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# Complete Response of Bone Metastasis in Non-small Cell Lung Cancer With Pembrolizumab: Two Case Reports

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**Abstract.** *Aim: To report two cases in which treatment with pembrolizumab for advanced non-small cell lung cancer (NSCLC) with bone metastasis of the long bone of the lower extremity in a state of impending fracture significantly ameliorated both lung tumor and bone metastasis. Case Report: Case 1 was a 74-year-old woman diagnosed with metastasis of NSCLC in the left tibia and case 2 was a 71-year-old man diagnosed with metastasis of NSCLC in the right femur; their bone metastases were in a state of impending fracture. Disease in both cases was already in stage IVB and they received systemic therapy using pembrolizumab, whilst the bone metastases were treated conservatively. After 3 months, both patients showed a complete response with remarkable osteosclerotic changes in bone metastases and the size of lung tumors was reduced. Conclusion: These results might imply a novel strategy for systemic treatment with pembrolizumab is required, even in case of impending fracture in advanced NSCLC.*

Lung cancer has the third highest rate of bone metastases after prostate cancer and breast cancer (1-3). A prospective cohort study (CSP-HOR13) of advanced-stage lung cancer (stages III and IV) showed bone metastasis at initial diagnosis in 48% of patients with stage IV non-small cell lung cancer (NSCLC) and 40% in those with extensive stage small-cell lung cancer (4). Bone metastases can cause skeletal-related events (SREs), such as severe bone pain, pathological fracture, spinal cord compression, and hypercalcemia (5), which significantly reduce the quality of life of these patients; moreover, their overall survival (OS) is shortened (6, 7). The prognosis of patients with bone metastases from lung cancer has been reported to be worse than that in other cancer types, such as prostate and breast, which have a high rate of bone metastasis (8). Severe SREs that significantly impair daily life may require surgery or radiation therapy to improve the quality of life of patients. Although bone-modifying agents (BMAs), such as denosumab and zoledronic acid, and molecule-targeted agents such as epithelial growth factor receptor (EGFR) inhibitors have shown effectiveness in bone metastases (9-11), prophylactic stabilization is usually needed in cases of impending fracture.

In recent years, immunotherapy has made remarkable progress in the treatment of cancer. In lung cancer, immune checkpoint inhibitors (ICIs) such as nivolumab and pembrolizumab, which target the programmed death-1 receptor (PD1)/PD-ligand 1 (PD-L1) pathway, have been reported to improve OS and progression-free survival more than conventional anticancer drugs (12-14). Although these ICIs have been used for advanced-stage NSCLC, there are few reports regarding their effectiveness for bone metastases. Herein, we report two cases in which treatment with pembrolizumab for advanced NSCLC with bone metastasis of long bones of the lower extremity in a state of impending fracture led to remarkable amelioration of both lung tumor and bone metastasis without prophylactic surgery.

*Case 1.* A 74-year-old woman who had no past medical history presented with left ankle pain and visited a nearby doctor. X-Ray showed a radiolucent finding in the left distal tibia (Figure 1A). She was then referred to our Department for suspected malignant bone tumor of the left tibia. Computed tomography (CT) showed osteolysis of the left distal tibia (Figure 1B). Mirels' score (15) was 11 points (lower extremity 2, moderate 3, lytic 3, and size 3), indicating an impending fracture. A bone scan and thallium scan showed

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*Key Words:* Non-small cell lung cancer, bone metastasis, pembrolizumab, immune checkpoint inhibitor, impending fracture.

