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Summary

Background Activating *FGFR2* mutations are found in 10–16% of primary endometrial cancers and provide an opportunity for targeted therapy. We assessed the safety and activity of dovitinib, a potent tyrosine-kinase inhibitor of fibroblast growth factor receptors, VEGF receptors, PDGFR-β, and c-KIT, as second-line therapy both in patients with *FGFR2*-mutated (*FGFR2*^{mut}) endometrial cancer and in those with *FGFR2*-non-mutated (*FGFR2*$^{non\text{-}mut}$) endometrial cancer.

Methods In this phase 2, non-randomised, two-group, two-stage study, we enrolled adult women who had progressive disease after first-line chemotherapy for advanced or metastatic endometrial cancer from 46 clinical sites in seven countries. We grouped women according to *FGFR2* mutation status and gave all women dovitinib (500 mg per day, orally, on a 5-days-on and 2-days-off schedule) until disease progression, unacceptable toxicity, death, or study discontinuation for any other reason. The primary endpoint was proportion of patients in each group who were progression-free at 18 weeks. For each group, the second stage of the trial (enrolment of 20 additional patients) could proceed if at least eight of the first 20 treated patients were progression free at 18 weeks. Activity was assessed in all enrolled patients and safety was assessed in all patients who received at least one dose of dovitinib. The completed study is registered with ClinicalTrials.gov, number NCT01379534.

Findings Of 248 patients with *FGFR2* prescreening results, 27 (11%) had *FGFR2*^{mut} endometrial cancer. Between Feb 17, 2012, and Dec 13, 2013, we enrolled 22 patients in the *FGFR2*^{mut} group and 31 patients in the *FGFR2*$^{non\text{-}mut}$ group. Seven (31·8%, 95% CI 13·9–54·9) patients in the *FGFR2*^{mut} group and nine (29·0%, 14·2–48·0) in the *FGFR2*$^{non\text{-}mut}$ group were progression-free at 18 weeks. On the basis of predefined criteria, neither group continued to stage two: seven (35%) of the first 20 patients in the *FGFR2*^{mut} group were progression free at 18 weeks, as were five (25%) of the first 20 in the *FGFR2*^{mut} population. Rates of treatment-emergent adverse events were similar between groups and events were most frequently gastrointestinal. Overall, the most common grade 3 or 4 adverse events suspected to be related to the study drug were hypertension (nine patients; 17%) and diarrhoea (five; 9%). The most frequently reported serious adverse events suspected to be related to study drug were pulmonary embolism (four patients; 8%), vomiting (four; 8%), dehydration (three; 6%), and diarrhoea (three; 6%). Only one death was deemed to be treatment-related: one patient in the *FGFR2*$^{non\text{-}mut}$ group died from cardiac arrest with contributing reason of pulmonary embolism (grade 4, suspected to be study drug related) 4 days previously.

Interpretation Second-line dovitinib in *FGFR2*^{mut} and *FGFR2*$^{non\text{-}mut}$ advanced or metastatic endometrial cancer had single-agent activity, although it did not reach the prespecified study criteria. Observed treatment effects seemed independent of *FGFR2* mutation status. These data should be considered exploratory and additional studies are needed.

Funding Novartis Pharmaceuticals.

Introduction

Endometrial cancer is the most common gynaecological malignancy in women in Europe and the USA.[1,2] Although most cases are detected at an early stage and cured with surgery alone or with adjuvant therapy, women with advanced or metastatic endometrial cancer have a poor prognosis, and few treatment options are available. Hormonal drugs or chemotherapies have little activity after first-line treatment, with median progression-free survival generally shorter than 3 months and median overall survival shorter than 12 months.[3–7] Thus, new treatment approaches are urgently needed.

Despite recent advances in the molecular characterisation of endometrial cancer, treatment strategies do not include target-based therapies.[8,9] Fibroblast growth factor receptor 2 (FGFR2) could be a novel molecular target.[10] Investigators have identified activating mutations in 10–16% of primary endometrial cancers, and these are more frequent in cancers of endometrioid histological subtype compared with serous or clear-cell subtypes.[8–10] Gain-of-function mutations in the kinase

Research in context

Evidence before this study

In February, 2015, we searched PubMed for papers with the search terms "endometrial" and "fibroblast growth factor receptor" with no limits on publication date or language. Before we started our study, retrospective analyses of endometrial tumours had identified activating mutations in *FGFR2*. These mutations had been targeted with fibroblast growth factor receptor (FGFR) inhibitors in preclinical, but not clinical, reports.

Added value of this study

Our search identified two clinical trials with inhibitors of FGFRs, nintedanib and brivanib, that were published after the start of our study. However, investigators for these trials did not prospectively group patients on the basis of *FGFR2* mutations and only nintedanib has an IC_{50} for FGFR2 that is similar to dovitinib (37 nmol/L *vs* 40 nmol/L), limiting comparison of these results. Therefore, to our knowledge, our study is the largest trial with an FGFR inhibitor and is the first of its kind to prospectively group patients with endometrial cancer on the basis of *FGFR2* status.

