Table S1. List of clinical trials involving immunomodulating agents or approaches in high-grade osteosarcoma (HGOS), which are either presently active or that have been concluded in the last 6 months without providing published results. In the "Indication" column, only the eligibility criteria for HGOS patients have been reported. Trials with available results have been described in the text.

Number referred in Figure 3	**Compound/Therapeutic strategy**	**Structure**	**Mechanism of action**	**Indication** **ClinicalTrials.gov NCT identifier (protocol acronym)** **Participating Countries**	**Stage of development** **(time period)**
1	**Mifamurtide** combined with post-operative chemotherapy	muramyl tripeptide linked to dipalmitoyl-phosphatidyl-ethanolamine to facilitate incorporation into liposomes	macrophage stimulant used with conventional drugs	HGOS metastatic at diagnosis or localized HGOS with poor histological response NCT03643133 (SARCOME 13) France	phase II recruiting no available results (10/2018 - 10/2028)
2	**Avelumab** (Bavencio®)	fully human monoclonal antibody against PD-L1	targeting PD-L1	recurrent or progressive HGOS NCT03006848 USA	phase II active, not recruiting no available results (02/2017-01/2023)
3	**ZKAB001** (STI-1014; STI-	fully human monoclonal	targeting PD-L1	recurrent or refractory	phase I/II

	A1014)	antibody against PD-L1		HGOS NCT03676985 China	recruiting no available results (10/2018 - 06/2023)
Number referred in Figure 3	**Compound/Therapeutic strategy**	**Structure**	**Mechanism of action**	**Indication** **ClinicalTrials.gov NCT identifier (protocol acronym)** **Participating Countries**	**Stage of development** **(time period)**
4	**ZKAB001** maintenance therapy after adjuvant chemotherapy	anti-PD-L1 antibody	targeting PD-L1	HGOS NCT04359550 China	phase III not yet recruiting no available results (06/2020 - 06/2023)
5	**Nivolumab** (Opdivo®) plus **Sunitinib** (Sutent®, previously known as SU11248) after standard treatment	Nivolumab: monoclonal antibody against PD-1 Sunitinib: RTK inhibitor	targeting PD-1 and RTK	advanced soft-tissue and bone sarcomas NCT03277924 (GEIS-52) Spain, Italy	phase I/II recruiting no available results (05/2017 - 09/2022)
6	**Nivolumab** (Opdivo®) and **Ipilimumab** (Yervoy®) plus cryotherapy	Nivolumab: monoclonal antibody against PD-1	targeting PD-1 (nivolumab) and CTLA-4 (ipilimumab)	Relapsed/refractory osteosarcoma	phase II recruiting

		Ipilimumab: monoclonal antibody against CTLA-4		NCT05302921 USA	no available results (02/2022 – 07/2025)
7	**Nivolumab** (Opdivo®) or **Nivolumab** (Opdivo®) and **Azacitidine**	Nivolumab: monoclonal antibody against PD-1	targeting PD-1	recurrent, resectable HGOS NCT03628209 USA	phase I/II recruiting no available results (10/2019 - 07/2022)

Number referred in Figure 3	Compound/Therapeutic strategy	Structure	Mechanism of action	Indication ClinicalTrials.gov NCT identifier (protocol acronym) Participating Countries	Stage of development (time period)
8	**Nivolumab** (Opdivo®) and **Regorafenib**	Nivolumab: monoclonal antibody against PD-1	targeting PD-1	recurrent, metastatic HGOS NCT04803877 (SARC038) USA	phase II recruiting no available results (06/2021 - 06/2026)
9	Combination of **Pembrolizumab** and **Cabozantinib**	Pembrolizumab: humanized IgG4 antibody directed against human cell surface receptor PD-1 Cabozantinib: multi-kinase inhibitor	potential immune checkpoint inhibitory and antineoplastic activities; blocking of PD-1 binding to its ligands, which results in the activation of T-cell-mediated immune responses against tumor cells	advanced HGOS NCT05182164 (PEMBROCABOSARC) France	phase II recruiting no available results (04/2022 - 10/2025)
10	**Atezolizumab** and **Cabozantinib** for the treatment of adolescents and young adults	Atezolizumab: monoclonal antibody against PD-L1 Cabozantinib: multi-kinase inhibitor	targeting PD-L1	locally advanced, metastatic, recurrent, refractory, or unresectable HGOS NCT05019703	phase II active, not recruiting no available results

				(TACOS) USA	(06/2022 - 12/2027)

