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Clinical Trial Results

Phase II Study of BEZ235 versus Everolimus in Patients with Mammalian Target of Rapamycin Inhibitor-Naïve Advanced Pancreatic Neuroendocrine Tumors

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Trial Information

- **ClinicalTrials.gov Identifier**: NCT01628913
- **Sponsor(s)**: Novartis Pharmaceuticals Corporation
- **Principal Investigator**: James C. Yao
- **IRB Approved**: Yes

Lessons Learned

- Treatment with BEZ235 has not been shown to demonstrate increased efficacy compared with everolimus and may be associated with a poorer tolerability profile.
- The hypothesis of dual targeting of the phosphatidylinositol 3-kinase and mammalian target of rapamycin pathways in patients with advanced pancreatic neuroendocrine tumors may warrant further study using other agents.

Abstract

Background. This phase II study investigated whether targeting the phosphatidylinositol 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) pathway via PI3K, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) inhibition using BEZ235 may be more effective than mTORC1 inhibition with everolimus in patients with advanced pancreatic neuroendocrine tumors (pNET) who are naïve to mTOR inhibitor therapy.

Methods. Patients with advanced pNET were randomized (1:1) to oral BEZ235 400 mg twice daily or oral everolimus 10 mg once daily on a continuous dosing schedule. The primary endpoint was progression-free survival (PFS). Secondary endpoints included safety, overall response rate (ORR), overall survival (OS), and time to treatment failure.

Results. Enrollment in this study was terminated early (62 enrolled of the 140 planned). The median PFS was 8.2 months (95% confidence interval [CI]: 5.3 to not evaluable [NE]) with BEZ235 versus 10.8 months (95% CI: 8.1–NE) with everolimus (hazard ratio 1.53; 95% CI: 0.72–3.25). The most commonly reported all-grade adverse events (>50% of patients regardless of study treatment relationship) with BEZ235 were diarrhea (90.3%), stomatitis (74.2%), and nausea (54.8%).

Conclusion. BEZ235 treatment in mTOR inhibitor-naïve patients with advanced pNET did not demonstrate increased efficacy compared with everolimus and may be associated with a poorer tolerability profile. ***The Oncologist*** 2018;23:766–e90

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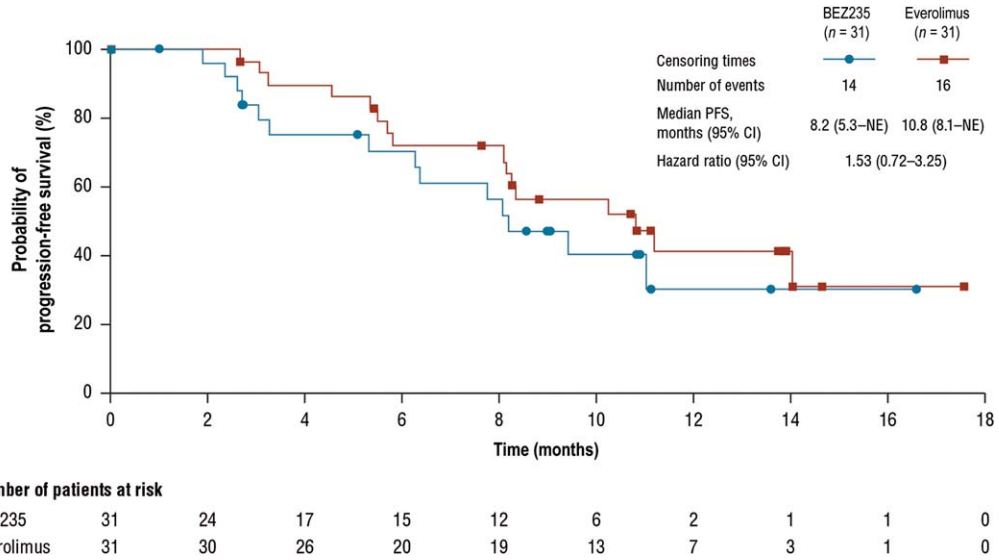

Figure 1. Kaplan-Meier plot of progression-free survival per local radiologic review.
Abbreviations: CI, confidence interval; NE, not evaluable; PFS, progression-free survival.