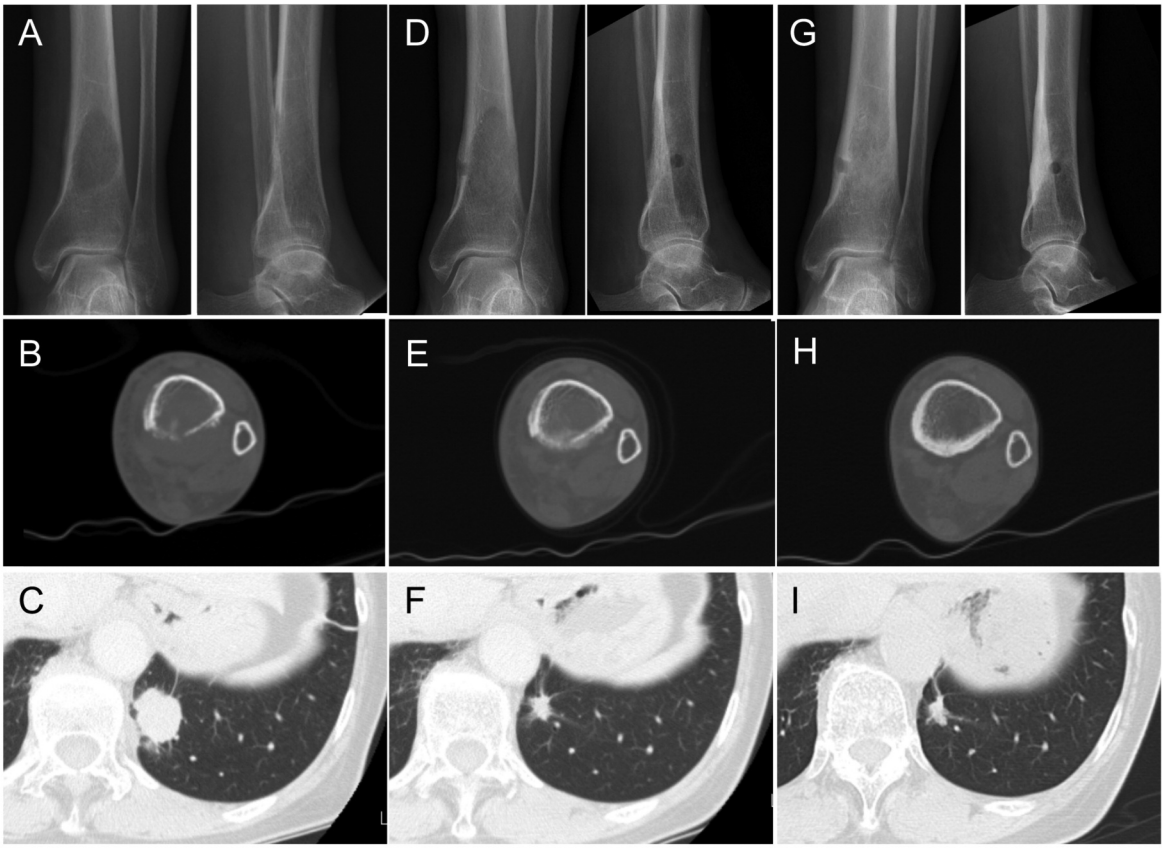


Figure 1. *Case 1: A 74-year-old woman who had no past medical history presented with left ankle pain. A pre-therapy X-ray showed a radiolucent lesion on the left distal tibia (A). computed tomography (CT) showed a thinning and partial defect of the cortical bone (B). CT of the chest revealed a lung tumor at the same time (C). Three months after initiating pembrolizumab, X-ray and CT showed a remarkable osteosclerotic change in the bone metastatic lesion (D, E). CT showed a reduction in the size of the lung tumor (F). After 19 months of pembrolizumab, X-ray and CT showed almost complete repair of the metastatic bony lesion (G, H), and CT showed shrinkage of the lung tumor (I).*

