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Phase I safety and pharmacokinetic study of SU-014813 in combination with docetaxel in patients with advanced solid tumours ☆,☆☆

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ABSTRACT

Background: In pre-clinical models enhanced anti-tumour activity was observed when SU-014813, an oral multi-targeted tyrosine kinase inhibitor was combined with docetaxel. This synergy might be explained by improvement of the penetration of cytotoxic agents into tumours as a result of both VEGFR and PDGFR inhibition. We assessed the maximal tolerated dose (MTD), evaluated the pharmacokinetics and preliminary anti-tumour efficacy of oral SU-014813 administered continuously in combination with docetaxel to patients with advanced solid tumours.

Methods: In this phase I study successive patient cohorts received docetaxel 60 or 75 mg/m^2 every 3 weeks in combination with chronic daily dosing of SU-014813. Dose limiting toxicity was assessed both in the first and second treatment cycle.

Results: Twenty-five patients were entered on study of which 24 started treatment. Dose limiting toxicities were prolonged neutropenia, neutropenic fever, fatigue and diarrhoea. Other toxicities included fatigue, alopecia, nausea, vomiting, anorexia, rash, hypertension and hair discolouration. The recommended phase II dose was determined to be docetaxel 75 mg/m^2 in combination with SU-014813 50 mg/day. There was no clinically relevant pharmacokinetic drug–drug interaction. Two patients (8%) achieved a partial response (PR) and 7 patients (29%) had stabilisation of their disease (SD) >6 months, for a clinical benefit rate of 37.5%. The activity observed in patients with melanoma and sunitinib refractory gastrointestinal stromal tumours (GIST) was particularly noteworthy.

Conclusions: Oral SU-014813 50 mg/day with docetaxel 75 mg/m^2 is a clinically feasible regimen with a manageable safety profile and anti-tumour activity. Further development is warranted in patients with melanoma and GIST.

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1. Introduction

Angiogenesis, the development of new blood vessels from existing vascular endothelium, plays a vital role in the growth, invasion and metastasis of human cancer. In this process at least three growth factors are known to be of crucial importance; the vascular endothelial growth factor (VEGF), the platelet derived growth factor (PDGF) and the basic fibroblast growth factor (bFGF). Over the past decade, inhibition of VEGF and its receptors have been successfully pursued as anti-cancer therapy.[1–4] The clinical relevance of inhibition of PDGF and bFGF is yet less well elucidated.

SU-014813 is an oral, indolinone based, multi-targeted tyrosine kinase inhibitor. *In vitro*, SU-014813 inhibited VEGFR-2, PDGFR-β and FLT3-ITD phosphorylation, with cellular IC_{50} values of 0.04, 0.02 and 0.05 μmol/L, respectively, and showed anti-tumour efficacy in tumour xenograft models.[5–8] SU-014813 has oral bioavailability of approximately 40% in mice. No active metabolite has been demonstrated for SU-014813 in pre-clinical studies. Sunitinib and SU-014813 receptor targets are similar, SU-014813 was developed as a follow-up compound to improve pharmacokinetics and safety characteristics.

SU-014813 was assessed as a single agent in a phase I trial studying dose ranges of 25–250 mg administered orally and daily for 4 weeks in 5 weeks cycles (4 + 1 schedule) and in a continuous daily schedule.[9] The recommended single agent dose for phase II studies is 100 mg administered continuously daily. Observed side-effects were mostly mild to moderate and included leucocytopenia, thrombocytopenia, hypertension, fatigue, diarrhoea, skin rash, hair discolouration and asymptomatic increase of plasma lipase levels. Pharmacokinetics increased in a dose-proportional manner and SU14813 was eliminated with a mean terminal half-life of 9–34 h. In preclinical models enhanced anti-tumour activity was observed when SU-014813 was combined with the cytotoxic agent docetaxel. Additionally, recently published data suggest a role for both VEGFR and PDGFR inhibition in improving the penetration of cytotoxic agents into tumours.[10–13] In tumours, the interstitial fluid pressure is frequently enhanced as compared to normal tissue. This pressure potentially acts as a barrier for tumour transvascular drug transport. Particularly PDGF beta is a mediator of tumour hypertension through this mechanism. The ratio of vascular volume to total tumour volume increased significantly ($P < .001$) following the administration of a PDGFR-β inhibitor, suggestive of recruitment of previously non-functioning vessels.[10] VEGF has been suggested to affect vascular permeability via various mechanisms. This combined effect could partly explain the improved delivery of cytotoxic drugs to the tumour in animal models.[11–13] Since SU-014813 is a potent inhibitor of both VEGFR and PDGFR, this was considered as an additional reason to combine the agent with cytotoxic drugs such as docetaxel.

