

Table S1 HER2-ADC combo in clinical development

No.	ADC generic name	ADC code No.	+ SM/LM/vaccine	Action	Company	Linker	Payload	DAR	Indication	Status	ClinicalTrials.gov Identifier
1	Trastuzumab deruxtecan	DS-8201a	Nivolumab	Anti-PD-1 mab	Daiichi Sankyo, Inc.; AstraZeneca; BMS	mc-GGFG-AM	Dxd	7-8	HER2+ breast cancer	Phase I	NCT03523572
2	Trastuzumab deruxtecan	DS-8201a	Pembrolizumab	Anti-PD-1 mab	Daiichi Sankyo, Inc.; AstraZeneca; Merck	mc-GGFG-AM	Dxd	7-8	Advanced/metastatic breast cancer	Phase I	NCT04042701
3	Trastuzumab deruxtecan	DS-8201a	Capecitabine	Antineoplastic agent	Daiichi Sankyo, Inc.; AstraZeneca	mc-GGFG-AM	Dxd	7-8	HER2-low advanced or metastatic breast cancer	Phase I	NCT04556773
4	Trastuzumab deruxtecan	DS-8201a	Durvalumab and paclitaxel	Anti-PD-L1 mab and antineoplastic agent	Daiichi Sankyo, Inc.; AstraZeneca	mc-GGFG-AM	Dxd	7-8	HER2-low advanced or metastatic breast cancer	Phase I	NCT04556773
5	Trastuzumab deruxtecan	DS-8201a	Capivasertib	AKT kinase inhibitor	Daiichi Sankyo, Inc.; AstraZeneca	mc-GGFG-AM	Dxd	7-8	HER2-low advanced or metastatic breast cancer	Phase I/II	NCT04538742
6	Trastuzumab deruxtecan	DS-8201a	Anastrozole	Nonsteroidal inhibitor	Daiichi Sankyo, Inc.; AstraZeneca	mc-GGFG-AM	Dxd	7-8	HER2-low advanced or metastatic breast cancer	Phase I	NCT04556773
7	Trastuzumab deruxtecan	DS-8201a	Fulvestrant	Steroidal antiestrogen	Daiichi Sankyo, Inc.; AstraZeneca	mc-GGFG-AM	Dxd	7-8	HER2-low advanced or metastatic breast cancer	Phase I	NCT04556773
8	Trastuzumab deruxtecan	DS-8201a	Durvalumab	Anti-PD-L1 mab	Daiichi Sankyo, Inc.; AstraZeneca	mc-GGFG-AM	Dxd	7-8	HER2+ metastatic breast cancer	Phase I/II	NCT04538742
9	Trastuzumab deruxtecan	DS-8201a	Paclitaxel	Antineoplastic agent	Daiichi Sankyo, Inc.; AstraZeneca	mc-GGFG-AM	Dxd	7-8	HER2+ metastatic breast cancer	Phase I/II	NCT04538742
10	Trastuzumab deruxtecan	DS-8201a	Pertuzumab	Anti-HER2 mab	Daiichi Sankyo, Inc.; AstraZeneca	mc-GGFG-AM	Dxd	7-8	HER2+ metastatic breast cancer	Phase I/II	NCT04538742
11	Trastuzumab deruxtecan	DS-8201a	Tucatinib	HER2 inhibitor	Daiichi Sankyo, Inc.; AstraZeneca	mc-GGFG-AM	Dxd	7-8	HER2+ metastatic breast cancer	Phase I/II	NCT04538742
12	Trastuzumab deruxtecan	DS-8201a	Ceralasertib	ATR kinase inhibitor	Daiichi Sankyo, Inc.; AstraZeneca	mc-GGFG-AM	Dxd	7-8	HER2+ advanced breast cancer	Phase I	NCT04704661
13	Ado-trastuzumab emtansine	T-DM1	Lapatinib and abraxane	EGFR/HER2 inhibitor and nonsteroidal inhibitor	Roche; ImmunoGen	SMCC	DM1	3.5	Metastatic HER2+ breast cancer	Phase I	NCT02073916
14	Ado-trastuzumab emtansine	T-DM1	Vinorelbine	Anti-mitotic chemotherapy	Roche; ImmunoGen	SMCC	DM1	3.5	Pre-treated HER2+ metastatic breast cancer	Phase I/II [†]	NCT02658084
15	Ado-trastuzumab emtansine	T-DM1	Pozotinib	Pan-EGFR inhibitor	Roche; ImmunoGen	SMCC	DM1	3.5	HER2+ breast cancer	Phase I [‡]	NCT03429101
