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Bone Metastases, Skeletal-Related Events, and Survival in Patients With Metastatic Non–Small Cell Lung Cancer Treated With Immune Checkpoint Inhibitors

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Abstract

Background: Bone metastases and skeletal-related events (SREs) are a frequent cause of morbidity in patients with metastatic non–small cell lung cancer (mNSCLC). Data are limited on bone metastases and SREs in patients with mNSCLC treated using immune checkpoint inhibitors (ICIs), and on the efficacy of bone-modifying agents (BMAs) in this setting. Here we report the incidence, impact on survival, risk factors for bone metastases and SREs, and impact of BMAs in patients with mNSCLC treated with ICIs in a multi-institutional cohort.

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Patients and Methods: We conducted a retrospective study of patients with mNSCLC treated with ICIs at 2 tertiary care centers from 2014 through 2017. Overall survival (OS) was compared between patients with and without baseline bone metastases using a log-rank test. A Cox regression model was used to evaluate the association between OS and the presence of bone metastases at ICI initiation, controlling for other confounding factors.

Results: We identified a cohort of 330 patients who had received ICIs for metastatic disease. Median patient age was 63 years, most patients were treated in the second line or beyond (n=259; 78%), and nivolumab was the most common ICI (n=211; 64%). Median OS was 10 months (95% CI, 8.4–12.0). In our cohort, 124 patients (38%) had baseline bone metastases, and 43 (13%) developed SREs during or after ICI treatment. Patients with bone metastases had a higher hazard of death after controlling for performance status, histology, line of therapy, and disease burden (hazard ratio, 1.57; 95% CI, 1.19–2.08; *P*=.001). Use of BMAs was not associated with OS or a decreased risk of SREs.

Conclusions: Presence of bone metastases at baseline was associated with a worse prognosis for patients with mNSCLC treated with ICI after controlling for multiple clinical characteristics. Use of BMAs was not associated with reduced SREs or a difference in survival.

Background

More than one-third of patients with metastatic non–small cell lung cancer (mNSCLC) will develop bone metastases during the course of their illness.[1] Development of bone metastases often leads to significant morbidity, with approximately 70% of patients needing opioids for pain.[2] The presence of bone metastases also increases the risk for skeletal-related events (SREs), including pathologic fracture. The prognostic significance of bone metastases with respect to mortality is unclear, with one recent meta-analysis of patients with mNSCLC treated with chemotherapy reporting that bone metastases were associated with improved overall survival (OS) compared with other metastatic sites.[3]

Few studies have evaluated the prognostic significance of bone metastases in the setting of immune checkpoint inhibitors (ICIs), although data show that bone metastases may be less responsive to ICIs.[4,5] Prior studies of bone metastases and immunotherapy have been limited to specific patient populations, including those receiving specific lines of therapy and types of ICI, and did not include assessment of SREs or impact of use of bone-modifying agents (BMAs).[6,7] Bone may represent an immunosuppressive tumor microenvironment, thereby limiting the efficacy of ICIs.[8] Mechanisms of immunosuppression include the disruption of the osteoblast–osteoclast remodeling cycle to induce a favorable growth environment for metastases, a decreased population of cytotoxic T cells and natural killer cells, and an increased population of suppressive immune cells, such as regulatory T cells and myeloid-derived suppressor cells.[9]

The FDA has approved the use of BMA, including bisphosphonates (pamidronate and zoledronic acid) and denosumab (a monoclonal antibody against RANKL), for the management of bone metastases in all solid tumors, and the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Non–Small Cell Lung Cancer (Version 6.2020) recommend consideration of these therapies in patients with mNSCLC who

have bone metastases.[10] Much of the data are extrapolated from large clinical trials in breast cancer, prostate cancer, and multiple myeloma. In lung cancer, zoledronic acid and denosumab reduce the risk of SREs[11,12] and serve as an adjunctive therapy to palliative radiation to control pain.[11] Retrospective analysis does not suggest that zoledronic acid improves survival in NSCLC, unlike in multiple myeloma, and an exploratory analysis suggested that denosumab was associated with an improvement in survival compared with zoledronic acid.[13,14] The ability of BMAs to prevent SREs, and their impact on survival in the era of ICIs in patients with mNSCLC has not been studied.

