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ORIGINAL ARTICLE

A drug–drug interaction study to assess the effect of the CYP1A2 inhibitor fluvoxamine on the pharmacokinetics of dovitinib (TKI258) in patients with advanced solid tumors

Vincent A. de Weger[1] · Sanjay Goel[2] · Roger von Moos[3] · Jan H. M. Schellens[1,4] · Nicholas Mach[5] · Eugene Tan[6] · Suraj Anand[6] · Jeffrey W. Scott[6] · Ulrik Lassen[7]

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Abstract

Purpose Dovitinib is an orally available multi tyrosine kinase inhibitor which inhibits VEGFR 1–3, FGFR 1–3, and PDGFR. This study was performed to investigate the potential drug–drug interaction of dovitinib with the CYP1A2 inhibitor fluvoxamine in patients with advanced solid tumors.

Methods Non-smoking patients of ≥ 18 years with advanced solid tumors, excluding breast cancer, were included. Patients were treated with a dose of 300 mg in 5 days on/2 days off schedule. Steady-state pharmacokinetic assessments of dovitinib were performed with or without fluvoxamine.

Results Forty-five patients were enrolled; 24 were evaluable for drug–drug interaction assessment. Median age was 60 years (range 30–85). At steady state the geometric mean for dovitinib (coefficient of variation%) of the area under the plasma concentration–time curve ($AUC_{0–72h}$) and maximum concentration (C_{max}) were 2880 ng/mL h (47%) and 144 ng/mL (41%), respectively. Following administration of dovitinib in combination with fluvoxamine the geometric mean of dovitinib $AUC_{0–72h}$ and C_{max} were 8290 ng/mL h (60%) and 259 ng/mL (45%), respectively. The estimated geometric mean ratios for dovitinib $AUC_{0–72h}$ and C_{max} (dovitinib + fluvoxamine vs. dovitinib alone) were 2.88 [90% confidence interval (CI) 2.58, 3.20] and 1.80 (90% CI 1.66, 1.95). This effect is considered a moderate drug–drug interaction.

Conclusions Fluvoxamine co-administration resulted in a 80% increase in C_{max} and a 188% increase in $AUC_{0–72h}$ of dovitinib. Given the increase in exposure to dovitinib observed, patients are at risk of dovitinib related toxicity. Dovitinib should, therefore, not be co-administered with moderate and strong CYP1A2 inhibitors, without dose reduction.

Keywords Drug–drug interaction · Dovitinib · Fluvoxamine CYP1A2 · TKI258

Abbreviations

AUC	Area under the plasma concentration–time curve
CLss/*F*	Apparent oral steady state clearance
C_{max}	Maximum plasma concentration
CV%	Coefficient of Variation%
CYP	Cytochrome P450 enzyme
DDI	Drug–drug interaction
ECOG	Eastern Cooperative Oncology Group
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
GIST	Gastro-intestinal stromal tumor
MTD	Maximum tolerated dose

✉ Jan H. M. Schellens
J.Schellens@nki.nl

1 Division of Clinical Pharmacology, The Netherlands Cancer Institute, Plesmanlaan 121, 1066CX Amsterdam, The Netherlands

2 Albert Einstein Cancer Center, Montefiore Medical Center, 111 E 210th Street, Bronx, NY 10567, USA

3 Department of Internal Medicine, Kantonsspital Graubünden, Loestrasse 170, 7000 Chur, Switzerland

4 Department of Pharmaceutical Sciences, Utrecht University, Universiteitsweg 99, 3584CG Utrecht, The Netherlands

5 Division of Oncology, University Hospital of Genève, Rue Gabrielle-Perret-Gentil 4, 1205 Geneva, Switzerland

6 Novartis Pharmaceuticals Corporation, 1 Health Plaza, East Hanover, NJ 07936, USA

7 Department of Oncology, Rigshospitalet, Blegsdamsvej 9, 2100 Copenhagen, Denmark

PDGF	Platelet-derived growth factor
PDGFR	Platelet-derived growth factor receptor
PK	Pharmacokinetics
PAS	Pharmacokinetic analyses set
TDM	Therapeutic drug monitoring
TK	Tyrosine kinase
T_{max}	Time to reach maximum plasma concentration
$T_{1/2}$	Terminal half-life
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

Introduction

The tyrosine kinases (TK) are important mediators of signal transduction in human cells. Activation of TK leads to diverse biological processes such as growth, differentiation, metabolism, and apoptosis. Activating mutations in TK are important drivers in the development of malignant disease. The multi-tyrosine kinase inhibitor (TKI), dovitinib (TKI258) binds to several TK including and primarily: the vascular endothelial growth factor receptors (VEGFR 1–3), fibroblast growth factor receptors (FGFR 1–3) and platelet-derived growth factor receptor (PDGFR), thereby disrupting the signaling by their respective growth factors, vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF) [1].

