A Phase II Study of BEZ235 in Patients with Everolimus-resistant, Advanced Pancreatic Neuroendocrine Tumours

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Abstract. *Background: This was a two-stage, phase II trial of the dual phosphatidylinositol 3-kinase/mammalian target of rapamycin inhibitor BEZ235 in patients with everolimus-resistant pancreatic neuroendocrine tumours (pNETs) (NCT01658436). Patients and Methods: In stage 1, 11 patients received 400 mg BEZ235 orally twice daily (bid). Due to tolerability concerns, a further 20 patients received BEZ235 300 mg bid. Stage 2 would be triggered by a 16-week progression-free survival (PFS) rate of ≥60% in stage 1. Results: As of 30 June, 2014, 29/31 patients had discontinued treatment. Treatment-related grade 3/4 adverse events were reported in eight (72.7%) patients at 400 mg and eight (40.0%) patients at 300 mg, including hyperglycaemia, diarrhoea, nausea, and vomiting. The estimated 16-week PFS rate was 51.6% (90% confidence interval=35.7-67.3%). Conclusion: BEZ235 was poorly tolerated by patients with everolimus-resistant pNETs at 400 and 300 mg bid doses. Although evidence of disease stability was observed, the study did not proceed to stage 2.*

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Pancreatic neuroendocrine tumours (pNETs) are rare malignancies, representing <2% of all pancreatic cancers (1). Several studies suggest that the annual incidence of pNETs, currently reported to be less than one in 100,000, is rising (1-4). pNETs tend to be slow-growing or indolent compared to other types of cancer, such as pancreatic adenocarcinoma, making early detection difficult. Most patients present with metastatic disease and have a poor prognosis, despite the increasing availability of treatment options (4).

Expression profiling studies have demonstrated an up-regulation of the phosphatidylinositol 3-kinase (PI3K) signaling pathway in primary pNET tissue (5), providing a rationale for targeting this pathway in patients with pNETs. The mammalian target of rapamycin (mTOR) inhibitor everolimus has demonstrated activity in patients with pNETs (6), and is approved for the treatment of progressive, advanced pNETs in the United States and Europe (7, 8), but *de novo* and acquired resistance to everolimus frequently result in disease progression (9). Somatostatin analogs, sunitinib, chemotherapy, and investigational peptide receptor radionuclide therapy represent alternative treatment options for these patients (10, 11). However, there are currently no internationally agreed treatment sequences in this setting (12). There remains a clinical need for novel therapies that can overcome mTOR inhibitor resistance and improve outcome in patients with advanced or metastatic pNETs.

Emerging evidence suggests that PI3K pathway activation may play a significant role in resistance to mTOR inhibitors (9).

The inability of everolimus to block mTOR complex (mTORC) 2-mediated activation of protein kinase B (AKT) may limit its efficacy (13). Everolimus has been shown to induce AKT phosphorylation *via* mTOR-dependent, negative feedback-induced activation of PI3K (14), raising the possibility that dual PI3K/mTOR inhibition may help to overcome resistance in patients with pNETs whose disease progresses on everolimus (13).

The oral ATP-competitive inhibitor BEZ235 (Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA) targets both class 1 PI3K and mTORC1/2 and has demonstrated potent antitumour activity in pre-clinical studies (15), making it a potential candidate for use in this setting.

This two-stage, prospective, phase II trial (CBEZ235F2201; NCT01658436) is the first to investigate dual PI3K/mTOR inhibition using BEZ235 monotherapy in patients with metastatic pNETs whose disease has progressed on or after treatment with mTOR inhibitors. The first stage consisted of a single-arm, open-label study, with an interim futility analysis after 16 weeks of treatment. If the stringent protocol-defined efficacy criteria were met during stage 1, a second, randomized stage was planned to investigate the combination of BEZ235 with best supportive care. Herein, we present results of the stage 1 interim futility analysis.

Patients and Methods

Patients. Patients 18 years of age or more, with histologically confirmed, low- or intermediate-grade [World Health Organization (WHO) 2010 classification grade 1 or 2], unresectable or metastatic pNETs with radiological evidence of disease progression (per investigator assessment) since last treatment were eligible. Patients were required to have disease progression while on mTOR inhibitor treatment or within 3 months of discontinuation. Prior or concurrent therapy with somatostatin analogs was permitted, provided dosing was stable for at least 2 months prior to study start and throughout the study. Other key inclusion criteria were WHO performance status ≤1, measurable disease per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 (16), and adequate bone marrow and organ function. Key exclusion criteria included prior treatment with a PI3K or AKT inhibitor for pNETs, more than three previous systemic treatment regimens for pNETs, or discontinuation of prior mTOR inhibitor therapy due to toxicity.

