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Phase II study of dual phosphoinositol-3-kinase (PI3K) and mammalian target of rapamycin (mTOR) inhibitor BEZ235 in patients with locally advanced or metastatic transitional cell carcinoma

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Objective

To assess, in a multicentre phase II trial, the safety and efficacy of BEZ235, an oral pan-class I phosphoinositol-3-kinase (PI3K) and mammalian target of rapamycin (mTOR) complex1/2 inhibitor, in locally advanced or metastatic transitional cell carcinoma (TCC) after failure of platinum-based therapy.

Patients and Methods

Patients with locally advanced or metastatic TCC progressing after platinum therapy were prospectively stratified by PI3K/Akt/mTOR pathway alterations, defined as PTEN loss and PIK3CA mutation. All patients received BEZ235 until progressive disease or unacceptable toxicity. The primary endpoint was the progression-free survival (PFS) rate at 16 weeks. This study was, however, closed prematurely because BEZ235 was withdrawn from further development.

Results

A total of 20 patients (18 without and two with PI3K/Akt/mTOR alterations) were enrolled and received BEZ235. One partial response (5%) and two cases of stable disease (10%) were observed, all in patients without PI3K/mTOR pathway alterations. The PFS rate at 8 and 16 weeks was 15 and 10%, respectively; the median (range) PFS was 62 (38–588) days (95% confidence interval [CI] 53–110); and the median (range) overall survival was 127 (41–734) days (95% CI 58–309). Among the 90% of patients who experienced drug-related adverse events of any grade, 50% experienced grade 3–4 adverse events, including stomatitis (15%), fatigue (5%), nausea (5%), diarrhoea (5%), renal failure (5%), cutaneous rash (5%), hepatotoxicity (5%) and hypertension (5%).

Conclusion

BEZ235 showed modest clinical activity and an unfavourable toxicity profile in patients with advanced and pretreated TCC; however, a minority of patients experienced a clinical benefit, suggesting that a complete blockade of the PI3K/mTOR axis could improve outcome in some specific patients. Furthermore, this study showed that molecular stratification of patients for personalized medicine before treatment is feasible.

Keywords

BEZ235, PI3K inhibitor, mTOR inhibitor, transitional cell carcinoma

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Introduction

Urothelial carcinoma, also known as TCC, is a common malignancy with >350 000 newly diagnosed cases and ~150 000 deaths each year worldwide [1]. Metastatic TCC has a poor prognosis, with a median survival that does not exceed 15 months [2]. Therapeutic options are limited and cisplatin-based chemotherapy is the only treatment that improves survival in the first-line setting; however, resistance occurs rapidly and second-line chemotherapy trials have unfortunately yielded discouraging results, with response rates of ~10–30%, progression-free survival (PFS) of between 2 and 3 months and a median survival of only 6–9 months [3–13]. In the last few decades, innovative targeted agents have been evaluated in clinical trials, but have also only resulted in modest anti-tumour activity [14–24].

The mammalian target of rapamycin (mTOR) protein plays a key role in cell growth, proliferation, survival and angiogenesis. mTOR exists as two distinct complexes, mTORC1 and mTORC2. After activation of growth factor receptors, phosphoinositol 3-kinase (PI3K) activates through phosphorylation Akt. To be fully active, Akt requires a second phosphorylation by mTORC2; it is then able to stimulate the rapamycin-sensitive complex mTORC1 as well as multiple mTORC1-independent survival processes. This PI3K/Akt/mTORC1 cascade is regulated by different mechanisms: the phosphatase PTEN antagonizes the PI3K activity, and a negative regulatory feedback loop exists between mTORC1 and PI3K [25,26].

The PI3K/Akt/mTOR pathway is frequently altered in TCC [27], providing the rationale to target this pathway as an anti-cancer technique. Among the most frequent anomalies are reduced PTEN expression, observed in up to 50% of TCCs, and an activating mutation of the *PIK3CA* gene encoding the catalytic subunit of PI3K, reported in 25% of TCCs [28,29]. Interestingly, several preclinical experiments showed that PTEN-deficient tumours and/or *PIK3CA* mutated tumours have enhanced sensitivity to mTOR inhibitors as a result of sustained activation of PI3K/Akt signalling [30,31].

