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Real-world efficacy and safety of belzutifan in patients with metastatic renal cell carcinoma: a multicenter retrospective study in Japan

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Abstract

Background

Belzutifan, a hypoxia-inducible factor-2α (HIF-2α) inhibitor, has recently become available for patients with previously treated metastatic renal cell carcinoma (mRCC). However, real-world evidence regarding its effectiveness and safety remains limited. We evaluated the clinical outcomes of belzutifan in Japanese patients with mRCC.

Methods

We retrospectively reviewed consecutive patients with mRCC treated with belzutifan at multiple institutions in Japan. Progression-free survival (PFS), overall survival (OS), objective response rate (ORR), disease control rate (DCR), and treatment-related adverse events (AEs) were evaluated. Survival outcomes were estimated using the Kaplan–Meier method, and exploratory Cox regression analyses were performed.

Results

Forty patients were included in the analysis. The ORR and DCR in the overall cohort were 10.0% and 35.0%, respectively, whereas among the 15 evaluable patients, the ORR and DCR were 26.7% and 80.0%, respectively. Median PFS was 6.0 months, while median OS was not reached. Treatment-related adverse events were generally manageable, with anemia being the most common toxicity. Exploratory analyses identified non-clear-cell histology and poor IMDC risk at belzutifan initiation as being associated with shorter PFS, while lymph node metastasis showed potential associations with poorer outcomes.

Conclusions

This multicenter real-world study suggests that belzutifan has clinical activity with a manageable safety profile in Japanese patients with previously treated mRCC. Exploratory analyses identified non-clear-cell histology and poor IMDC risk at belzutifan initiation as being associated with shorter PFS and suggested potential associations between lymph node metastasis, and unfavorable outcomes. These findings should be regarded as hypothesis-generating and warrant validation in larger prospective studies and may contribute to future patient selection strategies for HIF-2α inhibition.

Introduction

Renal cell carcinoma (RCC) accounts for approximately 2–3% of all adult malignancies, and nearly one-third of patients present with metastatic disease or eventually develop metastases after curative treatment (1). Although the introduction of immune checkpoint inhibitors (ICIs) and vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs) has substantially improved the prognosis of metastatic RCC (mRCC) (2, 3), most patients ultimately experience disease progression and require subsequent systemic therapies (4, 5). Recent real-world studies have highlighted the heterogeneity of outcomes following ICI-based

combination therapies and subsequent treatment strategies, emphasizing the importance of optimizing treatment sequencing in patients with mRCC (6–8). Therefore, the development of effective treatment strategies after failure of ICI- and VEGFR-targeted therapy remains an important unmet clinical need.

Belzutifan is a first-in-class hypoxia-inducible factor-2α (HIF-2α) inhibitor that selectively targets a key oncogenic pathway activated by von Hippel–Lindau (VHL) gene inactivation in clear-cell RCC (9). In the phase III LITESPARK-005 trial, belzutifan demonstrated superior progression-free survival and objective response rate compared with everolimus in patients previously treated with both ICIs and VEGFR-targeted therapy, leading to its approval as a standard treatment option for previously treated mRCC (10). These findings established HIF-2α inhibition as a novel therapeutic strategy in advanced RCC (11).

Despite these encouraging results, evidence regarding the effectiveness of belzutifan in routine clinical practice remains limited. Patients enrolled in prospective clinical trials are generally highly selected and may not fully represent those encountered in daily practice (12). In particular, because belzutifan has only recently become available in Japan, it is frequently introduced after multiple prior lines of systemic therapy, resulting in a patient population that may differ substantially from that included in pivotal clinical trials. Furthermore, clinical factors associated with durable benefit from belzutifan have not yet been well characterized.

Therefore, we conducted a multicenter retrospective study to evaluate the real-world efficacy and safety of belzutifan in Japanese patients with mRCC. In addition, we performed exploratory analyses to identify clinical characteristics associated with progression-free survival, with the aim of generating hypotheses for future studies investigating predictors of response to HIF-2α inhibition.

Materials and Methods

Study design and ethical considerations

This multicenter retrospective cohort study evaluated consecutive patients with mRCC who received belzutifan at participating institutions in Japan. Clinical information was retrospectively collected from institutional databases and electronic medical records. Demographic characteristics, clinicopathological findings, laboratory data, treatment history, metastatic sites, treatment response, survival outcomes, and treatment-related adverse events were extracted and analyzed.

