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Leveraging TROP2 Antibody-Drug Conjugates in Solid Tumors

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Abstract

Antibody-drug conjugates (ADCs) have become the cornerstone of effective therapeutics in solid and hematological malignancies by harnessing potent cytotoxic payloads with targeted tumoricidal delivery. Since the monumental shift occurred with HER2-targeted ADCs, the discovery of the TROP2 antigen has revolutionized the landscape of ADC development. Moving beyond the traditional ADC design, multiple novel ADCs have successfully shaped and improved survival outcomes in patients with various tumor histologies. Here we review and contrast the clinical impact of the well-known TROP2 ADCs currently in clinical use. We also shed light on upcoming investigational TROP2 ADCs showing promise with novel ADC platforms.

INTRODUCTION

Trophoblast cell surface antigen-2 (TROP2) is a type I cell surface glycoprotein first identified in human trophoblasts (1). It is also known by other names, such as membrane component chromosome 1 surface marker 1 (M1S1), cytoplasmic aspartate aminotransferase, gastrointestinal tumor-associated antigen GA7331, epithelial glycoprotein-1, and trichothiodystrophy-2, photosensitive (2). The TROP2 protein structure and the regulation of its expression were first explored by cloning the TROP2 gene in 1995 (3). TROP2 protein is encoded by the gene *TACSTD2* in chromosome 1p32.1. Although TROP2 is thought to play a crucial role in extracellular, transmembrane, and intracellular interactions to promote the cell cycle (4), its biological role is understudied.

TROP2 is mainly found in human epithelial tissue and is essential for embryo–fetal development (5). The expression of TROP2 is differentially upregulated in tumor tissue compared to normal tissues (6). TROP2 is a tumor-associated calcium signal transducer overexpressed in many epithelial cancers, and it stimulates cancer cell growth and is upregulated in a variety of human carcinomas (7–13). Multiple studies have demonstrated overexpression of TROP2 in various tumor types, predominantly in 78% of triple-negative breast cancers (TNBC), 64% of non-small cell lung cancers (NSCLC) of the adenocarcinoma subtype, and 75% in the squamous cell carcinoma (SCC) subtype 4, 14). **Figure 1** illustrates TROP2 expression in various tumor types. Stepan et al. described TROP2 mRNA and protein expression levels across normal human tissue and found expression in the stratified squamous epithelium of the cervix, esophagus, and skin, as well as in the cuboidal and columnar epithelium of breast, kidney, pancreas, bile ducts, and prostate, while no expression was noted in the brain, bone marrow, colon, heart, intestine, muscle, nerve, ovary, pituitary, spleen, testis, or thyroid (15).

In a meta-analysis involving 16 studies with >200 patients, increased TROP2 expression was associated with poor overall survival (OS) and disease-free survival (DFS) outcomes across several solid tumors (16). However, there are currently no standardized and internationally accepted guidelines for assessing TROP2 expression.

ANTITUMOR ACTIVITY OF VARIOUS TROP2 ANTIBODY-DRUG CONJUGATES ACROSS TUMOR TYPES

Sacituzumab Govitecan

Sacituzumab govitecan (SG; IMMU-132, Gilead/Immunomedics) is a first-in-class TROP2 ADC, where the monoclonal antibody (mAb) is cross-linked to a cleavable linker to SN-38 (7-ethyl-10-hydroxy-camptothecin) with a drug-to-antibody ratio (DAR) of 7.6:1. SN-38 is the active derivative of the topoisomerase I (TOP1) inhibitor irinotecan. Preclinical investigations using SN-38 covalently conjugated to a humanized anti-TROP2 antibody, hRS7, in five xenograft models demonstrated significant and specific antitumor effects in NSCLC and pancreatic and colorectal cancers (17). There are many reasons why SG became the frontline therapy in this class, including the fact that its SN-38 payload is threefold more potent than irinotecan's. Its hydrolyzable linker allows SN-38 to mediate a bystander effect, especially when TROP2 expression is heterogenous. It also has the highest DAR without compromising antibody binding or pharmacokinetic properties. The need for glucuronidation of SN-38 is lower, mediating a lower incidence of diarrhea classically seen with other TOP1 inhibitors (18). **Table 1** includes evidence of the clinical impact of SG on various tumor types.

DAR: drug-to-antibody ratio

The phase I/II IMMU-132-01 basket trial examined the safety and efficacy of SG in patients with advanced solid tumors. The strongest efficacy signals came out of the TNBC population,