Discussion

This phase II study aimed to investigate whether targeting the PI3K/mTOR pathway via PI3K, mTORC1, and mTORC2 adenosine triphosphate (ATP) site inhibition using BEZ235 is more effective than mTORC1 allosteric inhibition with everolimus in patients with advanced pNET who are naïve to mTOR inhibition therapy. However, emerging data suggesting an unfavorable safety profile and unpredictable bioavailability led to the sponsor's decision to halt the development of BEZ235 in all oncology indications including pNET, and enrollment in this study was terminated before the planned 70 patients had been randomized in each treatment arm and before a preplanned primary analysis after 70 disease progression events was reached.

The results of the study suggest that the efficacy of BEZ235 did not surpass that of everolimus in this setting (Fig. 1). The median PFS of 10.8 months observed with everolimus in this study is comparable to prior data in this setting (RADIANT-3 trial; [1]). The median PFS of 8.2 months observed with BEZ235 exceeded that of 4.6 months in the placebo arm of RADIANT-3, indicating some degree of efficacy [1]. ORR (9.7%) was similar in both groups, suggesting that a small degree of tumor shrinkage was observed with both treatments. Disease control rate was substantially lower with BEZ235 (61.3%) than with everolimus (90.3%), although the high rate of unknown tumor responses among patients in the BEZ235-treated group (25.8%) versus the everolimus-treated group (6.5%) precludes any meaningful comparison of disease stabilization between the groups. A small numerical difference in the estimated 6-month OS rate was observed with BEZ235 (96.6%) versus everolimus (90.3%), which should be interpreted with caution due to the early termination of the study, limited number of patients, and very few on-study deaths during the trial.

All adverse events (AEs) observed with BEZ235 and everolimus during the study were consistent with their known safety profiles and no unexpected events were reported [1–4]. However, this study indicated that BEZ235 was potentially less well tolerated than everolimus. More grade 3/4 AEs were reported with BEZ235 (83.9%) versus everolimus (71.0%) and discontinuations due to AEs were twice as frequent with BEZ235 versus everolimus (38.7 vs. 16.1%, respectively). The poor tolerability of BEZ235 versus everolimus may explain why patients randomized to this treatment were exposed to study medication for almost half the duration of time as those randomized to everolimus (22.9 vs. 39.4 weeks, respectively). This short duration of treatment time may have negatively impacted BEZ235 efficacy outcomes.

mTOR inhibitor-naïve patients with advanced pNET on treatment with BEZ235 did not demonstrate superior efficacy compared with everolimus and may have a poorer tolerability profile. However, the hypothesis of dual targeting of the PI3K and mTOR pathways in patients with advanced pNET may still warrant further study using other agents with more favorable safety profiles.

Trial Information	
Disease	Neuroendocrine
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	2 prior regimens
Type of Study – 1	Phase II
Type of Study – 2	Randomized
Primary Endpoint	Progression-free survival

Secondary Endpoint	Safety
Secondary Endpoint	Overall response rate
Secondary Endpoint	Overall survival
Secondary Endpoint	Time to treatment failure
Additional Details of Endpoints or Study Design The main analysis was originally intended to be performed after 70 patients had experienced progression of the disease or death due to any cause. Based on this, an indication for a longer PFS under BEZ235 would be achieved when the following two efficacy criteria are both met: (a) the estimated hazard ratio (HR) is $\leq$0.75 and (b) the posterior probability that the HR is $<$1 is at least 90%: Ppost (HR $<$1) $\geq$0.9. But due to early enrollment study termination on October 29, 2013, the 62 patients randomized were analyzed mainly for descriptive purpose after 6 months after the last patient started study treatment.	
Investigator's Analysis	Poorly tolerated/not feasible

Drug Information for Phase II Everolimus

Drug 1	
Generic/Working Name	Everolimus
Trade Name	Afinitor
Company Name	Novartis Pharmaceuticals Corporation
Drug Type	Targeted therapy
Drug Class	m-TOR
Dose	10 mg per flat dose
Route	p.o.
Schedule of Administration	Once daily, every day (28-day cycles)

Drug Information for Phase II BEZ235

Drug 1	
Generic/Working Name	BEZ235
Trade Name	Dactolisib
Company Name	Novartis Pharmaceuticals Corporation
Drug Type	Small molecule
Drug Class	PI3 kinase
Dose	400 mg per flat dose
Route	p.o.
Schedule of Administration	Twice daily, every day (28-day cycles)