Dovitinib has been investigated in three phase I dose-escalation trials and the dose of 500 mg on a 5 days on/2 days off schedule has been selected for the further clinical development [2–4]. Clinical development continued in both phase II and III trials in a variety of malignancies [e.g., renal cell carcinoma and gastro-intestinal stromal cell tumor (GIST)] [5–14].

Continuous daily dosing of dovitinib indicated that the drug has a time-dependent and nonlinear PK, which results in dose-dependent time to reach steady state, as well as dose-dependent accumulation at steady state and at the MTD of 500 mg on a 5 days on/days off schedule [15]. The plasma half-life of dovitinib at steady state is around 13 h [2, 5]. Dovitinib has a good oral bio-availability of around 75% and is extensively metabolized by the liver and excreted primarily via the feces [16]. Primary biotransformation in humans includes hydroxylation, *N*-oxidation, *N*-demethylation and direct glucuronidation of parent dovitinib. The biotransformation is to be attributed to the cytochrome P450 (CYP) enzymes CYP3A4 and CYP1A1/A2 (CYP1A), FMO3 and UGT [16]. In vitro dovitinib is metabolized by FMO3 (65–83%), CYP3A4 (17–35%), and inducible enzymes such as CYP1A1/1A2 [15] The metabolites of dovitinib are more than fivefold less pharmacologically active than the parent drug. Based on the human mass-balance and absorption excretion trial, as performed by Dubbelman et al. it is expected that CYP1A1/A2 accounts for approximately 1/3 of the in vivo metabolism of [14^C] dovitinib [16]. Since CYP1A2 is 28- to 126-fold more abundant than CYP1A1 in human livers, it is expected that this enzyme has a higher contribution to dovitinib metabolism [17].

In preclinical models, dovitinib was found to be a moderate CYP3A4 inhibitor and a strong CYP1A2 inducer, a moderate CYP2C19 inducer and a weak CYP2C9 inducer. The induction of CYP1A2 by dovitinib was further investigated in a drug–drug interaction (DDI) study with caffeine, which is a known CYP1A2 substrate. The area under the plasma concentration–time curve (AUC) for caffeine was reduced by 96% after co-administration of dovitinib [15]. This induction of CYP1A2 was further highlighted in a clinical phase I study in which the co-administration of dovitinib with erlotinib was investigated. The study was terminated early, because of a significant drug–drug interaction (DDI). Induction of CYP1A2 by dovitinib was the likely cause of this DDI, that resulted in a decrease of 97% in erlotinib concentrations [18], an effect that is comparable to the interaction observed in the study with caffeine.

To evaluate the effect of CYP1A2 inhibition on the metabolism of dovitinib, the strong inhibitor of CYP1A2, fluvoxamine [19, 20] was co-administered in this study. In preclinical human liver microsomal studies, fluvoxamine was shown to be a potent inhibitor of CYP1A2, with K_i values of 0.08–0.28 and 0.04 µM for caffeine and ethoxyresorufin, respectively [17, 21]. Fluvoxamine is, however, not a selective inhibitor of CYP1A2, as it is also an inhibitor of CYP3A4 [22, 23]. The metabolism of fluvoxamine primarily occurs via CYP2D6, but CYP1A2 is also involved. As was underscored by studies that showed that plasma fluvoxamine levels were significantly lower in cigarette smokers, a result that was attributed to CYP1A2 induction by cigarette smoking [24]. The half-life of fluvoxamine is around 10.5 h [24].

