Narrows 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
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[1] However, over 40000 American women were estimated to die from breast cancer in 2018[1], 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[1]. In fact, breast cancer continues to be the second leading cause of cancer death in the United States, despite the steady progress in survival[1]. 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[3,4] 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)[5-7]. Similar to the mechanism of T-DM1 activity, which relies upon directed delivery of a chemotherapeutic agent based on Her2neu overexpression[3], 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[8]. Although TNBC is identified in only 25%-30% of American breast cancer cases annually, these tumors continue to dominate the clinical and research landscape[8]. 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[8]. 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[8,12]. Recent data suggests that...
women who remain disease-free 5 years after treatment for TNBC have excellent disease free survival[12], 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[13]. 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, Cytoxan, and Taxol[13]. 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[14].

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[15].

Local-regional recurrences are generally treated with surgical resection followed by radiation, and often followed with additional chemotherapy[13]. 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[16,17]. 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[7,18].

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[5,7,19,20].

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[21].

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 metalloprotease 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[22-23]. 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[20]. 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 I SPIY-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[24] 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[25].

**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[22-24] 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 ≥ 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\(^a\) | TNBC expression\(^b\) | Normal tissue expression | Drug\(^c\) | Studies\(^d\) | Ref. |
|---------------|----------------------------------|------------------------|--------------------------|-----------|------------|-----|
| ANTXR1 (TEM8), Anthrax toxin receptor 1 | SPT1MP, integrin-like; Attachment, migration, progression | Protein, \(n = 23\), 100% stromal; very low in surrounding NB. | \(^1\)High: Gallbladder; Medium and low: Broadly expressed | CAR-T | Xenograft regression [34-36] |
| ICAM1, Intercellular adhesion molecule-1 | SPT1MP; Binds leukocyte adhesion protein LFA-1 (integrin \(\alpha\)L/\(\beta\)2) | mRNA, \(n = 6\) (cell lines), 60%; BC 25%. | \(^1\)High: Lung, kidney. Medium: Bone marrow and immune system, endometrium. Low: Cerebral cortex, colon, bladder, testis, fallopian tube | mAb: Enlimonab (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, \(n = 59\), increased relative to BC, \(n = 284\) and NB, \(n = 105\) | \(^2\)High and medium: Broadly expressed | Ib: OTSSP167 | Ib + radiation decreased xenograft growth [39,40] |
| MMP14, Matrix metallo-proteinase-14 | SPT1MP, Endopeptidase. Degrades extracellular matrix | mRNA, \(n = 5\), increased relative to BC, \(n = 14\) | \(^1\)High and medium: Broadly expressed | shRNA against FZD7 | Decreased xenograft growth [41] |
| MSLN, Mesothelin | Cell surface GPI anchor, secreted. Cell adhesion | ND, general increased in metastatic cancers | \(^3\)Medium and low: Broadly expressed | Humanized Fab Ab | Decreased progression and metastasis of syngeneic tumors [42] |
| GBP1, Guanylate-binding protein 1 | Cell surface lipid anchor, secreted. Hydrolyzes GTP to GMP. Host protection against pathogens | mRNA, \(n = 1512\), increased relative to BC, \(n = 1412\) and NB, \(n = 3887\) | \(^4\)Medium: Thyroid, appendix, small intestine. Low: Brain, testis, lung, GI tract, kidney, fallopian tube, endometrium, skin | None | Xenograft regression [43-47] |
| MST1R, Macrophage-stimulating protein receptor (RON) | SPT1MP, tyrosine kinase receptor. MST1 ligand. Proliferation, survival, migration, differentiation | Protein, \(n = 168\), 77% expression and 45% overexpression | \(^5\)High: Thyroid, lung, gallbladder, ovary, placenta. Medium: Broadly expressed | ADC: Zt/g4- MMAE (hAb from murine mAb conjugated to MMAE) | Xenograft regression [48-50] |
| MUC1, Mucin-1 | SPT1MP, extracellular or secreted. Adhesion, protective layer, progression, genotoxic stress response | Protein, \(n = 52\), 94% | \(^6\)High: Lung, gallbladder, GI tract, female tissues. Medium and low: Adrenal gland, bone marrow and immune, kidney, bladder, male tissues, skin | mAb: mAb-MMAE | PDX regression [51,52] |
| CDCA1, Cub domain-containing protein 1 | SPMP. Anchorage, migration, proliferation, differentiation | Protein, \(n = 100\), 57% | \(^7\)Medium and low: Broadly expressed | Ib: Glyco-conjugated palladium complex (Pd-Oqn) | Decreased metastasis [53-56] |

\(^a\)Protein type and function: ANT4, Anfrax, TEM8, Adhesion, migration, progression; ICAM1, Intercellular, adhesion, molecule-1; SPT1MP, Integrin, LFA-1; MMP14, Matrix, metallo-proteinase-14; MSLN, Mesothelin; GBP1, Guanylate, binding, protein-1; MST1R, Macrophage, stimulating, protein, receptor (RON); MUC1, Mucin, 1; CDCA1, Cub, domain-containing, protein 1.

\(^b\)TNBC expression: \(n\) indicates number of samples.

\(^c\)Drug: CAR-T, Cell, receptor, therapy; mAb: Monoclonal, antibody; Tlipo: Transfection, liposomes; Ib: Ibex.

\(^d\)Studies: Xenograft, regression; CAM, assay; Genetic, knockdown.

