Supplementary Figures and Tables

Apatinib plus camrelizumab (anti-PD1 therapy, SHR-1210) for advanced osteosarcoma (APFAO) progressing after chemotherapy: a single arm, open-label, phase 2 trial

Supplementary Figures

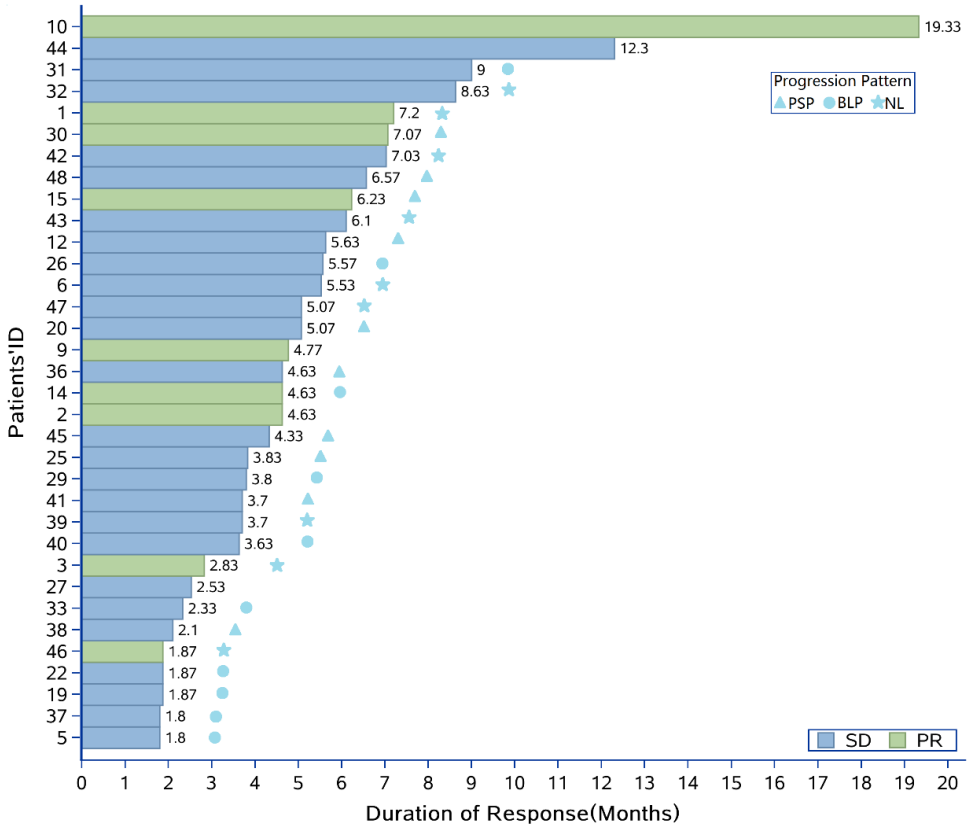

Figure S1 Duration of response. Eight patients were not included in the plot because they progressed at the time of first assessment, one patient withdrawal manifesting as stable disease at first evaluation but without further evaluation was either not included. The vertical coordinates stand for patients' identity number; the horizontal coordinates stand for duration of response; those with blue stripes stand for best overall response of stable disease; those with green stripes stand for best overall response of partial response. We divided patients' progression patterns into three types: Pulmonary lesions' Slow Progression (PSP, n=10), Bone Lesions' Progression (BLP, n=10), and stable disease with baseline lesions but progression with New Lesions (NL, n=9), which were respectively marked with triangle, roundness and star.

