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## Narrowing the focus: Therapeutic cell surface targets for refractory triple-negative breast cancer

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### Abstract

Triple-negative breast cancer (TNBC) is defined as a type of breast cancer with lack of expression of estrogen receptor, progesterone receptor and human epidermal growth factor 2 protein. In comparison to other types of breast cancer, TNBC characterizes for its aggressive behavior, more prone to early recurrence and a disease with poor response to molecular target therapy. Although TNBC is identified in only 25%-30% of American breast cancer cases annually, these tumors continue to be a therapeutic challenge for clinicians for several reasons: Tumor heterogeneity, limited and toxic systemic therapy options, and often resistance to current standard therapy, characterized by progressive disease on treatment, residual tumor after cytotoxic chemotherapy, and early recurrence after complete surgical excision. Cell-surface targeted therapies have been successful for breast cancer in general, however there are currently no approved cell-surface targeted therapies specifically indicated for TNBC. Recently, several cell-surface targets have been identified as candidates for treatment of TNBC and associated targeted therapies are in development. The purpose of this work is to review the current clinical challenges posed by TNBC, the therapeutic approaches currently in use, and provide an overview of developing cell surface targeting approaches to improve outcomes for treatment resistant TNBC.

**Key words:** Breast cancer; Triple negative; Biomarker; Cell surface; Targeted therapy; Chemorefractory

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**Core tip:** Triple-negative breast cancer continues to be a challenge in breast cancer therapeutics, as these heterogeneous tumors are refractory to many effective and well-tolerated standard treatments. Even more concerning is the subpopulation of these tumors that progress even on the most aggressive therapeutic regimens. The core of this work reviews the developing approaches for treatment-refractory triple-negative breast cancer and proposes cell-surface targeting as a novel modality for targeted treatment of resistant disease.

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## INTRODUCTION

Over the past decade, advances in breast cancer diagnostics, classification, and treatment have significantly improved outcomes and survival, with mortality rates from breast cancer decreasing by nearly 2% per year from 2006-2015<sup>[1]</sup>. However, over 40000 American women were estimated to die from breast cancer in 2018<sup>[1]</sup>, despite the fact that 95% of women diagnosed with nonmetastatic breast cancer receive curative treatment in the form of surgery, systemic therapy, and or radiation<sup>[2]</sup>. In fact, breast cancer continues to be the second leading cause of cancer death in the United States, despite the steady progress in survival<sup>[1]</sup>. The fact that uptake of breast cancer treatment is very high speaks to the ongoing challenge of treatment-resistant disease.

Advances in breast-cancer specific biomarkers have the potential to overcome resistance to all aspects of breast cancer treatment, not only with regards to systemic therapy, but also for local and regional treatments like surgery and radiation. The current focus of breast cancer biomarker therapeutic research focuses on cellular mechanisms of resistance to therapy<sup>[3,4]</sup> and the development of systemic agents inhibiting cellular pathways like mTOR, CDK4/6, and AKT. This approach has high potential for systemic agents, but limited use in regional therapeutics. In contrast, cell surface biomarkers have high potential for diagnostic and therapeutic applications. The most widely recognized use of cell surface biomarker targeting targets the human epidermal growth factor 2 (Her2) cell surface marker, for which monoclonal antibody drugs such as trastuzumab have revolutionized outcomes from cancers overexpressing this particular cell surface marker. Leveraging the specificity of cell surface targeting with the addition of a cytotoxic molecule represents the next wave of cancer therapeutics, as evinced by the clinical success of the trastuzumab-emtansine antibody drug conjugate, known as ado-trastuzumab emtansine (T-DM1)<sup>[5-7]</sup>. Similar to the mechanism of T-DM1 activity, which relies upon directed delivery of a chemotherapeutic agent based on Her2neu overexpression<sup>[3]</sup>, the addition of fluorescent or radioactive labelling of breast cancer specific cell surface markers may also be utilized in improving surgical visualization of tumors, or directed radiopharmaceutical use. However, cell surface markers have not been well characterized for other breast cancer subtypes or in the setting of treatment-refractory disease.

