

REVIEW

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Unlocking the potential of EphA2 with precision-guided cancer therapy: bicycle drug conjugates

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Abstract

Background Therapeutic advances have improved cancer survival outcomes for an increasing number of patients, but novel approaches are still urgently needed for patients who cannot tolerate, or do not respond to current treatments. Erythropoietin-producing hepatocellular receptor A2 (EphA2) is highly expressed in a variety of solid tumors, which is associated with poor prognosis, especially in tumors considered difficult-to-treat, such as pancreatic and head and neck cancer.

Main body EphA2 has emerged as a promising therapeutic target for the treatment of solid tumors; however, efficacy and safety issues have halted clinical development of previous EphA2-targeting agents including MEDI-547, DS-8895a, MM-310, and dasatinib. Despite these setbacks, interest in targeting EphA2 in solid tumors remains, with ongoing development of investigational therapies such as antibodies, antibody drug conjugates, EphA2 antagonists, peptide drug conjugates, bicyclic peptide drug conjugates, and tyrosine kinase inhibitors. Among these, BT5528, a Bicycle[®] Drug Conjugate (BDC), has shown an emerging differentiated safety profile, in contrast to prior EphA2-targeting agents, and promising antitumor activity in patients with advanced solid tumors. BT5528 comprises an EphA2-targeting bicyclic (Bicycle) peptide, linked to the cytotoxin monomethyl auristatin E (MMAE) via a valine-citrulline cleavable linker. The high specificity of BT5528 to EphA2, combined with its high affinity, enables precision-guided delivery of MMAE, while its peptidic nature results in rapid distribution and retention of MMAE within the tumor, limited systemic exposure, and liver-sparing renal elimination.

Conclusion The preclinical and emerging clinical data for BT5528 suggest that novel approaches to targeting EphA2 can achieve efficacy without the safety issues that plagued earlier agents. Here, we review EphA2 as a target and the historical and current clinical development of EphA2-targeting therapeutic agents.

Keywords Antibody drug conjugates, Bicycle[®] drug conjugate, BT5528, EphA2, Investigational therapies, Solid tumors

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Background

Despite significant therapeutic advances that have improved cancer survival outcomes for an increasing number of patients [1], novel approaches are still urgently needed for patients who cannot tolerate, or do not respond to current treatments, especially in tumors considered difficult to treat. Erythropoietin-producing hepatocellular receptor A2 (EphA2) is a member of the receptor tyrosine kinase family that is highly expressed in a variety of solid tumors and contributes to oncogenesis, tumor-associated angiogenesis, invasiveness, and metastasis [2–9]. Although EphA2 has long been recognized as a promising therapeutic target, its full potential in solid-tumors has yet to be realized, largely due to efficacy and safety challenges encountered in early clinical trials for EphA2-targeting agents [10–13]. In this article we explore the novel next-generation agents that we believe are poised to unlock the potential of EphA2 using multiple precision-guided approaches.

EphA2: a high-value target in oncology

Erythropoietin-producing hepatocellular receptors are the largest group of receptor tyrosine kinases. EphA2 signaling has been shown to regulate cell proliferation, survival, and migration via activation of the AKT-mTORC1 and RAS-ERK oncogenic pathways and the Wnt/ β -catenin signaling pathway [14–17]. EphA2 exhibits diverse biological functions [18], and while typically expressed at low levels in healthy tissues [19], immunohistochemistry studies of clinical tumor samples and pre-clinical cell lines have demonstrated that EphA2 is highly expressed in a variety of tumor types, with high EphA2 expression in clinical samples from bladder, brain, breast, head and neck, lung, prostate and pancreatic tumors [2–7, 20–34]. Pancreatic adenocarcinoma (PAAD), comprising mainly of pancreatic ductal adenocarcinoma (PDAC; >90%) [35], and head and neck squamous-cell carcinoma (HNSCC) were found to have among the highest EphA2 expression levels in a pan-tumor study [31].

Substantial evidence indicates that high expression of EphA2 is significantly correlated with higher tumor grade, later stage, increased likelihood of metastasis, and worse prognosis across multiple solid tumors [2–9, 31, 34, 36–38]. For example, in a study from The Cancer Genome Atlas (TCGA) database and the Genotype-Tissue Expression (GTEx) portal, a significant correlation between increasing pathological stage and EphA2 expression was reported among patients with PAAD; furthermore, those with high EphA2 expression had shorter overall survival and disease-free survival than those with low EphA2 expression [31]. Furthermore, immunohistochemical analysis of NSCLC tissue from patients revealed that high expression of EphA2 predicted disease relapse as well as the site of relapse [3]. Regarding

metastasis, high EphA2 levels were associated with brain metastases in patients with NSCLC, whereas low EphA2 expression correlated with no relapse, or the subsequent development of contralateral lung metastasis [3]. A number of studies in breast cancer, esophageal squamous cell carcinoma, colorectal carcinoma and HNSCC tissue suggest high EphA2 expression correlates closely with metastasis [4, 9, 38], providing further evidence for the role of EphA2 in tumor progression.

The prognostic significance of EphA2 combined with its characteristic tumor expression and localization patterns, positions EphA2 as an attractive target for novel anticancer therapies.

EphA2 in solid tumors: a historical challenge

Despite clinical interest in EphA2 as a target in oncology, investigational treatments have failed over the last fifteen years for both efficacy- and safety-related reasons (Table 1).

MEDI-547 (MedImmune)

MEDI-547 is an antibody drug conjugate (ADC) comprising the EphA2-targeting monoclonal antibody (mAb) 1C1 conjugated to the cytotoxin maleimidocaproyl-monomethyl auristatin phenylalanine (mcMMAF). In preclinical studies using nude mouse xenograft and rat syngeneic tumor models, MEDI-547 effectively inhibited the growth of EphA2-expressing tumors with no observable adverse effects in either model [39]. Similarly, MEDI-547 effectively inhibited endometrial cancer growth in mouse orthotopic xenograft tumor models without overt signs of toxicity, while also reducing metastatic spread [40].

Despite these promising preclinical findings, clotting abnormalities were reported in cynomolgus monkey, mouse, and rat models, and hematological toxicity was observed as a dose-limiting toxicity in human studies [50]. The first-in-human Phase 1 trial (NCT00796055) was terminated prior to enrollment of the second dose escalation cohort, due to bleeding and coagulation events in 5 of the 6 treated patients. As a result, further clinical investigation of MEDI-547 was discontinued [10, 50].

DS-8895a (Daiichi Sankyo)

DS-8895a, an afucosylated anti-EphA2 mAb, demonstrated increased in vitro antibody-dependent cell-mediated cytotoxicity (ADCC) and significantly inhibited tumor growth in EphA2-positive breast and gastric cancer xenograft mouse models [41]. In the first-in-human Phase 1 dose escalation/dose expansion study (NCT02004717), DS-8895a was generally well tolerated in patients with EphA2-positive esophageal and gastric cancers (dose expansion arm) when administered at 20 mg/kg. Infusion-related reactions were reported in

Table 1 Early EphA2-targeting agents in oncology

Agent/Class	MOA	Status	Reason for discontinuation
MEDI-547 (1C1-mcMMAF) [10, 39, 40] Antibody drug conjugate	A human immunoglobulin G1 mAb directed against EphA2 (1C1) conjugated to the microtubule inhibitor MMAF using a stable maleimidocaproyl (mc) linker Upon internalization of MEDI-547, mcMMAF is released from 1C1 by lysosomal degradation of the antibody component, leading to cell cycle arrest, microtubule disruption, and apoptotic cell death	Clinical development discontinued	Safety concerns (bleeding/coagulation events)
DS-8895a [11, 41, 42] Anti-EphA2 antibody	A humanized anti-EphA2 mAb that has been afucosylated to enhance ADCC	Clinical development discontinued	Insufficient efficacy (response not sufficient to induce strong tumor shrinkage, likely due to low tumor uptake)
MM-310 (EphA2-ILS-DTXp) [7, 12, 43–46] Antibody targeted nanoparticle	Liposomal formulation of a docetaxel prodrug conjugated to a high affinity signal-chain variable fragment targeting EphA2 Following accumulation of MM-310, docetaxel is released from MM-310 and accumulates at the tumor site, resulting in cell cycle arrest and the induction of cell death. MM-310 increases the half-life of docetaxel and provides enhanced and specific accumulation in EphA2-expressing tumors	Clinical development discontinued	Safety concerns (cumulative Grade 3 peripheral neuropathy)
Dasatinib [13, 47, 48] Kinase inhibitor	Inhibits EphA2 directly by preventing its activation through phosphorylation, blocking downstream signaling pathways	FDA and EMA approved for the treatment of Ph+ CML and ALL Clinical development discontinued in solid tumors	Poor efficacy in solid tumors

Source: Agents identified through Clinicaltrials.gov search for oncology [condition/disease] plus EphA2 [other terms] with completed/terminated/withdrawn/unknown status; agents from the following trials were identified in search but not included in table due to lack of available additional information: NCT05198843 (trial terminated); NCT02575261 (trial withdrawn); and NCT03423992 (unknown status; although results were published in 2021 from three patients proposing additional studies are needed [49]). ADCC, antibody-dependent cellular cytotoxicity; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; EphA2, erythropoietin-producing hepatocellular receptor A2; EMA, European Medicines Agency; FDA, Food and Drug Administration; mAb, monoclonal antibody; mcMMAF, maleimidocaproyl monomethylauristatin phenylalanine; MMAF, monomethylauristatin phenylalanine; MOA, mechanism of action; Ph+, Philadelphia chromosome-positive

40% of patients, but these were low grade and considered manageable [11]. Despite evidence of enhanced ADCC activity, DS-8895a did not induce strong tumor shrinkage, and all enrolled patients ultimately discontinued the study [11]. Subsequent investigation in a Phase 1 safety and bioimaging study of patients with advanced EphA2-positive cancers (NCT02252211) also failed to demonstrate adequate therapeutic efficacy of DS-8895a at 1 mg/kg and 3 mg/kg (as seen by ⁸⁹Zr-DS-8895a imaging), likely due to low tumor uptake [42]. Biodistribution data from this trial were central in stopping further clinical development of DS-8895a; biodistribution was a secondary endpoint alongside tumor uptake [bioimaging] and pharmacokinetics [42].

MM-310 (Merrimack Pharmaceuticals, Inc.)

MM-310 is a liposomal formulation of a docetaxel prodrug, conjugated to a high affinity single-chain variable fragment targeting EphA2, designed for sustained delivery of active drug to solid tumors [43, 44, 51]. Pre-clinical studies have demonstrated a strong correlation between EphA2 expression and the uptake or biodistribution of MM-310 [44, 45]. Multiple xenograft models have demonstrated that MM-310 has greater tumor

penetration and overall antitumor activity compared to its non-targeted counterpart or to free docetaxel, while maintaining a favorable toxicity profile [7, 44]. Specifically, MM-310 was able to overcome the hematological toxicity associated with free docetaxel, with no coagulopathies or bleeding events reported; this was correlated with reduced systemic exposure to docetaxel following MM-310 administration compared to administration of docetaxel alone [44, 52]. Again, despite these promising preclinical results, the first-in-human Phase 1 study for MM-310 (NCT03076372) was unable to reach an optimal therapeutic index. Cumulative Grade 3 peripheral neuropathy emerged as a significant safety concern, leading to termination of the study and the clinical development program for MM-310 [12, 46].

Dasatinib (Bristol-Myers Squibb)

Dasatinib is a kinase inhibitor that was developed to target Abl and Src protein tyrosine kinases; however, protein profiling studies have revealed that dasatinib interacts with more than 30 kinases, including EphA2 [47, 53]. Dasatinib is highly effective against Philadelphia chromosome-positive chronic myeloid leukemia and acute lymphoblastic leukemia and is approved in the US and

EU for both indications [13, 47, 54, 55]. Preclinical data demonstrate in vitro antitumor activity and direct EphA2 targeting by dasatinib in pancreatic cancer cell lines and murine xenograft models [48]. However, despite demonstrating clinical efficacy in blood tumors, clinical trials in solid tumors have been unsuccessful. Across 11 clinical trials involving 459 patients treated with dasatinib, no patient achieved a complete response, only 10 (2%) achieved a partial response, and 150 (33%) achieved stable disease as their best response [13].

Targeting EphA2 in solid tumors: a future success?

Despite setbacks with early EphA2-targeting agents, there remains significant interest in EphA2 as a therapeutic target across multiple solid tumor types. A review of manuscripts from PubMed and abstracts from relevant oncology congresses (November 2021 to July 2024) identified 26 manuscripts/congress abstracts reporting on 23 EphA2-targeting agents currently in preclinical or clinical development. These agents span a range of tumor types, including brain, breast, cervical, lung, melanoma, osteosarcoma, pancreatic, and prostate cancers. The agents currently in development belong to diverse drug classes, including EphA2-targeted antibodies, ADCs, EphA2 antagonists, peptide drug conjugates, bicyclic peptide drug conjugates, and tyrosine kinase inhibitors (Supplemental Methods; Supplementary Table S1). Several early phase clinical trials are currently ongoing (Table 2). Among these, the largest is evaluating BT5528, which has shown an emerging differentiated safety profile, promising antitumor activity in patients with advanced solid tumors, and has no treatment-related adverse events (TRAEs) of hemorrhage reported to date [56–59]. Clinical trial results for the other agents have not yet been published.

BT5528: making EphA2-targeting a reality

Bicycle® molecules represent a novel class of therapeutics currently under clinical evaluation that offer the manufacturing and pharmacokinetic advantages of small molecules with the high binding specificity of biologics [60–62], making them ideally suited for the targeted delivery of a variety of payloads to solid tumors. Bicycle molecules are based on short, synthetic, phage-derived peptides (typically 9–20 amino acids long) that are constrained by a molecular scaffold to form two stable loops, resulting in molecules that are stabilized in optimal binding conformations [63, 64]. Bicycle Drug Conjugate (BDC) molecules are a type of Bicycle molecule comprising a tumor-targeting bicyclic peptide conjugated to a payload, typically a cytotoxin.

BT5528 is an EphA2-targeting Bicycle Drug Conjugate (BDC) that comprises a Bicycle peptide that binds with high affinity and specificity to EphA2, linked to the

cytotoxin monomethyl auristatin E (MMAE) via a valine-citrulline cleavable linker (Fig. 1A) [60, 65]. BT5528 can deliver its MMAE payload via two mechanisms: 1) receptor-mediated internalization and payload release after endo-lysosomal trafficking and 2) bystander killing, which does not require internalization and occurs via extracellular release of MMAE into the tumor microenvironment or through diffusion from a cell where the MMAE was released intracellularly [65].

The Bicycle peptide component of BT5528 was selected from phage library screening of short peptides containing three strategically placed cysteine residues interspersed with random amino acids [66]. Further optimization of the Bicycle peptide utilized structure-guided and rational drug design principles. The final peptide has high affinity for the ligand-binding domain of EphA2, with a footprint that overlaps the binding site reported for endogenous ephrin ligands [67].

Key attributes of BT5528

BT5528 possesses key attributes that distinguish it as a promising potential EphA2-targeted therapy, distinct from those of previous EphA2-targeting agents that have had clinical development discontinued (see Table 1).

High affinity and specificity

BT5528 combines high specificity and affinity for EphA2, enabling precision-guided delivery of MMAE to the tumor (Table 3). Its binding affinity is similar to that of biologics; however, in contrast with previous EphA2-targeting agents, BT5528 is also highly specific for EphA2 (Table 3) [65]. In a protein array of 5528 proteins, 1 μ M of BT5528 was observed to bind exclusively to EphA2 (BicycleTx Ltd unpublished data). Furthermore, quantification of cell surface-bound MMAE using an anti-MMAE antibody and confocal high content screening demonstrated binding of BT5528 to the surface of HT-1080 cells expressing high levels of EphA2 [65].

Short plasma half-life

BT5528 has a short plasma half-life, with transient systemic exposure and rapid clearance of plasma MMAE (Fig. 1B) [65]. Minimizing systemic exposure of BT5528 reduces exposure of non-target healthy tissue to MMAE [65, 74] and may explain the lack of BT5528-related hematological toxicity. In translational non-human primate (NHP) studies, no evidence of bleeding or hemorrhage (assessed by clinical signs and histopathology) were observed at doses exceeding the maximum tolerated dose, with no effect on the coagulation parameters D-dimer, activated partial thromboplastin time, and prothrombin time (Fig. 1C) [65]. A similar lack of hematological toxicity was observed following treatment with MM-310, which has a slow-release EphA2-targeted liposomal formulation and limited systemic exposure to the

Table 2 Ongoing trials of EphA2-targeting oncology agents, by primary completion date (as of 15 September 2025)

Agent/Class	Trial (enrollment)	Tumor	Status	Endpoints	Estimated primary completion
P30-EPS vaccine Peptide-based tumor-associated antigen vaccine	NCT05283109 Interventional Ph 1 (N=24)	Grade IV malignant glioma	Active, not recruiting	Primary: DLTs Secondary: Change in mean fold increase in pp56-specific T cells and EphA2- or survivin-specific T cells; median survival; median PFS	April 2025 (actual)
EphA2-targeting DOPC-encapsulated siRNA siRNA	NCT01591356 Interventional Ph 1 (N=49)	Solid tumors	Active, not recruiting	Primary: Safety and tolerability; MTD Secondary: Changes in EphA2 expression; changes in endothelial and tumor cell apoptosis; BoR; DoR; TTP	April 2025
BT5528 Bicycle®Drug Conjugate	NCT04180371 Interventional Ph 1/2 (N≈288)	Advanced solid tumors associated with EphA2 expression	Recruiting	Primary: MTD, safety and tolerability (esc); ORR, DoR, CBR, PFS, OS (exp) Secondary: ORR, DoR, CBR, time to progression, PFS, OS (esc); safety; PK parameters; ADAs; association between EphA2 expression and response (exp)	October 2025 (Ph 1 data published [56])
TP53-EphA2-CAR-DC CAR-DC vaccine	NCT05631886 Interventional Ph 1 (N≈10) ^a	La/m solid tumors	Recruiting	Primary: Safety and tolerability; clinical response; immune response Secondary: PFS; OS, TTR; DoR; number and copy number of TP53-EphA2-CAR-DCs; level of cytokines in serum	December 2025
KRAS-EphA2-CAR-DC CAR-DC vaccine	NCT05631899 Interventional Ph 1 (N≈15)	La/m solid tumors	Recruiting	Primary: Safety and tolerability; clinical response; immune response Secondary: PFS; OS; TTR; DoR; number and copy number of KRAS-EphA2-CAR-DCs; level of cytokines in serum	December 2025
EphA2-targeted CAR-T cells and CAR-DCs CAR-DC and CAR-T cell therapy	NCT06972576 Interventional (N≈18)	Advanced NSCLC	Recruiting	Primary: Safety; MTD; remission rate Secondary: ORR; OS; DFS; in vivo persistence, immunophenotype, and functional activity of CAR-T cells and CAR-DCs following infusion; safety	April 2026
E-SYNC CAR-T Cells CAR-T cell therapy	NCT06186401 Interventional Ph 1 (N≈20)	EGFRvIII positive (+) glioblastoma	Recruiting	Primary: Safety and tolerability Secondary: Patients (%) who successfully receive E-SYNC T cells; primed E-SYNC T cells (%) in TILs vs PBMC	August 2026
TBVA-Dendritic Cell Vaccine DC vaccine	NCT05127824 Interventional Ph 2 (N≈42)	Non-metastatic ccRCC	Recruiting	Primary: Immune response; safety and tolerability, DLTs Secondary: Effect of treatment on markers of vascular normalization	December 2026
SC-102 Peptide drug conjugate	NCT06710158 Interventional Ph 1 (N≈120)	Advanced solid tumors	Recruiting	Primary: Safety and tolerability; MTD; ORR Secondary: PK parameters; ADAs; DoR; DCR	December 2026

Source: Unless otherwise stated, information sourced from <https://clinicaltrials.gov> by NCT number, searching 'EphA2' in 'other terms' and manually selecting ongoing trials in solid tumors

^aIncludes patients with relapsed/refractory lymphomas

ADA, antidrug antibodies; BoR, best overall response; CAR-DC, chimeric antigen receptor engineered dendritic cell; CAR-T, chimeric antigen receptor T-cell therapy; CBR, clinical benefit rate; ccRCC, clear cell renal cell carcinoma; CR, complete response; DC, dendritic cell; DCR, disease control rate; DFS, disease free survival; DLT, dose-limiting toxicity; DOPC, 1,2-dioleoyl-sn-glycero-3-phosphatidylcholine; DOR, duration of response; EGFRvIII, epidermal growth factor receptor variant III; esc, dose escalation; exp, dose expansion; la/m, locally advanced/metastatic; MTD, maximal tolerated dose; ORR, objective response rate; NSCLC, non-small cell lung cancer; OS, overall survival; PBMC, peripheral blood mononuclear cells; PFS, progression-free survival; Ph, Phase; PK, pharmacokinetics; PR, partial response; SD, stable disease; siRNA, small interfering ribonucleic acid; TBVA, tumor blood vessel antigen; TEAE, treatment-emergent adverse event; TIL, tumor-infiltrating lymphocyte; TTP, time to progression; TTR, time to response

payload docetaxel [44]. In contrast, the serum concentration of the EphA2-targeting ADC MEDI-547 (0.08 mg/kg) persists in patients after 3 days, and both treatment-related bleeding and coagulation events have been observed [10].

Small size

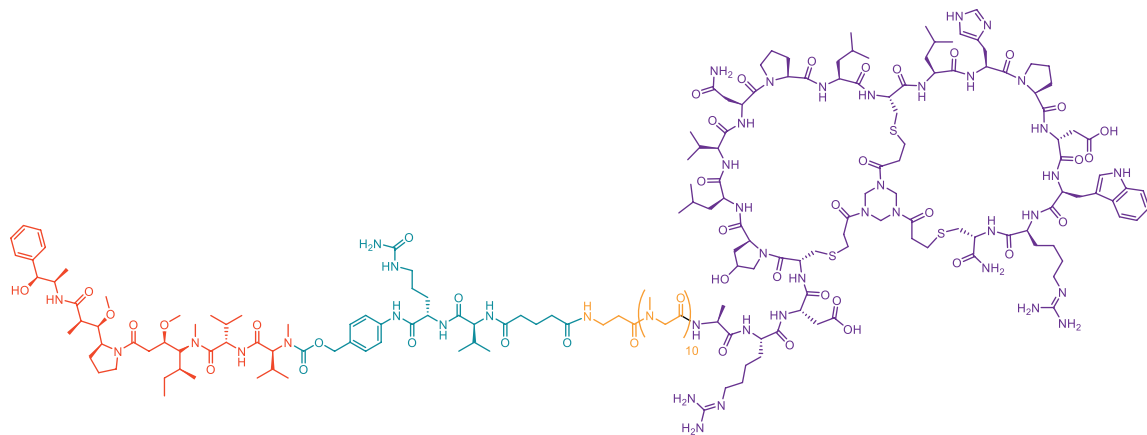
As a peptide-drug conjugate, with a low molecular weight of ~4.4 kDa, BT5528 is predominantly cleared through the kidney and bladder, with minimal exposure to the liver [60, 65]. Preclinical NHP toxicity studies for BT5528 demonstrated a lack of liver-related toxicity, with no changes in the liver enzymes alanine aminotransferase or aspartate

aminotransferase following either a low or high dose of BT5528 (Fig. 1C) [65].

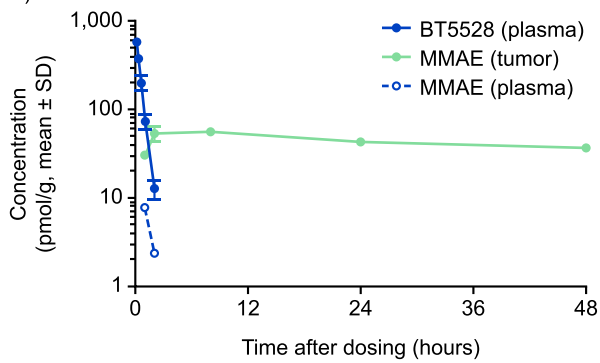
Rapid and extensive tumor distribution

Because of its low molecular weight, BT5528 is rapidly distributed, with rapid tumor uptake and retention of MMAE, at levels that exceed those in plasma circulation, persisting for at least 48 hours (Fig. 1B) [60, 65, 74, 75]. Due to the persistent tumor exposure to MMAE, antitumor activity of BT5528, has been demonstrated (Fig. 1D), including complete tumor regression correlating with EphA2 expression [65]. This has been shown in murine cell-line derived

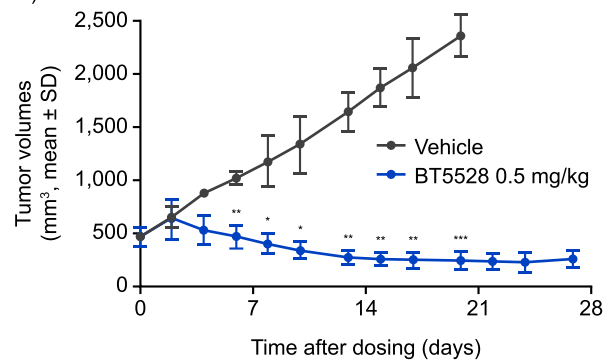
A)



B)



D)



C)

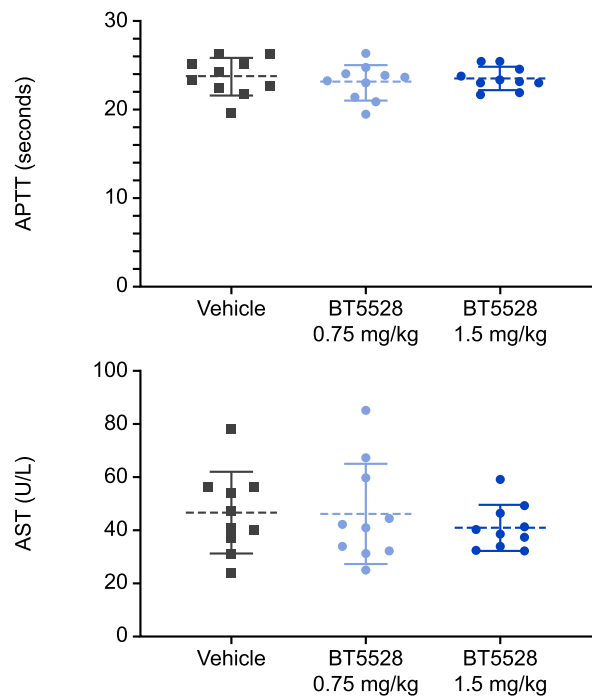
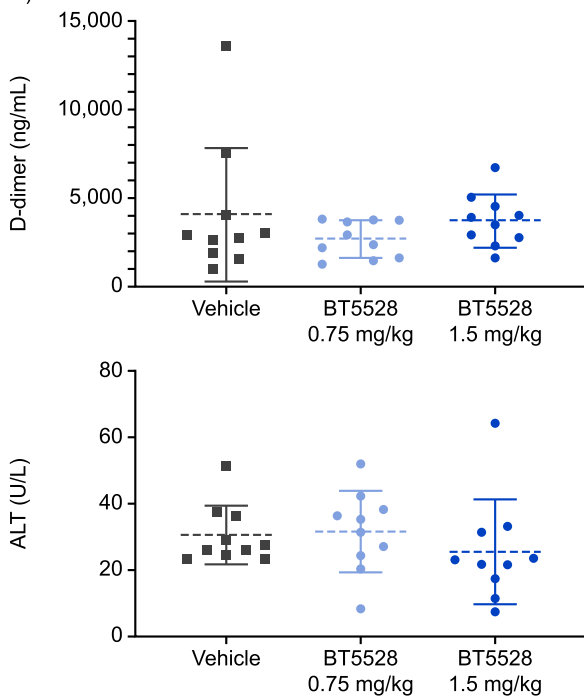


Fig. 1 (See legend on next page.)

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Fig. 1 Structure of BT5528 and key preclinical data. Source: Bennet et al. 2020 [65]. Reused with permission from *Mol Cancer Ther* [65]. **A) Structure of BT5528.** Purple: bicycle binder; orange: spacer (10 × sarcosine); cyan: cleavable linker, glutaryl-Val-Cit-PAB; red: cytotoxin MMAE; **B) Systemic clearance of BT5528 and MMAE.**^a BT5528 gives rise to transient MMAE levels in plasma: PK profiles of BT5528 and MMAE in plasma and MMAE in tumor samples following dosing with BT5528. Error bars indicate SD of $n=3$ (PC3 xenograft model; BT5528 IV 0.5 mg/kg); **C) Markers of hematologic and hepatic toxicity.**^b Clotting and liver parameters: BT5528 dosing to cynomolgus monkeys does not cause bleeding, coagulation, or liver toxicity: D-dimer, APTT, ALT, and AST responses (on day 32) following low (0.75 mg/kg) and high (1.5 mg/kg) BT5528 intravenous dosing to cynomolgus monkeys (three male and three female) on Days 1, 8, 15, 22, and 29; **D) BT5528 antitumor activity.**^d BT5528 gives rise to significant antitumor activity: tumor volume following BT5528 IV 0.5 mg/kg weekly (PC3 xenograft model). Error bars indicate SD of $n=3$ (*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$; two-way ANOVA with Sidak's multiple comparisons test).^a $n=3$; ^bCynomolgus monkeys (three male and three female) dosed with vehicle or BT5528 0.75 mg/kg or 1.5 mg/kg IV on Days 1, 8, 15, 22, and 29; ^cTumor volume in PC3 xenograft model (prostate cancer cell line) following dosing with vehicle or BT5528 0.5 mg/kg IV once weekly; error bars indicate SD of $n=3$ (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; two-way ANOVA). ALT, alanine aminotransferase; ANOVA, analysis of variance; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; D-Asp, D-aspartic acid; Harg, homoarginine; HyP, hydroxyproline; IV, intravenous; MMAE, monomethyl auristatin E; pHH3, phosphohistone H3; PK, pharmacokinetics; Sar, sarcosine; SD, standard deviation

and patient-derived xenograft models of multiple tumor types, including lung, breast, prostate, gastric, and sarcoma as well as difficult-to-treat and highly-resistant models of pancreatic disease and metastatic disease [76, 77]. In EphA2-expressing HT-1080 xenografts, complete regression was observed by Day 14 following exposure to BT5528 (3 mg/kg) once weekly [65], while in larger, more complex murine xenograft models of NSCLC and prostate cancer (LU-01-0251 and PC-3, respectively), complete regression was observed by Day 28 [65]. Of note, in patient-derived xenograft models, similar antitumor activity was observed for both small and large NSCLC tumors, despite the poor vasculature of large tumors, suggesting that BT5528 can achieve deep penetration into the tumor tissue [65]. It is anticipated that sensitivity to BT5528 will be retained upon re-challenge, as demonstrated in an NSCLC xenograft model with BCY6033, an EphA2-targeting BDC[™] molecule analogous to BT5528 [78].

In general, preclinical antitumor activity with BT5528 was at least as good as with ADCs: BT5528 induced tumor regression in the HT-1080 and PC-3 xenograft models that was comparable to an EphA2-targeted ADC (IC1-mcMMAF); however, faster and more complete antitumor activity was seen with BT5528 than the ADC for large NSCLC patient-derived tumors, despite equivalent antitumor activity in small tumors of the same type [65]. This difference may relate to extent of tumor uptake with Bicycle molecules versus antibodies: micro positron emission tomography (μ PET) imaging studies using a Gallium 68 (⁶⁸Ga) radiolabeled EphA2-targeting Bicycle binder BCY6164 (a close analogue of the peptide used in BT5528 conjugated to DOTA chelating group) in mice bearing subcutaneous HT-1080 xenografts, showed high and specific tumor targeting 1 hour post-dose [60, 65]; however, a biodistribution study of the antibody radionuclide conjugate ⁸⁹Zr-DS-8995a in patients demonstrated low tumor uptake associated with a low response [42].

Promising clinical progress with BT5528

Although preliminary, available clinical data for BT5528 are consistent with preclinical data and provide evidence of a promising efficacy-safety profile. These data suggest that

Bicycle technology may offer a means to effectively target EphA2 without the safety issues that have plagued available ADCs.

The first-in-human Phase 1/2 trial (NCT04180371) is being conducted to investigate the safety and tolerability of BT5528 in patients with advanced solid tumors known to express EphA2; the trial includes both dose escalation (2.2–8.5 mg/m² IV once weekly or 6.5–10.0 mg/m² IV every other week) and dose expansion (6.5 mg/m² IV every other week and 5 mg/m² IV once weekly) parts [56, 58, 59]. Early evidence from this ongoing study has shown BT5528 to be generally tolerable, with preliminary antitumor activity. To date, no treatment-related bleeding or hemorrhage events have been observed in dose escalation ($N=128$) [56, 58, 59], similar to MM-310 as discussed previously. Across the dose escalation and dose expansion parts of the study, 128 patients have received BT5528 monotherapy, with objective responses observed in urothelial carcinoma [UC], HNSCC, and ovarian cancer [58]. The greatest antitumor activity was observed in patients with UC; efficacy-evaluable patients in the 6.5 mg/m² once every 2 weeks and the 5 mg/m² once weekly cohorts achieved 45% and 27% objective response rates, respectively [58]. Gastrointestinal disorders were the most common TRAEs overall (64%), and the incidence of treatment-related peripheral neuropathy (TRPN) was 19% and 29% at the two doses tested (6.5 mg/m² IV every other week and 5 mg/m² IV once weekly, respectively), with no Grade ≥ 3 TRPN [57, 58]. In contrast, MM-310 was discontinued because of cumulative Grade 3 peripheral neuropathy [12, 46].

EphA2-targeted delivery of other payloads

While much focus has been on the delivery of chemotherapies as payloads, radionuclide-conjugated EphA2-targeted peptides are also in development for diagnostic and therapeutic use. Specifically, ¹⁷⁷Lu-RAYZ-6114 and -6283 have demonstrated high tumor uptake and ¹⁷⁷Lu-RAYZ-6114 inhibits tumor growth in vivo [79]. Furthermore, the EphA2-targeted radionuclide-peptide conjugate ^{99m}Tc-HYNIC-PEG4-EPH-3 has potential for diagnosis of tumor with high EphA2 expression due to its tumor-targeting capability [80].

Table 3 Key attributes of BT5528 and other EphA2-targeted agents

Entity/ Characteristic	BT5528	MEDI-547	DS-8895a	MM-310	Dasatinib
Affinity	K_D 0.88–2.67 nM (to purified EphA2 of human, mouse, rat, or cynomolgus monkey) [65]	K_D 0.59–1.33 nM (to purified EphA2 of human, mouse, rat or cynomolgus monkey) [39]	High affinity [68]	High affinity [19]	Sub micromolar affinity across kinases [69]
Specificity	High: only EphA2 (highly selective against > 5,000 other targets, including closely related human and rodent homologs [EphA3-7; EphB1; and EphB4] [65])	High: EphA2+FcR (specific binding to EphA2 vs any other EphA or EphB receptors; presence of Fc-binding domain on antibody) [39]	High: EphA2+FcR (specific binding to EphA2 vs proteins similar to the region containing the C-terminal FnIII domain of EphA2; binding affinity between Fc and Fc γ RIIIa) [41, 42]	High: EphA2 (specific binding to EphA2; no Fc binding as comprises only the high-affinity single-chain variable fragment of antibody) [43, 44]	Low (acts on multiple kinases including EphA2) [47]
Half-life	Short 0.3–0.6 hours (across preclinical studies in mouse, rat, and nonhuman primate) [65]	Long Data not available but expected to be consistent with other ADCs	Long ~10–14 days (patients with EphA2-positive esophageal and gastric cancer exposed to Cycle 1 at 20.0 mg/kg) [11]	Short ~13–18 hours (pre-clinical studies in dogs exposed to 5–15 mg/kg) [44]	Short 4.3 hours (patients with advanced solid tumors exposed to 100 mg twice daily) [70]
Size	~4.4 kDa ^a [65]	~150 kDa ^b [65] 11–12 nm hydrodynamic diameter ^b [71]	~150 kDa ^b [65] 11–12 nm hydrodynamic diameter ^b [71]	~100 nm hydrodynamic diameter ^c [72]	0.49 kDa ^a [73]
Tumor distribution	Rapid and extensive distribution with payload tumor retention [65]	Slow, limited distribution (poor extravasation due to large size) [65]	Slow, limited distribution (poor extravasation due to large size) [42, 65]	Rapid and extensive distribution (tumor vessels extravasate liposomes) [44, 71] with slow and sustained release of payload [44]	Rapid and extensive distribution [47]

^aHydrodynamic diameter not available

^bTypical molecular weight and hydrodynamic diameter for antibodies/ADCs [65]

^cTypical hydrodynamic diameter for a nanoliposome; molecular weight not available [72]

ADC, antibody drug conjugate; EphA2, erythropoietin-producing hepatocellular receptor A2; K_D , dissociation constant; kDa, kilodaltons

Leveraging the rapid and extensive targeted distribution of Bicycle molecules, the Bicycle Radionuclide Conjugate (BRC) BCY18469 is being explored preclinically, radiolabeled with positron-emitting radionuclide ⁶⁸Ga for PET imaging and with the photon-emitting indium-111 (¹¹¹In) for single photon emission computed tomography (SPECT) imaging [81]. SPECT imaging of [¹¹¹In]In-BCY18469 in a PC-3 xenograft model demonstrated good tumor uptake at 1 hour and roughly 50% retention at 24 hours post-injection, with clear contrast between the tumor versus surrounding tissue (Fig. 2) [81]. Similar research is ongoing with EphA2-targeting fluorine-18 [¹⁸F]-labeled and [⁶⁸Ga]-labeled bicyclic peptides for non-invasive detection of prostate-specific membrane antigen-negative prostate cancer and pancreatic adenocarcinoma [82, 83]. In addition, in a subcutaneous KPC model of pancreatic cancer, which replicates the treatment resistant nature of the disease, an [²²⁵Ac]-labeled bicyclic peptide significantly improved response and survival when compared to control groups [82]. These data highlight the potential value of EphA2 targeting radiopharmaceuticals.

Bicycle molecules can also be conjugated to immune-targeted Bicycle peptides to create Bicycle tumor-targeted immune cell agonists (Bicycle TICAs) [84, 85]. BCY12491, an EphA2- and CD137-targeting Bicycle TICA, exhibits highly potent activation of peripheral blood mononuclear cells in the presence of EphA2-expressing tumor cell lines, as well as CD8+ T cell-mediated tumor regression, immunologic memory, and significant modulation of the tumor microenvironment in preclinical murine syngeneic tumor models [85]. In addition, Bicycle TICAs that target both EphA2 and the natural killer (NK) cell surface receptor NKp46 (termed NK-TICA), have been found to drive potent activation and NK cell-mediated in vitro tumor cytotoxicity [84, 86]. Thus, Bicycle TICAs are well positioned to exploit the precision-targeted delivery of Bicycle molecules alongside immune cell agonism in the treatment of cancer.

Conclusions

In summary, EphA2 is a target of great interest in oncology. Historically, clinical development of EphA2-targeted therapies has been difficult, with issues in both efficacy and safety. Although several novel next-generation agents that

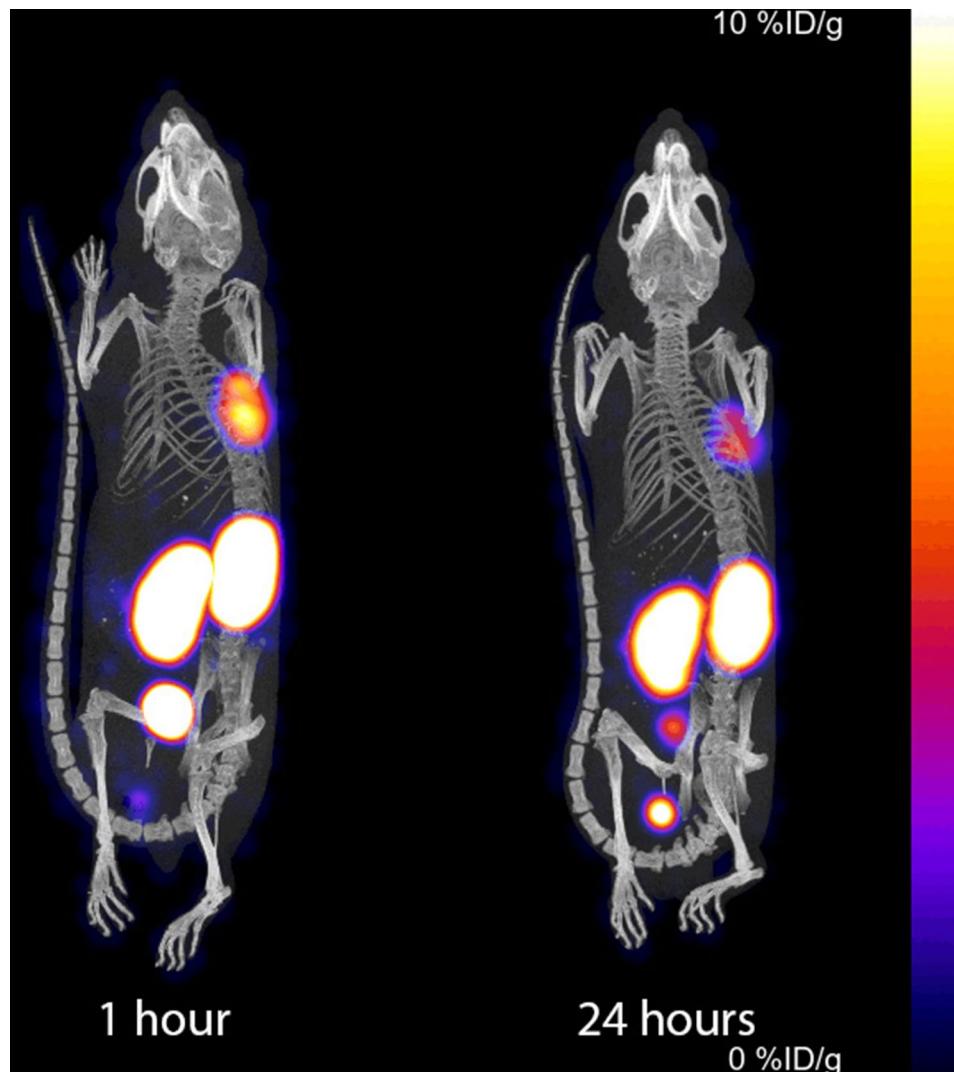


Fig. 2 SPECT imaging of [^{111}In]In-BCY18469 in a tumor xenograft mouse model. Source: El Fakiri et al. 2024 [81]. Reused with permission from *Theranostics*. SPECT/CT imaging was performed in three 5- to 8-week-old male athymic nude mice (Janvier Labs, UK) inoculated with PC-3 cells. Maximum intensity projection at 1 and 24 h p.i. of 230 pmol (5.3 ± 0.2 MBq) of [^{111}In]In-BCY18469

target EphA2 are in preclinical development, the BDC[®] molecule BT5528 is the only such agent to have reported promising antitumor activity and limited toxicity compared with previous EphA2-targeting investigational drugs. The ongoing work on BT5528, together with other Bicycle molecules, demonstrates potential for the targeting of EphA2 in the diagnosis and treatment of solid tumors.

Abbreviations

ADC	Antibody drug conjugate
ADCC	Antibody-dependent cell-mediated cytotoxicity
Bicycle TICAs	Bicycle [®] tumor-targeted immune cell agonists
BDC [®]	Bicycle [®] Drug Conjugate
BRC [®]	Bicycle [®] Radionuclide Conjugate
EphA2	Erythropoietin-producing hepatocellular receptor A2
HNSCC	Head and neck squamous-cell carcinoma
mAb	Monoclonal antibody
mcMMAF	Maleimidocaproyl monomethyl auristatin F
MMAE	Monomethyl auristatin E

NHP	Non-human primate
NK	Natural killer
NSCLC	Non-small cell lung cancer
PAAD	Pancreatic adenocarcinoma
PDAC	Pancreatic ductal adenocarcinoma
SPECT	Single photon emission computed tomography
TRAE	Treatment-related adverse events
UC	Urothelial carcinoma
μPET	Micro positron emission tomography

Supplementary information

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Supplementary material 1

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Data availability

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Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

GB, JR, and GM are employees of Bicycle Therapeutics and own stocks/stock options in the company.

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