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Research Paper

Tyrosine Kinase Inhibitors Outperform Immune Checkpoint Inhibitors in Bone-Predominant Metastatic Renal Cell Carcinoma: A Multicenter Real-World Analysis

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Abstract

Background: Bone-predominant metastatic renal cell carcinoma (mRCC) presents significant clinical challenges due to its associated morbidities and poor prognosis. Optimal first-line treatment remains unclear, largely because these patients are often excluded from clinical trials due to difficulties in measuring bone lesions. Emerging evidence suggests that bone metastases exhibit high angiogenesis gene signatures, potentially predicting favorable responses to tyrosine kinase inhibitors (TKIs).

Methods: We conducted a multicenter retrospective analysis of patients with bone-predominant mRCC treated at The Ohio State University Comprehensive Cancer Center and Fred Hutchinson Cancer Center from January 2008 to June 2021. Bone predominance was defined as having a greater number of osseous metastases compared to extra-osseous sites using computed tomography or bone scans. Patients receiving first-line TKIs or immune checkpoint inhibitors (ICIs) were included; those treated with combination TKI-ICI therapies were excluded due to limited numbers. Demographic, clinical, and treatment data were collected. Progression-free survival (PFS) and overall survival (OS) were analyzed using Kaplan-Meier methods and compared using the log-rank test. Univariate Cox regression analysis was conducted to identify factors associated with OS.

Results: A total of 69 patients with bone-predominant mRCC were identified, with 40 receiving TKIs and 29 receiving ICIs as first-line therapy. Baseline characteristics were comparable between groups. The median OS was significantly longer for patients treated with TKIs compared to those receiving ICIs (41.3 months vs. 19.3 months; log-rank $P = 0.036$). A trend toward improved median PFS was observed in the TKI group (7.9 months vs. 4.9 months; $P = 0.075$). Univariate analysis showed that treatment with ICIs was associated with an increased risk of death compared to TKIs (hazard ratio = 1.96; $P = 0.040$). Objective response rates were higher in the TKI group (22.9% vs. 12.0%), although this difference was not statistically significant ($P = 0.332$).

Conclusions: In this multicenter real-world analysis, first-line treatment with TKIs was associated with significantly improved OS compared to ICIs in patients with bone-predominant mRCC. These findings suggest that TKI-containing regimens may be the preferred front-line therapy for this patient subgroup. Prospective studies are warranted to validate these results and to optimize treatment strategies for bone-predominant mRCC.

Keywords: bone-predominant metastatic renal cell carcinoma, tyrosine kinase inhibitors, TKIs, immune checkpoint inhibitors, ICIs, overall survival, real-world multicenter analysis

Introduction

Renal cell carcinoma (RCC) comprises around 90% of kidney malignancies, with metastatic disease affecting approximately 60% of patients – either present at initial diagnosis (30%) or developing during disease progression (30%) [1-3]. Among patients with metastatic RCC (mRCC), bone

represents one of the most common sites of distant spread, affecting approximately 30-35% of patients [4-6]. Bone-predominant mRCC, characterized by a greater burden of osseous than extra-osseous metastases, presents unique clinical challenges [7-9]. These patients experience significant morbidity, including pathological fractures, spinal cord compression, and debilitating pain, which substantially impacts their quality of life [10, 11]. Moreover, the assessment and measurement of treatment response in bone metastases remains particularly challenging due to their largely non-measurable nature by conventional Response Evaluation Criteria in Solid Tumors (RECIST) [12, 13]. This not only complicates clinical decision-making but has historically led to the exclusion of these patients from many pivotal clinical trials, resulting in limited evidence to guide optimal treatment selection [14, 15].

The therapeutic landscape for mRCC has evolved dramatically over the past two decades, transitioning from cytokine-based therapies to more targeted and immunological approaches [16-20]. Tyrosine kinase inhibitors (TKIs), which target the vascular endothelial growth factor (VEGF) pathway, emerged as the first major breakthrough, with agents such as sunitinib demonstrating significant improvements in progression-free survival (PFS) (11 months vs. 5 months with interferon-alfa [IFN-α]) as first-line therapy [21]. More recently, immune checkpoint inhibitors (ICIs) have revolutionized mRCC treatment, either as monotherapy or in combination with other agents [22-24]. The combination of nivolumab plus ipilimumab has shown remarkable efficacy with a median overall survival (OS) of 47 months and a 42% objective response rate (ORR) in intermediate or poor-risk patients [25, 26]. These impressive outcomes have led current treatment guidelines to recommend ICI-based combinations as preferred first-line options for patients with intermediate- or poor-risk disease, while TKI monotherapy remains a standard option for favorable-risk patients [27].