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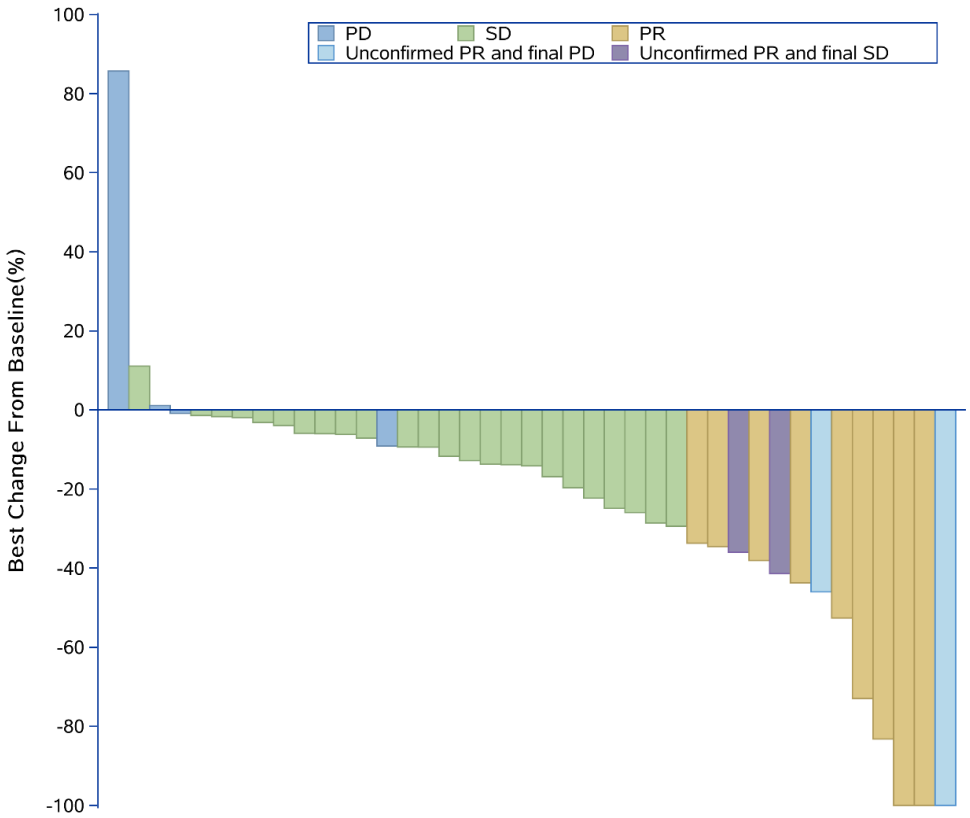

Figure S2 Waterfall plots for target lesions for the 41 patients.

