Name of the compound	Target	Linker	Payload	(DAR)
Trastuzumab emtasine (T-DM1)	HER2	MCC (non-cleavable)	DM1 (microtubule inhibitor)	3.5
Trastuzumab deruxtecan (T-DXd)	HER2	GGFG (cleavable)	DXd (topoisomerase I inhibitor)	8
Trastuzumab duocarmazine (SYD985)	HER2	VC (cleavable)	Duocarmycin (alkylating agent)	2.8
Sacituzumab govitecan (SG)	Trop2	Carbonate (cleavable)	SN38 (topoisomerase I inhibitor)	7.6
Datopotamab deruxtecan (Dato-DXd)	Trop2	Tetrapeptide-based (cleavable)	DXd (topoisomerase I inhibitor)	4
Patritumab deruxtecan (HER3-DXd)	HER3	Tetrapeptide-based (cleavable)	DXd (topoisomerase inhibitorI)	6

Table S1. ADCs structures. DAR, Drug-to-antibody ratio; GGFG, Gly-Gly-Phe-Gly; MCC, maleimidomethyl cyclohexane-1-carboxylate; VC, valine-citrulline.

Drugs	Most common grade 3 -4 AEs %	Start / End AE	Monitoring blood sample
T-DM1	Thrombocytopenia (45.1%)	Nadir day 8 Resolution at the next schedule dose	Routine blood test is recommended regularly before the first treatment, on the first day of each treatment cycle and at 30 days after drug administration.
T-DXd	Neutropenia (16%) Febrile neutropenia (1.1%)	The median time to onset was 54 days (range: 1 day to 18.0 months) and the median duration median first event was 22 days (range: 2 days to 9.0 months)	Monitor complete blood counts prior to initiation and prior to each dose, and as clinically indicated.
SG	Neutropenia (49.5%) Febrile neutropenic (6.6%)	The median time to the onset of neutropenia after the start of the first course of treatment was 15 days. The median duration of neutropenia was 8 days	Monitor blood cell counts periodically during treatment Indication for the count neutrophil Sacituzumab govitecan should not be administered if the absolute neutrophil count is below 1,500/mm3 on day 1 of any cycle or if the neutrophil count is below 1,000/mm3 on day 8 of any cycle
Dato-DXd	Anemia (4%)	Not reported	Not reported
Her3-DXd	Neutropenia (39.6%), Trombocytopenia (30.8%)	The median time to first onset was 8 days for thrombocytopenia and 12 days for neutropenia; the median duration was 8 days for both thrombocytopenia and neutropenia.	Not reported

Table S2. Common hematological AEs reported during treatment with ADCs, time of onset and monitoring blood test.

CTCAE v.6.0 GRADE	ANEMIA	PLATELET COUNT DECREASE	NEUTROPHIL COUNT
1	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L
2	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L
3	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L;	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L
4	Life-threatening consequences; urgent intervention indicated	<25,000/mm3; <25.0 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L

Table S3. Hematological toxicities grading according to CTCAE. LLN=lower limit of normal.

Dose reductions	
T-DM1 Starting dose: 3.6 mg/kg q3w	First level reduction: 3 mg/kg q3 w Second level reduction :2.4 mg/kg q3w Further reduction: Discontinue
T-DXd Starting dose: 5.4 mg/kg q3w	First level reduction: 4.4 mg/kg q3 w Second level reduction :3.2 mg/kg q3w Further reduction: Discontinue
SG Starting dose: 10 mg/Kg day 1;day 8 q3w	First level reduction: 25% Second level reduction :50% Further reduction: Discontinue
Dato-DXd Starting dose: 6 mg/kg q3w	Not reported
Her3-DXd Starting dose: 4.8 mg/kg and 6.4 mg/kg q3w	Not reported

Table S4. Dose modification of ADCs.

