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Are bone targeted agents still useful in times of immunotherapy? The SAKK 80/19 BTA pilot study

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ABSTRACT

Background: Patients with bone metastases from solid tumors often have additional treatment with bone targeted agents (BTAs) to avoid symptomatic skeletal events (SSEs) such as clinically significant pathological fracture leading toradiation therapy or surgery to the bone, spinal cord compression, or hypercalcemia. The absolute value of BTA treatment in the era of immunotherapy (IO) is unknown.

Methods: Patients with bone metastases treated with immunotherapy within the Alpine Tumor Immunology Registry were compared based on whether they received an additional BTA such as denosumab or zoledronic acid. The primary endpoint was time to first SSE. Continuous data were summarized as median and range, categorical data using frequency counts and percentages. Kaplan-Meier estimates were used to describe and visualize the effect of categorical variables.

Results: One hundred and ninety-seven patients with bone metastases and treatment with immunotherapy such as nivolumab (48 %), pembrolizumab (40 %), atezolizumab (12 %), ipilimumab (9 %) and other immunotherapy (5 %) were included. The most frequent tumor types were lung cancer (50 %), malignant melanoma (11 %), renal cell cancer (10 %) and bladder cancer (9 %), respectively. One hundred and twenty-two patients (62 %) received a BTA treatment (91 % denosumab). The median treatment duration of a BTA was 178 days (min: 1 day, max: 2010 days). Out of the 197 patients, 47 (24 %) experienced at least one SSE, 100 (51 %) had bone pain. Ten of the 122 patients (8 %) receiving a BTA developed osteonecrosis of the jaw (ONJ). The percentage of patients without an SSE at fixed time points was higher if treated with a BTA (e.g., at 6 months, 92 % [95 % CI: 84 % - 96 %] versus 88 % [95 % CI: 77 % - 94 %]), but no significant difference in time to first SSE (HR 0.69; 95 % CI 0.34–1.39, log-rank $p = 0.29$) or time to first bone pain (HR: 0.85; 95 % CI: 0.51–1.43, $p = 0.54$) between these two groups could be detected. There were differences in OS between patients treated with a BTA and patients not treated with a BTA (HR: 1.46; 95 % CI: 1.01–2.10, $p = 0.043$).

Conclusion: No significant difference in time to first SSE or bone pain was observed between patients who have received a BTA or not when treated with immunotherapy. Based on these retrospective results the indication of BTAs to reduce SSEs in cancer patients under treatment with immunotherapy needs further evaluation.

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1. Introduction

The occurrence of bone metastases is common among patients with solid tumors, frequently seen with specific cancer types such as breast-, prostate-, lung- and kidney cancer and is associated with additional pain and fatigue, impaired quality of life and skeletal complications (skeletal-related events [SREs] and symptomatic skeletal events [SSEs]) (Cleeland et al., 2016; Smith et al., 2015; Coleman, 1997). Several bone-targeting agents (BTAs) have been developed to restore the healthy equilibrium between bone resorption and formation. One class of BTAs are bisphosphonates (BPs) that bind to bone and slow down the bone resorption activity of osteoclasts. BPs are nowadays usually replaced by receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors (e.g., denosumab), which influence the differentiation, proliferation and survival of osteoclasts (Roodman, 2004). In the pre-immunotherapy period, these BTAs demonstrated greater effectiveness than BPs in breast and prostate cancer, while maintaining comparable efficacy in other types of solid tumors (Lipton et al., 2007).