Implications of all the available evidence

Although there was insufficient activity to proceed to stage two, dovitinib showed some activity in $FGFR2^{mut}$ and $FGFR2^{non\text{-}mut}$ patients. Therefore, FGFR-pathway inhibition remains promising. More potent and selective FGFR inhibitors could improve clinical activity and reduce toxicity in this population. Additional studies are necessary before implementation in the clinic.

domain (ie, N549K substitution) lead to ligand-independent activation of the receptor, whereas mutations in the extracellular ligand-binding domain (ie, S252W or P253R substitution) increase the affinity for fibroblast growth factors (FGFs).[8,10–12] Both types of mutations have been shown to be potentially oncogenic in endometrial cancer cell lines.[11] Importantly, *FGFR2* mutations are of independent prognostic relevance in early-stage endometrioid endometrial cancer, suggesting a role as oncogenic drivers.[12]

Dovitinib (TKI258) is a reversible ATP-competitive receptor tyrosine-kinase inhibitor that targets FGFR1, FGFR2, FGFR3, VEGFR1, VEGFR2, VEGFR3, PDGFR-β, c-KIT, and other kinases.[13] Dovitinib selectively inhibited the growth of endometrial cancer cell lines with *FGFR2* mutations by blocking FGFR2 signalling, inducing cell-cycle arrest, and increasing apoptosis.[14] In mice, dovitinib showed dose-dependent growth inhibition of both *FGFR2*-mutated ($FGFR2^{mut}$) and *FGFR2*-nonmutated ($FGFR2^{non\text{-}mut}$) endometrial xenografts.[14,15] These preclinical data suggest that dovitinib might act not only via direct anti-tumour effects (inhibition of FGFR2) but also through inhibition of the formation and maintenance of tumour vasculature (inhibition of VEGFR1, VEGFR2, VEGFR3, FGFR1, FGFR2, FGFR3, and PDGFR-β),[15] thereby providing rationale for evaluation of dovitinib in both $FGFR2^{mut}$ and $FGFR2^{non\text{-}mut}$ patient populations. We did a clinical study to evaluate the efficacy and safety of dovitinib as second-line therapy in patients with $FGFR2^{mut}$ or $FGFR2^{non\text{-}mut}$ advanced or metastatic endometrial cancer. Since *FGFR2* mutations are less frequent in endometrial cancer, it was necessary to accrue $FGFR2^{mut}$ and $FGFR2^{non\text{-}mut}$ groups separately to ensure an adequate number of evaluable patients.

Methods

Study design and participants

For this non-randomised, multicentre, open-label, two-group, two-stage, phase 2 trial, we enrolled women aged 18 years or older with advanced or metastatic endometrial cancer with progressive disease (per Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1) after first-line antineoplastic treatment (including at least one cytotoxic drug). We did not consider neoadjuvant and adjuvant treatments to be a previous line of treatment, unless the recurrence occurred at or within 6 months since the last administration of neoadjuvant or adjuvant chemotherapy. We did not consider hormonal therapy in any setting to be a line of treatment. Eligible histological disease types included endometrioid, serous, clear-cell, mucinous, adenosquamous, and mixed types. Key additional eligibility criteria included tissue specimen for *FGFR2* assessment, Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and at least one measurable lesion. Key exclusion criteria included more than one previous line of chemotherapy for advanced or metastatic disease, previous treatment with an FGFR inhibitor, known brain metastases, and impaired cardiac function or clinically significant cardiac disease. A full list is provided in the appendix.

See Online for appendix

The protocol and amendments were reviewed by each centre's independent ethics committee or institutional review board. All patients provided written informed consent. The trial was done in accordance with the ICH Harmonised Tripartite Guidelines for Good Clinical Practice, with applicable local regulations, and with the ethical principles of the Declaration of Helsinki.

Procedures

Patients were treated with 500 mg dovitinib (Novartis Pharmaceuticals, East Hanover, NJ, USA), orally on a 5-days-on and 2-days-off schedule until disease progression, unacceptable toxicity, death, or discontinuation from the study treatment due to any other reason. The dose and schedule for single-agent dovitinib were based on pharmacokinetic modelling and data from a phase 1 trial in patients with renal-cell carcinoma,

which showed steady state was achieved by the second week.[16,17] Investigators could manage dovitinib-related toxicities with dose interruptions (up to 21 days) or dose reductions (400 mg then 300 mg per day on the same schedule). Dose re-escalation was not permitted.

We classified women into two groups on the basis of *FGFR2* mutation status (*FGFR2*^{mut} or *FGFR2*$^{non\text{-}mut}$). We established *FGFR2* status by Sanger sequencing (on archival tumour blocks or fresh fixed tumour biopsies) of the five main hotspot mutation sites reported for endometrial cancer within exons 7, 8, 9, 11, and 13.[18] Tumour assessments were done with CT or MRI every 6 weeks until disease progression, with an additional assessment for complete response or partial response within 4 weeks after the criteria for response were first met.[19] Activity was assessed locally and reviewed centrally for all enrolled patients. Safety was assessed in all patients who received at least one dose of dovitinib and included monitoring of adverse events; haematology; blood chemistry; urinalysis; and regular vital signs, physical examination, performance status, electrocardiograph, and cardiac imaging assessments. Urinalysis, blood chemistry, and haematology were assessed on days 1, 33, and 43 after the start of treatment and every 21 days thereafter, with blood chemistry and haematology also being assessed on day 12. Adverse events were assessed according to Common Terminology Criteria for Adverse Events version 4.03 throughout the study and 30 days after the last dose of study treatment (on treatment). Blood samples for dovitinib trough concentrations were collected predose on day 5 of weeks 2, 4, and 6, and on day 1 every 12 weeks beginning week 13.