abnormal accumulation in the skull and left distal tibia (Figure 2A and B). Magnetic resonance imaging revealed brain and skull metastatic lesions (Figure 2C), and CT revealed lung masses (Figure 1C). A needle biopsy of the distal tibia was performed, and the pathological diagnosis was adenocarcinoma. The patient was referred to the Department of Respiratory Medicine of our hospital and diagnosed with lung adenocarcinoma (cT1cN2M1c, stage IVB, PD-L1 expression 75%; molecular testing for EGFR, receptor tyrosine kinase (ROS1), anaplastic lymphoma kinase (ALK), and BRAF were negative). The treatment plan was discussed between our Department and the Department of Respiratory Medicine. Although prophylactic stabilization was recommended according to Mirels' scoring system, radiation therapy for metastatic lesions of the brain and skull was performed after the multidisciplinary discussion. Systemic therapy was then administered using pembrolizumab 200 mg every 3 weeks and conservative treatment of the bone metastases (non-weight-bearing and 120 mg denosumab every month). Three months after initiating treatment with pembrolizumab, X-ray and CT showed a remarkable osteosclerotic change in the metastatic lesion of the distal tibia, and CT showed a reduction in the size of the lung tumor (Figure 1D-F). Treatment with pembrolizumab has continued for 19 months; X-ray and CT showed almost normal new bone formation at the bone metastatic lesion, which was considered as complete response according to the modified MD Anderson criteria (16), and CT showed maintenance of the shrinkage of the lung lesion (Figure 1G-I). She returned to normal life without weight restriction of her lower extremities at the latest follow-up.

*Case 2*. A 71-year-old man who had no past medical history complained of right thigh pain and a lung tumor was detected on CT (Figure 3C). He was referred to the Department of Respiratory Medicine of our hospital and diagnosed with lung adenocarcinoma with multiple pleural dissemination (cT4cN3M1c; stage IVB; PD-L1 expression >75%; molecular