We performed a dose-finding study of SU-014813 in combination with docetaxel in patients with solid tumours, with the primary objective to assess the maximal tolerated dose (MTD) of oral SU-014813 administered continuously in combination with docetaxel. Secondary objectives included (a) evaluation of pharmacokinetics drug interactions between SU-014813 and docetaxel and (b) to assess anti-tumour effects induced by the combination in the patients with measurable disease.

2. Patients and methods

2.1. Eligibility criteria

Patients with a cytologically or histologically confirmed diagnosis of an advanced and measurable or evaluable solid tumour were eligible. Additional criteria included: age ⩾ 18 years; ECOG performance status 0 or 1; an adequate bone marrow function (haemoglobin ⩾ 10 g/dL, platelet count ⩾ 100×10^9/L, absolute neutrophil count ⩾ 1.5×10^9/L), liver function (bilirubin ⩽ 1.5 the upper limit of normal (ULN), alanine aminotransferase and aspartate aminotransferase ⩽ 2.5 × ULN (5 × ULN in case of liver metastasis in the presence of a normal alkaline phosphatase), alkaline phosphatase ⩽ 2.5 × ULN (5 × ULN in case of bone or liver metastasis in the presence of a normal ALT/AST)) and renal function (serum creatinine ⩽ 1.5 × ULN) and a serum albumin ⩾ 3.0 g/dL.

Specific exclusion criteria included but were not limited to prior treatment with high-dose chemotherapy requiring stem cell rescue; prior treatment with docetaxel; prior irradiation to >25% of the bone marrow reserve; uncontrolled hypertension; presence of malabsorption due to prior surgery, gastrointestinal disease or an unknown reason or inability to take oral medication and/or CTCAE grade >2 neuropathy or oedema from any cause. This study was performed according to the principles defined by the Declaration of Helsinki in Rotterdam, The Netherlands and in Leuven, Belgium, and approved by the institutional ethics committees in both institutions. All the patients gave written informed consent prior to study entry.

2.2. Study design

SU-014813 (Pfizer Inc.) was supplied as gelatine capsules containing 25 mg or 50 mg of free base equivalent of SU-014813. The capsules were stored in opaque plastic bottles to protect the compound from light in a controlled room temperature of 20–25 °C. Commercially available docetaxel (Taxotere®) was supplied by the study centres and was stored between 2° and 25 °C in its original package to protect it from bright light. Patients received docetaxel as a 1 h intravenous infusion every 21 days starting from day 1 in cycle 1. SU-014813 was administered every morning on an empty stomach with a glass of water, about 2 h from food intake in cycles of 3 weeks starting from day 2 in cycle 1. Patients were to receive the combination SU-014813 and docetaxel for up to 6 cycles in the absence of any withdrawal criteria that would require treatment discontinuation. Individual treatment could be continued at the discretion of the treating physician in the presence of objective clinical benefit and the absence of unacceptable toxicity. Initially 3 patients were treated in each cohort starting with 50 mg SU-014813 and 60 mg/m^2 docetaxel. All the 3 patients were allowed to be enrolled simultaneously. Dose escalation of SU-014813 and docetaxel proceeded according to predefined dose levels.

Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (NCI CTCAE) Version 3.0.

