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Bone Metastases in Renal Cell Carcinoma: Impact of Immunotherapy on Survival

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Abstract. *Background/Aim: We performed a multicenter retrospective observational study to investigate the impact of immune checkpoint inhibitors (ICIs) on the survival of patients with bone metastases (BMs) from renal cell cancer (RCC). Patients and Methods: A total of 98 patients with metastatic RCC (mRCC) treated with ICIs were retrospectively enrolled. All patients received standard treatments with nivolumab alone or in combination with ipilimumab from December 2015 to March 2022. The primary endpoint was median overall survival (OS). Results: Forty-three patients (44%) had radiological evidence of BMs. No statistically significant difference in OS was reported between the BM population and the entire population (p=0.254). Conclusion: Our study suggests some degree of ICI activity to treat patients with BMs from RCC, historically associated with a poorer prognosis.*

Immune-checkpoint inhibitors (ICIs) have undoubtedly revolutionized metastatic renal cell carcinoma (mRCC) treatment (1); however, a significant proportion of patients with mRCC, harbouring some recognized negative prognostic factors, fails to respond to ICI therapy. In this case, approximately one third of patients with mRCC have bone metastases (BMs), which are associated with poor prognosis (2, 3). BMs from RCC are predominantly osteolytic and often associated with skeletal-related events (SREs), such as severe bone pain, pathological fractures, spinal cord compression, hypercalcemia, and need for radiotherapy or surgery (4). The median overall survival (OS) after diagnosis of BMs ranges from 12 to 28 months (2). Systemic treatments of BMs include inhibitors of bone resorption and anabolic signals, namely bone target agents (BTA) like zoledronic acid or nuclear factor-κ B ligand (RANK-L) inhibitor denosumab (5).

Data regarding the efficacy of ICIs in patients with BMs from RCC is sparse. In a CheckMate 9ER exploratory *post hoc* analysis of depth of response in target lesions by organ site, a higher proportion of patients experienced tumor shrinkage with nivolumab plus cabozantinib *versus* sunitinib across all organ sites assessed, including the bone (6). Subgroup analysis of patients with BMs treated with nivolumab on CheckMate 025 in the non-front-line setting showed increased overall response rates (ORR) compared to patients treated with everolimus (26 *vs.* 6%) (7). However, in a large tumor agnostic study, BMs were associated with decreased response to immunotherapy (8). Thus, the potential beneficial effect of ICIs on BMs is, at present, controversial and this is an urgent area for future study. Herein, we conducted a multicentric retrospective study to investigate the potential impact of ICI treatments on the overall survival (OS) of an Italian mRCC population bearing BMs.

Patients and Methods

A cohort of consecutive patients with a histologically confirmed diagnosis of RCC was retrospectively identified from the clinical registries of the Clinical Oncology Unit of Careggi University Hospital, Florence, Italy and the Unit of Medical Oncology of the

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Table I. *Characteristics of the entire study population.*

Characteristics	Frequency	Percentage
Age at RCC diagnosis (n=98)		
Median, 62 (41-82) years		
Sex (n=98)		
Male	76	78%
Female	22	22%
Histology (n=98)		
ccRCC	71	72%
nccRCC	27	28%
Sarcomatoid features		
Yes	10	10%
No	88	90%
IMDC risk group (n=93)		
Favourable	21	22%
Intermediate	64	69%
Poor	8	9%
ICIs		
Nivolumab	96	98%
Nivolumab plus ipilimumab	2	2%

RCC: Renal cell cancer; ccRCC: clear cell renal cell cancer; nccRCC: non clear cell renal cell cancer; IMDC: International Metastatic RCC Database Consortium; ICIs: immune checkpoint inhibitors.

Table II. *Characteristic of the bone metastases study population.*

Characteristics	Frequency	Percentage
Age at RCC diagnosis (n=43)		
Median, 64 (42-84) years		
Sex (n=43)		
Male	34	79%
Female	9	21%
Histology (n=43)		
ccRCC	32	74%
nccRCC	11	26%
Sarcomatoid features (n=43)		
Yes	5	12%
No	38	88%
IMDC risk group (n=41)		
Favourable	6	14%
Intermediate	31	72%
Poor	4	9%
ICIs (n=43)		
Nivolumab	42	98%
Nivolumab plus ipilimumab	1	2%

RCC: Renal cell cancer; ccRCC: clear cell renal cell cancer; nccRCC: non clear cell renal cancer; IMDC: International Metastatic RCC Database Consortium; ICIs: immune checkpoint inhibitors.

