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ORIGINAL ARTICLE

Phase 2 study of dovitinib in patients with relapsed or refractory multiple myeloma with or without t(4;14) translocation

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Abstract

Objectives: Approximately 15% of patients with multiple myeloma (MM) exhibit a t(4;14) translocation, which often results in constitutive activation of the receptor tyrosine kinase (RTK) fibroblast growth factor receptor 3 (FGFR3). This study evaluated the efficacy and safety of dovitinib, an RTK inhibitor with *in vitro* inhibitory activity against FGFR, in patients with relapsed or refractory MM with or without t(4;14) translocation. *Methods:* Adult patients with relapsed or refractory MM who had received ≥2 prior regimens were enrolled in this multicenter, 2-stage, phase 2 trial. Patients were grouped based on their t(4;14) status. Dovitinib (500 mg/day orally) was administered on a 5-days-on/2-days-off schedule. The primary endpoint was overall response rate by local investigator review (per International Myeloma Working Group criteria). In non-responding patients, treatment could continue with the addition of low-dose dexamethasone. *Results:* In total, 43 patients (median age, 63 years) were enrolled (13 t(4;14) positive, 26 t(4;14) negative, and 4 t(4;14) status non-interpretable). Patients had received a median of 5 prior regimens. Median duration of treatment was 8.7 weeks in the t(4;14)-positive group and 3.7 weeks in the t(4;14)-negative group. None of the patients on dovitinib had objective responses. The stable disease rate was 61.5% in the t(4;14)-positive group and 34.6% in the t(4;14)-negative group. Overall, 39 patients (90.7%) had adverse events suspected to be related to study drug, most commonly diarrhea (60.5%), nausea (58.1%), vomiting (46.5%), and fatigue (32.6%). *Conclusion:* Dovitinib showed no single-agent activity in relapsed or refractory MM but may stabilize disease in some t(4;14)-positive patients.

Key words phase 2; relapsed or refractory multiple myeloma; FGFR3; dovitinib; t(4;14) translocation

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Multiple myeloma (MM) is a neoplastic disorder of clonal B cells characterized by uncontrolled and aberrant proliferation of plasma cells within bone marrow, monoclonal protein in the blood or urine, and associated organ dysfunction (1). About 24 050 new cases of myeloma are estimated in 2014 in the United States (2), whereas the estimated number of new MM cases in Europe was 33 000 in 2012 (3). Over the past decade, the outcome of patients with MM has significantly improved with the development of immunomodulatory drugs (thalidomide, lenalidomide, and pomalidomide) and proteasome inhibitors (bortezomib and carfilzomib). However, despite these advances, nearly all patients with MM eventually relapse. Although patients can sometimes achieve subsequent responses with additional treatment regimens, these responses are often of shorter duration, necessitating novel treatment options for MM (4, 5).

The fibroblast growth factor (FGF) receptor (FGFR) signaling pathway is implicated in the pathogenesis of a variety of cancers including MM (6); FGFR signaling promotes tumor angiogenesis, and deregulated expression of FGFs leads to

tumor cell proliferation, survival, and chemoresistance (7). Approximately 15% of patients with MM exhibit a t(4;14) translocation (8), which often results in FGFR3 expression. FGFR3 is receptor tyrosine kinase (RTK) of the FGF family, consisting of 3 immunoglobulin-like extracellular domains, a transmembrane domain, and a split cytoplasmic tyrosine kinase domain. Following ligand stimulation, it signals primarily through the extracellular signal-regulated kinases 1 and 2, phosphatidylinositol 3-kinase, and phospholipase C-pathways (9–11). Furthermore, somatic mutation may occur after the translocation, resulting in the constitutive activation of FGFR3 (12). Patients with t(4;14) translocation appear to have a worse prognosis and shorter survival compared with patients without this translocation (13, 14). About 25% of patients lose FGFR3 protein expression over time, and Ras mutations common to almost 50% of patients with MM may circumvent FGFR3 signaling dependency (15, 16).

