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Recent therapeutic trends and promising targets in triple negative breast cancer

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ABSTRACT

Breast cancer accounts for 25% of all types of cancer in women, and triple negative breast cancer (TNBC) comprises around 15~20% of breast cancers. Conventional chemotherapy and radiation are the primary systemic therapeutic strategies; no other FDA-approved targeted therapies are yet available as for TNBC. TNBC is generally characterized by a poor prognosis and high rates of proliferation and metastases. Due to these aggressive features and lack of targeted therapies, numerous attempts have been made to discover viable molecular targets for TNBC. Massive cohort studies, clinical trials, and in-depth analyses have revealed diverse molecular alterations in TNBC; however, controversy exists as to whether many of these changes are beneficial or detrimental in caner progression. Here we review the complicated tumorigenic processes and discuss critical findings and therapeutic trends in TNBC with a focus on promising therapeutic approaches, the clinical trials currently underway, and potent experimental compounds under preclinical and evaluation.

Contents

1. Introduction

1.1. Histology of TNBC

The most prevalent cancer in women worldwide is breast cancer, which accounts for about 12% of all new cancer cases and 25% of all types of cancer in women (Ferlay et al., 2015). In the United States, breast cancer is the second leading cause of cancer death. Breast cancer can be categorized by histopathological type, grade, tumor stage, and the expression of receptor proteins and genes. These classification criteria are useful for establishing appropriate treatment strategies. There are four subtypes of breast cancer according to receptor status: luminal A (estrogen receptor (ER) positive, progesterone receptor (PR)

Abbreviation: TNBC, Triple negative breast cancer; BRCA, Breast Cancer gene; PARP, Poly ADP-ribose polymerase; TP53, Tumor protein p53; VEGF, Vascular endothelial growth factor; EGFR, Epidermal growth factor receptor; FGF, Fibroblast growth factor; PD1/PD-L1, Programmed cell death-receptor/ligand 1; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; AR, Androgen receptor; AMPK, AMP activated protein kinase; MTDH, Metadherin; MDM2, Mouse double minute 2 homolog; MTBP, Mdm2 binding protein; HSP90, Heat shock protein 90; ATR, Ataxia telangiectasia-mutated- and Rad3-related kinase; PLK1, Polo-like kinase 1; AurA, Aurora-Akinase; CHK1, Checkpoint kinase1; WEE1, Wee1-like protein kinase; CDC25, Cell division cycle 25c phosphatase.

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positive, and human epidermal receptor 2 (HER2) negative); luminal B (ER-positive and/or PR-positive, HER2-positive); HER2 overexpressing (ER-negative, PR-negative and HER2-positive); and triple negative (ER-negative, PR-negative, HER2 negative). Among these subtypes, triple negative breast cancer (TNBC), which accounts for about 15~20% of all breast cancer types, has no FDA-approved targeted therapies other than conventional chemotherapeutics and radiation therapy (Perou et al., 2000). The most important characteristics of TNBC are high proliferation and frequent metastasis to the lung and brain, unlike other types of breast cancers that metastasize mainly to bone and soft tissues (Dent et al., 2009). TNBCs are sub-grouped into seven classes: basal-like 1 (BL1), basal-like 2 (BL2), mesenchymal-like (M), mesenchymal stem-like (MSL), luminal androgen receptor (LAR), immunomodulatory (IM) and unstable (UNS) in accordance with gene expression profiling. This may correlate with therapeutic response to chemotherapeutics and radiotherapy (reviewed in (Kalimutho et al., 2015)). Given 1) high occurrence rate in young women (younger than 40 years), 2) absence of available targeted therapeutics, 3) low 5-year survival rate, 4) highest distant recurrence rate compared to other breast cancer subtypes, and 5) presentation of fetal metastatic diseases, which are accounted for major causes of death in breast cancer patients (Dent et al., 2009; Foulkes, Smith, & Reis-Filho, 2010), here we summarized the complicated metastasis process in TNBC and discuss about targets under clinical validation. Besides, this review also strived to introduce various experimental targets and potentially viable compounds that may have clinical application in future. We vigorously compared the diverse mode of action of each agent and how TNBC patients may benefit from them.

1.2. Influence of race and obesity on TNBC

Analysis of tumor genomic profiles, such as somatic mutations, genomic diversity, and gene expression using cancer genomic atlas (TCGA) data collected in 2010-2014 suggested a link between race and breast cancer recurrence: the incidence rate of TNBC was found to be almost three times higher in African-American patients than in white American patients. African-American patients had a higher risk of recurrence (10.6% vs. 4.6%) and TP53 gene mutations (42.9% vs. 27.6 %) than white American patients (Keenan et al., 2015). Among non-African-Americans, black women have been reported to suffer from a higher prevalence of TNBC than white women (Sachdev et al., 2010). Despite the high TNBC incidence in women of African ancestry or non-African-American black women, there has been controversy surrounding treatment and survival rates. Race was not a determinant of survival outcomes and failure patterns in studies of 448 non-Hispanic black and white American TNBC patients (Prasad et al., 2016) and 93 African-American and Caucasian American TNBC patients (Starlard-Davenport et al., 2013). TNBC patients at the MD Anderson Cancer Center who underwent conventional neo-adjuvant chemotherapy without any treatment disparities, showed similar clinical outcomes regardless of race (Dawood et al., 2009). However, there are several reports that African-American TNBC patients exhibited a worse survival than their white counterparts, even after adjusting for socioeconomic factors, delayed treatment, and tumor characteristics (Bauer, Brown, Cress, Parise, & Caggiano, 2007; Lund et al., 2009; Sachdev et al., 2010). Although the incidence of TNBC in African-American women is disproportionately high, there are no clear relationships between genetic differences and therapeutic outcomes or survival rates (Bauer et al., 2007; Dawood et al., 2009; Lund et al., 2009; Prasad et al., 2016; Starlard-Davenport et al., 2013). Therefore, much effort has been devoted to determining feasible targets for TNBC therapy through molecular characterization of TNBCs. In general, most of the attempts to demonstrate the characteristics of TNBC have relied on its biology. Interestingly, recent epidemiologic studies have shown that the microenvironment of the breast, especially obesity, can serve as an important key driving factor of TNBC. Typically, according to the Center for Disease Control and Prevention (CDC), women with body mass index (BMI) ≥ 30 kg/m^2 are classified as "obese" or "metabolically unhealthy." (CDC, 2019). The World Health Organization (WHO) defined women with a waist/hip ratio (WHR) higher than 0.85 as "abdominally obese" and reported high risk of various metabolic complications, including cancer, within this group (Mushtaq et al., 2011). According to diverse reports, the prevalence rates of TNBC and obesity are distinctively high in African-American women, suggesting the potential link between these two factors, as TNBC is more likely to develop in obese women (Bernstein, Teal, Joslyn, & Wilson, 2003; Carey et al., 2006; S.Y. Kim, Dietz, England, Morrow, & Callaghan, 2007; Vona-Davis et al., 2008). Thus, diverse studies such as Carolina Breast Cancer Study (stage 3, 2008 - 2014) (Millikan et al., 2008; Newman et al., 1995), Women's Contraceptive and Reproductive Experiences (CARE) Study (Berstad et al., 2010), Black Women's Health Study (BWHS) (Palmer, Adams-Campbell, Boggs, Wise, & Rosenberg, 2007; Rosenberg, Adams-Campbell, & Palmer, 1995), Women's Circle of Health Study (Ambrosone et al., 2009; McGee, Durham, Tse, & Millikan, 2013), and the African American Breast Cancer Epidemiology and Risk (AMBER) Consortium (Bandera et al., 2015; Kolonel et al., 2000; Palmer, Ambrosone, & Olshan, 2014) have been extensively conducted to explain the exact relationship of TNBC and obesity and how the obese state may contribute to the biology of TNBC. However, unfortunately, the results to date are considered rather complex and, at times, conflicting. The relationships are varied by race, ethnicity, and tumor subtype (Y.L. Liu, et al., 2018; Mamidi, Wu, & Tchounwou, 2018). When investigating the effect of obesity on TNBC, one of the biggest obstacles is that BMI and WHR (the general evaluation indices of obesity) are not sufficient as absolute markers to fully represent the metabolic health of individuals. There are other contributing risk factors than BMI and WHR, such as body composition and insulin sensitivity of peripheral muscle tissue, when assessing the influence of obesity on metabolic disorders (Dietze, Chavez, & Seewaldt, 2018). Several studies including AMBER Consortium have demonstrated that general and abdominal obesity can have different impacts on cancer depending on menopausal status (Bandera et al., 2015). The AMBER study concluded that there is substantial relevance of various mechanisms for the association of obesity with TNBC in African-American women. Therefore, when determining the biology of TNBC, it is necessary to comprehensively consider potential molecular mechanisms expected to be critically involved, along with anthropometric measurements. Recently, several studies have suggested possible mechanisms for the role of obesity in the initiation and progression of TNBC. The major findings involve: 1) Insulin-mediated activation of the PI3K/AKT/mTOR pathway preferably promoting glucose uptake and aerobic glycolysis in TNBC to increase the production rate of ATP and other metabolic precursors (Massihnia et al., 2016; Pelicano et al., 2014; Robey & Hay, 2009; Rose & Vona-Davis, 2012); 2) Activation of oncogenic signaling pathways such as STAT3, NF-κB, and EZH2/Wnt/β-catenin pathway through increased secretion of pro-inflammatory cytokines (IL-1β, IL-6, IL-8, IL-12, TNF-α, CCK2, and leptin) in obese adipose tissue (Creighton et al., 2009; Hartman et al., 2013; Paz-Filho, Mastronardi, Wong, & Licinio, 2012; Perez-Perez et al., 2017); and 3) Favorable microenvironment for cancer progression of increased epithelial growth factor (EGF) and tumor growth factor (TGFβ) through an alternative switch from tumoricidal M1 macrophage to tumorigenic M2 macrophage in cancer-associated adipocytes near breast tumor (Arendt et al., 2013; Colegio et al., 2014; DeNardo et al., 2011; Medrek, Ponten, Jirstrom, & Leandersson, 2012; Sica et al., 2008; Zeyda et al., 2007). All of the identified mechanisms eventually aggravate the malignant features of TNBC by accelerating mitochondrial dysfunction, proliferation, metastasis, invasion, and angiogenesis, which eventually lead to poor prognosis of patients. Since obesity can induce significant alterations in diverse cancer-related signaling pathways to promote tumor progression, biological measures are emphasized to be considered when evaluating the effect of obesity on TNBC, rather than simply measuring body shape. Therefore, in this review, we

