Rogaratinib in patients with advanced cancers selected by *FGFR* mRNA expression: a phase 1 dose-escalation and dose-expansion study

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Lancet Oncol 2019; 20: 1454–66

Published Online August 9, 2019 http://dx.doi.org/10.1016/S1470-2045(19)30412-7

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Summary

Background The clinical activity of fibroblast growth factor receptor (FGFR) inhibitors seems restricted to cancers harbouring rare *FGFR* genetic aberrations. In preclinical studies, high tumour *FGFR* mRNA expression predicted response to rogaratinib, an oral pan-FGFR inhibitor. We aimed to assess the safety, maximum tolerated dose, recommended phase 2 dose, pharmacokinetics, and preliminary clinical activity of rogaratinib.

Methods We did a phase 1 dose-escalation and dose-expansion study of rogaratinib in adults with advanced cancers at 22 sites in Germany, Switzerland, South Korea, Singapore, Spain, and France. Eligible patients were aged 18 years or older, and were ineligible for standard therapy, with an Eastern Cooperative Oncology Group performance status of 0–2, a life expectancy of at least 3 months, and at least one measurable or evaluable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. During dose escalation, rogaratinib was administered orally twice daily at 50–800 mg in continuous 21-day cycles using a model-based dose-response analysis (continuous reassessment method). In the dose-expansion phase, all patients provided an archival formalin-fixed paraffin-embedded (FFPE) tumour biopsy or consented to a new biopsy at screening for the analysis of *FGFR1–3* mRNA expression. In the dose-expansion phase, rogaratinib was given at the recommended dose for expansion to patients in four cohorts: urothelial carcinoma, head and neck squamous-cell cancer (HNSCC), non-small-cell lung cancer (NSCLC), and other solid tumour types. Primary endpoints were safety and tolerability, determination of maximum tolerated dose including dose-limiting toxicities and determination of recommended phase 2 dose, and pharmacokinetics of rogaratinib. Safety analyses were reported in all patients who received at least one dose of rogaratinib. Patients who completed cycle 1 or discontinued during cycle 1 due to an adverse event or dose-limiting toxicity were included in the evaluation of recommended phase 2 dose. Efficacy analyses were reported for all patients who received at least one dose of study drug and who had available post-baseline efficacy data. This ongoing study is registered with ClinicalTrials.gov, number NCT01976741, and is fully recruited.

Findings Between Dec 30, 2013, and July 5, 2017, 866 patients were screened for *FGFR* mRNA expression, of whom 126 patients were treated (23 *FGFR* mRNA-unselected patients in the dose-escalation phase and 103 patients with *FGFR* mRNA-overexpressing tumours [52 patients with urothelial carcinoma, eight patients with HNSCC, 20 patients with NSCLC, and 23 patients with other tumour types] in the dose-expansion phase). No dose-limiting toxicities were reported and the maximum tolerated dose was not reached; 800 mg twice daily was established as the recommended phase 2 dose and was selected for the dose-expansion phase. The most common adverse events of any grade were hyperphosphataemia (in 77 [61%] of 126 patients), diarrhoea (in 65 [52%]), and decreased appetite (in 48 [38%]); and the most common grade 3–4 adverse events were fatigue (in 11 [9%] of 126 patients) and asymptomatic increased lipase (in 10 [8%]). Serious treatment-related adverse events were reported in five patients (decreased appetite and diarrhoea in one patient with urothelial carcinoma, and acute kidney injury [NSCLC], hypoglycaemia [other solid tumours], retinopathy [urothelial carcinoma], and vomiting [urothelial carcinoma] in one patient each); no treatment-related deaths occurred. Median follow-up after cessation of treatment was 32 days (IQR 25–36 days). In the expansion cohorts, 15 (15%; 95% CI 8·6–23·5) out of 100 evaluable patients achieved an objective response, with responses recorded in all four expansion cohorts (12 in the urothelial carcinoma cohort and one in each of the other three cohorts), and in ten (67%) of 15 *FGFR* mRNA-overexpressing tumours without apparent *FGFR* genetic aberration.

Interpretation Rogaratinib was well tolerated and clinically active against several types of cancer. Selection by *FGFR* mRNA expression could be a useful additional biomarker to identify a broader patient population who could be eligible for FGFR inhibitor treatment.

Funding Bayer AG.

Research in context

Evidence before this study

We searched PubMed between Dec 30, 2003, and April 10, 2019, and congress proceedings of the American Association for Cancer Research, the American Society of Clinical Oncology, and the European Society of Medical Oncology Annual Meetings, for articles and abstracts relevant to the development of fibroblast growth factor receptor inhibitor drugs and related biomarkers using the search terms "fibroblast growth factor", "fibroblast growth factor receptor", "RNA in situ hybridisation", "gene fusion", "genomic alterations", "biomarker", "urothelial cancer", "non-small cell lung cancer", and "head and neck squamous cell carcinoma" (including abbreviations and related terminology) without any language restrictions. Our search results showed that predictive biomarkers for clinical development of fibroblast growth factor receptor (FGFR) inhibitor therapy have been based on genetic alterations—ie, gene copy number alterations (amplifications), fusions, or mutations.

Added value of this study

To our knowledge, this is the first-in-human phase 1 study for the pan-FGFR inhibitor rogaratinib. We demonstrated that patient selection on the basis of *FGFR1–3* mRNA expression from standard tumour biopsies is feasible and allows identification of a broader group of patients who could benefit from FGFR inhibitors. Rogaratinib had a favourable safety profile and clinical efficacy in patients with solid cancers selected by *FGFR1–3* mRNA expression.

Implications of all the available evidence

FGFR mRNA-based screening can detect a broader patient population eligible for rogaratinib treatment, which increases its overall clinical feasibility and potential benefit to patients with *FGFR*-positive cancers.

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Introduction

The fibroblast growth factor receptor (FGFR) is involved in tumour pathophysiology via regulation of cell proliferation and survival, apoptosis, metastasis formation, and angiogenesis.[1] The development of first-generation FGFR kinase inhibitors has been challenging because of poor selectivity, substantial heterogeneity of molecular characteristics for patient selection, and the occurrence of dose-limiting toxicity in early clinical trials.[2] Several potent and FGFR-selective small-molecule kinase inhibitors have been identified in phase 1 and 2 studies,[3–7] showing promising antitumour activity in solid malignancies, with manageable safety profiles in patients pre-selected on the basis of *FGFR* genetic alterations, including amplifications, translocations, or activating mutations in *FGFR1–4*. Overall, the prevalence of *FGFR* genetic alterations is low (1–20%), with *FGFR3* mutations in advanced urothelial carcinoma being most prominent.[1] However, the predictive value of *FGFR* gene copy number gain for clinical activity is unknown, exemplified by poor associations between *FGFR1* and *FGFR2* copy number alterations with *FGFR* mRNA or protein overexpression, and poor predictive value of clinical response.[8,9]

With the exception of *FGFR3* mutations in urothelial carcinoma, *FGFR* mutations have been poor predictors of FGFR inhibitor response in vitro[10] and in clinical trials,[4,5] although the oncogenic function of *FGFR* mutations was unknown before patient recruitment in these trials. By contrast, *FGFR* gene fusions were found to be strong predictors of clinical response.[7,11] However, beyond *FGFR2* gene fusions in intrahepatic cholangiocarcinoma, the prevalence of *FGFR* gene fusions is low in solid malignancies.[12]

Rogaratinib is a novel, highly specific, and potent orally available small molecule inhibitor of FGFR1–4 kinase activity.[13–15] High tumour *FGFR* mRNA expression has been explored as an alternative biomarker selection strategy in preclinical models. mRNA expression was strongly correlated with response to rogaratinib, independent of tumour type and *FGFR* subtype overexpression. In vitro, metabolism of rogaratinib is preferentially catalysed by cytochrome p450 3A4 (CYP3A4) and, to a lesser extent, by cytochrome p450 2C9 (CYP2C9) enzymes.[13–15]

In this first-in-human study, we report the safety, tolerability, pharmacokinetics, and recommended phase 2 dose of rogaratinib, and report preliminary clinical activity in patients selected by *FGFR* mRNA expression.