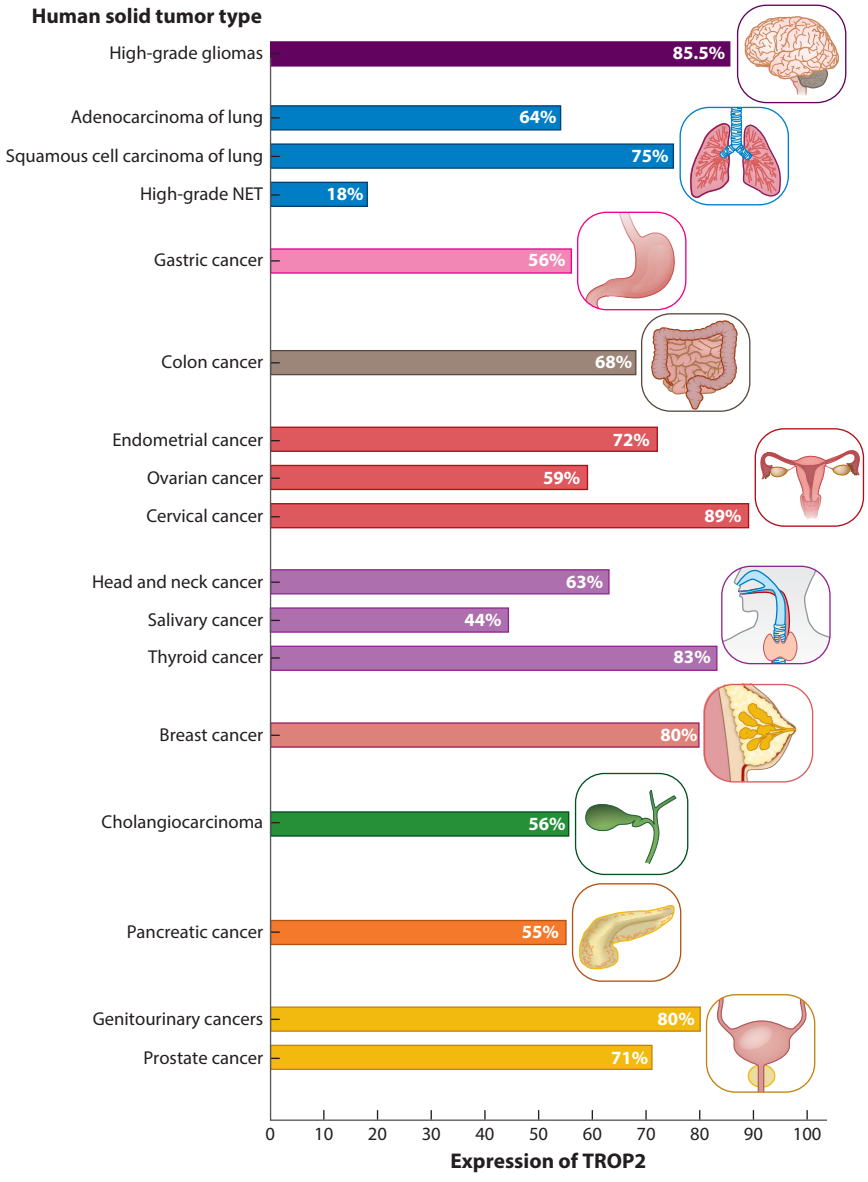

Figure 1

Distribution of TROP2 expression in various human solid tumors. Abbreviation: NET, neuroendocrine tumor. Figure adapted from Reference 4 with permission.

where among 108 patients, the objective response rate (ORR) was 33%. Median progression-free survival (PFS) was 5.5 months and median OS reached 13 months. In the metastatic urothelial carcinoma cohort of the same trial, the ORR for 45 patients was 28.9%, while 54 patients with hormone receptor–positive breast cancer (HR+ BC) had an ORR of 31.5% (19). In the NSCLC cohort, 54 patients were enrolled and the ORR was 16.7% [9 partial responses (PR)]. The median duration of response (DOR) was 6 months while the OS was 7.3 months and PFS was 4.4 months.

DOR: duration of response

HR+ BC: hormone receptor–positive breast cancer

Table 1 Clinical efficacy of TROP2 antibody-drug conjugates across tumor types

Tumor	Year	Phase	Drug	ORR	mDOR	mPFS	mOS	Trial
Multiple histologies	2015	I	SG	8% (2 PR; $n = 25$)	N/A	N/A	N/A	NCT01631552
UC	2015	I	SG	33% (2 PR; $n = 6$)	N/A	6.7–8.2 m	7.5–11.4 m	NCT01631552
TNBC	2017	I	SG	30% (2 CR + 19 PR; $n = 69$)	8.9 m	6 m	16.6 m	NCT01631552
NSCLC	2017	I	SG	19% (9 PR; $n = 47$)	6.0 m	5.2 m	9.5 m	NCT01631552
SCLC	2017	II	SG	14% (7 PR; $n = 50$)	5.7 m	3.7 m	7.5 m	NCT01631552
TNBC	2019	I/II	SG	33.3% (3 CR + 33 PR; $n = 108$)	7.7 m	5.5 m	13.0 m	NCT01631552
HR+/HER2− BC	2020	I/II	SG	31.5% (17 PR; $n = 54$)	8.7 m	5.5 m	12 m	NCT01631552
CRC	2021	I/II	SG	3.2% (1 PR; $n = 31$)	9.8 m	3.9 m	14.2 m	NCT01631552
Esophageal carcinoma	2021	I/II	SG	5.3% (1 PR; $n = 19$)	5.4 m	3.4 m	7.2 m	NCT01631552
Endometrial carcinoma	2021	I/II	SG	22.2% (4 PR; $n = 18$)	NR	3.2 m	11.9 m	NCT01631552
CRPC	2021	I/II	SG	9.1%; (1 CR; $n = 11$)	N/A	N/A	N/A	NCT01631552
TNBC	2021	III	SG	35% (CR/PR: N/A)	6.3 m	5.6 m	12.1 m	NCT02574455
UC	2021	II	SG	27% (6 CR + 25 PR; $n = 113$)	7.2 m	5.4 m	5.4 m	NCT03547973 (Cohort 1)[a]
HR+/HER2− BC	2022	III	SG	21% (2 CR + 55 PR; $n = 272$)	7.4 m	5.5 m	14.4 m	NCT03901339
UC	2023	II	SG	32% (12 PR; $n = 38$)	5.6 m	5.6 m	13.5 m	NCT03547973 (Cohort 2)[b]
UC	2023	II	SG + pembrolizumab	41% (8 CR + 9 PR; $n = 17$)	11.1 m	5.3 m	12.7 m	NCT03547973 (Cohort 3)[c]
UC	2023	I	SG + ipilimumab + nivolumab	41% (1 CR + 3 PR; $n = 9$)	9.2 m	8.8 m	NR	NCT04863885
NSCLC	2021	I	Dato-DXd	35% ($n = 34$)	9.5 m	N/A	N/A	NCT03401385
TNBC	2022	I	Dato-DXd	32% (1 CR + 13 PR; $n = 44$)	NR	4.3 m	12.9 m	NCT03401385
HR+/HER2− BC	2022	I	Dato-DXd	27% (11 PR; $n = 41$)	NR	8.3 m	NR	NCT03401385
NSCLC	2022	I	Dato-DXd + pembrolizumab +/− chemotherapy	Doublet: 37% Triplet: 41%	N/A	N/A	N/A	NCT04526691
TNBC	2022	I/II	Dato-DXd + durvalumab	73.6% (4 CR + 35 PR; $n = 53$)	N/A	N/A	N/A	NCT03742102

[a]PD after platinum and IO.

