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Clinical Trial Results

A Phase Ib Study of BEZ235, a Dual Inhibitor of Phosphatidylinositol 3-Kinase (PI3K) and Mammalian Target of Rapamycin (mTOR), in Patients With Advanced Renal Cell Carcinoma

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Trial Information

- **ClinicalTrials.gov Identifier:** NCT01453595
- **Sponsor(s):** Novartis
- **Principal Investigator:** Ana M. Molina
- **IRB Approved:** Yes

Lessons Learned

- Our results highlight additional toxicities of dual PI3K/mTOR inhibition in the clinical setting that were unforeseen from preclinical models.
- Because of toxicity and lack of efficacy, BEZ235 should not be further developed in the current formulation for patients with renal cell carcinoma.

Abstract

Background. Allosteric inhibitors of the mammalian target of rapamycin complex 1 (mTORC1) are approved for advanced renal cell carcinoma (RCC). Preclinical models have suggested that dual inhibition of phosphatidylinositol 3-kinase (PI3K) and mTOR kinase may establish superior anticancer effect. We aimed to establish safety for BEZ235, a potent inhibitor of both PI3K and mTOR, in advanced RCC.

Methods. Patients with advanced RCC who had previously failed standard therapy received escalating doses of BEZ235 in sachet formulation twice daily until progression or unacceptable toxicity. Primary endpoints were to identify the maximally tolerated dose (MTD) and to determine the recommended dose for the phase II study.

Results. The study was terminated early because of high incidence of dose-limiting toxicities (DLTs) across all dose levels tested. Ten patients were treated with BEZ235—six with clear cell and four with non-clear cell subtypes. Five of these patients suffered DLTs: 2 of 2 patients in the original 400 mg b.i.d. cohort, 1 of 6 in the 200 mg b.i.d. cohort, and 2 of 2 in the 300 mg b.i.d. cohort. DLTs included fatigue, rash, nausea and vomiting, diarrhea, mucositis, anorexia, and dysgeusia. Five patients were evaluable for response: Two had stable disease as best response, and three had progressive disease.

Conclusion. BEZ235 twice daily resulted in significant toxicity without objective responses; further development of this compound will not be pursued in this disease. ***The Oncologist*** 2016;21:787–788d

Discussion

A key element in the pathogenesis and sustainment of RCC is activation of the PI3K/Akt/mTORC pathway, which promotes tumor growth through its enhancing effects on both angiogenesis and tumor cell proliferation. Everolimus and temsirolimus, TORC1-specific allosteric mTOR inhibitors, are approved for use in advanced RCC [1–3]. Whether the addition of PI3K inhibition to mTOR inhibition is safe and improves outcomes is unknown. BEZ235 is an orally available PI3K, mTORC1, and mTORC2 inhibitor. We sought to investigate the safety and tolerability of BEZ235 in advanced RCC.

This was a single-center, phase Ib trial with the standard 3 + 3 dose escalation design set up to test twice-daily administration of BEZ235 across three dose levels. The study was conducted in patients with advanced RCC of any subtype previously treated with at least one systemic regimen; enrollment required Eastern Cooperative Oncology Group

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Table 1. Grade 3 or 4 adverse events of BEZ235

Adverse event	All grades, no. (%)	Grade 3 or 4, no. (%)
Diarrhea	9 (90)	2 (20)
Fatigue	9 (90)	2 (20)
Elevated lipase	4 (40)	1 (10)
Chest pain, noncardiac	4 (40)	1 (10)
Anemia	2 (20)	1 (10)
Increased alkaline phosphatase	2 (20)	1 (10)
Hyperuricemia	1 (10)	1 (10)
Rash, maculopapular	1 (10)	1 (10)

(ECOG) performance status 0–1 and adequate organ function. A total of 10 patients were enrolled. The first 2 patients in the initial 400 mg b.i.d. dosing cohort experienced DLTs (grade 3 fatigue and rash in 1 patient, and intolerable grade 2 nausea, vomiting, mucositis, and fatigue in the other), prompting de-escalation of dose. Per protocol, a 200 mg b.i.d. dosing cohort was opened, which ultimately enrolled 6 patients. Only 1 experienced a DLT (intolerable grade 2 mucositis), and with an amendment to the protocol, a third dosing cohort of BEZ235 300 mg b.i.d. was added. Two patients were enrolled at this dose level. Both experienced DLTs (1 patient had intolerable grade 2 anorexia and dysgeusia and grade 3 diarrhea; the other patient had intolerable grade 2 nausea and grade 3 fatigue).