Methods

Study design and participants

We did a phase 1, open-label, multicentre, non-randomised, dose-escalation and dose-expansion study in patients with advanced solid tumours at 22 academic medical centres in Germany, Switzerland, South Korea, Singapore, Spain, and France (appendix p 2). Eligible patients were aged 18 years or older with radiologically measurable or clinically evaluable tumours who were ineligible for standard therapy, an Eastern Cooperative Oncology Group performance status of 0–2, and life expectancy of at least 3 months. Patients had at least one measurable or evaluable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and had to have an archival or fresh tumour biopsy specimen available for *FGFR* mRNA expression. Eligible patients were required to have adequate bone marrow, liver, and renal function, which was defined as an absolute neutrophil count of 1500×10^9/L or higher; platelet count of $75\,000\times10^9$/L or higher; total serum bilirubin 1·5-times the upper limit of

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normal (ULN) or less (patients with known Gilbert syndrome were allowed if total bilirubin was <6 mg/dL); aspartate amino transferase, amino alanine transferase, and alkaline phosphatase up to 2·5×ULN (≤5×ULN in patients with liver involvement); lipase up to 5×ULN; Child-Pugh score not higher than B7; and glomerular filtration rate 30 mL/min per 1·73m² or higher according to the Modification of Diet in Renal Disease abbreviated formula.[16] Previous anticancer therapies were allowed with a wash-out period of five half-lives of the anticancer drugs or 6 weeks for mitomycin C, nitrosoureas, or monoclonal antibodies. Patients were ineligible if they had previously received FGFR-directed therapies. Full eligibility criteria are shown in the study protocol (appendix pp 66–72).

For the dose-escalation phase, patients with histologically or cytologically confirmed advanced solid tumours in whom standard-of-care treatment had failed were eligible. The dose-expansion phase consisted of three separate cohorts of patients with biomarker-positive non-small-cell lung cancer (NSCLC), head and neck squamous-cell carcinoma (HNSCC), and urothelial carcinoma. A fourth exploratory cohort enrolled additional biomarker-positive patients with any other type of solid cancer. Overexpression of tumour *FGFR* mRNA (*FGFR1*, *FGFR2*, or *FGFR3*) was mandatory for enrolment in the dose-expansion cohorts. Biomarker positivity was defined by *FGFR1–3* mRNA overexpression or, for urothelial carcinoma only, an activating point mutation in *FGFR3*.

The study was approved by independent ethics committees and institutional review boards at each study site, and by the appropriate regulatory authorities. The study was done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol (appendix p 23) and all protocol amendments were approved by the respective competent authorities and local review boards. All patients provided written, informed consent before study entry.

Procedures

In the dose-escalation phase, rogaratinib (Bayer AG, Berlin, Germany) was administered orally twice daily in continuous 21-day treatment cycles. The starting dose was 50 mg twice daily (liquid formulation; 10 mg/mL). At a dose of 100 mg twice daily or above, the formulation was changed to a tablet. One of the dose-escalation cohorts was a tablet bridging cohort, in order to compare the relative bioavailability of both formulations. In this bridging cohort, four patients were given a single dose of the tablet formulation 3 days before the start of cycle 1 (ie, day −3 of cycle 1), and then continued with the solution formulation (administered orally twice daily) starting on cycle 1, day 1, in continuous 21-day treatment cycles. Dose-escalation steps were 50 mg, 100 mg, 200 mg, 400 mg, and 800 mg twice daily using a model-based dose-response analysis (continuous reassessment method);[17] the effect of food on rogaratinib pharmacokinetics was assessed at the 800 mg dose level.

Dose escalation was planned to be continued until the maximum tolerated dose was reached, which was defined according to model-based predictions using the continuous reassessment method,[17] or if the selected dose level for the next cohort had already been given to nine patients. Without the occurrence of toxicities, dose escalation was to be stopped and the recommended phase 2 dose was to be determined based on pharmacokinetic or pharmacodynamic results. In this case, Bayesian dose-response or pharmacokinetic or pharmacodynamic modelling were planned to be done after selected cohorts to generate information for adaptive dose selection decisions. Treatment continued until disease progression, unacceptable toxicity, consent withdrawal, or study withdrawal at the investigator's discretion.

Model-based dose-response analysis of dose-limiting toxicity rates was used to guide dose-escalation decisions. The dose predicted to yield a 20% probability of dose-limiting toxicity was selected as a best candidate for the next cohort. A dose-limiting toxicity was defined as the occurrence of any of the following attributed to rogaratinib during cycle 1 of a particular dose level: absolute neutrophil count of less than $0·5×10^9$/L for more than 7 days; febrile neutropenia with absolute neutrophil count of less than $1×10^9$/L and a single body temperature reading of 38·3°C or higher, or a sustained body temperature of 38·0°C or higher for more than 1 h; platelet count of less than $25×10^9$/L; grade 3 haemorrhage associated with thrombocytopenia of grade 3 or worse; any National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade 3 or grade 4 non-haematological toxicity related to study drug (nausea and vomiting only if refractory to anti-emetics and for >48 h); or serum calcium phosphate product higher than 70 mg²/dL² (5·6 mmol²/L²) despite the use of standard phosphate binders given at the investigator's discretion. If at least one patient out of three or one out of four in a cohort were to have dose-limiting toxicities, or if at least two patients were to report drug-related adverse events of grade 2 or higher, any further dose escalation, de-escalation, or cohort expansion would be decided in consultation between all investigators and the sponsor after consideration of all available safety data of the previous cohorts. Any subsequent dose was planned to be selected to determine the maximum tolerated dose. Compliance of at least 80% was required, thus patients had to have documented intake of at least 80% of the planned study medication (ie, 32 doses or 16 days of treatment in cycle 1 with pharmacokinetic assessment and 34 doses or 17 days of treatment in more than two cycles and in cycle 1 without pharmacokinetic assessment).

Rogaratinib dose interruptions were allowed for up to 21 days in the event of drug-related toxicity of any grade. Up to two dose reductions were allowed for drug-related toxicities of grade 3 or worse severity (appendix pp 81–85).

Tumour response was assessed by local investigators, according to RECIST version 1.1 after 6 weeks, and then

every 9 weeks thereafter. Measurable lesions were assessed for objective response by CT or MRI. Responses were confirmed after 4 weeks or more by local CT or MRI assessment, or were otherwise marked as unconfirmed responses.

Safety evaluations included adverse events, vital signs, laboratory tests, and electrocardiograms at screening, during study treatment, and 30 days after the last dose. Laboratory monitoring was done weekly during cycles 1–12 and on days 1 and 11 for subsequent cycles. Adverse events were coded according to Medical Dictionary for Regulatory Activities (version 21.1) and graded using NCI-CTCAE (version 4.03).

Serial blood samples were collected on days 1 and 15 of cycle 1 for rogaratinib single-dose and multiple-dose pharmacokinetic assessments, which were planned in all patients in the dose-escalation cohort and in a subset of eight patients in the dose-expansion cohorts who consented to providing pharmacokinetic samples. Plasma rogaratinib concentrations were determined using a validated liquid chromatography–tandem mass spectrometry analytical method and pharmacokinetic parameters were estimated using non-compartmental methods (Phoenix WinNonlin software; version 5.3; Pharsight Corporation, St Louis, MO, USA) and population modelling.

All patients with valid pharmacokinetic measurements were included in a two-compartment model with first-order absorption using NONMEM software (version 7.3; ICON, Dublin, Ireland). This modelling approach was developed to address questions (not limited to the recommended phase 2 dose) that might have arisen during the study, per the original protocol. The contribution of covariates to interpatient variability was evaluated. The model was used for simulations of different dosing regimens. In the dose-expansion phase, all patients provided an archival formalin-fixed paraffin-embedded (FFPE) tumour biopsy or consented to a new biopsy at screening for the analysis of *FGFR* mRNA expression. All biopsies were screened for *FGFR1–3* mRNA expression using RNA in-situ hybridisation (RNAscope; Advanced Cell Diagnostics, Newark, CA, USA) and NanoString nCounter technology (NanoString Technologies, Seattle, WA, USA), depending on tissue availability and quality (appendix p 1). Urothelial carcinoma biopsies were additionally screened for *FGFR3* gene mutations using a commercially available reverse transcription PCR-based mutation assay (Qiagen, Hilden, Germany) and targeted next-generation sequencing (Illumina MiSeq; Illumina, San Diego, CA, USA) as previously described.[18] *FGFR* mRNA overexpression was defined as a normalised NanoString signal of more than 800 counts or an RNAscope predominant score of 3 or 4 based on in-vivo models.[14] The correlation between *FGFR3* gene mutations and *FGFR3* mRNA expression was assessed by correlating the *FGFR3* mRNA expression level determined by the NanoString assay with the absence or presence of *FGFR3* activating mutations detected by RT-PCR assay. Publically available RNAseq gene expression data from The Cancer Genome Atlas urothelial carcinoma dataset[19] were used for external validation.