Dovitinib, an RTK inhibitor, has demonstrated *in vitro* inhibitory activity against FGFR, vascular endothelial growth factor receptor (VEGFR), and platelet-derived growth factor receptor, with half minimal inhibitory concentration values of approximately 10 nM (17).

Tumor growth inhibition was observed with dovitinib treatment in xenograft tumor models of MM with activating FGFR3 mutations (8, 18), resulting in significant improvement in survival (8). Thus, the preclinical data established a rationale for studying dovitinib in patients with MM. The objective of this study was to evaluate the efficacy and safety of dovitinib in patients with relapsed or refractory MM with or without t(4;14) translocation.

Patients and methods

Patients

Adult patients (age ≥18 years), with cytopathologically or histologically confirmed relapsed or refractory MM according to International Myeloma Working Group (IMWG) criteria (19), who had received ≥2 prior therapy regimens including chemotherapy, autologous transplant, immunotherapy, or other investigational agents, were included. Other eligibility criteria were presence of measurable disease (serum M-protein ≥1 g/dL and/or urine M-protein ≥200 mg/24 h by protein electrophoresis) (20); World Health Organization (WHO) performance status of ≤2; and absolute neutrophil and platelet count ≥1000/mm^3 and ≥75 000/mm^3, respectively (or ≥750/mm^3 and ≥50 000/mm^3, respectively, if neutropenia and thrombocytopenia was clinically related to progressive myeloma with bone marrow infiltration), hemoglobin ≥8 g/dL, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3.0 × upper limit of normal (ULN), serum bilirubin ≤1.5 × ULN, and serum creatinine ≤2.0 × ULN (or 24-hour creatinine clearance ≥50 mL/min).

Patients were excluded if they had non-secretory or oligosecretory MM, symptomatic amyloidosis or plasma cell leukemia, previous allogeneic stem cell transplant with evidence of active graft-vs.-host disease requiring immunosuppressive therapy, history of another malignancy within 3 years prior to study entry (except cured basal cell carcinoma of the skin or excised *in situ* carcinoma of the cervix), impaired cardiac function or clinically significant cardiac diseases, uncontrolled hypertension defined as systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥100 mmHg with or without antihypertensive medication(s), treatment with therapeutic doses of warfarin, cirrhosis, chronic active hepatitis, or chronic persistent hepatitis, and other concurrent severe and/or uncontrolled concomitant medical conditions that could have caused unacceptable safety risks. Patients could not have undergone a major surgery ≤2 weeks prior to starting the study drug.

Study design and treatment

This was a multicenter, non-randomized, open-label, 2-stage, phase 2 trial. Efficacy and safety of the treatment was separately evaluated in the t(4;14)-positive or t(4;14)-negative groups of patients. The study objectives did not include direct comparisons of the two groups. At the baseline visit, the patients' bone marrow aspirate samples were analyzed for t(4;14) translocation status by cytoplasmic immunoglobulin-enhanced interphase fluorescent *in situ* hybridization (FISH; Vysis; Abbott Laboratories, Abbott Park, IL, USA), and they were assigned to either t(4;14)-positive or t(4;14)-negative groups. Patients were considered assessable if at least 100 clonal plasma cells from each slide could be scored. Bone marrow aspirate samples were analyzed for FGFR3 expression by flow cytometry, and the results were qualitatively expressed as positive or negative. Patients were assigned as t(4;14)-non-interpretable if there were too few plasma cells in the samples to provide an accurate assessment by FISH and flow cytometry and were not included in the primary and secondary efficacy analyses.

All patients received dovitinib at a dose of 500 mg/day orally on a 5-days-on/2-days-off schedule (dosing on days 1 to 5, 8 to 12, 15 to 19, and 22 to 26) every 28 days until progressive disease (PD), unacceptable toxicities, or patient's/investigator's decision to discontinue. The 500 mg/day orally on a 5-days-on/2-days-off dosing schedule was selected based on the phase 1/2 study of dovitinib in metastatic renal cell carcinoma (mRCC). In a Phase 1/2 dose escalation study, dovitinib at the dose of 500 mg on a 5-days-on/2-days-off schedule was generally well tolerated and showed antitumor activity in heavily pretreated patients with mRCC. Also, the pharmacodynamic analysis revealed VEGFR inhibition and FGFR inhibition (21). Further, dovitinib (500 mg/day on a 5-days-on/2-days-off schedule) was effective and tolerable in patients with advanced or metastatic RCC enriched for

patients previously treated with a VEGFR TKI and an mTOR inhibitor (22).