The study protocol was approved by the Institutional Review Board of Asahikawa Medical University (approval ID: C2542) and by the ethics committees of the participating institutions as required. Because of the retrospective nature of the study, the requirement for written informed consent was waived, and an opt-out approach was adopted according to institutional regulations. The study was conducted in accordance with the principles of the Declaration of Helsinki and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Patient selection

Patients were eligible if they had histologically confirmed mRCC and received at least one dose of belzutifan during the study period. Patients with incomplete clinical information or without evaluable follow-up after belzutifan initiation were excluded from the analysis.

Belzutifan was administered after prior systemic therapy according to routine clinical practice in Japan. Clinical variables collected at the initiation of belzutifan included age, sex, performance status, histological subtype, previous nephrectomy, laboratory findings, sites and number of metastatic organs, previous systemic therapies, and treatment line.

The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk classification was determined at the initiation of first-line systemic therapy. The number and distribution of metastatic organs were evaluated at belzutifan initiation. Primary renal tumors remaining in situ were recorded separately from local recurrence. Skeletal muscle and subcutaneous metastases were categorized as soft tissue metastases.

Treatment

Belzutifan was administered according to routine clinical practice at each institution. The starting dose, dose reductions, temporary interruptions, and treatment discontinuation were determined by the treating physician based on the patient's clinical condition and the occurrence of adverse events.

Treatment was continued until radiographic disease progression, unacceptable toxicity, death, or physician decision.

Outcome measures

The primary endpoint was progression-free survival (PFS), defined as the interval between belzutifan initiation and radiographic disease progression or death from any cause, whichever occurred first.

Secondary endpoints included overall survival (OS), objective response rate (ORR), disease control rate (DCR), and treatment-related adverse events.

Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. ORR was defined as the proportion of patients who achieved a complete response or partial response, whereas DCR included patients with complete response, partial response, or stable disease.

Treatment-related adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

Statistical analysis

Continuous variables are presented as median with interquartile range (IQR), whereas categorical variables are summarized as frequencies and percentages.

PFS and OS were estimated using the Kaplan–Meier method, and survival curves were compared using the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards regression models. Exploratory univariable analyses were performed to identify clinical factors associated with PFS. Variables showing potential clinical relevance or a univariable P value <0.10 were subsequently included in exploratory multivariable analyses.

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). All

statistical tests were two-sided, and a P value <0.05 was considered statistically significant.

Results

Patient characteristics

A total of 40 consecutive patients with mRCC who received belzutifan were included in this multicenter retrospective study (Table 1). The median age was 64 years (IQR, 58–72), and 30 patients (75.0%) were male. Clear-cell RCC accounted for 85.0% of cases, whereas six patients (15.0%) had non-clear-cell RCC. Prior nephrectomy had been performed in 29 patients (72.5%). At first-line systemic therapy initiation, IMDC risk was favorable in 9 patients (22.5%), intermediate in 21 (52.3%), and poor in 6 (15.0%). At belzutifan initiation, IMDC risk was favorable in 3 patients (7.5%), intermediate in 17 (42.5%), and poor in 11 (27.5%), whereas IMDC classification was unavailable in nine patients (22.5%). The median number of involved organs was 3 (IQR, 2–4). Lung (75.0%) and lymph node (52.5%) metastases were the most common metastatic sites.

Treatment exposure and antitumor activity

Treatment exposure and tumor responses are summarized in Table 2.

Belzutifan was administered as second-line in eight (20.0%), third-line in 12 (30.0%), fourth-line in six (15.0%), fifth-line in five (12.5%), and sixth-line or later in nine (22.5%), indicating that 80.0% of patients received belzutifan as third-line therapy or beyond.

Best overall response consisted of partial response in four patients (10.0%), stable disease in 10 (25.0%), and progressive disease in seven (17.5%), whereas 19 patients (47.5%) were not evaluable because radiological response assessment had not yet been completed. Consequently, the ORR and DCR in the overall cohort were 10.0% and 35.0%, respectively. Among the 15 evaluable patients, the ORR was 26.7% and the DCR was 80.0%.

Survival outcomes

Kaplan–Meier analyses demonstrated a median PFS of 6.0 months, whereas median OS had not been reached at the time of analysis (Figure 1).

Safety profile

Treatment-related adverse events are summarized in Table 3.

Treatment-related adverse events of any grade occurred in 29 patients (72.5%), and grade ≥3 adverse events occurred in 9 patients (22.5%). Anemia was the most common toxicity (55.0%), including grade ≥3 anemia in four patients (10.0%). Grade ≥3 hypoxia occurred in four patients (10.0%). No unexpected safety signals were observed.