Emerging biological insights suggest that bone metastases in RCC exhibit distinct characteristics that may influence treatment outcomes [8, 28]. Genomic analyses have revealed that bone metastases typically display elevated angiogenesis gene signatures compared to other metastatic organ systems, with the hypoxia-induced factor (HIF) signaling pathway playing a key role in these processes through upregulation of several growth factors including VEGF, platelet-derived growth factor (PDGF), and transforming growth factor-alpha (TGF-α) [29, 30]. Recent molecular analyses have further demonstrated

that bone metastases are enriched for polybromo 1 (PBRM1) and tumor protein p53 (TP53) mutations, predominantly express an angiogenic/stromal molecular subtype, and exhibit a distinct microenvironment characterized by increased endothelial cells and monocytic lineages [31]. This biological rationale is supported by preliminary clinical observations showing favorable responses to TKIs in patients with bone metastases, as these agents not only target tumor vasculature but may also modulate the bone microenvironment through effects on osteoclasts and osteoblasts [32, 33].

Recent clinical evidence reflects the complexity of optimal treatment selection in this population. A multi-institutional retrospective study demonstrated superior objective response rates with second-line TKIs compared to nivolumab in bone lesions [34], and studies of ICI combinations in mRCC found that patients with a higher burden of bone metastases demonstrated worse disease control rates (DCR) [35] and OS [9]. However, challenging these findings, a study of 98 mRCC patients suggested that bone metastases did not significantly impact OS in patients receiving ICI therapy [36], indicating that traditional assumptions about poor prognosis may need to be reevaluated in the immunotherapy era. Despite the improved survival times with modern therapies making optimal treatment selection increasingly crucial, robust real-world evidence directly comparing the efficacy of first-line TKIs versus newer immunotherapy approaches in bone-predominant disease remains limited.

To address this critical knowledge gap, we conducted a multicenter retrospective analysis comparing the effectiveness of first-line TKIs versus ICIs in patients with bone-predominant mRCC. By leveraging real-world data from two major academic cancer centers spanning over a decade, our study aimed to provide clinically relevant evidence to guide treatment selection for this challenging patient population.

Patients and Methods

Study population and treatment

We conducted a retrospective analysis of patients diagnosed with mRCC at The Ohio State University Comprehensive Cancer Center and the University of Washington Fred Hutchinson Cancer Center between January 2008 and June 2021. As shown in **Figure 1**, a total of 771 patients with mRCC were initially screened. Among these, 143 patients had bone metastases, and 69 patients were identified as having bone-predominant disease, defined as a greater number of osseous metastases compared to

extra-osseous metastases. These 69 patients were included in the study. Patients were stratified into two groups based on their first-line systemic therapy: those who received TKIs and those who received ICIs. The TKI group comprised 40 patients, while the ICI group included 29 patients. Patients who received combination therapies of TKIs and ICIs were excluded due to limited numbers. First-line TKIs administered included sunitinib, pazopanib, cabozantinib, sorafenib, axitinib, and tivozanib. In the ICI group, patients received either single-agent ICIs (nivolumab or pembrolizumab) or combination ICI therapy with nivolumab plus ipilimumab (**Supplemental Table 1**). This study was approved by the Institutional Review Boards of both participating institutions. Due to the retrospective nature of the study, the requirement for informed consent was waived.

Study design and assessments

Baseline demographic and clinical data were collected from electronic medical records, including age, gender, histology, Eastern Cooperative Oncology Group (ECOG) performance status, International Metastatic RCC Database Consortium (IMDC) risk category, prior nephrectomy status, and the number of metastatic organ systems. Treatment details, subsequent therapies, and responses were also recorded. Treatment responses were evaluated using RECIST version 1.1. ORR was defined as the proportion of patients achieving a complete response (CR) or partial response (PR). DCR included patients who achieved CR, PR, or stable disease (SD). PFS was defined as the time from the initiation of first-line therapy to documented disease progression or death from any cause. OS was defined as the time from the initiation of first-line therapy to death from any cause.