Previously, in a phase II trial in patients with metastatic TCC who had failed platinum, we evaluated the antitumoural efficacy of everolimus, a rampamycin derivative and allosteric oral mTORC1 inhibitor. Among the 37 enrolled patients, everolimus showed modest anti-tumour efficacy with a partial response rate of 5%, and a stable disease rate of 22%. The median progression-free survival (PFS) and overall survival (OS) were only 61 and 101 days, respectively [32]. Based on a retrospective observation that a loss of PTEN expression was seen only in patients resistant to everolimus, we showed *in vitro* and *in vivo* that PTEN loss could facilitate rapamycin-induced Akt activation, resulting in the stimulation of survival pathways and the development of rapamycin resistance. Furthermore, we showed that the addition of a PI3K inhibitor restored the sensitivity to rapamycin [33].

BEZ235 (Novartis, Cambridge, Massachusetts, United States of America) is a pan-class I PI3K inhibitor which targets the kinase activity of PI3K by competing with ATP for binding. BEZ235 also binds to the catalytic site of mTOR, inhibiting both mTORC1 and mTORC2 kinases [34]. In the present paper, we report the results of a phase II study evaluating the safety and activity of BEZ235 in patients with locally advanced or metastatic TCC and disease progression after platinum-based chemotherapy.

Patients and Methods

Eligibility

Eligible patients were required to have histologically or cytologically confirmed locally advanced or metastatic TCC, documented progression after first-line platinum-based chemotherapy (in the neoadjuvant/adjuvant setting or for distant metastases), disease not amenable to curative treatment, at least one measurable lesion according to the Response Evaluation Criteria In Solid Tumors (RECIST) 1.1, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1. An interval of at least 4 weeks since the last cytotoxic chemotherapy, biological therapy, surgery or radiotherapy was required. Patients were required to have an absolute neutrophil count >1 500/μL, haemoglobin >9 g/dL, platelet count >100 000/μL, serum creatinine <1.5 × the upper limit of normal (ULN), total bilirubin <1.5 × ULN, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <2.5 × ULN, fasting cholesterol <300 mg/dL and fasting triglycerides <2.5 × ULN.

Patients were excluded if they had received more than two systemic treatments for their metastatic disease or previous treatment with mTOR inhibitors. Patients were also ineligible if they had significant cardiovascular disease, active infection, known CNS metastases, autoimmune disease, or other malignancies within the previous 5 years, excluding adequately treated carcinoma *in situ* of the cervix, or basal or squamous cell skin cancer. The translational and clinical parts of the study were approved by an independent ethics committee and the Belgian health authority in accordance with European regulations, and conducted in accordance with the Declaration of Helsinki (October 2000).

Study Design

This was an open-label, multicentre, single-arm phase II study. Patients were prospectively stratified into two groups according to PI3K/Akt/mTOR pathway activation (loss of PTEN expression and/or *PIK3CA* activation vs no loss of PTEN expression and no *PIK3CA* activation). Patients

received BEZ235 monotherapy continuously until progressive disease or unacceptable toxicity.

Patients who received at least one dose of study medication were evaluable for the toxicity and safety profile. Baseline evaluation was carried out <2 weeks before inclusion and included medical history, physical examination, electrocardiogram, and chest and abdominal CT. Laboratory tests included full blood count, creatinine, total protein, albumin, bilirubin, AST and ALT, lactate dehydrogenase, alkaline phosphatase, serum-corrected calcium, fasting glucose, triglycerides and cholesterol. Imaging was repeated every 8 weeks and centrally reviewed. Adverse events were monitored throughout the study and recorded according to the National Cancer Institute Common Toxicity Criteria (version 3).

Treatment Administration

BEZ235 was administered orally and continuously at a starting dose of 300 mg twice daily. Although it was not a dose-escalation study, at day 15, based on a clinical evaluation of adverse events, the dose was adjusted for the rest of study. In the event of an adverse event ≤grade 1, the dose was increased to 400 mg twice daily; for any grade 2 adverse events, patients continued at 300 mg twice daily; and for adverse events ≥grade 3, BEZ235 was interrupted until resolution and then reintroduced at 200 mg twice daily.