[b]PD after IO but ineligible for platinum.

[c]PD after platinum but IO naive.

Abbreviations: BC, breast cancer; CR, complete response; CRC, colorectal cancer; CRPC, castration-resistant prostate cancer; Dato-DXd, datopotamab deruxtecan; HER2, human epidermal receptor 2; HR, hormone receptor; IO, immunotherapy; m, months; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; N/A, not applicable; NR, not reported; NSCLC, non–small cell lung cancer; ORR, objective response rate; PD, progressive disease; PR, partial response; SCLC, small cell lung cancer; SG, sacituzumab govitecan; TNBC, triple-negative breast cancer; TROP2, trophoblast cell surface antigen-2; UC, urothelial carcinoma.

In the small cell lung cancer (SCLC) cohort, 62 patients who received SG had an ORR of 17.7% while the median DOR was 5.7 months and OS was 7.1 months (19).

CT: chemotherapy

IO: immunotherapy

Based on efficacy signals seen in the IMMU-132-01 study, 468 metastatic TNBC patients enrolled in the phase III ASCENT trial (NCT02574455) to receive SG versus investigator's choice of chemotherapy (CT) with eribulin, vinorelbine, capecitabine, or gemcitabine (20). SG demonstrated a survival advantage in both median PFS (5.6 months versus 1.7 months) and median OS (12.1 months versus 6.7 months). In April 2021, the US Food and Drug Administration (FDA) approved SG for metastatic TNBC patients who have received ≥2 prior therapies. Treatment-related adverse events (TRAEs) of ≥ grade 3 were neutropenia (51%), leukopenia (10%), diarrhea (10%), and febrile neutropenia (6%). Diarrhea and myelosuppression are hallmarks of SN-38, a TOP1 inhibitor. However, only 5% of these patients discontinued the study due to toxicities, as they were treated successfully by using aggressive preemptive care (20). In light of this, the FDA recommends secondary prophylaxis with growth factor support and recommends withholding SG in the presence of an absolute neutrophil count below 1,500/mm^3 or neutropenic fever (21).

In the TROPHY-U-01 (NCT03547973) phase II study, 113 metastatic urothelial carcinoma patients with prior platinum-based CT and immunotherapy (IO) received SG. The ORR was 28%, and the median DOR was 6.1 months with median PFS 5.4 months and OS 10.9 months. The most common grade ≥3 TRAEs included decreased neutrophil count (35%), diarrhea (10%), and febrile neutropenia (10%) (22). These results led the FDA to grant accelerated approval in April 2021 to SG for patients with refractory urothelial carcinoma who had prior platinum-based therapy and either a programmed death receptor-1 (PD-1) or a programmed death-ligand 1 (PD-L1) inhibitor. In recently presented results from TROPHY-U-01 cohort 2 (NCT03547973), the ORR was 32%, median PFS was 5.6 months, and OS was 13.5 months (23).

Recently, the TROPiCS-02 (NCT03901339) phase III randomized controlled trial (RCT) in 543 patients with refractory human epidermal growth factor receptor 2 (HER2)–negative HR+ BC examined the survival benefit of SG against CT. With SG, the median PFS was 5.5 months [95% confidence interval (CI) 4.2, 7.0] and the median OS was 14.4 months while ORR was 21%. This led to FDA approval in February 2023 for sacituzumab govitecan-hziy for progression after receiving a cyclin D kinase 4/6 inhibitor, endocrine therapy, and taxane with at least two prior CTs in the metastatic setting (one of which could be in the neoadjuvant or adjuvant setting if recurrence occurred within 12 months).

In an early trial of SG, Heist et al. reported on 54 metastatic NSCLC patients who had received at least one line of prior therapy (24). Out of 47 patients evaluable for response, the ORR was 17%, median DOR 6.0 months, median PFS 5.2 months, and OS 9.5 months. Grade ≥3 TRAEs were neutropenia (28%), diarrhea (7%), nausea (7%), fatigue (6%), and febrile neutropenia (4%) (24).

The phase I/II IMMU-132-01 basket trial recruited 18 patients with endometrial carcinomas who were treated with SG and demonstrated an ORR of 22.2% (19, 25). Currently, a phase II study of SG in recurrent endometrial carcinoma patients who have at least 2+ expression of TROP2 on prescreening (NCT04251416) is enrolling patients and pending completion.

Since SN-38 has a hydrolyzable payload, previous preclinical studies showed SG activity in intracranial xenografts. One single-center study reported examining concentrations of SN-38 in tumors of patients undergoing craniotomy for breast cancer brain metastases (BCBM) ($n = 20$) or recurrent glioblastoma ($n = 10$), where one dose of SG (10 mg/kg) was given intravenously (IV) 24 h prior to craniotomy. Postoperatively, patients resumed SG at 10 mg/kg IV on days 1 and 8 of a 21-day cycle and were assessed for response or progression every third cycle by magnetic resonance imaging. SG achieved therapeutically relevant concentrations of SN-38 for BCBM. At

IHC: immunohistochemistry

ISH: in-situ hybridization

ILD: interstitial lung disease

12 weeks from the first postoperative cycle, two partial responses occurred in the BCBM arm (ORR 28%) and glioblastoma arm (ORR 50%) (26).

The NeoSTAR trial (NCT04230109) is a phase II study examining neoadjuvant SG for patients with localized TNBC. Interim results showed most patients (49/50) completed four cycles. Twenty-six patients underwent surgery after SG; pathological complete response with SG alone was 30% in 15 patients. The most common TRAEs were nausea (82%), fatigue (78%), alopecia (76%), and neutropenia (58%) (27).

Investigating adjuvant SG, the SASCIA (NCT04595565) study is a phase III RCT that is enrolling patients with HER2-negative [immunohistochemistry (IHC) 0/1+ in-situ hybridization (ISH) negative] HR+ BC who have residual disease after neoadjuvant CT. SASCIA will examine the impact on OS and DFS of SG versus investigator choice (capecitabine, carboplatin, cisplatin, or observation). An interim safety analysis showed that grade 3 and 4 TRAEs were seen in 66.7% of the SG arm and 20.9% of the capecitabine arm. Discontinuation secondary to treatment toxicities occurred in 13.6% of the SG and 9.4% of the capecitabine arm (28). Further ongoing studies being conducted with SG as monotherapy are described in **Table 2**.