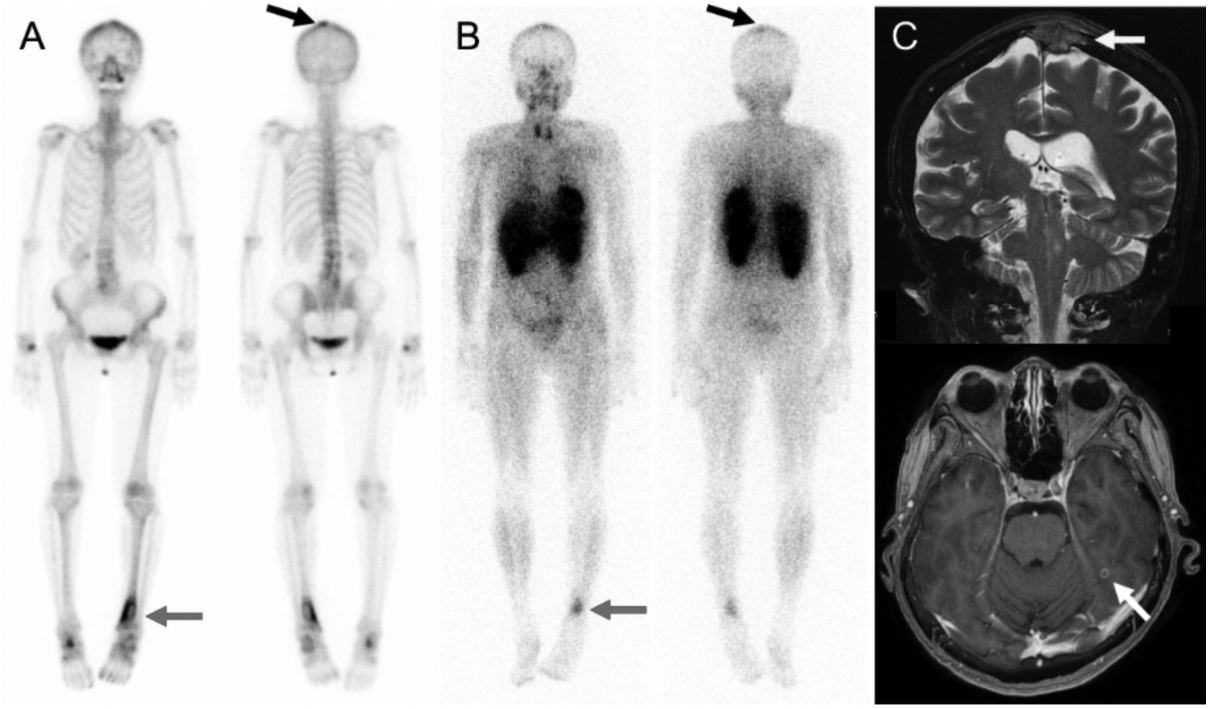


Figure 2. *Case 2: A 71-year-old man who had no past medical history complained of right thigh pain. Initial bone (A) and thallium (B) scans showed abnormal accumulation in the skull (black arrow) and left distal tibia (red arrow). Magnetic resonance imaging revealed metastatic lesions of the brain (white arrow) and skull (yellow arrow) (C).*

testing for EGFR, ROS1, ALK, and BRAF were negative). Positron-emission tomography showed standard uptake values of 11.8 for lung lesions and 9.2 for the right femur, and he was referred to our Department for investigation of bone metastasis (Figure 4A). X-Ray showed a radiolucent lesion (Figure 3A) and CT showed osteolysis in the right proximal femoral diaphysis (Figure 3B); and Mirels' score was 9 points (lower extremity 2, moderate 2, lytic 3, and size 2), indicating an impending fracture. After the multidisciplinary discussion, systemic therapy with 200 mg pembrolizumab, carboplatin area under the concentration-time curve of 5, and 500 mg/m$^2$ pemetrexed every 3 weeks was initiated. His right lower extremity was restricted from weight bearing, and 120 mg denosumab was administered every month. After four cycles of combined chemotherapy, X-ray and CT showed a remarkable osteosclerotic change in the metastatic lesion of the femur, and CT showed shrinkage of the lung tumor and residual pleural effusion (Figure 3D-F). Treatment with pembrolizumab has continued for 8 months; X-ray and CT showed almost normal new bone formation of the bone metastatic lesion, and CT showed continued shrinkage of the lung lesions (Figure 3G-I). Furthermore, positron-emission tomography revealed that the accumulation of lung lesions was reduced to a standard uptake value of 2.8, and that in the femur had disappeared (Figure 4B), therefore the response was judged as complete response (16). Currently, the patient has no pain and maintains normal life using a single cane.

## Discussion

The multidisciplinary approach with surgery, radiation therapy, and multi-agent chemotherapy has improved treatment outcomes in lung cancer (17). Moreover, the development of ICIs has led to a paradigm shift not only in lung cancer but also in other types of cancer (18, 19). ICIs or concomitant treatment with ICIs and chemotherapy have been reported to have a higher response rate and longer OS in patients with metastatic NSCLC compared with conventional anticancer drugs (in a phase 3 trial) (12-14, 20-22). Therefore, ICIs are expected to prolong the survival of patients with advanced NSCLC. However, there have been few reports regarding the therapeutic effect on and mechanism of ICIs in bone metastases, and the mechanism of action has not been clarified. Herein, we report two cases of advanced NSCLC with bone metastases treated with pembrolizumab-based systemic therapy which showed remarkable osteosclerotic changes in the bone metastatic lesions, in addition to the shrinkage of the primary lung lesions.