PTEN Status and *PIK3CA* Mutation

Once a patient was deemed eligible, the most recent paraffin-embedded tumour tissue specimen was sent to a centralized and certified laboratory (Institute of Pathology and Genetics, Gosselies, Belgium) to assess PTEN expression and *PIK3CA* mutation for stratification purposes.

PTEN immunochemistry was assessed by a PTEN monoclonal antibody (#9559; Cell Signaling, Danvers, MA, USA). Detection was carried out using a secondary horseradish peroxydase antibody. Staining intensity was defined as weak, intermediate or strong. The staining score was calculated based on the percentage of stained cells (%) with the formula (% weak ×2% intermediate ×3% strong). There was no loss of PTEN expression if at least 10% of the cells were weakly positive [35].

DNA was extracted from paraffin-embedded tumour tissue sections (Maxwell 16 FFPE Tissue LEV DNA Purification kit; Promega, Madision, WI, USA). Exons 9 and 21 of PIK3CA were amplified with forward primers GACAAAGAACA GCTCAAAGCA and AGCAAGAGGCTTTGGAGTA and reverse primers CACTTACCTGTGACTCCATAGAA and TTGTGTGGAAGATCCAATCCA, respectively (10 μM each). After a denaturation step at 95 °C for 5 min, 50 cycles were performed (denaturation at 95 °C for 15 s), annealing at 56 °C for 20 s and elongation for 15 s at 72 °C). Amplification products were purified (ExoSAP-it PCR Clean-up Kit; GE Healthcare, Little Chalfont, UK). Mutation identification was performed by dideoxy single base extension and termination of oligonucleotides in the presence of fluorescently labelled ddNTPs and DNA Polymerase (SNaPshot Multiplex System; Life Technologies, Waltham, MA, USA). Oligonucleotides for the detection of mutation at positions E542, E545 and H1047 were (T15)-TACACGAGA TCCTCTCTCT, (T25)-TCCTCTCTCTGAAATCACT and (T40)-TGAAACAAATGCCTGATGCAC, respectively. Fluorescent fragments were analysed by capillary electrophoresis on an ABI3130 (Applied Biosytems, Foster City, CA, USA).

Statistical Methods

Initially, the primary objective of the present study was to evaluate the efficacy of BEZ235 in terms of the rate of PFS at 16 weeks in patients with advanced or metastatic TCC previously treated with platinum-based therapy, with and without PI3K/Akt/mTOR pathway activation. Using a modified Simon Minimax two-stage testing procedure, the sample size required for the first step of this study was estimated to be 38 patients, or 19 per stratification group. This estimation was based on the following hypothesis: $P0 = 0.20$, $P1 = 0.40$, $\alpha = 0.1$ and $\beta = 0.1$. Patient characteristics, disease and treatment information were summarized using descriptive statistics (median and range for continuous variables, frequencies and percentages for categorical variables); however, after Novartis' decision to cease development of BEZ235, the study design had to be reviewed. The two groups according to the PI3K/Akt/mTOR pathway activation were merged, and the reported results are mainly descriptive.

The PFS rate was defined as the proportion of patients alive and progression-free at 16 weeks. Patients who did not progress were considered as having stable disease, a partial response or a complete response at 16 weeks, according to RECIST 1.1. Patients who were unable to be evaluated at 16 weeks, because of rapid clinical deterioration or death from any cause, or the start of an additional anti-tumour therapy, were considered as having progressive disease.

The definition used for PFS was the time interval between the date of inclusion and the date of progressive disease or death from any cause. If the patient did not meet the event (i.e. those lost to follow-up or those who had not relapsed or died), the survival time was censored on the date of last follow-up. OS was defined as the time interval between the date of inclusion and the date of death. If the patient did not die, the survival time was censored on the last date the patient was known to be alive, corresponding to the date of last follow-up. PFS and OS are summarized using

Kaplan–Meier curves. The median Kaplan–Meier estimate of PFS and OS are presented with 95% CIs, minimum and maximum.

Results

Patient Characteristics

Between March 2013 and October 2013, 20 patients from 10 centres were included. All patients had locally advanced or metastatic TCC and were previously exposed to platinum-based chemotherapy in the (neo)adjuvant and/or metastatic setting. The median (range) patient age was 66.5 (41–78) years, and the baseline ECOG performance status was 0 for 10 patients (50%) and 1 for 10 patients (50%).

