# Concepts and targets in triple-negative breast cancer: recent results and clinical implications

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***Abstract*:** Triple-negative breast cancer (TNBC) is a heterogeneous disease in which tumors are defined by lack of expression of the estrogen receptor (ER), the progesterone receptor (PR), and the human epidermal growth factor receptor 2 (HER2) receptor. No targeted therapies are available for the treatment of TNBC, and chemotherapy remains the standard of care. Gene expression profiling has identified six distinct molecular subtypes of TNBC. The identification of novel targets, coupled with the development of therapies for different subsets of TNBC, holds great promise for the future treatment of this aggressive form of breast cancer. This review focuses on novel therapies in development for the treatment of TNBC.

***Keywords:*** targeted therapy, therapeutic targets in triple-negative breast cancer, triple-negative breast cancer

## Introduction

### *Triple-negative breast cancer*

Triple-negative breast cancer (TNBC) is a heterogeneous disease that encompasses subsets of breast cancers defined by the lack of expression of the estrogen receptor, progesterone receptor, and the human epidermal growth factor receptor 2 (HER2) receptor. TNBC accounts for 15–20% of breast cancers and is more common in young women, individuals of African and Hispanic heritage, and in those with a *BRCA1* germline mutation [National Cancer Institute; Carey *et al.* 2006]. TNBC has a higher risk of both local and distant recurrence as compared to other subtypes of breast cancer. Cytotoxic chemotherapy remains the standard of care for the treatment of TNBC.

### *Molecular subtypes of triple-negative breast cancer*

TNBC shows a remarkable diversity of histologic patterns and subtypes. Using gene expression analysis from 386 tumors, Lehmann and colleagues identified six distinct TNBC molecular subtypes, each displaying a unique biology. These six TNBC molecular subtypes are the basal-like 1 (BL1), basal-like 2 (BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL), and the luminal AR (LAR) subtype. The BL1 subtype is characterized by elevated cell cycle and DNA damage response gene expression, while the BL2 subtype is enriched for growth factor signaling and myoepithelial markers. Both the M and MSL subtypes have elevated expression of genes involved in epithelial–mesenchymal transition (EMT) and growth factor pathways, but the MSL subtype has decreased expression of genes involved in proliferation. The IM subtype is composed of immune antigens and genes involved in cytokine and core immune signal transduction pathways. The LAR subtype is characterized by luminal gene expression and is driven by androgen receptor (AR) signaling. When comparing these triple-negative subtypes characterized by Lehmann and colleagues with the intrinsic subtypes first described by Perou (2010), investigators demonstrated that the BL1, BL2, IM, and M tumors cluster within the intrinsic basal-like subtype, while the MSL tumors cluster within the intrinsic normal-like subtype, and the LAR tumors primarily cluster in the intrinsic luminal and HER2 subtypes [Lehmann *et al.* 2011].

One hundred and sixty-three triple-negative tumors were included in The Cancer Genome Atlas (TCGA) project, and the median overall

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survival (OS) and disease-free survival (DFS) of patients with BL1, IM, and MSL tumors was nearly double that of patients with BL2, LAR, and M tumors. Furthermore, patients with tumors of the IM subtype had the best outcome [Mayer *et al.* 2014]. Masuda and colleagues performed a retrospective analysis of 130 TNBC cases treated with neoadjuvant doxorubicin, cyclophosphamide, and paclitaxel chemotherapy. Although the overall pathologic complete response (pCR) rate was 28%, there were subtype specific responses which differed substantially. The BL1 subtype achieved the highest pCR rate at 52%, and the BL2, LAR, and MSL subtypes had the lowest response (0%, 10%, 23%, respectively) [Masuda *et al.* 2013].

Thus, while many TNBCs share a number of genomic alterations, further analysis by triple-negative subtype suggests that not only do these subtypes differ in outcome, but they also likely differ in driver mutations. Better characterization of these recurrent alterations may lead to the development of novel targeted therapies.