Statistical analysis

Statistical analyses were performed using SPSS Biostatistics 27. Baseline characteristics were compared between the TKI and ICI groups using Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. Survival analyses for PFS and OS were conducted using the Kaplan-Meier method and compared with the log-rank test. A univariate Cox proportional hazards model was employed to assess the association of clinical variables with OS. Variables included in the model were treatment type (ICI vs. TKI), age, gender, histology (clear cell vs. non-clear cell), ECOG performance status, IMDC risk category, prior nephrectomy, and the number of metastatic organ systems. Response rates were compared using Fisher's exact test. All tests were two-sided, and a

P-value of less than 0.05 was considered statistically significant.
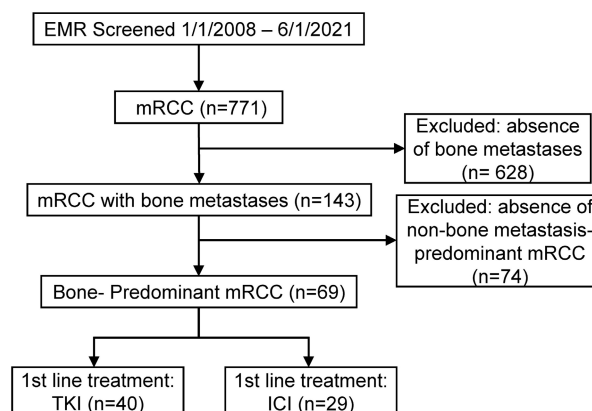
Figure 1. CONSORT diagram for patient selection in the retrospective cohort analysis. Abbreviations: EMR – electronic medical records; mRCC – metastatic renal cell carcinoma; TKI – tyrosine kinase inhibitor; ICI – immune checkpoint inhibitor.

Results

Demographics and clinical characteristics of bone-predominant mRCC patients

A total of 69 patients with bone-predominant mRCC were included in the analysis, with 40 patients receiving TKIs and 29 patients receiving ICIs as first-line therapy. The baseline demographic and clinical characteristics of these patients are summarized in **Table 1**. The median age was similar between the TKI and ICI groups (64.5 vs. 64 years, respectively; $P = 0.422$). The majority of patients were male (71.0%) and had clear cell histology (78.3%), with no significant differences between the treatment groups for gender ($P = 0.592$) or histology ($P = 0.690$). Most patients had an ECOG performance status of 0 or 1 (66.7%) and were classified as intermediate risk according to the IMDC criteria (58.0%), with comparable distributions across both groups. Notably, a higher proportion of patients in the TKI group had undergone prior nephrectomy compared to the ICI group (67.5% vs. 44.8%), approaching statistical significance ($P = 0.0842$). The number of metastatic organ systems was similar between groups ($P = 0.429$), with approximately 71.0% of patients having only one metastatic site (bone). Patients in the TKI group received an average of 2.36 subsequent lines of therapy compared to 1.38 in the ICI group (**Supplemental Table 2**). The median follow-up period was 20.6 months (IQR: 14.4-41.6 months) for the entire cohort, with 25.3 months (IQR: 16.5-67.2 months) for the TKI group and 17.3 months (IQR: 13.5-23.5 months) for the ICI group.

Table 1. Demographics and clinical characteristics of patients with bone-predominant mRCC stratified by treatment groups.

	Pts treated with TKI (n=40)	Pts treated with ICI (n=29)	*P* value	All patients (n=69)
Age (Median, IQR), years	64.5 (58.5-73.25)	64 (54-72)	0.422	64 (55-73)
Gender, n (%)			0.592	
Male	27 (67.5)	22 (75.9)		49 (71.0)
Female	13 (32.5)	7 (24.1)		20 (29.0)
Histology, n (%)			0.690	
Clear cell	31 (77.5)	23 (79.3)		54 (78.3)
Non clear cell	5 (12.5)	2 (6.9)		7 (10.1)
Unknown	4 (10.0)	4 (13.8)		8 (11.6)
ECOG, n (%)			0.770	
0/1	27 (67.5)	19 (65.5)		46 (66.7)
2/3	8 (20.0)	7 (24.1)		15 (21.7)
Unknown	5 (12.5)	3 (10.4)		8 (11.6)
IMDC, n (%)			0.816	
Favorable	2 (5.0)	1 (3.5)		3 (4.3)
Intermediate	24 (60.0)	16 (55.2)		40 (58.0)
Poor	9 (22.5)	9 (31.0)		18 (26.1)
Unknown	5 (12.5)	3 (10.3)		8 (11.6)
Nephrectomy, n (%)			0.0842	
Yes	27 (67.5)	13 (44.8)		40 (58.0)
No	13 (32.5)	16 (55.2)		29 (42.0)
# of metastatic organ systems, n (%)			0.429	
1	30 (75.0)	19 (65.5)		49 (71.0)
2/3	10 (25.0)	10 (34.5)		20 (29.0)