Out of the 20 patients, only two exhibited PI3K/Akt/mTOR pathway activation, both having PTEN loss of expression. No patients had *PIK3CA*-activating mutations. Based on the validated adverse risk factors for prognosis (ECOG status >0, haemoglobin <10 g/dL and liver metastases) [36], patients were organised into four risk groups according to the number of risk factors present (none, one, two or three). Baseline characteristics are described in Table 1. The CONSORT diagram is shown in Fig. 1.

Table 1 Baseline characteristics of patients.

Male/female, *n*	17/3
Median (range) age, years	66.5 (41–78)
ECOG performance status, *n* (%)	
0	10 (50)
1	10 (50)
Tumour differentiation grade at diagnosis, *n* (%)	
Good	1 (5)
Moderate	6 (30)
Poor	11 (55)
Unknown	2 (10)
Primary tumour, *n* (%)	
Bladder	12 (60)
Urothelial tract	8 (40)
Platinum-based chemotherapy, *n* (%)	
Adjuvant/neoadjuvant	17 (75)
Administered for metastatic disease	12 (60)
Platinum/gemcitabine regimen	18 (90)
MVAC regimen	2 (10)
One previous chemotherapy line for palliation	8 (40)
Two previous chemotherapy lines for palliation	5 (25)
Chemotherapy-free interval <6 months	16 (80)
Location of disease at inclusion, *n* (%)	
Non-visceral only (lymph nodes, bones, . . .)	7 (35)
Visceral (liver and lung)	13 (65)
Clinical stage at initial diagnosis (AJCC 2010), *n* (%)	
I	2 (10)
II	4 (20)
III	4 (20)
IV	9 (45)
Unknown	1 (5)
Metastatic site at inclusion, *n* (%)	
Lung	10 (50)
Liver	6 (30)
Lymph nodes	14 (70)
Bones	4 (20)
Other (bladder, ureter, kidney, spleen, prevesical)	5 (25)
Group risk factor according to Bellmunt et al.[36], *n* (%)	
0	8 (40)
1	5 (25)
2	6 (30)
3	1 (5)
Loss of PTEN expression, *n* (%)	2 (10)
PIK3CA mutation, *n* (%)	0 (0)

ECOG, Eastern Cooperative Oncology Group; AJCC, American Joint Cancer Classification; MVAC, methotrexate, vinblastine, adriamycin and cisplatin.

Toxicity and Adverse Events

In all, 18 patients (90%) experienced at least one drug-related adverse event (Table 2). Ten patients (50%) experienced drug-related grade 3–4 adverse events, including stomatitis (15%), fatigue (5%), nausea (5%), diarrhoea (5%), cutaneous disorder (5%), renal failure (5%), hepatotoxicity (5%) and hypertension (5%).

Of the 20 patients who started BEZ235 at 300 mg twice daily, only six were able to increase the dose to 400 mg twice daily at day 15. According to protocol, four remained on 300 mg twice daily because of grade 2 adverse events ($n = 2$) or following the investigator's decision ($n = 2$); four decreased to 200 mg twice daily because of grade 3 adverse events, and six stopped BEZ235 (two because of rapid progressive disease, three because of toxicity, and one patient by their own decision). During the study, treatment interruption and/or discontinuation occurred in 13 patients (65%) because of BEZ235-related adverse events. The reasons to definitively stop BEZ235 were as follows: progressive disease ($n = 13$, 65%), toxicity ($n = 6$, 30% including nausea [$n = 1$], diarrhoea [$n = 1$], stomatitis [$n = 2$], fatigue [$n = 1$] and liver toxicity [$n = 1$]), or patient refusal to continue ($n = 1$, 5%; Fig. 1).

Efficacy

Among the 20 treated patients, nine patients were deemed unevaluable by imaging at 8 weeks after discontinuing treatment for either rapid clinical deterioration ($n = 2$), adverse events related to BEZ235 ($n = 6$) or patient refusal ($n = 1$). Of the 20 patients, three patients, all harbouring no PI3K/Akt/mTOR pathway activation, were progression-free at 8 weeks and of these three patients, two were progression-free at 16 weeks, resulting in a PFS rate at 8 and 16 weeks of 15 and 10%, respectively. Overall best response, based on radiological evaluation only, was partial response for one patient (5%), stable disease for two patients (10%), and progressive disease for eight patients (40%). One of the two patients with stable disease experienced a minor response, with a maximum percentage reduction in the sum of the diameters of the target lesions of 26%. The median (range) PFS for all these 20 patients was 62 (38–588) days (95% CI 53–110) and the median (range) OS was 127 (41–734) days

Fig. 1 CONSORT diagram.