## Recent trial results

### *Platinum agents*

Platinum salts, including carboplatin and cisplatin, lead to DNA cross-link strand breaks, which may be especially important in cells that are deficient in homologous recombination repair mechanisms such as *BRCA1/2*-associated tumors and TNBCs. Platinum agents have been investigated for TNBC in the neoadjuvant setting and have shown higher pCR rates both in those with a *BRCA1* mutation carrier as well as those with sporadic TNBC [Byrski *et al.* 2010; Silver *et al.* 2010; Von Minckwitz *et al.* 2014; Sikov *et al.* 2015].

At the San Antonio Breast Cancer Symposium (SABCS) in 2015, updated results of the CALGB 40603 and GeparSixto studies were presented and further elucidate the role of carboplatin in TNBC. In the GeparSixto trial [ClinicalTrials.gov identifier: NCT01426880], patients with early stage TNBC were treated with neoadjuvant paclitaxel, nonpegylated liposomal doxorubicin, and bevacizumab with or without carboplatin. Addition of carboplatin to anthracycline/taxane based neoadjuvant chemotherapy was shown to improve the primary endpoint of pCR rate, defined as absence of invasive cancer in the breast and axilla (ypT0N0), in the TNBC cohort from 36.9% to 53.2% ($p = 0.005$). There was also an improvement in DFS in the TNBC subgroup from 76.1% to 85.8% with the addition of carboplatin (hazard ratio 0.56, $p = 0.035$) [Von Minckwitz *et al.* 2015]. Similarly, CALGB 40603 evaluated the addition of carboplatin or bevacizumab to neoadjuvant taxane and anthracycline-based chemotherapy, and found a significant improvement in pCR rate (defined as ypT0/isN0) from 41% to 54% ($p = 0.0029$) with the addition of carboplatin. However, when evaluated by treatment arm, neither carboplatin nor bevacizumab was associated with an improved event-free survival (EFS) or OS, although the study was underpowered to make this determination [Sikov *et al.* 2015]. In both studies, the addition of carboplatin resulted in higher rates of grade 3 or 4 hematologic toxicity, dose modification, and treatment discontinuation. Thus, the addition of carboplatin to taxane and anthracycline-based neoadjuvant chemotherapy comes at the cost of additional toxicity, and it is not yet clear if these higher pCR rates will translate to an improvement in relapse free or OS.

In the metastatic setting, the phase III TNT (Triple Negative Breast Cancer Trial) study compared carboplatin area under the curve (AUC) 6 every 3 weeks with docetaxel 100 mg/m$^2$ every 3 weeks as first-line treatment for advanced stage disease. In the overall population, at a median follow up of 11 months, outcomes were similar in terms of response rate (31.4% *versus* 35.6%, $p = 0.44$), progression-free survival (PFS) (4.5 *versus* 3.1 months), and OS (12.3 *versus* 12.4 months) between the docetaxel and carboplatin arms, respectively. However, *BRCA1/2* mutation carriers who received carboplatin experienced a significantly greater response than those who were treated with docetaxel (68% *versus* 33.3%, $p = 0.03$). The median PFS for patients with *BRCA1/2* mutations in the carboplatin group was 6.8 months compared with 3.1 months for the non-BRCA mutation carriers and 4.8 months *versus* 4.6 months among patients with and without *BRCA1/2* mutations treated with docetaxel. These data support the use of a platinum agent for metastatic TNBC in the setting of a *BRCA1/2* mutations [Tutt *et al.* 2014].

### *Poly(ADP-ribose) polymerase (PARP) inhibitors*

The PARP family of enzymes (primarily PARP1 and PARP2) plays an important role in the repair

of DNA single-strand breaks *via* the base-excision repair pathway. Through their binding to regions of DNA damage and their recruitment of other DNA repair enzymes to these sites, these proteins are instrumental in enabling single-strand DNA repair. In normal cells, base excision repair and homologous recombination are both mechanisms by which cells repair damaged DNA. In *BRCA1/2*-deficient tumors, however, homologous recombination does not proceed normally due to the loss of these important DNA repair proteins. PARP inhibition in the setting of BRCA1/2 deficient tumors leads to an accumulation of DNA single strand breaks that the cells are unable to repair, ultimately leading to cell death, a concept known as 'synthetic lethality'.

