haematologica
Journal of the Ferrata Storti Foundation

Tumor flare pain reaction following bispecific T-Cell engagers in multiple myeloma: a unique and underrecognized toxicity

by Gaspard Jadot, Anna Sabouret, Anne Couture, Louis Laflamme, Frédéric Larose, Imran Ahmad, Karim Benkirane, Jean-Sébastien Delisle, Isabelle Fleury, Silvy Lachance, Richard LeBlanc, Jean Roy, Stéphanie Thiant, Olivier Veilleux and Jean-Sébastien Claveau

Received: September 7, 2025.
Accepted: March 16, 2026.

Citation: Gaspard Jadot, Anna Sabouret, Anne Couture, Louis Laflamme, Frédéric Larose, Imran Ahmad, Karim Benkirane, Jean-Sébastien Delisle, Isabelle Fleury, Silvy Lachance, Richard LeBlanc, Jean Roy, Stéphanie Thiant, Olivier Veilleux and Jean-Sébastien Claveau. Tumor flare pain reaction following bispecific T-Cell engagers in multiple myeloma: a unique and underrecognized toxicity. Haematologica. 2026 Mar 26. doi: 10.3324/haematol.2025.289122 [Epub ahead of print]

Tumor flare pain reaction following bispecific T-Cell engagers in multiple myeloma: a unique and underrecognized toxicity

Gaspard Jadot[1], Anna Sabouret[1], Anne Couture[2], Louis Laflamme[2], Frédéric Larose[3], Imran Ahmad[1,4], Karim Benkirane[5], Jean-Sébastien Delisle[1,4], Isabelle Fleury[1], Silvy Lachance[1], Richard LeBlanc[1], Jean Roy[1,4], Stéphanie Thiant[1], Olivier Veilleux[1], Jean-Sébastien Claveau[1,4]

[1]Hematology-Oncology and Cell Therapy University Institute, Hôpital Maisonneuve-Rosemont, University of Montreal, Montreal, Quebec, Canada

[2]Nuclear Medicine Department, Hôpital Maisonneuve-Rosemont, University of Montreal, Montreal, Quebec, Canada

[3]Divison of hematology, Hôtel-Dieu de Lévis, CISSS de Chaudières-Appalaches, Lévis, Quebec, Canada

[4]Hôpital Maisonneuve-Rosemont Research Center, University of Montreal, Montreal, Quebec, Canada

[5]Biochemistry Laboratory, Hôpital Maisonneuve-Rosemont, University of Montreal, Montreal, Quebec, Canada

Author contributions: JSC and GJ designed the study ; JSC supervised the project ; GJ, AS, FL, IA, JSD, IF, RL, SL, JR, OV and JSC followed study patients; GJ, ST and JSC collected data and interpreted the results ; AC and LL analyzed the radiological images ; KB interpreted the laboratory tests and cytokine panel results ; GJ and JSC wrote the manuscript ; all authors revised and approved the manuscript.

Running title: Bispecific-Induced Acute Bone Pain in Myeloma

Corresponding author: Jean-Sébastien Claveau

Email: jean-sebastien.claveau@umontreal.ca

Data availability statement: data may be made available upon request to the corresponding author.

Ethics Declarations:

Competing interests: the authors declare no competing financial interests.

Acknowledgements: GJ is a Fellow of the Stem Cell Transplantation and Cell Therapy Program at the University of Montreal, Quebec, Canada. GJ gratefully acknowledges the support of the Belgian Hematology Society, the Salus Sanguinis Foundation, and the Maisonneuve-Rosemont Hospital Cancer Program, which provided funding for the fellowship during which this work was carried out.