The dose limiting toxicity (DLT) was defined in both the first and second cycle. Since SU-014813 was only administered from day 2 of the first cycle onwards, we assumed that a possible interaction between docetaxel and SU-014813 could only be fully evaluated during the second cycle since at that time steady state concentration of SU-014813 was present at the time of the administration of docetaxel. A DLT was defined as one of the following events: (1) febrile neutropenia, or grade 4 neutropenia lasting for $\geqslant$7 days, (2) grade $\geqslant$3 thrombocytopenia with bleeding or lasting $\geqslant$7 days; (4) grade 3 or 4 non-haematological toxicities including fatigue lasting for $\geqslant$7 days (except for skin discolouration, nausea, vomiting and diarrhoea without optimal supportive therapy and grade 3/4 hyperamylasemia without signs of pancreatitis), (5) grade $\geqslant$3 hypertension despite optimal treatment (i.e. combination of 2 anti-hypertensives) and (6) treatment discontinuation for $\geqslant$2 weeks because of drug related toxicity. Dose modifications to the next lower dose level were permitted once a patient had experienced a DLT.

If DLTs were observed in 1 out of 3 patients during the first or second cycle, up to 3 additional patients were to be treated at the same dose level. If 1 or none of these additional patients experienced DLT, the next dose level was to be studied. If more than one of the additional patients experienced DLT the maximum tolerated dose (MTD) had been exceeded and 3 more patients were to be treated at the next lower dose level, if only 3 patients were previously treated at that prior dose. If DLT had not been observed at the highest dose level for both docetaxel and SU-014813 then this dose would be considered the MTD.

If patients withdrew for reasons other than toxicity after completing only 1 cycle, they were to be replaced. In addition, patients who experienced significant toxicity attributed only to docetaxel necessitating dose reduction, were also to be replaced. Once the MTD was established an additional 9 patients would be enrolled at this dose level.

2.3. *Pretreatment and follow-up studies*

Before therapy, a complete medical history was taken and a physical examination was done including ECOG performance status, body weight, height and vital signs. A complete blood cell count including WBC differential and serum biochemistry, which included total bilirubin, serum transaminases, alkaline phosphatase, lactic dehydrogenase, amylase, lipase, albumin, sodium, potassium, chloride, calcium, phosphorus, blood urea nitrogen, creatinine, uric acid and glucose, were done as were urinalysis, triplicate 12-lead electrocardiograms and a pregnancy test (if applicable). The 12 lead electrocardiogram was repeated on day 1 of cycle 1 and subsequently if clinically indicated. Haematology and biochemistry assessments were performed on day 1, 8 and 15 (or more frequently if clinically indicated) of every cycle. Furthermore, weekly evaluations on day 1, 8 and 15 of each cycle included physical examination and toxicity assessments. Pre-medication with corticosteroids were allowed for 3 days, starting 1 day before day 1 of every cycle. Tumour imaging was performed within 14 days prior to study treatment, prior to cycles 3 and 5, at regular intervals thereafter, and at termination of study treatment.

In the protocol a PET assessment using radiolabelled docetaxel to measure tumour uptake of radiolabelled docetaxel was planned at MTD to study the influence of co-administration of SU-014813 on the tumoural uptake of docetaxel. Unfortunately no validated method for the radiolabelling of docetaxel could be developed and this part of the protocol was not carried out.

2.4. *Pharmacokinetic sampling and data analysis*

For docetaxel pharmacokinetic (PK) analyses, blood samples (5 mL) were collected using an indwelling i.v. canula in the opposite arm of infusion 15 min before dosing (time point 0) and 0.5, 1, 1.5, 3, 5, 7, 23 and 27 h after start of docetaxel infusion on day 1 of cycle 1 and 2. For SU-014813 PK, blood samples (2 mL) were collected before dosing and 1, 2, 4, 8 and 24 h after SU-014813 dosing on day 21 of cycle 1 and on day 1 of cycle 2. On day 1 of cycle 2, the day of the second docetaxel administration, SU-014813 was administered 1 h before docetaxel infusion. Additionally, trough samples for SU-014813 were collected prior to dosing on day 1 of all subsequent cycles. Blood samples for docetaxel as well as SU-014813 pharmacokinetic analyses were collected into appropriately labelled tubes containing sodium heparin and were kept at 4 °C until centrifugation within 30 min of collection at 1500*g* for 10 min. The plasma samples were divided into 2 aliquots (2 for docetaxel and 2 for SU-014813) and stored in appropriately labelled screw-cap polypropylene tubes at 20 °C or below until analysis.