The 100 mg dose of fluvoxamine is expected to achieve peak concentrations close to 0.1 µM [25] suggesting a sufficient inhibitory effect on CYP1A2, furthermore it was shown that at steady-state a fluvoxamine dose of 25 mg already inhibited about 75% of CYP1A2 [26]. Based on the approximately 1/3 of the metabolism of dovitinib that can be accounted for by CYP1A2, an increase of about 33% in dovitinib plasma concentrations was expected. The actual increase in exposure to dovitinib might be higher due to the inherent PK variability of dovitinib. Therefore, as a safety precaution, a reduced dose of 300 mg on a 5 days on/2 days off schedule was selected for the pharmacokinetic (PK) phase of this study, rather than the maximum tolerated dose (MTD) of 500 mg on a 5 days on/2 days off schedule.

Materials and methods

Patients

Patients with histological or cytological proof of advanced solid tumors, excluding breast cancer, were allowed to enroll in this study. Other inclusion criteria were provision of written informed consent prior to study start, age 18 years or older, an ECOG performance status ≤ 1, a life expectancy of ≥ 3 months, and laboratory values of the hematology, renal function and hepatic values within a safety threshold. Exclusion criteria were brain metastases, another active malignancy, and administration of other targeted therapy within the last 2 weeks prior to study start. Patients expected to receive or to use moderate to strong inhibitors/inducers of CYP3A4 or CYP1A2 (including tobacco) from 5 days prior to start for inhibitors and 30 days prior to study start for inducers until after completion of the PK phase were excluded. Alcohol use exceeding one drink a day was not allowed from 3 days prior to and until after completion of the PK phase, woman planning to become pregnant or woman pregnant or breast feeding were also not allowed to enroll.

Study design

The study was performed in two parts: in part I the effect of fluvoxamine co-administration on dovitinib pharmacokinetics was investigated. In this PK phase patients received dovitinib in a 5 days on 2 days off schedule at a daily dose of 300 mg. Blood samples for steady state PK for dovitinib were collected on days 19–22 (starting on week 3 day 5). On day 22 (week 4 day 1) patients started with a 100 mg QD fluvoxamine dose for one week (days 22–28). On day 26 (week 4 day 5), fluvoxamine was administered 5 min prior to dovitinib, and blood samples for PK for dovitinib were collected on days 26–29 (starting on week 4 day 5).Patients who completed and also who did not complete the PK phase were allowed to continue dovitinib treatment after a dosing interruption of 5–11 days, to give sufficient time for washout. Patients continued dovitinib at 500 mg QD in a 5 days on/2 days off schedule in the clinical treatment phase. Patients were allowed to continue dovitinib until disease progression or intolerable toxicity.

Evaluability criteria

A minimum of 16 evaluable patients were planned to be enrolled to determine the influence of fluvoxamine on the steady state PK of dovitinib. Patients were evaluable for the DDI part if two full PK profiles of dovitinib (dovitinib alone and dovitinib with fluvoxamine) were available. Full PK was defined as: a patient did not vomit within 4 h after receiving dovitinib on the days of blood collection for PK, did receive ≥ 7 of the first 10 scheduled doses of dovitinib, and did receive the next 4 consecutive days of dosing prior to the days of blood collection for PK. Additionally, the patient had to have taken fluvoxamine for 7 consecutive days following the completion of PK collection for dovitinib alone, with no vomiting within 4 h of fluvoxamine administration on the day of PK profile collection for dovitinib and fluvoxamine.

Safety evaluations

Safety assessments consisted of monitoring and recording of all AEs, including serious adverse events (SAE), the regular monitoring of electrocardiograms, cardiac imaging (using echocardiogram or multi gated acquisition (MUGA) scan), chest X-ray, hematology, serum chemistry, urinalysis, coagulation, thyroid function test, routine monitoring of vital signs (respiratory rate, weight, body temperature, sitting pulse and sitting blood pressure), and ECOG PS. Assessments were usually performed at Baseline/Screening, PK phase (Day 1, Day 12, Day 19, Day 26) and in the clinical phase (Week 1 Day 1, Week 4 Day 1 onwards every 4 weeks) and at the end of treatment.