\(^e\)Ref: Literature, reference.
PIM1, Serine/threonine-protein kinase pim-1  
Isoform 2: Cell surface, serine/threonine kinase. Proto-oncogene. Survival, proliferation, apoptosis  
mRNA, n = 123, increased relative to BC, n = 647  
\[^{1}\] Low: Broadly expressed  
Ib: AZD1208, PIM kinase inhibitors  
Stopped PDX growth; increased MYC expression; MYC-driven GEMM  

NECTIN4, Nectin-4  
SPT1MP. Cell adhesion  
mRNA, n = 1175, 61%. Protein, n = 61, 62%; NB, n = 2, 0%; ON, n = 30, 0%  
\[^{1}\] 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  

GPR55, G-protein coupled receptor 55  
MPMP, LPI receptor  
Protein, n = 27, 82%  
\[^{1}\] Broadly expressed, higher levels in bone marrow and immune system, lung, gall bladder, GI tract, bladder, female and male tissues. 72 organs, leukaocyte, brain, bone  
siRNA against GPR55  
Decreased xenograft growth  

LRP8, Low-density lipoprotein receptor-related protein 8  
SPT1MP, reelin and apolipoprotein E receptor  
mRNA, METABRIC data set, increased relative to BC  
\[^{1}\] High: Testis. Low: Placenta  
siRNA against LRP8; shRNA against LRP8: Inducible  
Knockdown in cells. Decreased tumorigenesis via Wnt signaling inhibition  

\[^{1}\] MPMP: Multi-pass membrane protein; PMP: Peripheral membrane protein; SPMP: Single-pass membrane protein; SPT1MP: Single-pass type I membrane protein.  
\[^{2}\] 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.  
\[^{3}\] 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.  
\[^{4}\] 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.  
\[^{5}\] Human Protein Atlas: Protein expression.  
\[^{6}\] Human Protein Atlas: mRNA expression.  
\[^{7}\] 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 | Expression in TNBC | Normal tissue expression | Targeted Drug | Clinical trials | Ref. |
|--------------|--------------------------|--------------------|--------------------------|---------------|-----------------|------|
| EGFR, Epidermal growth factor receptor | (1) SPT1MP, tyrosine kinase receptor; (2) IGF ligands; (3) RAS-RAF-MEK-ERK, PI3 kinase-AKT, PLCγ-PKC and STAT pathways | (1) Protein, n = 316, 37%. (2) Protein, n = 930, 54%. (3) Protein, n = 17, 89% | High: Placenta. Low: Bladder, liver, skeletal muscle, skin, testis, tonsil, vagina | Ib: Afinatinib, Gefitinib, Lapatinib. Ab: Cetuximab, MM 151 Ab mixture | Phase 2 | 104-107 |
| VEGFR1-3, Vascular endothelial growth factor receptors 1-3 | (1) SPT1MP, tyrosine kinase receptor; (2) VEGF A,B,C,D,PGF ligands; (3) Angiogenesis, lymphangiogenesis, cell survival, migration, chemotaxis, invasion, vascular development and permeability | (1) Genomic, increased copy number n = 87, 62%, (2) Genomic, increased copy number n = 35, 29% | 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 | 102-104 |
| FGFR1, Fibroblast growth factor receptor 1 | (1) SPT1MP, tyrosine kinase receptor; (2) FGF ligands; (3) Proliferation, migration | Genomic, increased mRNA, n = 103, 29% | High: Gallbladder, esophagus, fallopian tube, placenta. Medium and Low: Broadly expressed | | Phase 2 | 105-107 |
| GPNMB, Transmembrane glycoprotein NMB | (1) SPT1MP; (2) Possible melanogenic enzyme | mRNA, n = 103, 29% | High: Skin. Medium: Cervix, uterine, gallbladder. Low: Broadly expressed | ADC: Glembatumumab vedotin (CDX-011) | Phase 2 | 109 |
| TACSTD2, Tumor-associated calcium signal transducer 2 (Trop-2 receptor) | (1) SPT1MP; (2) Possible growth factor receptor | Protein, n = 96, 75% | Medium: Nasopharynx, bronchus, oral mucosa, esophagus, bladder, seminal vesicle, cervix, uterine, skin. Low: Multiple sites | ADC: Sacituzumab govitecan (IMMU-132) | Phase 2 | 101 |
| SLC39A6, Zinc transporter ZIP6 (LIV-1) | (1) MPM; (2) Possible zinc-influx transporter | Protein, n = 20, 65% | High: Adrenal gland, endometrium. Medium and low: Broadly expressed | ADC: SGN–Ab and human Ab-MMAE | Phase 1/2 | 122-124 |
| CD274, Programmed cell death 1 ligand 1 (PD-L1) | (1) SPT1MP; (2) Immune tolerance, antitumor immunity | Protein, n = 127, 30.7% | High: Lung, placenta. Medium: Lymph node, tonsil, spleen. Low: Appendix, colon | Ab: Avelumab, Atezolizumab, BMS-936559, Durvalumab, HLX20, LDP, LY300554. CAR-T. CSR-T | Phase 1, 2, 3 | 80-83 |

1 MPMP: Multi-pass membrane protein; SPMP: Single-pass membrane protein; SPT1MP: Single-pass type I membrane protein.
2 mRNA: Microarray, protein, immunohistochemistry; n: Number of patient specimens.
3 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.
4 Human Protein Atlas: Protein expression.
5 Human Protein Atlas: mRNA expression.
6 UniProt: mRNA expression.