2.5. *Data-analysis*

All patients who took at least one dose of SU-014813 were evaluable for all analyses. Descriptive statistics were used to analyse safety. Pharmacokinetic parameter estimates were

Table 1 – Patient baseline characteristics.

Characteristic	Number of patients
Age	
Mean (year)	54
Range (year)	32–75
Gender	
Male	18
Female	6
WHO PS	
0	4
1	15
2	5
Tumour type	
GIST	4
Melanoma	12
Miscellaneous	8
Prior treatment	
Radiotherapy	6
Systemic therapy	22
1–3 regimens	18
>3 regimens	4

determined from individual plasma concentration–time data using non-compartmental analyses (WinNonLin version 4.1).

3. Results

Patient baseline characteristics are presented in Table 1. Twenty-five patients were entered into the trial 24 of whom started study treatment. All 24 patients were evaluable for toxicity and PK analyses. All patients were Caucasian. At study cut-off, a total of 269 treatment cycles were administered, ranging from 2 to 45 cycles across the three dosing cohorts (2–45 in patients with malignant melanoma and 5–31 in patients with GIST).

In the patients included at the first dose level (SU-014813 50 mg + docetaxel 60 mg/m^2) no DLT was observed. In the second dose level (SU-014813 50 mg + docetaxel 75 mg/m^2) 1 DLT (neutropenia G4) was observed in one of the initial 3 patients treated, therefore 3 additional patients were included. At the third dose level (SU-014813 100 mg + docetaxel 75 mg/m^2) 1 DLT (neutropenic fever) was observed in one of the initial 3 patients. As per protocol, 3 additional patients were included 2 of which experienced a DLT (neutropenic fever and grade 3 diarrhoea). Since the MTD was exceeded 9 additional patients were then enrolled to a total of 15 patients at SU-014813 50 mg/day and docetaxel 75 mg/m^2, 5 of whom experienced a DLT (1 patient with grade 3 fatigue, 1 patient with neutropenic fever and grade 4 thrombocytopenia, 2 patients with prolonged neutropenia and 1 patient with both grade 3 fatigue, grade 3 colitis and neutropenic fever) in the first two treatment cycles. Since 5 out of a total of 15 patients experienced a DLT, which is 1/3 of the patients, this dose level, as per protocol, was defined as the recommended dose for further studies (Table 2).

Table 3 shows the most relevant treatment-related adverse events. The most common treatment-related grade 3 or 4 AEs were neutropenia and diarrhoea. While all patients at the recommended phase II dose level experienced grade 3–4 neutropenia, this was complicated by fever in 9 of the 111 administered cycles. Other toxicities included fatigue, alopecia, nausea, vomiting and anorexia. Side-effects attributed to SU-014813 consisted of diarrhoea, rash, hypertension and hair discolouration. Diarrhoea with abdominal discomfort was mainly observed in patients continuing on SU-014813 single agent therapy in whom the dose of SU-014813 was

Table 2 – Overview DLTs.

SU-014813 50 mg + D 75 mg/m^2 (N = 15)	1 pt: neutropenia G 4 >7 days	Cycle 1
	1 pt: fatigue G 3	Cycle 2
	1 pt: febrile neutropenia G 4, fatigue G 3, colitis G 3, stomatitis G 3	Cycle 1
	1 pt: neutropenia G 4 >7 days	Cycle 1
	1 pt: febrile neutropenia and thrombocytopenia G 4	Cycle 1
SU-014813 100 mg + D 75 mg/m^2 (N = 6)	1 pt: febrile neutropenia G 4	Cycle 2
	1 pt: febrile neutropenia G 3	Cycle 1
	1 pt: diarrhoea G 3	Cycle 2

D; docetaxel; N; number of patients; pt: patient; G: grade.

Table 3 – Most relevant treatment-related AEs per patient, all cycles.