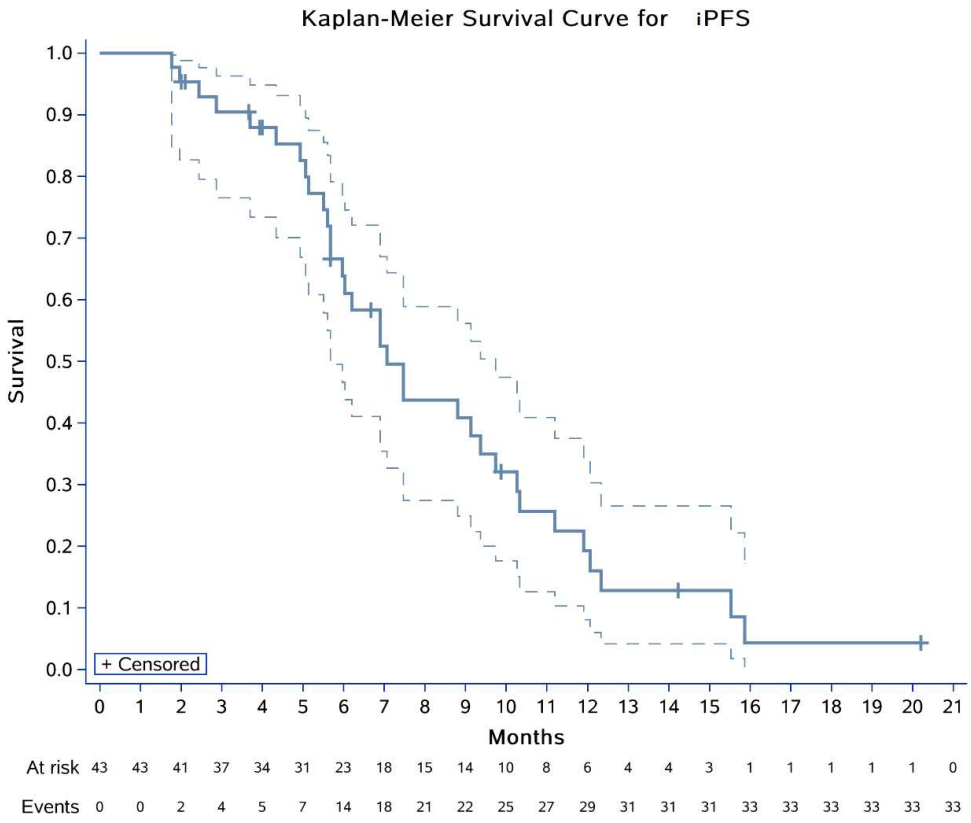

Figure S3 Kaplan-Meier plots for progression-free survival in 43 patients according to iRECIST.

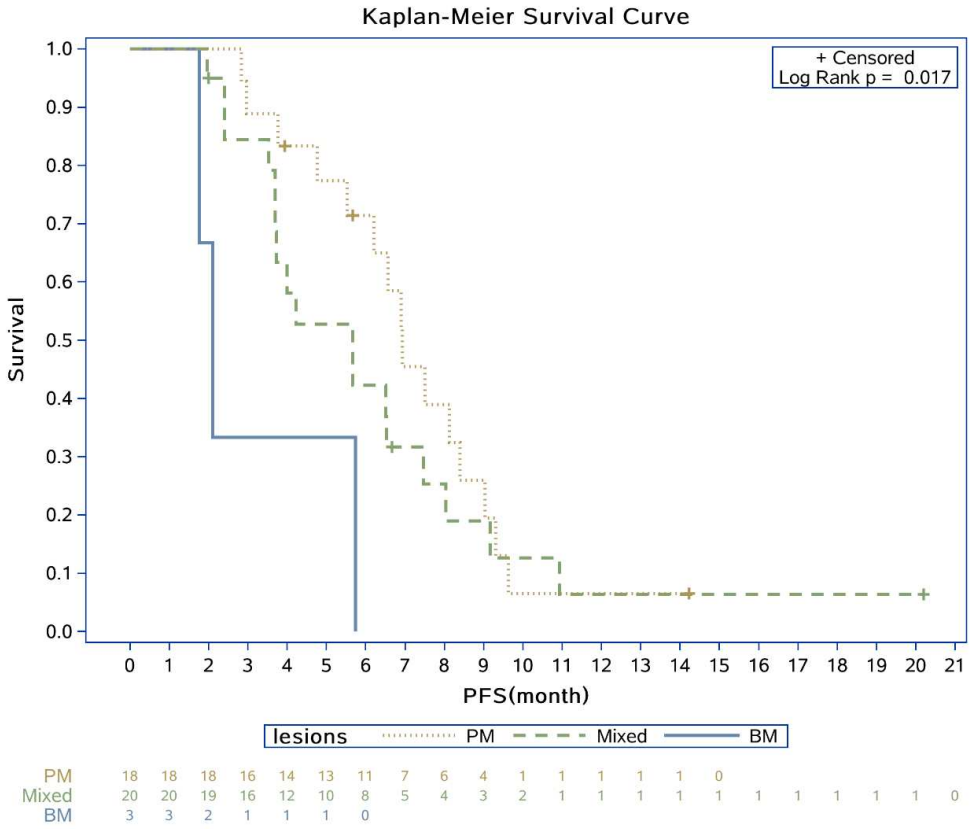

Figure S4 Kaplan-Meier plot for progression-free survival based on baseline lesions. We divided baseline lesions including target lesions and non-target lesions into three types: Pulmonary Metastasis only (PM, N=18); Bone Metastasis only (BM, N=3); Mixed type (Lung and bone or viscera) (Mixed, N=20). Log-rank test p=0·017. Crosses indicate censoring.