REFERENCES

1 Balko JM, Giltnane JM, Wang K, Schwarz LJ, Young CD, Cook RS, Owens P, Sanders ME, Kubo MG, Sánchez V, Kurupi R, Moore PD, Pinto JA, Doimi FD, Gómez H, Horiuchi D, Goga A, Lehmann BD, Bauer JA, Pietenpol JA, Ross JS, Palmer GA, Yelensky R, Cronin M, Miller VA, Stephens PJ, Artega CL. Molecular profiling of the residual disease of triple-negative breast cancers after neoadjuvant chemotherapy identifies actionable therapeutic targets. Cancer Discov 2014; 4: 232-245 [PMID: 24356096 DOI: 10.1158/2159-8290.CD-13-0286]

2 Miller KD, Siegel RL, Lin CC, Mariotto AB, Kramer JL, Rowland JH, Stein KD, Alteri R, Jemal A. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin 2016; 66: 271-289 [PMID: 27253694]
Tafreshi NK et al. Targeting refractory TNBC

DOI: 10.3322/caac.21149

3 Tang Y, Wang Y, Kiani MF, Wang B. Classification, Treatment Strategy, and Associated Drug Resistance in Breast Cancer. Clin Breast Cancer 2016; 16: 335-343 [PMID: 27208730 DOI: 10.1016/j.clbc.2016.05.012]

4 Brufsky AM. Long-term management of patients with hormone receptor-positive metastatic breast cancer: Concepts for sequential and combination endocrine-based therapies. Cancer Treat Rev 2017; 59: 22-32 [PMID: 28719836 DOI: 10.1016/j.ctrv.2017.06.004]

5 von Minckwitz G, Huang CS, Mano MS, Loibl S, Mamoussan EP, Untch M, Wolmark N, Rastogi P, Schneeweis A, Redondo A, Fischer HJ, Jacot W, Conin AK, Arce-Salinas C, Wagner JL, Jackisch C, DiGiovanna MP, Fasching PA, Crown JP, Widling P, Shao Z, Rota Caremoli E, Wu H, Lam LH, Tesarowski D, Smit M, Douweswale H, Singel SM, Geyer CE; KATHERINE Investigators. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med 2019; 380: 617-628 [PMID: 30516102 DOI: 10.1056/NEJMoa1814017]

6 Verma S, Miles D, Gianni L, Kroop IE, Welslau M, BaseIja L, Pegram M, Oh DY, Diwars V, Guardino E, Fang L, Lu MW, Olsen S, Blackwell K; EMILIA Study Group. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 2012; 367: 1783-1791 [PMID: 23020162 DOI: 10.1056/NEJMoa1209124]

7 Hurvitz SA, Martin M, Symmons WF, Jung KH, Huang CS, Thompson AM, Harbeck N, Valero V, Stroyakovskiy D, Wildiers H, Campone M, Boileau JF, Beckmann MW, Afenjar K, Fresco R, Helms HJ, Xu J, Lin YG, Sperano J, Slamon DS. Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with HER2-positive breast cancer (KRISTINE): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol 2018; 19: 115-126 [PMID: 29175149 DOI: 10.1016/S1470-2045(17)30716-7]

8 Gutzmer R, Rivolinski L, Leechenko E, Testori A, Utikal J, Ascierto PA, Demidov L, Grob JJ, Ridolfi R, Schadendorf D, Queirolo P, Santoro A, Loqui C, Dreno B, Hauschild A, Schulte E, Leisemple TP, Vanhoutte N, Salama B, Gilliet M, Jansjak S, De Sousa AL, Louahed J, Brichard VG, Lehmann FF. Safety and immunogenicity of the PRAME cancer immunotherapeutic in metastatic melanoma: results of a phase I dose escalation study. ESMO Open 2016; 1: e000608 [DOI: 10.1136/esmoopen-2016-000608]

9 Boyle P. Triple-negative breast cancer: epidemiological considerations and recommendations. Ann Oncol 2012; 23 Suppl 6: v7-v12 [PMID: 23012066 DOI: 10.1093/annonc/mds187]

10 Gierach GL, Burke A, Anderson WF. Epidemiology of triple negative breast cancers. Breast Dis 2010; 32: S-24 [PMID: 21062309 DOI: 10.1007/s10549-010-0315-5]

11 Prat A, Adamo B, Cheang MC, Anders CK, Carey LA, Perou CM. Molecular characterization of basal-like and non-basal-like triple-negative breast cancer. Oncologist 2013; 18: 123-133 [PMID: 23404817 DOI: 10.1634/theoncologist.2012-0397]

12 Reddy SM, Barcenas CH, Sinha AK, Hsu L, Moulder SL, Tripathy D, Hortobagyi GN, Valero V. Long-term survival outcomes of triple-receptor negative breast cancer survivors who are disease free at 5 years and relationship with low hormone receptor positivity. Br J Cancer 2018; 118: 17-23 [PMID: 29235566 DOI: 10.1038/bjc.2017.379]

13 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Breast Cancer. Plymouth Meeting, PA: National Comprehensive Cancer Network, 2019

14 Walsh EM, Shalaby A, O'Loughlin M, Webber MJ, Kerin MJ, Keane MM, Glynn SA, Callagy GM. Outcome for triple negative breast cancer in a retrospective cohort with an emphasis on response to platinum-based neoadjuvant therapy. Breast Cancer Res Treat 2019; 174: 1-13 [PMID: 30488345 DOI: 10.1007/s10549-018-5066-6]

15 Masuda N, Lee SJ, ObiSani S, Im YH, Lee ES, Yokota I, Kurei K, Im SA, Park BW, Kim SB, Yanagita Y, Ohno S, Takao S, Aogi K, Iwata H, Jeong J, Kim A, Park KH, Sasano H, Ohashi Y, Toi M. Adjuvant Capcitabine for Breast Cancer after Preoperative Chemotherapy. N Engl J Med 2017; 376: 2147-2159 [PMID: 28564564 DOI: 10.1056/NEJMoa1612645]