Pharmacokinetic measurements

Pharmacokinetic sampling for dovitinib was performed on days 19 and 26 at the following time points: pre-dose, 2, 4, 6, 9, 24, 48 and 72 h after administration. Non-compartmental PK analyses were conducted on the full PK profiles of dovitinib. The primary PK parameters determined were area under the plasma concentration time curve time = 0–72 h ($AUC_{0–72h)}$ and maximum plasma concentration (C_{max}) for dovitinib with and without fluvoxamine. Secondary PK parameters were $AUC_{0–24h}$, time to reach C_{max} (T_{max}), terminal half-life ($T_{1/2}$) and apparent oral steady state clearance (CLss/F).

Efficacy

The response to treatment was determined by the investigator using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. The local Investigator's measurements were used for analysis and for treatment decision making. Evaluation was performed using either CT or MRI scans every 8 weeks.

Statistical analyses

A formal statistical analysis was conducted to explore the relative bio-availability of dovitinib co-administered with fluvoxamine as compared to dovitinib alone. A linear mixed effects model was fitted to the log-transformed steady state PK parameters ($AUC_{0–72hr}$ and C_{max}). Treatment, as the fixed

effect, and patients as random effect were included in the model. For the mixed model analysis, dovitinib + fluvoxamine was the test treatment and dovitinib alone the reference. The model based, between-treatment mean differences (dovitinib + fluvoxamine − dovitinib alone) and the corresponding two-sided 90% confidence intervals (CIs) were calculated on the log-scale. The between-treatment differences and 90% CIs were then back transformed to the original scale to obtain the geometric mean ratios (dovitinib + fluvoxamine/dovitinib alone) and the corresponding 90% CIs. Steady state PK parameters for dovitinib were summarized by treatment. Safety of dovitinib was evaluated for the PK and clinical treatment phases together by summarizing the frequency and severity of AEs. Efficacy data are presented as assessed by the investigators.

Results

Overall, 45 patients were enrolled. Patients had a median age of 60 years (range 30–85), with more male (60%) than female (40%). All patients had a good performance status according to the Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1. The most common tumor types were colorectal cancer (14 patients), adenoid cystic carcinoma (5 patients), ovarian cancer (4 patients) and pancreatic cancer (4 patients). A more detailed overview of the patient characteristics is shown in Table 1.

Twenty-five patients completed the PK phase as per protocol, of which 24 were considered evaluable for the pharmacokinetic analysis set (PAS). Twenty patients discontinued prior to completion of the PK phase: 13 for adverse events, 3 due to non-compliance with study treatment and physician decision, 1 each due to progressive disease, protocol deviation and subject/guardian decision. In total 33 patients continued into the treatment phase. Reasons for treatment discontinuation in these patients were: progression of disease in 24 patients, adverse events in 5 patients, death, not treatment related, in 2 patients, and study termination by the sponsor (patients were allowed to continue on dovitinib in another protocol), in 2 patients.

Pharmacokinetics

The PK parameters of dovitinib when administered alone and with fluvoxamine are displayed in Table 2. At steady state after 3 weeks of treatment with dovitinib (Day 19) the geometric mean [coefficient of variation% (CV%)] of $AUC_{0–72h}$ and C_{max} was 2880 ng/mL h (47%) and 144 ng/mL (41%), respectively. Following administration of dovitinib in combination with fluvoxamine the geometric mean of dovitinib (Day 26) $AUC_{0–72h}$ and C_{max} increased to 8290 ng/mL h (60%) and 259 ng/mL (45%), respectively. The estimated geometric mean ratios for dovitinib $AUC_{0–72h}$ and C_{max} (dovitinib + fluvoxamine vs. dovitinib alone) were 2.88 (90% CI 2.58, 3.20) and 1.80 (90% CI 1.66, 1.95), respectively, as presented in Table 3. This indicates that fluvoxamine increased the dovitinib $AUC_{0–72h}$ by 188% and C_{max} by 80%, a 2.9- and 1.8-fold increase, respectively.

Based on the fold change, the interaction on C_{max} is considered a weak interaction as the increase is < twofold, however, the interaction on $AUC_{0–72h}$ is considered moderate as the increase was ≥ 2 and ≤ fivefold [27]. Consistent with increased $AUC_{0–72h}$ and C_{max}, geometric mean of dovitinib CLss/*F* decreased from 157 to 77 L h and $T_{1/2}$ increased from 14 to 20 h for dovitinib + fluvoxamine vs dovitinib alone, respectively.