Symptomatic CTRCD	Very severe	HF requiring inotropic support, mechanical circulatory support, or consideration of transplantation
	Severe	HF hospitalization
	Moderate	Need for outpatient intensification of diuretic and HF therapy
	Mild	no intensification of therapy required
Asymptomatic CTRCD	Severe	New LVEF reduction to <40%
	Moderate	New LVEF reduction by ≥10 percentage points to an LVEF of 40–49% New LVEF reduction by < 10 percentage points to an LVEF of 40– 49% AND either new relative decline in GLS by >15% from baseline New rise in cardiac biomarkers
	Mild	LVEF ≥ 50% AND new relative decline in GLS by <15% from baseline AND/OR new rise in cardiac biomarkers

Table S5. Cancer therapy related cardiac disfunction (CTRCD) according to the European Society of Cardiology (ESC).

Clinical condition	**Management**	**Causing Agent**
Dry eye	Topical lubricants	T-DM1 SYD985 T-DXd
Conjunctivitis	Topical lubricants Topical antibiotics Topical steroids Delay or stop the administration	T-DM1 SYD985
Keratitis	Topical lubricants Topical steroids (if ulcerative) Delay or stop the administration	T-DM1 SYD985
Cataract	Surgery	T-DM1
Tear duct stenosis/swelling	Topical diuretics and steroids Dacryocystostomy	T-DM1

Table S6. Management of ADCs-related eye disorders.

	Trial	**Investigational arm**	**Control arm**
T-DM1	TH3RESA [1]	2%	11%
	MARIANNE [2]	6.6% (T-DM1 alone) 9% (T-DM1 + pertuzumab)	59,8% (trastuzumab + taxane)
	I-SPY [3]	9.6% (T-DM1 + pertuzumab)	66.7% (paclitaxel + trastuzumab + pertuzumab) 67.7% (paclitaxel + trastuzumab)
	ATEMPT [4]	0.3%	41% (paclitaxel + trastuzumab)
T-DXd	DESTINY-Breast01 [5]	49.8%	N/A
	DESTINY-Breast03 [6]	36.2%	2.3% (grade 1; T-DM1)

	DESTINY-Breast04 [7]	37.7%	32.6% (chemotherapy)
SG	ASCENT [8]	47%	16% (chemotherapy)
	IMMU-132-01 [9]	38%	N/A
SYD985	NCT02277717 [10]	21% (grade 1) 18% (grade 2)	N/A
Dato-DXd	TROPION-PanTumor01 (BC subgroup) [11]	35%	N/A
HER3-DXd	U31402-A-U102 [12]	30-32%	N/A

Table S7. Incidence of alopecia during treatment with ADCs across trials. NA=Not applicable

	Trial	**Investigational arm**	**Control arm**
T-DM1	TH3RESA [1]	6% (1 case grade 3)	10%
	I-SPY [3]	15.4% (T-DM1 + pertuzumab)	33% (paclitaxel + trastuzumab + pertuzumab) 25.8% (paclitaxel + trastuzumab)
	EMILIA [13]	11.6%	27.5% (capecitabine + lapatinib)
SG	ASCENT [8]	12% (1 case grade 3)	5% (chemotherapy)
	IMMU-132-01 [9]	30% (2% grade 3)	N/A
SYD985	NCT02277717 [10]	3% (grade ≤2) 1 case (grade 3)	N/A

Table S8. Incidence of cutaneous rash during treatment with ADCs across trials. NA=Not applicable

Compound	**Year of the first PubMed publication**	**DLT in Phase I**	**Main toxicities in Phase II clinical trials**	**Year of the last fully published clinical trial.**
Myatansin (parent compound of emtansine)	1972 [14]	Fatigue, Nausea, Vomiting, Diarrhea [15]	Vomiting, Diarrhea, Lethargy, altered mentation [16]	1985 [17], Phase II
Exatecan Mesylate (parent compound of deruxtecan)	1995 [18]	Neutropenia [19]	Neutropenia, fatigue, nausea diarrhea [20]	2007 [21], Phase II*
Dolastatin (parent compound of vedotin)	1980 [22]	Neutropenia [23]	Neutropenia [24]	2009 [25], Phase I
Duocarmycin (parent compound of duocarmazine)	1980 [26]	Leukopenia, neutropenia and	Leukopenia, neutropenia,	2007 [29], Phase II

		thrombocytopenia [27]	thrombocytopenia, anemia [28]	

Table S9. Summary of selected prior investigations of intravenous formulations of currently available ADCs' payloads parent compounds. *Results of a phase III showing no advantage of adding intravenous exatecan to gemcitabine in advanced pancreatic cancer were published in 2006 [30].