Funding: none

Teclistamab (Tec) is the first B-cell maturation antigen-targeted bispecific T-cell engager approved for the treatment of relapsed/refractory multiple myeloma (MM), based on the MajesTEC-1 trial results[1]. In a population of 165 triple-class-exposed MM patients who had received at least three prior lines of therapy, Tec demonstrated a deep and durable response with an overall response rate of 63%, and a median progression-free survival of 11.3 months. Since its approval, Tec has been widely adopted in clinical practice, with real-world data showing comparable efficacy and a similar safety profile to the pivotal trial[2,3]. The typical toxicity profile (cytopenias, infections and cytokine release syndrome) of bispecific T-cell engagers is now well recognized, and specific measures are being implemented to mitigate these adverse events[4]. Nevertheless, additional toxicities have been reported with Tec**,** notably bone pain, which occurred in 17.6% of patients in the MajesTEC-1 trial (grade ≥ 3: 3.6%)[1]. We observed a higher frequency of severe bone pain in our cohort of patients treated with Tec, particularly during the step-up dosing phase. This raised concerns about a tumor flare reaction—an event rarely described with bispecific T-cell engagers—which we characterized as a tumor flare pain reaction, a clinical presentation that, to our knowledge, has not been previously reported. We therefore conducted a multicenter retrospective study to assess the incidence of tumor flare pain reactions associated with Tec, as well as to describe their clinical presentation and management. Informed consent was obtained from all patients, and the study protocols were approved by the institutional ethics committees.

From June 2024 to June 2025, a total of 40 relapsed/refractory MM patients were treated with Tec in two Canadian centers (Hôpital Maisonneuve-Rosemont in Montreal and Hôtel-Dieu in Lévis). They received Tec subcutaneously at the approved step-up doses of 0.06 mg/kg and 0.3 mg/kg on days +1 and +3, respectively, followed by a full dose of 1.5 mg/kg on day +5, then weekly until progression or unacceptable toxicity occurred. Every patient received tocilizumab prophylaxis (8 mg/kg, maximum 800 mg) before the first step-up dose. Other

premedication consisted of dexamethasone (16 mg), acetaminophen (1000 mg) and cetirizine (10 mg) before the step-up and the first full doses. Ninety percent (n=36) received their step-up dosing in the outpatient setting.

Ten patients (25%) receiving Tec developed acute bone pain (grade 3 according to CTCAE v5.0 grading criteria) during step-up dosing, consistent with a tumor flare pain reaction. Six were treated in an outpatient setting. All received standard premedication along with tocilizumab prophylaxis. There were 5 males, median age was 61 years (range: 41-79), and the majority had an IgG isotype (n=7). Three patients exhibited plasmablastic morphology, one had a history of plasma cell leukemia, and 9 presented an extramedullary disease. Patient characteristics are detailed in Supplemental Table 1. One patient was not evaluable for response due to oligo-secretory disease. Among the remaining patients, seven achieved at least a partial response, with an overall response rate of 78%. One patient experienced grade 2 cytokine release syndrome (n=1/10), and no cases of neurotoxicity were observed. Tumor flare pain reactions only occurred after the step-up or the first full dose. Median time before onset of pain was 4 days (range: 2-8) after the first Tec dose, and the median duration was 4 days (range: 1-6). All patients received opioid analgesia (subcutaneous hydromorphone 1-2 mg every 3-4 hours), pregabalin, and acetaminophen. Seven patients experienced rapid relief following dexamethasone administration (mostly 10 mg up to three times daily for 24-48h). Among the six treated as outpatients, 2 required hospitalization for optimal pain control. For example, one patient presented, approximately 12 hours after the second dose of Tec, with a sudden onset of severe pain in the sternum and thoracic spine. Pancorporeal MRI and monoclonal protein remained stable throughout the episode. The pain was rapidly relieved following a single dose of dexamethasone 20 mg intravenously (IV). For some patients, recurrence of bone pain occurred after subsequent doses during step-up dosing. However, episodes were successfully managed, and all patients were able to continue Tec. No episodes