Table 1 Patient demographics

	All patients ($n = 45$)
Age (years)	
Median (range)	60 (30–85)
Sex *n* (%)	
Female	18 (40%)
Male	27 (60%)
Race *n* (%)	
Caucasian	41 (91.1%)
Black	2 (4.4%)
Asian	2 (4.4%)
ECOG performance status: *n* (%)	
0	24 (53%)
1	21 (47%)
Tumor type	
Colorectal	14
Adenoid cystic carcinoma	5
Ovarian	4
Pancreatic	4
NSCLC	3
Urothelial cell carcinoma	3
Other	12

n number of patients, *NSCLC* non-small cell lung cancer

Safety

All patients included reported at least one adverse event suspected to be study drug related. The most commonly reported toxicities were diarrhea (60%), nausea (47%), and fatigue (45%). Fourteen patients (31%) discontinued the study drug due to adverse events regardless of study drug relationship. Forty percent of patients experienced grade ≥ 3 toxicity. The most common grade 3 toxicity was fatigue and occurred in 18% of patients; other grade 3 events included diarrhea and pulmonary embolism in 2 patients each. Additionally, 1 patient had

Table 2 Summary of dovitinib pharmacokinetic parameters by treatment (pharmacokinetic analysis set of dovitinib)

	$AUC_{0–72h}$ (ng/mL h)	$AUC_{0–24h}$ (ng/mL h)	C_{max} (ng/mL)	T_{max} (h)	$T_{1/2}$ (h)	CLss/*F* (L/h)
Dovitinib ($n=24$)						
Mean (CV%)	3180 (46%)	2240 (42%)	155 (39%)	3.97 (1.90–9.00)	14.4 (14%)	157 (41%)
Geo-mean (CV%)	2880 (47%)	2060 (43%)	144 (41%)	Median (range)	14.2 (14%)	145 (43%)
Dovitinib + Fluvoxamine ($n=24$)						
Mean (CV%)	9450 (48%)	5080 (50%)	281 (40%)	4.27 (1.75–9.00)	20.5 (25%)[a]	77.3 (48%)[a]
Geo-mean (CV%)	8290 (60%)	4600 (50%)	259 (45%)	Median (range)	19.9 (26%)[a]	69.8 (49%)[a]

CV% = Coefficient of variation (%); CV% = (SD/mean) × 100; CV% geo-mean = sqrt(exp(variance log-transformed data) − 1) × 100

$AUC_{0–72h}$ area under the plasma concentration time curve $t=0–72$ h, $AUC_{0–24h}$ area under the plasma concentration time curve $t=0–24$ h, C_{max} maximum plasma concentration observed, T_{max} time to reach C_{max}, $T_{1/2}$ terminal half-life, *CLss/F* apparent oral steady state clearance, *N* number of patients included in the analyses

[a]$n=19$

Table 3 Summary of statistical analysis of primary pharmacokinetics parameters for dovitinib (pharmacokinetic analysis set of dovitinib)

PK parameter (unit)	Treatment	*n*	Adjusted geo-mean	Comparison(s)	Treatment comparison 90% CI		
					Geo-mean ratio	Lower	Upper
$AUC_{0–72h}$ (ng/mL h)	Dovitinib	24	2880	Dovitinib + fluvoxamine: Dovitinib	2.88	2.58	3.20
	Dovitinib + fluvoxamine		8290				
C_{max} (ng/mL)	Dovitinib	24	144	Dovitinib + fluvoxamine: Dovitinib	1.80	1.66	1.95
	Dovitinib + fluvoxamine		259				

The model for log-transformed PK parameter $AUC_{0–72h}$ and C_{max} includes treatment as a fixed factor and patient as a random factor

Adjusted geo-mean, geo-mean ratio and 90% confidence interval (90% CI) are all determined from a mixed effect model and back transformed from log-scale

$AUC_{0–72h}$ area under the plasma concentration time curve $t=0–72$ h, C_{max} maximum plasma concentration observed, *N* Number of patients, *Geo-mean* geometric mean

a grade 4 hypertriglyceridemia. In Table 4 all adverse events suspected to be related to the study drug which occurred in > 5% of patients or are grade ≥ 3 are presented. Six (13.3%) on-treatment deaths (within 30 days of the last dose of dovitinib), all due to disease progression, occurred on study. Two additional deaths were reported which occurred more than 30 days after the last dose of dovitinib, one due to disease progression and one due to unknown causes.