16 Smith I, Procter M, Gelber RD, Guillaume SA, Feyereislova A, Dowsett M, Goldhirsch A, Untch M, Mariani G, Basaleska J, Kaufmann M, Cameron D, Bell R, Bergi J, Corleto E, Wang X, Harbeck N, Lopez RI, Mallmann P, Gelmon K, Willenek L, Wits E, Saujeda S, ovaria P, Piccart-Gebhart MJ, HERA study team. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. Lancet 2007; 369: 29-36 [PMID: 17208639 DOI: 10.1016/S0140-6736(07)60028-2]

17 Cameron D, Piccart-Gebhart MJ, Gelber RD, Procter M, Goldhirsch A, de Azambuja E, Castro G, Untch M, Smith I, Giannini L, Basaleska J, Al-Sahaf N, Lauer S, McDadden E, Leyland-Jones B, Bell R, Dowsett M, Jackisch C; Herceptin Adjuvant (HERA) Trial Study Team. 11 years’ follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. Lancet 2017; 389: 1195-1205 [PMID: 28215665 DOI: 10.1016/S0140-6736(16)3226-1]

18 von Minckwitz G, Procter M, de Azambuja E, Zardavas D, Benuyens M, Sieg V, Suter T, Arahanni A, Rouchet N, Clark E, Knott A, Lang I, Levy C, Yardley DA, Bines J, Gelber RD, Piccart M, Baselga J; APHINITY Steering Committee and Investigators. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. N Engl J Med 2017; 377: 122-131 [PMID: 28581536 DOI: 10.1056/NEJMoa1703643]

19 Montemurro F, Ellis P, Anton A, Wuerster L, Delalohe S, Bonnetterre J, Quenal-Tueux N, Linn SC, Ibraha N, Donica M, Lindegee N, Barrios CH. Safety of trastuzumab emtansine (T-DM1) in patients with HER2-positive advanced breast cancer: Primary results from the KAMILLA study cohort 1. Eur J Cancer 2019; 109: 92-102 [PMID: 30700254 DOI: 10.1016/j.ejca.2018.12.022]

20 Brias HA, Rudo HS, VukeliA SI, Vogel CL, Berson RA, Limentani S, Tan-Chiu E, Kroop IE, Michaelson RA, Girish S, Amler L, Zheng M, Chu YW, Klencke B, O'Shaughnessy JA. Phase II study of the antibody drug conjugate trastuzumab-DMI for the treatment of human epidermal growth factor receptor 2 (HER2)-positive breast cancer after prior HER2-directed therapy. J Clin Oncol 2011; 29: 398-405 [PMID: 21127293 DOI: 10.1200/JCO.2010.29.5865]

21 Zhao W, Kuai X, Zhou X, Jia L, Wang J, Yang X, Tian Z, Wang X, Lv Q, Wang B, Zhao Y, Huang W. Trop2 is a potential biomarker for the promotion of EMT in human breast cancer. Oncol Rep 2018; 40: 759-766 [PMID: 29901160 DOI: 10.3892/or.2018.6496]

22 Sussman D, Smith LM, Anderson ME, Dunilo S, Hunter HJ, Kostner M, Miyamoto JB, Nesterova A, Westendorf L, Van Epps HA, Whiting N, Benjamin DR. SGN-LIV1A: a novel antibody-drug conjugate targeting LIV-1 for the treatment of metastatic breast cancer. Mol Cancer Ther 2014; 13: 2991-3000
Quintero M, El-Haddad G, Wolin E, Hendifaar A, Yao J, Chasen B, Mitra E, Kunz PL, Culke MH, Jacene H, Bushnell D, O’Dorrisio TM, Baan RP, Kulkarni HR, Caplin M, Lebahi R, Hobday T, Delpassand E, Van Cutsem E, Benson A, Srigajakanthan R, Pavel M, Mora J, Berlin J, Grande E, Reed N, Seregini E, Öberg K, Lopera Sierra M, Santoro P, Thvenet T, Erion JL, Ruzinszewi P, Kwikkeeboom D, Krenning E; NETTER-1 Trial Investigators. Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors. N Engl J Med 2017; 376: 125-135 [PMID: 28076709 DOI: 10.1056/NEJMoa1607427

Yu L, Wang J. T cellredirecting bispecific antibodies in cancer immunotherapy: recent advances. J Cancer Res Clin Oncol 2019; 145: 941-956 [PMID: 30798356 DOI: 10.1007/s00432-019-02867-6

Shao F, Sun H, Deng CX. Potential therapeutic targets of triple-negative breast cancer based on its intrinsic subtype. Oncotarget 2017; 8: 73329-73344 [PMID: 29069872 DOI: 10.18632/oncotarget.20274

Zhang JF, Liu J, Wang Y, Zhang B. Novel therapeutic strategies for patients with triple-negative breast cancer. Onco Targets Ther 2016; 9: 6519-6528 [PMID: 27799799 DOI: 10.2147/OTT.S105716

Rose AA, Biondini M, Curiel R, Siegel PM. Targeting GPNNMB with glembatumum vedotin: Current developments and future opportunities for the treatment of cancer. Pharmacol Ther 2017; 179: 127-141 [PMID: 28546682 DOI: 10.1016/j.pharmthera.2017.05.010

Shvartsur A, Bonavida B. Trop2 and its overexpression in cancers: regulation and clinical/therapeutic implications. Genes Cancer 2015; 6: 84-105 [PMID: 26000093 DOI: 10.18632/genesandcancer.40