of recurrence were observed after cycle 1. A patient with plasma cell leukemia experienced bone pain on days +2, +4, +6, and +7 during the Tec step-up dosing. Each episode resolved following a 10 mg dose of IV dexamethasone. Paraprotein remained stable, while PET-CT showed multiple osteomedullary lesions with increased ^{18}F-FDG uptake involving notably the spine, ribs, long bones, and pelvis (Fig 1). Another patient presented lower back pain radiating to the left leg a few days prior to Tec initiation. MRI revealed compression of the L4 nerve root by a paravertebral lesion. Twenty-four hours after the second dose of Tec, the patient experienced a marked worsening of pain accompanied by left L4-distribution paraparesis, which was partially relieved with morphine. Dexamethasone was initiated, in addition to radiotherapy targeting the affected vertebrae, leading to pain relief and clinical improvement. The clinical presentation was suggestive of a tumor flare reaction. Following the third Tec dose, the patient developed severe bone pain in the pelvic and sternal regions, which was once again relieved by dexamethasone. Nine patients underwent imaging (PET-CT, CT, or MRI) during the pain episode, and three of them demonstrated radiologic findings that may represent pseudoprogression. Findings included an apparent increase in the size of an extramedullary muscular lesion (n=1), enlargement of extramedullary plasmacytomas involving the peritoneum (n=1), and the appearance of a new muscular lesion (n=1). Two of these three patients progressed within three months of initiating teclistamab.

Additionally, for three patients, a broad cytokine panel including tumor necrosis factor-αalpha, interferon-β, interleukins (IL)-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, and IL-1 was assessed during the pain episode. Cytokine analysis revealed that most values were within normal limits, except for IL-2 (approximately twice above the upper limit of normal), soluble IL-2 receptor (1.5 to 3 times above the upper limit of normal), IL-5 (eight times above the upper limit of normal), IL-10 (25 to 50 times above the upper limit of normal), and IL-6 (100 to 200 times above the upper limit of normal).

A tumor flare reaction, driven by acute immune infiltration and inflammation at tumor sites, can mimic disease progression, either clinically or radiologically. A transient increase in tumor size or the appearance of new lesions on imaging shortly after treatment initiation is referred to as pseudoprogression[5]. Tumor flare reaction has been well described in patients with solid tumors treated with immune checkpoint inhibitors as well as in chronic lymphocytic leukemia and non-Hodgkin's lymphoma following treatment with immunomodulatory drugs[5]. It typically occurs shortly after treatment initiation and resolve rapidly with appropriate management, particularly corticosteroids[5]. Tumor flare reactions are less commonly described in MM, with few cases reported following T-cell–redirecting therapies[2,6-9]. Nevertheless, in most of these cases, tumor flare reactions manifested as pseudoprogression, rather than as acute bone pain episodes, as observed in our cohort. In such situations, the prompt supportive care along with continuation of treatment may be appropriate[10].

We hypothesize that during step-up dosing, rapid and robust T-cell engagement triggers localized immune activation, infiltration of immune cells and cytokine-mediated inflammation in the bone marrow, resulting in acute bone pain driven by local inflammation. The consistent and rapid pain relief with dexamethasone, combined with PET-CT findings showing diffuse hypermetabolic marrow activity without new lesions or biochemical progression, supports the hypothesis that tumor flare pain reaction reflects a transient inflammatory process rather than true disease progression. However, in some patients, pseudoprogression and tumor flare pain reaction may occur simultaneously, underscoring the importance of correlating clinical, radiological, and biochemical data when evaluating early treatment-related events. Given the small sample size and retrospective design, identifying predictors of tumor flare pain reaction was not feasible. Notably, 90% of patients who experienced bone pain had extramedullary disease, suggesting a potential association

between high tumor burden, enhanced T-cell recruitment, and a more pronounced immune response.

While tocilizumab may be used prophylactically to reduce cytokine release syndrome and facilitate outpatient care, its impact on tumor flare pain reactions incidence remains unclear. Notably, all patients in our cohort who experienced tumor flare pain reactions had received prophylactic tocilizumab. If tocilizumab blocks the classical IL-6 signaling pathway, it may paradoxically enhance a trans-signaling pathway, activating sensory neurons via GP130 and promoting pain through the JAK2/STAT3 pathway, leading to edema and nociceptor sensitization[11,12]. Though speculative, this hypothesis is highly theoretical and has not been previously reported in studies evaluating prophylactic tocilizumab, warranting further investigation[13-16].