Although BTA treatment in principle is recommended by various guidelines to be initiated as soon as bone metastases are diagnosed and whether they are symptomatic or not, the optimal frequency and duration of BTA therapy over the longer term is still unknown (von Moos et al., 2019; Bouganim et al., 2011). According to international guidelines dose and dosing interval should be assessed on an individual patient basis including the risk for an SRE and the overall status of control of the tumor (Coleman et al., 2020). However, there is no validated tool to predict which patients will develop an SRE. On the one hand, in a Swiss survey one-third of the physicians treating patients with solid tumors and bone metastases reported reducing dosing frequency to once every 12 weeks after 2 years and 16 % reported implementation of 12-weekly dosing even after 1 year (Mark et al., 2020). On the other hand, evidence suggests that BTAs are routinely prescribed beyond the 1–2-year evaluation period of most registration randomized controlled trials and that, once started, they are rarely discontinued (Clemons et al., 2004; Holen and Coleman, 2010). Within this context, it is important to note that patients diagnosed with bone metastases limited to the skeleton often have a prolonged disease course (Rosen et al., 2003; Aapro et al., 2010), and up to 20 % of patients with metastatic bone disease survive for more than 5 years (Aapro et al., 2010). Physicians must, therefore, consider the implications of cumulative BTA dosing, as the risk of BTA-related adverse events (such as hypocalcemia, renal toxicity, osteonecrosis of the jaw (ONJ), atypical fractures and vascular events (Giordano et al., 2008; Arslan et al., 2011; John Camm, 2010; Wilkinson et al., 2010; von Moos et al., 2018; Gillessen et al., 2019)) is directly proportional to both drug potency and cumulative dose (Mariotti, 2008).

Survival data on the additional treatment of patients with bone metastases using BTAs were collected a decade ago and do not reflect the current therapeutic options for patients with solid tumors. In particular, the use of immunotherapy (IO) in various tumor types has revolutionized the treatment landscape in cancer care and significantly improved prognosis. Consequently, immunotherapy is now a crucial component in the first-line treatment of various solid tumors in the metastatic setting, such as lung carcinoma without an actionable driver mutation, malignant melanoma, or renal cell carcinoma (Planchard et al., 2018; Michielin et al., 2019; Powles et al., 2021). Retrospective data suggest that BTAs could potentially improve survival in NSCLC patients with bone metastases and treated with immunotherapy (Bongiovanni et al., 2021). Therefore, we aim to investigate the impact of BTAs on the outcome in patients with any solid tumors and bone metastases under immunotherapy.

2. Material and methods

2.1. Patients and inclusion criteria

Patients diagnosed with bone metastases undergoing immunotherapy within the SAKK 80/19 Alpine Tumor Immunology Registry were subjected to comparison based on whether they were administered an additional BTA such as denosumab or zoledronic acid or not.

2.2. Statistical analysis

The primary endpoint was time to first SSE. An SSE was defined as one of the following events: clinically significant pathological fracture, radiation therapy to the bone, surgery to the bone, or spinal cord compression. Any further events within 12 weeks after the occurrence of an SSE belonged to the initial SSE, and hence did not count as a second SSE. Time to first SSE was calculated as the time from the start date of the first immunotherapy line to the date of the first recorded SSE. Patients that did not experience any SSE were censored at the last date known to be alive. Patients in the BTA cohort that experienced an event before the BTA administration were excluded from the analysis. Secondary endpoints were overall survival (OS), time to first bone pain, time to first ONJ, and skeletal morbidity period rate (SMPR) after first immunotherapy line. OS was calculated as from the start date of the first immunotherapy line to the date of death. Time to first reported bone pain was the time from the start date of the first immunotherapy line to the date of the first bone pain event. Time to first ONJ was the time from the start date of the first immunotherapy line to the date of the first ONJ. Patients not experiencing an event were censored at the last date known alive. The SMPR was calculated using a revised event ratio method, as follows:

$$SMPR = \frac{number\ of\ 12\ week\ periods\ with\ SSEs + 1}{number\ of\ 12\ week\ periods\ since\ bone\ metastasis + 0.5}$$

Continuous data was summarized using median and range. Categorical data was summarized using frequency counts and percentages. The denominator for percentages was the number of patients in the corresponding group within the population of interest. For time-to-event endpoints, Kaplan-Meier estimates were used to describe and visualize the effect of the administration of BTA versus no BTA. Log-rank tests were used to compare the administration of BTA versus no BTA. Cox regression models were used to explore other covariates. For rates, the median and 95 % CI were estimated using the Hodges-Lehmann method, and a rank regression was used to compare patients receiving a BTA versus no BTA. All analyses were exploratory and hypothesis-generating in nature. Two-sided p-values were calculated but were not to be interpreted as confirmatory and were not corrected for multiple testing. All the analyses were conducted using SAS v.9.4 (SAS Institute Inc.) and R v.4.2.2 (R Core Team 2022).