	Neutropenia		Diarrhoea		Fatigue		Anorexia		Vomiting		Rash		Hypertension		Hair discolouration
Grade	1–2	3–4	1–2	3–4	1–2	3–4	1–2	3–4	1–2	3–4	1–2	3–4	1–2	3–4	1–2
SU-014813 50 mg + D 60 mg/m^2 (N = 3)	1	1	1	2	0	1	2	0	2	0	1	0	2	0	1
SU-014813 50 mg + D 75 mg/m^2 (N = 15)	0	15	10	2	7	3	10	1	7	0	10	0	2	0	1
SU-014813 100 mg + D 75 mg/m^2 (N = 6)	0	5	2	2	5	1	1	0	4	0	3	0	0	1	1

D: docetaxel; N: number of patients.

Table 4 – Relative and absolute dose intensity of docetaxel administered per dose level.

Dose level	Cycles administered	Relative dose docetaxel (%)	Actual dose docetaxel (mg/m^2)
SU-014813 50 mg + D 60 mg/m^2 (N = 3)	27	95.3	58.2
SU-014813 50 mg + D 75 mg/m^2 (N = 15)	111	90.8	66.3
SU-014813 100 mg + D 75 mg/m^2 (N = 6)	33	91.9	69.7

D: docetaxel; N: number of patients.

Table 5 – Plasma PK parameters of intravenous docetaxel in the presence and absence of SU-014813: geometric mean [95% CI].

Treatment group	Cycle day (*N*)	C_{max} (ng/mL)	AUC_{inf} (ng * h/mL)	$T_{½}$ (h)	CL/F (L/h)	V_z/F (L)
1. Docetaxel 60 mg/m^2 alone[a]	C1D1 (3)	2202 (1365, 3552)	2326	14.4	47.3	982
1. SU-014813 50 mg/day + docetaxel 60 mg/m^2[a]	C2D1 (3)	2266 (1499, 3427)	3305	8.7	33.3	417
2. Docetaxel 75 mg/m^2 alone[b]	C1D1 (13)	2421 (2048, 2860)	3148 (2152, 4606)	14.9 (10.3, 21.4)	43 (31.1, 59.6)	923 (561, 1516)
2. SU-014813 50 mg/day + docetaxel 75 mg/m^2[b]	C2D1 (13)	2848 (2340, 3465)	3428 (2252, 5219)	14.9 (11, 20.1)	37.4 (28.3, 49.2)	803 (480, 1344)
3. Docetaxel 75 mg/m^2 alone[c]	C1D1 (5)	1977 (584, 6691)	3385 (298, 38514)	15.9 (4, 63.6)	42.2 (3.3, 540)	970 (127, 7434)
3. SU-014813 100 mg/day + docetaxel 75 mg/m^2[c]	C2D1 (5)	2150 (1094, 4225)	3616 (895, 14602)	12 (4, 35.4)	36.7 (9.6, 140)	634 (167, 2402)

Abbreviations: AUC_{24} = area under the plasma concentration–time profile from time zero to 24 h; AUC_{inf} = area under the plasma concentration–time profile from time zero to infinity; C = cycle; C_{max} = maximum plasma concentration; D = day; PK = pharmacokinetic; $T_{½}$ = terminal half-life; T_{max} = time to C_{max}; CL/F = apparent oral clearance; V_z/F = apparent volume of distribution.

[a] 1D1 and C2D1 – $t_{½}$, CL, AUC_{inf} and V_z $n = 1$.

[b] Data from Subject 10021013 was excluded due to missing PK on C2 D1. C1D1 and C2D1 – $t_{½}$, CL, AUC_{inf} and V_z $n = 7$.

[c] Data from Subject 10021003 was excluded due to missing PK on C1D1. C1D1 and C2D1 – $t_{½}$, CL, AUC_{inf} and V_z $n = 3$.

Table 6 – Plasma PK parameters of SU-014813 in the absence and presence of docetaxel: geometric mean [95% CI].