Datopotamab Deruxtecan

Datopotamab deruxtecan (Dato-DXd; DS-1062, Daiichi Sankyo/AstraZeneca), an exatecan derivative, is a TROP2 ADC with humanized IgG1 mAb conjugated with TOP1 inhibitor. It is cross-linked via a tetrapeptide-based cleavable linker to reduced residues of cysteine with disulfide bonds of the mAb and has a DAR of 4 (29). It requires TROP2 expression on the cell surface for internalization into tumor cells and is then transported into the lysosomes by endocytosis, after which it undergoes proteolytic degradation (29). Notably, in vitro preclinical studies demonstrated that cytotoxic effects mainly were contributed by DXd due to the induction of DNA damage and apoptosis (29). The potency of this agent can be attributed to its preferential internalization into rapidly proliferative and highly TROP2-expressive cancer cells, prompt payload clearance, and durable linker that is only cleavable within the tumor environment (29). Dato-DXd has a long controlled release of its cytotoxic load; 5% is seen in the circulation after 3 weeks, in contrast to SG, where 90% of SN-38 is released in 72 h (30). However, the mAb component of SG has a higher affinity than Dato-DXd (0.3–27 nM Kd), likely in part to reduce the off-target toxicities. **Table 1** depicts the antitumor activity of Dato-DXd in various tumor types.

The phase I TROPION-PanTumor01 basket trial (NCT03401385) is evaluating the safety and efficacy of Dato-DXd in unresectable advanced NSCLC, TNBC, HR+ BC, SCLC, pancreatic adenocarcinoma, HER2-negative gastric/gastroesophageal junction cancer, esophageal cancer, head and neck squamous cell carcinoma, transitional cell carcinoma of the urothelium, and castration-resistant prostate cancer. It was recently reported that 44 patients in the TNBC cohort with a median of three prior therapies received Dato-DXd; ORR was 32% with 1 CR (complete response) and 13 PRs, while median DOR was not reached. The disease control rate (DCR) was noted to be 80%, while the median PFS and OS were 4.3 and 12.9 months, respectively. The ORR in TOP1 inhibitor–naive patients was 44% (12/27). Among all patients without prior TOP1 inhibitor ADC therapy ($n = 30$), the median PFS was 7.3 months and the median OS was 14.3 months. The most common treatment-emergent adverse events (TEAEs) were stomatitis (73%), nausea (66%), and fatigue (34%). Interstitial lung disease (ILD) was not seen in this study (31).

Similarly, in the HER2-low (IHC 1 positive or IHC positive/ISH negative) or HER2-negative (IHC 0) HR+ BC cohort, 41 patients with a median of five prior therapies received Dato-Dxd. The ORR was 27% (11 PRs), stable disease (SD) was 56%, DCR was 85%, and clinical benefit rate

Table 2 TROP2 antibody-drug conjugates under clinical investigation as monotherapy

Tumor type	Phase	TROP2 ADC	Intervention	Disease setting	Trial
HR+/HER2− BC TNBC	III	SG	SG versus capecitabine or carboplatin or cisplatin	Adjuvant	SASCIA (NCT04595565)
Glioblastoma	II	SG	SG	Advanced Refractory Metastatic	NCT04559230
Esophageal SCC Gastric adenocarcinoma Cervical cancer	II	SG	SG	Advanced Refractory Metastatic	NCT05119907
UC	II	SG	SG followed by radical cystectomy and pelvic nodal dissection	Neoadjuvant	NCT05581589
NSCLC HNSCC Endometrial cancer SCLC	II	SG	SG	Advanced Refractory Metastatic	NCT03964727
HER2− BC Brain metastases	II	SG	SG	Advanced Refractory Metastatic	NCT04647916
Muscle-invasive bladder cancer	II	SG	TURBT f/b SG f/b radical cystectomy	Neoadjuvant	NCT05226117
Endometrial cancer of epithelial origin with 2+ TROP2 expression	II	SG	SG	Advanced Refractory Metastatic	NCT04251416
UC	II	SG	Cohort 1: SG with prior PT and IO Cohort 2: SG with prior IO but PT ineligible	Advanced Refractory Metastatic	TROPHY U-01 (NCT03547973)
Multiple tumor types	I	SG	SG	Advanced Refractory Metastatic	NCT04617522
PD-L1− TNBC	III	SG	SG versus paclitaxel versus nab-paclitaxel versus gemcitabine + carboplatin	Advanced Refractory Metastatic	ASCENT-03 (NCT05382299)
NSCLC with prior PT and IO exposure	III	SG	SG versus docetaxel	Advanced Refractory Metastatic	EVOKE-01 (NCT05089734)
Metastatic CRPC progressed on second-generation AR therapy	II	SG	SG	Advanced Refractory Metastatic	NCT03725761
Endometrial cancer Metastatic CRPC Ovarian cancer CRC	II	Dato-DXd	Dato-DXd monotherapy Dato-DXd monotherapy Dato-DXd monotherapy Dato-DXd monotherapy	Advanced Refractory Metastatic	TROPION-PanTumor03 (NCT05489211)
TNBC	III	Dato-DXd	Dato-DXd versus paclitaxel; nab-paclitaxel; carboplatin; capecitabine; eribulin	Advanced Refractory Metastatic	TROPION-Breast02 (NCT05374512)
Stage I–III TNBC with residual disease	III	Dato-DXd	Dato-DXd + durvalumab versus Dato-DXd versus capecitabine +/− pembrolizumab	Adjuvant	TROPION-Breast03 (NCT05629585)
NSCLC with actionable genomic alterations	II	Dato-DXd	Dato-DXd	Advanced Refractory Metastatic	TROPION-Lung05 (NCT04484142)

(*Continued*)

Table 2 (*Continued*)