The study was reviewed by regulatory authorities and approved by the independent ethics committee or institutional review board of each participating centre. All patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki guidelines for Good Clinical Practice, as defined by the International Conference on Harmonisation.

Study design and treatment. This was a prospective, multicentre, two-stage, phase II study of single-agent BEZ235. In stage 1 (single-arm, open-label), patients received 400 mg oral BEZ235 solid dispersion system (SDS) sachet twice daily (*bid*) on a continuous dosing schedule in 28-day cycles. Due to tolerability concerns, the starting dose was reduced to 300 mg *bid*. Treatment continued until radiological evidence of disease progression (per RECIST v1.1), intolerable toxicity, death, withdrawal of consent, or loss to follow-up. Dose interruptions and dose reductions (in 100 mg increments) were permitted for patients with clinically significant adverse events (AEs) related to study treatment; up to two dose reductions were permitted, to a minimum dose of 100 mg *bid*.

An interim futility analysis was performed when 31 patients had been observed on treatment for at least 16 weeks. The primary endpoint of stage 1 was the 16-week progression-free survival (PFS) rate per RECIST v1.1; patients were considered 'progression free' if they had an overall lesion response of complete response (CR), partial response (PR), or stable disease (SD).

Secondary end-points included the frequency and severity of AEs, overall response rate (ORR; CR+PR), and disease control rate (DCR; CR+PR+SD), based on investigator assessment and RECIST v1.1. Stage 2 would investigate the safety and efficacy of best supportive care in combination with either BEZ235 or placebo.

Safety and efficacy assessments. Laboratory evaluations, physical examination, vital signs, weight, cardiac health, and WHO performance status were continuously monitored. AEs were recorded from the first dose to 30 days following the last dose of BEZ235 and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03 (17).

Assessments of antitumour activity were performed in all patients who received at least one dose of BEZ235. Tumour response was assessed locally during screening and every 8 weeks (±7 days) following treatment initiation, per RECIST v1.1.

Pharmacokinetic (PK) assessments. Venous blood samples for PK analyses were collected from 30 patients pre-dose on days 8, 15, and 22 of cycle 1, day 1 of cycle 2, and at the end of treatment. Analyses were performed using a validated liquid chromatography tandem mass spectrometric assay, with a lower limit of quantification of 1 ng/ml (18).

Statistical analyses. The full analysis set included all patients who had received at least one dose of study drug. Efficacy in stage 1 would trigger initiation of stage 2 and was demonstrated by a 16-week PFS rate of ≥60%, with a posterior probability of the 16-week PFS rate being ≥40% of at least 0.9 (derived from the Bayesian posterior distribution of PFS rate). Tolerability analyses, based on the number and frequency of AEs observed, were carried out on all patients who received at least one dose of study drug and had at least one post-baseline safety assessment.

Results

Patient characteristics and disposition. A total of 31 patients from 24 sites in eight countries were enrolled between November 30, 2012 and September 26, 2013. All patients received at least one dose of BEZ235 at 400 mg (n=11) or 300 mg (n=20; Table I) and were evaluable for safety and efficacy assessments. As of 30 June, 2014, 29 patients had discontinued from the study (Table II). The most common reasons for treatment discontinuation were progressive disease (PD) and AEs.

Safety and tolerability. The median duration of exposure to BEZ235 was 16.1 (range=2.1-66.6) weeks; 15.1 (range=

2.9-48.0) weeks for patients treated at 300 mg *bid* and 16.6 (range=2.1-66.6) weeks for those treated at 400 mg *bid*. Seventeen (85.0%) patients in the 300 mg *bid* group and eight (72.7%) in the 400 mg *bid* group experienced AEs leading to dose interruption or reduction.