As far as we are aware, only two cases have been reported of treatment with pembrolizumab leading to the complete

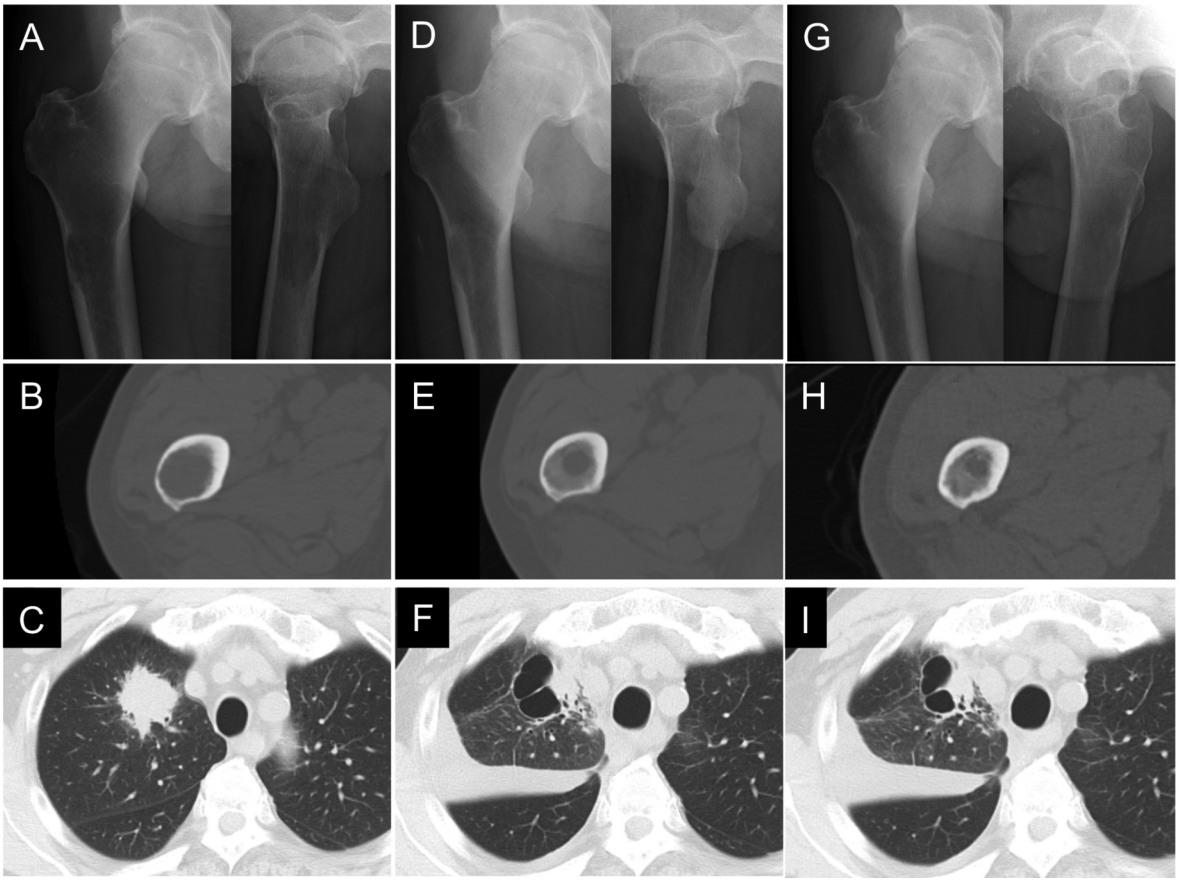


Figure 3. *Case 2: X-Ray of a 71-year-old man with right thigh pain but no past medical history showed a radiolucent lesion on the right proximal femur (A). Computed tomography (CT) showed a metastatic lesion in the medullary cavity and a thinning of cortical bone (B). CT of the chest revealed a lung tumor (C). Three months after initiating pembrolizumab, X-ray and CT showed a remarkable osteosclerotic change in the bone metastatic lesion (D, E) and CT showed shrinkage of the lung tumor and residual pleural effusion (F). After 8 months of pembrolizumab therapy, X-ray and CT revealed repair of the bony metastasis (G, H), and CT showed that the shrinkage of the lung tumor had been maintained (I).*