Number referred in Figure 3	Compound/Therapeutic strategy	Structure	Mechanism of action	Indication ClinicalTrials.gov NCT identifier (protocol acronym) Participating Countries	Stage of development (time period)
11	**Camrelizumab** in combination with neoadjuvant chemotherapy	Camrelizumab: humanized anti-PD1 IgG4 monoclonal antibody	targeting PD-1	locally resectable HGOS NCT04294511 China	phase II recruiting no available results (12/2019 - 09/2023)
12	**LN-145** or **LN-145-S1** after **Ipilimumab, Nivolumab,** cyclophosphamide IV and fludarabine IV and before Aldesleukin IV and **Nivolumab**	LN-145 is made by collecting Growing specialized white blood cells (T-cells) that are collected from the patient's tumor LN-145-S1 is made using a modified process that chooses a specific portion of the T-cells Ipilimumab: monoclonal antibody against CTLA-4 Nivolumab: monoclonal antibody against PD-1	T cells should specific targeting and killing of tumor cells targeting PD-1and CTLA-4	relapsed or refractory HGOS NCT03449108 USA	phase II recruiting no available results (04/2018 - 06/2024)
13	**Tislelizumab** in association	Human IgG4 monoclonal	targeting PD-1 in	bone metastatic cancers	phase II

	with chemotherapy	antibody against PD-1 combined with chemotherapy	association with chemotherapy	(including HGOS) NCT05241132 China	recruiting no available results (11/2021 – 10/2024)
Number referred in Figure 3	**Compound/Therapeutic strategy**	**Structure**	**Mechanism of action**	**Indication** **ClinicalTrials.gov NCT identifier (protocol acronym)** **Participating Countries**	**Stage of development** **(time period)**
14	**Niraparib** and **dostarlimab**	Niraparib: PARP inhibitor with potential antineoplastic activity Dostarlimab: PD-1 inhibitor	inhibition of PARP and PD-1	solid tumors (including HGOS) NCT04544995 France, Spain, UK	phase I recruiting no available results (10/2020 – 03/2030)
15	**Durvalumab** and **Oleclumab**	Oleclumab: Monoclonal Antibody MEDI9447 that inhibits the ectonucleotidase CD73 (also known as 5-nucleotidase) Durvalumab: Human Monoclonal antibody that blocks the interaction of PD-L1 with PD-1 and CD80 inhibiting the immune	help of the body's immune system in killing cancer cells interference with the ability of tumor cells to grow and spread	metastatic , recurrent or refractory HGOS NCT04668300 (DOSa) USA	phase II recruiting no available results (11/2020 - 06/2024)

		evading mechanisms			
16	**Durvalumab and tremelimumab**	Durvalumab: anti-PD-L1 IgG1monoclonal antibody Tremelimumab: anti-CTLA-4 human monoclonal antibody	targeting PD-L1 and CTLA-4	advanced or metastatic HGOS NCT02815995 USA	phase II recruiting no available results (08/2016 - 12/2022)

Number referred in Figure 3	Compound/Therapeutic strategy	Structure	Mechanism of action	Indication ClinicalTrials.gov NCT identifier (protocol acronym) Participating Countries	Stage of development (time period)
17	Humanized **anti-GD2 monoclonal antibody 3F8 (Hu3F8)** combined with GM-CSF	humanized anti-GD2 monoclonal antibody	targeting GD2 with the humanized antibody Hu3F8	recurrent HGOS NCT02502786 USA	phase II recruiting no available results (07/2015 - 07/2023)
18	**Dinutuximab** and **Magrolimab**	Dinutuximab beta: IgG1 chimeric monoclonal antibody against GD2 Magrolimab: A human monoclonal anti-CD47 antibody for the treatment of non-Hodgkin's lymphoma	targeting GD2 and CD47	recurrent or resectable HGOS NCT04751383 USA	phase I recruiting no available results (04/2021 - 01/2024)
19	**Pepinemab (VX15/2503)**	anti-SEMA4D monoclonal antibody	immunomodulation	recurrent or refractory HGOS and malignant solid tumors NCT03320330 USA	phase I/II active, not recruiting no available results

					(01/2018 - 12/2025)

Number referred in Figure 3	Compound/Therapeutic strategy	Structure	Mechanism of action	Indication ClinicalTrials.gov NCT identifier (protocol acronym) Participating Countries	Stage of development (time period)
20	**PLX3397** plus **Sirolimus**	PLX3397: inhibitor of of macrophage colony-stimulating factor receptor Sirolimus: immunosuppressive agent	PLX3397: selective inhibition of macrophages Sirolimus: immunosuppression	unresectable sarcomas (including HGOS) NCT02584647 USA	phase I/II recruiting no available results (11/2015 - 03/2024)
21	**Autologous tumour infiltrating lymphocytes** in association with cyclophosphamide and fludarabine	cellular immunological anticancer therapy	Novel immunotherapy based on tumour-infiltrating lymphocytes in patients non-responding to standard treatments	several solid tumors, including recurrent HGOS NCT03610490 USA	phase II active, not recruiting no available results (08/2018- 01/2025)
22	**Tumor infiltrating lymphocytes** plus **anti-CTLA-4** and **anti-PD-L1/L2**	Autologous tumor infiltrating lymphocytes after Ipilimumab and followed by Nivolumab	Cellular immunological anticancer therapy plus anti-CTLA-4 and anti PD-L1 and PD-L2 treatment	relapsed or refractory HGOS NCT03449108 USA	phase II recruiting no available results (04/2018 - 06/2024)