Archival tumour samples remaining from *FGFR2* screening were tested for mutations and copy number variations with the FoundationOne targeted next-generation sequencing cancer panel (Foundation Medicine, Cambridge, MA, USA) on the Illumina HiSeq 2000 platform. The assay sequenced the entire coding region of 287 genes known to be changed in cancer (T5a cancer gene panel), including *FGFR1, FGFR2, FGFR3, FGFR4,* and nine FGF genes (3, 4, 6, 7, 10, 12, 14, 19, and 23).[20]

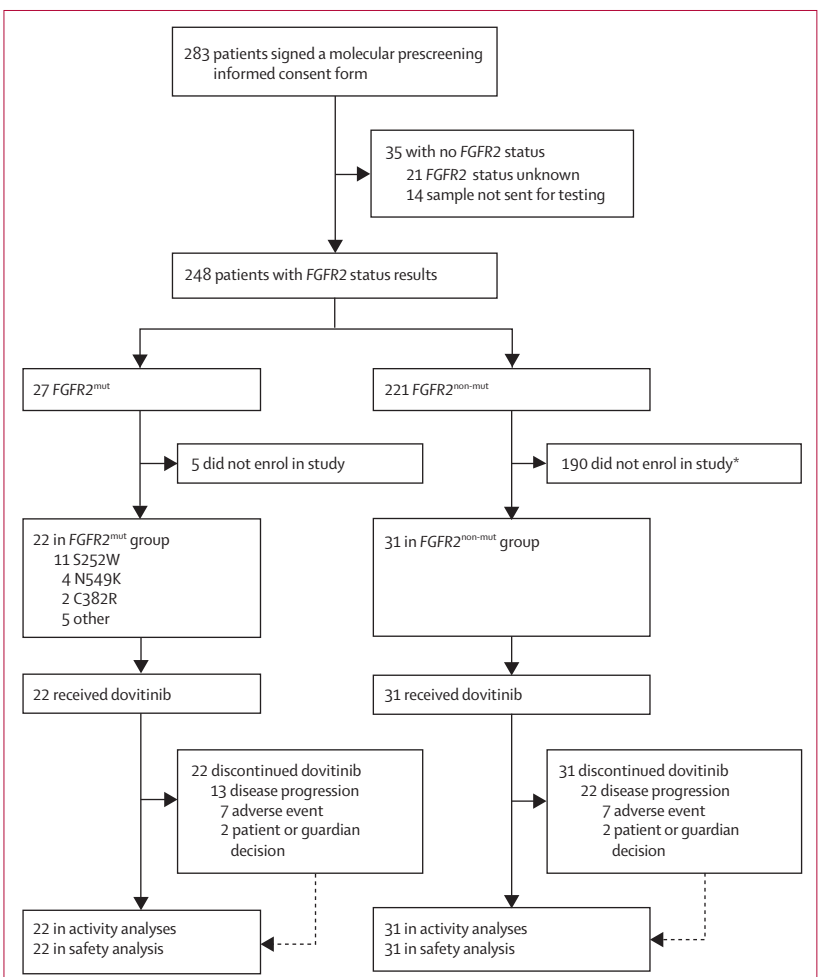

Figure 1: **Trial profile**
FGFR2^{mut}=*FGFR2*-mutated. *FGFR2*$^{non\text{-}mut}$=*FGFR2*-non-mutated. *We identified 166 patients after enrolment into the *FGFR2*$^{non\text{-}mut}$ group was complete.

Outcomes

The primary endpoint was the proportion of patients in each group who were progression free (by investigator assessment with RECIST version 1.1) at 18 weeks in the whole population of each group.[19] Published criteria consider the progression-free survival rate at a predefined timepoint an appropriate endpoint to identify a signal of biological activity in a phase 2 setting, and this early signal would inform further clinical development.[19] The key secondary endpoint was the proportion of patients who achieved an overall response (defined as a complete response or partial response). Additional secondary endpoints were the proportion of patients who achieved disease control (defined as overall response plus stable disease), duration of response, progression-free survival, overall survival, safety, tolerability, dovitinib trough concentrations, and pharmacodynamic changes from baseline.

Statistical analysis

We used a two-stage design for the *FGFR2*^{mut} group and the *FGFR2*$^{non\text{-}mut}$ group to inform a go or no-go decision for a larger, randomised phase 3 trial. At least 20 patients were to be enrolled per stage. Stage two could proceed if at least eight of the first 20 treated patients (40%) with measurable disease at baseline met the primary endpoint. If, at the end of stage 2, 50% or more patients were progression-free at 18 months (and there was ≥0·95 probability that the rate was >20%), then evidence of a dovitinib treatment effect was to be concluded because it would show a 50% or greater improvement in progression-free survival compared with historical controls of hormonal drugs and chemotherapies after first-line treatment, in which patients achieved progression-free survival of less than 3 months and

overall survival of less than 12 months.[3–7] Because of the small sample size, which was based on the statistical assumptions described above, we planned no multivariate analysis to model the *FGFR* mutation status and survival adjusting for baseline clinical parameters.

We used descriptive statistics to summarise the findings in both groups, including the primary endpoint of proportion of patients progression-free at 18-weeks. A 95% Clopper-Pearson (exact) CI was also calculated for primary endpoint. We used the Kaplan-Meier method to analyse progression-free survival and overall survival. Progression-free survival was defined as the time from the start date of study drug to the date of the first radiologically documented disease progression or death due to any cause. If a patient had not progressed or died at the date of analysis cutoff date or had received any further anticancer therapy, data was censored at the date of the last adequate tumour evaluation before the cutoff date or before the start of the new anticancer therapy date, whichever was earlier. Overall survival was defined as the time from the start date of the study drug to the date of death due to any cause. If a patient was not known to have died, then overall survival was censored at the last contact date. Data were analysed with SAS version 9.4.

The trial is registered with ClinicalTrials.gov, number NCT01379534.

Role of the funding source

The funder and the study steering committee participated in study design and data collection, analysis, and interpretation. Primary data were accessible to all authors. GEK had the final responsibility for the decision to submit for publication.

Results

283 patients from 46 sites in seven countries (appendix) consented to molecular prescreening (figure 1). Of the 248 patients with *FGFR2* mutational status results, 27 (11%) had mutations in the gene, most commonly S252W and N549K (figure 1). The remaining 221 patients were *FGFR2*$^{non\text{-}mut}$ (including 166 patients who were identified after enrolment to the group was closed).

