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Inhibition of hypoxia-inducible factor-2α in renal cell carcinoma with belzutifan: a phase 1 trial and biomarker analysis

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Author contributions

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Abstract

Hypoxia-inducible factor-2α (HIF-2α) is a transcription factor that frequently accumulates in clear cell renal cell carcinoma (ccRCC), resulting in constitutive activation of genes involved in carcinogenesis. Belzutifan (MK-6482, previously known as PT2977) is a potent, selective small molecule inhibitor of HIF-2α. Maximum tolerated dose, safety, pharmacokinetics, pharmacodynamics and anti-tumor activity of belzutifan were evaluated in this first-in-human phase 1 study (NCT02974738). Patients had advanced solid tumors (dose-escalation cohort) or previously treated advanced ccRCC (dose-expansion cohort). Belzutifan was administered orally using a 3 + 3 dose-escalation design, followed by expansion at the recommended phase 2 dose (RP2D) in patients with ccRCC. In the dose-escalation cohort ($n = 43$), no dose-limiting toxicities occurred at doses up to 160 mg once daily, and the maximum tolerated dose was not reached; the RP2D was 120 mg once daily. Plasma erythropoietin reductions were observed at all doses; erythropoietin concentrations correlated with plasma concentrations of belzutifan. In patients with ccRCC who received 120 mg once daily ($n = 55$), the confirmed objective response rate was 25% (all partial responses), and the median progression-free survival was 14.5 months. The most common grade ≥3 adverse events were anemia (27%) and hypoxia (16%). Belzutifan was well tolerated and demonstrated preliminary anti-tumor activity in heavily pre-treated patients, suggesting that HIF-2α inhibition might offer an effective treatment for ccRCC.

Improved understanding of the molecular biology of renal cell carcinoma (RCC) has resulted in substantial developments in treatment options. A crucial advancement in the understanding of ccRCC is the implication of the von Hippel–Lindau (*VHL*) gene in carcinogenesis, which, in turn, highlights the potential value of targeting the associated hypoxia response pathway[1].

The *VHL* gene is lost in approximately 90% of ccRCC tumors[2]. The VHL protein (pVHL) has multiple functions, but the role most directly associated with ccRCC carcinogenesis is its function as a subunit of the E3 ubiquitin ligase complex, which mediates the proteasomal degradation of HIF-2α[3,4]. Under hypoxic conditions, HIF-2α heterodimerizes with aryl hydrocarbon receptor nuclear translocator (ARNT, also known as hypoxia-inducible factor-1β) to form an active transcription factor (hypoxia-inducible factor 1) that upregulates expression of hypoxia-inducible genes, such as vascular endothelial growth factor (*VEGF*) and erythropoietin, to counteract hypoxia and increase oxygenation[5]. Under normal conditions, oxygen-dependent post-translational modifications on HIF-2α allow pVHL to recognize and target HIF-2α for rapid degradation. Loss of pVHL function in ccRCC is associated with a pseudohypoxic state, accumulation of HIF-2α and upregulation of downstream genes[6,7]. HIF-2α, therefore, presents a promising target for the treatment of tumors associated with pVHL dysfunction, such as ccRCC.

The oxygen-sensitive HIF-2α subunit and the ARNT subunit belong to the Per-ARNT-Sim (PAS) family and contain the PAS-A and PAS-B ligand-binding domains[8]. Identification of the PAS-B domain prompted the development of synthetic small molecules that occupy the pocket, which caused marked conformational changes that disrupt HIF-2α and

ARNT dimerization[8–10]. Therefore, drugs occupying this pocket disrupt HIF-2α/ARNT heterodimerization and, in turn, could inhibit HIF-2α target gene expression[8–10].

Initial investigation of HIF-2α inhibitors, such as MK-3795 (previously known as PT2385), in pre-clinical studies demonstrated promising results. MK-3795 strongly inhibited expression of HIF-2α–dependent genes in ccRCC cell lines and was associated with significant tumor regression in xenograft models[11]. A first-in-human dose-escalation and dose-expansion study investigating MK-3795 in 51 patients with heavily pre-treated ccRCC reported favorable safety and activity[9]. Subsequently, a more potent and selective second-generation small molecule HIF-2α inhibitor, belzutifan (MK-6482, previously known as PT2977), was developed. Belzutifan was approximately ten-fold more potent than MK-3795 in mouse xenograft models[7].

The objective of this study was to identify the maximum tolerated dose of belzutifan and evaluate the safety, pharmacokinetics, pharmacodynamics and anti-tumor activity of belzutifan in patients with advanced solid tumors, including ccRCC.

Results

Ninety-five patients were enrolled: 43 in the dose-escalation cohort and 52 in the dose-expansion cohort. The ccRCC cohort comprised 55 patients with RCC treated at the RP2D (n = 3 in the dose-escalation cohort and n = 52 in the dose-expansion cohort) (Extended Data Fig. 1).

Patient characteristics.

The median age of all patients in the dose-escalation cohort was 63 years (range, 27–84 years). Most patients (65%) were male and 98% had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 (Table 1). The most common cancers were renal (n = 22, 51%), brain (n = 5, 12%) and other (n = 7, 16%). The median number of previous treatments for all patients was three (range, 0–12).