Efficacy

The best tumor response while on study, as assessed by the investigators was partial response in three patients (adenoid cystic carcinoma, urothelial cell carcinoma and endometrial carcinoma, all in 1 patient). Nineteen patients had stable disease and 11 had progressive disease at the first evaluation. In Fig. 1 the time on the PK phase and the treatment phase is presented for all patients. Seven patients had prolonged benefit of dovitinib treatment and continued treatment with dovitinib > 6 months.

Discussion

The co-administration of fluvoxamine with dovitinib resulted in an increase in dovitinib $AUC_{0–72h}$ of 188% and C_{max} of 80%. Fluvoxamine is therefore considered to be a moderate inhibitor of dovitinib metabolism.

The increase in $AUC_{0–72h}$ observed in this study was far greater than expected. Based on the role of CYP1A2 in the metabolism of dovitinib, the increase was predicted to be about 33%. The increase of $AUC_{0–72h}$ was however 188%, about sixfold higher than expected. It is unlikely that the increase can entirely be attributed to CYP1A2 inhibition alone.

The precise importance of CYP1A2 and CYP3A4 in the metabolism of dovitinib after prolonged use is unclear. Over time CYP1A2 will be induced, whereas CYP3A4 will be inhibited by dovitinib. This likely results in a higher dependence on CYP1A2 for metabolism of dovitinib after prolonged use. Given the large drug–drug interaction observed it is likely that the 100 mg fluvoxamine dose has inhibited CYP1A2 entirely, even after the induction of CYP1A2 by dovitinib. Given the potential increase of metabolism via

Table 4 Adverse events (all grades, in > 5% of patients or grade ≥ 3), suspected to be related to the study drug, by preferred term and maximum grade

Preferred term	Grade 1 *n* (%)	Grade 2 *n* (%)	Grade 3 *n* (%)	Grade 4 *n* (%)	All grades *n* (%)
All patients (*n* = 45)					
Total	7 (15.6)	20 (44.4)	17 (37.8)	1 (2.2)	45 (100.0)
Diarrhea	16 (35.6)	9 (20.0)	2 (4.4)	0	27 (60.0)
Nausea	11 (24.4)	9 (20.0)	1 (2.2)	0	21 (46.7)
Fatigue	10 (22.2)	4 (8.9)	6 (13.3)	0	20 (44.4)
Vomiting	13 (28.9)	4 (8.9)	1 (2.2)	0	18 (40.0)
Decreased appetite	5 (11.1)	4 (8.9)	0	0	9 (20.0)
Weight decreased	3 (6.7)	6 (13.3)	0	0	9 (20.0)
Rash	5 (11.1)	2 (4.4)	0	0	7 (15.6)
Dysgeusia	6 (13.3)	0	0	0	6 (13.3)
Headache	1 (2.2)	4 (8.9)	0	0	5 (11.1)
Abdominal pain upper	4 (8.9)	0	0	0	4 (8.9)
Constipation	2 (4.4)	2 (4.4)	0	0	4 (8.9)
Dyspnea	3 (6.7)	1 (2.2)	0	0	4 (8.9)
Palmar-planter erythrodysaesthesia syndrome	2 (4.4)	1 (2.2)	1 (2.2)	0	4 (8.9)
Abdominal pain	1 (2.2)	1 (2.2)	1 (2.2)	0	3 (6.7)
Dry mouth	2 (4.4)	1 (2.2)	0	0	3 (6.7)
Hypertriglyceridemia	0	0	1 (2.2)	1 (2.2)	2 (4.4)
Pulmonary embolism	0	0	2 (4.4)	0	2 (4.4)
Stomatitis	1 (2.2)	0	1 (2.2)	0	2 (4.4)
Cholesterol increased (blood)	0	0	1 (2.2)	0	1 (2.2)
Epilepsy	0	0	1 (2.2)	0	1 (2.2)
Febrile neutropenia	0	0	1 (2.2)	0	1 (2.2)
Hypertension	0	0	1 (2.2)	0	1 (2.2)
Left ventricular dysfunction	0	0	1 (2.2)	0	1 (2.2)
Leukopenia	0	0	1 (2.2)	0	1 (2.2)