Zaman S, Jadid H, Denson AC; Gray JE. Targeting Trop-2 in solid tumors: future prospects. Onco Targets Ther 2019; 12: 1781-1790 [PMID: 30881031 DOI: 10.2147/OTT.S162447

Stawick AN, Ocean AJ, Shah MA, Guarino MJ, Picozzi VJ, Vahdat TL, Shokat KS, Govindan SV, Maliaak PL, Wegener WA, Hamburger SA, Sharkey RM, Goldenberg DM. First-in-Human Trial of a Novel Anti-Trop-2 Antibody-SN-38 Conjugate, Sacituzumab Govitecan, for the Treatment of Diverse Metastatic Solid Tumors. Clin Cancer Res 2015; 21: 3870-3878 [PMID: 25944802 DOI: 10.1158/1078-0432.CCR-14-3231

Taylor KM. A distinct role in breast cancer for two LIV-1 family zinc transporters. Biochem Soc Trans 2008; 36: 1247-1251 [PMID: 19021534 DOI: 10.1042/BST0361247

Gutwein LG, Al-Qurán SZ, Fernando S, Fletcher BS, Copeland EM, Grobmyer SR. Tumor endothelial marker 8 expression in triple-negative breast cancer. Anticancer Res 2011; 31: 3417-3422 [PMID: 21965755

Byrd TT, Fousek K, Pignata A, Szt C, Komlósi H, Szeleczsényi K, Baker JS, Hsu C, Diamond M, Basu N, Friedlander E, Celli B, Green A, Hsu E, Sherolgerät C, Winkler M, Baetens D, Mertens P, van der Wulp C, van den Broek P, Yap AP, von dem Bussche A, de la Rosette JJC, Shannon KM. Anti–vascular endothelial growth factor antibody bevacizumab in combination with paclitaxel or docetaxel as first-line treatment for advanced or metastatic triple-negative breast cancer: a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2017; 18: 1471-1483 [PMID: 28338287 DOI: 10.1016/S1470-2045(17)30297-3

Guo P, Huang J, Wang L, Jia D, Yang J, Dillon DA, Zarakowski D, Mao H, Moses MA, Auguste DT. ICAM-1 as a molecular target for triple negative breast cancer. Proc Natl Acad Sci USA 2014; 111: 14710-14715 [PMID: 25266762 DOI: 10.1073/pnas.1408556111

Guo P, Yang J, Jia D, Moses MA; Auguste DT. ICAM-1-Targeted, Lcn2 siRNA-Encapsulating Liposomes are Potent Anti-angiogenic Agents for Triple Negative Breast Cancer. Theranostics 2016; 6: 1-13 [PMID: 26722369 DOI: 10.7150/thno.12167

Speers C, Zhao SG, Kothari V, Santola A, Liu M, Wilder-Romans K, Evans J, Batra N, Bartelink H, Hayes DF, Lawrence TS, Brown PH, Pierce LJ, Feng FY. Maternal Embryonic Leucine Zipper Kinase (MELK) kinase holds promise as a new radiosensitizing target and biomarker in triple-negative breast cancer. Radiother Oncol 2016; 127647-127655 [PMID: 27225691 DOI: 10.1016/j.radonc.2015.12.018

Moreno CS. MELK kinase holds promise as a new radiosensitizer in triple-negative breast cancer. J Thorac Oncol 2016; 11: 1471-1482 [PMID: 27225691 DOI: 10.1016/j.jtho.2015.12.019

Yang L, Wu X, Wang Y, Zhang K, Wu J, Yuan YC, Deng X, Chen L, Kim CC, Lau S, Somlo G, Yen Y. FZD7 has a critical role in cell proliferation in triple negative breast cancer. J Thorac Dis 2016; 8: 4437-4446 [PMID: 25332620 DOI: 10.1159/000444145

Ling B, Watt K, Banerjee S, Newsted D, Truesdell P, Adams J, Sidhu SS, Craig AWB. A novel immunotherapy targeting MMP-14 limits hypoxia, immune suppression and metastasis in triple-negative breast cancer models. Oncotarget 2017; 8: 58372-58385 [PMID: 28938563 DOI: 10.18632/oncotarget.17702

Parinivasilitikul N, Blumenschein GR, Wu Y, Lei X, Chavez-Macgregor M, Smart M, Gonzalez-Angulo AM. Mesothelin expression and survival outcomes in triple receptor negative breast cancer. Clin Breast Cancer 2013; 13: 378-384 [PMID: 23810431 DOI: 10.1016/j.clbc.2013.05.001

Tchou J, Wang LC, Selven B, Zhang H, Conejo-Garcia J, Borghaei H, Kalos M, Vonderheide RH, Albeda SM, June CH, Zhang PJ. Mesothelin, a novel immunotherapy target for triple negative breast cancer. Breast Cancer Res Treat 2012; 133: 799-804 [PMID: 22418702 DOI: 10.1007/s10549-012-2814-8

Tohikian G, Brogi E, Kadota K, Catalano J, Akebi B, Norton L, Adusumilli PS, Wen HY. Mesothelin expression in triple negative breast carcinomas correlates significantly with basal-like phenotype, distant metastases and decreased survival. PLoS One 2014; 9: e114900 [PMID: 25506917 DOI: 10.1371/journal.pone.0114900

Ablewine C, Xiang L, Yamori T, Niederfeldner G, Bosslet K, Pastian I. Efficacy of RC7787, a next-generation mesothelin-targeted immunotoxin, against triple-negative breast and gastric cancers. Mol Cancer Ther 2014; 13: 2653-2661 [PMID: 25523997 DOI: 10.1158/1078-0415.MCT-14-0132

