Phase II study of pazopanib monotherapy in metastatic gastroenteropancreatic neuroendocrine tumours

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Background: Treatment options for patients with metastatic gastroenteropancreatic neuroendocrine tumours (GEP NETs) are still limited. We investigated the antitumour activity and safety profile of pazopanib – a multitarget drug with anti-angiogenic activity in patients with metastatic GEP NETs.

Methods: This was a nonrandomised, open-labeled, single-center phase II study. Pazopanib was orally administered at a dose of 800 mg daily continuously with a 28-day cycle. The primary end point was an objective response rate according to Response Evaluation Criteria in Solid Tumors (RECIST). The secondary end points were progression-free survival (PFS), overall survival (OS) and safety. An independent review of objective response was planned. The trial is registered with ClinicalTrials.gov, NCT number 01099540. Correlative biomarker analyses were performed.

Results: Between April 2010 and February 2012, a total of 37 patients were enrolled. Thirty-two percent of the enrolled patients had pancreatic primary and 22% of the patients had colorectal primary NETs. This phase II study demonstrated an objective response rate of 18.9% (7 of the 37, 95% CI 8.0–35.2) and a disease control rate (CR + confirmed PR + stable disease) of 75.7% (28 of the 37, 95% CI, 58.8–88.2) in metastatic GEP NETs. The independent review demonstrated a higher overall response rate of 24.3% (95% CI, 11.8–41.2%) with nine confirmed PRs.

Conclusion: Pazopanib showed a comparable efficacy to other targeted agents not only in pancreatic NETs but also in NETs originating from gastrointestinal (GI) tract.
Gastroenteropancreatic neuroendocrine tumours are known as hypervascular tumours with increased expressions of vascular endothelial growth factor (VEGF) and VEGF receptors (VEGFRs) (Terris et al, 1998), which are associated with poor prognosis. The presence of VEGFR-2 was detected in ~48% of carcinoid tumours, with the highest expression in foregut and hindgut carcinoids. A modest clinical activity with bevacizumab, a monoclonal antibody targeting VEGF, has been observed in advanced neuroendocrine tumours in phase II studies. A randomised phase II study that compared bevacizumab with interferon alpha treatment has demonstrated a response rate of 18% with a trend towards longer progression-free survival (PFS) (Yao et al, 2008b). Most recently, a phase II study on bevacizumab and temozolomide combination treatment showed a response rate of 15% and a median PFS of 11.0 months in 34 GEP NET patients including poorly differentiated (G3) NET (Chan et al, 2012). In pancreatic NET, continuous administration of sunitinib was compared with placebo in a phase III trial of 171 patients suffering from pancreatic NETs, and median PFS was significantly prolonged in the sunitinib arm (11.4 vs 5.5 months) (Raymond et al, 2011). On the basis of these data, sunitinib was approved in the United States for the treatment of progressive, well-differentiated pancreatic NET patients.

Pazopanib (GW786034; GlaxoSmithKline, Stevenage, UK) is a novel oral multilysated tyrosine kinase inhibitor with a wide range of activities that are mediated through VEGFR types 1, 2 and 3, platelet-derived growth factor receptors α and β, and stem-cell factor receptor (c-Kit) (Kumar et al, 2009; Hamberg et al, 2010). In a phase I pazopanib trial with 63 patients, one patient with neuroendocrine tumour (primary not specified) demonstrated a partial response (PR) to pazopanib (Hurwitzy et al, 2009). In a preliminary report on phase II pazopanib for pancreatic NETs, the response rate of 17% was reported (Phan et al, 2010).

In contrast to pancreatic NETs, there are very limited data on the efficacy of tyrosine kinase inhibitors in non-pancreatic NETs. Given the high incidence of non-pancreatic NETs, such as those originating from colorectum and small intestine, the antitumour efficacy of molecularly targeted agents should be tested in non-pancreatic NET patients, who could potentially benefit from TKIs. Hence, we designed a phase 2 study of pazopanib in patients with metastatic GEP NETs to assess the safety and efficacy of pazopanib.