Promising results have been achieved with PARP inhibitors in *BRCA1/2*-associated cancers. Olaparib is an oral PARP inhibitor approved by the US Food and Drug Administration (FDA) for the treatment of patients with *BRCA1/2* germline mutations and advanced ovarian cancer. PARP inhibitors have also been investigated in breast cancer with the most compelling evidence remaining in the subset of patients who harbor *BRCA1/2* germline mutations.

Olaparib has been investigated as monotherapy in a phase II study of patients with metastatic TNBC with germline *BRCA1/2* mutations. This study found that in patients with TNBC treated with olaparib 400 mg twice daily, the response rate was 54% (7/13) [Tutt *et al.* 2010]. Kaufman and colleagues also investigated olaparib in 298 patients with BRCA1/2-associated cancers, including 62 with metastatic breast cancer. In the 30 patients with ER-negative metastatic breast cancer, the response rate was 13.3% [95% confidence interval (CI) 3.8–30.7%]. The lower efficacy observed in the Kaufman study may be related to the inclusion of more heavily pretreated patients and those who had previously been exposed to platinum agents [Kaufman *et al.* 2015].

Veliparib, another oral PARP inhibitor, has also been studied in *BRCA1/2*-associated tumors. Coleman and colleagues reported data on veliparib efficacy as a single agent in gynecologic cancers, and demonstrated an overall response rate (ORR) of 26% [Coleman *et al.* 2015]. Veliparib in combination with temozolomide has been evaluated in a study of 41 patients with metastatic breast cancer. The response rate in *BRCA1/2* mutation carriers was 37.5% (3/8), including one complete response (CR) and two partial responses (PRs). There were no responses observed in non-*BRCA1/2* carriers (0/33) [Isakoff *et al.* 2010].

The prevalence of *BRCA1* and *BRCA2* mutations in patients diagnosed with TNBC is approximately 10% [Hartman *et al.* 2012]. Emerging data suggest that there are a number of traits shared by sporadic TNBCs and tumors which arise in patients with *BRCA1/2* mutations, and this 'BRCAness' has led to the exploration of PARP inhibition in the treatment of sporadic TNBC.

Several large studies are underway to further evaluate PARP inhibitors in both the adjuvant and neoadjuvant setting for TNBC. The adjuvant OlympiA trial [ClinicalTrials.gov identifier: NCT 02032823] is investigating the efficacy and safety of up to 12 months of adjuvant olaparib *versus* placebo in individuals with germline *BRCA 1/2* mutations and high-risk TNBC who have completed definitive local treatment.

In the neoadjuvant ISPY-2 trial, which uses an adaptive biomarker-based design, the combination of veliparib and carboplatin was added to weekly paclitaxel followed by doxorubicin and cyclophosphamide. The estimated pCR rate for this arm of the study was 52% [Rugo *et al.* 2013]. These promising results led to the 'graduation' of the veliparib/carboplatin arm to a randomized phase III trial. The ISPY-2 design did not evaluate the effect of veliparib or carboplatin individually, however this question is currently being addressed in a randomized phase III clinical trial [ClinicalTrials.gov identifier: NCT 02032277] which is evaluating the efficacy of adding carboplatin or carboplatin plus veliparib to taxane and anthracycline neoadjuvant chemotherapy for TNBC. The primary endpoint of this study is to compare pCR rates across the three different arms in both those with *BRCA1/2* germline mutations as well as those with sporadic TNBC. This study has recently completed accrual and results should be available in the summer of 2017.