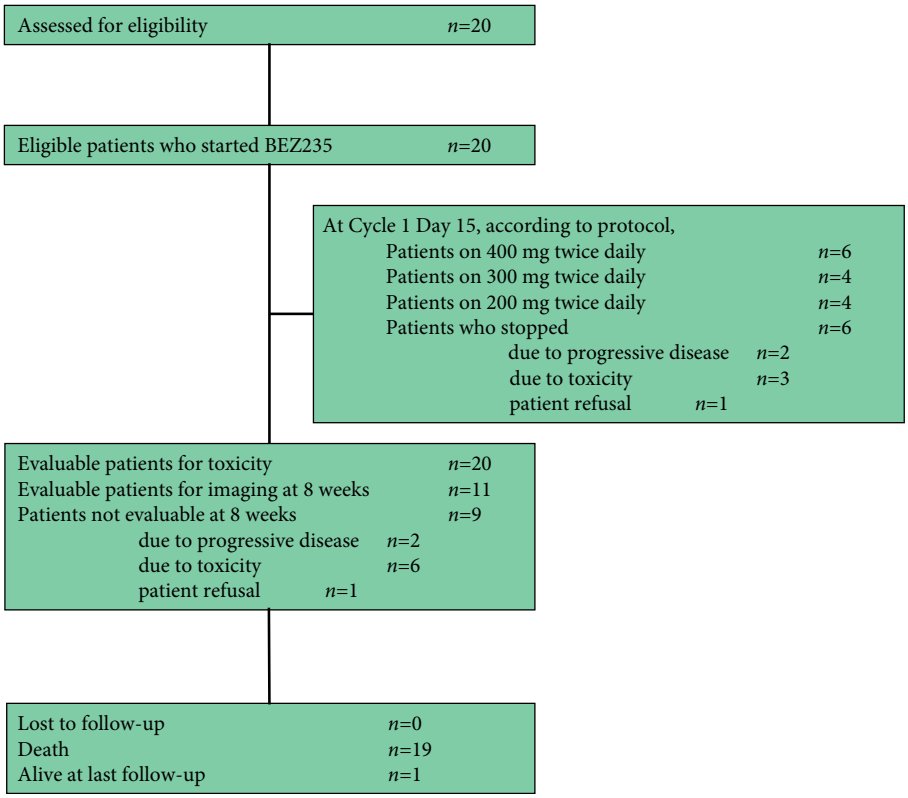


Table 2 Treatment-related adverse events.

Adverse event	Overall, *n* (%)	Grade 1–2, *n* (%)	Grade 3–4, *n* (%)
Fatigue	9 (45)	8 (40)	1 (5)
Nausea	7 (35)	6 (30)	1 (5)
Vomiting	4 (20)	4 (20)	0 (0)
Anorexia	6 (30)	6 (30)	0 (0)
Stomatitis	6 (30)	3 (15)	3 (15)
Diarrhoea	9 (45)	8 (40)	1 (5)
Hyperglycaemia	1 (5)	1 (5)	0 (0)
Rash/pruritus	8 (40)	7 (35)	1 (5)
Liver toxicity effects (ALT and AST)	1 (5)	0 (0)	1 (5)
Hypertension	2 (10)	1 (5)	1 (5)
Pyrosis/gastritis	3 (15)	3 (15)	0 (0)
Renal failure	2 (10)	1 (5)	1 (5)
Limb oedema	3 (15)	3 (15)	0 (0)
Confusion	2 (10)	2 (10)	0 (0)
Constipation	1 (5)	1 (5)	0 (0)
Fever	1 (5)	0 (0)	0 (0)
Malaise	1 (5)	0 (0)	0 (0)
Weight loss	4 (20)	4 (20)	0 (0)
Dry mouth	1 (5)	0 (0)	0 (0)

ALT, alanine transaminase; AST, aspartate transaminase.