As an exploratory objective, after disease progression on dovitinib monotherapy, patients had the option to continue treatment with the addition of low-dose dexamethasone (40 mg every 7 days), with M-protein levels at the time of progression considered as the new baseline.

Dose reductions [400 mg (first reduction) and 300 mg (second reduction)] were permitted for patients unable to tolerate the protocol-specified dosing schedule of dovitinib. No dose escalation was allowed once a patient was dose reduced. Dose reductions for dexamethasone were not permitted in the dexamethasone-supplemented dovitinib regimen.

All patients provided written informed consent. The study protocol and its amendments were approved by the independent ethics committees at each center. The study conformed to Good Clinical Practices guidelines and the ethical principles of the Declaration of Helsinki. The study was designed by the academic investigators and by representatives of the sponsor, Novartis Oncology.

Efficacy and safety assessments

The primary endpoint was extended overall response rate (ORR) by local investigator review. Extended ORR was defined as the rate of patients with ORR [best overall response of complete response (CR), very good partial response (VGPR), or partial response (PR)], plus patients with best overall response of minor response (MR) according to IMWG criteria (19). Secondary endpoints included safety and ORR and progression-free survival (PFS) by local investigator review. PFS was defined as the time from the start of treatment to the date of the first-documented PD or death due to any cause, as assessed by the investigator. If a patient had not progressed or died at the date of the analysis cutoff or when he/she received any further antineoplastic therapy, PFS was censored at the time of the last tumor assessment before the cutoff date or the antineoplastic therapy start date. Documentation of response in patients who opted to continue on a dexamethasone-supplemented dovitinib regimen was an exploratory objective. Patients were evaluated at the end of each cycle. Any response of MR or better had to be confirmed by the next set of evaluations 4 weeks later. Any response of PD had to be confirmed as soon as possible, preferably within 7 days after the observation.

Safety assessments consisted of collecting all adverse events (AEs) and serious AEs (SAEs), including the regular monitoring of laboratory tests, regular measurement of vital signs, weight, performance status, physical examination, and cardiac assessments (electrocardiogram, blood pressure, cardiac enzymes, and multigated acquisition/echocardiogram). All AEs were recorded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Statistical analysis

A 2-stage design (23) was used for each group to test the null hypothesis that the extended ORR is $\leq$10% using a 1-sided test with 10% level of significance and 90% power at the alternative extended ORR of 30%. The null hypothesis of extended ORR = 0.10 and the alternative of extended ORR = 0.30 were chosen with reference to the outcomes of single-agent phase 2 studies of lenalidomide and bortezomib in patients with relapsed or refractory MM (24, 25). For stage 1 enrollment, a total of 20 patients were planned in each group. If $\geq$3 patients had a response, an additional 20 patients were planned in stage 2 of that group. The null hypothesis was rejected at the 10% level of significance (1-sided) if there were $\geq$7 responders among all 40 patients at the end of stage 2. Kaplan–Meier product-limit method was performed to estimate median PFS.

Results

Patient characteristics

A total of 43 patients with relapsed or refractory MM were enrolled between May 28, 2010, and December 29, 2011. As of the latter date, only 13 patients were enrolled in the t(4;14)-positive group. Enrollment in the t(4;14)-positive group was closed due to lack of objective responses and slow rate of enrollment. Twenty-six patients were enrolled in the t(4;14)-negative group. The t(4;14) translocation status could not be determined in 4 patients; these patients were summarized in a non-interpretable group.