Exploratory analysis

Exploratory univariable Cox regression analyses are summarized in Table 4, and Kaplan–Meier curves are shown in Figure 2. Among the evaluated variables, non-clear-cell RCC showed the strongest association with shorter PFS (HR 6.87, 95% CI 1.81–26.03; P=0.001). Poor IMDC risk at belzutifan initiation also associated with

shorter PFS (HR 3.37, 95% CI 1.00–11.37; P=0.034). Lymph node metastasis showed a potential association with shorter PFS in the Cox proportional hazards model (HR 3.45, 95% CI 0.91–13.11; Cox P=0.061), while Kaplan–Meier analysis demonstrated a significant difference by the log-rank test (P=0.049). Elevated CRP also showed a trend toward shorter PFS, whereas the remaining variables were not significantly associated with PFS.

Discussion

To our knowledge, this is one of the first multicenter real-world studies evaluating belzutifan in Japanese patients with metastatic renal cell carcinoma. In this heavily pretreated cohort, belzutifan demonstrated clinical activity with a manageable safety profile. Exploratory analyses suggested that non-clear-cell histology was associated with shorter progression-free survival, while poor IMDC risk at belzutifan initiation and lymph node metastasis showed potential associations with poorer outcomes. In contrast, the number of involved metastatic organs was not associated with progression-free survival. Collectively, these findings suggest that patient and tumor characteristics at the initiation of belzutifan—including histological subtype, clinical risk status, and metastatic pattern—may be more informative than metastatic burden alone in determining the clinical activity of belzutifan.

A notable characteristic of the present cohort was the advanced treatment setting in which belzutifan was introduced. Eighty percent of patients received belzutifan as third-line therapy or later, and 35.0% received the drug as fifth-line therapy or beyond. Compared with the phase III LITESPARK-005 trial, our population therefore represents a substantially more heavily pretreated cohort encountered in routine clinical practice. Despite these differences, the median PFS observed in our study was broadly consistent with that reported in LITESPARK-005 (10). However, treatment efficacy should be interpreted cautiously because 62.5% of patients were not evaluable for radiographic response at the data cutoff owing to the short observation period. Among the 15 evaluable patients, the ORR and DCR were 26.7% and 80.0%, respectively, suggesting that the overall ORR of 10.0% underestimated the antitumor activity observed in assessable patients. Therefore, direct comparisons with prospective clinical trials should be made with caution.

One of the most notable findings of this study was the significantly shorter PFS observed in patients with non-clear-cell RCC. Belzutifan was developed primarily for clear-cell RCC, in which inactivation of the VHL gene leads to constitutive activation of the HIF-2α pathway (1). Therefore, reduced efficacy in non-clear-cell histologies is biologically plausible, although the molecular backgrounds of non-clear RCC are heterogeneous (13, 14). Because only six patients with non-clear-cell RCC were included in this study, this finding should be interpreted cautiously and regarded as hypothesis-generating. Nevertheless, our results suggest that histological subtype may represent an important factor influencing the clinical activity of belzutifan and warrant further investigation in larger multicenter cohorts.

Poor IMDC risk at belzutifan initiation also tended to be associated with shorter PFS. This finding suggests that the patient's clinical condition at the start of belzutifan therapy may remain relevant even in the era of HIF-2α inhibition. Because IMDC was originally developed as a prognostic model rather than a predictive biomarker (15), further studies are needed to determine whether it retains prognostic value or can aid treatment selection for belzutifan (16).

Interestingly, the number of involved metastatic organs was not associated with PFS in the present study. In contrast, histological subtype and the pattern of metastatic spread appeared to be more informative than metastatic burden alone. Although these findings should be interpreted cautiously because of the limited sample size, they raise the possibility that biological characteristics of the tumor may be more relevant than disease extent when selecting patients for belzutifan treatment.

The biological basis underlying the potential association between lymph node metastasis and shorter PFS remains unclear (17). Unlike immune checkpoint inhibitors, whose efficacy is strongly influenced by host immune responses, belzutifan primarily targets the HIF-2α pathway. Therefore, lymph node metastasis may reflect a biologically aggressive tumor phenotype rather than simply indicating advanced disease burden. Previous studies have suggested that lymph node metastases exhibit distinct molecular and immune microenvironmental characteristics, including altered angiogenic signaling (18, 19), metabolic reprogramming (20), and immune cell composition (21). Such biological features may influence sensitivity to HIF-2α inhibition; however, this hypothesis remains speculative and requires validation through translational studies incorporating molecular profiling and tumor microenvironment analyses.

Another noteworthy finding was the limited prognostic impact of conventional clinical biomarkers in this cohort. Although elevated CRP showed a trend toward shorter PFS in the univariable analysis, no robust association was identified. Systemic inflammatory markers have consistently been associated with outcomes in patients treated with immune checkpoint inhibitors and VEGF-targeted therapies (7, 22, 23). However, our findings suggest that predictors of clinical outcome during belzutifan treatment may differ from those established for other systemic therapies. Given the exploratory nature of the present analysis, these observations require confirmation in larger cohorts with longer follow-up.