Correlative laboratory analysis. Serum CgA was assayed before commencement of the study drug. Pretreated archival tissue was collected and assayed for Ki-67 and PHH3 expression by immunohistochemistry. Immunohistochemistry was performed in 4 μm sections of paraffin-embedded archival tissue on Leica BOND-MAX and BOND-III automated IHC staining systems (Leica Microsystems, Wetzlar, Germany). As a primary antibody, MIB1 (DAKO, Glostrup, Denmark; 1:300 dilution) was used for Ki-67 staining and 3H10 (Millipore, Bellerica, MA, USA; 1:2000 dilution) was used for PHH3. The staining of both Ki-67 and PHH3 was evaluated by counting positive cells, and the percentage of positive tumour cell nuclei was counted in at least 100 cells for each case (magnification × 400, field size 0.18 mm²) in selected ‘hot spot’ areas.

Statistics. To test the null hypothesis of response rate of 5% and an alternative of 25% with a type I error rate of 5% and type 2 of 10%, 30 patients were required. Considering a 15% drop-out rate, 35 patients were planned to be accrued. Progression-free survival and OS were estimated using the Kaplan–Meier method and compared by the log-rank test. The PFS was estimated from the date of the first administration of pazopanib to death, documented progression or the date of the last follow-up visit. The OS was defined as the time from the date of the first administration of pazopanib to death or the date of the last follow-up visit. All statistical analyses were performed using the SPSS software (IBM SPSS Statistics for Windows, Version 20.0; IBM Corp, Armonk, NY, USA).

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RESULTS

Patients and treatment outcome. Between April 2010 and February 2012, a total of 37 patients were enrolled. At the time of enrollment, 30 of the 37 patients had documented progressive diseases within 3 months and the other seven patients at the time of first diagnosis. Patient characteristics are shown in Table 1. Eight patients (22%) had G1, 16 (43%) had G2 and 13 (35%) had G3 GEP NETs originating from different primary sites, with pancreatic site (n = 12) being the most common one followed by colorectal site (n = 8, 22%). Other primary sites were stomach (n = 4), duodenum (n = 3), liver (n = 5) and gall bladder (n = 1); in four cases, primary sites were unknown. All patients had metastatic disease at the time of study treatment.

Of the 37 patients enrolled on to the study, 3 patients were not assessable for treatment response. By an intent-to-treat analysis including all patients, an overall response rate of 18.9% was demonstrated (95% CI, 8.0–35.2%), with zero CR and seven PRs. Stable disease (SD) was achieved in 21 (56.8%) patients. The overall disease-control rate (CR + PR + SD) was 75.7% (95% CI, 58.8–88.2%) (Table 2). Sixteen percent of the patients progressed to pazopanib. As shown in the waterfall plot (Figure 1A), tumour shrinkage of target lesions was observed in 22 patients (59.5%) when compared with the baseline tumour measurement according to RECIST 1.1. In three patients, more prominent tumour volume reduction was noted (by 37%, 45%, and 54%, respectively).

Table 1. Baseline characteristics of the patients (n = 37)