A majority of the patients were white (90.7%), had a WHO performance status of 1 (58.1%), and were refractory to last treatment (60.5%) (Table 1). Independent of translocation status, 12 patients (27.9%) had FGFR3 expression (9 in the t(4;14)-positive group, 2 in the t(4;14)-negative group, and 1 in t(4;14)non-interpretable group). Patients had received a median of 5 (range, 2–10) prior antineoplastic regimens.

Patient disposition

All 43 patients received dovitinib monotherapy (Table 2). The median duration of exposure to the study drug was 8.7 weeks and 3.7 weeks for the patients enrolled in t(4;14)-positive and t(4;14)-negative groups, respectively. Of the 27 patients with PD on dovitinib monotherapy, 6 patients continued on dovitinib with dexamethasone added [3 each in the t(4;14)-positive and t(4;14)-negative groups].

Table 1 Patient characteristics at baseline – dovitinib monotherapy

	t(4;14)-Positive *n* = 13	t(4;14)-Negative *n* = 26	t(4;14)-Non-interpretable *n* = 4	All patients *N* = 43
Median age (range), years	61 (47–69)	67 (29–84)	55 (40–66)	63 (29–84)
Sex, *n* (%)				
Female	6 (46.2)	10 (38.5)	4 (100)	20 (46.5)
Male	7 (53.8)	16 (61.5)	0	23 (53.5)
Race, *n* (%)				
White	12 (92.3)	23 (88.5)	4 (100)	39 (90.7)
Black	1 (7.7)	2 (7.7)	0	3 (7.0)
Asian	0	1 (3.8)	0	1 (2.3)
World Health Organization performance status, *n* (%)				
0	4 (30.8)	9 (34.6)	0	13 (30.2)
1	8 (61.5)	15 (57.7)	2 (50.0)	25 (58.1)
2	1 (7.7)	2 (7.7)	2 (50.0)	5 (11.6)
Median time since diagnosis (range), months	49.3 (24.9–84.3)	64.3 (15.8–246.0)	62.1 (58.8–140.1)	58.8 (15.8–246.0)
Number of prior lines of therapy, *n* (%)				
2	4 (30.8)	2 (7.7)	0	6 (14.0)
3	1 (7.7)	4 (15.4)	0	5 (11.6)
4	2 (15.4)	5 (19.2)	0	7 (16.3)
>4	6 (46.2)	15 (57.7)	4 (100)	25 (58.1)
Median prior lines of therapy (range)	4.0 (2–10)	5.0 (2–9)	7.0 (5–9)	5.0 (2–10)
Prior therapies, *n* (%)				
Corticosteroids	13 (100)	26 (100)	4 (100)	43 (100)
Bevacizumab	1 (7.7)	1 (3.8)	0	2 (4.7)
Bortezomib	13 (100)	24 (92.3)	4 (100)	41 (95.3)
Vorinostat	1 (7.7)	2 (7.7)	0	3 (7.0)
Lenalidomide	11 (84.6)	21 (80.8)	4 (100.0)	36 (83.7)
Thalidomide	6 (46.2)	16 (61.5)	4 (100.0)	26 (60.5)
Patients relapsed or refractory from last treatment, *n* (%)				
Refractory	7 (53.8)	16 (61.5)	3 (75.0)	26 (60.5)
Relapsed	6 (46.2)	10 (38.5)	1 (25.0)	17 (39.5)
FGFR3 expression, *n* (%)				
Yes	9 (69.2)	2 (7.7)	1 (25.0)	12 (27.9)
No	0	19 (73.1)	2 (50.0)	21 (48.8)
Unknown	4 (30.8)	5 (19.2)	1 (25.0)	10 (23.3)

FGFR3, fibroblast growth factor receptor 3.