In the ccRCC cohort, the median age was 62 years (range, 39–75 years), and most patients were male (n = 44; 80%), had an ECOG performance status score of 1 (n = 34, 62%) and were considered at intermediate/poor risk by International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria (n = 42, 76%) (Table 1). Patients previously received a median of three treatments; 50 patients (91%) received anti-VEGF agents; 44 patients (80%) received a checkpoint inhibitor; and 13 patients (24%) received a mammalian target of rapamycin (mTOR) inhibitor. Thirty-nine patients (71%) received both anti-programmed death 1 and anti-VEGF agents. Median follow-up, defined as the date from the first dose to the database cutoff date of June 1, 2020, was 27.7 months (range, 24.8–34.3 months). Treatment was ongoing for 11 patients (20%); the most common reason for treatment discontinuation was progressive disease (n = 33, 60%).

Pharmacokinetics and pharmacodynamics.

Pharmacokinetics and pharmacodynamics were assessed by dose cohort, including patients from both the dose-escalation and the dose-expansion cohorts (n = 95). Exposure to

belzutifan increased with dose (Supplementary Table 2), and area under the concentration curve from time 0 to the end of the dosing period increased over the dose range of 20–120 mg once daily but remained similar over the dose range of 120–240 mg once daily. Dose-normalized area under the concentration curve from time 0 to the end of the dosing period increased with dose from 20 to 120 mg but decreased from 120 to 240 mg once daily. Maximum concentration increased 38% in the 240-mg once-daily cohort compared to the 120-mg once-daily expansion cohort. Median plasma terminal half-life was 11.2–21.5 h, and median time to maximum observed plasma concentration was 1.0–2.0 h across dose levels. Moderate accumulation was observed with a mean accumulation ratio of 1.3–1.5 with once-daily dosing and 2.4 for 120-mg twice-daily dosing. Plasma concentrations of belzutifan and PT3317 by dose cohort over time are shown in Extended Data Figs. 2 and 3, respectively.

Reductions in plasma erythropoietin were observed at all dose levels (Extended Data Fig. 4), and plasma erythropoietin concentrations were significantly correlated with plasma concentrations of belzutifan. Decreases in erythropoietin concentrations from baseline were similar at doses of ≥120 mg once daily.

Safety.

No dose-limiting toxicities were observed in the dose-escalation cohort at doses up to 160 mg once daily. Treatment-related dose-limiting toxicities occurred in one of seven patients (14%) at 240 mg orally (grade 4 thrombocytopenia) and one of six patients (17%) at 120 mg twice daily (grade 3 hypoxia). The maximum tolerated dose was not reached. At data cutoff, treatment had been discontinued in 36 patients (84%). Treatment-emergent adverse events of any grade occurred in 42 of 43 patients (98%) and were considered treatment related in 31 of 43 patients (72%). Grade ≥3 treatment-related adverse events occurred in eight of 43 patients (19%) across dose levels. No patients died of treatment-related adverse events. Based on safety, pharmacokinetics and pharmacodynamics in the dose-escalation cohort, 120 mg once daily was selected as the RP2D.

All patients in the ccRCC cohort experienced at least one adverse event (Table 2). The most common all-grade adverse events were anemia (n = 42, 76%), fatigue (n = 39, 71%), dyspnea (n = 27; 49%) and nausea (n = 20, 36%). The most common grade ≥3 treatment-emergent adverse events were anemia (n = 15, 27%) and hypoxia (n = 9, 16%); all were grade 3 (Table 2). The median (range) time to the first grade ≥3 treatment-emergent adverse event was 1.8 months (range, 0.03–30.0 months). Of 42 patients with anemia, 28 (67%) received exogenous erythropoietin, and 15 (36%) underwent blood transfusion. No patients required dose reductions or discontinuations for anemia. Of the 17 patients with hypoxia, 11 (65%) received supplemental oxygen. Four other patients required supplemental oxygen because of dyspnea (n = 2), pneumonitis (n = 1) and sepsis (n = 1). Hypoxia usually resolved with supplemental oxygen therapy; six patients required a dose interruption, two patients required a dose reduction, and two patients discontinued treatment. Two patients experienced four grade 4 adverse events (sepsis (n = 2), hypercalcemia (n = 1), respiratory failure (n = 1)), and four patients experienced grade 5 adverse events (disease progression (n = 1), malignant neoplasm progression (n = 1), acute kidney injury (n = 1) and cardiac arrest

(*n* = 1)). Treatment-related adverse events occurred in 53 patients (96%); the most common (≥15%) were anemia (*n* = 39, 71%), fatigue (*n* = 31, 56%), dyspnea (*n* = 11, 20%), hypoxia (*n* = 10, 18%), peripheral edema (*n* = 9, 16%) and nausea (*n* = 8, 15%). Five patients (9%) required dose reductions because of treatment-related adverse events (depressed level of consciousness (*n* = 1), headache (*n* = 1), hypoxia (*n* = 2) and fatigue (*n* = 1)). Two patients (4%) discontinued belzutifan after treatment-related adverse events (both hypoxia). No treatment-related grade 4 or 5 events occurred.

Anti-tumor activity.

In the dose-escalation cohorts, responses (all partial) were observed in one of six patients (17%) at 120 mg once daily, two of six patients (33%) at 160 mg once daily, two of seven patients (29%) at 240 mg once daily and one of six patients (17%) at 120 mg twice daily. Median duration of response was not reached in any dose cohort in any patient who had a response. Five responses occurred in patients with RCC, and one response occurred in a patient with anaplastic ependymoma.