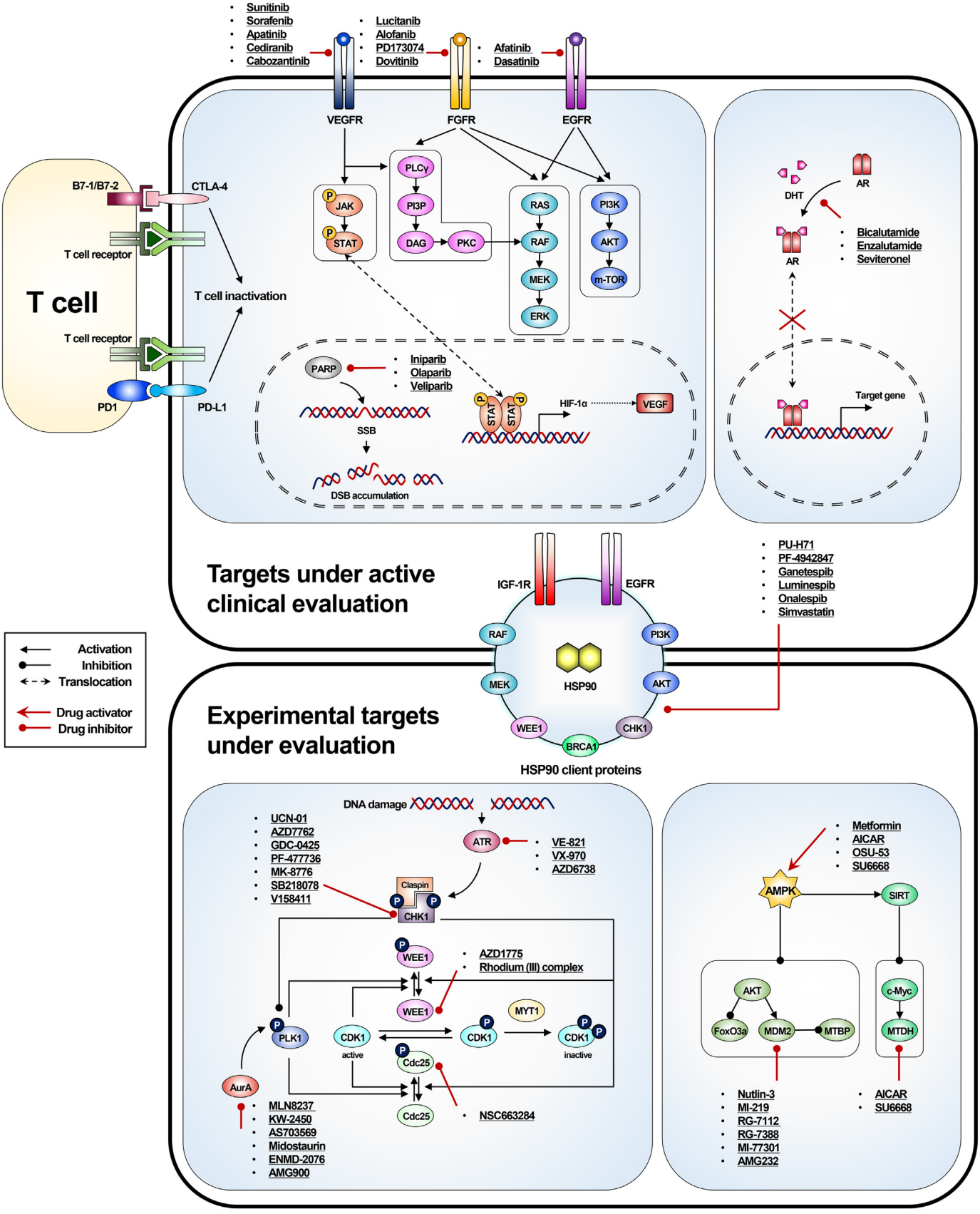


Fig. 1. Recent therapeutic trends and promising targets in triple negative breast cancer. Summary of TNBC-associated molecular targets and their small molecule inhibitors under active clinical (PARP, VEGF/VEGFR, EGF/EGFR, FGF/FGFR, AR, PD1/PD-L1 and CTLA-4) and preclinical evaluation (AMPK, MDM2/MTBP, MTDH, AurA, ATR, CHK1, WEE1, CDC25 and HSP90).

summarized the recent data on molecular targets associated with TNBC, regulators currently being investigated in clinical trials, and experimental drugs that have shown promising results in preclinical studies (Fig. 1).

2. Targets of TNBC under active clinical evaluation

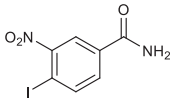
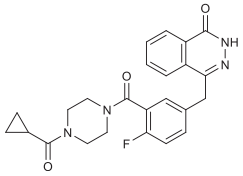
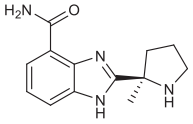
2.1. BRCA1/2 mutation and Poly ADP-ribose polymerase (PARP)