We examined the impact of bone metastases and SREs on OS in patients with mNSCLC treated using ICIs, and evaluated the use of BMAs and their impact on survival and SREs. In addition to corroborating prior published studies examining the prognostic significance of bone metastases and determining the prognostic impact of bone metastases in the setting of different treatment modalities, we also evaluated a cohort of patients with mNSCLC treated with chemotherapy alone in whom we also recorded the incidence of bone metastases.

Patients and Methods

ICI Cohort

All patients who received ICIs for mNSCLC at University of Michigan and The Ohio State University between 2014 and 2017 were included in this retrospective analysis. These studies were approved by the Institutional Review Boards of both institutions. Patient demographics, disease characteristics (stage, histology, genomic alterations, metastatic burden [defined as the number of metastatic organ systems involved: 1, 2, ≥2]), treatment received (including ICIs and BMAs), PD-L1 status when known, and response to treatment were all collected in a REDCap database.[15] The presence of bone metastases was assessed on routine imaging obtained as part of standard of care before ICI initiation; for the purpose of this study, we defined baseline bone metastases as the presence before initiation of ICI treatment. SREs included pathologic bone fracture, palliative osseous radiation, or surgical intervention. OS was calculated from the date of ICI initiation until the date of death from any cause or was censored at loss to follow-up. Median OS with 95% confidence intervals was estimated using the Kaplan-Meier method. OS was compared between patients with and without baseline bone metastases using a log-rank test. A Cox regression model was used to study the association between OS and baseline bone metastases, controlling for ECOG performance status, cancer histology, line of therapy, and metastatic burden. Patient characteristics were summarized and compared between those with and without SREs using the Fisher exact test for the categorical risk factors and the Kruskal-Wallis test for the continuous variables. All statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc).

Chemotherapy-Only Cohort

An independent cohort of patients with mNSCLC treated using chemotherapy alone at University of Michigan in 2014 through 2017 were included in this analysis, which was approved by the Institutional Review Board. Information on patient demographics, histology, and chemotherapy regimen used was collected. Patients were divided into those

with and without bone metastases, and OS data were collected. Patient date of death and time to progression were used to generate Kaplan-Meier plots of OS followed by log-rank tests. Date of death was used as a primary endpoint. Patients still alive were censored at the time of last follow-up. Median and 95% confidence intervals for OS were reported.

Results

Patient Characteristics

A total of 330 patients with mNSCLC who received ICIs were identified. Median age was 63.4 years, 156 patients (47%) were male, 289 (88%) were current or former smokers, 219 (66%) had adenocarcinoma histology, and 211 (64%) received nivolumab (Table 1). Of all patients included, 124 (38%) had baseline bone metastases at ICI initiation. There were no significant differences between patients with versus without bone metastases in terms of sex (P=.753), smoking status (P=.838), histology (P=.490), or line of therapy (P=.567) (see supplemental eTable 1, available with this article at JNCCN.org). Median OS for the entire cohort was 10 months (95% CI, 8.4–12.0). PD-L1 by tumor proportion score was positive in 68 patients (20.6%), negative in 28 (8.5%), and unknown in 234 (70.9%), with no significant differences between patients with versus without bone metastases (supplemental eTable 1). Of the 124 patients with baseline bone metastases, 65 had received prior radiation, and no significant difference in survival was observed in these patients compared with those who had not received radiation (P=.187).