All patients experienced at least one AE regardless of the study drug (Table III). Diarrhea, nausea, hyperglycaemia, stomatitis, and vomiting all occurred in ≥30% of patients. Most patients in the 300 mg *bid* group (n=19; 95.0%) and all patients in the 400 mg group (n=11; 100.0%) experienced at least one AE suspected to be related to study treatment. The most common (≥30%) treatment-related AEs were diarrhea, nausea, hyperglycaemia, and vomiting at 300 mg *bid*; and diarrhea, nausea, stomatitis, and vomiting at 400 mg *bid*. Treatment-related grade 3/4 AEs were reported in eight (40.0%) patients at 300 mg *bid* and eight (72.7%) of patients at 400 mg *bid* (Table III).

Serious AEs were reported in 13 (41.9%) patients; eight (40.0%) at 300 mg *bid* and five (45.5%) at 400 mg *bid* (Table IV). Only sepsis and abdominal pain were reported by more than one patient at 300 mg *bid*; all serious AEs reported in the 400 mg *bid* group were experienced by one patient each. Six (30.0%) and three (27.3%) patients experienced grade 3/4 serious AEs in the 300 mg and 400 mg *bid* groups, respectively.

Six (30.0%) and six (54.5%) patients in the 300 mg and 400 mg *bid* groups, respectively, discontinued due to AEs. The most frequent AEs leading to study drug discontinuation were hypertransaminasaemia (all grades n=2; grade 3/4 n=1; both in the 400 mg *bid* group) and hyperglycaemia (all grades n=2; grade 3/4 n=2; both in the 300 mg *bid* group). Other AEs leading to discontinuation were reported in one patient each.

One patient died during the study due to cardiac arrest, not suspected to be treatment-related by the investigator. This patient was a 49-year-old woman with liver metastases who had received BEZ235 300 mg *bid* for approximately 11 months. At the time of death, ongoing grade 3/4 AEs were increased γ-glutamyltransferase, vomiting, and abdominal pain, none suspected to be treatment-related by the investigator.

Efficacy. Response at 16 weeks was SD in 16 (51.6%) patients, PD in nine (29.0%) patients, and unknown in six (19.4%) patients. The estimated 16-week PFS rate was 51.6% (90% CI=35.7-67.3), with a posterior probability of the 16-week PFS rate being ≥40% of 0.9. The efficacy criteria for stage 1 were not met, and stage 2 was therefore not initiated.

Best overall response (BOR) was SD in 22 (71.0%) patients (Table V). Five patients had unknown BOR: one had SD before the first tumour assessment at 8 weeks, one discontinued BEZ235 and started antineoplastic treatment prior to the first assessment, one withdrew consent prior to first assessment, and two had no post-baseline assessments.

Table I. *Patient demographics and disease characteristics at baseline*.

	BEZ235 300 mg or 400 mg *bid* N=31
Median age (range), years	60.0 (26.0-80.0)
Male/female, n (%)	18 (58.1)/13 (41.9)
Tumour type, n (%)	
Non-functioning pNET	28 (90.3)
Insulinoma	1 (3.2)
Other	2 (6.5)
Type of lesions at baseline, n (%)	
Target only	7 (22.6)
Target and non-target	24 (77.4)
Metastatic sites, n (%)	
Liver	27 (87.1)
Lung	6 (19.4)
Anterior mediastinal lymph nodes	2 (6.5)
Bone	2 (6.5)
Mesenteric lymph nodes	2 (6.5)
Pelvic region	2 (6.5)
Peritoneum	2 (6.5)
Other*	12 (38.7)
Time since diagnosis, n (%)	
≤6 months	0
>6 months-≤2 years	8 (25.8)
>2-≤5 years	9 (29.0)
>5 years	14 (45.2)
Time since progression with mTOR inhibitor therapy, n (%)	
≤1 month	5 (16.1)
>1-≤2 months	12 (38.7)
>2-≤3 months	8 (25.8)
>3 months	5 (16.1)
Unknown	1 (3.2)

*Other metastatic sites include abdominal region, lumbar vertebrae, pelvis, sacrum, sternum and ribs, colon, gastro-hepatic lymph nodes, kidney, mediastinum lymph nodes, para-aortic lymph nodes, pelvic nodes, and stomach (all n=1 each). *bid*, Twice daily; *mTOR*, mammalian target of rapamycin; *pNET*, pancreatic neuroendocrine tumour.

Pharmacokinetics. Due to sparse sampling, non-compartmental PK parameters were not calculated. Plasma concentrations of BEZ235 at the protocol-defined time points are presented in Table VI, and show that BEZ235 reached steady state by day 8 of cycle 1, consistent with previously measured PK (18). Pre-dose concentrations of BEZ235 showed large intra- and inter-patient variability (as has previously been observed at this dose range).