3. Results

Baseline characteristics are given in Table 1. In total, 197 patients with bone metastases and treatment with immunotherapy such as nivolumab (48 %), pembrolizumab (40 %), atezolizumab (12 %), ipilimumab (9 %) and other immunotherapy (5 %) were included. Median follow-up time from the first diagnosis of bone metastasis is 4.8 years (95 % CI: 3.3 to 5.7 years) for the 197 patients. One hundred and twenty-two patients (62 %) received a BTA treatment (91 % denosumab). The median treatment duration of a BTA was 178 days (min: 1 day, max: 2010 days). The administration of BTA was unknown for 3 patients.

Out of the 197 patients, 33 patients (17 %) experienced at least one SSE after the first immunotherapy line, from which 2 patients (1 %) experienced at least one SSE before the BTA administration. The percentage of patients without an SSE at fixed time points was higher if treated with a BTA (e.g., at 6 months, 92 % [95 % CI: 84 % - 96 %] versus

Table 1
Baseline demographic and clinical characteristics.

Characteristic	BTA administered		
	No (N = 72)[a]	Yes (N = 122)[a]	Overall (N = 197)[a]
Age at tumor diagnosis median (range)	68 (33, 86)	63 (30, 87)	65 (30, 87)
Age at first bone metastasis median (range)	69 (38, 86)	63 (32, 87)	66 (32, 87)
Sex			
Female	27 (37.5 %)	56 (45.9 %)	85 (43.1 %)
Male	45 (62.5 %)	66 (54.1 %)	112 (56.9 %)
Smoking status			
Smoker	13 (18.1 %)	37 (30.3 %)	50 (25.4 %)
Ex-smoker	24 (33.3 %)	37 (30.3 %)	62 (31.5 %)
Never-smoker	28 (38.9 %)	42 (34.4 %)	72 (36.5 %)
Unknown	7 (9.7 %)	6 (4.9 %)	13 (6.6 %)
SSE before first immunotherapy			
Clinically significant pathologic bone fracture	1 (1.4 %)	1 (0.8 %)	2 (1.0 %)
Radiation to the bone	5 (6.9 %)	10 (8.2 %)	15 (7.6 %)
Spinal cord compression	0 (0.0 %)	2 (1.6 %)	2 (1.0 %)
Surgery to the bone	1 (1.4 %)	2 (1.6 %)	3 (1.5 %)
Bone pain before first immunotherapy	12 (16.7 %)	34 (27.9 %)	46 (23.4 %)
Tumor indication (ICD-10 Category term)			
Malignant neoplasm of bronchus and lung	31 (43.1 %)	67 (54.9 %)	99 (50.3 %)
Malignant melanoma of skin	7 (9.7 %)	15 (12.3 %)	22 (11.2 %)
Malignant neoplasm of kidney, except renal pelvis	7 (9.7 %)	11 (9.0 %)	19 (9.6 %)
Malignant neoplasm of bladder	13 (18.1 %)	5 (4.1 %)	18 (9.1 %)
Malignant neoplasm of breast	2 (2.8 %)	6 (4.9 %)	8 (4.1 %)
Other	12 (16.7 %)	18 (14.8 %)	31 (15.7 %)
Metastasis outside bone at tumor diagnosis			
Lymph nodes	17 (23.6 %)	51 (41.8 %)	69 (35.0 %)
Pulmonary	6 (8.3 %)	31 (25.4 %)	37 (18.8 %)
Hepatic	10 (13.9 %)	24 (19.7 %)	35 (17.8 %)
Adrenals	4 (5.6 %)	15 (12.3 %)	19 (9.6 %)
Brain	3 (4.2 %)	13 (10.7 %)	16 (8.1 %)
Pleura	5 (6.9 %)	9 (7.4 %)	14 (7.1 %)
Skin	0 (0.0 %)	2 (1.6 %)	2 (1.0 %)
Bone marrow	0 (0.0 %)	1 (0.8 %)	1 (0.5 %)
Other	6 (8.3 %)	25 (20.5 %)	31 (15.7 %)
Unknown	1 (1.4 %)	0 (0.0 %)	1 (0.5 %)

[a] n (%).