(95% CI 58–309). At the time of manuscript submission, only one patient who had stable disease without minor regression was alive. The baseline characteristics of the three patients with either stable disease or partial response are described in Table 3. The maximum percentage reduction in the sum of target lesion diameters for assessable patients is described in Fig. 2.

Discussion

In the present paper, we report the results of a clinical trial evaluating a dual PI3K-mTOR kinase inhibitor in patients with advanced TCC after failure of platinum-based chemotherapy. Although the study was prematurely stopped, BEZ235 showed some anti-tumour activity in this patient population, with a median PFS and OS of 62 days and 127 days, respectively.

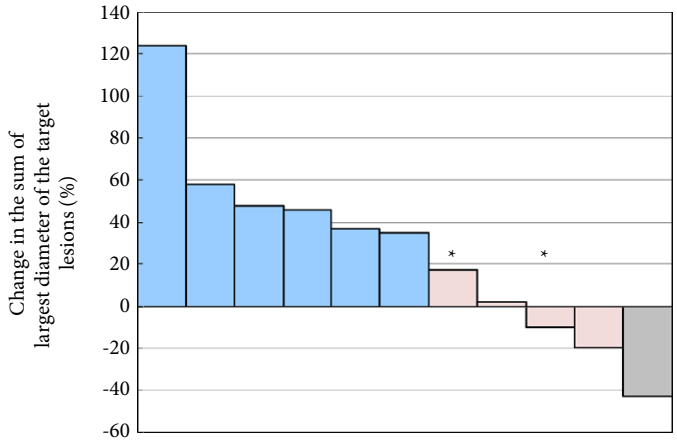
Among the 20 included patients, three achieved at least stable disease, including one partial response and one minor regression according to RECIST 1.1 criteria. These three patients had a long OS that may suggest that BEZ235 could have clinically relevant anti-tumoural activity in a minority of patients; however, because of the limited number of enrolled patients, it is difficult to firmly conclude that this prolonged survival is attributable to BEZ235 activity. Notably, one of these three patients, according to Bellmunt et al. [36], had poor prognostic factors, and two had aggressive disease with a chemotherapy-free interval of <6 months.

Table 3 Baseline characteristics of the 3 patients with either stable disease or partial response.

	Patient 1	Patient 2	Patient 3
Sex	Male	Male	Male
Age (years)	61	76	66
Initial diagnosis	Localised grade 3 bladder TCC 15 months prior to study enrollment	Localised grade 3 kidney TCC 15 months prior to study enrollment	Localised grade 3 bladder TCC 18 months prior to study enrollment
Initial treatment	Curative-intent neoadjuvant CG	Curative-intent adjuvant CG	Curative-intent neoadjuvant CG
Time interval between the curative intent surgery (cystectomy) and metastatic relapse	11 months	13 months	14 months
First-line palliative chemotherapy before study inclusion	Non-platinum chemotherapy (paclitaxel)	None	Non-platinum chemotherapy (paclitaxel)
Interval between the last chemotherapy (including platinum and non-platinum agent) administration and BEZ235 initiation	<6 months	12 months	<6 months
Prognosis group [36]	2 (ECOG 1, Hb<10 g/dl)	0	0
BEZ235 dose	400 mg	400 mg	200 mg
Reason for stopping treatment	Progressive disease	Progressive disease	Progressive disease
Maximum change in the sum of the largest diameters of the target lesions	−43%	−26%	+0.3%
PFS	193 days	116 days	131 days
OS	239 days	588 days	734 days
PI3K/Akt/mTOR pathway activation	No	No	No

CG, cisplatin/gemcitabine; mTOR, mammalian target of rapamycin; NE, not evaluable; OS, overall survival; PFS, progression-free survival; PI3K, phosphoinositol-3-kinase. As per guidelines, duration of response can only be calculated for patients whose best response was either a complete response or partial response.

Fig. 2 Waterfall plots showing the maximum percentage modification in the sum of the largest diameters of the 11 assessable patients. According to Response Evaluation Criteria In Solid Tumors 1.1, blue plots represent progressive disease, red plots represent stable disease, black plot represents partial response, and red plots* represent stable disease in target lesions but onset of new metastases.