Abbreviations: mRCC – metastatic renal cell carcinoma; TKI – tyrosine kinase inhibitor; ICI – immune checkpoint inhibitor; IQR – interquartile range
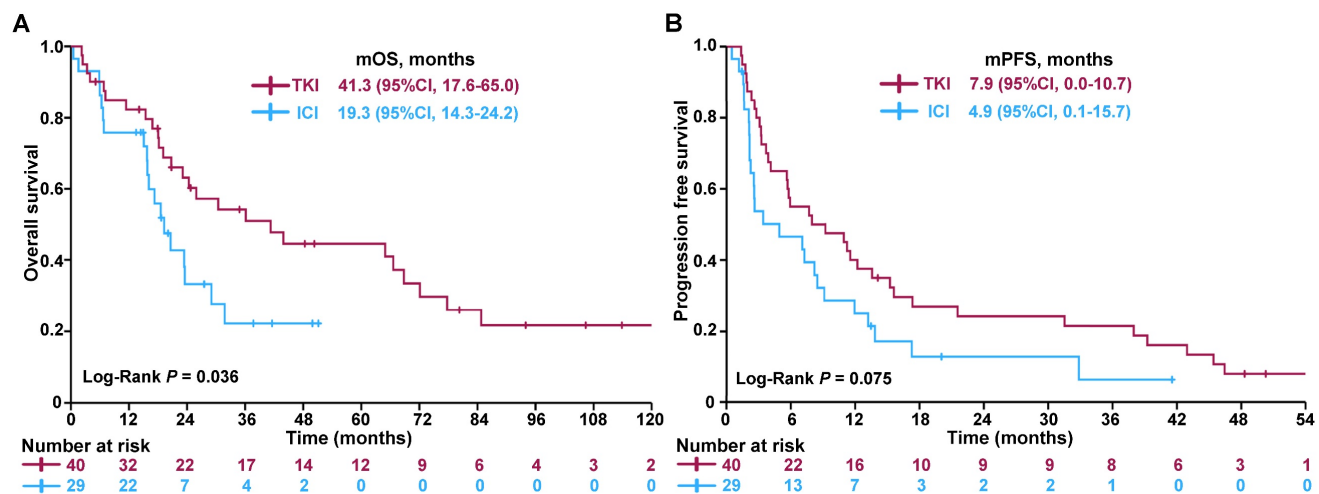
Figure 2. Kaplan-Meier survival curves comparing (A) OS and (B) PFS between patients treated with TKIs and ICIs. Abbreviations: OS – overall survival; PFS – progression-free survival; TKI – tyrosine kinase inhibitor; ICI – immune checkpoint inhibitor; CI – confidence interval.

Overall, there were no statistically significant differences in baseline characteristics between the TKI and ICI groups, suggesting that the cohorts were comparable for outcome analysis purposes.

Improved OS and trend toward better PFS in patients treated with TKIs

Patients with bone-predominant mRCC who received TKIs demonstrated significantly improved OS compared to those treated with ICIs. The median OS was 41.3 months for the TKI group versus 19.3 months for the ICI group (**Figure 2A**), with the difference reaching statistical significance (log-rank test, *P* = 0.036). In terms of PFS, there was a trend favoring the TKI group. The median PFS was 7.9 months for patients treated with TKIs compared to 4.9 months for those receiving ICIs (**Figure 2B**). Although this difference did not reach statistical significance (log-rank test, *P* = 0.075), it suggests a potential benefit of TKIs in delaying disease progression.

To identify factors associated with OS, a univariate Cox regression analysis was performed (**Table 2**). Treatment with ICIs (versus TKIs) was associated with a nearly two-fold increased risk of

death (hazard ratio [HR] = 1.96; 95% confidence interval [CI]: 1.03–3.71; *P* = 0.040). Additionally, non-clear cell histology was significantly associated with worse OS (HR = 0.30; 95% CI: 0.13–0.74; *P* = 0.009), indicating that patients with clear cell carcinoma had better survival outcomes. Other variables, such as age, gender, ECOG performance status, IMDC risk category, prior nephrectomy, and the number of metastatic organ systems, were not significantly associated with OS in this analysis.