Treatment group	Cycle day (*N*)	C_{max} (ng/mL)	T_{max}[a] (h)	AUC_{24} (ng * h/mL)	$T_{½}$ (h)	CL/F (L/h)	V_z/F (L)
1. SU-014813 50 mg/day alone[b]	C1D21 (2)	130.3	3 (2–4)	1310	9.7	38.8	535.5
1. SU-014813 50 mg/day + docetaxel 60 mg/m^2[b]	C2D1 (2)	108.5	1.5 (1–2)	1237	10.2	40.5	596.1
2. SU-014813 50 mg/day alone[c]	C1D21 (12)	101.3 (76.3, 134.6)	4 (1–8)	1258 (997, 1588)	12.3 (9.8, 15.4)	39.7 (31.5, 50.2)	657 (467, 924)
2. SU-014813 50 mg/day + docetaxel 75 mg/m^2[c]	C2D1 (12)	89.6 (70.8, 113.4)	2 (1–24)	1088 (910, 1300)	10.9 (8.7, 13.6)	46.0 (38.5, 54.9)	718 (544, 948)
3. SU-014813 100 mg/day alone[d]	C1D21 (6)	245.3 (170.6, 352.6)	1.5 (0–4)	2820 (1324, 6007)	8.6	35.3 (16.6, 75.5)	332
3. SU-014813 100 mg/day + docetaxel 75 mg/m^2[d]	C2D1 (6)	194.7 (112.7, 336.2)	1.5 (0–8)	3168 (1679, 5975)	4.8	31.6 (16.7, 59.5)	286

Abbreviations: AUC_{24} = area under the plasma concentration–time profile from time zero to 24 h; C = cycle; C_{max} = maximum plasma concentration; D = day; PK = pharmacokinetic; $T_{½}$ = terminal half-life; T_{max} = time to C_{max}; CL/F = apparent oral clearance; V_z/F = apparent volume of distribution.

[a] Median (range).

[b] Data from Subject 10011001 were excluded due to missing PK on C2 D1.

[c] Data from Subjects 10011012 and 10021011 were excluded due to missing PK on C1 D21. Data from Subject 10021013 were excluded due to missing PK on C2 D1; for C_{max}, AUC_{24}, T_{max} and CL/F $n = 12$; $t_{½}$ and V_z/F $n = 7$.

[d] For CL/F and AUC_{24} $n = 3$; for $t_{½}$ and V_z/F $n = 1$.

escalated to 100 or 150 mg/day and was often amenable to treatment with loperamide. Hypertension was easily manageable with antihypertensive agents.

The relative dose intensity of docetaxel at the recommended dose level was 86.4% over all cycles administered, resulting in an actual dose of 64.8 mg/m^2 docetaxel (Table 4). At the next lower dose level the achieved dose intensity for docetaxel was 57.0 mg/m^2. These data confirm that SU-014813 in combination with docetaxel 75 mg/m^2 is the recommended dose level for further studies.

3.1. *Pharmacokinetics*

A summary of the pharmacokinetic data of docetaxel and SU-014813 is given in Tables 5 and 6. Co-administration with SU-014813 did not affect the pharmacokinetics of docetaxel. The mean exposure for docetaxel (C_{max}, AUC_{24} and AUC_{inf}) as well as secondary parameters ($t_{½}$, CL/F, and V_z/F) were similar when administered with and without SU-014813. Furthermore, in general, co-administration with docetaxel did not affect the plasma pharmacokinetics of SU-014813. The mean exposure for SU-014813 (C_{max} and AUC_{24}) was similar when administered with and without docetaxel at both the 50 mg and the 100 mg dose levels, however, low to moderate variability was observed for the SU-014813 C_{max} and AUC_{24} values.

3.2. *Anti-tumour activity*

Overall, there were 2 patients (8%) achieving a confirmed partial response (PR) and 12 patients (50%) with stable disease (SD) for a clinical benefit rate (PR and SD >6 months) of