All 55 patients in the ccRCC cohort were evaluable for efficacy. The objective response rate was 25% (Table 3); all were partial responses. Thirty patients (54%) experienced a best response of stable disease, providing a disease control rate of 80% (Table 3). In 35 of 52 patients (67%) with baseline and post-baseline imaging assessments, target lesion size was reduced from baseline (Fig. 1a). Nineteen patients (35%) were treated with belzutifan beyond 12 months (Fig. 1b). Median duration of response was not reached; in ten of 14 responders (71%), duration of response was ≥6 months. Median progression-free survival was 14.5 months (95% confidence interval (CI), 7.3–not reached) (Fig. 1c). For patients with IMDC favorable (*n* = 13) and intermediate/poor (*n* = 42) risk, the objective response rate was 31% and 24%, respectively. Median progression-free survival was not reached and 11.0 months for patients with IMDC favorable and intermediate/poor risk, respectively.

Discussion

VHL loss of function, and the associated accumulation of HIF-2α, is an established oncogeneic event in ccRCC[6,7]. Targeting HIF-2α has emerged as a potential therapeutic strategy for ccRCC, and a previous phase 1 study in advanced ccRCC showed that the HIF-2α inhibitor MK-3795 was well tolerated, with some anti-tumor activity[9]. It was also observed that higher MK-3795 exposure was associated with longer progression-free survival, and a more potent and selective second-generation belzutifan was developed to overcome the pharmacokinetic limitations of MK-3795 (refs. [7,9]).

In this study, belzutifan had promising anti-tumor activity and was well tolerated. The maximum tolerated dose was not reached, and the RP2D of 120 mg once daily was determined based on pharmacokinetics, pharmacodynamics and safety. Furthermore, a previous study found that exposure to belzutifan increased with doses up to 120 mg once daily, although doses higher than 120 mg once daily did not provide markedly increased exposure[7]. Moreover, there was a reduction in erythropoietin with belzutifan at 120 mg once daily that was similar to the level of reduction in patients with high exposure to MK-3795. In this study, reductions in erythropoietin concentrations from baseline were similar across

doses ≥120 mg once daily, which further supports the RP2D dose of 120 mg once daily. With a median follow-up of 27.7 months in this study, the objective response rate was 25% and the disease control rate was 80% in patients with heavily pre-treated ccRCC treated at doses of 120 mg once daily. Median duration of response was not reached, and responses persisted for at least 6 months in 71% of responders. Median progression-free survival was 14.5 months. These results are especially notable given the heavily pre-treated population: 62% had previously received ≥3 therapies, and 91% experienced disease progression on previous anti-VEGF treatments.

Belzutifan had a distinct toxicity profile compared to that of other drugs used in a second-line setting for ccRCC; other profiles include cardiovascular or gastrointestinal adverse events associated with anti-VEGF agents and immune-related adverse events associated with checkpoint inhibitors[12,13]. Belzutifan was not associated with cardiovascular adverse events such as hypertension or other adverse events typical of the anti-VEGF class of agents[11]. In the dose-expansion cohort, the most common grade 3 adverse events in patients receiving belzutifan were hypoxia and the on-target adverse event of anemia. HIF-2α upregulates expression of genes encoding erythropoietin[14,15], and belzutifan produces rapid, pronounced decreases in erythropoietin, which can result in the development of anemia. In this study, anemia was well managed with erythropoietin replacement, and no patients required dose reductions or discontinuations because of anemia. Hypoxia, detected by pulse oximetry monitoring, likely occurs because HIF-2α inhibition impairs the pulmonary arterial vasoconstrictive response to ventilation/perfusion mismatch[16]. All but five hypoxia cases reported in this study were triggered by an acute event (for example, pneumonia or pleural effusion). Fifteen patients received supplemental oxygen and responded; most cases resolved with drug interruption.

The current study was limited by its open-label, single-arm design. However, the objective response rate (25%) and disease control rate (80%) observed in the ccRCC cohort of this study served as the rationale to evaluate belzutifan monotherapy compared to everolimus in an ongoing phase 3 trial of previously treated patients with advanced ccRCC (NCT04195750).

In conclusion, belzutifan had a favorable safety profile and showed promising anti-tumor activity in heavily pre-treated patients with ccRCC. This study validates the growing pre-clinical and clinical evidence that HIF-2α inhibition might offer an effective and well-tolerated treatment for patients with advanced ccRCC[9,17,18]. Additionally, belzutifan demonstrates anti-tumor activity by targeting the underlying pathophysiology of ccRCC, which makes it an attractive agent for future combinations.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-021-01324-7.

Methods

Trial oversight.

This ongoing study was designed by sponsor representatives and with academic advisors. The protocol and its amendments were approved by the appropriate institutional review board or independent ethics committee at each center: Integreview, WIRB, the University of Texas MD Anderson Center, Dana-Farber Cancer Institute, the University of Miami and Wake Forest University Health Sciences. The trial was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written informed consent. Data were collected by study investigators and site personnel. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication. The authors vouch for the completeness and accuracy of the reported data and attest that the trial was conducted per protocol.

Patients.