88 % [95 % CI: 77 % - 94 %]), but no significant difference in time to first SSE (HR 0.69; 95 % CI 0.34–1.39, log-rank $p = 0.29$) could be detected (Fig. 1).

An additional competing risk analysis, using death from any cause as a competing event to SSE, supported the results from the primary endpoint (HR 0.63; 95 % CI 0.32–1.25, $p = 0.19$). The median time to SSE was neither reached for patients administered with a BTA (95 % CI: NR - NR) nor for patients that did not receive a BTA (95 % CI: NR - NR). The percentage of patients that do not experience an SSE at various fixed time points for BTA-treated and not treated is presented in Table 2.

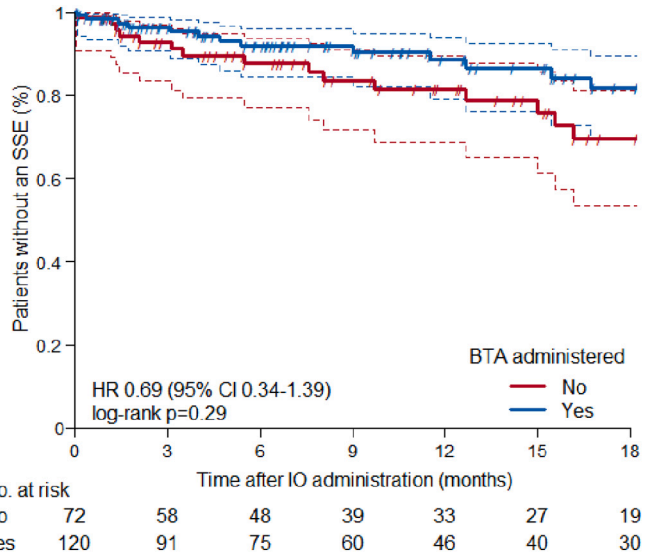

Fig. 1.. Time to first SSE by BTA administration.

Table 2
Percentage of patients without an SSE at 3, 6, 9, 12, and 18 months after bone metastasis by BTA.

Months	– BTA administered –		
	No (N = 72)[a]	Yes (N = 120)[a]	Overall (N = 197)[a]
3	92.7 % [83.4 %, 96.9 %]	96.4 % [90.6 %, 98.6 %]	95.1 % [90.7 %, 97.4 %]
6	87.7 % [76.9 %, 93.7 %]	91.9 % [84.3 %, 95.9 %]	89.8 % [84.0 %, 93.5 %]
9	83.7 % [71.5 %, 90.9 %]	91.9 % [84.3 %, 95.9 %]	88.1 % [81.9 %, 92.3 %]
12	81.4 % [68.7 %, 89.4 %]	88.5 % [79.2 %, 93.8 %]	84.3 % [77.1 %, 89.4 %]
18	69.6 % [53.4 %, 81.1 %]	81.6 % [69.2 %, 89.4 %]	75.4 % [65.9 %, 82.6 %]

[a] % [95 % CI].

The median OS for patients treated with a BTA was 0.9 years (95 % CI: 0.7 to 1.2 years) and 1.7 years (95 % CI: 1.3 to 2.5 years) for patients that did not receive any BTA (Fig. 2). There were differences in OS between patients treated with a BTA and patients not treated with a BTA (HR: 1.46; 95 % CI: 1.01–2.10, $p = 0.043$). OS results at year 1, 2 and 3 are shown in Table 3.

From the subgroup of the 89 NSCLC patients, the BTA administration was unknown for one patient. No differences for time to first SSE (HR: 1.39; 95 % CI: 0.38–5.13, $p = 0.62$) and OS (HR: 1.35; 95 % CI: 0.78–2.35, $p = 0.28$) by BTA administration were detected.