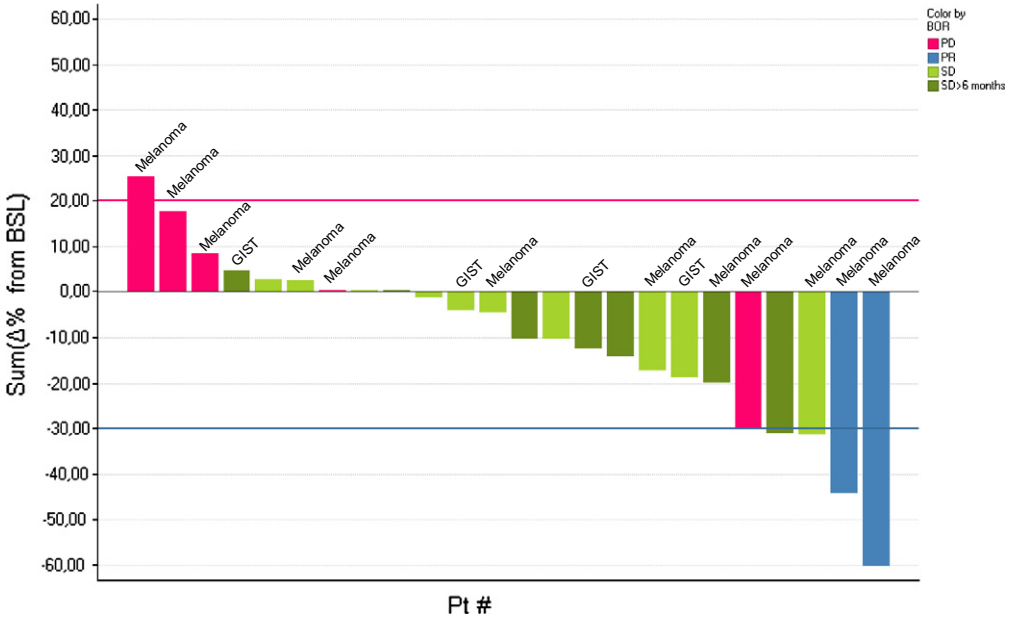

Fig. 1 – Waterfall plot percentage change in sum longest diameter tumour compared to baseline.

37.5% (95% CI 19–59%). Of the observed stable diseases 7 lasted more than 6 months (Fig. 1).

Interestingly, 6 out of 12 patients with melanoma showed clinical benefit. Two patients showed a partial response lasting for 36 and 114 weeks. Both patients received prior systemic therapy containing CDDP and DTIC with progression disease as best response. Both patient had liver metastases and one patient in addition pulmonary and lymphnode metastases. The remaining 4 patients showed disease stabilisation lasting for 12–135 weeks. In addition in 4 patients with GIST a disease stabilisation could be observed lasting for 15–93 weeks. All of them were imatinib refractory and 3 of also refractory to sunitinib.

4. Discussion

We performed a phase I dose-finding study on the combination of a multi-tyrosine kinase inhibitor SU-014813 and docetaxel, based on observed pre-clinical data showing additivity and the hypothesised increase of docetaxel uptake in tumour tissue due to the decrease in intratumoural interstitial fluid pressure induced by inhibition of VEGFR and/or PDGFR. Dose limiting side-effects at the recommended dose level of docetaxel 75 mg/m^2 and SU-014813 50 mg consisted of neutropenia, neutropenic fever, fatigue and diarrhoea. One of the intentions of this study was also to establish the compound as a better partner for combinations with taxanes compared to other similar multitargeted TKIs.

Neutropenic fever is a well known side-effect of docetaxel treatment. When administered at doses of 75–100 mg/m^2 single agent docetaxel induces grade 4 neutropenia in 78.6–88.5% of patients, complicated by fever in up to 14% of patients.[14–16] Furthermore grade 3–4 fatigue is observed in 14.5% of patients. Against this background toxicity the side-effect frequency in the present combination should be valued. At the recommended dose 86.7% of patients experienced grade 4 neutropenia. Neutropenic fever was observed in 8.1% of all administered cycles at the recommended dose (9 out of 111 cycles). While a control arm in the current study was obviously lacking, historical data on docetaxel suggest that the incidence of both toxicities are in a similar range as those observed on single agent docetaxel.