This first-in-human phase 1 study (NCT02974738) enrolled patients from seven centers (hospitals and cancer centers) between December 14, 2016, and September 19, 2018. The data cutoff for this report was June 1, 2020. Eligible patients were aged ≥18 years and had a histologic or cytologic diagnosis of locally advanced or metastatic solid tumor (dose-escalation cohort) or locally advanced or metastatic RCC with predominantly clear cell subtype who had previously received one or more treatments for ccRCC (dose-expansion cohort). Additional inclusion criteria were measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) and ECOG performance status score of 0 or 1[19]. Complete eligibility criteria are available in the study protocol, provided in the Supplementary Material.

Study design and treatment.

This study was conducted in two parts: a dose-escalation phase in patients with advanced solid tumors and a dose-expansion phase in patients with previously treated advanced ccRCC. The primary objective was to identify the maximum tolerated dose and the RP2D of belzutifan. Secondary end points included safety, pharmacokinetics, pharmacodynamics and anti-tumor activity of belzutifan.

In the dose-escalation phase, patients with advanced solid tumors were enrolled to sequential dose cohorts (3–6 patients per cohort) using a standard 3 + 3 design[20]. The first cohort received oral belzutifan at 20 mg once daily. In each subsequent cohort, the dose level was increased by 100% until the occurrence of dose-limiting toxicities considered at least possibly related to study drug. Thereafter, dose levels were increased by ≤50% until the maximum tolerated dose was reached. At each dose level, patients completed ≥3 weeks of treatment before escalation to the next dose level. Dose-limiting toxicities were predefined grade 3 or 4 adverse events that occurred during the first 21 d of treatment and had no clear alternative explanation, such as being disease related (Supplementary Table 1).

In the dose-expansion cohort, patients with previously treated advanced ccRCC were treated with belzutifan at the RP2D. Patients could continue to receive belzutifan in the absence of

unacceptable treatment-related toxicity or unequivocal disease progression for up to 1 year at the investigator's discretion and beyond 1 year with the agreement of the investigator and the sponsor.

Assessments.

Safety was assessed throughout the study and included analysis of adverse events, laboratory parameters, vital signs and electrocardiograms. Adverse events were coded using Medical Dictionary for Regulatory Activities terminology, and severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 or later.

Blood samples for pharmacokinetic analyses were obtained 1 before and 0.5, 1, 1.5, 2, 4, 6, 8, 12 and 24 h after belzutifan administration at the week 1 and 3 visits and before belzutifan administration at the week 2, 4, 5, 7, 9, 13 and 17 visits. Blood samples for pharmacodynamic assessment were obtained 1 h before and 4 and 8 h after belzutifan administration at the week 1 and 3 visits and before belzutifan administration at the week 2, 4, 5, 7, 9, 13, 17, 25, 33, 41 and 49 visits. Plasma concentrations of belzutifan and its metabolite, PT3317, were determined using validated liquid chromatography/mass spectrometry methods. Pharmacokinetic parameters analyzed included plasma terminal half-life ($t_{½\lambda z}$), time to maximum observed plasma concentration (T_{max}), maximum observed plasma concentration (C_{max}), area under the plasma concentration–time curve (AUC) from 0 to last measurable concentration (AUC_{0-t}), AUC over the dose interval (0–24 h for once-daily dosing; 0–12 h for twice-daily dosing; AUC_{t}) computed, total AUC from time 0 to infinity ($AUC_{0-\infty}$), portion of $AUC_{0-\infty}$ extrapolated beyond the last quantifiable time point ($\%AUC_{0-\infty}$ extrapolated), apparent clearance (CL/F) where F is the fraction of the dose absorbed, apparent volume of distribution (Vz/F) and accumulation ratio (R_{ac}), calculated by AUC_t at steady state/AUC_t after the first dose.

Tumor imaging by computed tomography or magnetic resonance imaging was performed at baseline, within 7 d before the week 9 visit and every 8 weeks thereafter. The same technique was used for imaging at baseline and each follow-up assessment. Tumor response per RECIST v1.1 was assessed by the investigators.

Statistical analysis.

The full statistical analysis plan is available in the Supplemental Material. The sample size required for the dose-escalation phase was based on the need to establish the maximum tolerated dose (3–48 patients, depending on the specific dose level determined in the dose-escalation phase). After determination of the maximum tolerated dose, the RP2D or both, up to 50 additional patients with diagnoses of advanced ccRCC were enrolled in the dose-expansion cohort.

Safety was assessed in all patients who received one or more doses of belzutifan. Pharmacokinetics were assessed in all patients who received one or more doses of belzutifan and had evaluable belzutifan, its primary metabolite PT3317 or both. Pharmacodynamics were assessed in all patients who received one or more doses of belzutifan and had evaluable pharmacodynamic data. Anti-tumor activity was assessed in all patients who received one

or more doses of belzutifan and had disease assessments at baseline and one or more post-baseline time points or who discontinued before their first post-baseline assessment because of death or documented disease progression.

Pharmacokinetic parameters were calculated by non-compartmental analysis using Phoenix WinNonlin (Certara, v6.3 or later) software. Non-pharmacokinetic statistical analyses were done using SAS version 9.4. Safety, pharmacokinetics, pharmacodynamics and tumor response were summarized descriptively. Duration of response and progression-free survival were estimated using the Kaplan–Meier method. No imputation of values was performed for missing data.