Between Feb 17, 2012, and Dec 13, 2013, we enrolled 22 patients in the *FGFR2*^{mut} group and 31 patients in the *FGFR2*$^{non\text{-}mut}$ group (table 1). Compared with the *FGFR2*$^{non\text{-}mut}$ group patients, those in the *FGFR2*^{mut} group were more likely to have an ECOG performance status of 0 and a longer median time since initial diagnosis, and more frequently had endometrioid endometrial cancers and well or moderately differentiated disease (table 1). As of the data cutoff, March 27, 2014, all patients had discontinued study treatment, most commonly due to progressive disease (66% [35 of 53]; figure 1).

Seven (31·8%, 95% CI 13·9–54·9) patients in the *FGFR2*^{mut} group and nine (29·0%, 14·2–48·0) in the *FGFR2*$^{non\text{-}mut}$ group were progression-free at 18 weeks (appendix). In the planned interim analysis, seven

	FGFR2^{mut} (n=22)	*FGFR2*$^{non\text{-}mut}$ (n=31)
Median age (years)	64·5 (40·0–78·0)	65·0 (36·0–80·0)
Age ≥65 years	11 (50%)	18 (58%)
Race		
White	20 (91%)	23 (74%)
Black	1 (5%)	4 (13%)
Asian	1 (5%)	1 (3%)
Pacific Islander	0	1 (3%)
Unknown	0	2 (6%)
ECOG performance status		
0	15 (68%)	14 (45%)
1	7 (32%)	17 (55%)
Predominant histological disease		
Endometrioid	19 (86%)	19 (61%)
Serous	1 (5%)	6 (19%)
Clear-cell adenocarcinoma	1 (5%)	6 (19%)
Mucinous adenocarcinoma	1 (5%)	0
Histological grade		
Well differentiated	3 (14%)	3 (10%)
Moderately differentiated	11 (50%)	7 (23%)
Poorly differentiated	7 (32%)	18 (58%)
Unknown	1 (5%)	3 (10%)
Adjuvant or neoadjuvant chemotherapy*	11 (50%)	13 (42%)
Recurrence within 6 months since last adjuvant or neoadjuvant chemotherapy	6 (27%)	10 (32%)
Median time since initial diagnosis (months)	33·3 (2·1–104·6)	16·4 (5·8–50·3)
Median time since most recent recurrence or relapse (months)	1·7 (0·5–3·6)	1·8 (0·1–4·5)

Data are median (range) or n (%). *FGFR2*^{mut}=mutated *FGFR2*. *FGFR2*$^{non\text{-}mut}$=non-mutated *FGFR2*. ECOG=Eastern Cooperative Oncology Group. *One patient in the *FGFR2*^{mut} group received neoadjuvant chemotherapy.

Table 1: **Baseline demographics and disease characteristics**

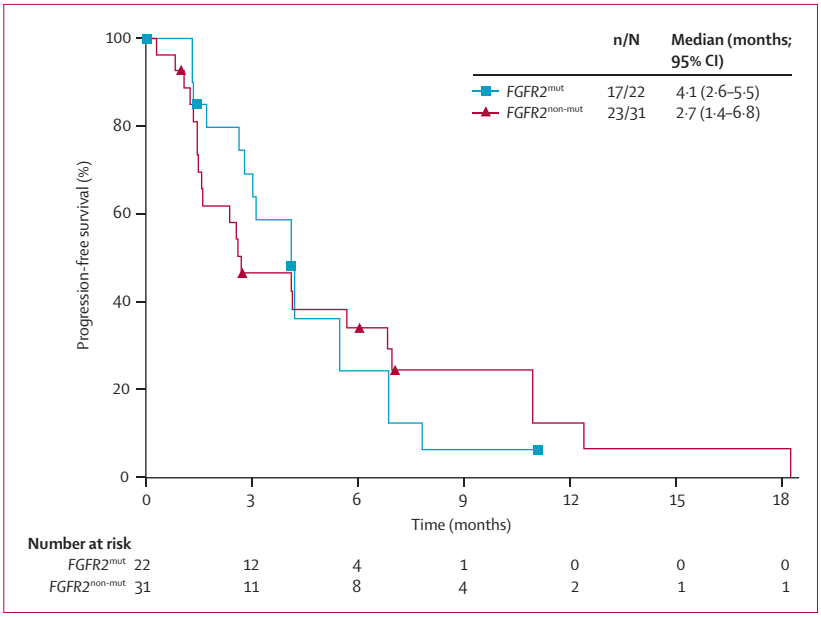

Figure 2: **Progression-free survival**

Symbols represent patients who were censored. FGFR2^{mut}=FGFR2-mutated. FGFR2$^{non\text{-}mut}$=FGFR2-non-mutated.