resolution of bone metastases (23, 24). Sidhu *et al*. reported a case of metastatic bone tumor of the scapula from poorly differentiated adenocarcinoma. This patient was treated with pembrolizumab following radiotherapy at 300 cGy. CT taken after 4 months revealed complete normalization of the scapula (23). Tang *et al*. presented poorly differentiated lung adenocarcinoma accompanied by fifth lumbar vertebral metastasis. This patient received pembrolizumab and radiotherapy for the metastatic lesion. CT taken after two cycles of pembrolizumab showed a partial response of lung tumor and metastatic tumor. Sclerotic change was also observed in the metastatic vertebra (24). Both cases showed sclerotic changes in bone metastases following pembrolizumab treatment without bone-modifying agents. Our two patients were treated with pembrolizumab and denosumab. The effect of denosumab against metastatic bone tumors from lung cancer has been reported in several articles (11, 25, 26). In these reports, denosumab has been reported to reduce the risk of developing SREs and prolong the OS of patients with NSCLC with bone metastases. However, there have been no reports of denosumab ameliorating impending fracture of the long bone of the lower extremity and avoidance of the need for prophylactic stabilization. Therefore, to our knowledge, our two cases are the first reported to show that pembrolizumab treatment for advanced NSCLC had a great therapeutic effect on lung lesions and bone metastases and ameliorated impending fracture of the long bone of the lower extremity.

Since the lower extremity is a weight-bearing limb, there is a high risk of pathological fractures while walking in daily life, and prophylactic surgery is recommended based on Mirels' score. Prophylactic stabilization is recommended for scores greater than 9 points (15). Prophylactic surgery in the state of impending fracture has been recommended because it results in less blood loss and better postoperative gait than

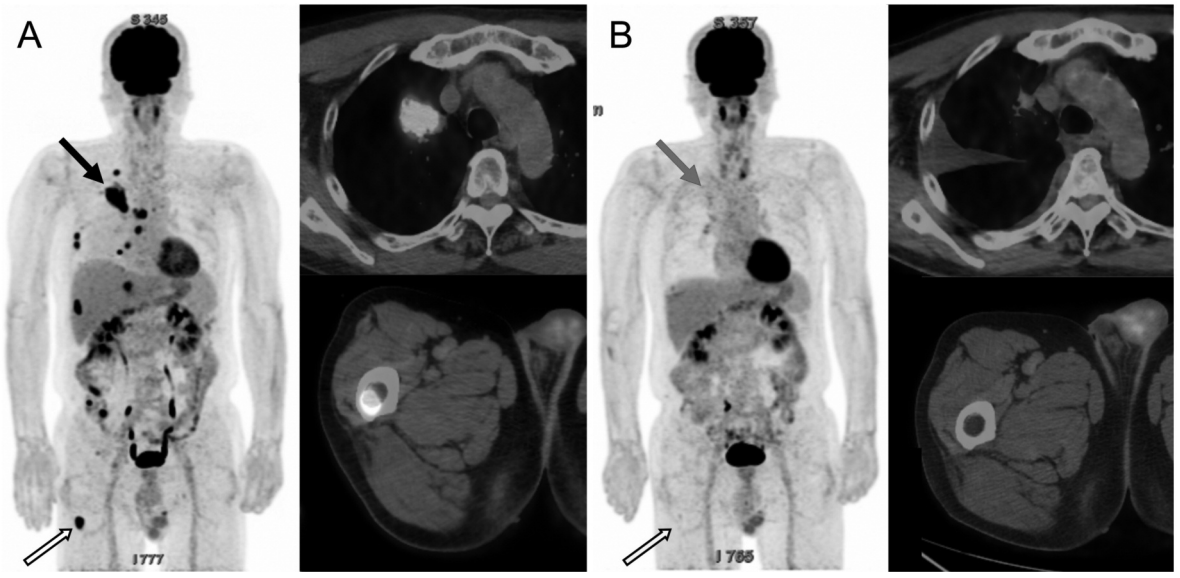


Figure 4. *Positron-emission tomography of case 2 showed standard uptake values of 11.8 for lung lesions (black arrow) and 9.2 for that of the right femur (white arrow) (A). After 8 months of pembrolizumab therapy, positron-emission tomography revealed that the accumulation of lung lesions (red arrow) was reduced to a standard uptake value of 2.8 and the accumulation of the femur (yellow arrow) had disappeared (B).*