Supplementary Tables

Table S1 Influential or promising ongoing immunotherapy trials on osteosarcoma

Name	Time	n	Organization	Disease for trials	Agents	Benefit from Cohorts	ORR	CBR at 6 months	mPFS	mOS
NCT00134030 (EURAMOS-1)*	2005–2011	1164	EURAMOS Intergroups	Initial-treated osteosarcoma	IFN-α-2b†	3 year-EFS HR 0.83; P=0.214	N/A	N/A	N/A	N/A
INT-0133‡	1993–2005	205	COG	Initial-treated Osteosarcoma	Mifamurtide§	5 year-EFS 42% vs. 26% (HR 0.72, P=0.23)	N/A	N/A	N/A	N/A
NCT00428272	2006–2011	24	NCI	Advanced Ewing sarcoma, osteosarcoma, neuroblastoma and rhabdomyosarcoma	HGS-ETR2¶	One osteosarcoma patient had SD for more than 1 year.	No response	N/A	N/A	N/A
NCT00743496	2008–2014	38	St. Jude Children's Research Hospital	Advanced Neuroblastoma, Melanoma, Osteosarcoma, Ewing Sarcoma	GD2 mAbs**	6/31 (19.4%) had PR for by MIBG score. Median duration of response was 3.4 months (range, 1.1 months to 2.3 years)	No response	N/A	N/A	N/A
NCT02500797 (Alliance A091401)††	2015–2017	85	A091401‡‡ and NCTN	Advanced sarcoma	Ipilimumab and nivolumab		No objective responses seen in the nine patients with bone sarcomas in either group	4 (10%) of 42 patients in nivolumab group and 6 (12%) of 42 patients in the combination group	1.7 (1.4–4.3) months in nivolumab group and 4.1 months (1.4–4.7) in the combination group	10.7 (5.5–15.4) months in nivolumab group and 14.3 months (9.6–not estimable) in the combination group
NCT02304458 (ADVL1412)§§	2015–2020	484	COG	Advanced sarcoma	Ipilimumab and nivolumab	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing
NCT02301039 (SARC028)¶¶	2015–2017	80	SARC***	Advanced sarcoma	Pembrolizumab		One (5%) of 22 patients	N/A	8 weeks (95%CI 7–9 weeks) for bone sarcomas	52 weeks (95%CI 40–72 weeks)
NCT01241162	2010–2016	15	University of Louisville	Advanced Neuroblastoma; Ewing Sarcoma; Osteogenic Sarcoma; Rhabdomyosarcoma; Synovial Sarcoma	Decitabine and autologous dendritic cell vaccine		1/10 patients who had a complete response	N/A	N/A	N/A
NCT01803152	2014–2019	56	Macarena De La Fuente	Advanced sarcoma	Dendritic Cell Vaccine and Gemcitabine	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing
NCT02982941	2016–2020	25	MacroGenics	Advanced Neuroblastoma; Rhabdomyosarcoma; Osteosarcoma; Ewing	Enoblituzumab (MGA-271) anti-B7-H3	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing

				Sarcoma; Wilms Tumor; Desmoplastic Small Round Cell Tumor	antibody					
Retrospective study	2015–2016	28	New York University Langone Medical Center	Advanced sarcoma	Pazopanib and nivolumab		One (25%) of 4 osteosarcoma patients	12 (50%) out of 24 patients (all sarcoma included)	N/A	N/A
NCT03190174	2017–2020	40	Sarcoma Oncology Research Center	Advanced Undifferentiated Pleomorphic Sarcoma; Liposarcoma; Chondrosarcoma; Osteosarcoma; Ewing Sarcoma	Nivolumab and ABI-009 (Nab-rapamycin)	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing
NCT03006848	2017–2021	40	St. Jude Children's Research Hospital	Advanced osteosarcoma	Avelumab (anti-PD-L1)	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing
NCT02982486	2017–2020	60	Assaf-Harofeh Medical Center	Advanced sarcoma	Nivolumab and ipilimumab	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing
NCT02815995	2016–2019	150	MDACC	Advanced and/or Metastatic Sarcoma	Durvalumab and tremelimumab	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing
NCT03012620	2017–2023	350	UNICANCER†††	Advanced Sarcoma	Pembrolizumab	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing
NCT03359018 (present study)	2018–2019	41	Peking University People's Hospital	Advanced osteosarcoma	Camrelizumab (SHR-1210) and apatinib		20.93% (9/43)	30.23% (13/43)	6.23 (95%CI 3.57, 8.90) months	11.27 (95%CI 8.07, 14.77) months

*European and American Osteosarcoma Study Group (EURAMOS) including the Children's Oncology Group (COG), Cooperative Osteosarcoma Study Group (COSS), European Osteosarcoma Intergroup (EOI), and Scandinavian Sarcoma Group (SSG). The EURAMOS-1 trial established largescale multinational cooperation in clinical trials for osteosarcoma.