In the United States, about 12-24% of breast cancer patients are classified as TNBC and they are more likely to exhibit germline mutations of *BRCA1/2*. Seventy percent of breast tumors with inherited *BRCA1* mutations and 16~23% of *BRCA2* mutated breast cancers are TNBCs (Perou et al., 2000; Stevens, Vachon, & Couch, 2013). Likewise, *BRCA* mutations are quite common in TNBC (Caldecott, 2008; Farmer et al., 2005; Livraghi & Garber, 2015; Perou et al., 2000; Stevens et al., 2013). Although some TNBC patients respond well to neoadjuvant anthracycline plus taxane (e.g. docetaxel and paclitaxel) regimens, most of the breast cancers with *BRCA1* mutations have been demonstrated to be less susceptible to taxanes than non-TNBCs despite their high proliferation rate and incidence of *TP53* mutations, which are predictors of favorable therapeutic response to taxanes (Reis-Filho & Tutt, 2008). One of the key features of *BRCA1/2* mutant breast cancer cells is homologous recombination (HR) deficiency. Lack of *BRCA1* or *BRCA2* results in inefficient activation of the HR DNA repair pathway, inhibiting restoration of replication. Thus, to maintain DNA integrity, HR-deficient cells rely on PARP-dependent secondary DNA repair pathways such as base excision repair (BER), single strand break repair (SSBR), and non-homologous end-joining (NHEJ), consequently making PARP1 activity essential in HR-lacking *BRCA1/2* mutant tumor cells. PARP1, the most well-studied member of the 18-member PARP family in humans is initially activated in response to DNA damage. These proteins synthesize ADP-ribose polymers, which induce assembly of the DNA repair complex at the damaged site. PARP expression is high in both TNBC and breast cancer cells treated with chemotherapeutics. Higher PARP expression was associated with worse clinical outcomes in early stage breast cancer and TNBC according to a meta-analysis that investigated the association between PARP expression and clinicopathologic features of breast cancers, including TNBC (Burkle & Virag, 2013; Qiao, Pan, Kou, Li, & Yang, 2017). Numerous attempts have been made to inhibit PARP in *BRCA*-mutant and triple negative (TN) breast cancers generally based on the idea that lack of HR may synergistically promote the accumulation of unrepaired SSBs induced by PARP inhibition. This results in collapse of replication fork, eventually leading to cancer cell death. The cytotoxicity is amplified when unrepaired SSBs are later converted to double strand breaks (DSBs) (Helleday, 2011; Livraghi & Garber, 2015; Patel, Sarkaria, & Kaufmann, 2011). A PARP1-deficient mouse model clearly verified the role of PARP1 in promoting DNA repair after exposure to ionizing radiation and alkylating agents (Burkle & Virag, 2013; Caldecott, 2008; Livraghi & Garber, 2015; Qiao et al., 2017). PARP1 inhibition alone augmented cytotoxicity in HR-deficient tumor cells, *BRCA1*$^{-/-}$ or *BRCA2*$^{-/-}$ cells, and *BRCA2*-deficient cell-xenografted mice, but had little effect on *BRCA2*-complemented or *BRCA2* wild-type cells (H.E. Bryant et al., 2005; Farmer et al., 2005; Patel et al., 2011). While PARP1 knockout mice survived in a healthy state, simultaneous depletion of PARP1 and *BRCA*1 significantly reduced the clonogenic survival of human cells, but that of PARP2 and *BRCA*2 did not (H.E. Bryant et al., 2005; de Murcia et al., 1997). PARP inhibitor combination therapy improves the susceptibility of TNBC cells to DNA-damaging chemotherapeutics. Further investigation is needed to maximize the therapeutic efficacy of PARP inhibitors toward *BRCA*-mutant TNBC patients in combination with diverse chemotherapeutic agents. It is necessary to determine what kinds of drugs should be used in combination with PARP inhibitors, and how to sequence the drug combinations (Sonnenblick, de Azambuja, Azim Jr., & Piccart, 2015). Ongoing clinical trials of PARP inhibitors co-administered with chemotherapeutics to treat TNBC are summarized below (Table 1). Combination of iniparib (BSI-201), an irreversible PARP inhibitor, with gemcitabine and carboplatin has been reported to delay TNBC progression and improve OS in clinical phase II studies (X. Liu, et al., 2012; J. O'Shaughnessy et al., 2011), but no synergistic effect was observed in phase III trials (J. O'Shaughnessy et al., 2014). Combination treatment of TNBC with iniparib and paclitaxel showed no difference compared to paclitaxel alone in phase II trials (Llombart-Cussac et al., 2015). Olaparib is the first FDA-approved orally active PARP inhibitor and was used in 2018 to treat germline *BRCA*-mutated, metastatic, and HER2-negative breast cancer (Le & Gelmon, 2018). A total of 15 clinical trials of olaparib monotherapy and combination therapy for TNBC are currently underway (Table 1): olaparib in combination with programmed cell death-ligand 1 (PD-L1) inhibitors such as durvalumab and atezolizumab in TNBC and platinum-treated mTNBC (Roviello et al., 2016; Solinas et al., 2017).; olaparib in combination with cediranib (AZD2171), an orally bioavailable inhibitor of VEGFR-2 tyrosine kinase (Wedge et al., 2005).; olaparib in combination with orally bioavailable pan-PI3K inhibitors such as buparlisib (BKM120) and alpelisib (BYL719) in recurrent TNBC (Geuna et al., 2015; Teo et al., 2017).; and olaparib in combination with oral mTORC1/2 inhibitor (vistusertib/AZD2014) or AKT inhibitor (capivasertib/AZD5363) (X.-D. Ma, Qiu, Yang, He, & Hu, 2016; Ocana & Pandiella, 2017). A phase I clinical trial of fluzoparib (also known as SHR3162 and HS10160), a selective oral inhibitor of PARP1/2 together with apatinib, a selective VEGFR inhibitor which is also orally bioavailable, is currently in the recruiting phase (NCT03075462). Information about the structure and chemistry of fluzoparib is currently not available. Combination treatment with olaparib and various inhibitors of PD-L1, VEGFR, PI3K, and AKT may effectively inhibit the growth of rapidly proliferating TNBC cells by affecting their blood supply and blocking the molecules required for cell growth. Veliparib is a well-studied PARP inhibitor (To et al., 2014). However, veliparib failed to improve outcomes in phase III trials when used in combination with carboplatin and paclitaxel in patients with squamous NSCLC and TNBC (Loibl et al., 2018).

2.2. Vascular Endothelial Growth Factor Receptor (VEGF/VEGFR)

The highly proliferative and metastatic characteristics of TNBC are well-recognized to be dependent on constant new vessel formation (Elkashif, McCarthy, & Buckley, 2018). Vascular Endothelial Growth Factor (VEGF) plays a central role as an essential mediator in tumor vascularization; therefore, the signaling pathway of VEGF is considered important in the pathophysiology of TNBC (Tang, Feng, & Yao, 2009). The VEGF family is comprised of six members; A, B, C, D, E (viral factora), and placental growth factor. They intensively interact with VEGF receptors, such as VEGFR-1, VEGFR-2, and VEGFR-3, to execute their functions (Achen & Stacker, 1998). VEGF, mostly referring to VEGF-A, initiate the angiogenic process in human by principally binding to VEGFR-2, promoting survival, proliferation, migration, and adhesion of endothelial cells (Iosifidou et al., 2009; Yadav, Chanana, & Jhamb, 2015). The STAT1/HIF-1alpha/VEGF-A axis is generally reported to be responsible for this process (Davuluri, Schiemann, Plow, & Sossey-Alaoui, 2014; Xiang, et al., 2014). In the obese state, elevated inflammatory cytokines (e.g. IL-1β, IL-6, IL-8, IL-12, TNF-α, CCK2, and leptin) in adipocytes induce VEGF production to further stimulate angiogenesis (Esquivel-Velazquez et al., 2015). Infiltrating immune cells and cancer-associated macrophages accumulate in the obese adipose tissue residing in the tumor stroma and increase the levels of pro-angiogenic factors including VEGF (Lin & Pollard, 2007). Experimentally, obese mice showed a higher level of VEGF in the serum compared to nonobese mice (Miyazawa-Hoshimoto et al., 2005). Women with high BMI also showed an increased plasma level of VEGF, which decreased with weight loss (Miyoshi et al., 2003). Specifically, in an obese condition, VEGF- and FGF-induced angiogenesis can be synergistically promoted by increased leptin, which also plays a key role in regulation of vascular

Table 1
Structures and efficacy of PARP inhibitors currently under clinical evaluation for TNBC