Discussion

The aim of this two-stage, phase II study was to evaluate the safety and efficacy of twice-daily BEZ235 in patients with advanced pNETs whose disease had progressed on everolimus. At the interim futility analysis, performed after 31 patients had been observed for at least 16 weeks on

Table II. *Patient disposition*.

	BEZ235 300 mg *bid* n=20	BEZ235 400 mg *bid* n=11	All N=31
Treatment, n (%)			
Treatment ongoing*	1 (5.0)	1 (9.1)	2 (6.5)
Treatment discontinued	19 (95.0)	10 (90.9)	29 (93.5)
Primary reason for treatment discontinuation, n (%)			
Progressive disease	11 (55.0)	4 (36.4)	15 (48.4)
Adverse event	6 (30.0)	5 (45.5)	11 (35.5)
Physician decision	1 (5.0)	0	1 (3.2)
Patient/guardian decision	0	1 (9.1)	1 (3.2)
Death	1 (5.0)	0	1 (3.2)

*Ongoing at time of data cut-off, 30 June, 2014. *bid*, Twice daily.

Table III. *Treatment-emergent adverse events (AEs) (≥10% overall)*.

	BEZ235 300 mg *bid* n=20		BEZ235 400 mg *bid* n=11		All N=31	
AE, n (%)	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Regardless of relationship to study drug						
Total	20 (100)	15 (75.0)	11 (100)	10 (90.9)	31 (100)	25 (80.6)
Diarrhea	16 (80.0)	1 (5.0)	6 (54.5)	2 (18.2)	22 (71.0)	3 (9.7)
Nausea	9 (45.0)	0	6 (54.5)	2 (18.2)	15 (48.4)	2 (6.5)
Hyperglycaemia	7 (35.0)	2 (10.0)	4 (36.4)	4 (36.4)	11 (35.5)	6 (19.4)
Stomatitis	6 (30.0)	0	5 (45.5)	1 (9.1)	11 (35.5)	1 (3.2)
Vomiting	6 (30.0)	2 (10.0)	4 (36.4)	1 (9.1)	10 (32.3)	3 (9.7)
Fatigue	6 (30.0)	0	3 (27.3)	0	9 (29.0)	0
Abdominal pain	6 (30.0)	2 (10.0)	2 (18.2)	0	8 (25.8)	2 (6.5)
Decreased appetite	6 (30.0)	0	2 (18.2)	0	8 (25.8)	0
Asthenia	4 (20.0)	0	3 (27.3)	1 (9.1)	7 (22.6)	1 (3.2)
Peripheral oedema	4 (20.0)	0	3 (27.3)	0	7 (22.6)	0
Upper abdominal pain	2 (10.0)	1 (5.0)	4 (36.4)	0	6 (19.4)	1 (3.2)
Pyrexia	5 (25.0)	0	1 (9.1)	0	6 (19.4)	0
Increased GGT	3 (15.0)	3 (15.0)	2 (18.2)	2 (18.2)	5 (16.1)	5 (16.1)
Constipation	3 (15.0)	0	2 (18.2)	1 (9.1)	5 (16.1)	1 (3.2)
Dyspnoea	4 (20.0)	0	1 (9.1)	0	5 (16.1)	0
Rash	2 (10.0)	0	3 (27.3)	0	5 (16.1)	0
Arthralgia	1 (5.0)	0	3 (27.3)	0	4 (12.9)	0
Dyspepsia	2 (10.0)	0	2 (18.2)	0	4 (12.9)	0
Decreased weight	2 (10.0)	0	2 (18.2)	0	4 (12.9)	0
Musculoskeletal pain	3 (15.0)	0	1 (9.1)	0	4 (12.9)	0
Suspected to be related to study drug						
Total	19 (95.0)	8 (40.0)	11 (100)	8 (72.7)	30 (96.8)	16 (51.6)
Diarrhea	15 (75.0)	0	6 (54.5)	2 (18.2)	21 (67.7)	2 (6.5)
Nausea	7 (35.0)	0	5 (45.5)	2 (18.2)	12 (38.7)	2 (6.5)
Stomatitis	5 (25.0)	0	5 (45.5)	1 (9.1)	10 (32.3)	1 (3.2)
Vomiting	6 (30.0)	1 (5.0)	4 (36.4)	1 (9.1)	10 (32.3)	2 (6.5)
Hyperglycaemia	6 (30.0)	2 (10.0)	3 (27.3)	3 (27.3)	9 (29.0)	5 (16.1)
Decreased appetite	5 (25.0)	0	2 (18.2)	0	7 (22.6)	0
Fatigue	5 (25.0)	0	2 (18.2)	0	7 (22.6)	0
Asthenia	2 (10.0)	0	3 (27.3)	1 (9.1)	5 (16.1)	1 (3.2)
Rash	2 (10.0)	0	3 (27.3)	0	5 (16.1)	0
Peripheral oedema	3 (15.0)	0	1 (9.1)	0	4 (12.9)	0