16	Ado-trastuzumab emtansine	T-DM1	Neratinib	EGFR/HER2 inhibitor	Roche; ImmunoGen	SMCC	DM1	3.5	Metastatic HER2+ breast cancer	Phase I/II	NCT02236000
17	Ado-trastuzumab emtansine	T-DM1	Standard endocrine therapy	Endocrine	Roche; ImmunoGen	SMCC	DM1	3.5	Operable HER2+/HR+ breast cancer	Phase II	NCT01745965
18	Ado-trastuzumab emtansine	T-DM1	Trastuzumab and pertuzumab (FDC SC)	Anti-HER2 mab	Roche; ImmunoGen	SMCC	DM1	3.5	HER2+/ER-/node-neg early breast cancer achieved pCR after neoadjuvant chemo & dual HER2 blockade	Phase II	NCT04675827
19	Ado-trastuzumab emtansine	T-DM1	Docetaxel	Antineoplastic agent	Roche; ImmunoGen	SMCC	DM1	3.5	HER2+ early breast cancer	Phase II	NCT04733118
20	Ado-trastuzumab emtansine	T-DM1	Docetaxel and Pertuzumab	Antineoplastic agent and anti-HER2 mab	Roche; ImmunoGen	SMCC	DM1	3.5	Advanced breast cancer	Phase I/II	NCT00934856
21	Ado-trastuzumab emtansine	T-DM1	Tucatinib	HER2 inhibitor	Roche; ImmunoGen	SMCC	DM1	3.5	Metastatic HER2+ breast cancer not received prior chemotherapy	Phase II	NCT00679341
22	Ado-trastuzumab emtansine	T-DM1	Docetaxel and Pertuzumab	Antineoplastic agent and anti-HER2 mab	Roche; ImmunoGen	SMCC	DM1	3.5	Advanced breast cancer	Phase I/II	NCT00934856
23	Ado-trastuzumab emtansine	T-DM1	Tucatinib	HER2 inhibitor	Roche; ImmunoGen	SMCC	DM1	3.5	Preventing relapses in patients with high risk HER2+ breast cancer	Phase III	NCT04457596
24	Ado-trastuzumab emtansine	T-DM1	Trastuzumab (SC)	Anti-HER2 mab	Roche; ImmunoGen	SMCC	DM1	3.5	Advanced or metastatic HER2+ breast cancer	Phase III	NCT03975647
25	Ado-trastuzumab emtansine	T-DM1	Pertuzumab	Anti-HER2 mab	Roche; ImmunoGen	SMCC	DM1	3.5	HER2+ metastatic breast cancer	Phase I	NCT02562378
26	Ado-trastuzumab emtansine	T-DM1	Non-pegylated liposomal doxorubicin	Anthracycline antibiotic with antineoplastic activity	Roche; ImmunoGen	SMCC	DM1	3.5	HER2+ advanced or metastatic breast cancer	Phase III	NCT02131064
27	Ado-trastuzumab emtansine	T-DM1	Pertuzumab	Anti-HER2 mab	Roche; ImmunoGen	SMCC	DM1	3.5	HER2+ breast cancer	Phase III	NCT01120184
28	Ado-trastuzumab emtansine	T-DM1	Trastuzumab (SC)	Anti-HER2 mab	Roche; ImmunoGen	SMCC	DM1	3.5	Pre-OP early-stage HER2+ breast cancer	Phase II	NCT02326974
29	Ado-trastuzumab emtansine	T-DM1	Pertuzumab	Anti-HER2 mab	Roche; ImmunoGen	SMCC	DM1	3.5	Stage I HER2+ invasive breast cancer	Phase II	NCT04893109
30	Ado-trastuzumab emtansine	T-DM1	Trastuzumab (SC)	Anti-HER2 mab	Roche; ImmunoGen	SMCC	DM1	3.5	Metastatic breast cancer	Phase I	NCT03032107
31	Ado-trastuzumab emtansine	T-DM1	Atezolizumab	Anti-PD-L1 mab	Roche; ImmunoGen	SMCC	DM1	3.5	HER2+ and PD-L1+ locally advanced or metastatic breast cancer	Phase III	NCT04740918