The absence of an apparent late plateau in the PFS curve should be interpreted with caution because the median follow-up remains relatively short and the survival curves are still immature. Nevertheless, compared with the LITESPARK-005 trial, our cohort consisted of substantially more heavily pretreated patients, with 80.0% receiving belzutifan as third-line therapy or later. Extensive prior systemic therapy may have contributed to the emergence of treatment-resistant tumor clones, thereby reducing the likelihood of durable disease control. These observations raise the possibility that earlier use of belzutifan may improve long-term outcomes, although this hypothesis requires prospective evaluation (24).

The safety profile observed in the present study was generally consistent with that reported in previous clinical trials and post-marketing experience (10). Anemia was the most common treatment-related adverse event and the principal cause of grade ≥ 3 toxicity, whereas severe hypoxia remained relatively uncommon. Importantly, no previously unrecognized safety signals were identified despite the inclusion of heavily pretreated patients treated in routine clinical practice. These findings support the manageable safety profile of belzutifan when appropriate monitoring and supportive care are provided.

This study has several limitations. First, its retrospective design introduces the possibility of selection bias and unmeasured confounding. Second, the relatively small sample size limited the statistical power of the exploratory analyses, particularly for subgroup analyses such as non-clear-cell RCC, and precluded robust multivariable modeling. Third, the follow-up period remains short because belzutifan has only recently become available in Japan, and 62.5% of patients had not yet undergone radiographic response assessment at the data

cutoff. Accordingly, both response and survival outcomes should be interpreted with caution. Fourth, most patients received belzutifan after multiple prior lines of systemic therapy, limiting direct comparison with prospective clinical trials. Finally, molecular biomarkers, including alterations in the VHL/HIF pathway and other genomic features, were not evaluated, and therefore the biological mechanisms underlying the observed findings remain speculative.

In conclusion, this multicenter real-world study suggests that belzutifan has clinical activity with a manageable safety profile in Japanese patients with previously treated metastatic renal cell carcinoma. Exploratory analyses identified non-clear-cell histology and poor IMDC risk at belzutifan initiation as being associated with shorter progression-free survival and suggested a potential association between lymph node metastasis and poorer outcomes; however, these findings should be regarded as hypothesis-generating. Larger prospective studies with longer follow-up are warranted to validate these observations and to establish clinically useful biomarkers for patient selection.

Declarations

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Author Contributions

KN conceived and designed the study. KN collected and interpreted the data and drafted the manuscript. All authors contributed to data acquisition, critically revised the manuscript for important intellectual content, and approved the final version of the manuscript.

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Data Availability

The datasets generated and/or analyzed during the current study are not publicly available because they contain information that could compromise patient privacy but are available from the corresponding author on reasonable request.

Conflict of Interest

Kazuyuki Numakura has received honoraria from MSD, Ono Pharmaceutical, Bristol Myers Squibb, Chugai Pharmaceutical, Pfizer, Eisai, Astellas Pharma, Janssen Pharmaceutical, Takeda Pharmaceutical, Bayer Yakuhin, and Merck Biopharma. The remaining authors declare that they have no conflicts of interest relevant to this study.

Ethics approval

The study protocol was approved by the Institutional Review Board of Asahikawa Medical University (Approval No. C2542) and was conducted in accordance with the Declaration of Helsinki and its later amendments.

Consent to participate

The requirement for written informed consent was waived because of the retrospective nature of this study. Instead, an opt-out approach was adopted in accordance with institutional regulations.

Consent for publication

Not applicable.