Number referred in Figure 3	Compound/Therapeutic strategy	Structure	Mechanism of action	Indication ClinicalTrials.gov NCT identifier (protocol acronym) Participating Countries	Stage of development (time period)
23	**Haploidentical transplant and donor NK cells**	cellular and adoptive immunotherapy	HLA-haploidentical hematopoietic cell transplantation followed by an early, post-transplant infusion of donor NK cells will influence the development of particular NK and T cell subtypes	HGOS NCT02100891 (STIR) USA	phase II not recruiting no available results (03/2014 - 12/2022)
24	**Transplantation with haploidentical donor peripheral blood stem cells** in conjunction with **Zoledronate**	cellular and adoptive immunotherapy	enhancement of tumor killing by combining transplantation with immunostimulating activity of zolendronic acid	pediatric patients with relapsed or refractory hematologic malignancies or high risk solid tumors, including HGOS NCT02508038 USA	phase I recruiting no available results (02-2016-11/2025)
25	Aerosolized **Aldesleukin**	Aldesleukin (also called Proleukin and recombinant human interleukin-2) is a form of interleukin-2 that is	Aldesleukin acts as immunomodulating agent, increasing the activity and growth of	metastatic osteosarcoma, stage IV HGOS NCT01590069	phase I not recruiting

		made in the laboratory.	white blood cells called T lymphocytes and B lymphocytes, which may help the immune system kill cancer cells	USA	no available results (06/2012- 12/2022)
Number referred in Figure 3	**Compound/Therapeutic strategy**	**Structure**	**Mechanism of action**	**Indication** **ClinicalTrials.gov NCT identifier (protocol acronym)** **Participating Countries**	**Stage of development** **(time period)**
26	**CRX100** combined with oncolytic virus CDSR	*ex vivo* generation of autologous CIK	anti-tumor activity of autologous CIK cells	relapsed or refractory HGOS NCT04282044 USA	phase I recruiting no available results (01/2021 - 03/2025)
27	**Dendritic Cell** and tumor cell vaccine	patient-derived dendritic cells vaccine (a type of white blood cells that helps fight infections obtained by leukapheresis) tumor cell vaccine: tumor cell lysate	dendritic cells vaccine followed by tumor cell vaccine with or without gemcitabine prior to dendritic cells vaccination	bone sarcoma NCT01803152 USA	phase I not recruiting no available results (01/2014- 07/2024)
28	4th generation safety-engineered **CAR T cells** targeting sarcomas	4th generation safety-engineered CAR T cells	CAR-IgT cells targeting sarcoma surface antigens	osteoid sarcomas, including HGOS	phase I/II recruiting

				NCT03356782 China	no available results (12/2017 - 12/2023)

Number referred in Figure 3	Compound/Therapeutic strategy	Structure	Mechanism of action	Indication ClinicalTrials.gov NCT identifier (protocol acronym) Participating Countries	Stage of development (time period)
29	**EGFR806 CAR T cell** immunotherapy	second generation EGFR-specific CAR T cells	administration of T cells derived from the participant's blood, which have been genetically modified to express either the EGFR receptor alone (EGFR806CAR(2G)-EGFRt) or in addition also the CD19 receptor (CD19CAR(2G)-T2A-HER2tG)	recurrent or refractory solid tumors, including HGOS NCT03618381 USA	phase I recruiting no available results (06/2019 - 06/2038)
30	**NY-ESO-1-specific CAR T cells**	CAR T cells targeting NY-ESO-1 positive cells	TCR affinity enhancing specific T cell therapy	bone sarcomas (including HGOS) stage IV or after failure of first-line treatment NCT03462316 China	phase I recruiting no available results (05/2018 - 02/2023)