Table 2. Univariate Cox regression analyses of clinical variables for predicting overall survival.

Variable	HR (95%CI)	*P* value
Treatment: ICI vs TKI	1.96 (1.03 - 3.71)	0.040
Age	1.00 (0.98 - 1.02)	0.670
Gender: male vs female	0.68 (0.37 - 1.26)	0.225
Clear cell: yes vs no	0.30 (0.13 - 0.74)	0.009
ECOG: 2/3 vs 0/1	1.44 (0.68 - 3.08)	0.345
IMDC: poor vs favorable/intermediate	3.20 (0.76 - 13.43)	0.112
Nephrectomy: yes vs no	0.72 (0.39 - 1.32)	0.288
# of metastatic organ systems: 2/3 vs 1	1.46 (0.78 - 2.72)	0.233

Abbreviations: HR – hazard ratio; CI – confidence interval; ICI – immune checkpoint inhibitor; TKI – tyrosine kinase inhibitor; ECOG – Eastern Cooperative Oncology Group; IMDC – International Metastatic RCC Database Consortium

These findings suggest that first-line treatment with TKIs may confer a survival advantage over ICIs in patients with bone-predominant mRCC and highlight the importance of histological subtype in predicting patient outcomes.

### Trend toward higher ORR and DCR with first-line TKIs

In patients with bone-predominant mRCC, first-line treatment with TKIs demonstrated a trend toward higher ORR and DCR compared to ICIs, although these differences were not statistically significant. Among the evaluable patients (*n*=60), none in either treatment group achieved CR. PR was observed in 22.9% of patients treated with TKIs (8/35) compared to 12.0% in the ICI group (3/25). SD was achieved by 37.1% of TKI-treated patients and 40.0% of ICI-treated patients. Progressive disease (PD) occurred in 40.0% of patients receiving TKIs and 48.0% of those receiving ICIs.

The ORR was higher in the TKI group (22.9%) compared to the ICI group (12.0%), but this difference did not reach statistical significance (*P* = 0.332). The DCR was also higher in the TKI group (60.0%) versus the ICI group (52.0%), with no statistically significant difference (*P* = 0.603). **Figure 3** illustrates the comparison of response rates between the two treatment groups. While the data suggest a potential advantage of TKIs in achieving tumor response and disease control, the lack of statistical significance indicates that larger studies are needed to confirm these trends.

Discussion

Bone-predominant mRCC poses significant treatment challenges, and the optimal first-line therapy for this subgroup has not been well established [7-9, 28]. While ICIs have shown promising results in mRCC overall [22-24], their effectiveness in bone-predominant disease remains uncertain due to limited evidence [9, 35, 36]. In this multicenter retrospective study, we evaluated the efficacy of first-line TKIs compared to ICIs in patients with bone-predominant mRCC. Our findings revealed a significant improvement in OS with TKI therapy, showing a median OS of 41.3 months versus 19.3 months with ICIs (*P* = 0.036). Additionally, there

A

TKI group: ORR = 22.9%; DCR = 60.0%

B

ICI group: ORR = 12.0%; DCR = 52.0%
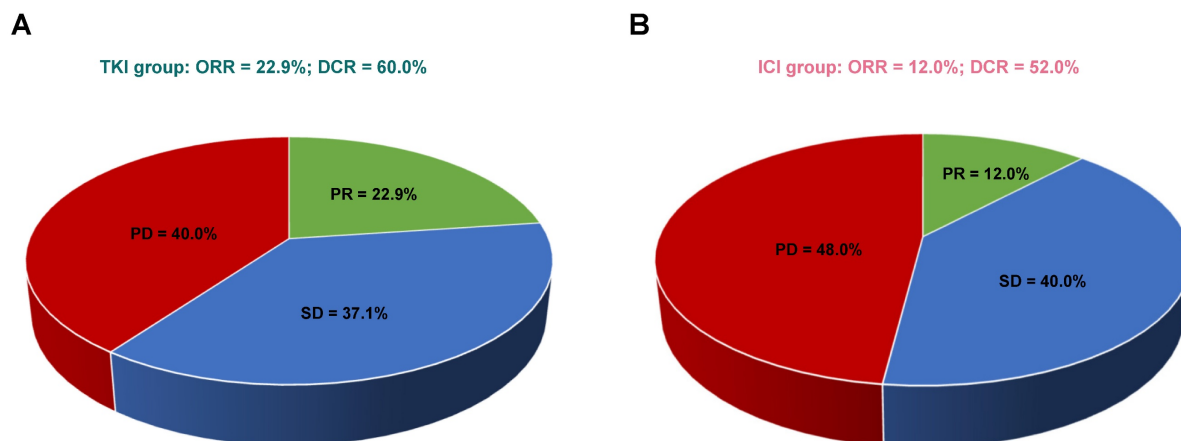
Figure 3. Comparison of response rates in patients receiving TKIs versus ICIs. (A) Response rates in the TKI group. (B) Response rates in the ICI group. Abbreviations: CR – complete response; PR – partial response; SD – stable disease; PD – progressive disease; ORR – objective response rate; DCR – disease control rate.