Morello A, Sadatulin M, Adusumilli PS. Mesothelin-Targeted CARs: Driving T Cells to Solid Tumors. Cancer Discov 2016; 6: 133-146 [PMID: 26503962 DOI: 10.1158/2159-8290.CD-15-0583

Quintarelli M, Adamek D, Reis LM, Ascencio CFR, Oliveira KRS, Gonçalves KA, Dias MM, Carazzolle MF, Dias SMG. Guanylate-binding protein-1 is a potential new therapeutic target for triple-
negative breast cancer. *BMJ Cancer* 2017; 17: 272 [PMID: 29115931 DOI: 10.1186/s12858-017-3726-2]

49 Suthe SR, Yao HP, Weng TH, Hu CY, Feng L, Wu ZG, Wang MH. RON Receptor Tyrosine Kinase as a Therapeutic Target for Eradicating of Triple-Negative Breast Cancer: Efficacy of Anti-RON ADC ZG4-MMAE. *Mol Cancer Ther* 2018; 17: 2654-2664 [PMID: 30275231 DOI: 10.1158/1535-7163.MCT-18-0522]

50 Yao HP, Feng L, Suthe SR, Chen LH, Weng TH, Hu CY, Jun ES, Wu ZG, Wang WL, Kim SC, Tong XM, Wang MH. Therapeutic efficacy, pharmacokinetic profiles, and toxicological activities of humanized antibody-drug conjugate ZG4-MMAE targeting RON receptor tyrosine kinase for cancer therapy. *J Immunother Cancer* 2019; 7: 75 [PMID: 30781169 DOI: 10.1186/s40425-019-0309-4]

51 Sirov A, Abdul-Karim FW, Miedler J, Feng N, Fu P, Gilmore H, Baar J. MUC1 is expressed at high frequency in early-stage basal-like triple-negative breast cancer. *Hum Pathol* 2013; 44: 2159-2166 [PMID: 23845471 DOI: 10.1016/j.humpath.2013.04.010]

52 Panchamoorthy G, Jin C, Raina D, Bharati A, Yamamoto M, Adeebeg D, Zhao Q, Bronson R, Jiang S, Li L, Suzuki Y, Tagle A, Ghoroghchian PP, Wong KK, Kharbanda S, Kufe D. Targeting the human MUC1-C oncoprotein with an antibody-drug conjugate. *JCI Insight* 2018; 3 [PMID: 29925694 DOI: 10.1172/jci.insight.99880]

53 Turdo F, Bianchi F, Gasparini P, Sandri M, Sasso M, De Cecco L, Forti L, Casalini P, Aiello P, Sifondrini L, Agresti R, Carcangiu ML, Plantamura I, Sozzi G, Tagliaferri E, Campiglio M. CDCP1 is a novel marker of the most aggressive human triple-negative breast cancers. *Oncotarget* 2016; 7: 69649-69665 [PMID: 27627601 DOI: 10.18632/oncotarget.11935]

54 Nakashima K, Uekita T, Yano S, Kikuchi JI, Nakanishi R, Sakamoto N, Fukumoto K, Nomoto A, Kawasaki K, Shibahara T, Yamaguchi H, Sakai R. Novel small molecule inhibiting CDCP1-PRKCI pathway reduces tumor metastasis and proliferation. *Cancer Sci* 2017; 108: 1049-1057 [PMID: 28256037 DOI: 10.1111/cas.13218]

55 Wright HJ, Police AM, Razorenova OV. Targeting CDCP1 dimerization in triple-negative breast cancer. *Cell Cycle* 2016; 15: 2385-2386 [PMID: 27362899 DOI: 10.1080/15384101.2016.1204849]

56 Wright HJ, Hou J, Xu B, Corsetti PM, Eto OA, Tromberg BJ, Razorenova OV. CDCP1 drives triple-negative breast cancer metastasis through reduction of lipid-droplet abundance and stimulation of fatty acid oxidation. *Proc Natl Acad Sci USA* 2017; 114: E6556-E6563 [PMID: 28793932 DOI: 10.1073/pnas.1703791114]

57 Braso-Maristany F, Filisito S, Catchpole S, Marlow R, Quist J, Francesch-Domench E, Plumab DA, Zakka L, Gzinaksa P, Luccardi G, Meier P, Gris-Oliver A, Cheang MCC, Perdrix-Rosell A, Shafat M, Noel F, Patel N, McEachern K, ScWit M, Castel P, Noor F, Biasu R, Maglia S, Sculean A, Serra V, Marra P, Grigoriadis A, Tutt AN. Erratum: PIM kinase regulates cell death, tumor growth and chemotherapy response in triple-negative breast cancer. *Nat Med* 2017; 23: 788 [PMID: 28586336 DOI: 10.1038/nm.4178]

58 Zhao W, Qin R, Li P, Yang J. PIM1: a promising target in patients with triple-negative breast cancer. *Med Oncol* 2017; 34: 142 [PMID: 28721678 DOI: 10.1007/s12323-017-0998-y]

59 Horiuichi D, Camarda R, Zhou Y, Yau C, Momcilovic O, Balakrishnan S, Corella AN, Eyob H, Kessenbrock K, Lawson DA, Marsh LA, Anderton BN, Rohrborg J, Kunder R, Bazarov AV, Yaspen W, McManus MT, Rugo HS, Werb Z, Goga A. PIM1 kinase inhibition as a targeted therapy against triple-negative breast tumors with elevated MYC expression. *Nature Med* 2016; 22: 1321-1329 [PMID: 27775070 DOI: 10.1038/nm.4211]