SRE Incidence and Risk Factors

SREs occurred in 43 patients in the entire cohort (13%), with a median time to SRE of 2.8 months. Histology, the presence of specific oncogenic mutations (*KRAS*, *EGFR*, *TP53*), sex, and age were not predictive for the development of SREs (Table 2). Median duration of ICI treatment in patients who developed SREs was 2.5 months (interquartile range, 1.3–7.9) and was not significantly different compared with those who did not develop SREs (2.3 months; IQR, 0.9–7.2; P=.790). The only predictive factors identified in the entire cohort were the presence of baseline bone metastases (P<.001) and the development or progression of bone metastases after ICI initiation (P<.001). Therefore, a subgroup analysis of risk factors for SREs was conducted only in the 124 patients with baseline bone metastases (Table 3). Age, sex, histology, mutational status, ECOG performance status, and PD-L1 were not associated with risk of SREs in patients with bone metastases.

BMA Use and SREs

Of the 124 patients with bone metastases at baseline, 65 (52%) received BMAs. There was no significant association between use of BMAs and development of SREs (P=.84).

Bone Metastases and Survival

Patients with baseline bone metastases had shorter survival compared with those without bone metastases, with a median OS of 5.9 months (95% CI, 4.2–7.8) versus 13.4 months (95% CI, 10.8–17.0; P<.001), respectively (Figure 1). Patients with baseline bone metastases also had a higher hazard of death than those without after controlling for ECOG performance status, histology, line of therapy, and metastatic burden (hazard ratio, 1.57;

95% CI, 1.19–2.08; *P*=.001). Development of SREs, irrespective of baseline bone metastases status, was associated with a shorter OS (median, 7.5 months [95% CI, 4.6–10.0] vs 10.6 months [95% CI, 8.4–12.8]; *P*=.041). Use of BMAs in 65 patients did not impact OS (*P*=.778), and the type of BMA used (bisphosphonates, n=37; denosumab, n=28) was not correlated with OS (*P*=.622).

Prognostic Significance of Bone Metastases in Patients Treated With Chemotherapy Alone

A total of 166 patients with mNSCLC treated with chemotherapy alone at the University of Michigan were evaluated in the chemotherapy-only cohort. Median age at chemotherapy was 66 years, 90 patients (54.2%) were male, 141 (85%) were former or current smokers, 131 (78.9%) had adenocarcinoma histology, and the most common treatment regimen was carboplatin/pemetrexed (supplemental eTable 2). There was no statistically significant difference in survival between patients with or without bone metastases treated with chemotherapy alone (median OS, 15.4 vs 12.8 months, respectively; *P*=.757; Figure 2).

Discussion

In our multi-institutional study of patients with mNSCLC treated with ICIs, the presence of bone metastases was an independent adverse prognostic factor associated with worse OS after controlling for ECOG performance status, cancer histology, and line of therapy. Our finding is strengthened by our observation that, when accounting for metastatic burden, the presence of bone metastases was still a negative prognostic factor. In a separate independent cohort of patients treated with chemotherapy only, we found that the presence of bone metastases did not have any prognostic significance with respect to survival, corroborating prior studies.[3] This analysis supports that bone metastases convey a different prognostic significance depending on treatment modality (chemotherapy vs immunotherapy) and adds to the literature supporting the negative impact of bone metastases in the era of checkpoint inhibition in mNSCLC. To our knowledge, this is the first study to show the negative impact of bone metastases regardless of line of therapy, and the first to explore the relationship between BMA use, SREs, and outcomes in these patients.

ICIs are now approved as first-line treatment either alone or in combination with chemotherapy for most patients with mNSCLC.[16] Emerging data suggest that different sites of metastases may portend different prognostic significance. In a large retrospective study of 1,025 patients with mNSCLC treated using ICIs, a multivariable analysis showed that brain metastases were not associated with worse OS,[17] similar to findings in patients treated with chemotherapy.[18] However, liver metastases, which are also common in mNSCLC, have been associated with poor prognostic significance in patients treated using both chemotherapy and ICIs.[4,9] Recently, malignant pleural effusion has also been shown to be a predictor of poor outcomes in patients treated with ICIs.[19,20] In addition to the sites of disease involved, several indices of inflammation derived from routine blood testing have also been explored,[21] although these biomarkers are broadly prognostic and do not seem to be specifically predictive for immunotherapy.