Tumor type	Phase	TROP2 ADC	Intervention	Disease setting	Trial
NSCLC with or without actionable genomic alterations	III	Dato-DXd	Dato-DXd versus docetaxel	Advanced Refractory Metastatic	TROPION-LUNG01 (NCT04656652)
HR+/HER2− BC	III	Dato-DXd	Dato-DXd versus capecitabine; gemcitabine; eribulin; vinorelbine	Advanced Refractory Metastatic	TROPION-Breast01
Multiple tumor types	I/II	SKB264	SKB264	Advanced Refractory Metastatic	NCT04152499
TNBC	III	SKB264	SKB264 versus eribulin; capecitabine; gemcitabine; vinorelbine	Advanced Refractory Metastatic	NCT05347134
Multiple tumor types	I	JS108	JS108	Advanced Refractory Metastatic	NCT04601285
Multiple tumor types	I	FDA018-ADC	FDA018-ADC	Advanced Refractory Metastatic	NCT05174637
Multiple tumor types	I	BAT8008	BAT8008	Advanced Refractory Metastatic	NCT05620017
Multiple tumor types	I	ESG401	ESG401	Advanced Refractory Metastatic	NCT04892342

Abbreviations: ADC, antibody-drug conjugate; AR, androgen receptor; BC, breast cancer; CRC, colorectal cancer; f/b, followed by; HER2, human epidermal growth factor receptor; HNSCC, head and neck squamous cell carcinoma; HR, hormone receptor; IO, immunotherapy; NSCLC, non–small cell lung cancer; PD-L1, programmed death-ligand 1; PT, platinum; SCC, squamous cell carcinoma; SCLC, small cell lung cancer; SG, sacituzumab govitecan; TNBC, triple-negative breast cancer; TROP2, trophoblast cell surface antigen-2; TURBT, transurethral resection of bladder tumor; UC, urothelial carcinoma.

(CR + PR + SD ≥6 months) was 41%. TEAEs of any grade were observed in 98% of patients, with 41% having TEAEs of grade ≥3; the most common TEAEs were stomatitis (80%), nausea (56%), and fatigue (46%). One patient developed keratitis ($n = 1$) while two patients developed pneumonitis ($n = 2$), of which one case was deemed grade 3. The median PFS was 8.3 months and, with a median follow-up of 13.7 months, the median DOR and median OS had not been reached (32).

In the NSCLC cohort of the TROPION-PanTumor01 trial with Dato-DXd, 180 patients were enrolled at dose levels of 4–8 mg/kg, and across dose cohorts, 76–88% of these patients had prior IO. The ORR was 22% at 4 mg/kg, 26% at 6 mg/kg, and 23.8% at 8 mg/kg. In the 6 mg/kg cohort, median PFS was 6.9 months, and median OS was 11.4 months. Grade 3–4 TRAEs were predominantly pneumonia, anemia, and decreased lymphocyte count. Across all three dose levels, six patients experienced ILD (two grade 3, one grade 4, and three grade 5). All grade 5 events occurred in the 8-mg/kg cohort (33). In the TROPION-PanTumor01 subset with actionable driver alterations ($n = 34$), Dato-DXd demonstrated durable efficacy with an ORR of 35% with a median DOR lasting more than 9 months (34).

The recommended phase II dose for Dato-DXd is 6 mg/kg every 3 weeks (35). Dato-DXd has an ILD risk that is mainly seen in NSCLC at higher doses than 6 mg/kg, likely due to deruxtecan payload. One systematic review analyzed 14 studies of trastuzumab DXd in various tumor types and found that the incidence of all-grade ILD/pneumonitis cases was 11.40% (136/1,193) (36). Although stomatitis is commonly seen, the implementation of steroid mouthwashes has mitigated its effects, with some evidence of impact on efficacy (37).

The TROPION PanTumor-03 phase II trial (NCT05489211) is currently investigating the safety, tolerability, and antitumor activity of Dato-DXd in advanced or metastatic endometrial cancer, gastric cancer, castration-resistant prostate cancer, ovarian cancer, or colorectal cancer as monotherapy or in combination with CT, IO, or AZD5305, which is a poly-(ADP ribose) polymerase 1 (PARP1) inhibitor.

The TROPION-Breast03 study (NCT05629585) is investigating the efficacy and safety of Dato-DXd as adjuvant therapy with or without durvalumab versus capecitabine with or without pembrolizumab in patients with stage I, II, or III TNBC who have residual invasive disease after surgery following neoadjuvant therapy. **Table 2** describes further ongoing studies being conducted with Dato-DXd as monotherapy.

SKB-264

SKB-264 (Klus Pharma) is an ADC designed against the TROP2 antigen using a belotecan-derived TOP1 inhibitor payload with a humanized IgG1 mAb (hRS7) having a DAR of 7.4. It has a cleavable complicated PEG8 (polyethylene glycol 8) and triazole-containing PABCpeptide-mc (p-aminobenzyl carbamate peptide maleimidocaproyl) linker.

SKB-264 is being investigated in a phase I/II clinical trial (NCT04152499) in patients with refractory solid tumors. Among 17 evaluable patients, the ORR was 41.2% and the DCR was 70.6%. Efficacy signals were seen predominantly in TNBC (ORR 40%; 1/1), ovarian cancer (ORR 60%; 2/5), and HR+ BC (ORR 100%; 1/1). The most common TEAEs were low-grade nausea and alopecia in >70% of patients; grade ≥3 TEAEs were neutropenia (28%) and leukopenia (22%) (38).

As of October 2022, 59 patients from the phase II dose expansion TNBC cohort received SKB-264 at SKB264 at 4 or 5 mg/kg every 2 weeks. Most had received ≥3 prior therapies. The confirmed ORR was 46.1% for the 4 mg/kg and 62.5% for the 5 mg/kg cohort. The most common ≥ grade 3 TRAEs were neutropenia (23.7%), anemia (20.3%), and thrombocytopenia (16.9%). No TRAEs leading to death or ILD were reported (39). Further ongoing studies being conducted with SKB-264 as monotherapy are described in **Table 2**.