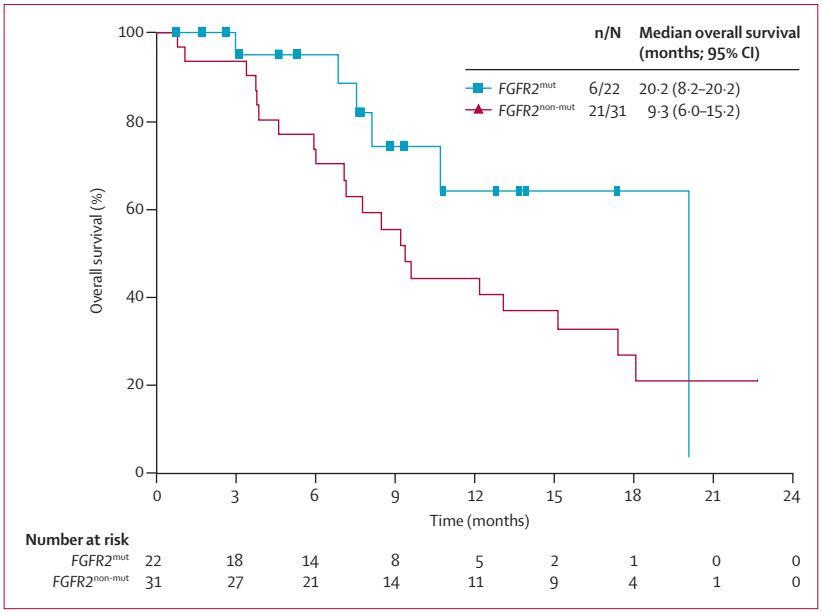

Figure 3: **Overall survival**
Symbols represent patients who were censored.

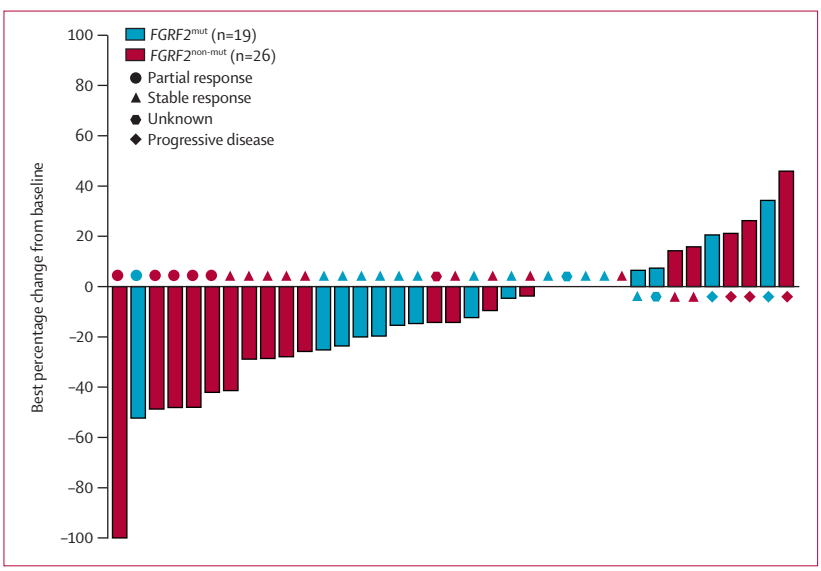

Figure 4: **Best change from baseline in target lesions**
Analysis excludes eight patients (two *FGFR2*^{mut} and six *FGFR2*$^{non\text{-}mut}$) for whom the best percentage change in target lesions was contraindicated by overall lesion response of progressive disease (three patients [one *FGFR2*^{mut} and two *FGFR2*$^{non\text{-}mut}$] had reductions in target lesions; the remaining five had increases in target lesions). *FGFR2*^{mut}=mutated *FGFR2*. *FGFR2*$^{non\text{-}mut}$=non-mutated *FGFR2*.

(35·0%, 95% CI 15·4–59·2) of the first 20 patients in the *FGFR2*^{mut} group and five (25·0%, 8·7–49·1) of the first 20 in the *FGFR2*^{mut} group were progression-free at 18 weeks. On the basis of the predefined criteria of a threshold of 40% rate, neither group of patients were continued to stage two of the study.

The median follow-up for progression-free survival in all patients was 2·7 months (IQR 1·3–5·5). The median progression-free survival by local investigator assessment was 4·1 months (95% CI 2·6–5·5) in the *FGFR2*^{mut} group and 2·7 months (1·4–6·8) in the *FGFR2*$^{non\text{-}mut}$ group (figure 2). The probability of being progression free at 18 weeks based on a Kaplan-Meier analysis was 47·8% (95% CI 24·8–67·7) in the *FGFR2*^{mut} group and 37·9% (19·7–56·0) in the *FGFR2*$^{non\text{-}mut}$ group (figure 2). The median follow-up for overall survival in all patients was 7·8 months (IQR 4·6–13·2). The median overall survival was 20·2 months (IQR 8·2–20·2) in the *FGFR2*^{mut} group and 9·3 months (6·0–15·2) in the *FGFR2*$^{non\text{-}mut}$ group (figure 3; appendix).

No patients achieved a complete response; however, six patients achieved a partial response (one in the *FGFR2*^{mut} group and five in the *FGFR2*$^{non\text{-}mut}$ group); thus the proportion of patients achieving an overall response was 5% (one of 22 patients) in the *FGFR2*^{mut} group and 16% (five of 31) in the *FGFR2*$^{non\text{-}mut}$ group. The duration of response was censored at 2·8 months in the patient with a partial response in the *FGFR2*^{mut} group because they started a new cancer treatment. In the five patients with partial responses in the *FGFR2*$^{non\text{-}mut}$ group, the median follow-up for duration of response was 2·8 months (range 2·8–6·9). Target lesion size (sum of longest diameters) was reduced in nine patients in the *FGFR2*^{mut} group and 14 patients in the *FGFR2*$^{non\text{-}mut}$ group (figure 4). 24 patients had stable disease as their best response (13 *FGFR2*^{mut}, 11 *FGFR2*$^{non\text{-}mut}$); 14 (64%) of 22 patients achieved a clinical benefit in the *FGFR2*^{mut} group, as did 16 (52%) of 31 of patients in the *FGFR2*$^{non\text{-}mut}$ group. The median follow-up for the duration of stable disease was 4·2 months (range 1·4–11·0) in the *FGFR2*^{mut} group and 5·8 months (2·3–18·2) in the *FGFR2*$^{non\text{-}mut}$ group (figure 5).