Name	Structure	Potency and clinical implication	NCT number	Clinical trial identifier
Iniparib		- Also known as BSI-201 and SAR240550 - Discovered as a β-nicotinamide adenine dinucleotide (NAD(+)) noncompetitive PARP inhibitor but shows low specificity due to its ability to form adducts with many cysteine-containing proteins	NCT00813956 NCT01045304 NCT01130259 NCT00938652 NCT01204125 NCT01173497	- Delays TNBC progression and improves OS in completed clinical phase II studies in combination with gemcitabine and carboplatin - Showed no synergistic effects in a phase III trial - Competed phase II trial of combination of iniparib with paclitaxel for TNBC showed no difference compared to paclitaxel alone - Competed phase II trial of iniparib + irinotecan but results have not been reported
Olaparib		- Also known as AZD2281, LYNPARZA™, and Ku-0059436 - Selective inhibitor of PARP1/2 - In 2018, first FDA-approved orally active PARP inhibitor to treat germline *BRCA* mutated, metastatic, and HER2-negative breast cancer	NCT00679783 NCT03544125 NCT02484404 NCT03167619 NCT02681562 NCT02484404 NCT03330847 NCT03109080 NCT02849496 NCT03150576 (PARTNER) NCT02789332 NCT01116648 NCT02498613 NCT01623349 NCT02898207 NCT02208375	- Phase I/II study to explore the efficacy of olaparib alone or in combination with durvalumab (MEDI4736, human monoclonal antibody against PD-L1) in TNBC and platinum-treated mTNBC - Phase II study to explore the efficacy of olaparib or olaparib in combination with AZD6738 (inhibitor of Ataxia-Telangiectasia Mutated (ATM) and Rad3--related protein kinase) and AZD1775 (WEE1 inhibitor) in TNBC - Phase I study of olaparib with radiation therapy in mTNBC or operated TNBC with residual disease after chemotherapy - Phase II study of olaparib with atezolizumab (anti--PD-L1, MPDL3280A) in TNBC - Phase II/III study of olaparib with paclitaxel and carboplatin in TNBC and/or germline *BRCA* mutated breast cancer - Phase I/II study of olaparib with cediranib maleate (AZD2171, orally active inhibitor of VEGFR tyrosine kinase in recurrent TNBC - Phase I study of olaparib with PI3K inhibitor, BKM120 or BYL719 in recurrent TNBC - Phase I study of olaparib with onalespib (AT13387, orally bioavailable heat shock protein 90 inhibitor) in TNBC - Phase I/II study of olaparib with vistusertib (AZD2014, oral mTORC1/2 inhibitor) or capivasertib (AZD5363, oral AKT inhibitor) in TNBC
Veliparib		- An orally active PARP1/2 inhibitor also known as ABT888 and 912444-00-9 - Reported in 2017 that veliparib failed in two phase III trials of combination therapy with carboplatin and paclitaxel in patients with squamous NSCLC and TNBC	Six completed and six under evaluation clinical trial studies involving veliparib for TNBC NCT01306032 NCT00892736 NCT01251874 NCT01281150 NCT01104259 NCT02985658 NCT01145430 NCT02158507 NCT00576654 NCT02595905 NCT02032277	- Completed phase II study of veliparib in combination with cyclophosphamide to allow a lower dose and fewer cyclophosphamide side effects but similar efficacy compared to cyclophosphamide monotherapy - Completed phase I study of veliparib alone - Completed phase I study veliparib in combination with carboplatin - Completed phase I study of veliparib with cisplatin plus vinorelbine in breast cancers including TNBC - Completed phase I study of veliparib with cisplatin plus vinorelbine in breast cancers including TNBC - Completed phase I study of veliparib with pegylated liposomal doxorubicin HCl in breast cancers including TNBC - Pilot study of veliparib with lapatinib (a dual tyrosine kinase inhibitor of EGFR and HER2) in mTNBC - Phase I study to determine the side effects and best dose of veliparib when combined with irinotecan HCl - Phase II study to compare efficacy of veliparib plus cisplatin to that of cisplatin alone in mTNBC and *BRCA* mutated breast cancer - Phase III study of veliparib plus carboplatin or carboplatin alone in TNBC

permeability and fenestration response in adipose tissue (Cao, Brakenhielm, Wahlestedt, Thyberg, & Cao, 2001). VEGF also elevates the levels of anti-apoptotic proteins such as Bcl2, XIAP, and survivin to maintain tumor vascularization. Thus, where VEGF is absent, newly generated blood vessels eventually collapse due to apoptosis of endothelial cells (S.B. Fox & Harris, 2004; H.P. Gerber et al., 1998; Olsson, Dimberg, Kreuger, & Claesson-Welsh, 2006). Generally, intratumor and serum levels of VEGF are remarkably elevated in TNBC compared to non-TNBC (54.3% vs. 22.9%) (Bahhnassy et al., 2015; Chanana et al., 2014; Linderholm et al., 2009), and VEGFR expression is about two-fold higher in metastatic breast cancer than in non-metastatic cancer (Roberti et al., 2012; Taha et al., 2009). Typically, VEGF level exhibits positive correlation with microvascular density (MVD), and it has been reported that upregulated mean MVD is a direct contributor to the highly aggressive and invasive features of TNBC and its poor prognosis (El-Arab, Swellam, & El Mahdy, 2012). Recent studies have

demonstrated unfavorable relations of high VEGF level to tumor size, tumor grade, and lymph node positivity in association with worse PFS and OS of TNBC patients (Bahhnassy et al., 2015; Chanana et al., 2014; Taha et al., 2009; Yadav et al., 2015). According to a cohort study, TNBC patients with higher VEGFR level also exhibited shorter DFS/DDFS and OS; 96 out of 564 TNBC patients with high VEGFR2 expression level showed significantly low 5- and 10-year survival rates (Ryden et al., 2009; Rydén, Jirström, Haglund, Stål, & Fernö, 2010). Therefore, several clinical trials have investigated the therapeutic benefits of bevacizumab-based regimens of a humanized monoclonal antibody drug targeting VEGF-A in TNBC patients (J. Crown, O'Shaughnessy, & Gullo, 2012). There have been some conflicting results regarding the efficacy of such treatment: a meta-analysis including 621 TNBC patients from three different clinical trials (ECOG-E2100; NCT00028990, AVADO; NCT00333775 and RIBBON-1; NCT00262067), and the RIBBON-2 trial (NCT00281697) demonstrated significant PFS and ORR improvements through bevacizumab combination therapies (Carpenter, Kesselheim, & Joffe, 2011; J. O'Shaughnessy et al., 2010; Robert et al., 2011; Schneider et al., 2013). However, some other trials including the latest BEATRICE study failed to show therapeutic advantages of bevacizumab in an adjuvant setting (Bidard et al., 2010; Cameron et al., 2013). Studies involving neoadjuvant settings also showed contradictory results: pathological complete response (pCR) rate was significantly increased (27.9% to 39.3%) with the use of bevacizumab in addition to epirubicin plus cyclophosphamide and docetaxel (GeparQuinto trial); however, adding bevacizumab to paclitaxel plus doxorubicin and cyclophosphamide regimen was ineffective in TNBC patients (CALGB 40603 trial) (B. Gerber et al., 2013; Seano et al., 2015). The NSABP-B40 study also exhibited negative results in TNBC patients (Burstein et al., 2008). Meanwhile, use of the mTOR inhibitors temsirolimus or everolimus with liposomal doxorubicin and bevacizumab (DAT/DAE) showed significant improvements in ORR (Basho et al., 2018). Due to this inconsistency on the therapeutic benefit of bevacizumab, initial FDA approval on 2008 for the use of this drug in the metastatic condition had been reversed on 2010.

Along with the antibody drugs, diverse VEGFR TKIs are also under clinical evaluation as another therapeutic option for TNBC. Sorafenib, an orally bioavailable tyrosine kinase inhibitor, initially induced a significant improvement in the median PFS of prespecified TNBC patients when added to capecitabine (phase II SOLTI-0701 trial; 2.5 *vs.* 4.3 months); however, it failed to show similar benefits in the confirmatory study (phase III RESILIENCE trial; 5.5 *vs.* 5.4 months) (Baselga et al., 2009; Baselga et al., 2014; Gelmon et al., 2012). There were also attempts to evaluate its efficacy in combination with bevacizumab (BRE06-109), but the study was terminated due to high toxicity (L.A. Mina et al., 2013). There are also on-going studies regarding the combinatory effect of VEGFR TKIs with PARP inhibitors; phase I study evaluating the efficacy of cediranib (AZD2171) with olaparib showed no clinical benefits to date (Liu et al., 2013), and another phase I trial of apatinib together with fluzoparib is currently recruiting patients.

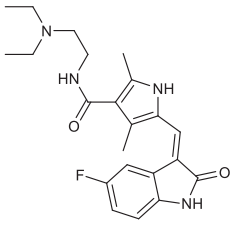
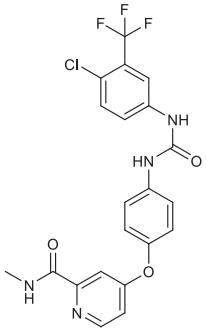
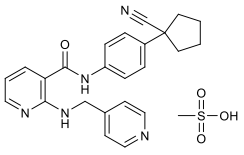
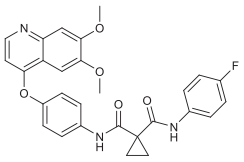
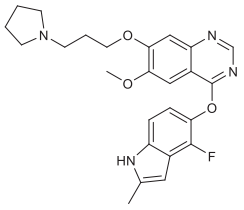
In addition to the approaches evaluating the combination effect of VEGFR TKIs, there are also trials investigating their therapeutic potential as a monotherapy. Apatinib alone has shown therapeutic benefits against metastatic TNBC (mTNBC), improving the PFS rate (X. Hu et al., 2014). Cabozantinib (XL184), a MET and VEGFR-2 inhibitor that significantly inhibited the growth and invasion of TNBC in preclinical models (Sameni et al., 2016), as a monotherapy, did not meet the primary endpoint (objective response rate) but did exhibit a clinical benefit rate of 34% and a median PFS of 2 months (S.M. Tolaney et al., 2017). A multi-center phase II trial of sunitinib (SU011248) monotherapy showed significant activity in mTNBC patients (15% RR; 3/20 patients); however, the follow up phase III trial of sunitinib and capecitabine combination therapy (NCT00435409) did not exhibit benefits in PFS of TNBC patients (Burstein et al., 2008; J.P. Crown et al., 2013). A phase I/II trial on locally advanced TNBC patients administered sunitinib in a neoadjuvant setting with paclitaxel and carboplatin (NCT00887575) has also failed to show benefits and is not recommended for further evaluations (Yardley et al., 2015). Sunitinib is also reported to inhibit platelet-derived growth factor receptor (PDGFR), c-Kit, and colony-stimulating factor 1 receptor (CSF-1R), which are strong regulatory factors of the vascular mimicry process (Gluz et al., 2009; Luan, Liu, Zhong, Yao, & Yu, 2015). TNBC generally possesses a unique ability of vascular mimicry in *in vitro* and *in vivo* xenograft models along with human samples. Vascular mimicry is usually responsible for blood lacunae formation around tumor cells and naturally serves as a negative predictor of prognosis. Blood lacunae are reported to be responsible for regrowth of TNBC after termination of sunitinib administration (D. Zhang et al., 2014). The mentioned compounds and related trials are well organized in Table 2.