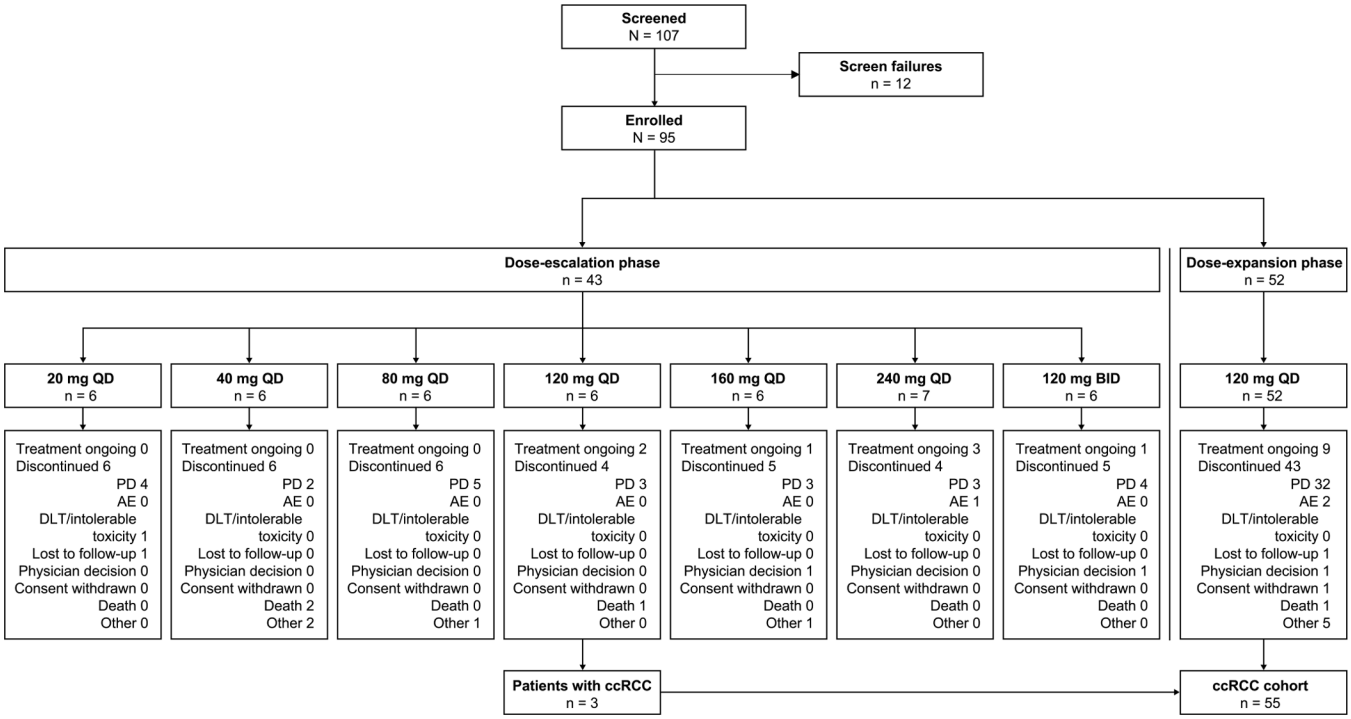
Reporting Summary.

Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

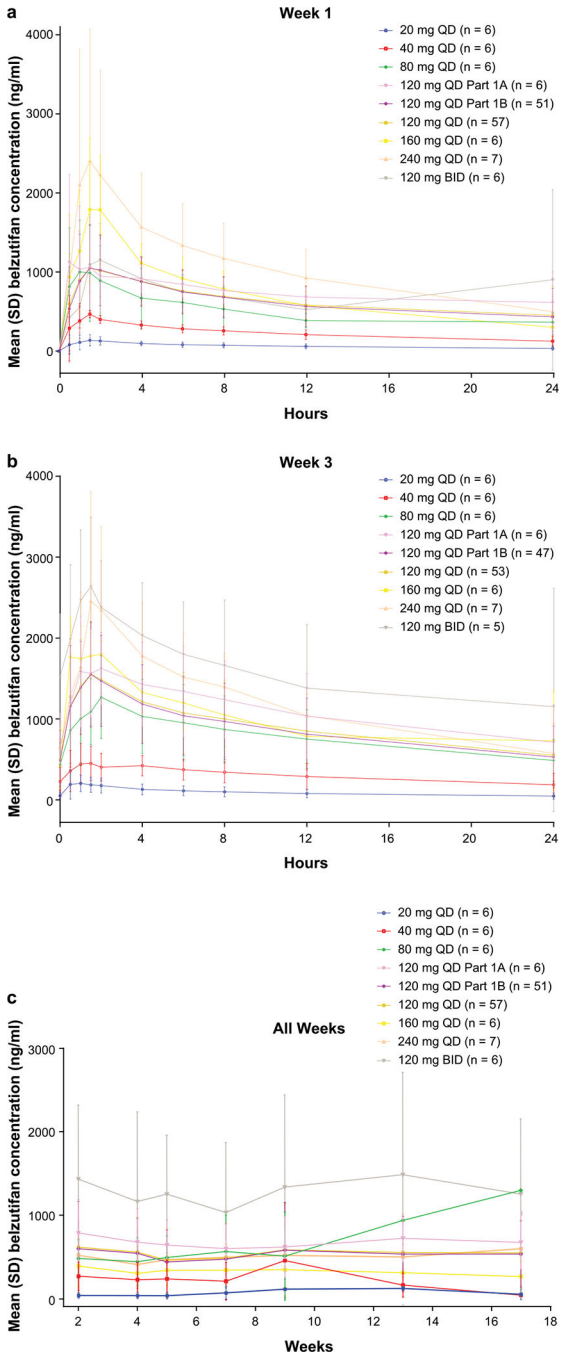
Merck Sharp & Dohme (MSD), a subsidiary of Merck & Co., Inc., is committed to providing qualified scientific researchers access to anonymized data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (available at http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the United States and European Union or after product development is discontinued. There are circumstances that might prevent MSD from sharing requested data, including country- or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data sharing agreement, MSD will either perform the proposed analyses and share the results with the requestor or will construct biomarker co-variates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