Serum phosphate and serum fibroblast growth factor 23 (FGF23) were applied as pharmacodynamic biomarkers; blood samples were taken at protocol-defined laboratory safety evaluations. Serum FGF23 concentrations were quantified using an enzyme-linked immunosorbent assay (Kainos Laboratories, Tokyo, Japan), which was developed into a clinical trial assay by a central laboratory (Nuvisan GmbH, Neu-Ulm, Germany).

Depending on tissue availability, additional post-hoc analyses, including targeted next-generation sequencing, whole-exome sequencing, RNA sequencing, fluorescence in-situ hybridisation assay (*FGFR* amplification), and the Archer FusionPlex panel (Archer, Boulder, CO, USA), were done on the latest available platform to confirm the absence or presence of *FGFR* genetic alterations as described previously,[20] as part of a hypothesis-generating post-hoc analysis of genomic markers. Tumour genomic DNA from all treated patients with urothelial carcinoma was assessed for mutations potentially associated with rogaratinib resistance, including *PIK3CA* and *RAS* hotspot mutations.[21] All biomarker assessments were done at a central laboratory (Targos Molecular Pathology GmbH, Kassel, Germany).

Outcomes

The primary endpoints were safety and tolerability, including determination of maximum tolerated dose and the occurrence of dose-limiting toxicities, and the pharmacokinetics of rogaratinib. Secondary endpoints were biomarker status, pharmacodynamic parameters, and tumour response (including progression-free survival and time to progression) in biomarker-selected expansion cohorts, and assessment of the relative bioavailability of the tablet formulation of rogaratinib in comparison with the solution formulation and the effect of food on pharmacokinetics, as part of prespecified pharmacokinetic characterisation.

Statistical analysis

Descriptive statistics were used to summarise demographics, baseline characteristics, adverse events, safety parameters, and response data, including the primary and secondary outcomes. No formal sample size calculation was done for this exploratory study. All patients who received at least one dose of study drug and who had available post-baseline efficacy data were included in efficacy analyses of all outcomes. All patients who completed cycle 1 of treatment or discontinued during cycle 1 due to an adverse event or dose-limiting toxicity were to be included in the evaluation of maximum tolerated dose. All patients who received at least one dose of rogaratinib were included in the safety analyses. All

	Dose-escalation cohort (n=23)	Dose-expansion cohort (n=103)				All enrolled patients (n=126)
		Urothelial carcinoma (n=52)	Head and neck squamous cell carcinoma (n=8)	Non-small-cell lung cancer (n=20)	Other solid tumours (n=23)	
Sex						
Men	14 (61%)	37 (71%)	8 (100%)	18 (90%)	14 (61%)	91 (72%)
Women	9 (39%)	15 (29%)	0	2 (10%)	9 (39%)	35 (28%)
Race						
White	19 (83%)	36 (69%)	7 (88%)	10 (50%)	15 (65%)	87 (69%)
Asian	4 (17%)	11 (21%)	1 (13%)	10 (50%)	8 (35%)	34 (27%)
Not reported	0	5 (10%)	0	0	0	5 (4%)
Age, years	62·0 (45·0–67·0)	67·5 (60·0–73·0)	67·0 (56·0–71·0)	61·0 (57·0–67·0)	62·0 (57·0–71·0)	63·5 (58·0–71·0)
ECOG performance status						
0	9 (39%)	13 (25%)	3 (38%)	6 (30%)	10 (43%)	41 (33%)
1	12 (52%)	37 (71%)	5 (63%)	12 (60%)	12 (52%)	78 (62%)
2	2 (9%)	2 (4%)	0	2 (10%)	1 (4%)	7 (6%)

Data are n (%) or median (IQR). ECOG=Eastern Cooperative Oncology Group.

Table 1: **Demographics, baseline characteristics, and tumour types (n=126; safety analysis set)**

analyses were done with SAS (version 9.4). No sensitivity analyses were done, and no formal interim analysis was planned. We did a hypothesis-generating post-hoc analysis of genomic markers, as described in the Procedures section. This study is registered with ClinicalTrials.gov, number NCT01976741.

Role of the funding source

The study funder was involved in study design, data analysis, writing of the report, and in the decision to submit the paper for publication. The funder had no role in data collection or data interpretation. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

Results

Between Dec 30, 2013, and July 5, 2017, 866 patients were screened for *FGFR1–3* mRNA expression (appendix p 2), of whom 813 had a valid *FGFR* test result (appendix p 21). 23 non-biomarker-selected patients with solid tumours were enrolled and treated in the dose-escalation phase and 103 patients with *FGFR* RNA-positive tumours were enrolled and treated in the dose-expansion phase, of whom 52 patients had urothelial carcinoma, 20 patients had NSCLC, eight patients had HNSCC, and 23 patients had other types of solid cancer. Patient demographics are summarised in table 1. Eleven (21%) of 52 patients in the urothelial carcinoma cohort in the dose-expansion phase had received previous immune checkpoint inhibitor therapy.

In the dose-escalation phase, four patients were assigned to rogaratinib 50 mg twice daily, four patients to 100 mg twice daily, four patients to 200 mg twice daily, three patients to 400 mg twice daily, four patients to 600 mg twice daily, and four patients to 800 mg twice daily. No dose-limiting toxicities were observed. Overall median duration of treatment (in all enrolled and treated patients) was 12 weeks (IQR 6·1–19·0). Median duration of treatment was 6·7 weeks (IQR 4–11) in the dose-escalation cohort. In the dose-expansion cohorts, median duration of treatment was 11·1 weeks (IQR 6–34) in the other solid tumours cohort, 15·1 weeks (7–25) in the urothelial carcinoma cohort, 6·3 weeks (2–19) in the HNSCC cohort, and 13·0 weeks (7–18) in the NSCLC cohort.

Treatment-emergent adverse events of any grade were reported in all 126 (100%) enrolled and treated patients, of whom 90 (71%) patients had a grade 3–5 adverse event. 114 (90%) of 126 patients had a treatment-related adverse event of any grade, and 36 (29%) had a grade 3–4 treatment-related adverse event. No treatment-related deaths occurred. The most common treatment-emergent adverse events were hyperphosphataemia (77 [61%] of 126 patients), diarrhoea (65 [52%]), and decreased appetite (48 [38%]; table 2; appendix pp 3–5). Management of hyperphosphataemia, which was expected based on the mode of action of the study drug due to renal FGFR1 inhibition, was guided by the study protocol and resulted in reversal of hyperphosphataemia within 1 week in all patients. The most common grade 3 or worse treatment-emergent adverse events were fatigue (12 [10%] of 126 patients) and asymptomatic increased lipase (ten [8%] of 126 patients). 40 (32%) of 126 patients had dose reduction and a relative dose intensity of 87·9% (SD 15·7) was reached for the whole study population (n=126). 38 (37%) of 103 patients in the dose-expansion cohorts had a dose reduction and a relative dose intensity of 86·3% (SD 16·3) was reached for these cohorts.

