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

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- 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
(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.

**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)                |

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### Patient Characteristics

| Characteristic                  | Value |
|--------------------------------|-------|
| 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**

| Parameter                          | Value |
|------------------------------------|-------|
| 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 amylose 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%        |
| Condition                        | Grade 80% | Grade 20% | Grade 0% | Grade 0% | Grade 0% | Grade 0% | Grade 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%      |
| Hyponatremia                     | 90%       | 10%       | 0%       | 0%       | 0%       | 0%       | 10%      |
| Hypernatremia                    | 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%      |
| Urinary 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   |

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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

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 intratissue 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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