Extended Data



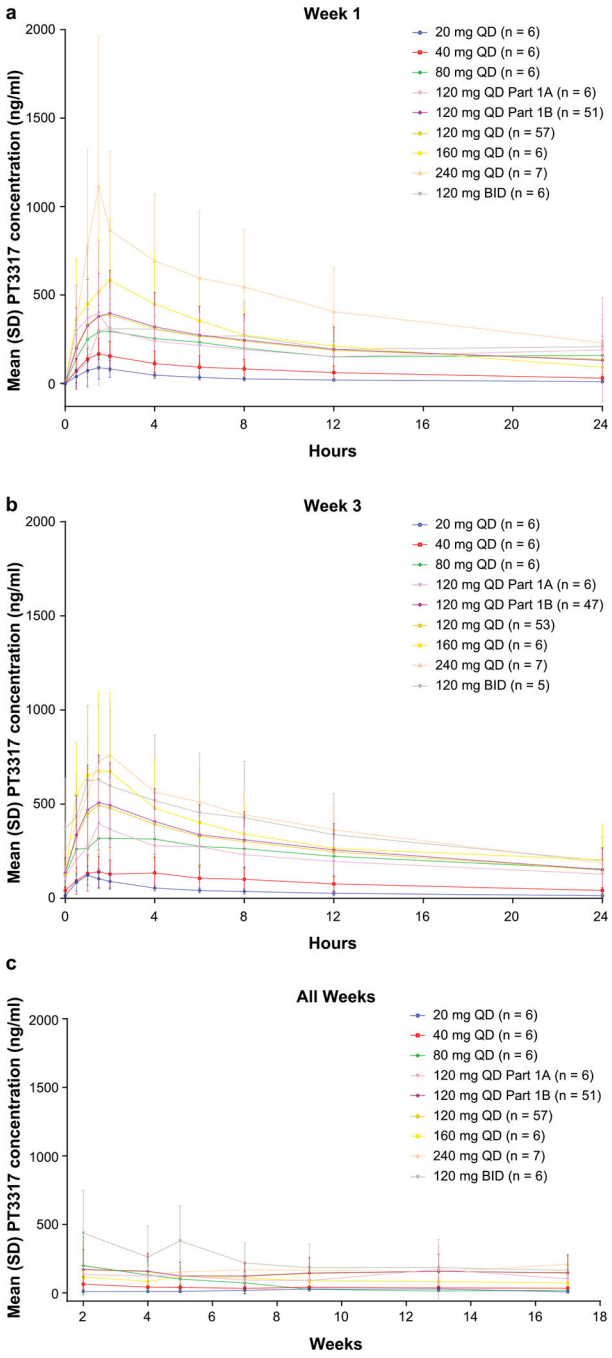
Extended Data Fig. 1 |. Patient disposition.

AE: adverse event; BID: twice daily; ccRCC: clear cell renal cell carcinoma; DLT: dose-limiting toxicity; QD: once daily; PD: progressive disease.