Sixty-seven patients (34 %) had bone pain after the first immunotherapy line, of which 8 had bone pain before the first administration of BTA. The median time to first bone pain was 54.5 months (95 % CI: 22.0 to NR months) for patients receiving a BTA and 31.0 months (95 % CI: 15.7 to NR months) for patients not receiving a BTA (Fig. 3). There were no differences in the time to first bone pain between patients treated with a BTA and patients not treated with a BTA (HR: 0.85; 95 % CI: 0.51–1.43, $p = 0.54$).

The median time to the first ONJ was not reached. Ten of the 122 patients (8 %) receiving a BTA developed an ONJ compared to one of 72 patients (1 %) not receiving a BTA. The median SMPR was 0.32 (95 % CI: 0.28–0.38). Two patients experienced an SSE before the administration of a BTA, and hence they were excluded from the SMPR analysis. Patients receiving a BTA had a median SMPR of 0.35 SSEs per 12-weeks (95 % CI: 0.28–0.44 SSEs per 12-weeks), while patients that did not

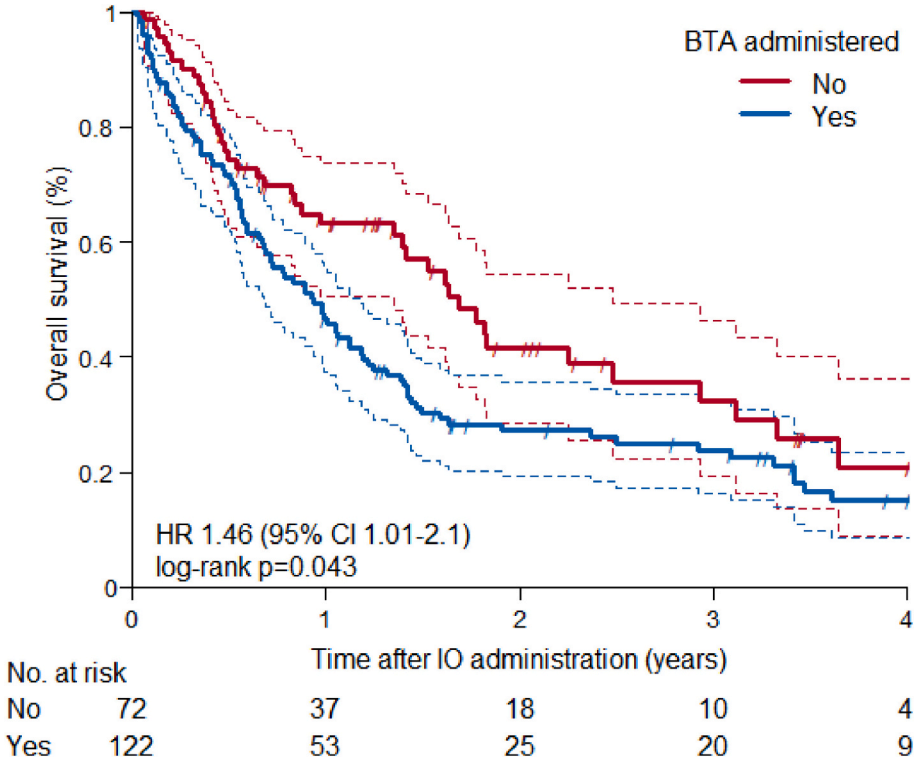

Fig. 2.. OS from bone metastasis by BTA.

Table 3
OS results in patients treated and not treated with a BTA at year 1, 2 and 3.

