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

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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**
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