Preclinical data suggest that the bone tumor microenvironment is immunosuppressive, thereby potentially negating the effect of ICIs.[8] Although prior studies have shown that liver

and brain metastases hold the same prognostic significance irrespective of treatment type, in our study, bone metastases stand out given their different impact depending on treatment modality.

Current clinical practice, informed by the NCCN Guidelines,[10] recommends the use of specific antineoplastic therapy in eligible patients with mNSCLC; bisphosphonates or denosumab may be considered for those with bone metastases.[16] Although zoledronic acid has been shown to delay time to SRE, it has not been shown to improve OS.[22] Denosumab was shown to be noninferior to zoledronic acid with respect to delaying the onset of SREs, and a subgroup exploratory analysis suggested an OS advantage compared with zoledronic acid.[11] In preclinical models and small studies, synergy between BMAs and ICIs has also been suggested.[23,24] In our study, however, we found no association between BMA use and incidence of SREs, and observed no impact on survival. Although the overall number of patients who received BMAs was small, the lack of an association with incidence of SREs lends further credence to our finding that the presence of bone metastases conveys a negative prognostic significance with the use of immunotherapy in terms of both morbidity and mortality. Finally, the use of BMAs in just more than half of patients with bone metastases suggests widespread variability in the use of BMAs in patients with mNSCLC and bone metastases. Although the differing patterns of BMA use have been observed in prior studies,[25] as the median duration of survival continues to improve with the changing treatment landscape for mNSCLC,[26] the ability to delay and prevent SREs will remain vital to minimize these life-changing or life-limiting events.

Although our study is the largest study to address this question, a major limitation is its retrospective nature. Most patients received ICIs as second-line therapy, but the standard of care over the past 2 years has moved to ICIs as first-line treatment (either alone or in combination with chemotherapy). Therefore, our observation needs to be validated in the present treatment paradigm. We also did not specifically evaluate patients with bone metastases as the sole site of metastatic disease. The lack of known PD-L1 status for all patients is a further limitation. Finally, we did not measure response in the bone, which can be problematic with current imaging techniques.[27]