The median exposure to dovitinib was 15·9 weeks (range 0·6–50·7) in the *FGFR2*^{mut} group and 11·1 weeks (0·3–77·1) in the *FGFR2*$^{non\text{-}mut}$ group. More than a third of all patients were treated for less than 6 weeks, and stopped the study drug before the first scheduled assessment of response (eight [36%] of 22 patients in the *FGFR2*^{mut} group, and 11 [35%] of 31 patients in the *FGFR2*$^{non\text{-}mut}$ group; table 2). Across both groups, the main reasons for discontinuation of patients within 6 weeks of treatment (n=19) were adverse events (ten [19%] patients), disease progression (seven [13%]), and patient or guardian decision (two [4%]). Across both groups, 20 (38%; six in *FGFR2*^{mut} group and 15 in *FGFR2*$^{non\text{-}mut}$) patients had dose reductions and 33 (62%; 14 in *FGFR2*^{mut} group and 19 in *FGFR2*$^{non\text{-}mut}$) patients had at least one dose delay or interruption. The geometric mean values and range of dovitinib trough concentrations were similar between the two groups. Consistent with the 5-days-on and 2-days-off schedule, trough concentrations on day 5 were generally greater than those on day 1 (appendix).

Adverse events were similar between the groups and most commonly gastrointestinal (table 3). The most common adverse events suspected to be related to study

drug (any grade) were diarrhoea, vomiting, nausea, fatigue, and rash (table 3). The most common suspected grade 3 or 4 events were hypertension, diarrhoea, fatigue, rash, hypertriglyceridaemia, lipase increase, and pulmonary embolism. Adverse events led to dose interruptions, dose reductions, or both in 36 (68%) patients, most commonly due to vomiting (12 [23%] patients), diarrhoea (11 [21%]), nausea (nine [17%]), fatigue (seven [13%]), and hypertension (seven [13%]). The most frequently reported serious adverse events suspected to be related to study drug were pulmonary embolism (four [8%]), vomiting (four [8%]), dehydration (three [6%]), and diarrhoea (three [6%]). The most common adverse events (irrespective of study drug relationship) that led to discontinuation were deep vein thrombosis, pulmonary embolism, and small-intestinal obstruction (two patients [4%] for each).

No patient had a QTcF interval longer than 480 ms, and none of the 52 patients with baseline electrocardiograms had an increase from baseline of longer than 60 ms. Additionally, none of the patients who had both pre-treatment and post-treatment echocardiograms (n=19) or multiple-gated acquisition scans (n=5) had a 20% or greater decrease from baseline cardiac ejection fraction.

Of the five on-treatment deaths, four patients died due to endometrial cancer and one died due to an adverse event suspected to be treatment-related. In this *FGFR2*$^{non\text{-}mut}$ patient, the primary reason for death was cardiac arrest with contributing reason of grade 4 pulmonary embolism, suspected to be study drug related, which occured 4 days previously.

48 (91%) patients enrolled in the study had tissue samples available for exploratory biomarker analysis, of which 44 samples were available for next-generation sequencing for somatic gene alterations. Beyond the known *FGFR2* mutations, we did not identify molecular abnormalities in FGF receptors or ligands (data not shown).

Discussion

Second-line dovitinib showed some clinical activity in *FGFR2*^{mut} and *FGFR2*$^{non\text{-}mut}$ advanced or metastatic endometrial cancer. To our knowledge, this is the first report showing activity of a single-agent tyrosine-kinase inhibitor in patients with recurrent advanced or metastatic *FGFR2*^{mut} endometrial cancer. Indeed, about a third of patients receiving second-line dovitinib in the *FGFR2*^{mut} group were progression-free at 18 weeks. Although this group did not continue to stage two based on the predefined 40% threshold, the proportion of patients who achieved clinical benefit was 64%, progression-free survival was 4 months, and the median overall survival was 20 months. Given the poor efficacy of alternative treatment options for recurrent advanced or metastatic endometrial cancer that has progressed after first-line chemotherapy, the clinical activity for dovitinib in the *FGFR2*^{mut} group seems to be clinically meaningful.

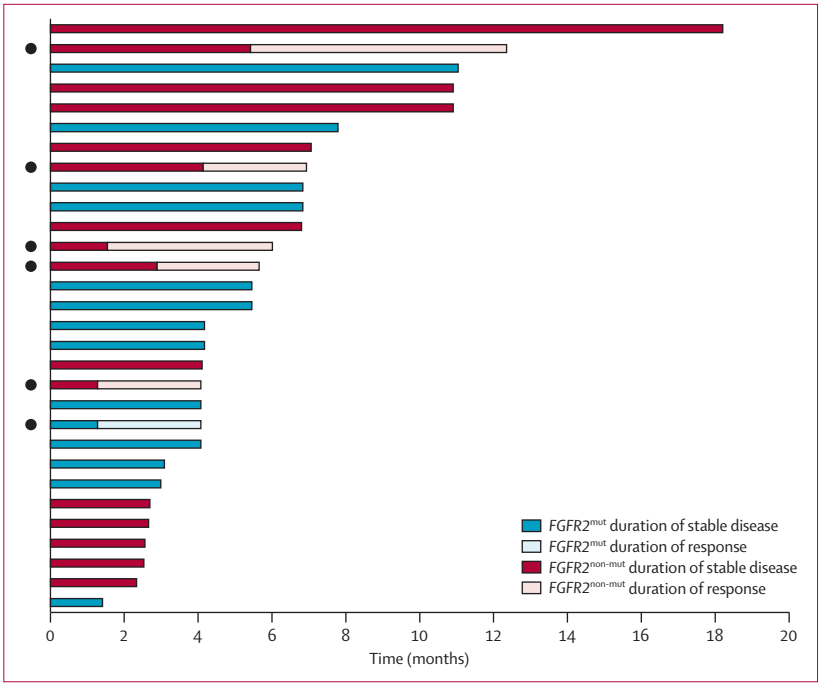

Figure 5: **Duration of stable disease and response**
Black circles indicate patients with confirmed partial responses. Duration of stable disease includes duration of response. *FGFR2*^{mut}=mutated *FGFR2*. *FGFR2*$^{non\text{-}mut}$=non-mutated *FGFR2*.