Although we describe tumor flare pain reaction in MM patients treated with Tec, this may apply to other bispecific T-Cell engagers. We observed this phenomenon in another patient treated with talquetamab, after prophylactic tocilizumab, who experienced grade 3 pelvic and spinal pain on days +4 and +5, following the second step-up dose, with rapid relief following dexamethasone administration. Pain recurred on days +5 and +6 after the third dose and was successfully managed with dexamethasone 10 mg IV every 8 hours for 24 hours. PET-CT imaging showed moderate to high ^{18}F-FDG uptake in the axial and proximal appendicular skeleton (Fig 2).

In conclusions, our finding come from a retrospective study with a small number of patients and therefore cannot be extrapolated to all individuals experiencing bone pain during step-up dosing. Acute bone pain should always prompt evaluation for alternative causes, particularly disease progression. Nonetheless, clinicians should be aware that tumor flare pain reaction appears to be an under-recognized yet clinically relevant adverse event during T-cell engagers

step-up dosing, often presenting as acute, severe bone pain without evidence of true disease progression. Early recognition and management are crucial to avoid unnecessary treatment discontinuation or hospitalization. Clinicians should remain vigilant, particularly in patients with high tumor burden or extramedullary disease**.** In this setting, corticosteroids - particularly dexamethasone - have shown rapid and consistent efficacy, highlighting their central role in managing tumor flare reaction. Prospective studies are needed to confirm our observations, clarify the underlying pathophysiological mechanisms, identify risk factors, and guide optimal pain relief strategies.

References:

1. Moreau P, Garfall AL, Van De Donk NWCJ, et al. Teclistamab in Relapsed or Refractory Multiple Myeloma. N Engl J Med. 2022;387(6):495-505.

2. Mohan M, Monge J, Shah N, et al. Teclistamab in relapsed refractory multiple myeloma: multi-institutional real-world study. Blood Cancer J. 2024;14(1):35.

3. Dima D, Davis JA, Ahmed N, et al. Safety and efficacy of teclistamab in patients with relapsed/refractory multiple myeloma: a real-world experience. Transplant Cell Ther. 2024;30(3):308.e1-308.e13.

4. Rodriguez-Otero P, Usmani S, Cohen AD, et al. International Myeloma Working Group immunotherapy committee consensus guidelines and recommendations for optimal use of T-cell-engaging bispecific antibodies in multiple myeloma. Lancet Oncol. 2024;25(5):e205-e216.

5. Taleb B. A. Tumour flare reaction in cancer treatments: a comprehensive literature review. Anticancer Drugs. 2019;30(9):953-958.

6. Nagarajan C, Eu Jo MW, Martin TG. BCMA Directed Bispecific Antibody Induced Tumor Flare in Multiple Myeloma. Clin Lymphoma Myeloma Leuk. 2024;24(7):488-490.

7. Forsberg M, Beltran S, Goldfinger M, et al. Phenomenon of tumor flare with talquetamab in a patient with extramedullary myeloma. Haematologica. 2024;109(7):2368-2371.

8. Jamet B, Bodet-Milin C, Moreau P, Kraeber-Bodéré F, Touzeau C. 2-[18F]FDG PET/CT Flare-up Phenomena Following T-Cell Engager Bispecific Antibody in Multiple Myeloma. Clin Nucl Med. 2023;48(5):e230-e231.

9. Leipold A, Werner R, Duell J, et al. Pseudoprogression and Sarcoidosis-like Phenomena after CART-Cells and Bispecific Antibodies in Multiple Myeloma. Blood. 2022;140(Supplement 1):10020-10021.