were trends toward enhanced PFS, ORR, and DCR in the TKI group, although these differences did not reach statistical significance. Univariate analysis confirmed the survival advantage of TKI treatment (HR 1.96 for ICI vs. TKI, $P = 0.040$) and identified clear cell histology as a significant prognostic factor (HR 0.30, $P = 0.009$). These results offer valuable insights into the potential benefits of TKI therapy over ICIs for managing bone-predominant mRCC.

The superior OS observed with TKIs in bone-predominant mRCC may be attributed to the unique biological characteristics of bone metastases. Bone lesions in RCC are known to exhibit high angiogenesis gene signatures, including upregulation of VEGF, PDGF, and TGF-α [29, 30]. This angiogenic phenotype is further supported by the recent molecular analysis by Gulati et al. [31], which demonstrated that bone metastases have distinct genomic and transcriptomic features, with significant enrichment of PBRM1 mutations (59.6%) and TP53 mutations (22.9%). Notably, bone metastases showed higher expression of PDL1 and PDL2 compared to primary kidney tumors and were predominantly characterized by the angiogenic/stromal molecular subtype. The study also revealed that bone metastases had a greater abundance of endothelial cells and cells of monocytic lineage in their microenvironment, along with increased fibroblast populations. These molecular features, particularly the angiogenic/stromal signature, may explain the enhanced efficacy of TKIs in bone metastases. Moreover, TKIs may exert additional effects within the bone microenvironment. They can modulate bone remodeling by inhibiting osteoclast-mediated bone resorption and affecting osteoblast function [32, 33]. The study's finding of increased expression of extracellular matrix reorganization genes (including ASPN, DCN, COL6A3, and COL11A1) in bone metastases suggests active remodeling of the bone microenvironment, which may be particularly susceptible to TKI intervention [31, 37]. The potential synergy between TKIs and bone-targeted therapies, such as bisphosphonates or denosumab, could further enhance therapeutic efficacy, although this warrants further investigation.

The relatively lower efficacy of ICIs compared to TKIs in patients with bone-predominant mRCC observed in our study may be attributed to the immunologically "cold" nature of bone metastases [38, 39]. The bone marrow microenvironment is enriched with immunosuppressive cells, such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), which inhibit effective antitumor immune responses [40-42]. Additionally, limited infiltration of cytotoxic T lymphocytes (CTLs)

into bone lesions may further reduce the effectiveness of ICIs, which depend on reinvigorating the host immune system to combat tumor cells [43-45]. This biological rationale aligns with clinical observations from prior studies. Clinical research examining ICI combination therapies in mRCC has demonstrated an inverse relationship between bone metastatic burden and treatment outcomes, with higher bone involvement correlating with reduced DCR [35] and OS [9]. However, a multicenter study by Gambale et al., which analyzed 98 mRCC patients treated with ICIs, reported no statistically significant difference in OS between patients with and without bone metastases ($P = 0.254$) [36]. This discrepancy likely stems from differences in study populations; the Gambale et al. cohort included patients with mixed metastatic patterns and lower bone-specific burden, while our study focused on bone-predominant disease. Furthermore, the Gambale study suggested that factors such as neutrophil-to-lymphocyte ratio (NLR) and basal calcemia levels significantly influenced OS in patients with bone metastases, underscoring the complex interplay between systemic inflammatory markers and treatment outcomes [36].