In particular, triple-negative breast cancer (TNBC) continues to pose a therapeutic challenge for women, as their outcomes are not improved by hormonal suppression or Her2neu targeted agents, and systemic therapy continues to be a backbone of standard chemotherapy agents with variable effects on short and long-term response<sup>[8]</sup>. Although TNBC is identified in only 25%-30% of American breast cancer cases annually, these tumors continue to dominate the clinical and research landscape<sup>[9]</sup>. Particularly challenging are women whose disease is refractory to standard therapy in the neoadjuvant or adjuvant setting. TNBC has a markedly poorer 5-year survival, approximately 75%, compared to 90% for hormone responsive breast cancers, with peak hazard rates for breast cancer related death at 7.5% per year 2 years after diagnosis<sup>[10]</sup>. Given the ongoing problem of treating this particular breast cancer subtype, biomarker discovery for TNBC is an ongoing area of interest among many investigators. It is important to note that TNBC is clearly an umbrella term encompassing a minority of all breast cancers, but representing a widely heterogeneous group on a molecular and biologic level, which translates to great variation in short and long-term therapeutic outcomes<sup>[8,11,12]</sup>. Recent data suggests that



women who remain disease-free 5 years after treatment for TNBC have excellent disease free survival<sup>[12]</sup>, so clearly not all TNBCs are the same. With this in mind, biomarker discovery for TNBCs should focus on lesions that are treatment refractory, as evinced by disease progression on chemotherapy or even residual tumor after receipt of neoadjuvant chemotherapy.

## CURRENT TREATMENTS FOR RESISTANT TRIPLE-NEGATIVE BREAST CANCER

Curative, localized, TNBC is generally treated with multimodal therapy, including surgery, chemotherapy, and radiation<sup>[13]</sup>. First-line curative systemic therapy involves chemotherapy, often given in the preoperative neoadjuvant setting, as a complete pathologic response to therapy at the time of surgery confers better prognosis. Standard chemotherapy agents include Adriamycin, Cytosan, and Taxol<sup>[13]</sup>. Additional chemotherapy agents, including carboplatin or gemcitabine, may also be considered as part of an initial therapy regimen for refractory disease; emerging data suggests that the addition of platinum-based agents may increase the rate of pathologic complete responses to chemotherapy at the time of surgical resection, and are the focus of several ongoing clinical trials<sup>[14]</sup>.

Resistant disease can be identified in patients with residual disease in the breast or regional nodes at the time of surgery or may present as a recurrence either regionally or at a distant metastatic site after curative therapy. Patients with residual disease after neoadjuvant chemotherapy and surgery are now being considered for additional adjuvant systemic therapy with capecitabine, as a recent publication suggests that this is a safe adjuvant therapeutic option with improved disease free and overall survival in this population. Radiation to the breast/chest wall, with or without the nodal basins, is also generally incorporated in the treatment plan<sup>[15]</sup>.

Local-regional recurrences are generally treated with surgical resection followed by radiation, and often followed with additional chemotherapy<sup>[13]</sup>. Distant metastases are generally treated systemically only, but there are no universally effective systemic therapies for long-term suppression of TNBC due to intolerance of prolonged therapy, and this population is the subject of multiple ongoing clinical trials due to the paucity of effective, tolerable therapy. In general, surgical resection or local radiation are reserved for symptomatic lesions and palliative procedures.

## THE CASE FOR CELL-SURFACE TARGETING IN BREAST CANCER

The introduction of trastuzumab, which received food and drug administration (FDA) approval in September of 1998, revolutionized the approach to solid tumor treatment. Trastuzumab is a monoclonal antibody targeting Her-2, a cell-surface receptor overexpressed in approximately 30% of breast cancers, and markedly improved the disease-free survival and overall survival of women with breast cancers with overexpression of HER-2 in multiple clinical trials; this effect appears to be quite durable, with a marked improvement in outcomes even after 11 years of followup<sup>[16,17]</sup>. Trastuzumab was the first in its class of targeted cancer therapeutics; since its introduction, pertuzumab, another monoclonal inhibitor of Her-2, has been added to the standard regimen for treatment of women with Her-2 positive breast cancers in the neoadjuvant, adjuvant, and metastatic settings<sup>[7,18]</sup>.