| Characteristic                | Number (%) |
|------------------------------|------------|
| Age (years)                  |            |
| Median range                 | 55         |
| 19–71                        |            |
| Sex                          |            |
| Male                         | 25 (68)    |
| Female                       | 12 (32)    |
| ECOG performance status      |            |
| 0                            | 4 (11)     |
| 1                            | 33 (89)    |
| Histology                    |            |
| Well-differentiated neuroendocrine tumour, G1 | 8 (22) |
| Well-differentiated neuroendocrine carcinoma, G2 | 16 (43) |
| Poorly differentiated neuroendocrine carcinoma, G3 | 13 (35) |
| Prior treatment              |            |
| Recurrence after curative surgery | 5 (14) |
| Palliative surgery           | 9 (24)     |
| Palliative radiotherapy      | 3 (8)      |
| Palliative chemotherapy      | 14 (38)    |
| None                         | 19 (51)    |
| Primary site                 |            |
| Pancreas                     | 12 (32)    |
| Colorectum                   | 8 (22)     |
| Stomach                      | 4 (11)     |
| Duodenum                     | 3 (8)      |
| Liver                        | 5 (14)     |
| Gall bladder                 | 1 (3)      |
| Unknown                      | 4 (11)     |
| Number of metastatic sites   |            |
| 1                            | 17 (46)    |
| 2                            | 13 (35)    |
| ≥3                           | 6 (16)     |
| Metastatic sites             |            |
| Liver                        | 32 (89)    |
| Distant lymph nodes          | 16 (43)    |
| Lung                         | 6 (16)     |
| Bone                         | 2 (5)      |
| Chromogranin level at baseline (n = 29) | ng ml⁻¹ |
| Median, range                | 110, 30–800|

Table 2. Response according to RECIST (version 1.1) and survival outcome

| Response                        | Number of patients (%), 95 CI |
|---------------------------------|------------------------------|
| Complete response               | 0 (0%)                       |
| Confirmed partial response      | 7 (18.9%, 8.0–35.2)          |
| Confirmed stable disease        | 21 (56.8%, 39.5–72.9)        |
| Progressive disease             | 6 (16%, 6.25–32.0)           |
| Withdrawal without evaluation   | 3 (8.1%)                     |
| Disease control rate (CR + PR + SD) | 28 (75.7%, 58.8–88.2)       |

Abbreviations: CI = confidence interval; RECIST = response evaluation criteria in solid tumors

Figure 1. A waterfall plot demonstrating the maximum reduction in tumour size (A) by site investigators and (B) after independent review.
according to the RECIST criteria version 1.1. A separate independent review was performed by an expert radiologist who was blinded of the treatment response or treatment outcome (Figure 1B). The independent review demonstrated a higher overall response rate of 24.3% (95% CI, 11.8–41.2%), with nine confirmed PRs. A disease-control rate (CR + PR + SD) from an independent review was 73% (95% CI, 55.9–86.2%). Hence, there was no significant difference in the overall response rate between investigators and an independent radiologist (18.9% and 24.3%, respectively). After a median follow-up duration of 31.2 months (range, 13.5–100 months), the median PFS was 9.1 months (95% CI 4.9–13.3 months) (Figure 2). The median OS was not reached at the time of analysis.

Toxicity. The safety population included patients who were treated with at least one dose of the study drug. In total, 37 patients were evaluable for toxicities (Table 3). The most common grades 3 and 4 AEs were proteinuria (11%), neutropaenia (8%), hypertension (5%), diarrhoea (5%), anorexia (5%), abdominal pain (5%) and AST/ALT elevation (5%). There was no treatment-related mortality.

Biomarker analysis. All biomarker analyses were preplanned. Baseline serum CgA level before the study treatment was measured in 29 patients. The median CgA value for this study population was 110 ng ml⁻¹ (range, 30–800 ng ml⁻¹). Patients with low CgA level (< median CgA level) demonstrated a trend towards prolonged survival (median OS 11.7 months) (P = 0.080) (Figure 3A). Expression levels of Ki-67 and PHH3 were significantly correlated with statistical significance (Spearman’s R correlation coefficient 0.79, P < 0.001). The survival according to the Ki-67 index and PHH3 is shown in Figure 3. Baseline FDG-PET scans were obtained in 18 patients. The maximum standardised uptake value (SUVmax) among all hypermetabolic lesions, the average SUV (SUVave) of those lesions and the sum of total lesion glycolysis (TLG) of each hypermetabolic were evaluated. Higher SUVave ≥ 3.8 was associated with considerably poorer OS following pazopanib treatment (median OS 10.8 months vs not reached in patients with SUVave < 3.8, P = 0.039, Figure 3D). However, SUVmax and TLG did not show significant association with treatment response.