To date, there is no established predictive biomarker associated with response to mTOR inhibitors or dual PI3K-mTOR kinase inhibitors. The initial purpose of the present study was to evaluate the efficacy of BEZ235 in patients prospectively stratified into two different molecular subgroups: patients with PI3K/Akt/mTOR activation, and patients without PI3K/Akt/mTOR activation. In this design, activation of the PI3K/Akt/mTOR pathway was determined as a loss of PTEN expression and/or *PIK3CA*-activating mutation. In our patient population, of the 20 included patients, only two (10%) were observed to have a loss of PTEN expression; no *PIK3CA*-activating mutation was detected. This frequency is low compared with previous reports [27–29,32] and may be explained by the limited number of enrolled patients in this small phase II trial, and the poorly standardized protocols for molecular screening among laboratories. These protocols vary in terms of choice of antibody, methods of tissue fixation, duration of incubation and scoring methods. There is also a large variability in interpretation and scoring of protein expression in terms of either intensity of staining or distribution/subcellular localization. Furthermore, PTEN expression and *PIK3CA* mutation were carried out on the primary tumours for the majority of patients, and not on metastases, resulting in potential bias. Because of the premature closure of the study and the limited number of patients in the group with PI3K/Akt/mTOR activation, it is impossible to compare the two groups; however, the present study showed that prospective molecular stratification of patients with advanced TCC is feasible.

The toxicity profile of BEZ235 was unfavourable: 90% of all patients experienced a drug-related adverse event, of which 50% were grade 3–4 adverse events. This toxicity resulted in a high rate of premature drug cessation and the inability of ~50% of patients to receive their day 15 per-protocol dose of at least 300 mg of BEZ235 twice daily, which was recommended in the phase I study [37]. Whether the inability of half of our patients to reach this dose is the reason behind BEZ235's modest anti-cancer activity remains to be determined. This unfavourable toxicity profile also

reflects the challenge associated with the development of newer drugs in TCC. This patient population is known to have multiple comorbidities and, after having received multiple previous lines of cytotoxic treatment, is especially vulnerable. There is an urgent need to improve study design and adapt inclusion criteria in order to avoid the risk of increased toxicity in this heavily pretreated and frail population.

Although direct comparison between different phase II trials is difficult, complete blockade of the PI3K/Akt/mTOR pathway does not seem to be more efficient than allosteric mTORC1 inhibition in terms of clinical activity in patients with advanced TCC after failure of platinum-based chemotherapy [32]. Even if most of the patients treated in the present study had an ECOG performance status of 0 or 1 at inclusion, the rate of patients (45%) who did not reach the 8-week evaluation point, because of rapid clinical progression or toxicity, was high. This reflects the fragility of this heavily pretreated population of patients with an aggressive cancer. Moon et al. [38] recently showed that BEZ235 could synergistically potentiate cisplatin-mediated apoptosis and cell cycle arrest without any paradoxical Akt activation in cisplatin-resistant human bladder cancer cells, but that it had only modest activity as monotherapy in this same setting. Furthermore, large interpatient variability in pharmacokinetics was observed with BEZ235, probably resulting in infra-therapeutic dosing in some patients [39]. Different innovative agents are currently under evaluation in advanced TCC, including PI3K inhibitors (BKM-120, Novartis, Cambridge, MA, USA) and mTORC1-2 kinase inhibitors (AZD8055, AstraZeneca, Alderley Park, UK), and the results are awaited. The outcomes of these studies may assist in determining the benefit of inhibiting different targets belonging to the same signalling pathway.

In conclusion, we found limited activity of BEZ235 in our population of patients with advanced TCC who had failed platinum-based chemotherapy. This study showed that molecular stratification of patients for personalized medicine before treatment is feasible.

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Conflict of Interest

Jean-Pascal Machiels has received research grants from Novartis, Janssen and Bayer. The remaining authors have no conflicts of interest to declare.

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Abbreviations: PI3K, phosphoinositol-3-kinase; mTOR, mammalian target of rapamycin; PFS, progression-free survival; OS, overall survival; ECOG, Eastern Cooperative Oncology Group; RECIST, Response Evaluation Criteria In Solid Tumors; ULN, upper limit of normal; ALT, alanine transaminase; AST, aspartate transaminase.