†Pegylated interferon alfa-2b (IFN-α-2b).

‡Intergroup Study 0133 containing Children's Cancer Group (CCG) and the Pediatric Oncology Group (POG).

§Liposomal muramyl tripeptide phosphatidylethanolamine (L-MTP-PE).

¶HGS-ETR2 (Lexatumumab) targets a protein called the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptor that is located on the surface of some tumor cells. When the TRAIL receptor is activated, it can cause the tumor cell to self-destruct.

**A glycosphingolipid that is expressed on the cell surface of limited normal adult tissue: the central nervous system, peripheral nerves, skin melanocytes, and mesenchymal stromal cells.

††Randomized Phase II Study of Nivolumab With or Without Ipilimumab in Patients with Metastatic or Unresectable Sarcoma.

‡‡Alliance Clinical Trials in Oncology Group.

§§A phase 1/2 study of nivolumab in children, adolescents, and young adults with recurrent or refractory solid tumors as a single agent and in combination with ipilimumab.

¶¶A Phase II Study of the Anti-PD1 Antibody Pembrolizumab (MK-3475) in Patients with Advanced Sarcomas.

***The Sarcoma Foundation of America, the QuadW Foundation, Ewan McGregor, and Pittsburgh Cure Sarcoma.
†††Fédération Nationale de Centres de Lutte Contre les Cancers (UNICANCER).
COG, Children's Oncology Group; MDACC, M.D. Anderson Cancer Center; Nab-rapamycin, nanoparticle albumin-bound rapamycin; N/A, not available; NCI, National Cancer Institute; NCTN, the National Clinical Trials Network.

Table S2 Efficacy of apatinib and camrelizumab combination treatment in patients with advanced osteosarcoma

	Overall (n=43)
Confirmed objective response*	9 (20.9%)
Complete response	0 (0.0%)
Partial response	9 (20.9%)
Stable disease ≥8 weeks	26 (60.5%)
Progressive disease	8 (18.6%)
ORR in evaluable 41 patients	22.0% (9.3%, 34.6%)
DCR in evaluable 41 patients	85.4% (70.8%, 94.4%)
CBR in evaluable 41 patients	31.7% (23.5%, 60.3%)
Median time to response	1.8 (1.2, 2.0)
Duration of response	
KM median (month)	6.2 (3.6, 8.9)
Ongoing, *n*/*N* (%)	1/9 (11.1%)
ITT progression-free survival	
KM median	6.2 (4.0, 6.9)
4 months	66.3% (49.8%, 78.5%)
6 months	50.9% (34.6%, 65.0%)
ITT overall survival	
KM median	11.3 (8.1, 14.8)
Patients' status at last follow-up	
AWD	12 (27.9%)
DOD	28 (65.1%)
Lost to follow-up	3 (7.0%)
Progression-free survival according to iRECIST	
KM median	7.5 (6.0, 9.7)
6 months	65.3% (47.8%, 78.2%)

Data are n (%), % (95%CI), or months (95%CI).
*Response was assessed in all enrolled patients.
AWD, alive with disease; CBR, clinical benefit rate; DCR, disease control rate; DOD, died of disease; iRECIST, guidelines for response criteria for use in trials testing immune-therapeutics; ITT, intention-to-treat population; KM, Kaplan Meier; NR, not reached; ORR, overall response rate.