	– BTA administered –		
Years	No (N = 72)	Yes (N = 122)	Overall (N = 197)
1	63.3 % [50.5 %, 73.6 %]	46.8 % [37.6 %, 55.5 %]	51.8 % [44.4 %, 58.7 %]
2	41.7 % [28.4 %, 54.5 %]	27.2 % [19.3 %, 35.7 %]	31.7 % [24.7 %, 38.9 %]
3	32.4 % [19.3 %, 46.3 %]	23.8 % [16.2 %, 32.2 %]	26.6 % [19.8 %, 33.8 %]

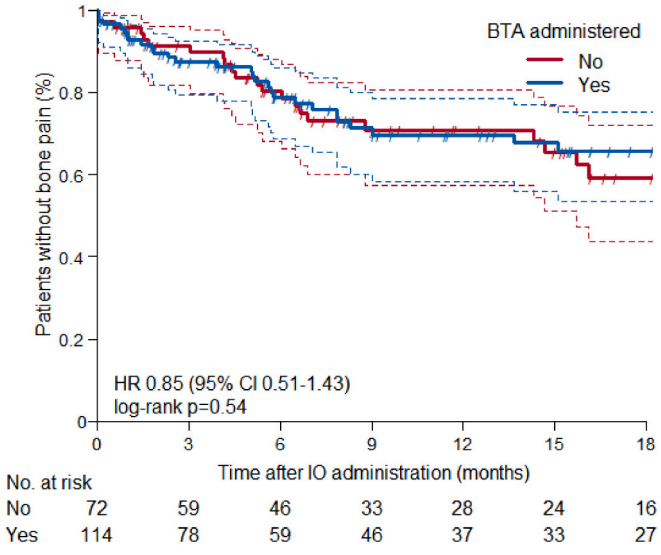

Fig. 3.. Time to first bone pain after bone metastasis by BTA.

receive a BTA had a median SMPR of 0.28 SSEs per 12-weeks (95 % CI: 0.23–0.35 SSEs per 12-weeks). The difference in SMPR between patients treated with a BTA versus patients not treated with a BTA was 0.03 (95 % CI: −0.10 - 0.03, $p = 0.35$).

To adjust for imbalances due to the non-randomized nature of the study, sensitivity analyses were performed. Propensity scores were estimated using the R package weights adjusting for the variables age, sex, smoking status, tumor indication, location of metastases, SSE before immunotherapy, bone pain before immunotherapy and BTA treatment. Based on these weights, inverse probability of treatment weighted (IPTW) survival curves were estimated using the R package adjusted curves. The curves look comparable to the non-weighted curves. The difference between the treated and untreated groups are a bit smaller than in the non-weighted curves for time to SSE but very similar for OS (data not shown).

4. Discussion

immunotherapy has significantly improved the outcome especially the survival time of patients with metastatic solid tumor diseases, especially in the first-line treatment setting of advanced NSCLC, melanoma, and renal cell carcinoma (Planchard et al., 2018; Michielin et al., 2019; Powles et al., 2021; Bongiovanni et al., 2021). Given the frequent occurrence of bone metastases in these tumor types, it is advised to incorporate osteoprotective treatment involving denosumab or BPs alongside antitumor therapy to mitigate SSEs (Coleman et al., 2020). Preclinical research provides further evidence of an immunomodulatory effect of BTAs, such as zoledronate which highlights the ability to enhance the antitumor efficacy of PD-1 blockade (Li et al., 2018). Zoledronate, a nitrogen-containing BP, hinders farnesyl pyrophosphate synthesis in the mevalonate pathway. This inhibition results in elevated levels of isopentenyl pyrophosphate in tumor cells, making them susceptible to targeting by gamma delta T cells. This mechanism contributes to innate immunity (Peters et al., 2020). The discovery of communication between T-cells and dendritic cells initially occurred

through the process of signaling, which involves the binding of the RANK to its ligand, RANKL. RANKL triggers the activation of osteoclasts to facilitate bone resorption and also plays a role in the development of the mammary gland and secondary lymph nodes (Kong et al., 1999). RANKL exhibits significant immune-modulating effects, as its interaction with its receptor leads to the induction of T-reg cells and promotes chemo-resistance by activating multiple signal transduction pathways (Peters et al., 2019; van Dam et al., 2019). As a result, inhibiting RANKL enhances immune responses and shows potential as an immunotherapeutic agent for cancer treatment. Expressions of RANK and RANKL have been noted in certain tumor types, with early clinical data indicating a potential anti-tumor effect of inhibitors targeting the RANK pathway such as denosumab (Peters et al., 2019). Bongiovanni et al. demonstrated a synergistic effect of BTAs with immunotherapy in a retrospective study, including a positive impact on bone response rates and even survival in patients with NSCLC and bone metastases. However, this study did not mention a reduction in SSEs with regards to the combination of BTAs and immunotherapy (Bongiovanni et al., 2021).