Per the dose escalation scheme, no additional patients were enrolled in the 300 mg b.i.d. cohort; rather, 2 additional patients would have been required in the 200 mg b.i.d. cohort to establish an MTD. Given the notable extent of toxicities and difficulty with patient retention, a decision was made to close the trial.

Overall, treatment with BEZ235 was poorly tolerated: 50% of patients developed grade 3–4 adverse events (Table 1), and 50% of patients came off the study because of toxicities. No objective responses were observed in the five evaluable patients. Two of these patients had stable disease and three patients had progression as best response. Poor tolerance limited the ability to assess whether dual inhibition of PI3K and mTOR with BEZ235 is effective in patients with RCC. There is currently no evidence to support its continued investigation in this disease.

Trial Information

Disease	Renal cell carcinoma – clear cell
Disease	Renal cell carcinoma – non-clear cell
Stage of disease / treatment	Metastatic / Advanced
Prior Therapy	No designated number of regimens
Type of study - 1	Phase I
Type of study - 2	3 + 3
Primary Endpoint	Recommended Phase II Dose
Primary Endpoint	Maximum Tolerated Dose
Secondary Endpoint	Tolerability
Secondary Endpoint	Safety
Additional Details of Endpoints or Study Design	This was originally designed as a phase Ib/II study; however, no patients were enrolled into the phase II part because of premature closure of the study.
Investigator's Analysis	Poorly tolerated/not feasible

Drug Information

Drug 1	
Generic/Working name	BEZ235
Company name	Novartis
Drug type	Small molecule
Drug class	mTOR inhibitor
Dose	Milligrams per flat dose
Route	Oral
Schedule of Administration	Twice daily

Dose Escalation Table

Dose Level	Dose of Drug: BEZ235	Number Enrolled	Number Evaluable for Toxicity
1	400 mg b.i.d.	2	2
−1	200 mg b.i.d.	6	6
−1a	300 mg b.i.d.	2	2

Patient Characteristics	
Number of patients, male	8
Number of patients, female	2
Stage	IV
Age	Median (range): 62 years (47–76 years)
Number of prior systemic therapies	Median (range): 3 (2–5)
Performance Status: ECOG	0 — 4 1 — 6 2 — 0 3 — 0 Unknown — 0
Cancer Types or Histologic Subtypes	Clear cell, 6 Unclassified, 2 Papillary, 1 Chromophobe, 1

Primary Assessment Method	
Control Arm: Total Patient Population	
Number of patients screened	15
Number of patients enrolled	10
Number of patients evaluable for toxicity	10
Number of patients evaluated for efficacy	5
Response assessment CR	$n = 0$ (0%)
Response assessment PR	$n = 0$ (0%)
Response assessment SD	$n = 2$ (20%)
Response assessment PD	$n = 3$ (30%)
Response assessment OTHER	$n = 5$ (50%)

Adverse Events

Adverse Events occurring in any patient, in any cycle

Name	*NC/NA	1	2	3	4	5	All Grades
Fatigue	10%	40%	30%	20%	0%	0%	90%
Diarrhea	10%	50%	20%	20%	0%	0%	90%
Nausea	20%	60%	20%	0%	0%	0%	80%
Vomiting	50%	40%	10%	0%	0%	0%	50%
Hyperglycemia	50%	40%	10%	0%	0%	0%	50%
Mucositis oral	50%	30%	20%	0%	0%	0%	50%
Hyperkalemia	50%	50%	0%	0%	0%	0%	50%
Creatinine increased	50%	40%	10%	0%	0%	0%	50%
Lipase increased	60%	30%	0%	10%	0%	0%	40%
Noncardiac chest pain	60%	30%	0%	10%	0%	0%	40%
Platelet count decreased	70%	10%	20%	0%	0%	0%	30%
Dyspnea	70%	30%	0%	0%	0%	0%	30%
Weight loss	70%	30%	0%	0%	0%	0%	30%
Hypocalcemia	70%	30%	0%	0%	0%	0%	30%
Serum amylase increased	70%	30%	0%	0%	0%	0%	30%
Alanine aminotransferase increased	70%	30%	0%	0%	0%	0%	30%
Blood bilirubin increased	70%	20%	10%	0%	0%	0%	30%
Hypoglycemia	80%	20%	0%	0%	0%	0%	20%
Cough	80%	20%	0%	0%	0%	0%	20%
Alkaline phosphatase increased	80%	10%	0%	10%	0%	0%	20%
Anemia	80%	0%	10%	10%	0%	0%	20%