32	Ado-trastuzumab emtansine	T-DM1	Pertuzumab	Anti-HER2 mab	Roche; ImmunoGen	SMCC	DM1	3.5	HER2+ Breast Cancer at high risk of recurrence following preoperative therapy	Phase III	NCT04873362
33	Ado-trastuzumab emtansine	T-DM1	Ribociclib	CDK4/6 inhibitor	Roche; ImmunoGen	SMCC	DM1	3.5	HER2+ and HER2- breast cancer	Phase I	NCT02605915
34	Ado-trastuzumab emtansine	T-DM1	Afatinib	EGFR/HER2 inhibitor	Roche; ImmunoGen	SMCC	DM1	3.5	Advanced/metastatic HER2+ breast cancer	Phase I/II	NCT02657343
35	Ado-trastuzumab emtansine	T-DM1	Venetoclax	Bcl-2 inhibitor	Roche; ImmunoGen	SMCC	DM1	3.5	HER2+ breast cancer with active brain metastases	Phase II	NCT04158947
36	Ado-trastuzumab emtansine	T-DM1	Copanlisib	PI3K inhibitor	Roche; ImmunoGen	SMCC	DM1	3.5	HER2+ Advanced or Metastatic breast cancer	Phase I/II [§]	NCT04298918
37	Ado-trastuzumab emtansine	T-DM1	Pictilisib	PI3K α/δ inhibitor	Roche; ImmunoGen	SMCC	DM1	3.5	Pretreated unresectable locally advanced or metastatic HER2+ breast cancer	Phase I/II [§]	NCT04042051
38	Ado-trastuzumab emtansine	T-DM1	Palbociclib	CDK4/6 inhibitor	Roche; ImmunoGen	SMCC	DM1	3.5	HER2+ breast cancer received trastuzumab-based therapy	Phase I	NCT00928330
39	Ado-trastuzumab emtansine	T-DM1	Palbociclib	CDK4/6 inhibitor	Roche; ImmunoGen	SMCC	DM1	3.5	Metastatic HER2+ breast cancer	Phase II	NCT03530696
40	Ado-trastuzumab emtansine	T-DM1	Paclitaxel	Nonsteroidal inhibitor	Roche; ImmunoGen	SMCC	DM1	3.5	Locally Advanced or metastatic HER2+ breast cancer	Phase I/II	NCT00951665
41	Ado-trastuzumab emtansine	T-DM1	Paclitaxel and Pertuzumab	Nonsteroidal inhibitor and anti-HER2 mab	Roche; ImmunoGen	SMCC	DM1	3.5	Locally advanced or metastatic HER2+ breast cancer	Phase I/II	NCT00951665
42	Ado-trastuzumab emtansine	T-DM1	Capecitabine	Antineoplastic agent	Roche; ImmunoGen	SMCC	DM1	3.5	Locally advanced or metastatic HER2+ breast cancer	Phase II [¶]	NCT01702558
43	Ado-trastuzumab emtansine	T-DM1	Palbociclib and Letrozole	CDK4/6 inhibitor and nonsteroidal inhibitor	Roche; ImmunoGen	SMCC	DM1	3.5	ER+ and HER2+ metastatic breast cancer	Phase I/II	NCT03709082
44	Ado-trastuzumab emtansine	T-DM1	Abemaciclib	CDK4/6 inhibitor	Roche; ImmunoGen	SMCC	DM1	3.5	HER2+ metastatic breast cancer	Phase II	NCT04351230
45	Ado-trastuzumab emtansine	T-DM1	Lapatinib and Abraxane	EGFR/HER2 inhibitor and nonsteroidal inhibitor	Roche; ImmunoGen	SMCC	DM1	3.5	HER2+ breast cancer	Phase II	NCT02073487
46	Ado-trastuzumab emtansine	T-DM1	Alpelisib	PI3K α inhibitor	Roche; ImmunoGen	SMCC	DM1	3.5	HER2+ metastatic breast cancer progressed after treatment with trastuzumab and paclitaxel	Phase I	NCT02038010
47	Ado-trastuzumab emtansine	T-DM1	Utomilumab	Anti-4-1BB mab	Roche; ImmunoGen	SMCC	DM1	3.5	HER2+ advanced breast cancer	Phase I	NCT03364348
48	Ado-trastuzumab emtansine	T-DM1	Neratinib	EGFR/HER2 inhibitor	Roche; ImmunoGen	SMCC	DM1	3.5	HER2+ breast cancer and brain metastases	Phase II	NCT01494662; NCT04856475