Conclusions

Our study contributes to the increasing body of evidence showing that the benefit of ICIs is partly determined by the involved site(s) of disease. In our study, patients treated with ICIs who had bone metastases had shorter survival than those without, and may represent a population at risk of poor outcomes from ICIs to be considered for further study. Finally, use of BMAs was not associated with a reduced risk of SREs or survival, although the patterns of use varied significantly.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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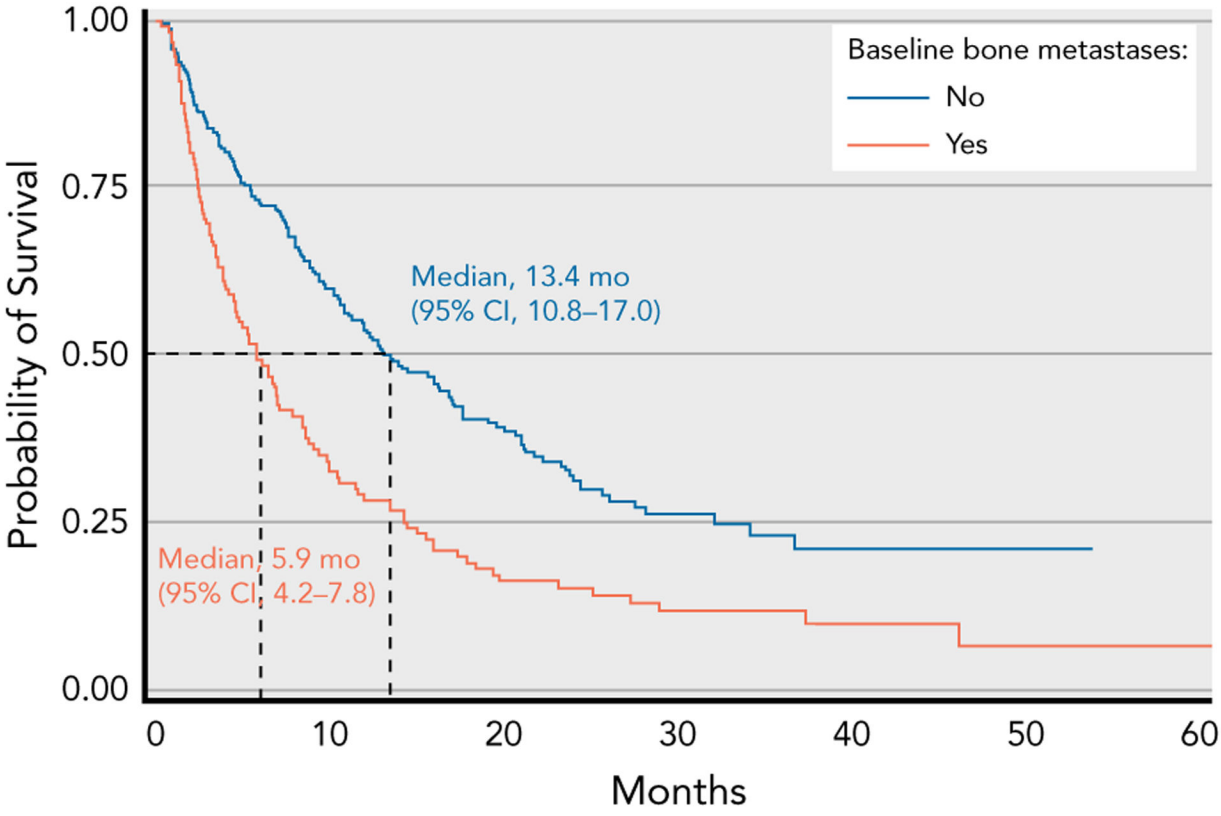

Figure 1.

Kaplan-Meier curve of patients with mNSCLC treated using ICIs. Patients with bone metastases before ICI initiation had a statistically significant worse OS than those without bone metastases. Abbreviations: ICI, immune checkpoint inhibitor; mNSCLC, metastatic non–small cell lung cancer; OS, overall survival.