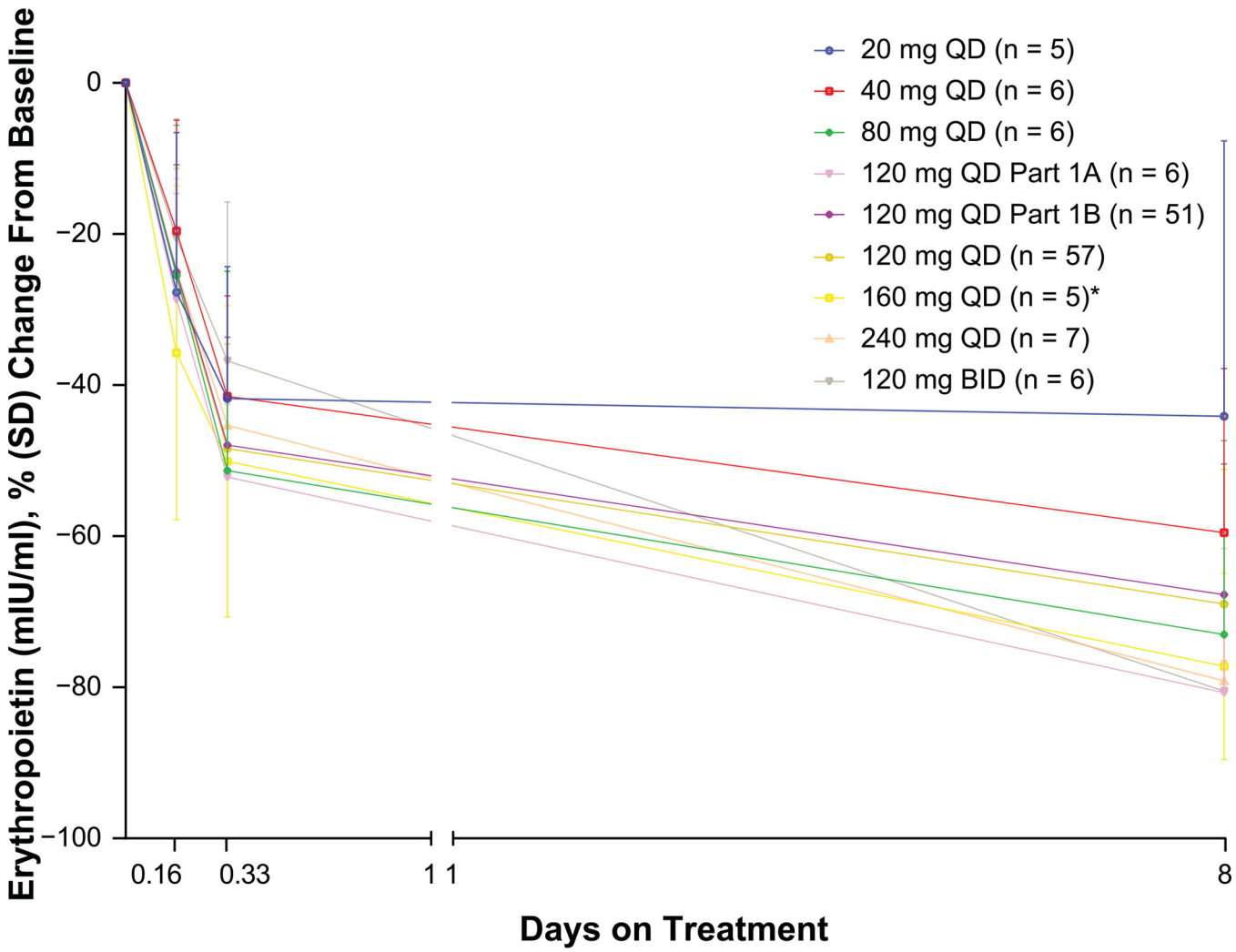
Extended Data Fig. 2 |. Mean (SD) plasma concentrations of belzutifan at (a) week 1, (b) week 3, and (c) all weeks.

BID: twice daily; QD: once daily; SD: standard deviation. n includes patients who had a predose assessment and at least one postdose assessment. Data are presented as mean values ± SD.



Extended Data Fig. 3 |. Mean (SD) plasma concentrations of PT3317 at (a) week 1, (b) week 3, and (c) all weeks.

BID: twice daily; QD: once daily; SD: standard deviation. n includes patients who had a predose assessment and at least one postdose assessment. Data are presented as mean values ± SD.



Extended Data Fig. 4 |. Mean (SD) percentage change in erythropoietin (mIu/ml) from baseline for the first 8 days.

BID: twice daily; QD: once daily; SD: standard deviation. n includes patients who had a predose assessment and at least one postdose assessment. *Erythropoietin concentration from baseline for the 160-mg QD dose cohort is based on the values after excluding one patient who had a very low erythropoietin baseline measurement of 2.8 mIU/ml, which is lower than the typical lower value of normal physiological reference range (3.5 mIU/ml) and very close to the lower limit of quantitation of 2.5 mIU/ml. This possibly erroneous low baseline value resulted in apparent large increases in percentage change from baseline in all the postbaseline values for this patient.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Competing interests

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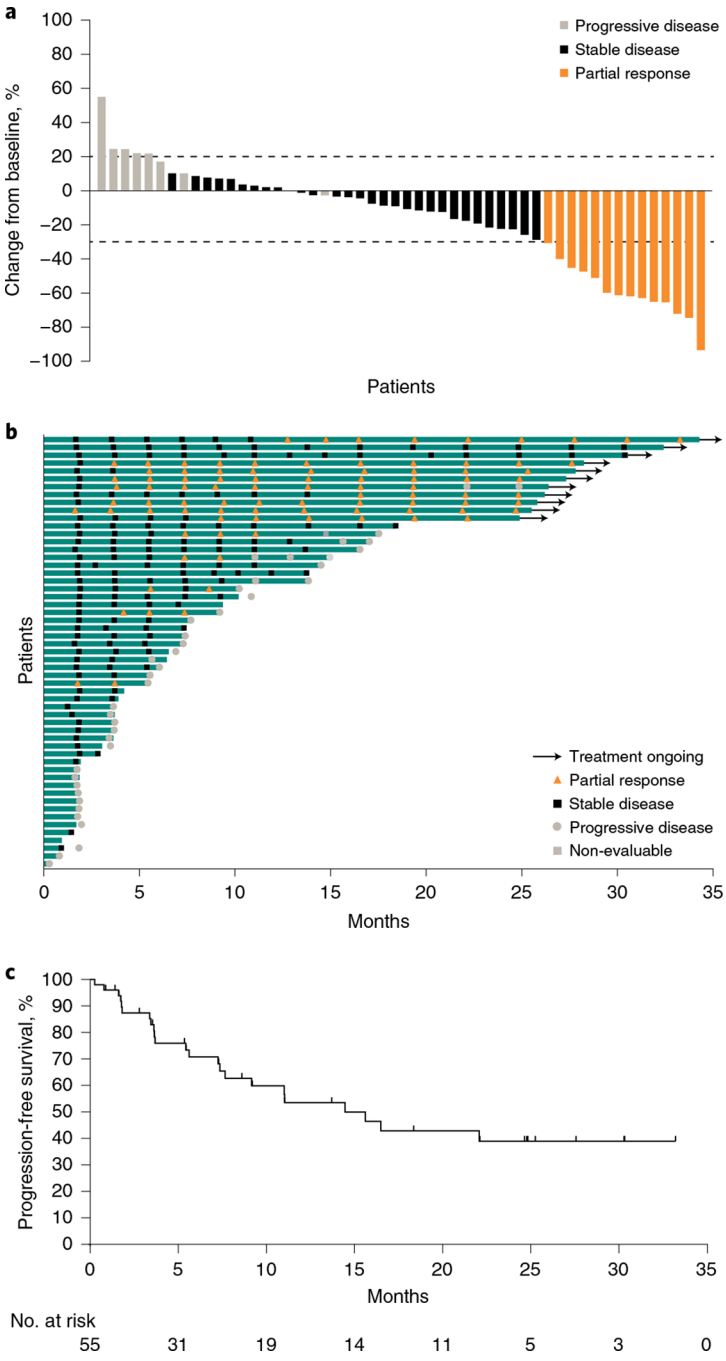