In our Alpine Tumor Immunology Registry, no significant difference in time to first SSE and bone pain was observed in different tumor types between patients who have received a BTA or not when treated with immunotherapy. Nevertheless, there were some differences in OS in favor of the patients not treated with a BTA. These findings are inline with the phase III SPLENDOUR trial, where denosumab added to chemotherapy did not improve OS with respect to chemotherapy alone in patients with advanced NSCLC (Peters et al., 2020). Furthermore, there were no differences in the time to first bone pain between patients treated with a BTA and patients not treated with a BTA. This is of significant clinical importance, as bone pain greatly impacts quality of life and patients never return to the level of bone pain before the event (von Moos et al., 2016). In contrast, 8 % of patients with additional BTA therapy experienced an ONJ in our registry for a median treatment duration of about 6 months. This could suggest a higher risk of ONJ when immunotherapy and BTAs are combined. Considering the cumulative incidence of ONJ occurrence (Peters et al., 2019), the omission or at least delayed administration of BTAs could substantially reduce the frequency of ONJ.

Our study has several limitations, primarily due to a small sample size and the retrospective nature of the analysis. In addition, it concerns a highly heterogeneous patient group with various tumor types and different treatment durations. However, after conducting an adjustment of imbalances analysis, no relevant difference in the outcome between the compared groups could be identified.

Although showing actually worse OS in our cohort of patients treated with BTAs, the interpretation of these results should be done with caution as a selection bias among treating physicians cannot be ruled out, as patients who are perceived as high risk for an SSE may be more likely to be treated with a BTA than those deemed low risk. This and the fact that this is an exploratory analysis may have lead to a poorer outcome. Clues to this can be found in the baseline characteristics (Table 1), which indicate that patients with bone pain before immunotherapy initiation were more frequently treated with BTA compared to those without baseline bone pain (27.9 versus 16.7 %). Notwithstanding these limitations, our data questions the hypothesis that BTAs enhance the effectiveness of immunotherapy on the outcome of patients with solid tumors and bone metastases. Larger prospective datasets or randomized clinical trials are essential to establish more robust evidence regarding the potential of BTAs in the era of immunotherapy.

5. Conclusions

We observed no significant benefit of additional BTAs in patients with solid tumors and bone metastasis when treated with immunotherapy.

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CRediT authorship contribution statement

Michael Mark: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Alfonso Rojas Mora:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Thomas Winder:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Anastasios Stathis:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Andreas Jakob:** Writing – review & editing, Writing – original draft, Validation, Project administration, Investigation, Formal analysis, Data curation, Conceptualization. **Gisela Müller:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Stefanie Hayoz:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Patrick Reimann:** Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Ulf Petrausch:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Data curation, Conceptualization. **Roger von Moos:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

Michael Mark: advisory role: Janssen, Roche, Takeda, BMS, MSD, Astra Zeneca, Merck; research grant: Gilead Science; travel grant: Jannsen, Astra Zeneca, Roche, Takeda, Amgen.

Anastasios Stathis: Travel Grant: Astra Zeneca, Incyte; advory role: Janssen, Roche; Expert Testimony: Bayer, Eli Lilly; financial interest: Abbvie, ADC Therapeutics, Amgen, Astra Zeneca, Bayer, Cellestia, Incyte, Loxo Oncology, Merck MSD, Novartis, Pfizer, Philogen, Roche (all institutional).

Andreas Jakob: employment: Tumor Zentrum Aarau; advisory role: Janssen Cilag, MSD; research funding: Roche, Lilly, Novartis, Daiichi Sankyo; Travel Grant: MSD, Janssen Cilag,

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Data availability

Data will be made available on request.

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