University Hospital of Pisa, Italy. All included patients had started nivolumab alone or in combination with ipilimumab as standard treatment for mRCC between December 2015 and March 2022. An institutional review board approval was obtained at each center prior to data collection onset and all selected patients had signed an informed consent for clinical data collection and use for research purposes. Data cut-off was November 2022.

Primary endpoint was OS, the time from first diagnosis to death from any cause.

All statistical analyses were conducted using the R software v4.3.0 (9) and the packages survival v3.5-5 (10), survminer v0.4.9 (11) and dplyr v1.1.2 (12). Significance was concluded at $p<0.05$. Categorical data were reported as percentages, while continuous data were reported as median and range. When necessary, the median value of continuous data was selected as cut-off value.

Differences in continuous data in the same sample but different times were estimated with a paired samples *t*-test. When appropriate, *p*-values were corrected for multiple hypothesis testing with the Bonferroni method. Survival rate between different groups was estimated with the Kaplan-Meier method and log-rank test.

Results

Baseline demographic features. In total, 98 patients with mRCC treated with ICIs were enrolled in the study. The basal clinical and pathological features of the entire population are described in Table I. The median age at diagnosis was 62 years and 78% of patients were male (n=76). Forty-three patients (44%) had radiological evidence of BMs; among these, 5 patients (12%) had a diagnosis of clear cell (cc) RCC with sarcomatoid features (Table II). Most patients (84%) had extraosseous metastases. In addition, among patients with evidence of BMs, 35 patients (81%) received the radical nephrectomy and 9 patients (21%) resection of BMs (Table II).

The onset of BMs and the diagnosis of primary RCC were mostly metachronous (98%). With regards to the number of BMs, 13 patients (30%) had solitary BMs and 30 patients (70%) had multiple BMs. Thirteen patients (30%) had more than five BMs. The prevalent BM site was the spine (57%), while 43% of patients the appendicular skeleton, including 33.4% with both axial and appendicular colonization (Table III). Twelve patients received BTA, including zoledronic acid (82%, n=10/12) or denosumab (18%, n=2/12). Regarding systemic treatments, 98% of patients with BMs (n=42/43) received second line and subsequent therapy with nivolumab, whereas 1 patient out of 43 underwent first line therapy with nivolumab plus ipilimumab within an Italian Expanded Access Program (Table II). As shown in Table I, 26% (n=11/43) of patients with BMs developed one SRE. Pathological fractures occurred in 100% (n=11) of patients with experienced SREs. Among patients who experienced one SRE, only 2 (2%) were previously treated with BTA such as bisphosphonates (Table III).

Actuarial overall survival. At the time of data lock, 45 patients were deceased and 52 were still alive, while one was lost to follow-up. The median OS was 30 months for the overall population. No statistically significant difference in OS was found between the BM population and the entire