### *Glucocorticoid receptor antagonists*

Up to 40% of breast cancers have been shown to express the glucocorticoid receptor (GR), and overexpression correlates with increased risk of relapse for early-stage, ER-negative breast cancer. The GR has been shown in preclinical studies to play an important role in breast cancer biology,

particularly in ER-negative breast cancer cell lines. GR activation is thought to initiate potent antiapoptotic signaling pathways in breast epithelial cells *via* transcriptional regulation of genes encoding cell survival pathway proteins [Mikosz *et al.* 2001]. In patients with breast cancer with early stage ER-positive tumors, high tumor GR expression is associated with a longer time to relapse. In ER-negative breast cancers, however, high tumor GR mRNA expression correlates with a decrease in time to relapse for both chemotherapy naïve and chemotherapy treated early stage patients, suggesting a role for GR in tumor aggressiveness and resistance to chemotherapy [Pan *et al.* 2011].

Preclinical studies have demonstrated that pretreatment with a GR antagonist, mifepristone, potentiates the efficacy of chemotherapy in GR-positive TNBC as well as in GR-positive ovarian cancer [Skor *et al.* 2013; Stringer-Reasor *et al.* 2015]. This hypothesis has subsequently been evaluated in a randomized phase I trial of nab-paclitaxel with or without mifepristone for advanced breast cancer [ClinicalTrials.gov identifier: NCT02046421]. Six of nine patients enrolled in this study were found to be GR positive by immunohistochemistry (IHC). Of these six patients, two had a CR, two a PR, two stable disease (SD), and one progressive disease (PD). Neutropenia occurred at both dose levels of nab-paclitaxel studied in this trial but was easily managed with dose reduction or growth factor administration [Nanda *et al.* 2013]. Based on this small study, GR antagonism using mifepristone appears promising, and a randomized phase II of nab-paclitaxel with and without mifepristone will begin enrollment soon. In addition, GR antagonism with mifepristone is also being investigated in combination with other chemotherapy agents for both advanced TNBC and ovarian cancer.

### *Androgen receptor antagonists*

The proportion of tumors expressing AR varies depending on breast cancer receptor status. In TNBC, the prevalence of AR positivity is approximately 10–20% [Niemeier *et al.* 2010; Choi *et al.* 2015]. The LAR subtype of TNBC is characterized by luminal gene expression profiling, and is enriched for expression of AR and its gene targets [Lehmann *et al.* 2011]. These observations have led to a number of studies investigating AR antagonism in advanced TNBC.

Antiandrogen agents have been studied for advanced AR-positive TNBC. Bicalutamide, an oral nonsteroidal antiandrogen, was evaluated in a phase II study by Gucalp and colleagues. In this study, 452 patients with TNBC were screened for AR expression and 12% tested positive for AR [Gucalp *et al.* 2013]. Twenty-six patients with metastatic, AR-positive (defined as IHC $>10\%$ nuclear staining) TNBC were subsequently enrolled and were treated with bicalutamide 150 mg daily. A clinical benefit rate (CBR) (defined as CR + PR + SD $>6$ months) of 18% (95% CI 6–37%) was reported. The most common treatment-related adverse events (AEs) were fatigue, hot flashes, limb edema, and elevation of liver function tests.

Enzalutamide, a next-generation oral antiandrogen, has also been evaluated in advanced AR-positive TNBC. In a study by Traina and coinvestigators, patients with AR-positive metastatic TNBC were treated with enzalutamide 160 mg once daily. In the 26 patients evaluable for the primary endpoint of CBR, the CBR was 42% (95% CI 24–62%), including one CR and one PR. Of the 404 patients screened, 55% were found to express AR [Traina *et al.* 2014], which is much higher than what was seen in the Gucalp study. Of note, these studies used different antibodies for staining, and different cutoffs for determining AR positivity (the Gucalp study used a cutoff of $>10\%$ while the Traina study used a cutoff of $>1\%$ positivity), which likely accounts for the differences in AR positivity between these two studies.