Table 2 Patient disposition

	t(4;14)-Positive *n* = 13	t(4;14)-Negative *n* = 26	t(4;14)-Non-interpretable *n* = 4	All patients *N* = 43
Dovitinib monotherapy				
EOT, *n* (%)	13 (100)	26 (100)	4 (100)	43 (100)
Primary reason for EOT, *n* (%)				
Disease progression	7 (53.8)	20 (76.9)	0	27 (62.8)
Adverse event (s)	4 (30.8)	3 (11.5)	3 (75.0)	10 (23.3)
Subject withdrew consent	2 (15.4)	3 (11.5)	1 (25.0)	6 (14.0)
Dovitinib plus dexamethasone				
EOT, *n* (%)	3 (23.1)	3 (11.5)	0	6 (14.0)
Primary reason for EOT, *n* (%)				
Disease progression	2 (15.4)	3 (11.5)	0	5 (11.6)
Adverse event(s)	1 (7.7)	0	0	1 (2.3)

EOT, end of treatment.

As of March 22, 2013 (final database lock), all patients discontinued the study drug (including those receiving the dovitinib/dexamethasone combination regimen). The most frequently reported reasons for discontinuing dovitinib monotherapy were disease progression in 27 patients (62.8%) and AEs in 10 patients (23.3%). The reasons to stop the dovitinib/dexamethasone regimen were disease progression for 5 patients and AEs for 1 patient.

Efficacy

None of the patients on dovitinib monotherapy had MR, PR, VGPR, or CR (Table 3); hence, the ORR (≥PR) and extended ORR (≥MR) were 0%. Overall, 20 patients (46.5%) had stable disease (SD).

Eight patients (61.5%) in the t(4;14)-positive group had SD. The median PFS per local investigator assessment was 2.6 months [95% confidence interval (CI): 0.9–3.9] in the t(4;14)-positive group in patients treated with dovitinib monotherapy (Fig. 1).Of the 3 patients in the t(4;14)-positive group who continued on the dexamethasone-supplemented treatment regimen, 1 patient had SD, 1 patient had PD, and the response was not evaluable for the remaining 1 patient.

Nine patients in the t(4;14)-negative group (34.6%) had SD. The median PFS per local investigator assessment was 0.9 months (95% CI: 0.8–1.7) in the t(4;14)-negative group in patients treated with dovitinib monotherapy (Fig. 1A). Of the 3 patients in the t(4;14)-negative group, 1 patient had PR and 2 patients had SD.

As the number of responders in each group failed to meet the criteria for study continuation to stage 2 (≥3 responders from stage 1), the study was terminated. Among the 12 patients with detectable FGFR3 expression, 58.3% had SD, whereas the SD rate in the 21 patients without FGFR3 expression (excluding patients with unknown expression) was 42.9%. The median PFS was 1.77 months [95% CI: 0.39–3.88]) in patients who had FGFR3 expression and 0.9 months [95% CI: 0.82–1.77] in patients who did not have FGFR3 expression (Fig. 1B).

Safety

Overall, 39 patients (90.7%) treated with dovitinib monotherapy had AEs suspected to be related to study drug (Table 4). The safety profiles were similar for the t(4;14)-positive and t(4;14)-negative groups. The most frequently reported AEs suspected to be related to study drug were diarrhea (60.5%), nausea (58.1%), vomiting (46.5%), fatigue (32.6%), and thrombocytopenia (20.9%). The most frequently reported grade 3 or 4 treatment-related AEs were diarrhea (20.9%), thrombocytopenia (16.3%), and fatigue (14.0%). Diarrhea was the most commonly reported grade 3 or 4 SAE occurring in 4 of the 8 patients (9.3%) with SAEs suspected to be related to study drug. For the 6 patients who continued on the dovitinib and dexamethasone combination, AEs and SAEs were primarily gastrointestinal related.

In the overall population, the most common AEs leading to discontinuation of dovitinib monotherapy were diarrhea (11.6%), vomiting (7.0%), and fatigue (4.7%). Overall, 26 patients treated with dovitinib monotherapy had AEs requiring a dose adjustment or study drug interruption, most commonly diarrhea (23.3%), nausea (9.3%), and vomiting (9.3%). A total of 12 patients (27.9%) on dovitinib monotherapy had a dose change: 6 patients (14.0%) required 1 dose change, and 6 patients (14.0%) required ≥2 dose changes. The median daily dose remained 500 mg/day in all the groups.