10. Chari A, Krishnan A, Rasche L, et al. Clinical management of patients with relapsed/refractory multiple myeloma treated with talquetamab. Clin Lymphoma Myeloma Leuk. 2024;24(10):665-693.e14.

11. Schaper F, Rose-John S. Interleukin-6: biology, signaling and strategies of blockade. Cytokine Growth Factor Rev. 2015;26(5):475-487.

12. Quarta S, Vogl C, Constantin CE, Üçeyler N, Sommer C, Kress M. Genetic evidence for an essential role of neuronally expressed IL-6 signal transducer gp130 in the induction and maintenance of experimentally induced mechanical hypersensitivity in vivo and in vitro. Mol Pain. 2011;7:73.

13. Scott SA, Marin EM, Maples KT, et al. Prophylactic tocilizumab to prevent cytokine release syndrome (CRS) with teclistamab: A single-center experience. Blood Cancer J. 2023;13(1):191.

14. Korst CLBM, Groen K, Bosman PWC, et al. Prophylactic tocilizumab reduces the incidence of cytokine release syndrome in relapsed/refractory myeloma patients treated with teclistamab: Implications for outpatient step□up dosing. Hemasphere. 2024;8(7):e132.

15. Kowalski A, Lykon J, Diamond B, et al. Tocilizumab Prophylaxis for Patients with Relapsed or Refractory Multiple Myeloma Treated with Teclistamab, Elranatamab or Talquetamab. Blood. 2024;144(Supplement 1):932.

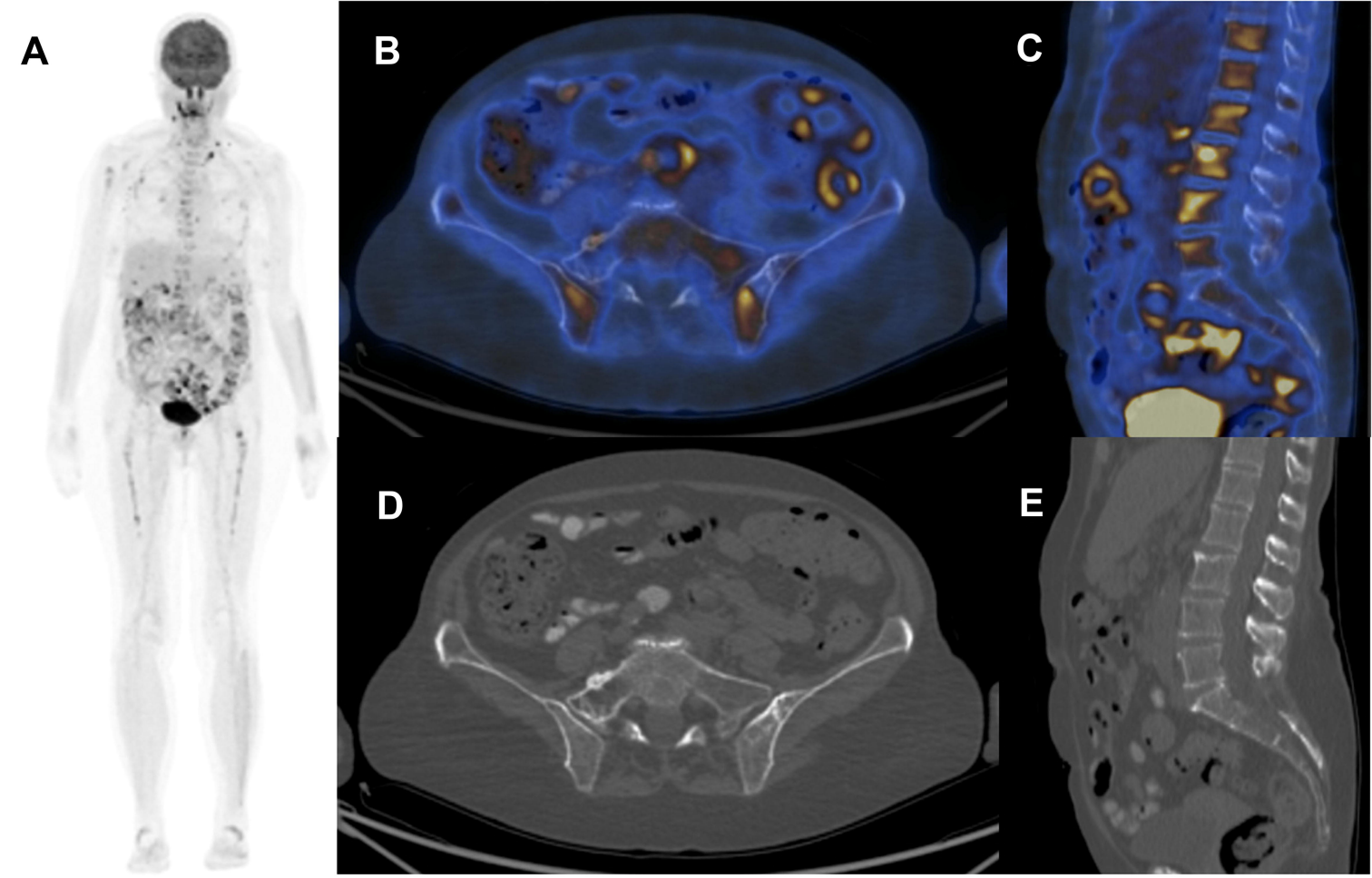
16. Van De Donk NWCJ, Garfall AL, Benboubker L, et al. Longer-term follow-up of patients (pts) receiving prophylactic tocilizumab (toci) for the reduction of cytokine release syndrome (CRS) in the phase 1/2 MajesTEC-1 study of teclistamab in relapsed/refractory multiple myeloma (RRMM). J Clin Oncol. 2024;42(16_suppl):7517.