Clinically, individuals with AR-negative, triple-negative tumors have a higher likelihood of achieving a pCR with neoadjuvant chemotherapy than those with AR-positive triple-negative tumors [Loibl *et al.* 2011]. Patients with an AR-positive TNBC, however, have a significantly better DFS and OS than those with AR-negative disease [Loibl *et al.* 2011]. Masuda and colleagues conducted a retrospective study of 130 pretreatment biopsies from patients treated with anthracycline and taxane-based neoadjuvant therapy. While the overall pCR was 28%, patients with the LAR subtype had a poorer response to chemotherapy than other subtypes, with only 10% achieving a pCR [Masuda *et al.* 2013]. These findings suggest that patients with AR-positive TNBC do not receive the same benefit from standard chemotherapy than those with AR-negative TNBC, and alternative strategies,

perhaps incorporating antiandrogen agents are needed.

### *Immune checkpoint inhibitors*

Over the last few years, drugs targeting the programmed death receptor 1 (PD-1)/ programmed death ligand 1 (PD-L1) axis have been investigated in multiple tumor types and early studies have shown promising safety and efficacy when used to treat advanced TNBC. PD-1 is expressed primarily by activated T cells, and binding of PD-1 to its ligands PD-L1 or PD-L2 has been show to impair T-cell function. PD-L1 is overexpressed by tumor cells and macrophages, and tumors can coopt the PD-1/PD-L1 pathway to evade immune surveillance. Once the PD-1/ PD-L1 interaction is blocked, preexisting anticancer T cells can have their effector function rapidly restored [Chen and Mellman, 2013].

The rationale for investigating immune checkpoint inhibitors in TNBC stems from a number of key observations made over the past decade. Loi and colleagues have observed that ER-negative breast cancers have a higher density of tumor infiltrating lymphocytes (TILs) than their ER-positive counterparts [Loi *et al.* 2014]. TNBCs also have a higher mutational load compared with their ER-positive counterparts, and have been proposed as a mechanism for increased immunogenicity [Wang *et al.* 2014]. Additionally, gene expression profiling of TNBCs has identified an immunomodulatory subtype that is characterized by increased expression of genes involved in T-cell function [Lehmann *et al.* 2011].

Thus far, three agents, pembrolizumab, atezolizumab, and avelumab, have been studied in early phase studies in TNBC.

*Pembrolizumab.* Pembrolizumab (MK-3475) is a highly selective, humanized immunoglobulin (Ig) G4-κ monoclonal antibody with activity against PD-1 and has been approved for treatment of metastatic melanoma and lung cancer. The KEYNOTE-012 study was a multicohort, phase Ib study of pembrolizumab in patients with PD-L1-positive advanced solid tumors, including triple-negative breast, head and neck, urothelial, and gastric cancers. Results of the TNBC cohort were initially presented at the SABCS in December 2014, and were published in May 2016. The TNBC cohort evaluated patients with recurrent or metastatic TNBC who were PD-L1 positive (defined by >1% of tumor cells in the stroma staining positive using the Merck 22C3 antibody). Of the 111 patients prescreened for the study, 58.6% had tumors positive for PD-L1 expression. A total of 32 patients (median age 50.5 years, range 29–72) were enrolled in the study and evaluated for safety and efficacy. Patients were heavily pretreated, with almost 90% of patients having received therapy for early stage disease, and 47% of patients having three or more prior therapies for metastatic disease. Treatment-related AEs were common, but generally mild and easily managed. The most common treatment-related AEs included arthralgias (18.8%), fatigue (18.8%), myalgias (18.8%), and nausea (15.6%) [Nanda *et al.* 2016].

Pembrolizumab was associated with an ORR of 18.5%, with one patient having a CR and four patients having a PR. Responses were durable, with the median response duration not reached (range 15 to >47 weeks) and three responders remaining on treatment for at least 12 months [Nanda *et al.* 2016]. Phase II [ClinicalTrials.gov identifier: NCT02447003] and phase III [ClinicalTrials.gov identifier: NCT02555657] studies of pembrolizumab are currently underway.