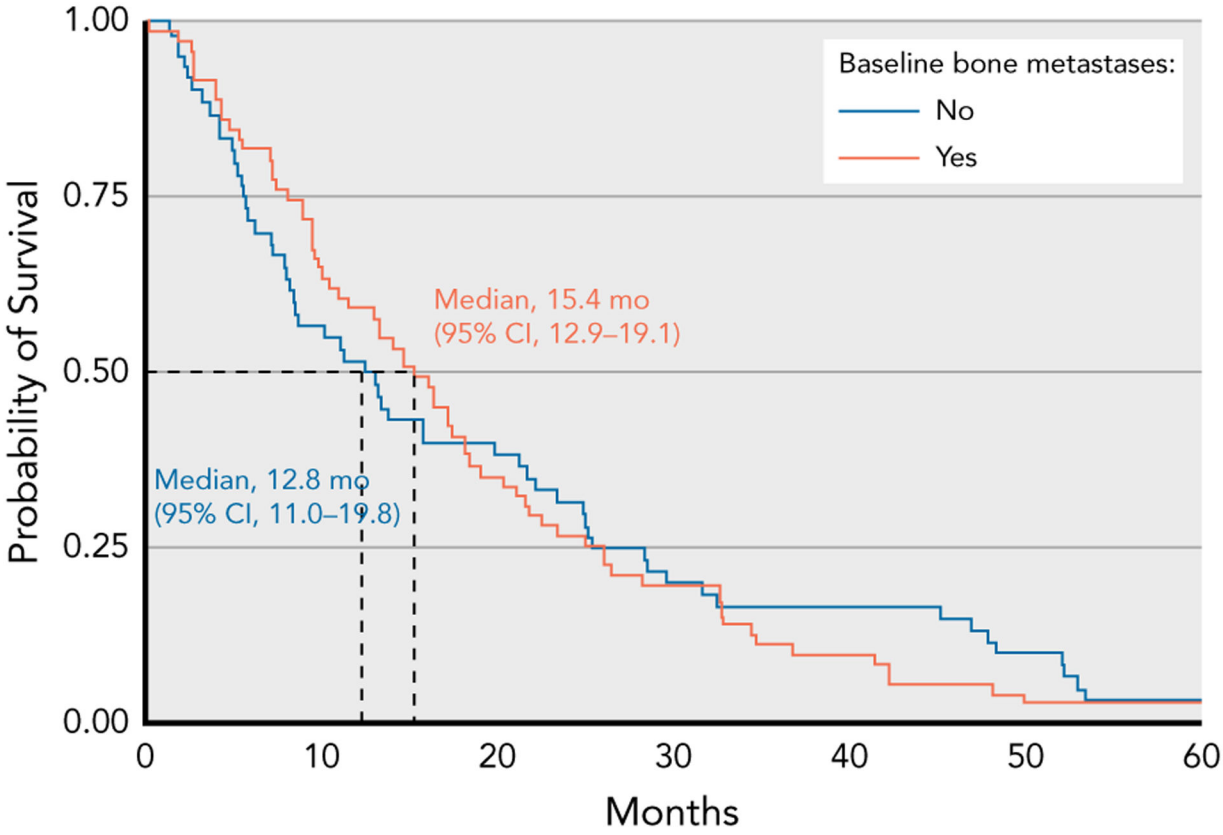

Figure 2.

Kaplan-Meier curve of patients with mNSCLC treated using chemotherapy alone. There was no difference in OS regardless of the presence of bone metastases.

Abbreviations: mNSCLC, metastatic non–small cell lung cancer; OS, overall survival.

Table 1.

Characteristics of Patients With mNSCLC Treated Using ICIs

	n (%)
Total, N	330
Median age at ICI, y	63.4
Sex	
Male	156 (47)
Female	174 (53)
Smoking	
Never	41 (12)
Current/Former	289 (88)
Histology	
Adenocarcinoma	219 (66)
Squamous	86 (26)
Other	25 (8)
Line of ICI	
First	91 (28)
Second	160 (48)
≥Third	79 (24)
Type of ICI	
Nivolumab	211 (64)
Pembrolizumab	55 (17)
Atezolizumab	22 (6)
Other	42 (13)
Baseline BM	124 (38)

Abbreviations: BM, bone metastases; ICI, immune checkpoint inhibitor; mNSCLC, metastatic non–small cell lung cancer.

Table 2.

Risk Factors for Development of SREs

Characteristic	No SRE n (%)	SRE n (%)	Total n (%)	*P* Value
Total	287 (87)	43 (13)	330 (100)	
Age at ICI, y				.758
Median (IQR) [min, max]	63.4 (57–71.9) [33.9, 88]	64.9 (58–71.1) [39.7, 91.7]	63.4 (57–71.7) [33.9, 91.7]	
Duration of treatment, mo				.790
Median (IQR) [min, max]	2.3 (0.9–7.2) [0.4, 46.5]	2.5 (1.3–7.9) [0.5, 42.5]	2.3 (0.9–7.20 [0.4, 46.5]	
Baseline BM				<.0001
No	196 (68)	10 (23)	206 (62)	
Yes	91 (32)	33 (77)	124 (38)	
Histology				.755
Adenocarcinoma	190 (66)	29 (67)	219 (66)	
Squamous cell	74 (26)	12 (28)	86 (26)	
Large cell	11 (4)	0 (0)	11 (3)	
Adenosquamous	5 (2)	1 (2)	6 (2)	
NSCLC, NOS	7 (2)	1 (2)	8 (2)	
Development of BM on ICI				<.0001
No	250 (87)	6 (14)	256 (78)	
Yes	37 (13)	37 (86)	74 (22)	
BMA use				.840
Yes	47 (72)	18 (28)	91 (73)	
No	44 (75)	15 (25)	33 (27)	
KRAS mutation				1.000
No	211 (74)	32 (74)	243 (74)	
Yes	76 (26)	11 (26)	87 (26)	
EGFR mutation				1.000
No	279 (97)	42 (98)	321 (97)	