Conflicting results regarding the efficacy of anti-VEGF therapies have demonstrated possible mechanisms of diverse intrinsic and acquired refractoriness to anti-VEGF inhibitors. Generally, tumor cells aggressively uptake various VEGF-substitutable pro-angiogenic factors that are alternatively secreted by stromal and bone-marrow-derived cells to avoid the anti-angiogenic activities of the drugs and maintain their vascularization process (Loges, Schmidt, & Carmeliet, 2010; Relf et al., 1997; Yoshiji, Harris, & Thorgeirsson, 1997). One of the recently reported mechanisms suggested obesity as an important resistance-inducing factor of anti-VEGF agents, since multiple inflammatory and pro-angiogenic factors are elevated under an obese condition. A phase II clinical study on a neoadjuvant setting of bevacizumab has revealed that women in an obese state (BMI ≥ 25 kg/m^2) tended to exhibit more profound hypoxia in the tumor, along with higher serum concentrations of IL-6 and FGF-2. Interestingly, IL-6 production was significantly elevated in the obese mouse model of ER+ breast cancer. However, in an obese TNBC mouse model, FGF-2 was upregulated rather than IL-6 and played a key role in impaired drug efficacy of VEGF inhibitor. FGF2 expression mostly occurred in adipocytes of the tumor periphery and activated cancer-associated fibroblasts. Metformin-mediated downregulation of FGF2 expression resensitized the efficacy to anti-VEGF agents by attenuating the AKT, MAPK, and STAT3 signaling pathways (Incio et al., 2018). As stated in this paper, different breast cancer subtypes can be engaged into separate microenvironmental conditions that induce anti-VEGF resistance. Thus, efforts to develop alternative strategies to overcome this therapeutic limitation should focus on tailored regulation of abnormal tumor microenvironment to a normal state based on specific understanding of the ample crosstalk between cancer biology and the microenvironment.

2.3. Epidermal Growth Factor Receptor (EGF/EGFR)

Although the mechanism of EGFR overexpression in TNBC has not been completely defined, many studies have demonstrated a correlation between TNBC and EGFR expression. About 36% to 89% of TNBC patients express EGFR (Changavi, Shashikala, & Ramji, 2015; D. Liu, et al., 2012; Nakai, Hung, & Yamaguchi, 2016; Park et al., 2014). EGFR protein overexpression in TNBC is proportional only to high *EGFR* gene copy number, not *EGFR* mutation (Park et al., 2014). Unlike the frequent mutations of *EGFR* in non-small cell lung cancer (NSCLC), a recent study revealed that *EGFR* mutations are rare in TNBC patients (A. Kim, Jang, Lee, & Bae, 2017; Lynch et al., 2004). EGFR overexpression frequently takes place in *BRCA1*-associated breast cancers, of which 75% have been identified as TNBCs. EGFR-overexpressing TNBCs are widely considered as basal-like high-grade carcinomas *BRCA*1 binds to the miR-146a promoter, leading to an increase in transcriptional levels of miR-146a. miR-146a binds to the 3′UTR of *EGFR* to promote its mRNA degradation. *BRCA*1 and miR-146a deficiency leads to an increase in EGFR and p-EGFR (Y1068) expression, which may partially explain the mechanism of EGFR overexpression in TNBC (Kumaraswamy et al., 2015; Nakai et al., 2016). This EGFR overexpression is negatively associated with the disease-free survival of TNBC patients (Changavi et al., 2015; D. Liu, et al., 2012; Nakai et al., 2016; Park et al., 2014). For the reasons described above, EGFR has emerged as an important therapeutic target in TNBC.

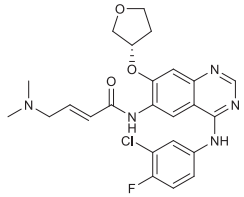
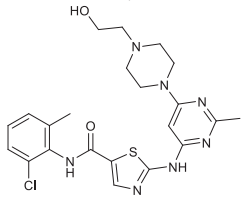
Table 2
Structures and efficacy of VEGF/VEGFR inhibitors (TKI) currently under clinical evaluation for TNBC

Name	Structure	Potency and clinical implication	NCT number	Clinical trial identifier
Sunitinib (Sutent®)		- Orally bioavailable multi-TKI targeting KIT, FLT3, RET, VEGFR2, and PDGFRB - Also known as SU011248 - Significantly inhibits the proliferation, invasion, and apoptosis resistance in TNBC cell lines and *in vivo* xenograft mouse model - Inhibits platelet-derived growth factor receptor (PDGFR), c-Kit and colony-stimulating factor 1 receptor (CSF-1R), strongly suppressing vascular mimicry	NCT00078000	- Multi-center phase II trial of sunitinib (SU011248) monotherapy showed significant activity against mTNBC patients (15% RR)
			NCT00887575	- Phase I/II trial on locally advanced TNBC patients administering sunitinib in a neoadjuvant setting with paclitaxel and carboplatin failed to show clinical benefits
			NCT00435409	- Follow up phase III trial of sunitinib and capecitabine combination therapy did not exhibit benefit in PFS of TNBC patients
			NCT00246571	- Clinically not effective as monotherapy in randomized phase II study comparing the efficacy with single-agent
Sorafenib		- Orally bioavailable multi-TKI targeting VEGFR1/2/3, PDGFRB, RAF, KIT, and FLT-3	NCT01194869	- Phase II Neoadjuvant Trial of Sorafenib in Combination with Cisplatin Followed by Dose Dense Paclitaxel for ER-, PR-, Her2- (Triple Negative) Early-Stage Breast Cancer
			NCT02624700	- Phase II Study of Pemetrexed and Sorafenib for Treatment of Recurrent or Metastatic Triple Negative Breast Cancer
			SOLTI-0701	- Significant improvement in the median PFS (2.5 vs. 4.3 months) of prespecified TNBC patients when added to capecitabine
			NCT01234337	- Failed to show similar benefits in the phase III confirmatory study with the PFS of 5.5 vs. 5.4 months (RESILIENCE trial)
			NCT00493636	- There were also attempts to evaluate its efficacy in combination with bevacizumab (BRE06-109) but was terminated due to the high toxicity.
Apatinib		- Orally bioavailable, highly potent tyrosine--kinase inhibitor targeting VEGFR2 - significant anti-tumor effect of apatinib + CPT-11 (irinotecan) + S-1 (tegafur) regimen against brain metastasis in TNBC patient	NCT01176669	- Phase II study of apatinib as monotherapy on heavily pretreated patients with metastatic triple-negative breast cancer (mTNBC) showed clinical benefit: ORR of 10.7%; CBR of 25.0%; PFS 3.3 month; OS 10.6 month
			NCT03075462	- Phase I open, non-randomized, multi-center study to assess the safety and efficacy of Fluzoparib given in combination with apatinib in TNBC patients: recruiting
			NCT03394287	- Phase II study on apatinib plus SHR-1210 (PD-1 antibody drug) in advanced TNBC patients: recruiting
			NCT03348098	- Phase II study of neoadjuvant therapy with apatinib and paclitaxel in locally advanced TNBC: recruiting
			NCT03254654	- Phase II randomized study of vinorelbine plus apatinib versus vinorelbine in advanced TNBC as a second- or third-line therapy: recruiting
			NCT03650738	- Phase II open clinical study of apatinib plus albumin paclitaxel and carboplatin regimen in neoadjuvant setting for TNBC: recruiting
			NCT03243838	- Phase I/II study on low-dose apatinib with neoadjuvant chemotherapy in the treatment of early TNBC (LANCET): yet recruiting
Cabozantinib		- MET and VEGFR2 inhibitor also known as XL184 - Significantly inhibited the growth of MET--positive TNBC cell lines in their 3D culture model and also *in vivo* xenograft model - No anti-cancer effects against MET-negative TNBC cells	NCT01738438	- Phase II study of cabozantinib for metastatic TNBC (mTNBC) as a monotherapy: clinical benefit rate of 34% and a median PFS of 2.0 months
			NCT03316586	- Phase II study of cabozantinib plus nivolumab combination therapy on metastatic TNBC (mTNBC): recruiting
			NCT03170960	- Phase Ib study of cabozantinib plus atezolizumab combination regimen against inoperable locally advanced or metastatic TNBC: recruiting
Cediranib (AZD2171)		- Oral VEGRF1/2/3 inhibitor (pan-VEGFR) - Inhibits the VEGF-A-mediated VEGFR1 Y1048 and Y1053 phosphorylation in AG1-G1-Flt1 (human angioma cell)	NCT01116648	- Phase I/II study of olaparib + cediranib on TNBC: no clinical benefit
			NCT02498613	- Another Phase II trial of olaparib + cediranib on TNBC: recruiting
			NCT02484404	- Phase I/II study on the efficacy of durvalumab (MEDI4736; anti-PDL1 drug) plus cediranib regimen: recruiting