60 M-Rabet M, Cabaud O, Josselin E, Finetti P, Castellano R, Farina A, Agivan-Couquiaud E, Saviane G, Collette Y, Viens P, Goncalves A, Gineciter C, Charafle-Jauffret E, Birnbaum D, Olive D, Bertucci F, Lopez M. Nectin-4: a new prognostic biomarker for efficient therapeutic targeting of primary and metastatic triple-negative breast cancer. *Ann Oncol* 2017; 28: 769-776 [PMID: 27909879 DOI: 10.1093/annonc/mdw678]

61 Andradas C, Blasco-Benito S, Castillo-Llusa S, Dillenburg-Pilla P, Diez-Alarica R, Juanes-Garcia A, Garcia-Taboada E, Hernando-Llerente R, Soriano J, Hamann S, Wenners A, Alkautou I, Klapper W, Rocken C, Bauer M, Arnold N, Quintanilla M, Megas D, Vicente-Manzanares M, Uriglen L, Gutkind JS, Guzmán M, Pérez-Gómez E, Sánchez C. Activation of the orphan receptor GPR55 by lysophosphatidylinositol promotes metastasis in triple-negative breast cancer. *Oncotarget* 2016; 7: 47565-47575 [PMID: 27340777 DOI: 10.18632/oncotarget.10206]

62 Lin CC, Lo MC, Moody R, Jiang H, Harouaka R, Stevens N, Tinsley S, Gasparyan M, Wieha M, Sun D. Targeting LRP8 inhibits breast cancer stem cells in triple-negative breast cancer. *Cancer Lett* 2018; 438: 165-173 [PMID: 30227220 DOI: 10.1016/j.canlet.2018.09.022]

63 Maire V, Mahmood F, Rigaill G, Ye M, Brisson A, Nématti F, Gentien D, Tucker GC, Roman-Roman S, Dubois T. LRP8 is overexpressed in estrogen-negative breast cancers and a potential target for these tumors. *Cancer Med* 2019; 8: 325-336 [PMID: 30575334 DOI: 10.1002/cam4.1923]

64 Baselga J, Albanell J, Ruiz A, Lluch A, Gascón P, Guillén V, González S, Saulea S, Martínom I, Tabernero JM, Kochler MT, Rojo F. Phase II and phase III studies with the monoclonal antibody cetuximab with cisplatin versus cisplatin alone in patients with metastatic breast cancer. *J Clin Oncol* 2005; 23: 3523-3533 [PMID: 15939921 DOI: 10.1200/JCO.2005.08.326]

65 Baselga J, Gómez P, Greil R, Braga S, Climent MA, Wardley AM, Kaufman B, Stemmmer SM, Pego A, Chan A, Goeminne JC, Graas MP, Kczak A, Corcuro M, Kennedy MJ, Corral C, Garin E, Galvez J, Melezinková H, Awada A. Randomized phase II study of the anti-epidermal growth factor receptor monoclonal antibody cetuximab with cisplatin versus cisplatin alone in patients with metastatic triple-negative breast cancer. *J Clin Oncol* 2013; 31: 2586-2592 [PMID: 23733761 DOI: 10.1200/JCO.2012.46.2401]

66 Bernsdorf M, Ingvar C, Heggens L, Tuxen MK, Jakobsen EH, Saetersdal A, Kimper-Karl ML, Kroman N, Balslev E, Ejlertsen B. Effect of adding gefitinib to neoadjuvant chemotherapy in estrogen receptor negative early breast cancer in a randomized phase II trial. *Breast Cancer Res Treat* 2011; 126: 463-470 [PMID: 21234672 DOI: 10.1007/s10549-011-1352-2]

67 Carey LA, Rugo HS, Marcon PK, Mayer EL, Esteva FJ, Ma CK, Liu MC, Storniolo AM, Rimawi MF, Forero-Torres A, Wolf AC, Hoblady TJ, Ivanova A, Chiu WK, Ferraro M, Burrows E, Bernard PS, Hoadley KA, Perou CM, Winer EP. TBCRC 001: randomized phase II study of cetuximab in combination with carboplatin in stage IV triple-negative breast cancer. *J Clin Oncol* 2012; 30: 2615-2623 [PMID: 22866533 DOI: 10.1200/JCO.2010.34.5579]

68 Changavi AA, Shashikala A, Rajani AS. Epidermal Growth Factor Receptor Expression in Triple Negative and Nontriple Negative Breast Carcinomas. *J Lab Physicians* 2015; 7: 79-83 [PMID: 26417156]
Cancer Manag Res, Borcherding N, Zhang W. The clinical promise of immunotherapy in triple-negative breast cancer. Cancer 2007; 109: 25-32 [PMID: 17146782 DOI: 10.1002/cncr.22381]

Rakha EA, El-Sayed ME, Green AR, Lee AH, Robertson JF, Ellis IO. Prognostic markers in triple-negative breast cancer. Cancer 2007; 109: 25-32 [PMID: 17146782 DOI: 10.1002/cncr.22381]

Rakha EA, Elsheikh SE, Alexsandarany MA, Habashi HO, Green AR, Pwee DG, El-Sayed ME, Bentiasouma A, Brunet JS, Akseen LA, Evans AJ, Blaney R, Reis-Filho JS, Fouliès WD, Ellis IO. Triple-negative breast cancer: distinguishing between basal and nonbasal subtypes. Clin Cancer Res 2009; 15: 2302-2310 [PMID: 19318481 DOI: 10.1186/1475-2840-7-2132]