In total, 4 patients died within 30 days following the last treatment dose on dovitinib monotherapy; the reasons for deaths were disease progression (3 patients) and cardiopulmonary arrest (1 patient). The patient who died due to cardiopulmonary arrest had discontinued study drug because of disease progression on day 25 and started melphalan 2 days later. The patient's condition deteriorated; under mechanical ventilation, cardiogenic shock was experienced 10 days after last dose of the study drug, which was followed by cardiopulmonary arrest 24 days after the last dose of the study drug. A total of 2 patients died within 30 days following the

Table 3 Overall response to dovitinib monotherapy, assessed by local review

Overall response, *n* (%)	t(4;14)-Positive *n* = 13	t(4;14)-Negative *n* = 26	t(4;14)-Non-interpretable *n* = 4	All patients *N* = 43
Complete response	0	0	0	0
Very good partial response	0	0	0	0
Partial response	0	0	0	0
Minor response	0	0	0	0
Stable disease	8 (61.5)	9 (34.6)	3 (75.0)	20 (46.5)
Progressive disease	4 (30.8)	13 (50.0)	1 (25.0)	18 (41.9)
Not determined	1 (7.7)	4 (15.4)	0	5 (11.6)
Extended overall response rate	0	0	0	0
Overall response rate	0	0	0	0

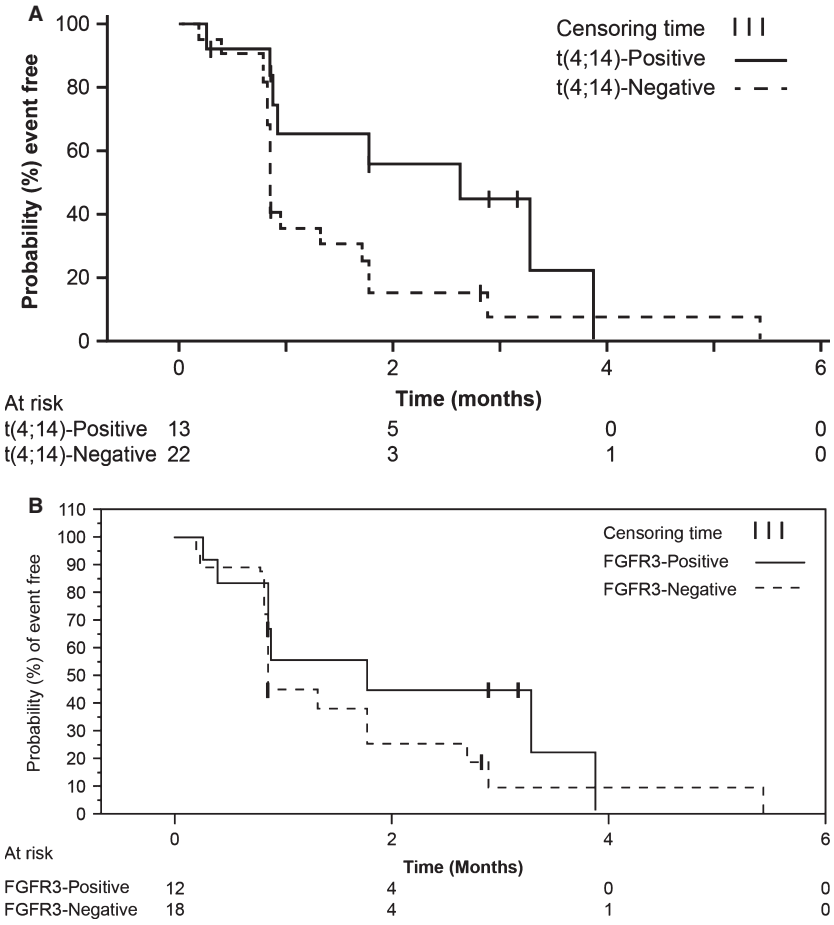

Figure 1 Kaplan–Meier median progression-free survival by local investigator review – dovitinib monotherapy by (A) t(4;14) translocation status and (B) FGFR3 expression status.