Building on the success of Her-2 targeting, T-DM1 received FDA approval in 2013 for use in treating refractory, metastatic Her2 positive breast cancers. T-DM1 is an antibody-drug conjugate, which further augments the cytotoxicity of trastuzumab by conjugation of the antibody to a tubulin inhibitor molecule, and has been demonstrated to improve outcomes for trastuzumab-resistant disease, with recent expansion to use in women with residual disease after neoadjuvant chemotherapy in combination with trastuzumab and pertuzumab<sup>[5,7,19,20]</sup>.

Two cell-surface targeted antibody-drug conjugates are currently in clinical trials for pretreated and treatment refractory breast cancer. The most developed of these is Sacituzumab govitecan (IMMU-132), which is currently enrolling for an international phase III trial for treatment refractory or relapsed TNBC (ASCENT study; ClinicalTrials.gov ID NCT02574455). IMMU-132 is a conjugate of a humanized antitrophoblast cell-surface antigen 2 (Trop-2) monoclonal antibody hRS7 IgG1k to SN-38. SN-38 is an active metabolite of irinotecan, a topoisomerase I inhibitor. This is joined by a cleavable CL2A linker, which enables release of SN-38 both intracellularly

as well as in the extracellular tumor microenvironment after binding to Trop-2, facilitating destruction of IMMU-132-bound cells as well as adjacent tumor cells. Trop-2 is expressed on the cell surface of 75% of TNBC patients<sup>[21]</sup>.

Also, in early phase trials is ladiratuzumab vedotin (SGN-LIV1a), another antibody-drug conjugate targeting LIV-1, which is a multi-span transmembrane protein. This protein acts as a metalloproteinase as well as a zinc transporter, and is highly expressed in multiple malignancies, including metastatic estrogen-receptor positive and TNBC, as well as melanoma, prostate, and pancreatic cancer. The anti-LIV-1 antibody is linked to monomethyl auristatin E (MMAE), which disrupts microtubules<sup>[22,23]</sup>. Although LIV-1 is expressed in 65% of TNBC patients, it is expressed in normal tissue, with up to 50% 1-2 intensity staining in normal breast on IHC<sup>[22,24]</sup>. SGN-LIV1a is currently in Phase I and Phase II breast cancer trials. The Phase I trials enroll patients with metastatic/locally advanced breast cancer both in the United States (ClinicalTrials.gov identifier NCT03310957) as well as internationally (ClinicalTrials.gov identifier NCT03310957). SGN-LIV1a is also in a randomized multicenter international Phase Ib/II trial for metastatic/unresectable TNBC (Morpheus-TNBC, ClinicalTrials.gov identifier NCT3424005), as well as the adaptive randomized neoadjuvant ISPY-2 trial in the United States (ClinicalTrials.gov identifier NCT01042379), which is not limited to triple negative disease.

In addition to the targeting approaches currently being applied to breast cancer, novel targeted therapies are being developed that have shown efficacy against other cancer types that could be applied to breast cancer. For example, targeted radionuclide therapies such as Lutathera®, which has demonstrated efficacy in the treatment of mid-gut neuroendocrine tumors<sup>[25]</sup> and has been approved by the FDA, could be applied to breast cancer. Bispecific antibodies that target immune checkpoint modulating antibodies to the tumor cell-surface are another example of targeted therapies that could be applied to breast cancer<sup>[26]</sup>.