Andre F, Job B, Dessen P, Tordai A, Michiels S, Liedtke C, Richon C, Yan K, Wang B, Vassal G, Delalonde S, Hortobagyi GN, Symmans WF, Lazar V, Pusztai L. Molecular characterization of breast cancer with high-resolution oligonucleotide comparative genomic hybridization array. Clin Cancer Res 2009; 15: 441-451 [PMID: 19147748 DOI: 10.1186/1475-2840-7-1791]

Linderholm BK, Hellborg H, Johansson U, Eklundberger G, Skoog L, Lehllii J, Lewensohn R. Significantly higher levels of vascular endothelial growth factor (VEGF) and shorter survival times for patients with primary operable triple-negative breast cancer. Ann Oncol 2009; 20: 1639-1646 [PMID: 19549711 DOI: 10.1093/annonc/mdp062]

Liu JF, Tolaney SM, Birrer M, Fleming GF, Buss MK, Dahlberg SE, Lee H, Whalen C, Tybkurski K, Winer E, Ivy P, Matulonis UA. A Phase 1 trial of the poly(ADP-ribose) polymerase inhibitor olaparib (AZD2281) in combination with the anti-angiogenic cediranib (AZD2171) in recurrent epithelial ovarian or triple-negative breast cancer. Eur J Cancer 2013; 49: 2972-2978 [PMID: 23810467 DOI: 10.1016/j.ejca.2013.05.020]

Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. Nature 2012; 490: 61-70 [PMID: 23600897 DOI: 10.1038/nature11412]

Turner N, Lambros MB, Horlings HM, Pearson A, Sharpe R, Nutrjan R, Geyer FC, van Kooiwenhove M, Krek S, Mackay A, Ashworth A, van de Vijver MJ, Castagnone SR. Integrative molecular profiling of triple-negative breast cancers identifies amplicon drivers and potential therapeutic targets. Oncogene 2010; 29: 2013-2023 [PMID: 20101236 DOI: 10.1038/onc.2009.489]

Soria JC, DeBraud F, Bahleda R, Adamo B, Andre F, Dienstmann R, Delmonte A, Cereda R, Issacson J, Litter J, Allen A, Dubois F, Baba C, Robert R, D’Incalci M, Zuccheti M, Camboni MG, Tabernero J. Phase IIa study evaluating the safety, efficacy, pharmacokinetics, and pharmacodynamics of atezolizumab in advanced solid tumors. Ann Oncol 2014; 25: 2244-2251 [PMID: 25193991 DOI: 10.1093/annonc/mda359]

Abu-Khalaf MM, Mayer IA, Tankersley C, Moy J, Allen AR, Vogel CL, Holmes FA, Nanda R, Miller K, Patel R, Pusztai L, Arteaga CL. A phase 2, randomized, open-label study of lucitanib in patients with FGF receptor-positive and FGF receptor-negative breast cancer. J Clin Oncol 2015; 33 suppl 15: TP5628 [DOI: 10.1200/jco.2015.33.15_suppl.tps5628]

Liu JF, Tolaney SM, Birrer M, Fleming GF, Buss MK, Dahlberg SE, Lee H, Whalen C, Tybkurski K, Winer E, Ivy P, Matulonis UA. A Phase 1 trial of the poly(ADP-ribose) polymerase inhibitor olaparib (AZD2281) in combination with the anti-angiogenic cediranib (AZD2171) in recurrent epithelial ovarian or triple-negative breast cancer. Eur J Cancer 2013; 49: 2972-2978 [PMID: 23810467 DOI: 10.1016/j.ejca.2013.05.020]

Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumours. Nature 2012; 490: 61-70 [PMID: 23600897 DOI: 10.1038/nature11412]

Turner N, Lambros MB, Horlings HM, Pearson A, Sharpe R, Nutrjan R, Geyer FC, van Kooiwenhove M, Krek S, Mackay A, Ashworth A, van de Vijver MJ, Castagnone SR. Integrative molecular profiling of triple-negative breast cancers identifies amplicon drivers and potential therapeutic targets. Oncogene 2010; 29: 2013-2023 [PMID: 20101236 DOI: 10.1038/onc.2009.489]

Soria JC, DeBraud F, Bahleda R, Adamo B, Andre F, Dienstmann R, Delmonte A, Cereda R, Issacson J, Litter J, Allen A, Dubois F, Baba C, Robert R, D’Incalci M, Zuccheti M, Camboni MG, Tabernero J. Phase IIa study evaluating the safety, efficacy, pharmacokinetics, and pharmacodynamics of atezolizumab in advanced solid tumors. Ann Oncol 2014; 25: 2244-2251 [PMID: 25193991 DOI: 10.1093/annonc/mda359]

Abu-Khalaf MM, Mayer IA, Tankersley C, Moy J, Allen AR, Vogel CL, Holmes FA, Nanda R, Miller K, Patel R, Pusztai L, Arteaga CL. A phase 2, randomized, open-label study of lucitanib in patients with FGF receptor-positive and FGF receptor-negative breast cancer. J Clin Oncol 2015; 33 suppl 15: TP5628 [DOI: 10.1200/jco.2015.33.15_suppl.tps5628]

Rose AA, Grosset AA, Dong Z, Russo C, Macdonald PA, Bertos NR, St-Pierre Y, Simantov R, Hallett M, Park S, Kwon Y. Recent therapeutic trends and promising targets in triple negative breast cancer. Future Oncol 2019; 15: 1951-1961 [PMID: 30977385 DOI: 10.2217/fon-2019-0059]

Hwang SY, Park S, Kwon Y. Recent therapeutic trends and promising targets in triple negative breast cancer. Pharmacol Ther 2019; 199: 30-57 [PMID: 30825473 DOI: 10.1016/j.pharmthera.2019.02.006]