Six patients permanently discontinued study treatment due to drug-related adverse events. All six patients were treated in the dose-expansion phase. Reasons for discontinuation were decreased neutrophil count in

	Grade 1–2	Grade 3	Grade 4	Grade 5
Hyperphosphataemia	76 (60%)	1 (1%)	0	0
Diarrhoea	62 (49%)	3 (2%)	0	0
Decreased appetite	45 (36%)	3 (2%)	0	0
Fatigue	30 (24%)	11 (9%)	0	1 (1%)*
Nausea	35 (28%)	2 (2%)	0	0
Constipation	32 (25%)	1 (1%)	0	0
Anaemia	17 (13%)	8 (6%)	1 (1%)	0
Dry mouth	26 (21%)	0	0	0
Alopecia	25 (20%)	0	0	0
Arthralgia	25 (20%)	0	0	0
Dysgeusia	25 (20%)	0	0	0
Urinary tract infection	14 (11%)	8 (6%)	0	0
Increased aspartate aminotransferase	20 (16%)	1 (1%)	0	0
Back pain	19 (15%)	2 (2%)	0	0
Dyspnoea	12 (10%)	6 (5%)	0	2 (2%)*
Stomatitis	19 (15%)	0	0	0
Increased alanine aminotransferase	16 (13%)	2 (2%)	0	0
Increased blood creatinine	16 (13%)	2 (2%)	0	0
Dry skin	18 (14%)	0	0	0
Increased lipase	8 (6%)	10 (8%)	0	0
Cough	16 (13%)	1 (1%)	0	0
Hypercalcaemia	14 (11%)	1 (1%)	1 (1%)	1 (1%)
Pyrexia	17 (13%)	0	0	0
Vomiting	14 (11%)	2 (2%)	0	0
Dry eye	14 (11%)	0	0	0
Insomnia	14 (11%)	0	0	0
Abdominal pain	12 (10%)	1 (1%)	0	0
Increased amylase	10 (8%)	2 (2%)	1 (1%)	0
Asthenia	12 (10%)	1 (1%)	0	0
Haemoptysis	10 (8%)	3 (2%)	0	0

Data are n (%). Adverse events were coded according to the Medical Dictionary for Regulatory Activities (version 21.1). CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events. *Associated with disease progression.

Table 2: **Treatment-emergent adverse events by CTCAE grade observed in more than 10% of all patients (safety analysis set; n=126)**

two patients (one patient with urothelial carcinoma and one with other solid tumours); stomatitis, neuropathic pain, and nail dystrophia in one patient with urothelial carcinoma; nail discoloration and nail ridging in one patient with urothelial carcinoma; retinopathy in one patient with urothelial carcinoma; and fatigue in one patient with urothelial carcinoma.

Serious adverse events assessed by the investigator as related to rogaratinib treatment were reported in five patients in the dose-expansion cohorts (diarrhoea and decreased appetite in one patient with urothelial carcinoma, acute kidney injury in one patient with NSCLC, hypoglycaemia in one patient with other solid tumours, retinopathy in one patient with urothelial carcinoma, and vomiting in one patient with urothelial carcinoma).

22 patients died during study treatment or within 30 days after permanent study treatment discontinuation. 19 deaths were caused by events associated with disease progression. One patient in the dose-escalation cohort had fatal hypercalcaemia and two patients with urothelial carcinoma died of sudden death. None of these events were considered to be treatment related, as per investigator assessment.

Geometric mean plasma rogaratinib concentrations are shown in figure 1A. In the dose-escalation cohorts, rogaratinib was rapidly absorbed at all dose levels, with a median time to maximum concentration of 2 h (range 0·5–4·0; appendix p 6); thereafter, rogaratinib concentrations declined, with a mean half-life of 12·8 h (SD 5·9; figure 1A). After twice-daily multiple dosing, a mean accumulation ratio of 1·3 (SD 0·39) was estimated on day 15, indicating a 30% increase in plasma rogaratinib exposure in patients who provided pharmacokinetic samples on both day 1 and day 15 in the dose-escalation cohorts (figure 1A). A less than proportional increase in rogaratinib plasma exposure was observed at doses higher than 200 mg (figure 1A, 1B; appendix p 6). Assuming saturable absorption, the population pharmacokinetic model showed that the fraction absorbed decreased with increasing rogaratinib doses, and simulations indicated no clinically relevant increase in exposure above a dose of 800 mg (data not shown). The bioavailability of solution and tablet formulation were assessed after single 100 mg rogaratinib administration and plasma exposure to rogaratinib was similar as assessed in the bridging cohort (data not shown). Administration of rogaratinib after a high-fat meal had no clinically relevant effects on pharmacokinetics (data not shown).

Since no dose-limiting toxicities were observed up to a dose of 800 mg twice daily, the maximum tolerated dose could not be determined using the posterior dose-limiting toxicity rates of the Bayesian response analysis. Therefore, we applied a modelling approach to determine the recommended phase 2 dose of rogaratinib on the basis of physicochemical properties and pharmacokinetic and pharmacodynamic data.

Preclinical models[15] determined that efficacious rogaratinib exposure could be reached with 600 mg twice daily dosing. In view of the involvement of FGFR1 in regulation of renal phosphate retention, increased serum phosphate was used as a pharmacodynamic biomarker (figure 1B).[22] Increased serum phosphate concentration was observed at doses higher than 400 mg twice daily (figure 1C). Phosphate binders were used when serum calcium phosphate product exceeded 70 mg^2/dL^2. Serum FGF23 did not provide any additional functional insight with regard to the recommended phase 2 dose (appendix p 16). Serum phosphate concentrations (half maximal effective concentration 46 mg×h/L) were positively correlated with drug exposure at steady state (steady state area under the plasma concentration–time curve [AUC_{ss}]; appendix pp 16, 17). AUC_{ss} was not associated with