## TNBC CELL-SURFACE TARGETS AND TARGETED THERAPIES

Although, cell-surface targeted therapies have been successful for breast cancer in general, there are currently no approved cell-surface targeted therapies specifically indicated for TNBC. However, there are a number of cell-surface targets that have been identified as candidates for treatment of TNBC and associated targeted therapies are in development. **Table 1** lists targets that have been identified as specific for TNBC and corresponding therapies are currently being tested in pre-clinical studies. **Table 2** lists cell-surface targets and targeted therapies that are candidates for treatment of TNBC that have been tested in clinical trials. Of these, epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptors 1-3, GPNMB, Trop-2 receptor and LIV-1 targeted therapies have been reviewed<sup>[27-33]</sup> and only EGFR, vascular endothelial growth factor receptors 1-3 and programmed death ligand 1 have published clinical trials that specifically included patients with TNBC (**Table 2**).

As development of a targeted therapy requires a significant expense in funds and effort, there are a few major prerequisites that should be considered prior to development of a cancer targeted therapy. First, it is important to understand the intensity and breadth of expression of the target marker in the tumor tissue to be targeted, *i.e.*, treatment resistant TNBC. Since, mRNA levels are not necessarily proportional to protein levels, a necessary step in the validation of putative targets involves the confirmation of protein levels on the surface of tumor cells in patient specimens. It is necessary to evaluate target expression in patient specimens instead of cultured cell lines, because cell lines are cultured in medium that is not representative of the tumor microenvironment and will not likely be representative of expression in patient tumors. It is notable that of the targets identified in **Tables 1** and **2**, only 52% (11/21) have confirmed protein expression in TNBC patient specimens, and only 24% (5/21) of these were evaluated in sample sets of  $n \geq 100$ . Of the targets characterized with larger sample sets, protein expression was reported to be observed in 31%-77% of the samples studied. However, the intensity of expression was typically not indicated. For only 3 of these targets, elevated expression relative to surrounding normal breast tissue was reported. The ratio of expression of the target in normal tissues of concern for toxicity relative to tumor expression is another factor that can influence dose limiting toxicity and therapeutic window. Per The Human Protein Atlas, all of the targets that had confirmed protein expression in patient TNBC specimens, had medium or high expression in tissues of concern for toxicity or were broadly expressed in normal tissues. Exceptions were EGFR which only has low expression in the liver and mesothelin which only has low expression in the bronchus,