Activated partial thromboplastin time prolonged	80%	20%	0%	0%	0%	0%	20%
Cholesterol high	80%	20%	0%	0%	0%	0%	20%
Hypertriglyceridemia	80%	20%	0%	0%	0%	0%	20%
Dysgeusia	80%	10%	10%	0%	0%	0%	20%
Hypoalbuminemia	80%	20%	0%	0%	0%	0%	20%
Constipation	80%	20%	0%	0%	0%	0%	20%
Hyperuricemia	90%	0%	0%	0%	10%	0%	10%
Rash, maculopapular	90%	0%	0%	10%	0%	0%	10%
Hypophosphatemia	90%	0%	10%	0%	0%	0%	10%
INR increased	90%	0%	10%	0%	0%	0%	10%
Hypoalbuminemia	90%	0%	10%	0%	0%	0%	10%
Hypercalcemia	90%	0%	10%	0%	0%	0%	10%
Anorexia	90%	0%	10%	0%	0%	0%	10%
Hypothyroidism	90%	0%	10%	0%	0%	0%	10%
Conjunctivitis	90%	10%	0%	0%	0%	0%	10%
Pruritus	90%	10%	0%	0%	0%	0%	10%
Peripheral sensory neuropathy	90%	10%	0%	0%	0%	0%	10%
Aspartate aminotransferase increased	90%	10%	0%	0%	0%	0%	10%
Allergic rhinitis	90%	10%	0%	0%	0%	0%	10%
Dry skin	90%	10%	0%	0%	0%	0%	10%
Hypomagnesemia	90%	10%	0%	0%	0%	0%	10%
Hyponatremia	90%	10%	0%	0%	0%	0%	10%
Cholesterol high	90%	10%	0%	0%	0%	0%	10%
Constipation	90%	10%	0%	0%	0%	0%	10%
Skin infection	90%	10%	0%	0%	0%	0%	10%
Fever	90%	10%	0%	0%	0%	0%	10%
Back pain	90%	10%	0%	0%	0%	0%	10%
Dizziness	90%	10%	0%	0%	0%	0%	10%
Abdominal pain	90%	10%	0%	0%	0%	0%	10%
Urinary frequency	90%	10%	0%	0%	0%	0%	10%
Hypernatremia	90%	10%	0%	0%	0%	0%	10%
Chills	90%	10%	0%	0%	0%	0%	10%
Urine discoloration	90%	10%	0%	0%	0%	0%	10%
Dry skin	90%	10%	0%	0%	0%	0%	10%
White blood cell decreased	90%	10%	0%	0%	0%	0%	10%
Erythema multiforme	90%	10%	0%	0%	0%	0%	10%

Adverse Events Legend
*No Change From Baseline/No Adverse Event

Serious Adverse Events

Name	Grade	Attribution
Noncardiac chest pain	3	Possible
Fatigue	3	Unrelated
Abdominal pain	3	Unrelated
Pleural effusion	3	Unrelated

Dose-Limiting Toxicities

Dose Level	Dose of Drug: BEZ235	Number Enrolled	Number Evaluable for Toxicity	Number with a Dose-Limiting Toxicity	Dose-Limiting Toxicity Information
1	400 mg b.i.d.	2	2	2	Grade 3 fatigue, grade 3 rash, intolerable grade 2 nausea and vomiting, intolerable grade 2 fatigue, intolerable grade 2 oral mucositis
−1	200 mg b.i.d.	6	6	2	Grade 3 fatigue, grade 3 rash, intolerable grade 2 nausea, intolerable grade 2 vomiting, intolerable grade 2 oral mucositis, intolerable grade 2 fatigue
−1a	300 mg b.i.d.	2	2	1	Intolerable grade 2 oral mucositis

Assessment, Analysis, and Discussion

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

Although the mammalian target of rapamycin (mTOR) inhibitors everolimus and temsirolimus are approved for the treatment of advanced renal cell carcinoma (RCC), significant tumor reductions and prolonged responses are seen in only a minority of patients [1–3]. There are several proposed mechanisms of resistance that could account for their limited activity. First, inhibition of mammalian target of rapamycin complex 1 (mTORC1) has been shown to prompt feedback activation of PI3K/Akt, which, in turn, could also activate other kinases [4]. Second, mTOR exerts its multiple functions as part of two distinct multiprotein complexes, mTORC1 and mTORC2, both with defined pro-oncogenic roles in human cancer. Everolimus and temsirolimus are allosteric inhibitors of mTORC1 but leave mTORC2 unaffected. There is thought to be cross-talk between the two complexes; hence, inhibition of mTORC1 could result in compensatory upregulation of mTORC2 activity [5]. A third proposed mechanism involves activation of the mitogen-activated protein kinase signaling pathway via mTORC1 inhibition [6].