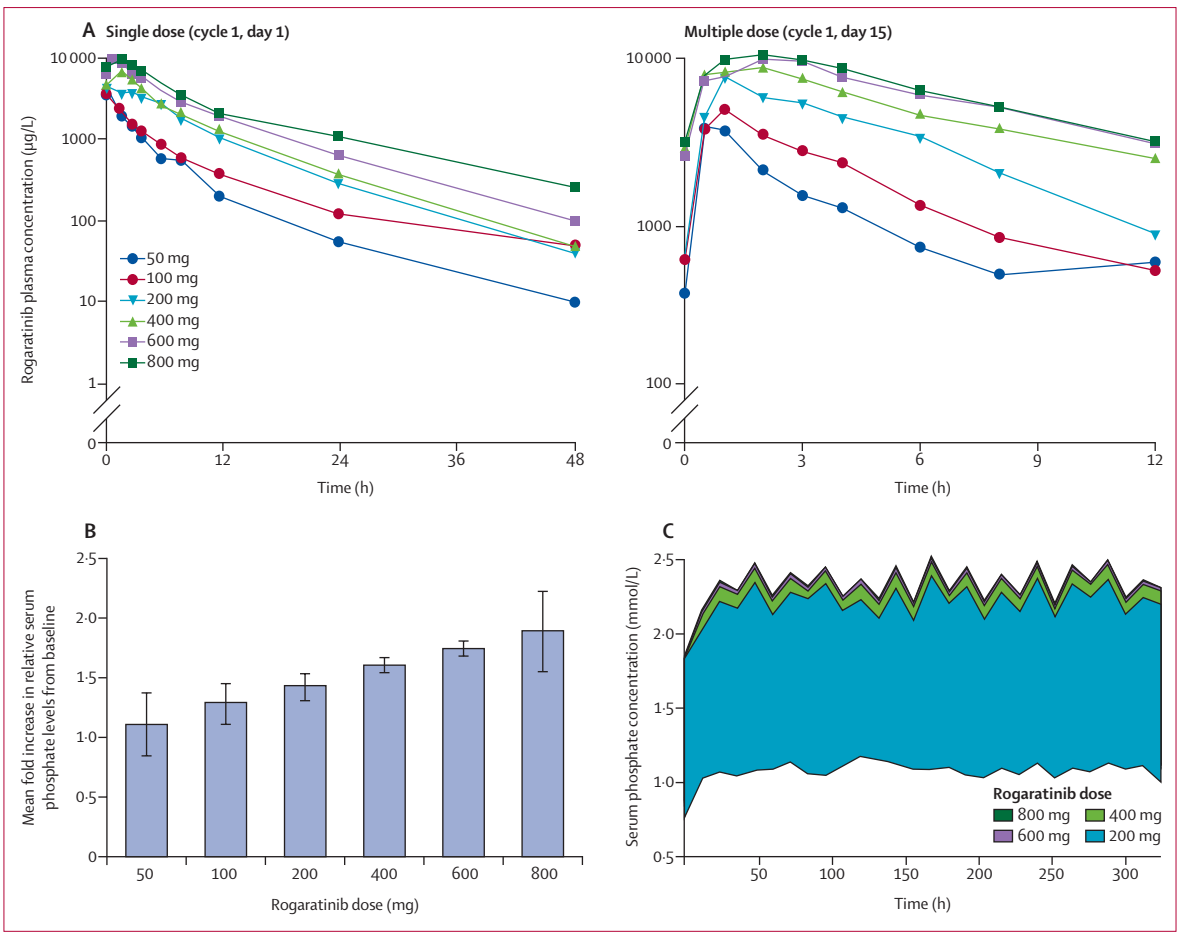

Figure 1: **Pharmacokinetic profile of rogaratinib and pharmacodynamic effects on serum phosphate concentrations**
(A) Single-dose (after day 1 dose) and multiple-dose (after day 15 dose) geometric mean plasma rogaratinib concentration over time (50 mg [single dose, n=3; multiple dose, n=4], 100 mg [n=4; n=3], 200 mg [n=4; n=3], 400 mg [n=3; n=3], 600 mg [n=4; n=4], and 800 mg [n=51; n=42]). (B) Dose-dependent increase in mean relative serum phosphate concentration compared with baseline. All patients from the dose-escalation cohorts were included. Error bars show standard error. (C) Simulated 90% CIs of serum phosphate concentration based on the minimum plasma concentration from the five dose-escalation cohorts (200 simulations). The profiles for the different doses are stacked from 200 mg to 800 mg; 800 mg is not visible because it is stacked behind 600 mg.

change in tumour size, serum calcium concentrations, or the occurrence of any adverse event (appendix pp 16–20). Based on these findings, doses of rogaratinib were not further escalated and 800 mg twice daily was selected as the recommended phase 2 dose, which was the dose used in the dose-expansion cohorts.

For the dose-expansion cohorts, 828 (96%) of the 866 analysed specimens were archived FFPE samples, with a median biopsy age of 11·7 months (IQR 4·7–25·2) before study entry. On-study biopsies were obtained from the remaining 38 (4%) of 866 patients. 744 (86%) of the 866 analysed biopsies originated from the primary tumour site and 122 (14%) of the 866 biopsies were taken from metastatic lesions. 433 (50%) of all 866 analysed biopsies were taken at the time of initial diagnosis; the remainder were taken after one or more lines of systemic anticancer therapy. Overall, 126 *FGFR*-positive patients consented to be screened for enrolment to treatment and, of those, 23 patients did not meet the clinical eligibility criteria. Thus, 103 *FGFR*-positive patients were finally selected and treated with rogaratinib in the dose-expansion cohorts. Of these patients, 34 (33%) provided a biopsy from a metastatic lesion or a lymph node; the remaining biopsies were from primary tumours. The provided biopsy was taken at diagnosis in 36 (35%) of 103 patients, with the remaining biopsies taken later in the disease course.

The prevalence of *FGFR1–3* mRNA-positive samples among major tumour types from the dose-expansion cohorts is summarised in figure 2 and the appendix (pp 7–10). The urothelial carcinoma cohort was the largest cohort screened, and 328 (96%) of 342 samples provided a valid *FGFR* test result. Samples from 164 (50%) of 328 patients with urothelial carcinoma were considered *FGFR* mRNA-positive (figure 3A). *FGFR3* mRNA overexpression was the most common alteration, found in 138 (84%) of 164 biomarker-positive urothelial carcinoma samples. Nine (5%) of 164 samples had

FGFR1 mRNA overexpression and 17 samples (10%) were positive for several *FGFR* subtypes including *FGFR2*, which was only detected when co-expressed with other subtypes. Activating *FGFR3* mutations were detected in 18 (11%) of 164 patients with urothelial carcinoma, of which all samples had *FGFR3* mRNA overexpression. The correlation between mutational status and *FGFR3* mRNA expression was confirmed using the publicly available external dataset obtained from The Cancer Genome Atlas (figure 3B).

In the dose-escalation phase, 21 (91%) of 23 enrolled patients were evaluable for response per RECIST version 1.1. Of these 21 patients, no patients achieved an objective response, and ten (48%) had stable disease, of whom three patients (one patient given rogaratinib 200 mg twice daily, one patient given rogaratinib 400 mg twice daily, and one patient given rogaratinib 800 mg twice daily) had minor reductions in target lesion size (range –2 to –9%).

All 103 treated patients with *FGFR1–3* mRNA-positive tumours in the dose-expansion cohorts received rogaratinib at the recommended phase 2 dose of 800 mg twice daily, and 100 of these patients were evaluable for response assessment per RECIST version 1.1 (51 patients with urothelial carcinoma, seven patients with HNSCC, 20 patients with NSCLC, and 22 patients with other solid tumour types). Three patients were withdrawn from the study before the first RECIST evaluation because of grade 3 adverse events (fatigue in two patients [one patient with urothelial carcinoma and one patient with other solid tumours] and dysphagia in one patient with HNSCC). Of the 100 patients who were evaluable for response assessment, 15 patients (15%; 95% CI 8·6–23·5) achieved an objective response and 71 (71%; 55·8–75·2) achieved disease control (an objective response or stable disease). One patient (1%) had a complete response (this patient had urothelial carcinoma), 14 (14%) had a partial response, 56 (56%) had stable disease, and 29 patients (29%) had progressive disease. Of the 29 patients with progressive disease, three patients had early clinical disease progression and no CT scan was done. Ten (67%) of 15 *FGFR* mRNA-positive patients without apparent *FGFR* genetic alterations achieved an objective response, including a patient with squamous NSCLC, a patient with adenoid cystic carcinoma of the tongue, and a patient with *FGFR3* mRNA-positive HNSCC; the seven remaining patients had urothelial carcinoma.

The highest level of rogaratinib activity was observed in the urothelial carcinoma cohort (figure 4A), in which 51 (98%) of 52 patients were evaluable for response. Of these 51 patients, 12 (24%) patients had an objective response (one patient had a complete response and 11 patients had a partial response, of which nine could be confirmed), 25 (49%) had stable disease (thus, 37 [73%] of 51 patients achieved disease control), and 14 (27%) had progressive disease. One partial response was observed in an *FGFR1* mRNA-positive patient with urothelial carcinoma, whereas all other patients with urothelial carcinoma with an objective response were *FGFR3* mRNA-positive. In a post-hoc analysis, 18 (35%) of 52 patients with urothelial carcinoma also had underlying *FGFR* DNA alterations: two (4%) had an *FGFR3* fusion and 16 (31%) had tumour *FGFR3*-activating point mutations (appendix pp 11, 12). Of the 11 *FGFR3* mRNA-positive patients with urothelial carcinoma who achieved an objective response, six had no *FGFR* genetic alterations as confirmed by retrospective orthogonal tumour genomic DNA testing. In the urothelial carcinoma cohort, 11 patients with no substantial clinical benefit to previous immune checkpoint inhibitors (ten had progressive disease and one had stable disease as their best response) were enrolled. With rogaratinib treatment, three of these patients achieved an objective response and six patients had objective shrinkage of target lesions.