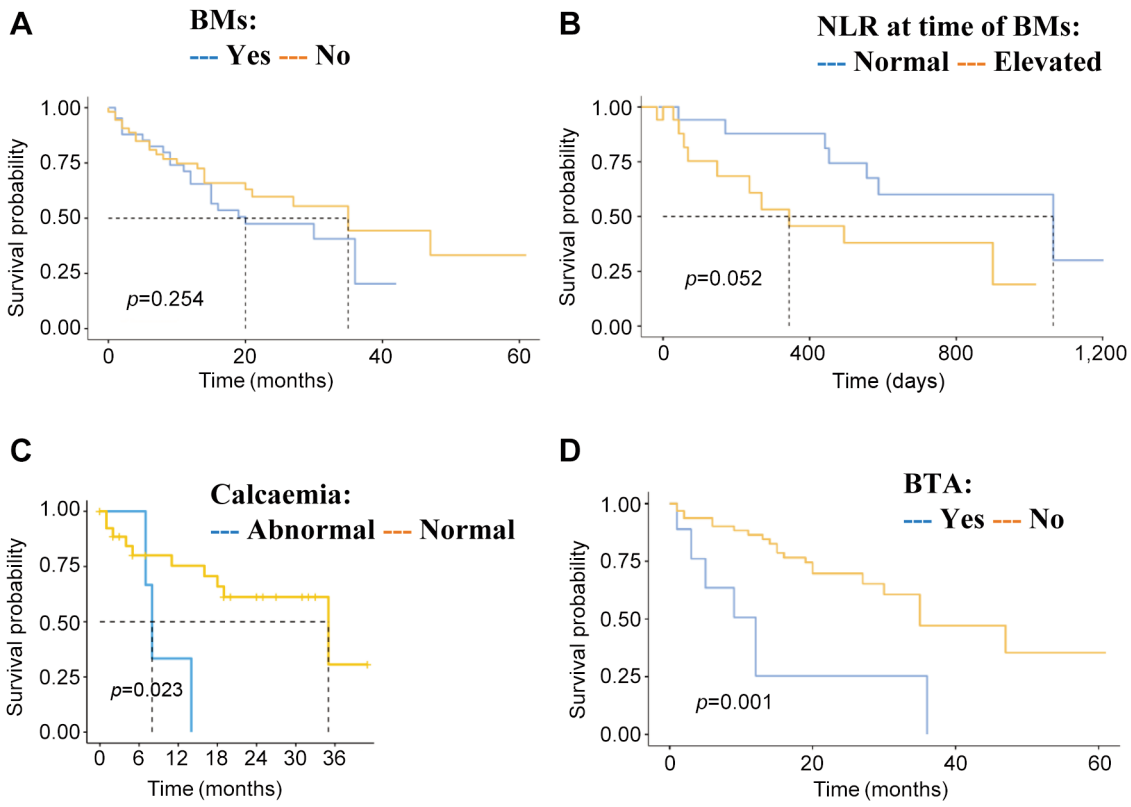

Figure 1. *Overall survival of study population. A) Overall survival according to presence or absence of bone metastases. B) Overall survival according to value of basal neutrophil/lymphocyte ratio (NLR) among bone metastases patients. C) Overall survival according to basal calcaemia among bone metastases patients. D) Overall survival according to use of bone resorption inhibitors [bone target agents (BTA)] among patients with bone metastases.*

population (p=0.254) (Figure 1A). A better OS was found for patients with normal neutrophil lymphocyte ratio (NLR) at baseline rather than patients with to elevated NLR (36.0 months *vs*. 12.0 months, p=0.023). Among patients with BMs, those with a normal NLR at the time of BMs detection at baseline had better survival than those with an elevated NLR (p=0.052) (Figure 1B). In the BM population, better OS was associated with normal basal calcaemia (35.0 months *vs*. 8.0 months, p=0.023; Figure 1C). In addition, the use of BTA was associated with worse OS in the BM population (12 months *vs*. 35 months, p=0.001) (Figure 1D).

Discussion

BMs are frequently developed in cancer and have a negative impact on the quality of life and survival. BMs are considered an independent risk factor for decreased survival (3). However, the results of our analysis do not support this conclusion and suggest a positive effect of immunotherapy. In support of our results, a subgroup analysis of CheckMate 025 trial showed that median OS of patients with BMs was 18.5 months [95% confidence interval (CI)=10.2–not reached] with nivolumab and 13.8 months (95%CI=7.0-16.4) with everolimus (6). Although BM is a poor prognostic factor for RCC, the ICIs provide hope for RCC patients with BMs. In addition, our literature research identified three case reports showing radiological complete response of BMs from RCC upon ICIs treatment (13-15). Finally, BTA may be recommended. Although our analysis showed an apparently detrimental effect of BTA during immunotherapy, this result deserves further consideration. In the real-world setting, the use BTA is often reserved for advanced BMs. Thus, the cohort of patients treated with BTA is probably a "negative" selected population. Furthermore, of the 12 patients who received BTA in our study, 10 received bisphosphonates whereas only 2 patients received denosumab, in absence of data suggesting a synergistic effect between bisphosphonates and ICIs. In a small retrospective analysis, there was an increased survival trend in patients taking BTA, both zoledronic acid and denosumabin in combination with tyrosine kinase inhibitor (TKI) (sunitinib or pazopanib) *versus* TKI alone: 29.6 months (95%CI=7.2-51.9) *versus*