*Atezolizumab.* Atezolizumab (MPDL3280A) is an engineered human monoclonal antibody targeting PD-L1. The efficacy of atezolizumab has been demonstrated in numerous tumor types, including bladder cancer, non-small cell lung cancer, renal cell carcinoma, and melanoma. Emens and colleagues presented data from the TNBC cohort of a phase Ia study, which included 54 patients with TNBC. The TNBC cohort initially included patients with PD-L1-positive tumors, but was later amended to also allow PD-L1 negative tumors. PD-L1 expression was performed using the SP142 antibody and positivity was defined using a cutoff for positivity of at least 5%. The median age of participants was 53 years and 89% of patients had been exposed to at least four systemic therapies. Treatment-related AEs were common, with 63% of patients experiencing a treatment-related AE of any grade. These were typically grade 1–2 and easily managed, with the most common AEs including fatigue, nausea, and pyrexia [Emens *et al.* 2014].

Building on the promising results of atezolizumab as a single agent, Adams and colleagues presented the first combination trial of atezolizumab with nab-paclitaxel in patients with metastatic TNBC.

Thirty-two patients were enrolled in this single-arm study and were evaluated for safety. The median age of study participants was 55.5 years (range 32–84), and at a median follow up of 5.2 months, the ORR was 41.7%. In the PD-L1-positive cohort, the ORR was 77.8% [Adams *et al*. 2015]. Fifty-six percent of patients who participated in the trial experienced grade 3 or 4 hematologic toxicity, however these were manageable and did not result in study discontinuation. Based on these results, the combination of atezolizumab and nab-paclitaxel is currently being evaluated in a phase III study [ClinicalTrials.gov identifier: NCT02425891] for frontline treatment of patients with metastatic TNBC.

*Avelumab.* Avelumab (MSB0010718C) is a fully human anti-PD-L1 IgG1 antibody that was recently studied in locally advanced or metastatic breast cancer in the phase Ib JAVELIN study. A total of 168 patients were enrolled in this study (median age 55 years; median of three prior lines of therapy). Forty-one percent of patients had hormone receptor (HR) positive disease, 33.9% of patients had TNBC, and 15.5% had HER2-positive breast cancer. Treatment-related AEs were common and occurred in 71.4% of patients, with the most common being fatigue, nausea, and infusion-related reactions. Treatment-related AEs of grade 3 or higher occurred in 24 patients (14.3%) and included fatigue, anemia, increased Gamma-glutamyl transpeptidase (GGT), and autoimmune hepatitis.

The unconfirmed ORR for the entire cohort was 5.4%, with one CR and eight PRs. SD was observed in 40 patients (23.8%) for an overall disease control rate of 29.2%. Notably, there were responders in all breast cancer types (HR positive, TN, and HER2 positive). Of the 57 patients with TNBC, there were five PRs (8.8%, 95% CI 2.9 – 19.3) PD-L1 expression was evaluable in 136 patients. Among all patients with PD-L1 expressing immune cells within the tumor, 33.3% (4 of 12) had PRs. In patients with TNBC who had PD-L1-positive tumors, 44.4% (4 of 9) had PRs, compared with 2.6% (1 of 39) for TNBC- and PD-L1-negative tumors [Dirix Ly *et al*. 2015].

Based on the studies reported to date, blockade of the PD-1/PD-L1 axis has demonstrated promising efficacy and durable responses in advanced TNBC. In addition, treatment with these immune checkpoint agents appears well tolerated, with the majority of side effects being mild and easily managed. A number of studies of PD-1 and PD-L1 inhibitors in combination with chemotherapy, radiation therapy, targeted therapy, and other checkpoint inhibitors are ongoing, and these combination approaches hope to build on the promising single agent responses observed thus far.

