol 199(5):665–678. https://doi.org/10.1111/bjh.18370
32. Jain P, Kantarjian HM, Ghorab A et al (2017) Prognostic factors and survival outcomes in patients with chronic myeloid leukemia in blast phase in the tyrosine kinase inhibitor era: Cohort study of 477 patients. Cancer 123(22):4391–4402. https://doi.org/10.1002/cncr.30864
33. Ren X, Pan X, Zhang Z et al (2013) Identification of GZD824 as an orally bioavailable inhibitor that targets phosphorylated and nonphosphorylated breakpoint Cluster region – Abelson (Bcr-Abl) kinase and overcomes clinically acquired mutation-Induced Resistance against Imatinib. J Med Chem 56:879–894. https://doi.org/10.1021/jm301581y
34. Jiang Q, Li Z, Qin Y et al (2022) Olverembatinib (HQP1351), a well-tolerated and effective tyrosine kinase inhibitor for patients with T315I-mutated chronic myeloid leukemia: results of an open-label, multicenter phase 1/2 trial. J Hematol Oncol 15:113. https://doi.org/10.1186/s13045-022-01334-z
35. Jabbour E, Oehler VG, Koller PB et al Olverembatinib after failure of tyrosine kinase inhibitors, including Ponatinib or Asciminib: a phase 1b Randomized Clinical Trial. JAMA Oncol 11(1):28–35. https://doi.org/10.1001/jamaoncol.2024.5157
36. PF-114 phase -3 clinical trial https://grls.rosminzdrav.ru/CIPermissionMini.aspx?CIStatementGUID=3fcf1320-4c3d-490b-9300-004bd84dc733_CIPermGUID=a0f27ea3-cfd1-4593-a506-5f377a7e04d5

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