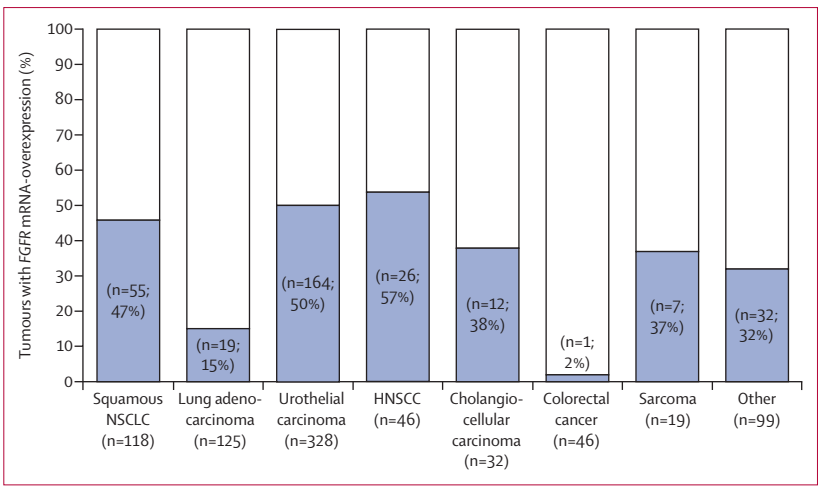

Figure 2: **Prevalence of *FGFR1–3* mRNA overexpression in various solid malignancies**
Solid tumour types for which at least 15 biopsies were obtained during prescreening are presented. The total number of biopsies per tumour type with a valid *FGFR* test result is shown on the x-axis. Shaded areas represent the proportion of samples that were *FGFR1–3* mRNA-positive. HNSCC=head and neck squamous-cell carcinoma. NSCLC=non-small-cell lung cancer.

In the other dose-expansion cohorts, excluding two patients for whom data was not available (one in the HNSCC cohort and one in the other solid tumours cohort), three patients had a partial response (one in the NSCLC cohort, one in the HNSCC cohort, and one in the other solid tumours cohort), 31 patients had stable disease (15 in the NSCLC cohort, two in the HNSCC cohort, and 14 in the other solid tumours cohort), and 15 had progressive disease (four in the NSCLC cohort, four in the HNSCC cohort, and seven in the other solid tumours cohort; appendix p 22).

Of the 121 patients in the dose-escalation and dose-expansion cohorts with available progression-free survival data, median progression-free survival was 93 days (95% CI 61–102) with a median follow-up time of 32 days (IQR 25–36). Median progression-free survival was 45 days (95% CI 41–88) in the dose-escalation cohort.

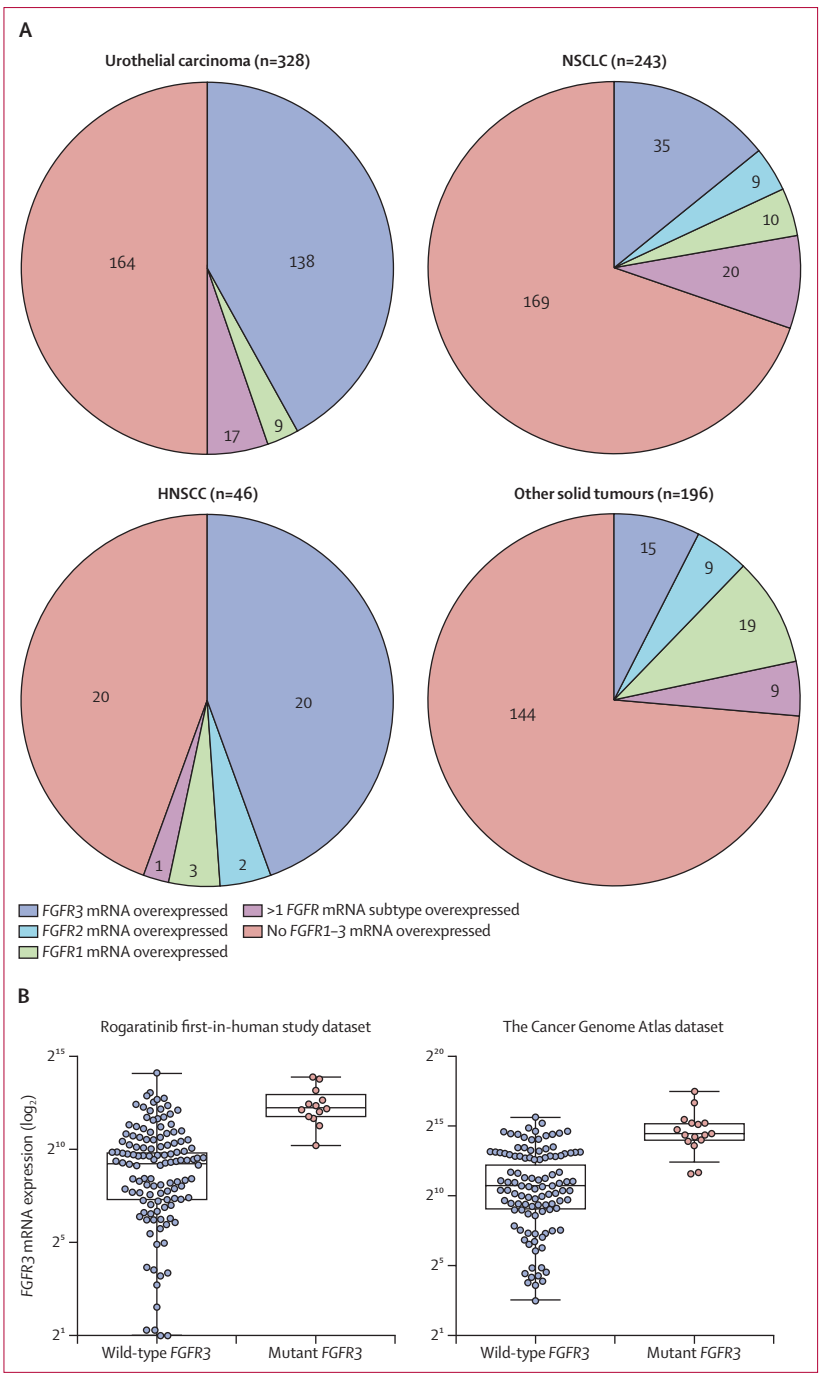

Figure 3: **Prevalence of *FGFR1–3* mRNA overexpression by tumour type at prescreening**
(A) *FGFR1–3* mRNA overexpression in patients by solid tumour type. (B) Wild-type and mutant *FGFR3* mRNA expression. Of the 164 *FGFR3* mRNA-positive tumours, 138 samples had a valid *FGFR3* mRNA test result as determined by NanoString assay and a valid mutation test result. All 13 *FGFR3*-mutant cases also had high *FGFR3* mRNA expression. Similarly, all 16 *FGFR3*-mutant urothelial carcinoma samples in The Cancer Genome Atlas dataset (n=125) had high *FGFR3* mRNA expression determined by RNA sequencing (*FGFR3* mutant, n=16; wild-type, n=109). HNSCC=head and neck squamous-cell carcinoma. NSCLC=non-small-cell lung cancer.

In the dose-expansion cohorts, median progression-free survival was 47 days (38–231) in the other solid tumours cohort, 100 days (57–143) in the urothelial carcinoma cohort, 44 days (24–144) in the HNSCC cohort, and 98 days (46–108) in the NSCLC cohort. Median time to progression was 47 days (95% CI 38–231) in the other solid tumours cohort, 100 days (57–109) in the urothelial carcinoma cohort, 68 days (35–295) in the HNSCC cohort, and 100 days (46–126) in the NSCLC cohort.

Additional exploratory post-hoc *FGFR* DNA analyses for patients with NSCLC, HNSCC, and other solid tumours given rogaratinib 800 mg twice daily in the expansion cohorts are presented in the appendix (pp 13–15).

To further support the biomarker selection strategy for rogaratinib treatment based on high *FGFR* mRNA expression without mandatory *FGFR* genetic alterations, we did a post-hoc analysis of the urothelial carcinoma cohort. No differences in median progression-free survival were identified between *FGFR* mRNA-positive patients (n=18) and those without underlying *FGFR* genetic aberrations (n=33; median progression-free survival 90 days [95% CI 42–143] *vs* 105 days [64–149]) or in the proportion of patients who achieved an objective response (five [28%] of 18 patients [95% CI 9·7–53·5] *vs* seven [21%] of 33 patients [9·0–38·9]; figure 4B). Additionally, no difference in tumour response (ie, percentage change in tumour size of target lesions from baseline) was identified between these two groups (figure 4C).

An exploratory post-hoc analysis was done in patients with urothelial carcinoma to evaluate a panel of potential FGFR-inhibitor resistance mutations, including hotspot mutations of *HRAS*, *NRAS*, *KRAS*, and *PIK3CA*. Our study identified no such mutations in patients with urothelial carcinoma who had an objective response. By contrast, four (29%) of 14 patients with urothelial carcinoma who had progressive disease harboured a mutation in one or more of these genes (data not shown).