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment at the maximum severity grade. *bid*, Twice daily; GGT, γ-glutamyltransferase.

Table IV. *Serious treatment-emergent adverse events (AEs), regardless of relationship to study drug.*

	BEZ235 300 mg *bid* n=20		BEZ235 400 mg *bid* n=11		All N=31	
AE, n (%)	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Total	8 (40.0)	6 (30.0)	5 (45.5)	3 (27.3)	13 (41.9)	9 (29.0)
Sepsis	2 (10.0)	2 (10.0)	0	0	2 (6.5)	2 (6.5)
Abdominal pain	2 (10.0)	1 (5.0)	0	0	2 (6.5)	1 (3.2)
Cardiac arrest	1 (5.0)	1 (5.0)	0	0	1 (3.2)	1 (3.2)
Constipation	0	0	1 (9.1)	1 (9.1)	1 (3.2)	1 (3.2)
Hepatic pain	0	0	1 (9.1)	1 (9.1)	1 (3.2)	1 (3.2)
Hyponatremia	1 (5.0)	1 (5.0)	0	0	1 (3.2)	1 (3.2)
Infection	1 (5.0)	1 (5.0)	0	0	1 (3.2)	1 (3.2)
Spinal cord compression	0	0	1 (9.1)	1 (9.1)	1 (3.2)	1 (3.2)
Staphylococcal infection	1 (5.0)	1 (5.0)	0	0	1 (3.2)	1 (3.2)
Systolic dysfunction	0	0	1 (9.1)	1 (9.1)	1 (3.2)	1 (3.2)
Ventricular hyperkinesia	0	0	1 (9.1)	1 (9.1)	1 (3.2)	1 (3.2)
Vomiting	1 (5.0)	1 (5.0)	0	0	1 (3.2)	1 (3.2)
Anaemia	1 (5.0)	0	0	0	1 (3.2)	0
Cholestasis	0	0	1 (9.1)	0	1 (3.2)	0
Diarrhoea	0	0	1 (9.1)	0	1 (3.2)	0
Erysipelas	1 (5.0)	0	0	0	1 (3.2)	0
Pyrexia	1 (5.0)	0	0	0	1 (3.2)	0
Spinal column stenosis	1 (5.0)	0	0	0	1 (3.2)	0

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment at the maximum severity grade. *bid*, Twice daily.

treatment, the estimated PFS rate was 51.6%. This was below the pre-defined threshold of 60% (corresponding to a median PFS of 5.5 months), which was established in the trial design as a preliminary sign of efficacy, based on the median PFS of 4.6 months observed in the placebo arm of the RADIANT-3 trial (19). The study therefore did not proceed to stage 2.

Although no patients achieved a confirmed CR or PR, SD was observed in 16 (51.6%) patients, suggesting that BEZ235 treatment had a modest antitumour effect. Treatment efficacy may have been limited by the high rate of AE-related discontinuations and the high PK variability. Alternatively, the modest efficacy results might suggest that the PI3K pathway is not the sole driver of disease progression in this setting, despite evidence of its activation in a significant proportion of everolimus-resistant pNETs (13).

The starting dose of BEZ235 400 mg *bid* was chosen based on results from a phase I dose-escalation study of single-agent BEZ235 (20); however, there were no data available regarding the safety profile of BEZ235 in patients previously treated with everolimus. Since BEZ235 and everolimus both target the PI3K pathway and have partially overlapping toxicity profiles, a strict dose reduction plan was implemented to manage treatment-related AEs. The high rates of AEs observed at the outset of this study consequently led to a starting dose reduction to 300 mg *bid*, which was still expected to inhibit mTORC1/2 according to previous pharmacodynamic data (18, 20). As 300 mg *bid* was the first dose reduction level recommended for AE management, many patients who had initiated treatment at 400 mg *bid* had already been reduced to this dose level.