n number of patients

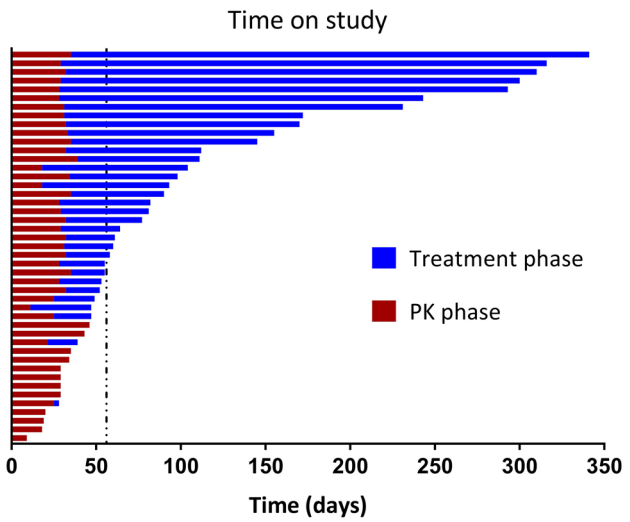

Fig. 1 Time on study. Time on study for all 45 patients enrolled. In red the duration patients were in the pharmacokinetic phase (PK) and in blue the time patients continued in the treatment phase. The dashed vertical line represents the first scheduled tumor assessment (8 weeks)

CYP1A2, the inhibition by fluvoxamine might explain at least in part the higher than expected change in both $AUC_{0–72h}$ and C_{max}.

Another potential contributing factor is the additional inhibition on CYP3A4 caused by fluvoxamine, as it is not only an inhibitor of CYP1A2 but also a CYP3A4 inhibitor. The combination of CYP1A2 and CYP3A4 inhibition might together provide the explanation for the 188% increase in the dovitinib $AUC_{0–72h}$.

Since both fluvoxamine and dovitinib are partially metabolized by CYP1A2 saturation of this enzyme may have occurred as a result of the inhibition of CYP1A2, which could have led to higher fluvoxamine levels, potentially resulting in more extensive inhibition of CYP3A4. This inhibition may have further decreased dovitinib metabolism. A drug interaction in which CYP2D6 is involved is not expected, as dovitinib is not known to inhibit or induce this enzyme [28].

A limitation of this study is that plasma concentrations of fluvoxamine were not measured. This would have added

valuable information on whether there was an effect of dovitinib on fluvoxamine plasma exposure, as this might partially explain the large effect observed. Given the design of the study a comparison of toxicity in weeks 3 and 4 of the study is not possible. The toxicity in week 4 would be overestimated as a result of carry-over of toxicity that has started in the first 3 weeks. A comparison with other studies is difficult as patients were treated at a relative low-dose of dovitinib for which limited safety data is available. The overall toxicity profile observed in this study was however in line with previous studies and no new safety signals were observed.

A 188% increase in $AUC_{0–72h}$ could result in dovitinib related adverse events. To mitigate this risk, commonly used drugs such as ciprofloxacin and oral contraceptives, that are strong and moderate CYP1A2 inhibitors, respectively, should not be given with dovitinib, or a dose reduction of dovitinib should be applied. The dovitinib dose should be reduced to 1/3 of the standard dose, given the 2.9-fold increase in $AUC_{0–72h}$ observed in this study after the combined administration of fluvoxamine and dovitinib. Further studies are needed to investigate the role of CYP3A4 inhibition to further identify the mechanism behind the large increase in $AUC_{0–72h}$ observed in this study.

Conclusion

The DDI observed in this study is of clinical relevance given the potential increase in plasma exposure to dovitinib, as this might result in increased dovitinib related toxicity. Prior to start of a moderate to strong CYP1A2 inhibitor dovitinib treatment should be stopped or the dose should be reduced, to mitigate the risk of toxicity.

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Compliance with ethical standards

Ethical standards The study was performed in compliance with the Declaration of Helsinki and its amendments. All patients provided informed consent prior to participation. The study was registered in clinicaltrials.gov (identifier: NCT01700270).

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Conflict of interest Jeffrey Scott, Arnand Suraj and Eugene Tan are employees of Novartis Pharmaceuticals. The other authors declare that they have no competing interests.

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