Discussion

Rogaratinib treatment in patients selected by *FGFR* overexpressing cancers resulted in a manageable safety profile and encouraging antitumour activity, even in patients refractory to immune checkpoint inhibitors. Our data suggest that *FGFR* mRNA positivity could be a clinically useful biomarker in addition to genetic alterations, identifying more patients who are likely to be susceptible to FGFR inhibition.

Considering their pleiotropic effects in cancer development and progression, FGFRs are promising drug targets for a broad range of cancers. The therapeutic window of currently available FGFR inhibitors is restricted by effects in non-malignant tissues. Accordingly, strategies have been devised to identify malignancies that are more susceptible to FGFR inhibition. So far, oncogenic *FGFR* gene fusions or activating *FGFR3* mutations have been validated as predictors for clinical activity of FGFR inhibitors.[4] However, these genetic aberrations have only been identified in a small number of patients with specific cancer types.[12]

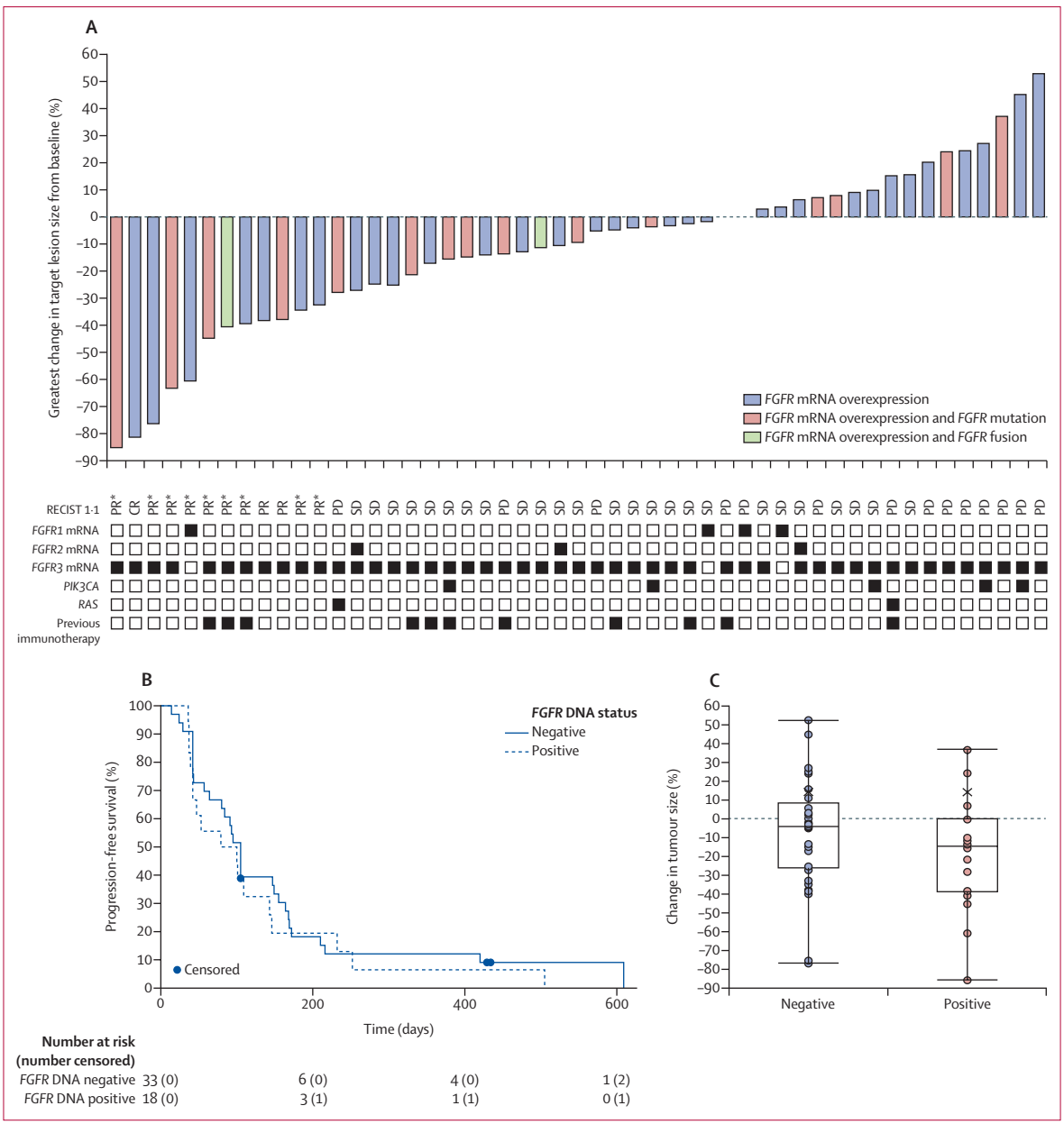

Figure 4: **Tumour responses to rogaratinib in the urothelial carcinoma dose-expansion cohort (n=52)**
(A) Waterfall plot of all patients with urothelial carcinoma who were evaluable for at least one response assessment (51 [98%] of 52 patients). 12 patients had an objective response. White square denotes biomarker negative. Black square denotes biomarker positive. (B) Kaplan-Meier plot of progression-free survival by FGFR DNA status. 17 events occurred in *FGFR* mRNA-positive patients with underlying genomic alterations (n=18) and 31 events occurred in *FGFR* mRNA-positive patients without underlying genomic alterations (n=33). (C) Box plot of best change in tumour size by *FGFR3* DNA status. Box and whisker plots indicate median with IQR (boxes), 1·5 × the IQR (whiskers), geometric mean (crosses), and individual values (circles). CR=complete response. PD=progressive disease. PR=partial response. RECIST=Response Evaluation Criteria in Solid Tumors. SD=stable disease. *Confirmed partial response.

We have coordinated clinical development of rogaratinib, a novel, highly selective, and potent oral pan-FGFR inhibitor,[23] with an innovative biomarker strategy to broaden the spectrum of patients who might benefit from treatment. Preclinical studies identified tumour *FGFR1–3* mRNA expression as a robust predictor of rogaratinib response, including in models devoid of *FGFR* gene aberrations.[14] This first-in-human phase 1 study established safety and tolerability of rogaratinib, and explored its clinical activity in patients selected by *FGFR* mRNA expression levels in tumour biopsies.

Rogaratinib was well tolerated, and no dose-limiting toxicities were observed up to a dose of 800 mg twice daily in continuous 21-day treatment cycles. As expected for FGFR inhibitors because of their mode of action,

rogaratinib induced dose-dependent hyperphosphataemia (figure 1B, appendix pp 16–17) in patients treated with doses higher than 400 mg twice daily, due to on-target inhibition of the FGF23–FGFR1–Klotho pathway involved in renal phosphate homeostasis.[22] The observed hyperphosphataemia is consistent with results from other recently developed FGFR inhibitors.[4,5]

In the overall study population, 15% of evaluable patients achieved an objective response, which compares favourably with the proportion of responses observed with other selective pan-FGFR inhibitors in early clinical trials, such as AZD4547 (8%),[3] infigratinib (8–15%),[4,7] and erdafitinib (21·7%).[5] By contrast with our study, patients with urothelial carcinoma in other trials were selected based on *FGFR3*-activating mutations or *FGFR2/3* gene fusions. The proportion of patients with urothelial cancer selected by *FGFR* mRNA overexpression who achieved an objective response with rogaratinib (24%) was similar to the proportion of patients selected by *FGFR* genetic alterations responding to other FGFR inhibitors (21% with pemigatinib,[24] 25·4% with infigratinib[25]), whereas the most potent FGFR inhibitor, erdafitinib, has been associated with a higher proportion of patients achieving an objective response (40%).[26] Our *FGFR* mRNA-based screening identified a broader proportion (up to 50%) of *FGFR* mRNA-positive patients in the overall urothelial carcinoma patient population, including patients with and without apparent *FGFR* genetic alterations.