	FGFR2^{mut} (n=22)	*FGFR2*$^{non\text{-}mut}$ (n=31)
Median exposure (weeks)	15·9 (0·6–50·7)	11·1 (0·3–77·1)
Duration of exposure		
<6 weeks	8 (36%)	11 (35%)
6 weeks to <12 weeks	2 (9%)	7 (23%)
12 weeks to <18 weeks	3 (14%)	4 (13%)
≥18 weeks	9 (41%)	9 (29%)
Median relative dose intensity	96·8%	94·8%

Data are median (range) or n (%), unless otherwise indicated. *FGFR2*^{mut}=mutated *FGFR2*. *FGFR2*$^{non\text{-}mut}$=non-mutated *FGFR2*.

Table 2: **Exposure to study drug**

Although the frequency of *FGFR2* mutations in our cohort is consistent with that of earlier reports (11–16%), previous studies included only patients with primary endometrial cancer and focused on endometrioid endometrial cancer and so might have had more mutations.[8,10–12] The mutation frequency in our study of advanced endometrial cancer was at the low end of the range, which could reflect the high proportion of tumours with serous and clear-cell histology findings, which are usually not *FGFR2*^{mut}. S252W, which was the most commonly identified mutation in the *FGFR2*^{mut} group, enables the receptor to bind FGF2 and FGF9, leading to autocrine activation of FGFR2.[10] Mutations in the kinase domain were identified in six tumours, and five additional mutations were noted in the transmembrane domain or

	Grade 1 or 2	Grade 3	Grade 4
Vomiting	32 (60%)	2 (4%)	0
Diarrhoea	31 (58%)	5 (9%)	0
Nausea	31 (58%)	2 (4%)	0
Fatigue	19 (36%)	4 (8%)	0
Appetite decrease	15 (28%)	0	0
Skin rash	14 (26%)	4 (8%)	0
Blood alkaline phosphatase increase	9 (17%)	2 (4%)	0
Weight decrease	9 (17%)	0	0
Headache	8 (15%)	0	0
Anaemia	7 (13%)	2 (4%)	0
Dyspepsia	6 (11%)	0	0
Hypertriglyceridaemia	5 (9%)	3 (6%)	1 (2%)
Asthenia	5 (9%)	1 (2%)	0
Alanine aminotransferase increase	4 (8%)	2 (4%)	0
Lymphopenia or lymphocyte count decreased	4 (8%)	2 (4%)	0
Pain in extremity	4 (8%)	2 (4%)	0
Hypomagnesaemia	4 (8%)	1 (2%)	0
Deep vein thrombosis	3 (6%)	0	2 (4%)
γ-glutamyltransferase increase	3 (6%)	1 (2%)	0
Hyponatraemia	3 (6%)	1 (2%)	0
Aspartate aminotransferase increase	2 (4%)	2 (4%)	0
Hypercholesterolaemia	2 (4%)	1 (2%)	0
Hypokalaemia	2 (4%)	0	1 (2%)
Peripheral oedema	2 (4%)	1 (2%)	0
Hypertension	1 (2%)	9 (17%)	0
Dehydration	1 (2%)	3 (6%)	0
Thrombocytopenia	1 (2%)	3 (6%)	0
Amylase increased	1 (2%)	0	1 (2%)
Blood bilirubin increase	1 (2%)	1 (2%)	0
Acneiform dermatitis	1 (2%)	1 (2%)	0
Muscular weakness	1 (2%)	1 (2%)	0
Lipase increase	0	2 (4%)	2 (4%)
Pulmonary embolism	0	2 (4%)	2 (4%)
Female genital tract fistula	0	2 (4%)	0
Cardiac arrest	0	0	1 (2%)
Cerebrovascular accident	0	1 (2%)	0
Erythema multiforme	0	1 (2%)	0
Gastrointestinal haemorrhage	0	1 (2%)	0
Hypovolemia	0	1 (2%)	0
Jaundice	0	1 (2%)	0
Pain of skin	0	1 (2%)	0
Peripheral ischaemia	0	1 (2%)	0
Right ventricular failure	0	1 (2%)	0
Syncope	0	1 (2%)	0
Transaminase increased	0	1 (2%)	0
White blood cell count decrease	0	1 (2%)	0

Data are n (%). All patients (n=53). Shows adverse events suspected to be related to study drug, and includes grade 1 or 2 events recorded in more than 10% of patients, and any grade 3 or 4 events.

Table 3: **Treatment-emergent adverse events**

the extracellular third immunoglobulin domain. Although inhibition of FGFR2 kinase activity in endometrial carcinoma cell lines bearing the S252W (ligand-binding domain) or N549K (kinase domain) mutation have been well studied, less is known about the transforming ability and functional relevance of the other mutations. In our study, we were not able to detect an association between the type of *FGFR2* mutation and clinical response to dovitinib; however, this finding could be due to the small number of samples available for analysis.