Our findings carry important clinical implications for managing bone-predominant mRCC. The significant OS benefit observed with TKIs suggests that TKI-containing front-line therapy may be the preferred treatment option for this patient subgroup. This is particularly relevant given that current guidelines often recommend ICI-based combinations as first-line therapy for intermediate- and poor-risk patients [27]. Notably, potential confounding factors such as prior nephrectomy and histology do not appear to explain the OS advantage observed with TKIs. While a higher proportion of patients in the TKI group underwent nephrectomy (67.5% vs. 44.8%), univariate analysis did not support nephrectomy as a significant factor for improved OS ($P = 0.288$). Nonetheless, we recognize that cytoreductive surgery may offer survival benefits in well-selected patients and could be subject to selection bias (i.e., patients with better performance status and fewer metastatic sites may be more likely to undergo nephrectomy). Future prospective studies are needed to clarify whether nephrectomy confers additional benefit in this subgroup. Similarly, although clear cell histology was associated with better survival outcomes (HR = 0.30; $P = 0.009$), the proportion of clear cell carcinoma was slightly lower in the TKI group (77.5% vs. 79.3%). A brief descriptive review of our data indicated that clear cell tumors generally had longer OS in both arms, but definitive subgroup analyses were limited by the modest sample sizes. These findings suggest that the observed OS benefit is

likely attributable to the initial choice of therapy rather than these variables. Additionally, patients in the TKI group received more subsequent lines of therapy on average compared to the ICI group (2.36 vs. 1.38), as shown in Supplemental Table 2, which might have contributed to the improved OS. However, the univariate analysis did not show that prior nephrectomy or the number of metastatic organ systems significantly affected survival, reinforcing that the initial choice of therapy plays a crucial role in patient outcomes.

Our study has several strengths and limitations that warrant discussion. The key strengths include its multicenter design and use of real-world data from two major academic centers, enhancing the generalizability of our findings. By focusing on the specific population of bone-predominant mRCC—a group often excluded from clinical trials—we address a critical gap in the literature. The long follow-up period allows for a comprehensive assessment of survival outcomes. However, important limitations should be considered when interpreting our results. The retrospective nature introduces potential selection biases and limits the ability to establish causality. The modest sample size ($n = 69$) may reduce the statistical power to detect significant differences in PFS and response rates and precludes robust multivariate analyses due to the risk of overfitting. Furthermore, the evolving treatment landscape during the study period may also affect the applicability of our findings. Specifically, we excluded patients who received TKI-ICI combination therapies (due to limited numbers), which is a significant limitation in light of modern practice, where regimens such as axitinib plus pembrolizumab have become first-line standards. As a result, our findings primarily inform the comparison between TKI monotherapy and ICI monotherapy, and it is unclear how they might translate to combination approaches. Prospective studies evaluating TKI-ICI combinations in bone-predominant disease will be essential to determine whether our results extend to current therapeutic regimens. It is also noteworthy that the TKI group had a longer median follow-up (25.3 vs. 17.3 months), which may partially account for the observed OS advantage. Further follow-up of the ICI cohort is necessary to determine whether this survival gap persists over time. Finally, we lacked molecular or advanced imaging data to confirm the angiogenesis signatures or immune profiles of bone metastases, which could have provided mechanistic insights into our clinical observations.

In conclusion, our study suggests that first-line treatment with TKIs offers a significant survival advantage over ICIs in patients with bone-predominant mRCC. These findings have important implications for treatment selection and highlight the need for personalized approaches based on metastatic patterns and tumor biology. Until prospective data are available, clinicians should consider TKI-containing regimens as the preferred front-line option for this patient population. Further research is essential to validate these results and to optimize therapeutic strategies for bone-predominant mRCC.

Supplementary Material

Supplementary tables.
https://www.jcancer.org/v16p4047s1.pdf

Acknowledgments

Author contributions

Conceptualization: LM, JG, YY; Methodology: LM, JG, ML, YY; Data collection: LM, SP, JG, ML, MN, DO, EG; Data analysis and interpretation: LM, JG, YY; Original draft preparation: LM, YY; Manuscript review and editing: All authors.

Competing Interests

Dr. Yuanquan Yang, the corresponding author, reports the following: Advisory Board: Exelixis, Eisai, Xencor; Consulting and Honoraria: The Whiteoak Group, AstraZeneca; Grants: NCI K12CA133250, Gateway for Cancer Research Foundation; Research support to institution: Incyte, Amgen, Novartis, Recordati Rare Diseases, Xencor, Taiho Oncology, AstraZeneca.

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