**DISCUSSION**

This phase II pazopanib study demonstrated a PR rate of 18.9% (7 of the 37, 95% CI 8.0–35.2) and a disease-control rate of 75.7% (28 of the 37, 95% CI, 58.8–88.2) in metastatic GEP NETs. This study is the first one to assess the antitumour activity and safety profile of pazopanib in metastatic GEP patients including NETs arising from nonpancreatic GI tract. Currently, the only available data on the efficacy of molecular targeted agents focus on G1 and G2 tumour pancreatic NETs.

The modest overall response rate of 18.9% and high disease-control rate of 75.7% concur with the recently reported response patterns of everolimus (Yao et al, 2011b) and sunitinib for pancreatic NETs (Raymond et al, 2011). Everolimus monotherapy (10 mg daily) was compared with the best supportive care alone in

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**Table 3. Overview of adverse events**

| Number of patients (%) | Total n = 37 |
|-----------------------|-------------|
| **All-grade AE**       | 36 (97%)    |
| **Grade 3,4 AE**       | 15 (41%)    |
| AEs leading to treatment discontinuation | 4 (11%) |
| AEs leading to death on treatment | 0 (0%) |

**Toxicity profile**

| Number of patients (%) |
|------------------------|
| All grades             |
| Grade 3/4              |

**Haematologic**

|                  | Number of patients (%) |
|------------------|------------------------|
| Anaemia          | 3 (8)                  |
| Neutropenia      | 9 (24)                 |
| Thrombocytopenia | 4 (11)                 |

**Non-haematologic**

|                  | Number of patients (%) |
|------------------|------------------------|
| Hypertension     | 12 (32)                |
| Proteinuria      | 11 (30)                |
| Skin rash        | 12 (32)                |
| Hand-foot syndrome | 20 (54)               |
| Diarrhoea        | 18 (49)                |
| Anorexia         | 17 (46)                |
| Mucositis        | 15 (41)                |
| Alopecia         | 7 (19)                 |
| Fatigue          | 8 (22)                 |
| Nausea           | 18 (49)                |
| Pruritus         | 4 (11)                 |
| Abdominal pain   | 19 (51)                |
| AST/ALT elevation | 6 (16)                |
| Hyperglycaemia   | 3 (8)                  |
| Hypokalemia      | 1 (3)                  |

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Figure 2. Survival curves (A) overall survival; (B) progression survival.
the placebo-controlled RADIANT-3 trial of 410 patients with advanced progressing pancreatic NET (Yao et al, 2011b). Everolimus was associated with a significant prolongation in the median PFS (11.0 vs 4.6 months, HR for progression 0.35, 95% CI 0.27–0.45). However, the confirmed objective PR was attained only in 5% and stable disease in 73% for everolimus treatment (Yao et al, 2008a). Another phase III trial that compared sunitinib with placebo in pancreatic neuroendocrine tumours demonstrated a lower response rate of 9.3% (95% CI, 3.2–15.4) and stable disease in 63% of sunitinib-treated patients (Raymond et al, 2011). The objective-confirmed response rate in this study (18.9%) is substantially higher than those reported in the two trials (5–9.3%). One of the plausible explanations for higher response rate achieved with pazopanib would be high number of patients with colorectal NETs, other targeted agents not only in pancreatic NETs but also in NETs originating from GI tract. In selected G3 patients, pazopanib may be considered as a treatment option in salvage setting. Genomic profiling to identify signal that predicts response to pazopanib in GEP NETs is currently ongoing.

In conclusion, pazopanib showed a comparable efficacy to other targeted agents not only in pancreatic NETs but also in NETs originating from GI tract. In selected G3 patients, pazopanib may be considered as a treatment option in salvage setting. Genomic profiling to identify signal that predicts response to pazopanib in GEP NETs is currently ongoing.

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DISCLAIMER

This was an investigator-sponsored trial and the company was not involved in study design or manuscript writing.
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