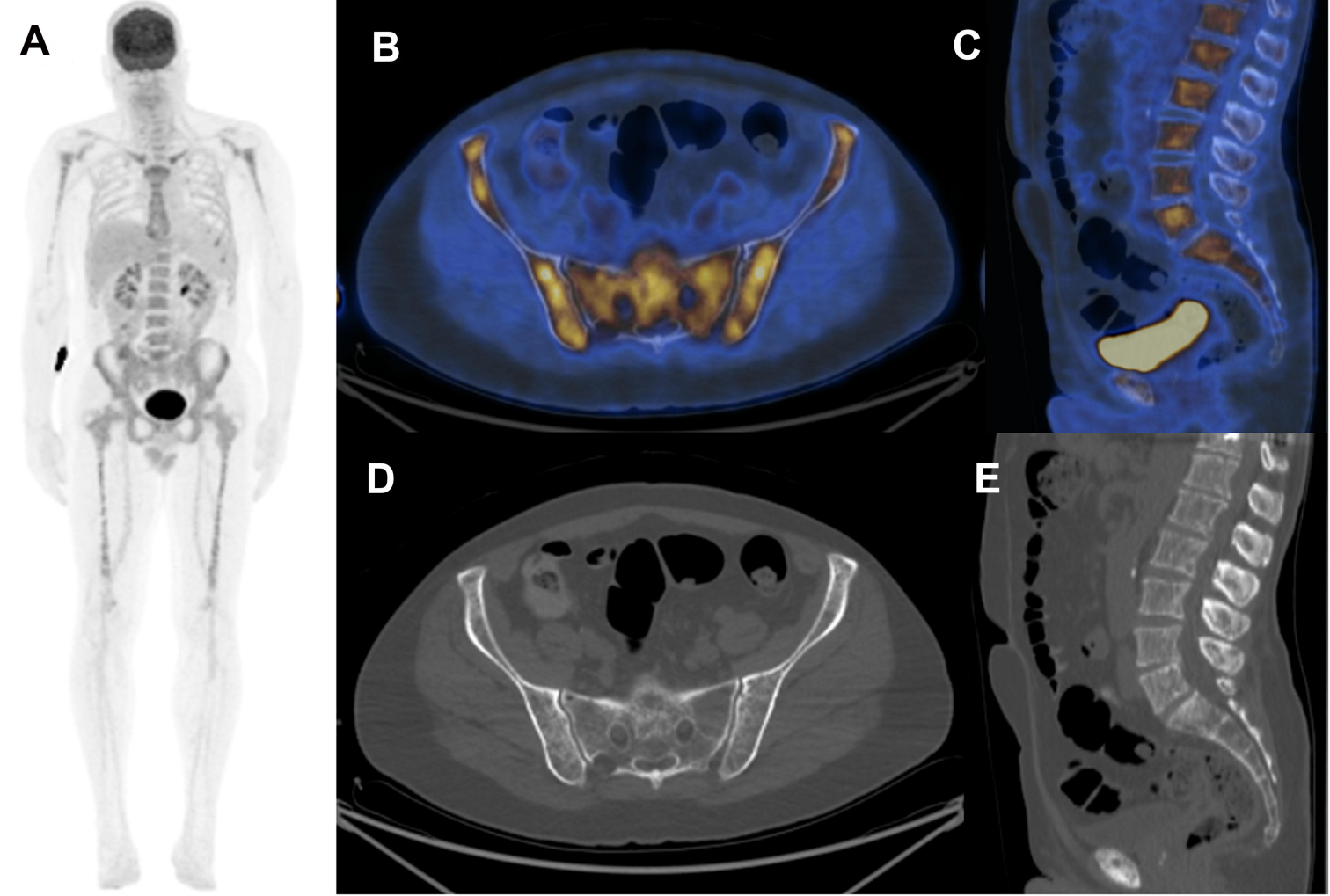
Figure 1: PET-CT imaging during a diffuse bone pain episode in a patient undergoing teclistamab step-up dosing.