Other TROP2 Antibody-Drug Conjugates

RN927C/PF 06664178 (Pfizer/Rinat) is made of an anti-TROP2 IgG1 antibody with a degradable linker and a payload containing the auristatin antitubulin agent (40). RN927C demonstrated tumoricidal activity in pancreatic, lung, ovarian, and TNBC mouse models when compared with paclitaxel or gemcitabine (40). RN927C was explored in a phase I study (NCT02122146) where, among 31 patients with advanced solid tumors, SD was seen in 11 patients (39%). The study was terminated early because of minimal antitumor activity and excessive toxicities including neutropenia and skin rash (41). BAT8008 (Bio-Thera) is a novel TROP2 ADC that has a degradable linker and TOP1 inhibitor warhead, with a DAR of 6. Preclinical studies showed that BAT8008 demonstrated direct tumor suppression in cell lines and also had additive bystander effects in cell lines and pancreatic cancer mouse models (42). A multicenter, open-label, dose-escalation and -expansion phase I trial (NCT05620017) is currently underway to explore the safety and efficacy of BAT8008. JS-108 (DAC-002) is an ADC designed against TROP2 composed of a noncleavable linker with an antitubulin payload (4). The safety and efficacy of JS-108 are being investigated in a phase I, open-label, first-in-human clinical study in advanced solid tumors (NCT04601285). FDA018 is a novel ADC targeting TROP2 being developed with an unrevealed payload and linker currently undergoing a phase I dose-escalation study to evaluate safety and efficacy (NCT05174637). ESG401 (Sorrento) is also an ADC with a humanized mAb against TROP2

with the same payload as SG but with an unrevealed linker. ESG401 is now being explored in a phase I/II study of subjects with advanced or metastatic solid tumors (NCT04892342). DB-1305 is an ADC targeting TROP2 with a novel TOP1 inhibitor, P1021, via an enzymatically cleavable tetrapeptide linker. Preclinical studies demonstrate selective cytotoxicity in TROP2-expressing cells when compared with Dato-DXd, with further bystander effects (43). DB-1305 is currently being explored in a phase I/IIa trial to evaluate its safety and tolerability in subjects with advanced solid tumors (NCT05438329).

TROP2 ANTIBODY-DRUG CONJUGATES AND COMBINATION THERAPY

ADCs are proposed to increase neoantigen load via tumoricidal cell death and could favorably alter the tumor immune microenvironment by promoting T cell infiltration of the tumor site, thereby enhancing the responsiveness to anti–PD-1/L1 therapy (44). Another avenue of synthetic lethality exploration is combining ADCs with PARP and TOP1 inhibitors to amplify payload-induced cell death through inhibition of the DNA damage repair pathway. Notably, the combination of SG with olaparib or talazoparib demonstrated tumor suppression in vitro and in vivo in *BRCA1/2*-mutant and *BRCA1/2*-wildtype TNBC xenografts without myelosuppression (45). Ongoing combination studies with various TROP2 ADCs are noted in **Table 3**.

Combination with Sacituzumab Govitecan

In this section, we explore select clinical trials that have investigated the combination of sacituzumab govitecan and various checkpoint inhibitors.

Immunotherapy. Several studies are now underway to examine the synergy of IO and SG clinically. Recently, interim efficacy and safety results have been reported on cohort 3 of TROPHY-U-01; SG with pembrolizumab in IO-naive patients with metastatic urothelial carcinomas who progressed after platinum-based CT was explored. The ORR was 41%, with a median DOR of 11.1 months and a median PFS of 5.3 months, while the median OS was 12.7 months. Grade ≥3 TRAEs occurred in 61% of patients, predominantly neutropenia (37%), leukopenia (20%), diarrhea (20%), and febrile neutropenia (10%) (46). In a novel concept using two ADCs, a phase I trial (NCT04724018) is now examining SG with enfortumumab vedotin in metastatic urothelial carcinomas. Another ongoing phase I/II study (NCT04863885) is examining SG with ipilimumab and nivolumab in therapy-naive cisplatin-ineligible patients with metastatic urothelial carcinoma; this study has completed the dose-escalation phase. Recently presented results revealed an ORR of 66.6% among four patients (1 CR and 3 PR; $n = 9$). The DOR was 9.2 months while the median PFS was 8.8 months and the median OS was not reached. The recommended phase II dose of SG was identified as 8 mg/kg in combination with ipilimumab 3 mg/kg + nivolumab 1 mg/kg as first-line therapy for cisplatin-ineligible metastatic urothelial carcinoma (47).

DNA Damage and Repair Inhibitors

In preclinical TNBC models, SN-38 binds at the TOP1 enzyme–DNA interface to prevent DNA religation and to lock the enzyme into TOP1 cleavage complexes. In addition, PARP was required for clearance of stabilized TOP1 cleavage complexes (48). Consequently, a phase 1b study combining SG with talazoparib in patients with TNBC (NCT04039230) was initiated and is now in the dose-expansion phase. The recommended phase II dose is 10 mg/kg on days 1 and 8 IV combined with talazoparib orally as 1 mg on days 15–21 every 3 weeks (49). Based on a similar foundation, a combination with an ataxia telangiectasia and Rad3 related (ATR) kinase inhibitor (berzosertib)

Table 3 Combinations of TROP2 antibody-drug conjugates under clinical investigation