Patient Characteristics for Phase II Everolimus

Number of Patients, Male	15
Number of Patients, Female	16
Age	Median: 57
Performance Status: ECOG	0 — 20 1 — 11 2 — 0 3 — Unknown —

Patient Characteristics for Phase II BEZ235

Number of Patients, Male	17
Number of Patients, Female	14
Age	Median: 56 years
Performance Status: ECOG	0 — 20 1 — 10 2 — 1 3 — Unknown —

Primary Assessment Method for Phase II Everolimus	
Title	Total patient population
Number of Patients Screened	31
Number of Patients Enrolled	31
Number of Patients Evaluable for Toxicity	31
Number of Patients Evaluated for Efficacy	31
Evaluation Method	Response Evaluation Criteria in Solid Tumors (RECIST) 1.0
Response Assessment CR	*n* = 0 (0%)
Response Assessment PR	*n* = 3 (9.7%)
Response Assessment SD	*n* = 25 (80.6%)
Response Assessment PD	*n* = 1 (3.2%)
Response Assessment OTHER	*n* = 2 (6.5%)
(Median) Duration Assessments PFS	10.8 months
(Median) Duration Assessments Duration of Treatment	39.4 weeks

Primary Assessment Method for Phase II BEZ235	
Title	Total patient population
Number of Patients Screened	31
Number of Patients Enrolled	31
Number of Patients Evaluable for Toxicity	31
Number of Patients Evaluated for Efficacy	31
Evaluation Method	RECIST 1.0
Response Assessment CR	*n* = 0 (0%)
Response Assessment PR	*n* = 3 (9.7%)
Response Assessment SD	*n* = 16 (51.6%)
Response Assessment PD	*n* = 4 (12.9%)
Response Assessment OTHER	*n* = 8 (25.8%)
(Median) Duration Assessments PFS	8.2 months
(Median) Duration Assessments Duration of Treatment	22.9 weeks

Treatment-Emergent Adverse Events (>15%)

	BEZ235 (*n* = 31), *n* (%)		Everolimus (*n* = 31), *n* (%)	
Adverse event	**All grades**	**Grade 3/4**	**All grades**	**Grade 3/4**
Any event	31 (100)	26 (83.9)	30 (96.8)	22 (71.0)
Diarrhea	28 (90.3)	5 (16.1)	17 (54.8)	1 (3.2)
Stomatitis	23 (74.2)	4 (12.9)	20 (64.5)	2 (6.5)
Nausea	17 (54.8)	2 (6.5)	10 (32.3)	0
Vomiting	15 (48.4)	2 (6.5)	7 (22.6)	1 (3.2)
Asthenia	13 (41.9)	5 (16.1)	13 (41.9)	1 (3.2)
Abdominal pain	12 (38.7)	3 (9.7)	8 (25.8)	0
Rash	11 (35.5)	0	13 (41.9)	0
Hyperglycemia	10 (32.3)	5 (16.1)	11 (35.5)	2 (6.5)
Appetite decreased	9 (29.0)	2 (6.5)	13 (41.9)	1 (3.2)
Pyrexia	9 (29.0)	1 (3.2)	4 (12.9)	0
Anemia	8 (25.8)	2 (6.5)	11 (35.5)	3 (9.7)
Fatigue	7 (22.6)	3 (9.7)	10 (32.3)	2 (2.5)
Blood creatinine increased	6 (19.4)	0	2 (6.5)	0

Headache	6 (19.4)	0	7 (22.6)	0
Edema peripheral	6 (19.4)	0	11 (35.5)	4 (12.9)
Pruritus	6 (19.4)	0	2 (6.5)	0
Abdominal pain upper	5 (16.1)	1 (3.2)	5 (16.1)	0
ALT increased	5 (16.1)	3 (9.7)	3 (9.7)	1 (3.2)
Dysgeusia	5 (16.1)	0	3 (9.7)	0
Constipation	4 (12.9)	0	5 (16.1)	0
Epistaxis	4 (12.9)	0	5 (16.1)	0
Weight decreased	4 (12.9)	0	6 (19.4)	1 (3.2)
Cough	3 (9.7)	0	8 (25.8)	0
Dyspnea	2 (6.5)	1 (3.2)	5 (16.1)	1 (3.2)
Nasopharyngitis	2 (6.5)	0	5 (16.1)	0
Dry skin	0	0	8 (25.8)	0
Hypertriglyceridemia	0	0	5 (16.1)	2 (6.5)
Platelet count decreased	0	0	7 (22.6)	0
Pneumonitis	0	0	5 (16.1)	1 (3.2)

Abbreviation: ALT, alanine aminotransferase.