As a single agent SU-014813 was studied in a 4 weeks on-1 week off schedule and in a continuous dosing schedule. The recommended dose for the 4 weeks on-1 week off schedule is 200 mg/day with fatigue as the main DLT. For the chronic dosing schedule the recommended dose was determined as 100 mg/day with diarrhoea as DLT.[9] Aside from fatigue and diarrhoea treatment-related adverse events constituted of skin rash, hypertension, mild myelosuppression and hair discolouration.[9] These side-effects are in line with the toxicity observed in the present study.

The observed safety profile for the combination of SU-014813 and docetaxel is comparable to the side-effects of the combination of sunitinib and docetaxel.[17,18] Also for this combination neutropenia, fatigue and diarrhoea constituted the main side-effects. In contrast to the present study the sunitinib–docetaxel combination appeared to be associated with more than the expected myelosuppression as compared to single agent docetaxel treatment and required the introduction of growth factor support in order to tolerate a dose of 60 mg/m^2 docetaxel in combination with sunitinib 37.5 mg/day for two weeks on one week off at least in one study.[17] In combination with prednisone docetaxel 75 mg/m^2 and sunitinib 37.5 mg/day day 1–14 was administered in patients with hormone refractory prostate cancer without growth factor support. However, 65% of the patients required either a dose reduction of sunitinib or docetaxel due to experienced toxicity.[18]

Despite the observed toxicity, the tolerance of the combination SU-014813 and docetaxel seemed acceptable. At the recommended dose level the median number of days on

treatment was 91 (range 37–959) and 5 out of 15 patients completed 6 or more combination cycles. Also in the study combining docetaxel and sunitinib 12 out of 40 patients at the recommended dose level were able to receive the planned 6 cycles.[17] Probably this is both indicative of the activity of both combinations and the absence of cumulative toxicity.

A clinically relevant PK interaction between SU-014813 and docetaxel was not observed at the recommended dose, similar to the observations with sunitinib and docetaxel.[17]

While one should always caution against over-interpretation of anti-tumour activity in the highly selected phase I study population, we consider some of our observations in the present study interesting. Six out of 12 patients with melanoma showed clinical benefit consisting of PR in 2 and prolonged SD in 4 patients. Previously reported anti-tumour activity of docetaxel in melanoma ranged from 14% to 17%.[19,20] A randomised phase II study on the combination of SU-014813 and docetaxel seems therefore warranted.

Furthermore 4 patients with GIST achieved durable disease stabilisation despite being refractory to previous imatinib (4pts) and sunitinib (3pts). Docetaxel was never tested in this patient population, but in general cytotoxic treatment is considered poorly active in GIST. The profile of SU-014813 is not sufficiently different from sunitinib to explain the mentioned responses in sunitinib refractory patients. One might therefore hypothesise that in line with pre-clinical data, SU-014813 induced a higher tumoural delivery of docetaxel due the decrease in intratumoural interstitial fluid pressure induced by the inhibition of VEGFR and/or PDGFR. This remains to be elucidated and should be addressed during further development of this combination. In addition, the response rate observed in the phase II study in prostate cancer combining docetaxel, prednisolone and sunitinib showed a promising response rate of 39% compared to 12% response rates in historical data.[18,21] In the first randomised study in breast cancer patients also an increase in response rate was observed in the combined treatment arm (51% versus 39%). However, this increase in response rate did not translate in an increase in progression free survival nor in overall survival.[22]

In conclusion a tolerable dose of the combination of SU14813 and docetaxel could be identified, that yielded interesting anti-tumour activity in a subset of patients. This combination warrants exploration in subsequent randomised phase II studies.

Conflict of interest statement

M. de Jonge: none declared; H. Dumez: none declared; J. Kitzen: non declared; B. Beuselinck: non declared; J. Verweij: Received honoraria for active participation in educational events organised for/by Pfizer; Department has received honoraria for entering patients in Pfizer trial; R Courtney: holds stock in Pfizer and is an employee of Pfizer and is currently conducting research sponsored by the company. A Battista: holds stock as a Pfizer employee; N. Brega: holds stock as a Pfizer employee; P. Schöffski: Received honoraria for active participation in educational events organised for/by Pfizer; received research grants for laboratory work by Pfizer; Department has received honoraria for entering patients in Pfizer trial; PI for Pfizer clinical studies.

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