Table S3 Adverse events that arose in at least one patient

	All, n (%)	**Grade 1, n (%)**	**Grade 2, *n* (%)**	**Grade 3, n (%)**	**Grade 4, n (%)**
Sum of all	43 (100.0)	42 (97.7)	43 (100.0)	29 (67.4)	6 (14.0)
Hypothyroidism	35 (81.4)	34 (79.1)	0 (0.0)	1 (2.3)	0 (0.0)
Hypertriglyceridemia	33 (76.7)	24 (55.8)	7 (16.3)	3 (7.0)	0 (0.0)
ALP increased	31 (72.1)	21 (48.8)	8 (18.6)	4 (9.3)	0 (0.0)
Platelet count decreased	30 (69.8)	14 (32.6)	4 (9.3)	2 (4.7)	0 (0.0)
Blood LDH increased	27 (62.8)	26 (60.5)	0 (0.0)	1 (2.3)	0 (0.0)
Diarrhea	23 (53.5)	11 (25.6)	11 (25.6)	3 (7.0)	0 (0.0)
Hand-foot syndrome	22 (51.2)	13 (30.2)	7 (16.3)	2 (4.7)	0 (0.0)
Blood bilirubin increased	22 (51.2)	14 (32.6)	13 (30.2)	4 (9.3)	0 (0.0)
Pain in extremity	20 (46.5)	4 (9.3)	16 (37.2)	2 (4.7)	0 (0.0)
Anorexia	20 (46.5)	10 (23.3)	7 (16.3)	3 (7.0)	0 (0.0)
AST increased	18 (41.9)	16 (37.2)	1 (2.3)	1 (2.3)	1 (2.3)
ALT increased	17 (39.5)	14 (32.6)	1 (2.3)	1 (2.3)	1 (2.3)
Leukopenia	17 (39.5)	4 (9.3)	12 (27.9)	1 (2.3)	2 (4.7)
Hypokalemia	17 (39.5)	17 (39.5)	0 (0.0)	0 (0.0)	0 (0.0)
Rash	15 (34.9)	7 (16.3)	7 (16.3)	2 (4.7)	0 (0.0)
Weight loss	15 (34.9)	7 (16.3)	5 (11.6)	3 (7.0)	0 (0.0)
Cough	12 (27.9)	6 (14.0)	5 (11.6)	1 (2.3)	0 (0.0)
Hypercholesteremia	12 (27.9)	10 (23.3)	2 (4.7)	0 (0.0)	0 (0.0)
Wound dehiscence	11 (25.6)	3 (7.0)	3 (7.0)	5 (11.6)	1 (2.3)
Proteinuria	11 (25.6)	5 (11.6)	5 (11.6)	1 (2.3)	0 (0.0)
Mucositis oral	11 (25.6)	6 (14.0)	3 (7.0)	2 (4.7)	0 (0.0)
Hypertension	10 (23.3)	4 (9.3)	3 (7.0)	2 (4.7)	0 (0.0)
Pneumothorax	10 (23.3)	3 (7.0)	4 (9.3)	2 (4.7)	1 (2.3)
Nausea	9 (20.9)	5 (11.6)	3 (7.0)	1 (2.3)	0 (0.0)
Abdominal pain	8 (18.6)	4 (9.3)	2 (4.7)	2 (4.7)	0 (0.0)
Myalgia	8 (18.6)	3 (7.0)	5 (11.6)	0 (0.0)	0 (0.0)
Arthralgia	7 (16.3)	4 (9.3)	3 (7.0)	0 (0.0)	0 (0.0)
Vomiting	6 (14.0)	3 (7.0)	2 (4.7)	1 (2.3)	0 (0.0)
Toothache	6 (14.0)	2 (4.7)	2 (4.7)	2 (4.7)	0 (0.0)
Hemorrhoidal hemorrhage	6 (14.0)	2 (4.7)	3 (7.0)	1 (2.3)	0 (0.0)
Sinus tachycardia	5 (11.6)	2 (4.7)	3 (7.0)	0 (0.0)	0 (0.0)
Fever	5 (11.6)	3 (7.0)	2 (4.7)	0 (0.0)	0 (0.0)
Backache	5 (11.6)	2 (4.7)	3 (7.0)	0 (0.0)	0 (0.0)
Fatigue	4 (9.3)	1 (2.3)	2 (4.7)	1 (2.3)	0 (0.0)
Headache	4 (9.3)	1 (2.3)	3 (7.0)	0 (0.0)	0 (0.0)
Electrocardiogram QT corrected interval prolonged	3 (7.0)	2 (4.7)	1 (2.3)	0 (0.0)	0 (0.0)
Paresthesia	3 (7.0)	2 (4.7)	1 (2.3)	0 (0.0)	0 (0.0)
Proteinuria	3 (7.0)	1 (2.3)	2 (4.7)	0 (0.0)	0 (0.0)
Peripheral neuroinflammation	3 (7.0)	2 (4.7)	0 (0.0)	1 (2.3)	0 (0.0)
Dysphasia	3 (7.0)	0 (0.0)	2 (4.7)	0 (0.0)	0 (0.0)
Chest pain	3 (7.0)	3 (7.0)	0 (0.0)	0 (0.0)	0 (0.0)
Epistaxis	2 (4.7)	2 (4.7)	0 (0.0)	0 (0.0)	0 (0.0)
Non-cardiac chest pain	2 (4.7)	1 (2.3)	1 (2.3)	2 (4.7)	0 (0.0)
Abdominal distension	2 (4.7)	1 (2.3)	0 (0.0)	1 (2.3)	0 (0.0)
Hyperuricemia	2 (4.7)	2 (4.7)	0 (0.0)	0 (0.0)	0 (0.0)