Table 4 Adverse events suspected to be related to study drug – Dovitinib monotherapy (≥10% patients)

	t(4;14)-Positive *n* = 13		t(4;14)-Negative *n* = 26		t(4;14)-Non-interpretable *n* = 4		All patients *N* = 43	
Preferred term	Any grade *n* (%)	Grade 3/4 *n* (%)	Any grade *n* (%)	Grade 3/4 *n* (%)	Any grade *n* (%)	Grade 3/4 *n* (%)	Any grade *n* (%)	Grade 3/4 *n* (%)
Total	12 (92.3)	8 (61.5)	23 (88.5)	12 (46.2)	4 (100)	2 (50.0)	39 (90.7)	22 (51.2)
Diarrhea	7 (53.8)	3 (23.1)	16 (61.5)	6 (23.1)	3 (75.0)	0	26 (60.5)	9 (20.9)
Nausea	7 (53.8)	1 (7.7)	14 (53.8)	2 (7.7)	4 (100)	0	25 (58.1)	3 (7.0)
Vomiting	6 (46.2)	1 (7.7)	11 (42.3)	2 (7.7)	3 (75.0)	0	20 (46.5)	3 (7.0)
Fatigue	4 (30.8)	3 (23.1)	10 (38.5)	3 (11.5)	0	0	14 (32.6)	6 (14.0)
Thrombocytopenia	4 (30.8)	3 (23.1)	3 (11.5)	2 (7.7)	2 (50.0)	2 (50.0)	9 (20.9)	7 (16.3)
Decreased appetite	2 (15.4)	1 (7.7)	5 (19.2)	1 (3.9)	0	0	7 (16.3)	2 (4.7)
Dehydration	1 (7.7)	0	5 (19.2)	4 (15.4)	0	0	6 (14.0)	4 (9.3)
Anemia	2 (15.4)	2 (15.4)	2 (7.7)	1 (3.8)	1 (25.0)	0	5 (11.6)	3 (7.0)
Neutropenia	3 (23.1)	3 (23.1)	2 (7.7)	1 (3.8)	0	0	5 (11.6)	4 (9.3)
Dyspepsia	0	0	2 (7.7)	0	2 (50.0)	0	4 (9.3)	0
Asthenia	0	0	3 (11.5)	0	0	0	3 (7.0)	0
Rash	2 (15.4)	0	1 (3.9)	1 (3.8)	0	0	3 (7.0)	1 (2.3)
Weight decreased	0	0	3 (11.5)	0	0	0	3 (7.0)	0

last dose on dovitinib plus dexamethasone combination therapy; 1 of these patients died due to disease progression, and the other patient died due to intestinal perforation secondary to disease progression. None of these 6 deaths were suspected to be related to study drug.

There was no evidence of QTcF increase from baseline of >60 ms. One patient experienced a >20% decrease in left ventricular ejection fraction.

Hematologic abnormality shifts were mostly grade 1 or 2. Eleven patients (25.6%) had grade 3 decreased neutrophils,

12 patients (27.9%) had grade 3 decreased hemoglobin, and 12 patients (27.9%) had grade 3 decreased white blood cells. A total of 6 patients (14.0%) experienced grade 3 decreased lymphocytes and 1 patient (2.3%) experienced grade 4 decreased lymphocytes. Furthermore, grade 3 and 4 decreased platelet count was reported in 9 patients (20.9%) and 10 patients (23.3%), respectively.

Grade 3 increases in ALT and AST were reported in 3 patients (7.3%) and 2 patients (4.7%), respectively, while for bilirubin, no increase of more than grade 1 was found.