BEZ235 is a novel, orally available imidazoquinoline that potently and reversibly inhibits class I PI3K and mTOR kinase, hence suppressing downstream effects of both mTORC1 and mTORC2. BEZ235 has been demonstrated to inhibit its putative targets and block tumor growth in preclinical models of various malignancies [7, 8]. In RCC cell lines and xenografts, when compared with rapamycin, BEZ235 treatment resulted in greater reduction in tumor cell proliferation and more complete suppression of Akt and other pathways downstream of PI3K [9]. The first-in-human phase I study of BEZ235, in gelatin capsule form, in advanced solid tumors demonstrated high inter- and intrapatient pharmacokinetic variability [10]. A solid dispersion system sachet was developed to decrease variability, and a maximum tolerated dose (MTD) of 1600 mg once daily was established; however, the safety of twice daily dosing warranted further investigation [11]. In this phase Ib trial, we sought to investigate the safety of BEZ235 sachet twice daily in patients with advanced RCC.

The results of this trial highlight that promising preclinical data and sound biological rationale do not always translate into successful development of a novel agent. We encountered dose-limiting toxicities at all dose levels tested on the trial; no objective responses were seen. The trial was closed early because of poor tolerance, a recommended phase II dose was not defined, and a planned expansion cohort did not open.

The adverse event profile of the study drug was largely class specific (i.e., similar to what has been seen with other PI3K/TORC1/TORC2 inhibitors). The challenges around drug tolerance encountered in this trial with BEZ235 parallel the experience across other malignancies. A parallel phase I study of BEZ235 in sachet formulation given twice daily also showed considerable toxicity, although it established an MTD of 300 mg twice daily [12]. A phase II trial of BEZ235 with the same dosing regimen in transitional cell carcinoma showed modest clinical activity but an unfavorable toxicity profile, with 50% of patients experiencing grade 3–4 toxicities [13]. Another phase II trial of the drug at twice daily 300-mg or 400-mg doses in patients with advanced pancreatic neuroendocrine tumors also had a high rate of toxicity and did not proceed to further investigation [14].

The strategy of dual mTOR/PI3K inhibition for advanced RCC has been pursued with other agents. A randomized trial of GDC-0980, another dual pan-PI3K and MTORC1/2 inhibitor, versus everolimus in patients with metastatic RCC showed that GDC-0980 had a higher rate of grade 3–4 adverse events (31% vs. 12%), and did not show benefit compared with everolimus [15]. A randomized phase II trial of AZD2014, a dual TORC1/TORC2 inhibitor, compared with everolimus, in RCC reported better patient tolerance. The study suggested that the AZD2014 group had fewer grade 3–4 adverse events than the everolimus group [16]. Disappointingly, however, the trial was terminated early when an early interim analysis suggested inferior outcome with AZD2014, including for the primary endpoint of progression-free survival (hazard ratio: 2.8; 95% confidence interval: 1.2–6.5; $p = .01$), and potentially also for overall survival (hazard ratio: 3.1; 95% confidence interval: 1.1–8.4; $p < .02$).

It seems unlikely that a challenging safety profile alone might account for such differences in cancer-specific outcome. Some have proposed that dual mTORC1/2 inhibition upregulates FOXO activity, which, in turn, may upregulate receptor tyrosine kinase expression [17, 18]. Regardless, in aggregate, our data do not support the strategy of broader mTOR/PI3K pathway inhibition in advanced RCC. Certainly, in

the case of BEZ235, added target-specific toxicity got in the way of meaningful improvement in anticancer effect.

Disclosures

Ana M. Molina: Novartis, Eisai (C/A); **Chung-Han Lee:** Pfizer, Eisai (RF); **Darren R. Feldman:** Novartis (RF); **Robert J. Motzer:** Pfizer, Novartis, Eisai (C/A), Pfizer, Bristol-Myers Squibb, Genentech/Roche, Eisai Inc. (RF); **Martin H. Voss:** GlaxoSmithKline, Novartis, Calithera, Natera, Exelixis (C/A), Bristol-Myers Squibb (RF). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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