In preclinical models, antitumour activity of rogaratinib strongly correlated with high tumour *FGFR1–3* mRNA expression and was independent of tumour type or FGFR subtype.[14] Therefore, we analysed all tumour biopsies obtained during the prescreening phase for *FGFR1–3* mRNA expression. The FGFR4 subtype was excluded from analysis because few *FGFR4* mRNA-positive tumours were identified during the assay validation phase. Tumour-agnostic *FGFR1–3* mRNA expression-based screening identified around 2–3 times more patients as *FGFR*-positive, and eligible for rogaratinib treatment, in all cancers evaluated (50% in urothelial carcinoma), than that reported for the prevalence of *FGFR* genetic alterations (21% in urothelial carcinoma[19,26]). The higher proportion of *FGFR*-positive patients identified by our screening approach can be explained by the overexpression of FGFRs independent of apparent genetic alterations—eg, epigenetic dysregulation, transcriptional dysregulation, or non-coding alterations.[27,28] The importance of these non-genetic mechanisms is corroborated by preclinical data showing that nearly half of the tested infigratinib-sensitive cell lines have no apparent *FGFR* genetic alterations.[29] We observed high *FGFR3* mRNA expression in patients with urothelial carcinoma harbouring *FGFR3* gene mutations or fusions in our population and in a dataset obtained from The Cancer Genome Atlas. Screening for *FGFR* RNA expression in addition to multiplex profiling of genomic biomarkers, which is now broadly done across many cancer entities, might increase the likelihood of a given patient benefiting from FGFR-directed targeted therapy.

The potential of our tumour-agnostic biomarker approach is highlighted by responses observed for the first time, to our knowledge, in tumours without apparent *FGFR* genetic alterations, including tumours positive for FGFR subtypes that have not yet been reported to be drug-sensitive by *FGFR* DNA-based screening: *FGFR1* mRNA-positive urothelial carcinoma, *FGFR3* mRNA-positive HNSCC, and *FGFR1* mRNA-positive adenoid cystic carcinoma. No differences were observed in the proportion and extent of best tumour response between patients with *FGFR* mRNA-positive and DNA-positive urothelial carcinoma compared with patients with only *FGFR* mRNA-overexpressing urothelial carcinoma. The prevalence of *FGFR3* mRNA-positive tumours in advanced, muscle-invasive urothelial carcinoma was substantially higher in our study (50%) than that of *FGFR* DNA alterations (around 20%) reported previously.[4,26,30,31]

This difference is particularly important, since treatment options for patients with urothelial carcinoma remain scarce. *FGFR* positivity was confirmed as a molecular hallmark of the luminal-papillary subtype of urothelial carcinoma that is characterised by a low level of T-cell infiltration and low *PD-L1* expression, thus deriving the smallest benefit of immune checkpoint inhibitor treatment.[32] Our finding that rogaratinib induced objective responses and shrinkage of target lesions in patients with urothelial carcinoma in whom previous treatment with immune checkpoint inhibitors had no benefit supports the use of FGFR inhibitor treatment over checkpoint inhibition for FGFR-positive patients with urothelial carcinoma who have progressed on prior platinum-based therapies, which is consistent with other studies.[4,26]

Several mechanisms of resistance to FGFR-directed therapy have been postulated on the basis of preclinical findings, including *PIK3CA* and *RAS* hotspot activating mutations[21] or MET overexpression.[14] Retrospective analysis of tumour genomic DNA obtained before rogaratinib treatment identified *PIK3CA* or *RAS* mutations in four of 14 patients with urothelial carcinoma who had progressive disease, however, no such mutations were detected in patients who had an objective response. Excluding patients with *PIK3CA* or *RAS* mutations from the urothelial carcinoma cohort increased the proportion of patients who achieved an objective response in our study from 24% to 27%. A fully automated companion diagnostics assay to detect *FGFR1* and *FGFR3* mRNA expression is currently in development (NCT03410693).

Limitations of this study include the small sample size for some of the tumour types evaluated, and the lack of genomic data for all patients. Additionally, the cutoff values used to determine *FGFR* mRNA overexpression have not yet been clinically validated.

Overall, the clinical application of *FGFR* mRNA overexpression as a novel biomarker enables the

identification of more patients who could benefit from FGFR inhibition. Rogaratinib is currently being investigated in several ongoing clinical trials as a monotherapy (NCT03762122, NCT03410693) and in combination with immune checkpoint inhibitors (NCT03473756) or targeted therapies (NCT03517956, NCT03088059). In summary, rogaratinib treatment in patients selected by overexpression of *FGFR1–3* mRNA is a promising new option in precision oncology for the treatment of advanced cancers.

Contributors

MSchu, PR, OB, MO, and PE designed the study. All authors generated the data. MSchu, JG, SB, HN, MO, PE, and MJ reviewed the data and wrote the report.

Declaration of interests

PR, SB, OB, HN, MO, and PE are employees of Bayer AG. HN, MO, and PE are shareholders of Bayer AG. JG is employed by BAST, which received funding from Bayer AG. PE has a patent pending (20180333418). MSchu is a consultant (compensated) for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb (BMS), Novartis, and Roche; has received honoraria for continuing medical education presentations from AbbVie, Alexion, Boehringer Ingelheim, BMS, Celgene, Lilly, Merck Sharp & Dohme (MSD), Novartis, and Pierre Fabre; and has received research funding (to his institution) from AstraZeneca, Boehringer Ingelheim, BMS, and Novartis. BCC reports research funding from AstraZeneca, Bayer, Champions Oncology, Dizal Pharma, Dong-A ST, Janssen, MOGAM Institute, MSD, Novartis, Ono, and Yuhan; has acted as a consultant for AstraZeneca, BMS, Boehringer Ingelheim, Janssen, Lilly, MSD, Novartis, Ono, Pfizer, Roche, Takeda, and Yuhan; has stock ownership in TheraCanVac Inc; and has received royalties from Champions Oncology. CMS has received personal fees from BMS and Celgene, outside the submitted work. AN reports personal fees from BMS, Oryzon Genomics, and Roche, and personal fees and non-financial support from Boehringer Ingelheim and Pfizer, outside the submitted work. RAS reports grants from AstraZeneca, and personal fees from AstraZeneca, BMS, Boehringer Ingelheim, Celgene, MSD, Novartis, Pfizer, Roche, Taiho, Takeda, and Yuhan, outside the submitted work. PAC reports personal fees and non-financial support from AstraZeneca; personal fees from Amgen and Roche; and grants, personal fees, and non-financial support from MSD and Novartis, outside the submitted work. LN reports grants from Bayer, during the conduct of the study; grants and personal fees from BMS and Janssen; grants, personal fees, and non-financial support from Novartis and Pfizer; grants from MSD; personal fees from Roche and Takeda; and personal fees and non-financial support from Boehringer Ingelheim and Celgene, outside the submitted work. MScho reports grants from Bayer, during the conduct of the study; grants from AstraZeneca, Bayer, BMS, MSD, Novartis, and Sanofi, outside the submitted work; and has received honoraria from AstraZeneca, Bayer, BMS, EDAP-TMS, MSD, Novartis, Sanofi, and Takeda, outside the submitted work. RC reports personal fees from Astellas, AstraZeneca, Bayer, BMS, MSD, and Roche, outside the submitted work. HR, DT, NP, SHP, PG, and MJ declare no competing interests.

Data sharing

Availability of study data will be determined according to Bayer's commitment to the EFPIA/PhRMA Principles for Responsible Clinical Trial Data Sharing. This pertains to scope, time point, and process of data access. Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications approved in the USA and European Union (EU) as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the EU and US regulatory agencies on or after Jan 1, 2014. Interested researchers can make a request via www.clinicalstudydatarequest.com to access anonymised patient-level data and supporting documents. Data will be available no later than within 1 year of study completion. Data access will be granted for anonymised patient-level data, protocols, and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

Acknowledgments

This study was funded by Bayer AG. We thank all patients and their families for supporting this study. We thank Sandra Hildebrandt, Frieder Wolff, Simone Behre, Dubravka Pavic-Sladoljev, Corinna Helmbrecht, and Stephanie Kerpen for their operational support. We also thank Jack Adams (Complete HealthVizion, Manchester, UK), who provided medical writing assistance on the basis of detailed discussion and feedback from all the authors, which was funded by Bayer AG.

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