Number referred in Figure 3	Compound/Therapeutic strategy	Structure	Mechanism of action	Indication ClinicalTrials.gov NCT identifier (protocol acronym) Participating Countries	Stage of development (time period)
31	Feasibility and safety study of **fluorescein-specific (FITC-E2) CAR T cells** in combination with parenterally administered folate-fluorescein (UB-TT170)	ex-vivo expanded autologous T cells genetically modified to express an antiFL(FITC-E2) CAR	evaluation of the pharmacokinetics of UB-TT170 in combination with the anti-FL(FITC-E2) CAR T cells	recurrent, refractory HGOS NCT05312411 USA	phase I recruiting no available results (05/2022 - 04/2040)
32	**CAR T cells targeting GD2** with interleukin-15 plus iCaspase 9 and Cyclophosphamide	CAR T cells	targeting GD2	relapsed or refractory HGOS NCT03721068 USA	phase I recruiting no available results (02/2019 - 06/2039)
33	**GD2-targeted modified T-cells (GD2CART)** and Cyclophosphamide	GD2-targeted CAR T-cells	immune cell therapy based on GD2-CAR-expressing autologous T-lymphocytes (GD2CART)	relapsed, refractory HGOS NCT04539366 (GD2-CAR PERSIST) USA	phase I recruiting no available results (06/2021 - 08/2024)

Number referred in Figure 3	Compound/Therapeutic strategy	Structure	Mechanism of action	Indication ClinicalTrials.gov NCT identifier (protocol acronym) Participating Countries	Stage of development (time period)
34	**Anti-GD2 CAR T cells**	GD2-targeting CAR T cells (GD2-CART01)	single infusion of GD2-CART01	recurrent GD2 positive HGOS NCT03373097 Italy	phase I/II recruiting no available results (01/2018 - 01/2027)
35	**C7R-GD2 CAR T cells** with or without cyclophosphamide and fludarabine	CAR T cells targeting GD2	cellular immunological anticancer therapy, targeting GD2 C7R gives the cells a constant supply of cytokine and helps them to survive for a longer period of time	relapsed HGOS NCT03635632 USA	phase I recruiting no available results (04/2019 – 12/2037)
36	**iC9-GD2-CAR-VZV-CTLs**	CAR consisting of an anti-GD2 antibody called 14g2a (GD2-CAR), containing parts of the CD28 and OX40 genes, which can stimulate T cells to make them live	treatment with GD2-T cells (also called iC9-GD2-CAR-VZV-CTLs) in combination with a varicella zoster vaccine and	refractory or metastatic GD2-positive HGOS NCT01953900 (VEGAS)	phase I active, not recruiting no available results

		longer	lymphodepleting chemotherapy	USA	04/2014 - 10/2034)

Number referred in Figure 3	Compound/Therapeutic strategy	Structure	Mechanism of action	Indication ClinicalTrials.gov NCT identifier (protocol acronym) Participating Countries	Stage of development (time period)
37	**CD276-targeted CAR T** administered intravenous and local tumor injection	CAR T cells targeting CD276	targeting CD276, which is highly expressed on the surface of HGOS cells but not in normal peripheral cells or tissues	HGOS NCT04864821 China	early phase I not yet recruiting no available results (05/2021 - 05/2023)
38	Multiple **sarcoma-specific CAR-T cells** and sarcoma vaccines	CAR-T cells against GD2, PSMA, Her2, CD276 or other markers and vaccines	multiple CAR T cells with low dose chemotherapy followed by maintenance sarcoma vaccines	relapsed or late stage Osteoid sarcoma NCT04433221 China	phase I/II recruiting no available results (07/2020 - 12/2023)
39	**B7-H3-CAR T** cells in association with cyclophosphamide, MESNA and fludarabine	cellular immunological anticancer therapy	CAR T cells targeting B7-H3 antigen	HGOS NCT04897321 USA	phase I recruiting no available results (06/2022 – 03/2027)

Number referred in Figure 3	Compound/Therapeutic strategy	Structure	Mechanism of action	Indication ClinicalTrials.gov NCT identifier (protocol acronym) Participating Countries	Stage of development (time period)
40	**B7-H3-CAR T** cells	cellular immunological anticancer therapy	CAR T cells targeting B7-H3 antigen	recurrent/refractory HGOS NCT04483778 USA	phase I recruiting no available results (07/2020 – 12/2040)

Legend: B7H3 or CD276: CD276 molecule; CAR: Chimeric antigen receptor; CIK: Cytokine induced killer cells; CTLA4: Cytotoxic T-Lymphocyte Associated Protein 4; EGFR: Epithelial growth factor receptor; GD2: Disialoganglioside 2; Her2 (ERBB2): Erb-B2 receptor tyrosine kinase 2; NK: Natural killer; PARP: Poly ADP-ribose polymerase; PD-1: Programmed cell death-1; PD-1L, PD-L1: Programmed death-ligand 1; PD-2L, PD-L2: Programmed death-ligand 2; PSMA: Prostate-specific membrane antigen; RTK: Tyrosine kinase; SEMA4D: Semaphorin 4D; TAMs: Tumor associated macrophages.