Post-marketing pharmacovigilance reports

A pharmacovilance study based on the FDA Adverse Event Reporting System (FAERS) database described post-marketing AEs incidence with T-DM1 and T-DXd. Most reported AEs occurring during T-DM1 treatment were thrombocytopenia, hepatic toxicity (ranging from liver enzymes alteration to hepatic cirrhosis, portal hypertension, and nodular regenerative hyperplasia), and peripheral neuropathy, while nausea, ILD/pneumonia and fatigue were the most frequently reported toxicity with T-DXd [31].

We further searched through the European Union Drug Regulating Authorities Pharmacovigilance (EudraVigilance) database, where 3686 cases of toxicity associated to T-DM1 administration were reported post-marketing, 192 related to cardiac disorders (whose 186 described as severe). A total of 1597 cases of toxicity were registered with T-DXd, 40 (2.5%) reported as cardiotoxicity. Whereas, 15 cases of cardiac disorders out of a total of 773 post-marketing toxicities were reported with the use of SG [32]. According to the same database [32], GI disorders represented the 21.5% and 27% of the suspected adverse reaction with T-DXd and SG, respectively. For these drugs, GI toxicity represents the third most common reported AE. Regarding T-DM1, GI disorders are on seventh place in the 15.7% of reporting. Nausea and vomiting are respectively the 61.2% and 25.2% of GI disorders reported with T-DXd treatment, in particular the 13.3% and 5.4% of all suspected AE. Nausea is the 27% of suspected GI disorders related to SG treatment and the 7.3% of total reports, while vomiting is the 9.4% of GI and 2.5% of whole reports. Nausea accounts to 29.4% of GI disorders reported with T-DM1 treatment (4.6% of total reports) while vomiting represents the 16% (2.5% of total reports). Diarrhea represents the 66% of the GI disorders reported for SG (17.8% of total reports), the 25.2% for T-DM1 and 17.5% for T-DXd (about 4% of total reports for both drugs). Stomatitis represents <1% of AEs reported with T-DM1, T-DXd and SG. Laboratory alterations are the second most common AE reported in patients treated with T-DM1 (22.1%). AST and ALT increase are respectively 8.3% and 7.6% of these alterations reported. Overall, alterations of liver enzymes (reported as "hepatic enzymes increased", "liver function test abnormal", "transaminase elevation", etc.) are about 42% of these reports and about 12% of all T-DM1 suspected AE reports. Moreover, there are 53 reports of NRH in patients treated with T-DM1, none of them was fatal. Only 1 case of NRH is reported in this database regarding patients treated with T-DXd. To date, no cases are reported with SG. Hepatobiliary disorders are reported in 12.1% of patients treated with T-DM1, 3.6% for T-DXd and 1.4% for SG. At the last update of the post-marketing analysis (April 2023) led by EudraVigilance, the cases of ILD reported in the toxicity group respiratory, thoracic, and mediastinal disorders were 619 related to T-DM1, 563 cases related to T-DXd, and 49 cases related to SG. Four patients treated with SG reported eye disorders (dry eye, blurred vision, ulcerative keratitis, eyelid disorders and visual impairment, the latter registered as "fatal"). Less than 1.5% (19 patients) of the AEs reported during T-DXd treatment were referred as eye disorders (of note, among the others, blindness, cataract, eye hematoma, punctate keratitis, uveitis, corneal epithelial microcysts, and pinguecula were described). Different ocular AEs are described as occurred in 126 patients treated with T-DM1 in the same database. Finally, regarding embryo-fetal toxicity, in the post-marketing setting, oligohydramnios, sometimes associated with pulmonary hypoplasia, has been reported in pregnant women treated with trastuzumab[32].

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