References

1. Rose TL, Kim WY. Renal Cell Carcinoma: A Review. JAMA. 2024;332(12):1001-10.
2. Nishimoto K, Kimura G, Sazuka T, Hamamoto S, Nozawa M, Numakura K, et al. The Effectiveness and Safety Profile of Nivolumab-Plus-Ipilimumab in Previously Untreated Japanese Patients With Advanced or Metastatic Renal Cell Carcinoma (J-ENCORE Study). Int J Urol. 2025;32(8):961-72.
3. Ishihara H, Katsurayama N, Nemoto Y, Mizoguchi S, Nakayama T, Fukuda H, et al. Midterm Outcomes of Combination Therapy With Immune Checkpoint Inhibitors and VEGFR-TKIs in Real-World Patients With Advanced Renal Cell Carcinoma. Int J Urol. 2026;33(3):e70444.
4. Mori K, Numakura K, Matsushita Y, Kojima T, Osawa T, Sazuka T, et al. Primary resistance to nivolumab plus ipilimumab therapy affects second-line treatment outcomes in patients with metastatic renal cell carcinoma. Cancer Sci. 2025;116(2):444-52.
5. Sazuka T, Tatsugami K, Shirotake S, Hamamoto S, Nozawa M, Numakura K, et al. Outcomes of Nivolumab-Plus-Ipilimumab in Metastatic Renal Cell Carcinoma: Second Interim Analysis of the J-ENCORE Study. Int J Urol. 2026;33(1):e70281.
6. Kikuta M, Naito S, Osawa T, Numakura K, Narisawa T, Takai Y, et al. Real-world short-term outcomes and treatment regimen comparisons in patients with metastatic renal cell carcinoma treated with first-line immune combinations. BMC Cancer. 2025;25(1):117.
7. Matsushita Y, Kojima T, Osawa T, Sazuka T, Hatakeyama S, Goto K, et al. Prognostic outcomes in patients with metastatic renal cell carcinoma receiving second-line treatment with tyrosine kinase inhibitor following first-line immune-oncology combination therapy. Int J Urol. 2024;31(5):526-33.
8. Tanaka R, Shinohara M, Kawashima Y, Sekine Y, Narita S, Kobayashi S, et al. Deferred Cytoreductive Nephrectomy in Unresectable/Metastatic Renal Cell Carcinoma: A Real-World Multicenter Retrospective Study. Int J Urol. 2026;33(1):e70356.
9. Jonasch E, Donskov F, Iliopoulos O, Rathmell WK, Narayan VK, Maughan BL, et al. Belzutifan for Renal Cell Carcinoma in von Hippel-Lindau Disease. N Engl J Med. 2021;385(22):2036-46.
10. Choueiri TK, Powles T, Peltola K, de Velasco G, Burotto M, Suarez C, et al. Belzutifan versus Everolimus for Advanced Renal-Cell Carcinoma. N Engl J Med. 2024;391(8):710-21.

11. Saad E, Machaalani M, McDermott DF, Choueiri TK. The clinical landscape of HIF2alpha inhibitors in oncology. Nat Rev Clin Oncol. 2026;23(7):501-19.
12. Van Spall HG, Toren A, Kiss A, Fowler RA. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. JAMA. 2007;297(11):1233-40.
13. Kim CM, Vocke C, Torres-Cabala C, Yang Y, Schmidt L, Walther M, et al. Expression of hypoxia inducible factor-1alpha and 2alpha in genetically distinct early renal cortical tumors. J Urol. 2006;175(5):1908-14.
14. Albiges L, Flippot R, Rioux-Leclercq N, Choueiri TK. Non-Clear Cell Renal Cell Carcinomas: From Shadow to Light. J Clin Oncol. 2018:JCO2018792531.
15. Ko JJ, Xie W, Kroeger N, Lee JL, Rini BI, Knox JJ, et al. The International Metastatic Renal Cell Carcinoma Database Consortium model as a prognostic tool in patients with metastatic renal cell carcinoma previously treated with first-line targeted therapy: a population-based study. Lancet Oncol. 2015;16(3):293-300.
16. Fallah J, Heiss BL, Joeng HK, Weinstock C, Gao X, Pierce WF, et al. FDA Approval Summary: Belzutifan for Patients with Advanced Renal Cell Carcinoma. Clin Cancer Res. 2024;30(22):5003-8.
17. Numakura K, Sekine Y, Hatakeyama S, Muto Y, Sobu R, Kobayashi M, et al. Primary resistance to nivolumab plus ipilimumab therapy in patients with metastatic renal cell carcinoma. Cancer Med. 2023;12(16):16837-45.
18. Fukata S, Inoue K, Kamada M, Kawada C, Furihata M, Ohtsuki Y, et al. Levels of angiogenesis and expression of angiogenesis-related genes are prognostic for organ-specific metastasis of renal cell carcinoma. Cancer. 2005;103(5):931-42.
19. Kroeger N, Seligson DB, Klatte T, Rampersaud EN, Birkhauser FD, Rao PN, et al. Clinical, molecular, and genetic correlates of lymphatic spread in clear cell renal cell carcinoma. Eur Urol. 2012;61(5):888-95.
20. Xu YY, Cheng GB, Li XY, Zeng XX, Wu SY. A novel angiogenesis-related gene signature predicting prognosis in clear cell renal cell carcinoma. Sci Rep. 2025;16(1):788.
21. Sobottka B, Vetter V, Banaei-Esfahani A, Nowak M, Lorch A, Sirek A, et al. Immune Phenotype-Genotype Associations in Primary Clear Cell Renal Cell Carcinoma and Matched Metastatic Tissue. Mod Pathol. 2024;37(10):100558.
22. Konishi S, Hatakeyama S, Numakura K, Narita S, Inoue T, Saito M, et al. Validation of the IMDC Prognostic Model in Patients With Metastatic Renal-Cell Carcinoma Treated With First-Line Axitinib: A Multicenter Retrospective Study. Clin Genitourin Cancer. 2019;17(5):e1080-e9.
23. Numakura K, Kobayashi M, Muto Y, Sekine Y, Takahashi M, Kashima S, et al. First-line axitinib therapy is less effective in metastatic renal cell carcinoma with spindle histology. Sci Rep. 2020;10(1):20089.
24. Agarwal N, Brugarolas J, Ghatalia P, George S, Haanen JB, Gurney H, et al. Randomized phase II dose comparison LITESPARK-013 study of belzutifan in patients with advanced clear cell renal cell carcinoma. Ann Oncol. 2024;35(12):1148-56.