Assessment, Analysis, and Discussion

Completion	Study terminated before completion
Terminated Reason	Toxicity
Investigator's Assessment	Poorly tolerated/not feasible

Two targeted agents have been approved for the treatment of locally advanced and metastatic pancreatic neuroendocrine tumors (pNET) based on improvements in progression-free survival versus placebo: everolimus, a mammalian target of rapamycin (mTOR) inhibitor, and sunitinib, a multitargeted tyrosine kinase inhibitor. Everolimus therapy has demonstrated considerable clinical benefit in the treatment of advanced pNET. However, de novo and acquired resistance to therapy have been observed. Such resistance may stem from enhanced activation of the phosphatidylinositol 3-kinase (PI3K)/mTOR pathway [5–7]. Everolimus specifically inhibits the mTOR complex 1 (mTORC1) but does not block mTOR complex 2 (mTORC2)-mediated activation of AKT. It is postulated that activation of AKT by way of insulin-like growth factor 1/insulin-like growth factor 1 receptor and mTORC2 signaling activation due to the inhibition of S6 kinase (S6K) negative feedback are mechanisms of everolimus treatment resistance [1, 8]. Samples from patients with advanced solid tumors and neuroendocrine tumors have shown that treatment with everolimus led to increases in activated AKT through the silencing of an S6K-dependent negative feedback-induced loop, especially in patients with clinical responses [9, 10]. Therefore, it is possible that targeting the PI3K/mTOR pathway via PI3K, mTORC1, and mTORC2 inhibition may circumvent treatment resistance and improve outcomes for patients with pNET compared with inhibition of mTORC1 alone.

These observations provided impetus for the development of dual PI3K/mTOR inhibitors such as dactolisib (BEZ235), SAR245409 (XL765), BGT226, and apitolisib (GDC-0980), which have subsequently been evaluated in a variety of solid tumors [2, 12–15]. BEZ235 is a novel pan-class I PI3K inhibitor that also inhibits mTORC1 and mTORC2 [16]. BEZ235 inhibits kinase activity by binding to the ATP-binding cleft of these enzymes, which occurs through a different mechanism to allosteric inhibition by everolimus, thus avoiding potential rapamycin complex binding site mutations [17].

In preclinical studies, BEZ235 was shown to have potent antitumor activity resulting in Gap 1 phase (G1) phase cell cycle arrest in vivo that was synergistic with the activity of other anticancer drugs, including everolimus [18, 19]. Furthermore, BEZ235 overcame long-term acquired everolimus resistance in human pNET cell lines, leading to further clinical evaluation of this compound in clinical trials [20]. In the clinical setting, a phase I study involving patients with advanced solid tumors treated with BEZ235 as a single agent demonstrated both clinical activity (45% had stable disease) and acceptable tolerability [2].

The safety and tolerability profile of BEZ235 observed in this study was consistent with the known experience, with no new signal identified. However, treatment with BEZ235 single agent 400 mg bid was accompanied with toxicity requiring frequent treatment modifications and discontinuations in this population with advanced pNET. Adverse events that were frequently reported in phase I studies with the other dual PI3K/mTOR inhibitors in development (XL765, GDC-0980, GSK2126458, and PF-04691502) were similar to those seen in this phase I trial of BEZ235, including nausea, vomiting, diarrhea, anorexia, and skin disorders [2]. Taken together, dual inhibition of PI3K-mTOR was associated with higher incidences of toxicity [21]. The shorter duration of treatment of BEZ235 (22.9 weeks) compared with everolimus (39.4

weeks) because of poor tolerability may have negatively impacted BEZ235 efficacy outcomes. Efficacy may also have been restricted by the high intra- and interpatient pharmacokinetic variability with BEZ235 administration observed in previous clinical studies [2, 4, 22, 23], and bioavailability issues [24]. In conclusion, the results of this study suggest that the modest efficacy and poor tolerability of pan-PI3K inhibitors and dual PI3K/mTOR inhibitors may limit further clinical development of these compounds.

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Disclosures

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