49	Ado-trastuzumab emtansine	T-DM1	Taselisib	PI3K $\alpha/\delta/\gamma$ inhibitor	Roche; ImmunoGen	SMCC	DM1	3.5	Advanced HER2+ breast cancer	Phase I	NCT02390427
50	Ado-trastuzumab emtansine	T-DM1	Taselisib and Pertuzumab	PI3K $\alpha/\delta/\gamma$ inhibitor and anti-HER2 mab	Roche; ImmunoGen	SMCC	DM1	3.5	Advanced HER2+ breast cancer	Phase I	NCT02390427
51	Ado-trastuzumab emtansine	T-DM1	TPIV100 and Sargramostim	HER2/neu peptide vaccine	Roche; ImmunoGen	SMCC	DM1	3.5	HER2+ stage II-III breast cancer with residual disease after chemotherapy and surgery	Phase II	NCT04197687
52	Ado-trastuzumab emtansine	T-DM1	Metronomic temozolomide	DNA replication inhibitor	Roche; ImmunoGen	SMCC	DM1	3.5	HER2-positive breast cancer brain metastases	Phase I/II	NCT03190967
53	Ado-trastuzumab emtansine	T-DM1	Brachyury-TRICOM and M7824	Vaccine expressed brachyury and T-cell co-stimulatory molecules; anti-PD-L1/TGF β Trap fusion protein	Roche; ImmunoGen	SMCC	DM1	3.5	Advanced breast cancer	Phase I	NCT04296942
54	Ado-trastuzumab emtansine	T-DM1	Brachyury-TRICOM, M7824 and Entinostat	Vaccine expressed brachyury and T-cell co-stimulatory molecules; anti-PD-L1/TGF β Trap fusion protein; HDAC1/HDAC3 inhibitor	Roche; ImmunoGen	SMCC	DM1	3.5	Advanced breast cancer	Phase I	NCT04296942
55	Ado-trastuzumab emtansine	T-DM1	DZD1516	HER2 tyrosine kinase inhibitor	Roche; ImmunoGen	SMCC	DM1	3.5	HER2+ metastatic breast cancer	Phase I	NCT04509596
56	Ado-trastuzumab emtansine	T-DM1	Pyrotinib	Pan-erbB receptor tyrosine kinase inhibitor	Roche; ImmunoGen	SMCC	DM1	3.5	HER2+ metastatic breast cancer	Phase II	NCT04769050
57	NA	PF-06804103	Palbociclib and letrozole	CDK4/6 inhibitor and	Pfizer	val-cit	Aur0101	4	HER2+ and negative breast cancer	Phase I	NCT03284723
58	Vic-trastuzumab duocarmazine	SYD985	Paclitaxel	Nonsteroidal inhibitor	Synthon Biopharmaceuticals BV	vc-Seco	DUBA	2.8	HER2+ breast cancer	Phase I	NCT04602117
59	Vic-trastuzumab duocarmazine	SYD985	Niraparib	PARP inhibitor	Synthon Biopharmaceuticals BV	vc-Seco	DUBA	2.8	Advanced or metastatic breast cancer	Phase I	NCT04235101
60	NA	BDC-1001	Pembrolizumab	Anti-PD-1 mab	Bolt Biotherapeutics	non-cleavable linker	T785 (TLR7/8 agonist)	NA	HER2+ and low breast cancer	Phase I/II	NCT04278144
61	NA	SBT6050	Pembrolizumab	Anti-PD-1 mab	Silverback Therapeutics	a TLR8 linker	TLR8 agonist	NA	Advanced HER2 expressing solid tumors	Phase I	NCT04460456

[†], terminated due to low accrual and toxicity concerns; [‡], terminated due to dose limiting toxicity; [§], terminated due to no benefit-risk impact; [¶], terminated due to no time to finish the trial in a reasonable timeframe; [¶], terminated due to 70% of participants had a PFS event. ADC, antibody drug conjugate; DAR, drug to antibody ratio.