Anti-EGFR-targeted therapies, such as small molecular tyrosine kinase inhibitors (TKIs) and monoclonal antibodies (mAbs), either alone or in combination with conventional chemotherapies, have been used to treat TNBC (Corkery, Crown, Clynes, & O'Donovan, 2009; Nakai et al., 2016).

However, some clinical trials of EGFR inhibitors in patients with TNBC have reported poor response rates and a high incidence of recurrence. A large subset of TNBC patients who did not respond to this therapy eventually developed untreatable metastatic disease. Although anti-EGFR-targeted therapies have been used clinically for the

Table 3
Structures and efficacy of EGFR inhibitors currently under clinical trial evaluation for TNBC

Name	Structure	Potency and clinical implication	NCT number	Clinical trial identifier
Afatinib (Gilotrif®)		- Pan-HER tyrosine kinase inhibitor (TKI) - Used for the treatment of non-small cell lung cancer (NSCLC) with mutations in the *EGFR* gene	NCT02511847	- Currently under phase II study to evaluate the efficacy of the combination of afatinib and weekly paclitaxel for patients with TNBC - This is the only clinical trial for TNBC patients, although afatinib has been studied in numerous clinical trials
Dasatinib (Sprycel®)		- Pan-Src tyrosine kinase inhibitor - Prevents nuclear translocation of EGFR and sensitizes TNBC cells to cetuximab - Inhibits c-Src phosphorylation (p-c-Rrc-Y419) induced by the interaction between syndecan--binding protein (SDCBP) and c-Src and inhibits proliferation of TNBC cells	NCT02720185 NCT00371254	- Under phase II study to evaluate efficacy and safety in nuclear EGFR positive TNBC - Phase II of dasatinib monotherapy for patients with metastatic TNBC (mTNBC) completed. The efficacy of dasatinib monotherapy is limited in TNBC

treatment of NSCLC and colorectal cancer (CRC), none have yet been approved for the treatment of TNBC. Several EGFR inhibitors are currently in clinical trials as listed on the U.S. National Institutes of Health (NIH) website www.clinicaltrials.gov (Table 3). Afatinib is a tyrosine kinase inhibitor that forms an irreversible covalent bond to cysteine residues of both EGFR and HER2 (D. Li, et al., 2008). Afatinib alone may be active in TNBC, but co-administration of afatinib with dasatinib may exert a synergistic antiproliferative effect through efficient inhibition of both ERK and Akt signaling (Canonici et al., 2016). Dasatinib, an inhibitor of Src family kinases, inhibits c-Src phosphorylation (p-c-Rrc-Y419) induced by the interaction between syndecan-binding protein (SDCBP) and c-Src. Expression levels of SDCBP in TNBC patient tissues are consistent with the level of p-c-src-Y419 and are positively correlated with the histologic grade of the tumors. Dasatinib inhibits proliferation and cell cycle progression of TNBC cells, both of which are accelerated by SDCBP overexpression (Qian et al., 2017). Dasatinib also prevents nuclear translocation of EGFR in nuclear EGFR-positive TNBCs, eventually sensitizing TNBC cells to cetuximab, an EGFR-targeting mAb drug (Brand et al., 2014). There are ongoing clinical investigations on the therapeutic improvement of mTNBC patients through co-administration of cetuximab with ixabepilone, a microtubule-targeted drug, and MM-121 (seribantumab), an ErbB3 mAb, on mTNBC (Lopus et al., 2015; Schoeberl et al., 2010; Tredan et al., 2015); Lapatinib, gefitinib, and erlotinib act as EGFR TKIs by binding to the ATP-binding site of EGFR and their antitumor efficacy in EGFR-positive TNBC patients is under clinical investigation (Kobayashi & Hagiwara, 2013; Lynch et al., 2004; Wood et al., 2004); Studies are also underway to test the clinical anticancer effects of inhibiting EGFR downstream signaling molecules such as PI3K, MEK1/2, and Akt with various combinations of PI3K, MEK1/2, and/or Akt inhibitors. Furthermore, a variety of techniques have been developed to efficiently reduce EGFR expression in TNBCs. EGFR-targeted small interfering RNA (siEGFR) transfection via cell-penetrating peptide (CPP)-loaded nanobubbles significantly reduced mRNA and protein expression of EGFR in TNBC cells, overall inhibiting the growth of TNBC xenograft tumors (Jing et al., 2016). Unimolecular micelle nanoparticles containing a strong TNBC cell growth inhibitor, aminoflavone, showed enhanced cellular uptake and strong growth inhibitory effects in TNBC cells when conjugated with GE11, a 12-amino acid peptide targeting EGFR. These nanoparticles also displayed *in vivo* growth inhibitory effects in an orthotopic TNBC xenograft model (Brinkman et al., 2016).