Sore throat	2 (4.7)	2 (4.7)	0 (0.0)	0 (0.0)	0 (0.0)
Pruritus	2 (4.7)	1 (2.3)	0 (0.0)	1 (2.3)	0 (0.0)
Pharyngolaryngeal pain	2 (4.7)	1 (2.3)	1 (2.3)	0 (0.0)	0 (0.0)
Insomnia	2 (4.7)	2 (4.7)	0 (0.0)	0 (0.0)	0 (0.0)
Hypersomnia	2 (4.7)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
Hoarseness	2 (4.7)	1 (2.3)	1 (2.3)	0 (0.0)	0 (0.0)
Stomach pains	2 (4.7)	1 (2.3)	0 (0.0)	1 (2.3)	0 (0.0)
Dysuria	2 (4.7)	0 (0.0)	1 (2.3)	1 (2.3)	0 (0.0)
Pleural effusion	2 (4.7)	0 (0.0)	2 (4.7)	0 (0.0)	0 (0.0)
Limb edema	2 (4.7)	0 (0.0)	2 (4.7)	0 (0.0)	0 (0.0)
Vitiligo	1 (2.3)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
Back pain	1 (2.3)	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)
Constipation	1 (2.3)	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)
Hypophysitis	1 (2.3)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
Cholecystitis	1 (2.3)	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)
Hypoalbuminemia	1 (2.3)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)
Seizure	1 (2.3)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)
Hepatic failure	1 (2.3)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)
Anal mucositis	1 (2.3)	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)
Perianal ulcer	1 (2.3)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)
Perianal abscess	1 (2.3)	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)
Hypercalcemia	1 (2.3)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
Arthritis	1 (2.3)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)
Anaphylaxis	1 (2.3)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)
Dyspnea	1 (2.3)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
Jaundice	1 (2.3)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)
Perineal ulcer	1 (2.3)	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)
Hyperthyroidism	1 (2.3)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
Oral hemorrhage	1 (2.3)	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)
Pneumonitis	1 (2.3)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)
Cerebral hemorrhage	1 (2.3)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)
Urine output decreased	1 (2.3)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)
Urinary frequency	1 (2.3)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
Skin ulceration	1 (2.3)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
Fracture	1 (2.3)	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)
Flank pain	1 (2.3)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
Buttock pain	1 (2.3)	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)
Gastric perforation	1 (2.3)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)
Periodontal disease	1 (2.3)	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)
Pancreatitis	1 (2.3)	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)
Loss of consciousness	1 (2.3)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
Productive cough	1 (2.3)	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)
Pain in extremity	1 (2.3)	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)
Rash pustular	1 (2.3)	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)
Muscle pain	1 (2.3)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
Urethritis	1 (2.3)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
Hemangioma	1 (2.3)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
Neutropenia	1 (2.3)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase.