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Original Article

The role of Trop2 in prostate cancer: an oncogene, biomarker, and therapeutic target

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Abstract: Prostate cancer remains the second leading cause of cancer-associated deaths amongst American men. Trop2, a cell surface glycoprotein, correlates with poor clinical outcome and is highly expressed in metastatic, treatment-resistant prostate cancer. High levels of Trop2 are prognostic for biochemical recurrence. Trop2 regulates tumor growth and metastatic ability of prostate cancer. Moreover, overexpression of Trop2 drives the transdifferentiation to neuroendocrine phenotype in prostate cancer. In addition, Trop2 is overexpressed across epithelial cancers and has emerged as a promising therapeutic target in various solid epithelial cancers. The FDA (Food and Drug Administration) recently approved the use of a Trop2-targeting ADC (antibody-drug conjugate), Sacituzumab Govitecan (IMMU-132), for metastatic, triple-negative breast cancer with at least two prior therapies. Here, we review the role of Trop2 in prostate tumorigenesis and its potential as a promising biomarker and therapeutic target for prostate cancer.

Keywords: Trop2, Trop-2, TACSTD2, prostate cancer, NEPC, metastasis, biomarker, sacituzumab govitecan, trodelvy, IMMU-132, antibody-drug conjugate (ADC)

Introduction

The American Cancer Society estimates that prostate cancer accounts for approximately 1 in every 5 cancer diagnoses in men [1]. About 191,930 new prostate cancer cases are predicted to occur in 2020, followed by approximately 33,330 prostate cancer deaths [1]. Although the 5-year survival rate for patients with localized prostate cancer is about 99% due to early diagnosis and treatments such as radical prostatectomy and radiation, this survival rate drastically deceases to about 31% for patients with metastatic prostate cancer [1-3]. Castration-resistant prostate cancer (CRPC) emerges post multiple rounds of anti-androgen therapies and is characterized by aggressive clinical course [2, 3]. Although the predominant histological variant of CRPC is adenocarcinoma positive for androgen receptor (AR) (CRPC-Adeno), 30-40% of CRPCs exhibit either loss of AR and presence of neuroendocrine phenotype (neuroendocrine prostate cancer, NEPC) or loss of AR and lack of neuroendocrine phenotype (double negative prostate cancer, DNPC) [2-7]. NEPC and DNPC are highly aggressive, metastatic, and not responsive to therapies targeting AR-signaling axis [2-7].

Trophoblast cell-surface antigen 2 (Trop-2; Trop2) is also known as tumor-associated calcium signal transducer (TACSTD2), membrane chromosome 1 surface marker 1 (M1S1), gastrointestinal tumor-associated antigen 733-1 (GA733-1), and epithelial glycoprotein-1 (EGP-1). Trop2 is overexpressed in localized prostate cancer relative to normal prostate tissues, and it is even higher in metastatic CRPC and NEPC, suggesting that Trop2 is involved in prostate cancer development and progression [8-10]. It has been reported that high levels of Trop2 are also predictive for prostate cancer recurrence [9]. Trop2 was shown to enhance prostate cancer growth, metastasis, and treatment resistance [8-10]. Trop2 also promotes treatment resistance via AR loss and stem cell self-renewal and contributes to prostate cancer progression into the currently untreatable NEPC subtype [9, 11].

Trop2-targeting antibody-drug conjugate Sacituzumab govitecan is now FDA approved for

treatment of triple negative breast cancer. Since Trop2 is a critical player in prostate cancer metastasis and progression, targeting Trop2 via Sacituzumab govitecan could serve as a potential therapy for advanced prostate cancer subtypes. This study provides a review on the role of Trop2 in prostate cancer by describing the role of Trop2 in prostate tumorigenesis and the potential of Trop2 as a promising biomarker and emerging therapeutic target for prostate cancer.

Trop2 structure and function

Trop2 is about 46-kDa, single pass glycoprotein that was first described as a surface marker for human trophoblast cells. Trop2 is composed of 323 amino acids and contains a 248 amino acid extracellular domain, a hydrophobic transmembrane domain, and a short cytoplasmic tail [12]. The extracellular domain of Trop2 is composed of GA733 type-1 and thyroglobulin type-1A motifs, both of which are also identifiable in Trop2 homolog, Trop-1/EpCAM (epithelial cell adhesion molecule) [13]. The intron-less TACSTD2 (Trop2 gene) is located on chromosome 1p32. The 35 kDa de-glycosylated Trop2 polypeptide can undergo post-translational, N-linked glycosylation. The cytoplasmic domain of Trop2, which is 26-amino acids in length, contains a phosphatidyl-inositol 4,5-bisphosphate binding site (PIP_2) and can be phosphorylated by protein kinase C (PKC) at the serine 303 position [10, 14, 15] (**Figure 1**). This phosphorylation site enables Trop2 to act as a Ca^{2+} signal transducer [15, 16] (**Figure 1**). Trop2-induced Ca^{2+} delivery has been associated with cell cycle propagation through mitogen-activated protein kinase signaling cascade (MAPK) [17] (**Figure 1**).

Trop2 as a diagnostic and prognostic biomarker for prostate cancer

Trop2 expression is elevated in prostate cancer relative to benign and normal prostate tissues [8-10]. Elevated levels of Trop2 also correlate with poor patient outcome and more aggressive clinical course [9, 18]. Normal prostate tissues contain the lowest levels of Trop2, and Trop2 levels increase in localized, organ-confined prostate cancer and peak in advanced, metastatic prostate cancer with extra-capsular extension [8-10]. The differential expression of Trop2 throughout prostate cancer progression establishes Trop2 as a potential biomarker candidate for early detection of clinically significant localized prostate cancer and metastatic prostate cancer. Elevated Trop2 levels also correlate with post-radial-prostatectomy biochemical recurrence as well as advanced, aggressive, and metastatic phenotypes such as CRPC-adeno and NEPC [8-10]. The positive correlation between Trop2 levels and prostate cancer aggressiveness, and recurrence risk, suggests its utility as a promising biomarker for significant prostate cancer.

Trop2 is a regulator of prostate cancer growth and metastasis

Trop2 regulates cancer proliferation, migration, invasion, and metastasis [9, 10, 14, 17, 18]. Loss of Trop2 expression is sufficient to reduce prostate cancer tumor growth and to decrease cell migration, invasion, and metastasis while Trop2 overexpression has the opposite effect to promote tumor growth and metastasis [9, 10, 18]. The onset of cancer metastasis depends on the loss of intercellular contact, the ability to migrate through the extracellular matrix (ECM), as well as the capacity to invade surrounding tissues by migrating and penetrating through the external capsule [19]. The integrin family of proteins are responsible for mediating interactions between cells and the ECM. Integrins together with fibronectin, a major component of the ECM, serve as key players in cell adhesion, cell migration, cell differentiation, and cell growth [8, 20-23]. Trop2 binds to and co-localizes with β1 integrins at the cell leading edges and prevents the recruitment of β1 integrins into focal adhesion (FA) sites [10, 24] (**Figure 1**). This relocation of β1 integrins and reconstitution of FAs is accomplished by Trop2-driven displacement and hyperphosphorylation of focal adhesion kinase (FAK) (**Figure 1**). FAK is a downstream target of integrin-mediated signaling, and the modulation of this β1-RACK1-FAK-Src signaling axis inhibits β1 integrin-mediated cell adhesion to fibronectin, causing cells to detach from its surrounding ECM and migrate [10, 24, 25] (**Figure 1**).

Similar to β1, α5 is also re-localized from FAs to the leading edge upon Trop2 up-regulation [10] (**Figure 1**). α5 subunit is a promoter of colonization and metastasis in breast and renal cell carcinomas [26, 27] and is essential for migra-

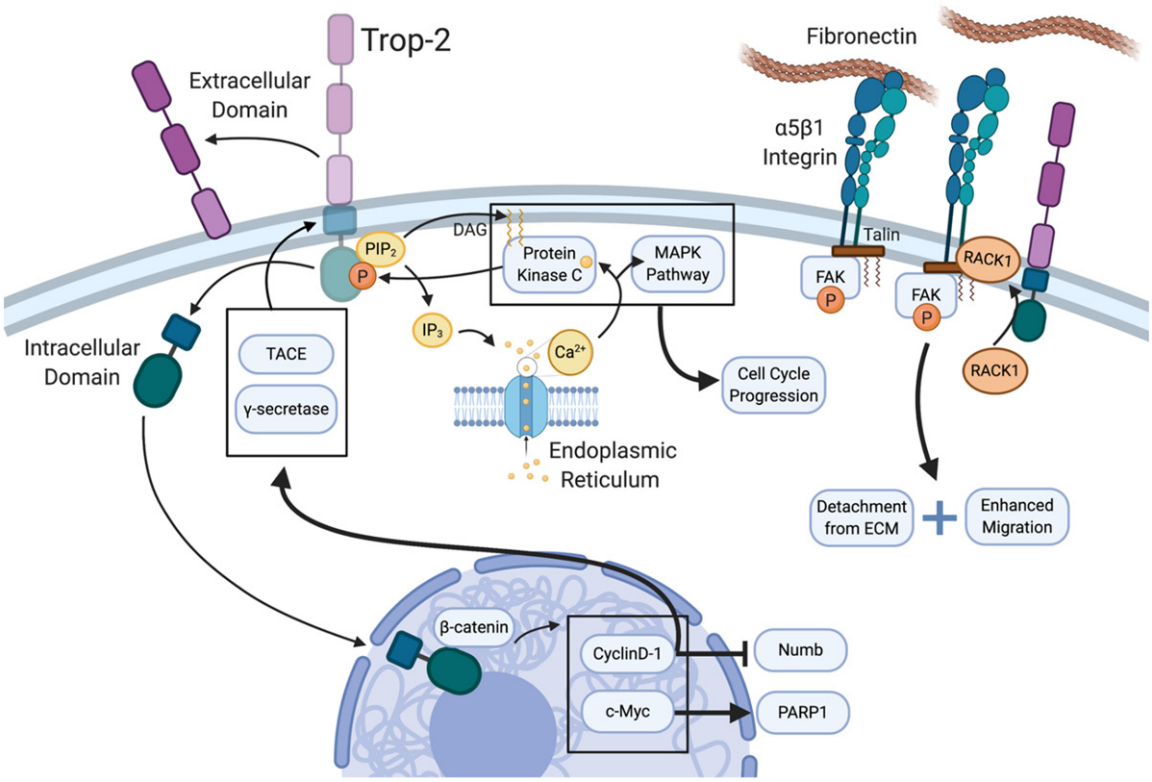

Figure 1. Trop2 signaling. Trop2 contains a hydrophobic transmembrane domain, an extracellular domain, and an intracellular domain. Its cytoplasmic domain plays an important role in signaling and contains a PIP_2 binding sequence. When PIP_2 binds to Trop2, the intracellular domain of Trop2 can also be phosphorylated by protein kinase C (PKC). This fosters PIP_2 cleavage by phospholipase C and releases IP_3 (inositol 1,4,5-triphosphate) into the cytoplasm, leaving DAG (deacylglycerol) on the plasma membrane. The IP_3 generates Ca^{2+} release from the endoplasmic reticulum and enables more PKC activation for Trop2 phosphorylation and the promotion of the MAPK pathway [17, 146]. As PKC and mitogen-activated protein kinases (MAPKs) such as ERK1/2 are recruited in this transmembrane calcium signal transduction, they contribute towards cancer cell growth via cell cycle regulations [17]. Trop2 is cleaved into two parts, an intra- and an extracellular domain, via regulated intramembrane proteolysis, which involves TNF-α converting enzyme (TACE), γ-secretase, presenilin 1 (PS-1), and presenilin 2 (PS-2) [58]. The intracellular domain is released into the nucleus while the extracellular domain is either released into the cytoplasm or lingers on the membrane. In the nucleus, β-catenin colocalizes with the Trop2 intracellular domain to upregulate Cyclin D1 and c-myc, which fosters cell growth. The surge in c-myc has been associated towards PARP1 upregulation [100], while the upregulation of Cyclin D1 is significant for cell growth enhancement, the increasing the expression of enzymes in Trop2 proteolysis (PS2 and TACE), and the inhibition of Numb, an inhibitor against the Trop2 proteolytic complex [83]. Trop2 is also responsible for fostering cell motility via β1 integrin-RACK1-FAK-Src signaling axis [8, 9, 24]. Trop2 re-localizes β1 integrins from FAs to the leading edge and recruits RACK1 into the cell membrane, which prevents the α5β1 integrin complex from binding to fibronectin [24]. By forming a complex with β1 integrin and talin, Trop2 activates FAK to reduce cell adhesion and to promote motility [24].

tion and chemotactic affinity towards the bone marrow microenvironment in prostate cancer [28]. This Trop2-induced α5 and β1 up-regulation is associated with prostate cancer metastatic ability as α5 and β1 subunits are both significantly upregulated in metastatic prostate cancer [8]. Interestingly, high-Trop2-expressing prostate cancer cells foster more liver and bone metastases compared to non-Trop2-expressing prostate cancer cells [9]. Bone metastasis is the most ubiquitous metastatic site amongst prostate cancer patients while liver metastasis is associated with shorter survival time [29]. The co-localized α5 and β1 integrins assemble into the α5β1 heterodimer, which is highly associated with Trop2 in the leading edge [8, 10] (**Figure 1**). The α5β1 heterodimer has been suggested to stimulate angiogenesis, to promote invasive and migratory phenotypes, and to regulate prostate cancer progression and metastasis [8, 10, 25, 28]. Lastly, Trop2 expression is elevated in distant metastatic

sites of human prostate cancer [9, 10]. Taken together, these studies demonstrate that elevated Trop2 expression drives migration and invasion abilities, thereby fostering prostate cancer metastasis.

Trop2 in exosomes

Trop2, β1, and α5 subunits are also detected in exosomes purified from Trop2-positive prostate cancer cells [8]. Vesicles with abundant levels of Trop2, α5, and β1, are sufficient to induce migration of Trop2-negative, non-migratory prostate cancer cells on fibronectin [8]. Studies have suggested a positive correlation between exosomes and metastasis as exosomes enable intercellular communication between tumor and stroma without requiring direct contact between cells [30-43]. Exosomes can also disseminate genetic materials and signaling molecules in order to remodel the microenvironment for colonization and metastasis outside of the primary tumor [43-50]. Since Trop2-positive exosomes can enhance motility in non-migratory prostate cancer cells, they may contribute towards colonization and metastasis by enabling the migration of neighboring tumor cells away from the primary intracapsular tumor. Targeting Trop2-positive exosome transmission and its associated motility may have therapeutic potential against prostate cancer tumor progression and metastasis.

Trop2 and epithelial to mesenchymal transition (EMT)

Trop2 has been shown to stimulate the phosphorylation of p-21-activated kinase 4 (PAK4) [10]. The PAK4 kinase is activated via Ser^{474} phosphorylation and is upregulated in breast, ovarian, and prostate cancers [51]. PAK4 is a critical promoter of prostate cancer progression via EMT regulation, and its silencing reduces prostate cancer EMT, invasion, and metastasis [51, 52]. PAK4 stabilizes Slug, an EMT regulator, by binding to and phosphorylating it [52]. The phosphorylation of Slug leads to enhanced EMT and cancer metastasis [52]. Trop2 is positively correlated with PAK4 and thereby correlates with elevated expression of Slug and mesenchymal traits [53]. Trop2 silencing may reduce or enhance EMT which suggests the role of Trop2 in EMT may be dependent on the cancer type [54-56].

Trop2 in prostate cancer cell of origin and prostate cancer stem cells

Trop2 has been associated with prostate stem cells in both mouse and human prostate [57-59]. Trop2-expressing cells express high levels of stem cell regulator Sox2 and exhibit stem cell like activity such as self-renewal and tissue regeneration in the prostate [57-60]. Trop2 downregulation in Trop2-expressing cells leads to a decrease in self-renewal and tissue regeneration ability of prostate stem/progenitor cells, demonstrating the functional role of Trop2 in these cells [58]. Trop2-expressing cells have been identified as efficient targets for prostate cancer initiation upon various oncogenic stimuli [61-64]. An expansion of Trop2-expressing luminal progenitor cells with age has been reported and suggested to have potential implications in the risk for prostate cancer initiation [65].

Studies proposed that cancer stem cells (CSCs) are a crucial source of therapy resistance in prostate cancer due to their survival and self-renewal abilities [66]. CSCs are able to replenish the heterogenous cell populations in tumors and are therefore involved in tumor progression, metastasis, and resistance against androgen deprivation therapy [11, 66-79]. As a result, CSCs are associated with worse clinical outcome and prostate cancer progression [11, 69, 70, 72, 73, 76, 79, 80]. Trop2 is a putative marker for tumor-initiating cells and plays a significant role in treatment resistance since the population of Trop2-expressing cells increases after anti-androgen treatment [11, 59]. Androgen-sensitive cells with elevated Trop2 expression exhibit enhanced survival and regrowth after chemotherapy, and androgen-independent cells with high Trop2 level demonstrate enhanced self-renewal [11].

The crosstalk between Trop2, c-Myc, and PARP1 may serve as an avenue for pluripotency and stemness. Trop2 has been suggested as a co-transcriptional factor for c-Myc, which is also up-regulated in prostate cancer [9, 58]. C-Myc binds to the promoter of PARP1 gene and serves as a key transcription factor for PARP1 expression, which plays a role in pluripotency and stem cell reprogramming [81, 82]. Moreover, Trop2 can be activated via a proteolytic cleavage by γ-secretase cleavage complex

(PS1, PS2) and TACE (ADAM17) [58]. The cleavage of Trop2 leads to the release of the intracellular domain of Trop2 into the nucleus, and the accumulation of Trop2 intracellular domain in cancer is sufficient to acquire self-renewal properties [58]. The proteolytic cleavage and activation of Trop2 also requires Cyclin D1 [83]. Cyclin D1 regulates PS2 and TACE, both of which are essential components for Trop2 proteolytic cleavage [83]. Cyclin D1 also enables Trop2 proteolytic cleavage and activation by reducing the expression of Numb, a negative regulator of Trop2 proteolytic cleavage complex [83]. As a result, patients that exhibit increased cyclin D1 expression, reduced Numb expression, and elevated intracellular Trop2 expression are at a higher risk of therapy resistance and cancer recurrence [83].

Trop2 fosters the development of aggressive NEPC phenotype

Recent studies have identified Trop2 as a driver of aggressive neuroendocrine phenotype [9]. Overexpression of Trop2 is sufficient to lead to a decrease in AR levels, resistance to androgen ablation, and up-regulation of NEPC markers such as CD56, synaptophysin (SYP), and chromogranin-A (CHGA) [9]. Trop2 overexpression reduces the expression of androgen responsive genes (ARGs) and luminal markers, especially AR, which leads to resistance to androgen deprivation therapies [9].

Trop2 has been suggested to regulate lineage plasticity. DNA replication and chromosome organization are the most intensified networks associated with Trop2 overexpression [9]. Elevated expression of Sox2, c-Myc, Ezh2, and Oct2/4 is also observed in Trop2-overexpressing prostate cancer cells [9]. Sox2 and Ezh2 have been associated with lineage plasticity and contribute towards resistance to anti-androgen therapies [84-96]. They also foster NEPC development through the loss of luminal markers (AR and CK8) and the gain of basal-cell marker p63 [84-96]. Furthermore, Trop2-positive human luminal epithelial cells are more likely to develop neuroendocrine phenotype upon oncogenic stimuli [97]. However, Trop2-induced neuroendocrine phenotype may depend on the genetic context and variance that exist between different prostate cancer cell lines [9]. These findings suggest that the ability of Trop2 to promote the NEPC phenotype may depend on specific genetic context that is yet to be unveiled [9].

Proteomic profiling was performed on Trop2-driven NEPC, and PARP1 (Poly (ADP-Ribose) polymerase 1) was identified as the most elevated protein upon Trop2 overexpression [9]. PARP1 enzyme is involved in transcriptional regulation by regulating replication fork, thereby modulating DNA replication, DNA repair, and cell apoptosis [98, 99]. PARP1 inhibitors repress cell proliferation, tumor growth, and metastasis in high-Trop2 expressing prostate cancer cells and reduce the expression of NEPC markers [9, 100]. PARP1 inhibitors can revert the Trop2-driven NEPC phenotype, which suggests the critical role of PARP1 in Trop2-driven tumor growth, metastasis, and NEPC phenotype [9]. This was further demonstrated when PARP1 inhibitors failed to impact non-Trop2-expressing prostate cancer xenografts [9]. As a result, PARP1 inhibitors could be applied as a novel therapy for high-Trop2-expressing NEPC patients. PARP1 has been shown to promote prostate cancer growth and metastasis [101, 102]. PARP1 inhibitors are FDA approved for treatment of patients with a few cancer types including patients with metastatic CRPC [103-111].

Trop2 in other epithelial cancers

Trop2 levels are found elevated in numerous cancers including lung, breast, gallbladder, colorectal, gastric, renal and others [15, 112]. Trop2 expression positively correlates with p53 mutation and enhances cell proliferation, migration, and invasion in lung adenocarcinoma [113, 114]. While an increase in Trop2 expression significantly associates with disease-specific mortality in lung adenocarcinoma, this correlation does not occur in squamous cell carcinoma, suggesting that the function of Trop2 may depend on the lung cancer subtype [115].

Trop2 has also been proposed as a potential EMT promoter in gallbladder cancer and breast cancer, and high levels of Trop2 associate with metastasis and the ER-/PR-/HER2- (triple-negative) breast cancer [56, 116]. Photoimmunotherapy (PIT) utilizing Trop2-targeting monoclonal antibody proved to be efficacious against the tumor growth of cholangiocarcinoma and pancreatic carcinoma [117]. Trop2 expression

correlates with MMP2 expression in thyroid cancer [118]. Since MMP2 drives invasion and migration, Trop2 upregulation predisposes thyroid cancer towards metastasis [118]. Trop2-driven invasion has been suggested to depend on ERK and JNK signaling pathways, both of which are mitogen-activated protein kinases (MAPK) that enhance MMP2 expression [118]. It was shown that Trop2 regulates colon cancer growth and invasion, and antibody targeting Trop2 decreases tumor cell invasiveness [119]. Trop2 further impacts cell cycle and apoptosis in gallbladder cancer by reducing PTEN expression and phosphorylation, and Trop2 increases AKT phosphorylation and PI3K/AKT signaling, which enhances proliferation, tumor growth, migration, and metastasis in gallbladder cancer [120].

Trodelvy (sacituzumab govitecan-hziy) anti-Trop2 ADC

Due to its overexpression across epithelial cancers, Trop2 has been recognized as a promising therapeutic target. Immunomedics developed an ADC that conjugated humanized anti-Trop2 antibody to SN-38 topoisomerase inhibitor [15, 121-134]. Trop2-targeting ADC is called sacituzumab govitecan (IMMU-132; sacituzumab govitecan-hziy; Trodelvy™), and it has demonstrated promising therapeutic potential against various solid cancers [15]. Sacituzumab govitecan was approved by the FDA in April of 2020 for the treatment of patients with metastatic, triple-negative breast cancer who have received two or more prior therapies (NCT01631552) [130, 135]. Results from phase I/II clinical trials have determined the recommended treatment dosage as 10 mg/kg on day 1 and day 8 of repeated 21-day treatment cycles until disease progression or intolerable toxicity [130, 135, 136]. Sacituzumab govitecan is currently undergoing various clinical trials for metastatic breast cancer, urothelial cancers, advanced solid tumors such as non-small cell lung cancer, castration-resistant prostate cancer, and various epithelial cancers (**Table 1**).

Sacituzumab govitecan uses an optimized, cleavable, CL2A linker to connect the anti-Trop2 antibody (humanized RS7) to SN-38 (govitecan) [130, 137]. SN-38 is a cytotoxic topoisomerase I inhibitor and an active metabolite from irinotecan [123, 138, 139]. Studies comparing various SN-38 release rates determined that maximum potency is achieved through an intermediate SN-38 release rate, which is accomplished by the cleavability and pH-sensitivity of the drug-antibody-linker CL2A [15, 123, 137].

Sacituzumab govitecan has an orphan drug status for SCLC in the United States and pancreatic cancer in both US and EU, and the FDA had already granted sacituzumab govitecan the breakthrough therapy designation for mTNBC as well as accelerated status for mTNBC, locally advanced or metastatic urothelial cancer, metastatic non-small cell lung cancer (NSCLC), and small-cell lung cancer (SCLC) [140]. In fact, studies indicate that a smaller amount of SN-38 administered to the tumor through sacituzumab govitecan is much more effective than a much larger dose of irinotecan or a combination of hRS7 IgG and SN-38 [137].

Sacituzumab govitecan has demonstrated therapeutic potential against various solid cancers and is currently explored across various cancers (**Table 1**). Combination therapies with sacituzumab govitecan and various compounds are also being examined. Studies disclosed that the functional expression of ABCG2, an efflux pump in the ATP-binding cassette (ABC), actively discharges the sacituzumab govitecan drug compound and fosters cellular chemotherapy resistance to SN-38 [122]. Combination therapy of sacituzumab govitecan and ABC transporter inhibitor, YHO-13351, demonstrated improved therapeutic efficacy and survival outcome in ABCG2-induced-SN-38-resistent human gastric cancer xenograft [122]. In addition, studies suggest that disturbances of DNA topoisomerase I (Top1) can also be a potential source of cellular SN-38 resistance [122]. Top1 is a topoisomerase that functions as an inhibition target for SN-38 and other camptothecins [122, 141]. Interestingly, PARP enzymes have been revealed to catalyze the binding between ADP-ribose polymers (PAR) and Top1. This binding reduces the camptothecins-induced Top1 commitment to Top1 cleavage complexes, which contributes towards reduced camptothecin efficacy [142]. Moreover, sacituzumab govitecan and SN-38 both foster an up-regulation of p53 and $p21^{WAF1/Cip1}$. This p53 and $p21^{WAF1/Cip1}$ up-regulation results in the activation of caspase as well as the cleavage and activation of PARP1 [137, 143], which is associ-

Table 1. Clinical Trials of Sacituzumab Govitecan (IMMU-132) as of September, 2020

Study Identifier	Cancer Type	Phase	Status	Objective
NCT04230109	Triple-Negative Breast Cancer	II	Recruiting	Assess IMMU-132 in various localized triple negative breast cancer (TNBC)
NCT02574455	Triple-Negative Breast Cancer	III	Active, Not Recruiting	Assess IMMU-132 in refractory or relapsing metastatic TNBC after at least 2 prior chemotherapies
NCT04454437	Triple-Negative Breast Cancer	II	Not Yet Recruiting	Assess the efficacy and safety of IMMU-132 in TNBC patients with at least two prior chemotherapies
NCT04039230	Triple-Negative Breast Cancer	I & II	Recruiting	Testing IMMU-132 in combination with the Poly (Adenosine Diphosphate [ADP]-Ribose) Polymerase (PARP) Inhibitor Talazoparib
NCT04468061	PD-L1-negative Triple-Negative Breast Cancer	II	Recruiting	Testing the safety and efficacy of IMMU-132 in metastatic, PD-L1-negative triple-negative breast cancer
NCT04448886	HR+/HER2- Metastatic Breast Cancer	II	Not Yet Recruiting	Assess the safety and effectiveness of IMMU-132 with or without Pembrolizumab in metastatic breast cancer
NCT03901339	HR+/HER2- Metastatic Breast Cancer	III	Recruiting	Compare the efficacy and safety of Sacituzumab Govitecan against TPC
NCT03964727	-Metastatic Non-Small Cell Lung -Head and Neck Squamous Cell -Endometrial Cancer	II	Temporarily Suspended	Assess IMMU-132 in adult subjects with Trop-2^{high} metastatic solid tumors
NCT04527991	Metastatic or Locally Advanced Unresectable Urothelial Cancer	III	Not Yet Recruiting	Assess IMMU-132 in urothelial cancers that have progressed after prior therapy with platinum-based regimen and anti-programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) therapy
NCT03547973	Metastatic Urothelial Cancer	II	Recruiting	Assess IMMU-132 in metastatic urothelial cancer that failed platinum-based regimen or anti-PD-1/PD-L1 based immunotherapy
NCT04251416	Endometrial Carcinoma	II	Recruiting	Assess IMMU-132 in subjects with persistent or recurrent endometrial carcinoma
NCT03995706	Glioblastoma	I	Recruiting	Assess IMMU-132 in Glioblastoma with breast brain metastasis
NCT01631552	-Gastric Adenocarcinoma -Esophageal Cancer -Hepatocellular Carcinoma -Non-small Cell Lung -Small Cell Lung -Ovarian Epithelial -Stage IV Breast -Triple Negative Breast -Head and Neck Squamous Cell -Hormone-refractory Prostate Cancer -Renal Cell Cancer -Urinary Bladder Neoplasms -Cervical Cancer -Endometrial Cancer -Follicular Thyroid Cancer -Glioblastoma -Pancreatic Cancer	I & II	Active, Not Recruiting	Assess the safety and tolerability of IMMU-132 in patients with advanced epithelial cancers
NCT03725761	Metastatic Castration-Resistant Prostate Cancer	II	Suspended (accrual goal met)	IMMU-132 in patients with metastatic castration-resistant prostate cancer that progressed on abiraterone or enzalutamide
NCT03337698	Metastatic Non-Small Cell Lung Cancer	I & II	Recruiting	Evaluate the efficacy, safety, and pharmacokinetics of multiple immunotherapy-based treatment combinations in metastatic non-small cell lung cancer (Atezolizumab + Sacituzumab Govitecan)
NCT03424005	Triple-Negative Breast Cancer	I & II	Recruiting	Evaluate the efficacy and safety of multiple immunotherapy-based treatment combinations in metastatic or inoperable locally advanced TNBC (Atezolizumab + Sacituzumab Govitecan)

ated with programmed cell death [133, 144]. As a result, treatment combining either SN-38 or sacituzumab govitecan with PARP1 inhibitors demonstrated synergy in 4 out of 5 osteosarcoma cell lines [145] and fostered synergistic growth inhibition and antitumor effects in TNBC cell lines and tumors [133]. The combination treatment of sacituzumab govitecan and PARP inhibitors is currently undergoing phase I/II clinical trial (NCT04039230) for patients with metastatic breast cancer. In addition, PARP1 and Top1 have also been proposed as potential contributors towards camptothecin resistance. These contributors towards camptothecin resistance may serve as potential candidates to target in combination therapy with sacituzumab govitecan since SN-38 is also a camptothecin.

DS-1062 Trop2-targeting ADC

In addition to sacituzumab govitecan, Daiichi Sankyo Company has developed another Trop2-targeting DXd ADC called DS-1062. Instead of SN-38, DS-1062 utilizes a cytotoxic DNA topoisomerase I inhibitor and a derivative from exatecan called DXd. The topoisomerase I inhibitor is linked to the Trop2 monoclonal antibody by a tetrapeptide-based linker (@NIH Drug Dictionary). The drug-to-antibody ratio (DAR) has been set to four in order to optimize the benefit-risk ratio for the intended patient population. Upon administration, DS-1062 binds to Trop2 receptors on tumor cell surface and internalizes into the cell when lysosomal enzymes break the linker to release DXd (@ https://www.daiichisankyo.com). DS-1062 is currently undergoing phase I clinical trial in non-small cell lung cancer (NSCLC) and triple negative breast cancer (NCT03401385) to determine the recommended dosage, safety, and tolerability. It is also under phase II clinical trial for NSCLC patients with actionable genomic alterations (NCT04484142) and phase I clinical trial in advanced/metastatic NSCLC for combination therapy with pembrolizumab (NCT04526691).

Conclusion

The significance of Trop2 in cancer therapy is evident through its prognostic value and therapeutic potential across several cancer types. In prostate cancer, Trop2 serves as a biomarker, an oncogene, and a potential therapeutic target. Trop2 plays a critical role in the progression of prostate cancer, and has therefore been identified as a promising therapeutic target for advanced prostate cancers. As a result, various Trop2-targeting ADCs such as sacituzumab govitecan and DS-1062 may serve as potential therapy against advanced prostate cancers. The availability of Trop2-targeting ADCs makes Trop2 an accessible and promising target for treatment of patients with advanced metastatic prostate cancers. Additional Trop2-targeting or Trop2-related therapies are still awaiting to be applied and unveiled. Novel diagnostic tools utilizing the variation in Trop2 expression across prostate cancers may also contribute towards the timely diagnosis of invasive prostate cancers and predict patient response to Trop2-targeting therapies.

Disclosure of conflict of interest

None.

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