Discussion

Approximately 15% of patients with MM exhibit a t(4;14) translocation (8), which often results in FGFR3 expression. Loss of FGFR3 expression is, however, evidenced during disease progression in approximately 25% of patients, leading some to believe that the reciprocal of the t(4;14) translocation that results in MMSET protein activation may be the dominant molecular event (15, 16). Treatment of patients with MM bearing the t(4;14) translocation (one of the 'high-risk' cytogenetic factors) is challenging, as early and aggressive relapse is common (26). Although development of immunomodulatory agents and proteasome inhibitors has dramatically improved the outlook for patients with MM, including t(4;14), prognosis in this MM subset remains poor overall (27). Dovitinib, an RTK inhibitor, demonstrated *in vitro* cytotoxicity and tumor growth inhibition in xenograft tumor models of MM with activating FGFR3 mutations (8, 18). Based on these preclinical findings, we evaluated the efficacy and safety of dovitinib in patients with relapsed or refractory MM with and without t(4;14) translocation.

In the present study, although none of the patients on dovitinib monotherapy had ORR (≥PR) or extended ORR (≥MR), 20 patients (46.5%) had SD. Although the t(4;14) translocation predicts poor prognosis in patients with MM (28), it is of interest that the proportion of patients with SD during study treatment was numerically higher in the t(4;14)-positive group (61.5%) than the t(4;14)-negative group (34.6%). These results need to be interpreted cautiously as the sample size was small, and the study objectives did not include direct comparison the t(4;14)-positive or t(4;14)-negative groups of patients. Furthermore, the median PFS in the t(4;14)-positive and t(4;14)-negative group was 2.6 months and 0.9 months, respectively. These results raise the possibility that dovitinib has some biologic activity in relapsed or refractory MM patients with t(4;14) translocation, a hypothesis that could be explored in combination studies with other agents, such as proteasome inhibitors or by studying similar agents earlier in the disease course. Although patient populations from different studies cannot be compared, it is interesting to note that carfilzomib as a single agent produced a median PFS of 3.5 months in patients with relapsed and refractory MM with high-risk cytogenetics (29). In a randomized phase 2 study comparing pomalidomide plus low-dose dexamethasone vs. pomalidomide alone in patients with relapsed and refractory MM, the median PFS was 2.7 months in patients treated with pomalidomide alone (30), which is similar to the median PFS in the t(4;14)-positive group in our study.

Monotherapy has generally not proven to be effective in patients with MM; thus, combination regimens have been the mainstay of effective therapy in MM. In this study, results were perhaps more promising in patients with t(4;14) or FGFR3 overexpression, and further *in vitro* and xenograft studies may suggest a role for using dovitinib in combination regimens for t(4;14)-positive patients.

The safety results in our study were in line with the known safety profile of dovitinib or were not unexpected in patients with relapsed or refractory MM. The most commonly affected primary system organ class (≥10%) for AEs suspected to be related to study drug was gastrointestinal disorders. Gastrointestinal toxicity remains a challenge, and timely monitoring and supportive care during dovitinib treatment may alleviate these symptoms.

In summary, dovitinib was found to have no or minimal single-agent activity in relapsed or refractory MM irrespective of t(4;14) status. However, the higher rate of disease stabilization, the longer exposure duration, and longer PFS in the t(4;14)-positive group may provide support for exploring the inclusion of dovitinib in a combination therapy regimen in this high-risk patient population, particularly those patients with earlier-stage disease who retain expression of FGFR3 and lack Ras or other genomic mutations that render FGFR3 redundant. Success is only likely in patients meeting these criteria who are still at least partially dependent on FGFR3 signaling.

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Conflict of interest and sources of funding

CS has received honoraria from Novartis. DR has received research funding from Novartis, Millennium, Janssen, and Celgene; honoraria from Novartis, Janssen, and Celgene; and consultancy from Janssen and Celgene. MB has served on advisory boards for Novartis, Janssen-Cilag, Celgene, Amgen, and Bristol-Myers Squibb; and speakers' bureau for Janssen-Cilag, Celgene, and Amgen. AS has received personal fees from Novartis. NC has nothing to disclose. PS has received grants and personal fees from Celgene, Janssen, Millennium, and Onyx; and has served on advisory boards for Novartis. GK, CC, MC, and JC are employees of

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