Fig. 1 |. Efficacy results of the ccRCC cohort.

a, Maximum change from baseline in target lesions. **b**, Duration of treatment. **c**, Kaplan–Meier estimate of progression-free survival. Data in **a**–**c** are in the ccRCC cohort; data in **a** includes patients who had a baseline and an evaluable post-baseline assessment (*n*â€‰=â€‰52).

Table 1 |

Baseline demographics and disease characteristics

Characteristic	Dose-escalation cohort (*n* = 43)	ccRCC cohort (*n* = 55)
Age, median (range), years	63 (27–84)	62 (39–75)
Sex, no. (%)		
Female	15 (35)	11 (20)
Male	28 (65)	44 (80)
ECOG performance status score, no. (%)		
0	14 (33)	20 (36)
1	28 (65)	34 (62)
2	1 (2)	1 (2)
Tumor type, no. (%)		
Renal	22 (51)	54 (98)
Brain	5 (12)	—
Lung	3 (7)	—
Esophageal	1 (2)	—
Gastric	1 (2)	—
Liver	1 (2)	—
Ovarian	1 (2)	—
Pancreatic	1 (2)	—
Prostate	1 (2)	—
Other	7 (16)	1 (2)[a]
Prior systemic therapies, median (range)	3 (0–12)	3 (1–9)
Number of prior systemic therapies, no. (%)		
0	3 (7)	0 (0)
1	5 (12)	8 (15)
2	9 (21)	13 (24)
≥3	26 (60)	34 (62)
Prior anti-cancer therapies, no. (%)		
VEGF/VEGFR	25 (58)	50 (91)
Checkpoint inhibitor	26 (60)	44 (80)
Investigational/other	23 (53)	16 (29)
mTOR inhibitor	10 (23)	13 (24)
Cytokine	10 (23)	10 (18)
IMDC risk category, no. (%)		
Favorable	—	13 (24)
Intermediate/poor	—	42 (76)

VEGFR, vascular endothelial growth factor receptor.

[a]Patient was classified as having predominantly ccRCC with papillary features.

Table 2 |

Incidence of all-cause adverse events ≥20% in the ccRCC cohort

Adverse event, no. (%)	ccRCC cohort (*n* = 55)			
	Grade 1	Grade 3	Grade 4	All grades or 2
Any	16 (29)	33 (60)	2 (4)	55 (100)
Anemia	27 (49)	15 (27)	0 (0)	42 (76)
Fatigue	36 (65)	3 (5)	0 (0)	39 (71)
Dyspnea	24 (44)	3 (5)	0 (0)	27 (49)
Nausea	19 (35)	1 (2)	0 (0)	20 (36)
Cough	17 (31)	0 (0)	0 (0)	17 (31)
Hypoxia	8 (15)	9 (16)	0 (0)	17 (31)
Vomiting	16 (29)	0 (0)	0 (0)	16 (29)
Edema peripheral	15 (27)	0 (0)	0 (0)	15 (27)
Arthralgia	14 (25)	0 (0)	0 (0)	14 (25)
Blood creatinine increased	13 (24)	1 (2)	0 (0)	14 (25)
Headache	13 (24)	1 (2)	0 (0)	14 (25)
Dizziness	13 (24)	0 (0)	0 (0)	13 (24)
Back pain	11 (20)	1 (2)	0 (0)	12 (22)
Diarrhea	12 (22)	0 (0)	0 (0)	12 (22)
Hyperkalemia	11 (20)	1 (2)	0 (0)	12 (22)
Constipation	12 (22)	0 (0)	0 (0)	12 (22)
Dehydration	10 (18)	1 (2)	0 (0)	11 (20)

Table 3 |

Best objective response per RECIST v1.1 in the ccRCC cohort

Efficacy parameter, no. (%) [95% CI]	**ccRCC cohort, *n* = 55**
Objective response rate	14 (25) [15–39]
Complete response	0 (0)
Partial response	14 (25)
Stable disease	30 (54)
Disease control rate	44 (80) [67–90]
Progressive disease	8 (15)
Non-evaluable	3 (5)

Disease control rate = complete response + partial response + stable disease.