**Table 1 Pre-clinical studies targeting the cell-surface of triple negative breast cancer**

Gene, Protein	Protein type and function <sup>1</sup>	TNBC expression <sup>2</sup>	Normal tissue expression	Drug <sup>3</sup>	Studies <sup>4</sup>	Ref.
ANTXR1 (TEM8), Anthrax toxin receptor 1	SPT1MP, integrin-like; Attachment, migration, progression	Protein, <i>n</i> = 23, 100% stromal; very low in surrounding NB. Protein, BC tissues, <i>n</i> = 120, NB, <i>n</i> = 33, increased in invasive BC	<sup>6</sup> High: Gallbladder; Medium and low: Broadly expressed	CAR-T	Xenograft regression	[34-36]
ICAM1, Interleukin adhesion molecule-1	SPT1MP; Binds leukocyte adhesion protein LFA-1 (integrin $\alpha$ L/ $\beta$ 2)	mRNA, <i>n</i> = 6 (cell lines), 60%; BC 25%. Protein, <i>n</i> = 6 (cell lines), increased expression	<sup>5</sup> High: Lung, kidney. Medium: Bone marrow and immune system, endometrium. Low: Cerebral cortex, colon, bladder, testis, fallopian tube	mAb: Enlimomab (murine mAb against the human ICAM1); TLipo: Lipocalin-2 siRNA payload	CAM assay; decreased xenograft angiogenesis	[37,38]
MELK, Maternal embryonic leucine zipper kinase	PMP, serine/threonine kinase. Cell cycle regulation, stem-cell self-renewal, apoptosis, splicing regulation, radiation resistance	mRNA, <i>n</i> = 59, increased relative to BC, <i>n</i> = 284 and NB ( <i>n</i> = 105)	<sup>5</sup> High and medium: Broadly expressed	Ib: OTSSP167	Ib + radiation decreased xenograft growth	[39,40]
FZD7, Frizzled-7	MPMP, Wnt protein receptor. Possibly signals polarity during morphogenesis, differentiation	mRNA, <i>n</i> = 5, increased relative to BC, <i>n</i> = 14	<sup>5</sup> High and medium: Broadly expressed	shRNA against FZD7	Decreased xenograft growth	[41]
MMP14, Matrix metallo-proteinase-14	SPT1MP, Endopeptidase. Degrades extracellular matrix	ND, general increased in metastatic cancers	<sup>5</sup> Medium and low: Broadly expressed	Humanized Fab Ab	Decreased progression and metastasis of syngeneic tumors	[42]
MSLN, Mesothelin	Cell surface GPI anchor, secreted. Cell adhesion	Protein, <i>n</i> = 109, 34%. Protein, <i>n</i> = 99, 67% mRNA, <i>n</i> = 226, increased relative to BC, <i>n</i> = 88	<sup>6</sup> Broadly very low to non-expressed. <sup>7</sup> 120 organs: (1) Lung, mesothelial cells, uterus; (2) Low in heart, kidney and placenta	ADC: RG7787, Ab fragment/pseudomonas exotoxin A. CAR-T (TNBC not tested)	Xenograft regression	[43-47]
GBP1, Guanylate-binding protein 1	Cell surface lipid anchor, secreted. Hydrolyzes GTP to GMP. Host protection against pathogens	mRNA, <i>n</i> = 1512, increased relative to BC, <i>n</i> = 1412 and NB, <i>n</i> = 3887	<sup>5</sup> Medium: Thyroid, appendix, small intestine. Low: Brain, tonsil, lung, GI tract, kidney, fallopian tube, endometrium, skin	None	Expression controlled by EGFR. Knockdown decreased cell growth	[48]
MST1R, Macrophage-stimulating protein receptor (RON)	SPT1MP, tyrosine kinase receptor. MST1 ligand. Proliferation, survival, migration, differentiation	Protein, <i>n</i> = 168, 77% expression and 45% overexpression	<sup>5</sup> High: Thyroid, lung, gallbladder, ovary, placenta. Medium: Broadly expressed	ADC: Zt/g4- MMAE (hAb from murine mAb conjugated to MMAE)	Xenograft regression	[49,50]
MUC1, Mucin-1	SPT1MP, extracellular or secreted. Adhesion, protective layer, progression, genotoxic stress response	Protein, <i>n</i> = 52, 94%	<sup>5</sup> High: Lung, gallbladder, GI tract, female tissues. Medium and low: Adrenal gland, bone marrow and immune, kidney, bladder, male tissues, skin	ADC: mAb-MMAE	PDX regression	[51,52]
CDCP1, CUB domain-containing protein 1	SPMP. Anchorage, migration, proliferation, differentiation	Protein, <i>n</i> = 100, 57%	<sup>5</sup> Medium and low: Broadly expressed	Ib: Glyco-conjugated palladium complex (Pd-Oqn)	Decreased metastasis	[53-56]



PIM1, Serine/threonine-protein kinase pim-1	Isoform 2: Cell surface, serine/threonine kinase. Proto-oncogene. Survival, proliferation, apoptosis	mRNA, <i>n</i> = 123, increased relative to BC, <i>n</i> = 647	<sup>5</sup> Low: Broadly expressed	Ib: AZD1208, PIM kinase inhibitors	Stopped PDX growth; increased MYC expression; MYC-driven GEMM	[57-59]
NECTIN4, Nectin-4	SPT1MP, Cell adhesion	mRNA, <i>n</i> = 1175, 61%. Protein, <i>n</i> = 61, 62%; NB, <i>n</i> = 2, 0%; ON, <i>n</i> = 30, 0%	<sup>5</sup> Medium: Tonsil, oral mucosa, esophagus, bladder, breast, placenta, skin. Low: Pancreas, kidney, female and male tissues	ADC: hAb-MMAE	Rapid, complete, durable responses in PDXs	[60]
GPR55, G-protein coupled receptor 55	MPMP, LPI receptor	Protein, <i>n</i> = 27, 82%	<sup>6</sup> Broadly expressed, higher levels in bone marrow and immune system, lung, gall bladder, GI tract, bladder, female and male tissues. <sup>7</sup> 72 organs, leukocyte, brain, bone	shRNA against GPR55	Decreased xenograft growth	[61]
LRP8, Low-density lipoprotein receptor-related protein 8	SPT1MP, reelin and apolipoprotein E receptor	mRNA, METABRIC data set, increased relative to BC	<sup>5</sup> High: Testis. Low: Placenta	siRNA against LRP8; shRNA against LRP8: Inducible	Knockdown in cells. Decreased tumorigenesis <i>via</i> Wnt signaling inhibition	[62,63]