Tumor type	Phase	TROP2 ADC	Intervention	Disease setting	Trial
Immunotherapy					
Endometrial cancer	II	Dato-DXd	Dato-DXd + durvalumab, Dato-DXd + durvalumab +AZD5305	Advanced Refractory Metastatic	TROPION-PanTumor03 (NCT05489211)
Gastric cancer			Dato-DXd + chemotherapy (capecitabine or 5-FU) + nivolumab		
NSCLC (treatment naive or received only first-line therapy with no IO exposure)	I	Dato-DXd	Dato-DXd + durvalumab; Dato-DXd + durvalumab + carboplatin; Dato-DXd + MEDI5752 +/− carboplatin	Advanced Refractory Metastatic	TROPION-Lung04 (NCT04612751)
NSCLC without actionable genomic alterations	III	Dato-DXd	Dato-DXd 6.0 mg/kg + durvalumab + carboplatin +/− cisplatin or carboplatin and pemetrexed +/− paclitaxel and carboplatin	Advanced Refractory Metastatic	AVANZAR (NCT05687266)
Stage I–III TNBC with residual disease	III	Dato-DXd	Dato-DXd + durvalumab versus Dato-DXd versus capecitabine +/− pembrolizumab	Adjuvant	TROPION-Breast03 (NCT05629585)
NSCLC with PD-L1 TPS ≥50%	III	SG	SG + pembrolizumab versus pembrolizumab	Advanced Refractory Metastatic	KEYNOTE D46/EVOKE-03 (NCT05609968)
TNBC	II	SG	Arm B: SG + avelumab	Advanced Refractory Metastatic	InCITe (NCT03971409)
UC without PD following completion of 4–6 cycles of first-line chemotherapy	II	SG	Group B: Maintenance therapy with avelumab + SG	Advanced Refractory Metastatic	JAVELIN Bladder Medley (NCT05327530)
NSCLC with prior PT or IO exposure	I	Dato-DXd	Dato-DXd + pembrolizumab +/− carboplatin/cisplatin	Advanced Refractory Metastatic	TROPION-Lung02 (NCT04526691)
NSCLC in first-line therapy-naive setting	III	Dato-DXd	Dato-DXd + pembrolizumab + platinum chemotherapy (cisplatin or carboplatin) versus Dato-DXd + pembrolizumab versus pembrolizumab + pemetrexed + platinum chemotherapy (cisplatin or carboplatin)	Advanced Metastatic	TROPION-Lung07 (NCT05555732)
UC	II	SG	Cohort 4/5: SG + cisplatin f/b maintenance with avelumab/zimberelimab IV in PT-naive mUC	Advanced Refractory Metastatic	TROPHY U-01 (NCT03547973)
			Cohort 6: SG + zimberelimab +/− domvanalimab in PT-naive Muc		
NSCLC with PD-L1 TPS ≥50%	III	Dato-DXd	Dato-DXd + pembrolizumab versus pembrolizumab	Advanced Refractory Metastatic	TROPION-Lung08 (NCT05215340)
UC	I/II	SG	SG + ipilimumab and nivolumab IV f/b nivolumab + RP2D dosing of SG	Advanced Refractory Metastatic	NCT04863885
NSCLC	II	SG	SG + pembrolizumab + /− carboplatin or cisplatin	Advanced Refractory Metastatic	EVOKE-02 (NCT05186974)

(*Continued*)

Table 3 (*Continued*)

Tumor type	Phase	TROP2 ADC	Intervention	Disease setting	Trial
TNBC	III	SG	SG + pembrolizumab versus pembrolizumab versus pembrolizumab + capecitabine	Adjuvant	ASCENT-05 (NCT05633654)
PDL-1+ TNBC	III	SG	SG + pembrolizumab versus pembrolizumab +/− paclitaxel; nab-paclitaxel; gemcitabine + carboplatin	Advanced Refractory Metastatic	ASCENT-04 (NCT053822860)
Small-molecule therapeutics					
Multiple tumor types HRD cancers SCLC EP-SCNC	I/II	SG	SG + berzosertib	Advanced Refractory Metastatic	NCT04826341
TNBC	II	SG	SG + trilaciclib	Advanced Refractory Metastatic	NCT05113966
TNBC	I/II	SG	SG + talazoparib	Advanced Refractory Metastatic	NCT04039230
HR+/HER2− BC TNBC	I	SG	SG + alpelisib	Advanced Refractory Metastatic	ASSET (NCT05143229)
Endometrial cancer	II	Dato-DXd	Dato-DXd + AZD5305, Dato-DXd + durvalumab +AZD5305	Advanced Refractory Metastatic	TROPION-PanTumor03 (NCT05489211)
Metastatic CRPC			Dato-DXd + AZD5305		
Ovarian cancer			Dato-DXd + AZD5305		
NSCLC (treatment naive or received only first-line therapy with no IO exposure)	I	Dato-DXd	Dato-DXd + AZD5305 +/− carboplatin	Advanced Refractory Metastatic	TROPION-Lung04 (NCT04612751)
Multiple tumor types	I/II	Dato-DXd	Module 5: AZD5305 + Dato-DXd	Advanced Refractory Metastatic	PETRA (NCT04644068)
NSCLC with EGFR mutation (progressed on first-line osimertinib)	II	Dato-DXd	Module 10: Osimertinib + Dato-DXd	Advanced Refractory Metastatic	ORCHARD (NCT03944772)
ADCs					
Metastatic UC (progressed on platinum-based chemotherapy and PD-1/L1 inhibitors	I	SG	SG + enfortumab vedotin	Advanced Refractory Metastatic	The Double Antibody Drug Conjugate (DAD) Phase I Trial (NCT04724018)

Abbreviations: 5-FU, fluorouracil; ADC, antibody-drug conjugate; CRPC, castration-resistant prostate cancer; EGFR, epidermal growth factor receptor; EP-SCNC, extra-pulmonary small cell neuroendocrine cancer; f/b, followed by; HER2, human epidermal growth factor receptor; HR, hormone receptor; HRD, homologous recombination-deficient; IO, immunotherapy; IV, intravenous; mUC, metastatic urothelial carcinoma; NSCLC, non–small cell lung cancer; PD, progressive disease; PD-L1, programmed death-ligand 1; RP2D, recommended phase 2 dose; SCLC, small cell lung cancer; SG, sacituzumab govitecan; TNBC, triple-negative breast cancer; TPS, tumor proportion score; TROP2, trophoblast cell surface antigen-2; UC, urothelial carcinoma.

and SG is currently being evaluated in SCLC, extrapulmonary small cell neuroendocrine cancer, and homologous recombination-deficient cancers (NCT04826341). Investigations of SG in combination with DNA damage and repair (DDR) inhibitors are also ongoing. The phase Ib SEASTAR study (NCT03992131) examined the safety and antitumor activity of rucaparib with SG. In arm B, six patients (three with DDR aberrations) enrolled demonstrated dose-limiting toxicities across two dose levels due to grade 4 neutropenia. Grade ≥3 TEAEs included neutropenia in five patients and leukopenia in two patients. Three confirmed PRs (TNBC, ovarian, and endometrial cancer) were reported. Notably, these patients were refractory to prior PARP inhibitors (50).