Tables

Table 1. Baseline patient characteristics (N = 40)

Age, years (IQR)		69	(63.5 -75.5)
Sex(%)			
	Male	30	(75.0)
	Female	10	(25.0)
Comorbidities (%)			
	Hypertension	20	(50.0)
	Chronic kidney disease	17	(42.5)
	Diabetes mellitus	18	(45.0)
Histology (%)			
	Clear-cell RCC	33	(82.5)
	Non-clear-cell RCC	6	(15.0)
Sarcomatoid/rhabdoid features (%)		2	(5.0)
Prior nephrectomy (%)		29	(72.5)
IMDC risk group			
at first-line therapy initiation			
	Favorable	9	(22.5)
	Intermediate	21	(52.5)
	Poor	6	(15.0)
	Missing/unknown	4	(10.0)
at belzutifan initiation			
	Favorable	3	(7.5)
	Intermediate	17	(42.5)
	Poor	11	(27.5)
	Missing/unknown	9	(22.5)
Karnofsky Performance Status (IQR)		80	(70 - 90)
Hemoglobin (IQR)	g/dL	11.5	(10.3 - 13.6)
eGFR (IQR)	mL/min/1.73 m²	45.7	(27.9 - 57.9)
CRP (IQR)	mg/dL	0.98	(0.11 - 2.22)
Sites of metastasis at belzutifan initiation (%)			
	Lung	30	(75.0)

	Lymph node	21	(52.5)
	Primary kidney	15	(37.5)
	Bone	13	(32.5)
	Pancreas	7	(17.5)
	Liver	6	(15.0)
	Adrenal gland	5	(12.5)
	Soft tissue	4	(10.0)
	Brain	1	(2.5)
	Other sites	9	(22.5)
Number of involved organs at belzutifan initiation (%)			
	1	8	(20)
	2	8	(20)
	3	15	(37.5)
	≥4	9	(22.5)
	Median (IQR)	3	(2 - 3)

CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IQR, interquartile range; RCC, renal cell carcinoma.

Table 2. Belzutifan treatment exposure and clinical outcomes

Variable		N	%
Treatment line			
	2nd line	8	20.0
	3rd line	12	30.0
	4th line	6	15.0
	5th line	5	12.5
	≥6th line	8	20.0
	Missing	1	2.5
Best overall response			
	CR	0	0
	PR	4	10.0
	SD	10	25.0
	PD	7	17.5
	Not evaluable	19	47.5
Objective response rate		4	10.0
Disease control rate		14	35.0
Treatment status		18	45.0
	Due to progressive disease	14	35.0
	Due to adverse events	2	5.0
	Due to death	1	2.5
	Ongoing treatment	20	50.0
	Missing	3	7.5

CR, complete response; DCR, disease control rate; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Objective response rate (ORR) was defined as the proportion of patients who achieved a complete or partial response. Disease control rate (DCR) was defined as the proportion of patients who achieved a complete response, partial response, or stable disease.

Table 3. Treatment-related adverse events during belzutifan treatment (N = 40)

Adverse event	Any grade		Grade ≥3	
	N	%	N	%
Any adverse event	29	72.5	9	22.5
Anemia	22	55.0	4	10.0
Hypoxia	4	10.0	4	10.0
Edema	2	5.0	1	2.5
Hepatic dysfunction	2	5.0	1	2.5
Interstitial pneumonia†	1	2.5	1	2.5
Thrombocytopenia	1	2.5	1	2.5
Renal dysfunction	1	2.5	0	0
Decreased appetite	1	2.5	0	0
Fever	1	2.5	0	0
Rash	1	2.5	0	0
Palpitations/Dizziness	1	2.5	0	0
Nausea	1	2.5	0	0
Syncope/Hypotension	1	2.5	0	0

Treatment-related adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0.