<sup>1</sup>MPMP: Multi-pass membrane protein; PMP: Peripheral membrane protein; SPMP: Single-pass membrane protein; SPT1MP: Single-pass type I membrane protein.

<sup>2</sup>mRNA: Microarray, protein, immunohistochemistry; *n*: Number of patient specimens; ND: Not determined; NB: Normal breast tissue; BC: Non-TNBC breast cancers; ON: Other normal tissues.

<sup>3</sup>Ib: Small molecule inhibitor; Ab: Antibody; hAb: Human/humanized; mAb: Monoclonal; CAR-T: CAR-T cells; TLipo: Targeted liposomes; shRNA: Short hairpin RNA; siRNA: Small inhibitory RNA; ADC: Antibody-drug conjugate; MMAE: Monomethyl auristatin E.

<sup>4</sup>CAM: Chick chorioallantoic membrane assay; xenograft: Human TNBC cell lines grown as tumors in immunocompromised mice *in vivo*; PDX: Patient derived xenografts using TNBC tumor or metastasis specimens; GEMM: Genetically engineered mouse model.

<sup>5</sup>Human Protein Atlas: Protein expression.

<sup>6</sup>Human Protein Atlas: mRNA expression.

<sup>7</sup>UniProt: mRNA expression.

nasopharynx and oral mucosa. Finally, it is important that the target expression be representative of the untreatable fraction of TNBC, *i.e.*, the patients with resistant disease. None of the target identification studies included TNBC specimens known to be resistant to standard therapy.

## CONCLUSION

Novel effective therapies are needed for the treatment of chemotherapy resistant TNBC which has an extremely poor prognosis. Cell-surface targeted therapies have demonstrated efficacy in the treatment of breast cancer in general, *e.g.*, the Her2 inhibiting antibody Trastuzumab, or the antibody-drug conjugate T-DM1. However, there are no targeted therapies that are specific for the effective treatment of resistant TNBC. Although some TNBC targets have been identified, few have been well characterized in terms of intensity and breadth of expression in TNBC patient specimens, nor in terms of expression in normal tissues of concern for toxicity. The ratio of expression in tumor versus normal tissues is a key factor in the therapeutic window observed for a corresponding targeted therapy. Some protection of normal tissues may be observed due to the relatively low permeability of vasculature in most normal tissues relative to tumor vasculature. However, this is not the case for some key clearance organs, *i.e.*, kidney and liver, which also have permeable vasculature. Systematic studies to discover cell-surface therapeutic targets for resistant TNBC are greatly needed. Once validated, novel and effective targeted therapies may be developed for resistant TNBC tumors and metastases.