### Antibody drug conjugates

*IMMU 132.* Trop-2 is expressed in a wide range of tumor types, including TNBC. Trop-2 is essential for anchorage independent cell growth and tumorigenesis, and overexpression of this transmembrane protein has been linked to a poor prognosis [Ambrogi *et al.* 2014]. Sacituzumab govitecan (IMMU-132) is an anti-trop-2/SN-38 antibody–drug conjugate made from a humanized anti-Trop-2 monoclonal antibody (hRS7) conjugated with the active metabolite of irinotecan, SN-38 [Cardillo *et al.* 2015; Goldenberg et al. 2015a; Sharkey *et al.* 2015; Starodub *et al.* 2015]. Results from a multicenter phase II study suggest that sacituzumab govitecan (IMMU-132) may be effective in patients with metastatic TNBC. The ORR to IMMU-132 among 58 patients with heavily pretreated TNBC was 31% with two CRs. The clinical benefit ratio, defined as CR + PR + SD greater than 6 months, was 49%, with 63% of patients having SD for over 4 months. The median PFS was 7 months, and median OS had not yet been reached. Grade 3–4 toxicities included neutropenia (26%), febrile neutropenia (2%), diarrhea (2%), anemia (4%), and fatigue (4%). No patient discontinued therapy due to toxicity [Bardia *et al*. 2015]. IMMU-132 recently received fast track designation from the FDA pending a randomized phase III trial to further evaluate its efficacy for metastatic TNBC. Additional combinatorial strategies incorporating IMMU-132 are ongoing. Preclinical studies have showed promising results when targeting the PARP DNA repair pathway in BRCA 1/2 mutant TNBC tumors by combining IMMU-132 therapy with either taxane-based therapy or PARP inhibitors, and further investigation is underway [Goldenberg *et al*. 2015b].

*Glembatumumab vedotin.* Glycoprotein NMB (gpNMB) is a type I transmembrane protein overexpressed in 40–60% of breast cancers. gpNMB is believed to be a negative prognostic marker in breast cancer and overexpression is thought to promote invasion, decrease apoptosis, and promote angiogenesis [Rose *et al.* 2010]. Glembatumumab vedotin (CDX-011 or CR011-vcMMAE) is an antibody drug conjugate that combines a

fully human monoclonal antibody against gpNMB and a potent microtubule inhibitor, monomethyl auristatin E (MMAE). Glembatumumab vedotin works by binding to gpNMB, and upon internalization, releasing MMAE resulting in tumor cell death by microtubule inhibition [Bendell *et al.* 2014; Yardley *et al.* 2015].

The EMERGE study investigated the activity of glembatumumab vedotin in 124 patients with refractory breast cancer. The agent was overall well tolerated, with the most frequent treatment-related AEs consisting of rash, neutropenia, and neuropathy. In a subset analysis of the EMERGE trial, ORR was 30% (7/23) for glembatumumab *versus* 9% (1/11) for investigator's choice of treatment in tumors with gpNMB overexpression (defined as ⩾25% of tumor epithelium expressing gpNMB). ORR in the TNBC cohort was 18% (5/28) for those treated with glembatumumab and 0% (0/11) for patients treated with investigator's choice. Interestingly, in the small subset of TNBC patients whose tumors also overexpressed gpNMB, the ORR with glembatumumab was 40% (4 of 10) [Yardley *et al.* 2015]. A larger, randomized, phase II study (METRIC) has been initiated to confirm these findings and is ongoing. The METRIC study plans to randomize 300 women with gpNMB overexpressing metastatic TNBC to receive glembatumumab vedotin or capecitabine.

## Conclusion

TNBC is a heterogeneous disease for which the standard treatment remains cytotoxic chemotherapy. Advances in the field over the last few years have demonstrated that multiple TNBC subtypes exist. With this knowledge has come an explosion of targeted therapies in development for the different subsets of TNBC. The treatment of TNBC will continue to evolve as we identify actionable targets. As we develop novel agents aimed at these targets, it will be equally as important to identify biomarkers predictive of response to these therapies to fully realize the promise of precision medicine for TNBC.

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