Table III. *Characteristics of metastatic disease in the bone metastases (BMs) study population.*

Characteristics	Frequency	Percentage
Presence of extraosseous mts (n=43)		
No	7	16
Yes	36	84
Time of BMS diagnosis (n=43)		
Synchronous	18	42
Metachronous	25	58
Sites of BMs (n=42)		
Axial	24	56
Appendicular	4	9
Both	14	33
Number of BMS (n=42)		
Single site	13	30
<5	16	37
≥5	13	30
Calcaemia at BMs diagnosis (n=34)		
<ULN	30	70
≥ULN	4	9
Use of BTA (n=43)		
No	31	72
Bisphosphonates	10	23
Denosumab	2	5
Palliative RT (n=41)		
Yes	36	88
No	5	12
SRE (n=42)		
Yes	11	26
No	31	74

Mts: Metastases; BMs: bone metastases; RT: radiotherapy; BTA: bone target agents; SRE: skeletal related events.

13.8 months [(95%CI=12.3-15.2), hazard ratio (HR)=1.66, 95%CI=0.62-4.45, p=0.31] (16). Although there have been no reports on the combined treatment for BMs from RCC, denosumab has been licensed for the treatment of mRCC and the combined of systemic treatment (TKI, ICIs) and denosumab may be recommended in RCC with BMs data in preclinical mouse tumor models and some retrospective studies enrolling patients with lung cancer and melanoma suggest synergistic effects of the combined administration of ICIs and denosumab (17). Regarding RCC, a phase II study (NCT03280667) is ongoing. Additionally, combination of local treatment on BMs (radiotherapy or surgery) ant immunotherapy could improve overall survival in patients with mRCC (18).

In line with what was expected, our study showed a negative correlation between high NLR (≥3) and survival. Local and systemic inflammation may lead to a neutrophilia leading to the suppression of the cytolytic activity of immune cells like lymphocytes, natural killer cells and activated T cells (19).

The alteration of peripheral blood biomarkers including NLR can represent a systemic inflammatory response. Several studies have demonstrated that NLR is a negative prognostic biomarker associated with a worse OS in mRCC in the pre-immunotherapy era (20). A recent review and meta-analysis, which explored the utility of NLR in patients with mRCC treated with ICIs, revealed that the high NLR group at baseline or pre-therapy had a shorter OS than the low NLR group (combined HR=2.23; 95%CI=1.84-2.70; p<0.001). Furthermore, a decrease in NLR during treatment was a predictor of a longer OS (HR=0.34; 95%CI=0.20-0.56; p<0.001) (20). Therefore, NLR, similarly others factors like serum C-reactive protein (CRP), neopterin, and urinary neopterin, lower serum albumin and hemoglobin concentration, could be considered a reliable biomarkers of activation of immune response, associated with outcome in mRCC patients treated with ICI immunotherapy (21).

Our study suggests some degree of ICI activity in the treatment of patients with BMs from RCC, which were historically associated with a poorer prognosis. Hopefully, the new standard of care based on combination therapies (like ICIs and TKIs) would improve more the OS of mRCC, even when BMs is present (22). Due to the exiguity of the examined population and the retrospective nature of our analysis, additional studies must be performed to shed light in the evaluation of the response of BMs to ICI treatment.

Conflicts of Interest

The Authors declare that the research was conducted in the absence of commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' Contributions

All the Authors contributed to the preparation of this work and read and approved the final manuscript. EG, SP, and LA contributed to study conception and design. EG, VEP, VR, EF, AB, AS, LG, MMM, and SP were responsible for collecting the data, analysis, and drafting the first copy. EG, EF, and SP were responsible for editing the manuscript. LA, EG, and SP were responsible for the final editing and preparation of the manuscript for submission.

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