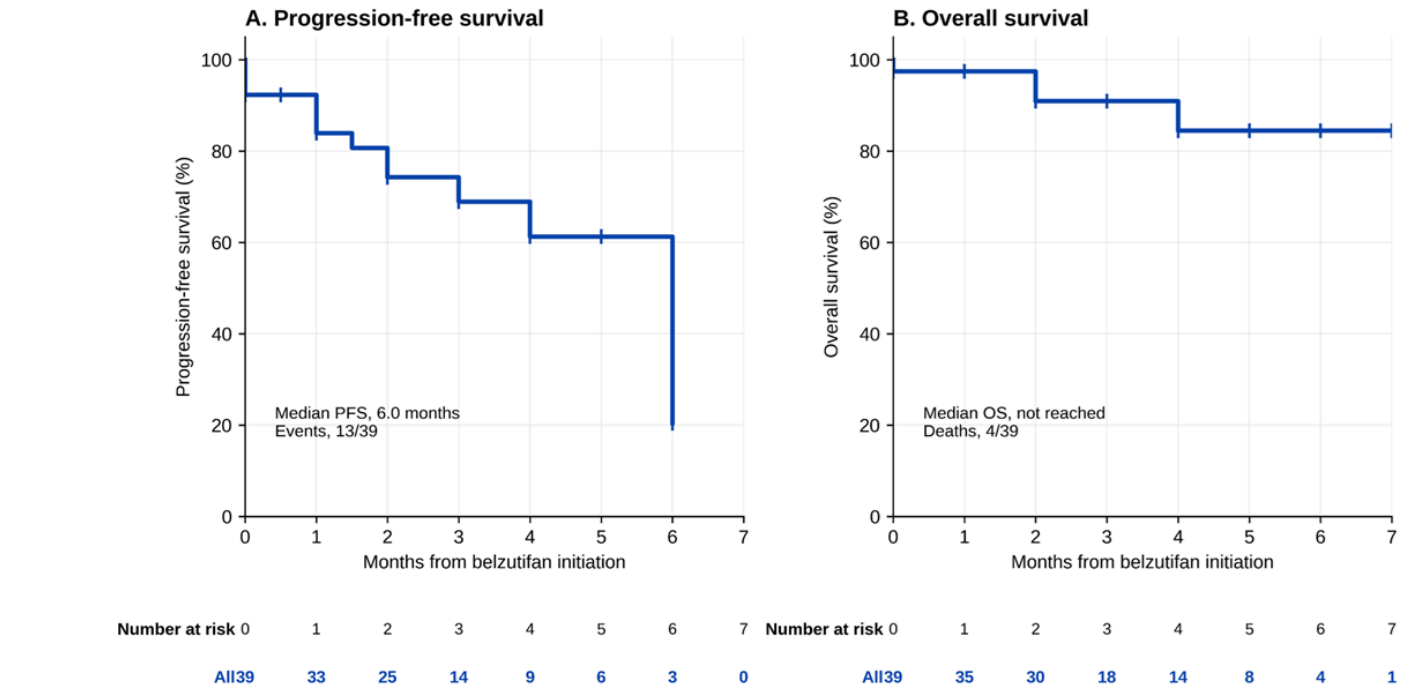
Table 4. Exploratory univariable Cox regression analysis of factors associated with progression-free survival

Variable	N	HR (95% CI)	Cox P value	Log-Rank P value
IMDC poor at belzutifan initiation	11	3.37 (1.00–11.37)	0.050	0.034
IMDC poor at first-line initiation	6	0.65 (0.08–5.13)	0.683	0.672
Hemoglobin <10 g/dL	5	2.61 (0.54–12.64)	0.210	0.205
CRP ≥2.0 mg/dL	11	2.47 (0.82–7.43)	0.071	0.075
Non-clear-cell RCC	6	6.87 (1.81-26.03)	0.001	0.001
Involved organs ≥3	20	1.36 (0.45–4.07)	0.470	0.564
Pancreatic metastasis	7	1.47 (0.39–5.53)	0.539	0.563
Bone metastasis	13	2.10 (0.70–6.35)	0.129	0.150
Liver metastasis	6	2.98 (0.78–11.40)	0.104	0.086
Lung metastasis	29	0.55 (0.18–1.68)	0.247	0.254
Lymph node metastasis	20	3.45 (0.91–13.11)	0.061	0.049
Belzutifan ≥4th line	19	0.44 (0.13–1.52)	0.147	0.173
Prior cabozantinib-containing therapy	14	1.42 (0.43–4.70)	0.762	0.556
Prior ICI-containing therapy	14	0.67 (0.18–2.46)	0.596	0.520

CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; ICI, immune checkpoint inhibitor; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; RCC, renal cell carcinoma; PFS, progression-free survival.