2.4. Fibroblast Growth Factor Receptor (FGF/FGFR)

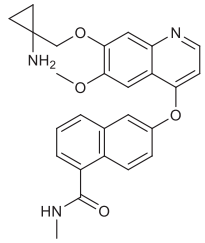
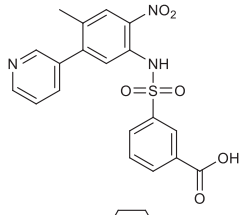
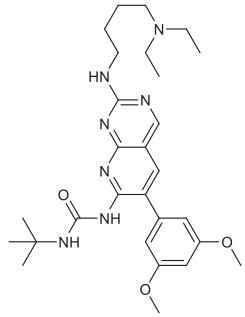
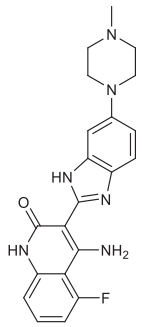
Like other receptor tyrosine kinase (RTK) targets, such as EGF and VEGF, fibroblast growth factor (FGF) has also been studied as a therapeutic target for TNBC patients (S. Wang & Ding, 2017). The FGF family consists of 22 subtypes with structural similarity (Eswarakumar, Lax, & Schlessinger, 2005). They regulate essential cellular processes such as survival, proliferation, migration, differentiation, and metabolism by interacting with four different membrane-bound tyrosine kinase FGF receptors (FGFRs) (Boilly, Vercoutter-Edouart, Hondermarck, Nurcombe, & Le Bourhis, 2000; N. Turner & Grose, 2010). Generally, they initiate the activation of intracellular MAPK, AKT, and STAT signaling pathways, which are mainly involved in the cellular proliferation and survival process (Beenken & Mohammadi, 2009; Boilly et al., 2000; Eswarakumar et al., 2005; Furdui, Lew, Schlessinger, & Anderson, 2006; Muller, Meyer, & Werner, 2012; Turner & Grose, 2010). A subset of TNBC patients is reported to carry gene amplification of *FGFR1* and/or *FGFR2* along with protein overexpression of FGFR1, FGFR2, and FGF2 (H.J. Lee et al., 2014; N. Turner et al., 2010). Particularly, the expression of FGFR1 has been analyzed to be an independent prognostic marker for the overall survival of TNBC patients. Specific knockdown of FGFR1 in several TNBC cell lines with elevated level of FGFR1 significantly suppressed cell migration, partially supporting the therapeutic potential of targeting FGF/FGFR in TNBC patients (C.L. Cheng et al., 2015; N. Turner et al., 2010). FGFs are generally bound to the cell membrane matrix; however, a small proportion of FGFs is released as a soluble form to serve as an autocrine regulator (D'Amore, 1990). The conventionally (e.g., FGF1) and unconventionally (e.g., FGF2) secreted FGFs respectively interact with FGFR3 and FGFR1 on the tumor to facilitate a cancer-associated fibroblast (CAF)-mediated enhancement of tumor cell invasion. CAFs, the activated form of fibroblasts in tumor stroma, intensively secrete growth factors, such as TGFβ and FGF, stimulating tumorigenesis and metastasis of cancer cells along with microenvironmental events such as extracellular matrix (ECM) remodeling, epithelial to mesenchymal transition (EMT), and angiogenesis (Erdogan & Webb, 2017; Kalluri & Zeisberg, 2006; Luo, Tu, Liu, & Liu, 2015). Recent analysis has revealed that TNBCs exhibit a significantly higher expression level of CAF-related proteins than the luminal types (J.H. Lee, Kim, & Koo, 2018). There are *in vitro* and *in vivo* studies demonstrating how the CAF-induced FGF/FGFR signaling directly contributes to the aggressiveness of TNBC, providing a basis for targeting FGF/FGFR in TNBC. CAF activation upregulates FGF5 secretion and collagen deposition, increasing the level of cancer stem cells (CSCs) directly associated with the highly metastatic and chemoresistant features of TNBC (Cazet et al., 2018; Hui et al., 2018). *In vitro* studies on the inhibition of FGF/FGFR signaling in 4T1 (murine TNBC cell line) using dovitinib (TKI258); an FGFR, VEGFR, and PDGFR inhibitor (Dey et al., 2010); and MDA-MB-231 (human TNBC cell line) with FGF2-neutralizing antibody (Suh, Kim, & Surh, 2016) have revealed significant reduction in the downstream mediators of FGFR, including phospho-fibroblast growth factor receptor substrate 2 (p-FRS2), phospho-AKT (p-AKT), and particularly matrix metalloprotease-9 (MMP9), which plays

an essential role in the metastasis and angiogenesis of TNBC. Significant attenuation of PI3K/AKT signaling induces downregulation of cyclin D1, which leads to a strong anti-proliferative effect via G1 arrest. All of these anti-tumor effects were confirmed in a mouse TNBC xenograft model (Dey et al., 2010). There have been several efforts to evaluate FGFR-targeting inhibitors against TNBCs. To date, a phase II clinical trial of lucitanib (E-3810), an FGFR1-3 and VEGFR1-3 inhibitor (NCT02202746), is the only FGFR-regarding study conducted on metastatic TNBC patients. The clinical trial has recently been completed (September 2018), but the final results have not been announced. Preclinical studies of lucitanib plus paclitaxel combination showed significant tumor regression in advanced-stage TNBC xenograft mouse models (Bello et al., 2013; Neophytou, Boutsikos, & Papageorgis, 2018), supporting the idea of targeting FGF in TNBC. FGFR signaling was also evaluated to be responsible for the elevation of drug-resistant CSC induced by PI3K/mTOR inhibition; thus, it has been suggested that co-administering lucitanib with mTOR inhibitors may serve as another promising option for TNBC treatment (Bhola et al., 2016). Although FGFR inhibitors are not actively assessed in clinical practice, there are many preclinical studies providing insights into targeting FGF in TNBCs. In *in vivo* and *in vitro* studies, treatment with alofanib (RPT835), a pan-FGFR inhibitor, inhibited cancer proliferation and migration of TNBC cell lines and patient-derived xenograft models (Tsimafeyeu et al., 2016), and PD173074, a pan-FGFR inhibitor, showed anti-cancer effects against *FGFR*-amplified TNBC cell lines (Ye et al., 2014). Several preclinical studies have demonstrated that PD173074 suppressed the growth of TNBC cells in *in vitro* and *in vivo* (Sharpe et al., 2011;N. Turner et al., 2010); moreover, dovitinib (TKI258), an FGFR, VEGFR, PDGFR inhibitor, showed potent anti-cancer effects on FGFR1 amplified advanced breast cancer (André et al., 2013; Perez-Garcia, Munoz-Couselo, Soberino, Racca, & Cortes, 2018). This was under clinical evaluation with fulvestrant against HER2- metastatic breast cancer; however, the study was terminated due to low effectiveness (NCT01528345) (Andre et al., 2013; Sobhani et al., 2018). Another trial testing aromatase inhibitor for metastatic breast cancer (NCT01484041) has also been terminated; to date, only one trial for metastatic inflammatory breast cancer is still active (NCT01262027) (S. Wang & Ding, 2017). The mentioned compounds and related trials are well listed in Table 4.

2.5. Androgen receptor (AR)

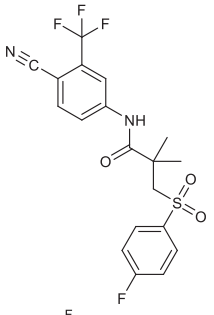
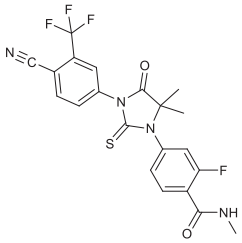
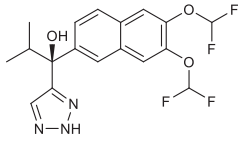
AR is a member of the nuclear steroid hormone receptor family, which includes the ER and PR. ER and PR are considered important

Table 4
Structures of small molecular FGFR inhibitors currently under evaluation for TNBC

Name	Structure	Potency and clinical implication	NCT number	Clinical trial identifier
Lucitanib (E-3810)		- FGFR1/2/3, VEGFR1/2/3, and CSF-1 oral inhibitor - Could be co-administered with 5-fluorouracil, cisplatin, and paclitaxel with a good safety profile - Lucitanib plus paclitaxel regimen induced superior tumor regression in advanced-stage TNBC xenograft mouse models - Lucitanib plus paclitaxel combination also reduces the levels of MMPs and tumor collagen IV - Implicated as a countermeasure of mTOR inhibition-mediated upregulation of CSCs	NCT02202746	- Phase II study of oral lucitanib in FGF aberrant mTNBC regarding its safety and efficacy - This trial has recently been completed (September 2018), but the final results have not been announced.
Alofanib (RPT835)		- Oral pan-FGFR inhibitor - Binds to extracellular domain of FGFR2 and inhibits phosphorylation of FRS2α - Shows FGFR level-dependent inhibitory activity against cell and tumor growth; FGFR2 with high expression of SUM 52PE (IC_{50}=16 nM) and low expression of HS578T (IC_{50}=0.21 μM)		
PD173074		- Oral pan-FGFR inhibitor - Showed anti-cancer effect against FGFR-amplified basal-like TNBC cell lines - Highly sensitive in anchorage-independent growth conditions - Induces cell cycle arrest and apoptosis by attenuating the MAPK and AKT signaling pathways - Significantly reduces tumor growth in an *in vivo* xenograft model - Decreases the myeloid-derived suppressor cells (MDSCs) in blood, spleen, and tumor, enhancing the infiltration rate of $CD4^+/CD8^+$ lymphocytes		
Dovitinib (TKI258)		- FGFR, VEGFR, PDGFR inhibitor - Showed potent anti-cancer effect on FGFR1 amplified advanced breast cancer. - Decreases FRS2 phosphorylation and suppresses the activity of ERK1/2, PLCγ, and AKT pathways, inducing apoptosis *in vitro* - Inhibited tumor growth and lung metastasis in an *in vivo* mouse xenograft model accompanied by downregulation of MMP9	NCT01528345 NCT01484041 NCT01262027	- Phase II trial of dovitinb with fulvestrant in $HER2^-/HR^+$ postmenopausal breast cancer patients that have evidence of disease progression on or after prior endocrine therapy: terminated due to low effectiveness - Phase I/II trial of TKI258 in combination with an aromatase inhibitor in mBC patients: terminated - Phase II study of TKI258 as salvage therapy in stage IV HER2-negative inflammatory breast cancer (IBC) and local or distant relapse patients: active - No clinical trials for TNBC

