

# Limited Data from Clinical Trials Assessing Immunotherapy Effects on Bone Metastases

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## Introduction

Bone metastases are a significant cause of mortality in many major cancers, including prostate, breast and lung cancer (1, 2). They are difficult to treat and their response rate to standard-of-care therapies is low. Immunotherapies have been approved as stand-alone therapies or in combination with other therapies for the treatment of advanced or metastatic triple-negative breast cancer (TNBC), prostate cancer, lung cancer and melanoma patients. It is unclear if the approved immunotherapies affect bone metastases.

## Materials and Methods

In this study, relevant scientific publications were evaluated for feasibility to perform a meta-analysis about immunotherapy efficacy on bone metastases. A PubMed search for approved immunotherapies for TNBC, prostate cancer, lung cancer and melanoma on September 21, 2020 resulted in 561 relevant scientific publications. From these, the criteria for selection of publications for this study were:

- 1) Patients had detectable bone metastases
- 2) Patients received at least one immunotherapy treatment
- 3) Therapy effects for bone metastases was followed
- 4) The study was published between 2010-2020

Based on these criteria only six eligible studies were identified.

Currently approved immunotherapies in the above-mentioned cancer indications used in the search (3) :

- **TNBC:** atezolizumab (Tecentriq), pembrolizumab (Keytruda)
- **Prostate cancer:** pembrolizumab
- **Lung cancer:** atezolizumab, durvalumab (Imfinzi), ipilimumab (Yervoy), nivolumab (Opdivo), pembrolizumab
- **Melanoma:** aldesleukin (Proleukin), atezolizumab, avelumab (Bavencio), cemiplimab (Libtayo), ipilimumab, nivolumab, and pembrolizumab

## Main Findings

### Triple-negative breast cancer

Schmid and co-workers reported prespecified second interim overall survival analysis from the IMpassion130 phase 3 trial evaluating the efficacy of atezolizumab and nab-paclitaxel in advanced or metastatic TNBC patients (reference 4, Table 1). Majority of the patients had 0-3 metastatic sites and about 30% (27-32%) had bone metastases at baseline. When looking at PD-L1 positive patients with bone metastases, median overall survival of patients treated with atezolizumab and nab-paclitaxel was 19.1 months, compared to 11.5 months in patients treated with placebo and nab-paclitaxel.

### Prostate cancer

KEYNOTE-199 phase 2 update reported by Antonarakis and co-workers evaluated efficacy of pembrolizumab in treatment-refractory metastatic castration-resistant prostate cancer patients within PD-L1 status defined cohorts and in bone-predominant disease regardless of PD-L1 expression. In patients treated with pembrolizumab, disease control rate according to PCWG3-modified RECIST was 13%, 18% and 39%, and median overall survival was 9.5, 7.9 and to 14.1 in the study cohorts (reference 5, Table 2).

### Lung cancer

Pawel and co-workers published results of long-term survivors of the OAK phase 3 study (6). In this study, atezolizumab treatment showed a survival benefit over docetaxel treatment in advanced non-small-cell lung cancer patients. Long-term survivors (over 24 months) had fewer bone metastases at baseline. Long-term survivors treated with atezolizumab had less new metastatic lesions compared to non-long-term survivors, whereas the incidence was similar in patients treated with docetaxel. Furthermore, atezolizumab-treated long-term survivors had less bone and liver metastases.

### Melanoma

Lee and co-workers studied metastasis-related responses in melanoma patients in KEYNOTE-001 phase 1 study (7). Only 1% of the patients had bone metastases at baseline and none of them had a complete response to pembrolizumab, compared to 65% and 49% complete responses in liver and lung metastases, respectively. Furthermore, Sundahl and co-workers studied ipilimumab in combination with radiation in metastatic melanoma patients in a phase 1 study (8). Four (31%) of these patients had bone metastases among other metastases, and all of them developed a progressive disease. Da Gama Duarte and co-workers studied ipilimumab in combination with intralesional Bacillus Calmette-Guérin in advanced metastatic melanoma patients in a phase 1 pilot study (9). However, the trial was discontinued because the treatment was not tolerated and clinical benefits were not observed.

TABLE 1. Modified from IMpassion130 study (4)

	Patients with bone metastases		Patients without bone metastases	
	Atezo + NP	Placebo + NP	Atezo + NP	Placebo + NP
OS (months), Intention-to-treat	16.8	14.9	22.1	20.1
OS (months), PD-L1 positive	19.1	11.5	27.3	20.1

Abbreviations: Atezo = atezolizumab, NP = nab-paclitaxel, OS = overall survival.

TABLE 2. Modified from KEYNOTE-199 study (5)

	Pembrolizumab treatment		
	Patients without bone metastases, PD-L1 positive	Patients without bone metastases, PD-L1 negative	Patient with bone metastases, PD-L1 unselected
DCR (%)	13	18	39
OS (months)	9.5	7.9	14.1

Abbreviations: DCR = disease control rate, OS = overall survival.

## Summary

Only about 1% (6/561) of publications with approved immunotherapies in breast, prostate and lung cancer and melanoma patients reported results on bone metastases. Therefore, no conclusions can be drawn about the efficacy due to the limited number of eligible studies.

## Future Directions

Currently, some T-cell targeting immunotherapies have been approved for patients with bone metastases. However, as observed in this study, the efficacy of immunotherapies against bone metastases is currently not known. Therefore, research efforts should be addressed towards tumor microenvironment in bone to characterize immune landscape, determine immune heterogeneity and assess predictive biomarkers. Better understanding of the milieu may open new opportunities such as targeting natural killer cells, myeloid-derived suppressor cells, macrophages and dendritic cells (10).

Clinical trials with immunotherapies specifying effects on bone metastases are warranted as they would allow to better understand metastasis-specific responses, improve patient selection in future clinical studies, and ultimately help in providing more effective treatments for patients with life-threatening bone metastases.

## References

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