Dovitinib preclinical activity is not restricted to $FGFR2^{mut}$ cell lines—$FGFR2^{non\text{-}mut}$ endometrial cancer xenografts exhibited complete tumour regressions in long-term in-vivo studies,[14] potentially showing dovitinib's anti-angiogenic activity.[15] In our study, around 29% of individuals with tumours that were $FGFR2^{non\text{-}mut}$ were progression-free at 18 weeks and the probability of being progression free at 18 weeks based on Kaplan-Meier analysis was 37·9%. Although, the proportion of patients achieving a clinical benefit in the $FGFR2^{non\text{-}mut}$ group (52%) could be seen as promising (especially since high-grade tumours were included), responses were short lasting. Nonetheless, the observed clinical activity is similar to what has been reported for hormonal drugs or chemotherapies after first-line treatment of advanced or metastatic endometrial cancer.[3–7] Since this activity was similar to that seen in the $FGFR2^{mut}$ group, testing for *FGFR2* mutations would not be a useful enrichment strategy if dovitinib was to be used clinically. The shorter overall survival in the $FGFR2^{non\text{-}mut}$ group (compared with the $FGFR2^{mut}$ group) could be attributed to the more adverse prognostic tumour characteristics in the former. Although these data need to be interpreted with caution because of the small number of patients in each group and the overlapping confidence intervals, they are of particular interest because next-generation sequencing did not identify molecular abnormalities of the other FGF receptors or ligands. Thus, activity in patients with $FGFR2^{non\text{-}mut}$ tumours might be reflective of the anti-angiogenic effects of dovitinib.

Bevacizumab inhibition of the VEGF pathway has shown clinical activity in endometrial cancer.[21] However, anti-angiogenic escape can occur via activation of several pathways, including those involving platelet-derived growth factor and FGF.[22] Although sunitinib, a VEGFR1, VEGFR2, VEGFR3, and PDGFR-β[23] inhibitor, also demonstrated activity in this population, the ability of dovitinib to potently inhibit FGFR1, FGFR2, and FGFR3 might provide broader protection against anti-angiogenic escape.

Unfortunately, our study was not able to establish whether the effects seen in the $FGFR2^{mut}$ group were due to FGFR2 inhibition only or also due to the anti-angiogenic effects from FGFR1, FGFR2, FGFR3, VEGFR1, VEGFR2, VEGFR3, and PDGFR-β as seen in the $FGFR2^{non\text{-}mut}$ group. A clinical trial with a more potent and selective FGF receptor inhibitor such as

BGJ398 or JNJ-42756493 would allow for better assessment of FGF receptor-dependent growth inhibition.[24,25] Thus additional studies are needed with more specific FGFR2 inhibitors before FGFR2 testing could be used clinically. Another limitation is that more than a third of the study patients in both groups had drug exposure of less than 6 weeks and stopped the study drug before the first assessment of treatment response. The trial staffs' lack of experience in the management of mild or moderate class-specific treatment-related side-effects early in the trial might have contributed to this high rate of patient discontinuation.

Although cross-trial comparisons must be made with caution, and despite the described limitations, in comparison to previous studies we believe our study is the most robust analysis of an inhibitor of FGF receptors in patients with *FGFR2*^{mut} endometrial cancer. Investigators have previously reported results of a phase 2 study of brivanib, an inhibitor of VEGF receptor and FGF receptor, in patients with recurrent or persistent endometrial cancer after one or two cytotoxic regimens.[26] 19% of these patients receiving brivanib achieved an overall response, and they had a progression-free survival rate at 6 months of 30·2% (90% CI 18·9–43·9).[26] However, the effect of FGFR2 inhibition in that study is not clear because only three patients had *FGFR2* mutations.[13,27] In another phase 2 study of single-agent nintedanib (an inhibitor of VEGF, platelet-derived growth factor, and FGF receptors that has a similar half maximal inhibitory concentration against FGFR2 as has dovitinib)[28] 9·4% of patients with recurrent or persistent, previously treated endometrial cancer achieved an overall response, and the progression-free survival rate at 6 months was 21·9%.[29] However, tissue specimens were not collected and *FGFR2* status of patients was not known.

The safety results in this study are consistent with the known safety profile of dovitinib. The most common adverse events were gastrointestinal (diarrhoea, vomiting, and nausea), with most events mild to moderate (grade 1 or 2) and manageable with dose adjustments or interruptions. The rate of thromboembolic events was higher in this study compared with that reported in other dovitinib studies.[30,31] However, venous thromboembolism is thought to be a comorbidity in women with gynaecological cancers, especially in patients with advanced or metastatic tumours.[32]

In our study, second-line dovitinib in *FGFR2*^{mut} advanced or metastatic endometrial cancer had single-agent activity, but did not meet the endpoint for stage two of the trial. These data should be considered exploratory and additional studies are needed. Importantly, our findings emphasise the need for further study of drugs that selectively target FGFR2 in patients with endometrial cancer, but they also underscore the call to further study multikinase inhibitors targeting both FGF and VEGF pathways in *FGFR2*$^{non\text{-}mut}$ advanced or metastatic endometrial cancer.

Contributors

NF, GEK, MS, and AU contributed to the study design. NF, PCF, AAG, GEK, RK, PSL, DL, and RPR collected data. PCF, AAG, GEK, RK, PSL, DL, KM, RPR, MS, AU, and YW analysed and interpreted the data. GEK, RK, and MS searched the literature. GEK and RK developed figures. All authors drafted or approved the final version of the manuscript.

Declaration of interests

Novartis Pharmaceuticals funded the study. AAG reports funding from Novartis Pharmaceuticals for study funding (paid to his institution) and honoraria for participation in an advisory board. PSL reports research funding from Novartis Pharmaceuticals. KM, MS, AU, and YW are employees of Novartis Pharmaceuticals. NF, PCF, GEK, RK, DL, and RPR declare no competing interests.

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