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Characteristic	No SRE n (%)	SRE n (%)	Total n (%)	*P* Value
Yes	8 (3)	1 (2)	9 (3)	
TP53 mutation				.842
No	226 (79)	33 (77)	259 (78)	
Yes	61 (21)	10 (23)	71 (22)	
Sex				.625
Male	134 (47)	22 (51)	156 (47)	
Female	153 (53)	21 (49)	174 (53)	
ECOG performance status				.811
Missing	4 (1)	0 (0)	4 (1)	
0	50 (18)	7 (16)	57 (17)	
1	161 (57)	23 (53)	184 (56)	
≥2	72 (25)	13 (30)	85 (26)	
Smoking status				.804
Never	35 (12)	6 (14)	41 (12)	
Current/Former	252 (88)	37 (86)	289 (88)	

Abbreviations: BM, bone metastases; BMA, bone-modifying agent; ICI, immune checkpoint inhibitor; IQR, interquartile range; max, maximum; min, minimum; NOS, not otherwise specified; NSCLC, non–small cell lung cancer; SRE, skeletal-related event.

Table 3.

Risk Factors for Development of SREs in Patients With Baseline Bone Metastases

Characteristic	No SRE n (%)	SRE n (%)	Total n (%)	*P* Value
Total, n	91	33	124	
Age at ICI, y				.473
Median (IQR) [min, max]	63.2 (56.3–71.3) [33.9, 86.8]	65 (57.4–71.1) [39.7, 91.7]	63.5 (56.8–71.2) [33.9, 91.7]	
Sex				.694
Male	45 (49.5)	15 (45.5)	60 (48.4)	
Female	46 (50.5)	18 (54.5)	64 (51.6)	
Histology				.675
Adenocarcinoma	60 (65.9)	22 (66.7)	82 (66.1)	
Squamous	21 (23.1)	9 (27.3)	30 (24.2)	
Other	10 (11.0)	2 (6.1)	12 (9.7)	
KRAS mutation				.665
No	67 (73.6)	23 (69.7)	90 (72.6)	
Yes	24 (26.4)	10 (30.3)	34 (27.4)	
EGFR mutation				.790
No	89 (97.8)	32 (97)	121 (97.6)	
Yes	2 (2.2)	1 (3.0)	3 (2.4)	
Smoking status				.876
Never	12 (13.2)	4 (12.1)	16 (12.9)	
Current/Former	79 (86.8)	29 (87.9)	108 (87.1)	
ECOG PS				.995
Missing	2 (2.2)	0 (0.0)	2 (1.6)	
0	13 (14.3)	5 (15.2)	18 (14.5)	
1	49 (53.8)	18 (54.5)	67 (54.0)	
2	25 (27.5)	9 (27.3)	34 (27.4)	
≥3	2 (2.2)	1 (3.0)	3 (2.4)	
PD-L1				.133

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Characteristic	No SRE n (%)	SRE n (%)	Total n (%)	*P* Value
Missing	70 (76.9)	21 (63.6)	91 (73.4)	
Negative	10 (11.0)	2 (6.1)	12 (9.7)	
Positive	11 (12.1)	10 (30.3)	21 (16.9)	

Abbreviations: ICI, immune checkpoint inhibitor; IQR, interquartile range; PS, performance status; SRE, skeletal-related event.