Hazard ratios (HRs) were estimated using univariable Cox proportional hazards regression analysis. P values were calculated using the log-rank test.

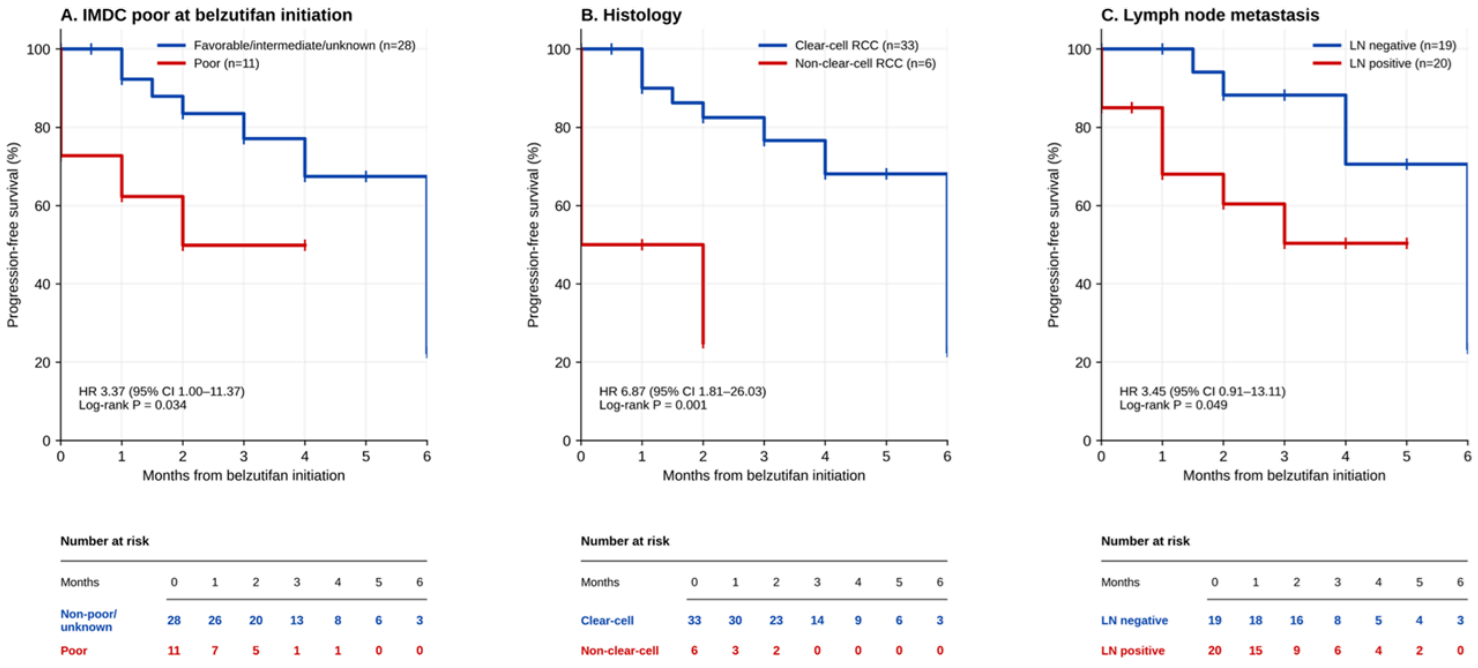
Figures



PFS, progression-free survival; OS, overall survival.

Figure 1

Kaplan–Meier estimates of progression-free survival (A) and overall survival (B) in the overall study population. Vertical tick marks indicate censored observations.



IMDC, International Metastatic Renal Cell Carcinoma Database Consortium;
LN, lymph node;RCC, renal cell carcinoma; HR, hazard ratio; CI, confidence interval.

Figure 2

Kaplan–Meier analyses of progression-free survival according to exploratory clinical factors.

(A) Clear-cell versus non-clear-cell renal cell carcinoma.

(B) IMDC favorable/intermediate/unknown versus poor risk at belzutifan initiation.

(C) Presence versus absence of lymph node metastasis at belzutifan initiation.

Hazard ratios (HRs) were estimated using univariable Cox proportional hazards regression models. P values shown in the panels were calculated using the log-rank test. Vertical tick marks indicate censored observations.