Table V. *Summary of best overall response per local assessment.*

	BEZ235 300 mg or 400 mg *bid* N=31
Patients with measurable disease at baseline, n (%)	31 (100)
Best overall response, n (%)	
Complete response (CR)	0
Partial response (PR)	0
Stable disease (SD)	22 (71.0)
Progressive disease (PD)	4 (12.9)
Non-CR/Non-PD	0
Unknown	5 (16.1)
Overall response rate (CR+PR), n	0
Disease control rate (CR+PR+SD), n (%), 90% CI	22 (71.0%), 54.8-83.9%

bid, Twice daily; CI, confidence interval; CR, complete response; PD, progressive disease; PR, partial response.

Table VI. *Summary of BEZ235 plasma concentrations (ng/ml) by timepoint (pharmacokinetics analysis set).*

Cycle/day	Parameter	BEZ235 300 mg *bid* n=20	BEZ235 400 mg *bid* n=11	All N=31
Cycle 1 Day 8	n	17	5	22
	Median (range)	239.0 (6.6-1970.0)	193.0 (16.5-321.0)	235.0 (6.6-1970.0)
	gMean (CV%)	–	–	153.7 (314.5)
Day 15	n	19	8	27
	Median (range)	46.8 (0-1730.0)	37.0 (0-833.0)	45.6 (0-1730.0)
	gMean (CV%)	–	–	114.8 (343.4)
Day 22	n	12	6	18
	Median (range)	64.5 (0-2190.0)	451.5 (110.0-813.0)	131.0 (0-2190.0)
	gMean (CV%)	–	–	173.1 (344.5)
Cycle 2 Day 1	n	18	6	24
	Median (range)	70.6 (0-1690.0)	192.7 (5.7-772.0)	83.7 (0-1690.0)
	gMean (CV%)	–	–	106.1 (446.9)

bid, Twice daily; CV%, coefficient of variation; gMean, geometric mean.

The median duration of exposure in the two dose groups was similar, and there was a high rate of dose interruption, dose reduction, and discontinuation due to AEs in both groups. Gastrointestinal-related AEs were common in both dose groups, and may have been related to BEZ235 administration *via* the oral SDS sachet. Careful and prompt AE management were key to maintaining adequate exposure to BEZ235 throughout the study. In line with previous studies of BEZ235 and other mTOR inhibitors, stomatitis was frequently observed but was readily managed with good oral hygiene techniques and topical corticosteroids (18, 21). While discontinuation may be justified in response to some AEs (such as hypertransaminasaemia), closer cooperation between oncologists and endocrinologists, or more frequent assessments of blood glucose levels, may result in fewer discontinuations for manageable 'on-target' AEs, such as hyperglycaemia (22-24).

In conclusion, this is the first study of a dual PI3K/mTOR inhibitor in patients whose disease has progressed on everolimus. Our conclusions regarding the efficacy of BEZ235 are limited by the high intra- and inter-patient PK variability, making it difficult to establish concentration–response relationships, as well as by the challenging toxicity profile, which restricted treatment duration. The modest efficacy of BEZ235 observed in stage 1 was primarily based on disease stability, and was insufficient to trigger the initiation of stage 2; results are consistent with studies of single-agent PI3K pathway inhibitors in other malignancies, which have also reported limited activity (23, 25-28). Given the association between PI3K pathway activation and mTOR inhibitor resistance (13, 14), further investigation of better-tolerated PI3K pathway inhibitors, in combination with other agents, is warranted in patients with advanced pNETs who progress after mTOR inhibitor treatment.

Conflicts of Interest

CV has received honoraria from Bayer, Novartis, and Ipsen. EB has received funding to attend ASCO 2013 and ESMO 2015. LA has received honoraria from Roche, Novartis, Ipsen, Merck, and Eli Lilly. MS has received research funding from Novartis. NF has received honoraria from Ipsen and Novartis, and research funding from Novartis. RB reports research funding from Novartis. WWdH has received research funding from Ipsen and Novartis. DD, ST, and PA are employees of Novartis. CM is an employee and shareholder of Novartis. All remaining authors (AT, HL, JC, MHK, MR, RAH, SKL) have declared no conflicts of interest. The study was funded by Novartis Pharmaceuticals Corporation and designed in conjunction with the steering committee. All authors had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

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