Multiple osteomedullary lesions with ^{18}F-FDG uptake are noted, notably involving the proximal right humeral diaphysis, the sternum, thoracolumbar spine, ribs, sacrum, iliac bones, left femoral neck, and diffusely the bilateral femoral diaphyses (A-C). A SUVmax of 5.7 is observed in the posterior aspect of the left iliac bone (B). No clear corresponding lesions are visible on low-dose CT (D and E).

Figure 2: PET-CT findings in a patient with acute bone pain during talquetamab initiation.

PET imaging (A) demonstrates moderate to high, minimally heterogeneous ^{1} F-FDG uptake in the axial and proximal appendicular skeleton, with SUVmax of 5.9 in the posterior right iliac bone (B) and 6.1 in the L4 vertebral body (C). Low-dose CT images (D, E) show numerous small lytic bone lesions without clear predominance.


A
B
C
D
E


A
B
C
D
E

Supplemental Table 1 – Characteristics of patients with acute tumor flare pain reaction following treatment with teclistamab

Median age in years (range)	61 (41-79)
Biological male sex - no. (%)	5 (50)
Race - no (%) White Black	 9 (90) 1 (10)
≥1 Extramedullary plasmacytoma - no. (%)	9 (90)
High-risk cytogenetic profile - no./total no. (%)	3/9 (33.3)
International Staging System class - no./total no. (%) ISS 1 ISS 2 ISS 3	 4/9 (44.4) 3/9 (33.3) 2/9 (22.2)
Revised International Staging System (R-ISS) class - no./total no. (%) R-ISS 1 R-ISS 2 R-ISS 3	 1/7 (14.3) 5/7 (71.4) 1/7 (14.3)
Renal clairance ≤30mL/min - no. (%)	0 (0)
Median time since diagnosis - years (range)	2.2 (0.6-9.2)
Median no. of previous lines of therapy (range)	3 (2-5)
Triple class exposure - no. (%)	10 (100)
Prophylactic use of tocilizumab - no. (%)	10 (100)