pathological fracture (27, 28). Therefore, in our two cases, it was considered that prophylactic surgery should be performed to prevent pathological fractures, since bone metastasis in a state of impending fracture of the lower extremity had been diagnosed. However, case 1 had metastases of the brain and skull, and case 2 had multiple pleural disseminations without systemic treatment against primary tumors. Since these situations were most severe for the patients and they needed systemic treatment immediately, the bone metastases were instead treated conservatively. Treatment with pembrolizumab led to complete response with massive osteosclerotic changes of bone metastases; thus, surgery for impending fractures was not necessary as of the latest follow-up. In addition, pembrolizumab also reduced the size of lung tumors and maintained stable disease long-term (more than 6 months). From the standpoint of orthopedic oncologists, even in cases of impending fracture in advanced NSCLC with bone metastases, systemic therapy using pembrolizumab would be a possible first treatment, with careful conservative follow-up. Subsequently, in case the metastatic lesion progresses, prophylactic surgery should be recommended to prevent pathological fracture.

Regarding the effect of ICIs on bone metastases from other types of cancer, there are a few reports on melanoma, renal cell carcinoma and uterine carcinosarcoma; however, the mechanism of ICIs on bone metastases has not been clarified (29-32). In our cases, denosumab was initiated at the same time as the treatment with pembrolizumab, and the bone metastases may have been affected by denosumab. Angela *et al*. reported that 62% of patients with stage IV melanoma with bone metastases had osteosclerotic changes of bone metastatic lesions by concomitant therapy with PD1 inhibitor and denosumab (29). Ahern *et al*. reported that concomitant therapy with ICIs and denosumab showed a higher antitumor effect than ICI monotherapy in animal experiments (33). Furthermore, Yano *et al*. reported that the abscopal effects of ICIs and local radiotherapy were effective for bone metastasis of advanced or recurrent uterine carcinosarcoma (32). Further investigation is necessary to verify the effect and mechanism of ICIs with or without denosumab and abscopal effects of ICIs and radiotherapy on bony metastasis from NSCLC. Our findings suggest that treatment with pembrolizumab for advanced NSCLC with bone metastases in a state of impending fracture might avoid the need for prophylactic surgery; therefore, systemic treatment for primary tumor lesions should be prioritized even in such cases.

## Conclusion

We presented two cases where treatment with pembrolizumab for NSCLC with long bone metastasis in the lower extremity in a state of impending fracture led to remarkable amelioration of both the primary lung lesion and bony metastasis without prophylactic surgery. Although careful assessment of bony metastasis is mandatory, these

results suggest a novel strategy for prioritizing systemic treatment with pembrolizumab even in cases of impending pathological fracture in advanced NSCLC.

## Conflicts of Interest

The Authors declare that they have no conflicts of interest.

## Authors' Contributions

Conceptualization: Yohei Asano and Akihiko Takeuchi. Data curation: Yohei Asano, Akihiko Takeuchi, Katsuhiro Hayashi, Shinji Miwa, Kentaro Igarashi, Hirotaka Yonezawa, Yoshihiro Araki, Sei Morinaga, Kazuo Kasahara and Takashi Sone. Investigation: Yohei Asano and Akihiko Takeuchi. Project administration: Akihiko Takeuchi. Writing – original draft: Yohei Asano. Writing – review and editing: Norio Yamamoto, Akihiko Takeuchi and Hiroyuki Tsuchiya. All Authors approved the final version of the article.

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