Table 2 Clinical studies targeting the TNBC cell surface

Gene, Protein	Protein type and function <sup>1</sup>	Expression in TNBC <sup>2</sup>	Normal tissue expression	Targeted Drug <sup>3</sup>	Clinical trials	Ref.
EGFR, Epidermal growth factor receptor	(1) SPT1MP, tyrosine kinase receptor; (2) EGF ligands; (3) RAS-RAF-MEK-ERK, PI3 kinase-AKT, PLCγ-PKC and STAT pathways	(1) Protein, <i>n</i> = 316, 37%. (2) Protein, <i>n</i> = 930, 54%. (3) Protein, <i>n</i> = 17, 89%	<sup>4</sup> High: Placenta. Low: Bladder, liver, skeletal muscle, skin, testis, tonsil, vagina	Ib: Afatinib, Gefitinib, Lapatinib. Ab: Cetuximab, MM 151 Ab mixture	Phase 2	[64-71]
VEGFR1-3, Vascular endothelial growth factor receptors 1-3	(1) SPT1MP, tyrosine kinase receptors; (2) VEGF A,B,C,D,PGF ligands; (3) Angiogenesis, lymphangiogenesis, cell survival, migration, chemotaxis, invasion, vascular development and permeability	(1) Genomic, increased copy <i>n</i> = 87, 62%; (2) Genomic, increased copy, <i>n</i> = 35, 29%	<sup>6</sup> VEGF1: 220 organs-lung, placenta, liver, kidney, heart, brain. VEGF2: 208 organs, lung, cornea, broadly expressed. VEGF3: 121 organs-liver, muscle, thymus, placenta, lung, testis, ovary, prostate, heart, kidney	Ib: Cediranib, Apatinib, Lucitanib	Phase 2	[72-74]
FGFR1, Fibroblast growth factor receptor 1	(1) SPT1MP, tyrosine kinase receptor; (2) FGF ligands; (3) Proliferation, migration	Genomic, increased copy, <i>n</i> = 76, 9%; mRNA, <i>n</i> = 56, 4%	<sup>4</sup> High: Gallbladder, esophagus, fallopian tube, placenta. Medium and Low: Broadly expressed	Ib: Lucitanib	Phase 2	[75-78]
GPNMB, Transmembrane glycoprotein NMB	(1) SPT1MP; (2) Possible melanogenic enzyme	mRNA, <i>n</i> = 103, 29%	<sup>5</sup> High: Skin. Medium: Cervix, uterine, gallbladder. Low: Broadly expressed	ADC: Glematumumab vedotin (CDX-011)	Phase 2	[79]
TACSTD2, Tumor-associated calcium signal transducer 2 (Trop-2 receptor)	(1) SPT1MP; (2) Possible growth factor receptor	Protein, <i>n</i> = 96, 75%	<sup>4</sup> Medium: Nasopharynx, bronchus, oral mucosa, esophagus, bladder, seminal vesicle, cervix, uterine, skin. Low: Multiple sites	ADC: Sacituzumab govitecan (IMMU-132)	Phase 2	[21]
SLC39A6, Zinc transporter ZIP6 (LIV-1)	(1) MPMP; (2) Possible zinc-influx transporter	Protein, <i>n</i> = 20, 65%	<sup>4</sup> High: Adrenal gland, endometrium. Medium and low: Broadly expressed	ADC: SGN-Ab and human Ab-MMAE	Phase 1/2	[22,24]
CD274, Programmed cell death 1 ligand 1 (PD-L1)	(1) SPT1MP; (2) Immune tolerance, antitumor immunity	Protein, <i>n</i> = 127, 30.7%	<sup>4</sup> High: Lung, placenta. Medium: Lymph node, tonsil, spleen. Low: Appendix, colon	Ab: Avelumab, Atezolizumab, BMS-936559, Durvalumab, HLX20, LDP, LY3300054. CAR-T. CSR-T	Phase 1, 2, 3	[80-85]

<sup>1</sup>MPMP: Multi-pass membrane protein; SPMP: Single-pass membrane protein; SPT1MP: Single-pass type I membrane protein.

<sup>2</sup>mRNA: Microarray, protein, immunohistochemistry; *n*: Number of patient specimens.

<sup>3</sup>Ib: Small molecule inhibitor; Ab: Inhibitory monoclonal antibody; ADC: Antibody-drug conjugate; hAb: Humanized antibody; CAR-T: CAR-T cells; CSR-T: Chimeric switch receptor modified T cells.

<sup>4</sup>Human Protein Atlas: Protein expression.

<sup>5</sup>Human Protein Atlas: mRNA expression.

<sup>6</sup>UniProt: mRNA expression.

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