Combination with Datopotamab Deruxtecan

This section explores select clinical trials that have investigated the combination of datopotamab deruxtecan and various checkpoint inhibitors.

Immunotherapy. The BEGONIA phase Ib/II trial (NCT03742102) showed that Dato-DXd combined with durvalumab in advanced TNBC unselected for PDL1 or TROP2 expression demonstrated an impressive ORR of 73.6% among 53 patients (4 CRs; 35 PRs). The most common all-grade TRAEs were nausea (57.4%), stomatitis (55.7%), alopecia (45.9%), and fatigue (39.3%). The incidence of discontinuation due to TRAE was 6.6%. Grade 1 ILD was noted in two patients (3.3%), and both of these ILD cases were adjudicated as treatment related (51).

The phase I TROPION-Lung02 trial is examining the safety and efficacy of Dato-DXd in combination with pembrolizumab with or without platinum CT (NCT04526691). In the doublet group (without CT), among 40 patients, the ORR was 37%; in the triplet group, among 48 patients, the ORR was 41%. The most common TRAEs in both groups were stomatitis (56% and 29%), nausea (41% and 48%), and fatigue (25% and 36%) in the doublet and triplet group respectively. Four patients developed ILD events (two grade 1–2 and two grade 3) (NCT04526691, 52).

PARP inhibitors. Yuca et al. examined the efficacy of Dato-DXd in breast cancer patient–derived xenografts and its synergy with PARP inhibitors (53). The TROP2 expression was associated with increased tumor suppression compared to the control ADC with a deruxtecan payload, while the combination of Dato-DXd and olaparib demonstrated greater activity than monotherapy in the majority of the breast cancer mouse models (53).

The phase I/II PETRA trial (NCT04644068) in Module 5 is currently exploring the safety and efficacy of a highly potent selective PARP-1 inhibitor, AZD5305, in combination with Dato-DXd in a dose-escalation design in various solid tumors (54). Potent synergy of poly-ADP ribose polymerase (PARP) inhibitors primarily depends on PARP1 inhibition (55). It is well known that PARP2 is crucial in mediating erythropoiesis (56). Hence, in the design of combinatory regimens, PARP1 inhibitors have great potential for synthetic lethality.

Designing ADC combination regimens needs to account for overlapping and mutually exclusive toxicities of the drugs involved while investigating preclinical and early efficacy signals of synergy between them.

BIOMARKERS OF RESPONSE AND RESISTANCE

Although TROP2 expression, SLFN11 expression, and homologous repair defects have all been associated preclinically with efficacy of TROP2 ADCs or TOP1 inhibitors, no predictive biomarkers for therapeutic targeting of various TROP2 ADCs have been clinically validated at this time. Shee et al. demonstrated that SLFN11 mRNA expression is a biomarker of sensitivity to an array of DNA-damaging chemotherapeutics across lung, breast, and ovarian cancers (57). Cardillo et al. also demonstrated preclinical evidence where SG conferred antitumor activity

compared to irinotecan in DDR-proficient and -deficient models expressing varying levels of Trop-2 (58). Also, preclinical TNBC models demonstrated that BRCA aberrations combined with high SLFN11 expression and RB1 expression resulted in high sensitivity to TOP1 inhibitors (59). It should be noted that the quantification of TROP2 expression has not been standardized by IHC or other scoring systems (57). An exploratory biomarker analysis based on the ASCENT trial evaluated if TROP2 expression impacted clinical efficacy. Among 290 patients with evaluable specimens, tumor cell membrane TROP2 expression was categorized based on a histochemical score (H-score). The study population was stratified into high (>300), medium (100–200), and low (0–100) H-score categories. In the SG cohort, patients with tumors with high H-scores demonstrated a numerically higher ORR than those with medium H-scores (44% versus 22%), but in both groups SG resulted in a higher ORR than physician-choice CT. Patients with high H-scores had a better OS at 14.2 months compared to the low-H-score patients at 9.3 months, although this difference was not statistically significant. Similar results were seen regardless of germline BRCA aberrations (60).

In patients with low HER2 expression (HER2 0–1+ IHC or 2+ IHC without overexpression by ISH), SG demonstrated similar survival outcomes with statistical significance with median PFS in HER2 low at 6.4 months and 5.0 months in HER2 0 group. However, the control group had a median PFS of 4.2 months and received physician choice of CT (61).

Recently, TROP2 expression and survival outcomes were reported from the TROPiCS-02 study in HR+ BC among 238 patients with evaluable specimens. More than 90% of the patients had a TROP2 H-score > 0 while less than 50% had an H-score < 100 and more than 50% had an H-score > 100. The median PFS and OS were higher with SG than with CT but did not differ significantly between the high- and low-H-score groups. In patients who received SG, the ORR ranged from 18% to 24% in both H-score groups. This led the authors to conclude that SG impacted efficacy independent of TROP2 expression (62).

There is limited knowledge about mechanisms of resistance to ADCs overall, especially for TROP2 ADCs. A recent case study demonstrated that mutations in *TOP1*, encoding TOP1, and mutations in *TACSTD2*, encoding TROP2, may represent mechanisms of resistance to SG, suggesting that sensitivity to payload as well as downregulating of target membrane localization may be different mechanisms of resistance (63).

CONCLUSION

Targeting TROP2 expression in various solid tumors using an ADC platform has become a highly successful approach with promise to impact survival outcomes of many tumor types. However, further advances in designing precision novel targeted payloads, minimizing on-target and off-target toxicities in ADC platforms, and determining predictors of response are required. Exploration of a combinatory approach to harness the potential of ADCs with other classes of anticancer agents can continue to shift the paradigm of cancer therapy.

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