prognostic and predictive biomarkers in breast cancers. AR-positive breast cancers are most likely to be diagnosed as ER-positive, PR-positive, and HER2-negative. They are typically characterized by small tumor size, low histological grade and stage, and greater response to hormonal therapy than chemotherapy (R. Hu et al., 2011). Although the AR is an important component of the steroid hormone receptor, little is known about its biological roles in TNBC. AR expression is observed in 25% to 75% of TNBCs, and its expression level is highest in the luminal androgen receptor (LAR) subtype of TNBC (Rampurwala, Wisinski, & O'Regan, 2016; Zuo, Wilson, Cicek, & Harigopal, 2018). As reported by Rampurwala *et al.,* many studies have demonstrated a relationship between AR expression and the clinical prognosis of TNBC, but there are still many conflicting results (Rampurwala et al., 2016). This section highlights recent ongoing studies regarding diverse perspectives on the role of AR in TNBC. Multiple reports have suggested that positivity for AR expression is associated with increased mortality rate in ER-negative breast cancer and TNBC patients, while it serves as a favorable prognostic factor associated with 30% reduced mortality in ER-positive breast cancer patients (R. Hu et al., 2011). There are also several studies that have demonstrated AR expression in TNBC as an advantageous prognostic factor associated with lower mitotic rate, better overall survival, and disease-free survival compared to AR-negative TNBCs (X.Q. Hu, Chen, Ma, & Jiang, 2017; Zuo et al., 2018). Conversely, there are also conflicting results insisting that distant metastatic disease is more likely to develop in patients with AR-positive TNBCs with lower intratumoral expression of AR (Sutton et al., 2012). When AR expression is coupled with mutation of *PIK3CA* mainly in the kinase domain, the expression level of AR serves as an unfavorable prognostic predictor in TNBC. TNBCs with mutated *PIK3CA* were shown to express higher levels of the AR than TNBCs with wild-type *PIK3CA*. Since both *PIK3CA* mutation alone and *PIK3CA* mutation with AR positivity have been proven to be negative prognostic factors for TNBC, AR-positive patients with *PIK3CA* mutation may significantly benefit from AR inhibition (Gonzalez-Angulo et al., 2009). Despite the discrepancies regarding the relationship between AR expression and the clinical features of TNBC, it has recently been suggested that blocking the AR pathway may be a promising method to treat metastatic AR-positive TNBC patients, because the recurrence rate of these patients was greater than 22.5% within 5 years in cases when they were only applied to conventional chemotherapeutic agents (Arce-Salinas, Riesco-Martinez, Hanna, Bedard, & Warner, 2016; Doane et al., 2006; Gucalp et al., 2013; B.D. Lehmann et al., 2011; A. Mina, Yoder, & Sharma, 2017; Proverbs-Singh, Feldman, Morris, Autio, & Traina, 2015; Rampurwala et al., 2016; T.A. Traina et al., 2018; T.A. Traina et al., 2015). Three nonsteroidal antiandrogen drugs, namely bicalutamide, enzalutamide, and seviteronel are in clinical trials as monotherapy or in combination with CDK4/6 inhibitors listed in Table 5 (Arce-Salinas et al., 2016; Bardia et al., 2018; Gucalp et al., 2013; Gucalp & Traina, 2017; B.D. Lehmann et al., 2011; Traina et al., 2018; T.A. Traina et al., 2015). Bicalutamide and enzalutamide are orally active androgen antagonists which androgen-competitively bind to the cytosolic AR to inhibit AR nuclear translocation, AR cofactor recruitment, and AR binding to androgen response elements on DNA (Arce-Salinas et al., 2016; Gucalp et al., 2013; B.D. Lehmann et al., 2011; Rampurwala et al., 2016; T.A. Traina et al., 2015). Seviteronel is an orally active inhibitor of androgen biosynthesis by inhibiting lyase-selective CYP17, which is the major rate-limiting enzyme in the androgen biosynthesis pathway (Bardia et al., 2018; Rafferty, Eisner, Moore, Schotzinger, & Hoekstra, 2014). Due to the inherently high proliferation rate of TNBCs, several CDK4/6 inhibitors such as palbociclib (NCT02605486) and ribociclib (NCT03090165) in combination with the AR antagonist bicalutamide are being investigated in clinical trials. Whether AR-targeted therapy is an effective target treatment strategy for patients with AR-expressing TNBCs will soon become apparent depending on the results of the currently active clinical trials.

Table 5
Structures and efficacy of AR inhibitors currently under clinical evaluation for TNBC

Name	Structure	Potency and clinical implication	NCT number	Clinical trial identifier
Bicalutamide (Casodex®)		- First FDA-approved orally active, androgen antagonist for treatment of advanced prostate cancer - Binds to cytosolic ARs and competitively inhibits the mode of action of the AR - Provides palliative benefit for TNBC patients - Has a more effective therapeutic effect on the LAR subtype of TNBC in *in vitro* assays	NCT03055312 NCT03090165 NCT02605486 NCT02348281	- Phase III study to compare the efficacy of bicalutamide with conventional chemotherapy as a first-line treatment for AR positive mTNBC - Phase II study of bicalutamide in combination with ribociclib orally available inhibitors of CDK4/6 for treatment of advanced AR positive TNBC - Phase II study of bicalutamide in combination with palbociclib, orally available inhibitors of CDK4/6 for treatment of advanced AR positive TNBC - Phase II completed to assess the efficacy and safety of bicalutamide for treatment of AR positive mTNBC
Enzalutamide (Xtandi®)		- Second-generation nonsteroidal antiandrogen showing 5-fold greater binding affinity to cytosolic AR than bicalutamide	NCT01889238 NCT02750358 NCT02457910 NCT02689247 NCT02457910	- Phase I/II study of enzalutamide for treatment of advanced AR positive TNBC - Phase II study of enzalutamide in combination with paclitaxel in TNBC - Phase I/II study of enzalutamide in combination with taselisib, PIK3CA inhibitor, in AR positive TNBC
Seviteronel		- Also named VT-464 and INO464 - Nonsteroidal antiandrogen that inhibits androgen biosynthesis by selectively inhibiting cytochrome P450c17a (CYP17) 17,20-lyase (lyase) - First approved for the treatment of castration-resistant prostate cancer in 2016 and then received fast-track designation for breast cancer in 2017	NCT02580448	- Under phase I/II studies to determine safety, pharmacokinetics, pharmacodynamics, efficacy, and activity of seviteronel in patients with advanced breast cancers including TNBC

2.6. Immunotherapy: PD1/PD-L1 and CTLA-4

Immunotherapy has recently emerged as a promising new therapeutic approach for TNBC. Among the reported immunotherapeutic targets, programmed cell death (PD1) receptor and its ligand PD-L1 are the two most frequently identified markers; together, they serve as an immune checkpoint, negatively regulating the activation of T cells (Isha Dua, 2017). PD-L1 expression, which significantly promotes cancer progression, is relatively upregulated in TNBC patients compared to non-TNBC populations (Collignon, Lousberg, Schroeder, & Jerusalem, 2016; Jia et al., 2017). According to a tissue microarray analysis on 105 TNBC specimens, 19% of the samples were PD-L1 positive (Mittendorf et al., 2014). Also, tumor infiltration of lymphocytes, the rate of which generally correlates with the expression level of PD-L1, has been evaluated to be relatively upregulated in TNBCs than other BC subtypes, consequently increasing the susceptibility of TNBCs to immunotherapies (Adams et al., 2014; Sikandar, Qureshi, Naseem, Khan, & Mirza, 2017). Furthermore, due to the high genomic instability and elevated genetic mutation frequencies, TNBCs are highly increased in immunogenicity, which also makes TNBC an apparent candidate cancer subtype predestined for immunomodulation (Banerji et al., 2012; Budczies et al., 2015; Y. Wang, et al., 2014). Phase I clinical trials on mTNBC patients treated with pembrolizumab (FDA-approved; PD1 monoclonal antibody drug; KEYNOTE-012 trial; NCT01848834) or atezolizumab (IgG1 PD-L1 monoclonal antibody drug; GO27831 trial; NCT01375842) have exhibited optimistic results with ORR of 18.5% and 33%, respectively. Since monotherapies of immunomodulators have presented some promising results against diverse TNBC patients, there are continuous efforts to additionally identify effective immune checkpoint targets, such as cytotoxic T lymphocyte-associated antigen 4 (CTLA-4). CTLA-4, a constitutively expressed molecule in regulatory T cells (Treg), also functions as a down-regulator of immune responses by transmitting inhibitory signals to T cells and is relatively upregulated in *BRCA1*-mutated TNBC compared to non-mutated cases (Nolan, et al., 2017). Inhibition of CTLA-4 primarily induces anti-tumor T cell priming to enhance T cell activation in draining lymph nodes (Beavis et al., 2018). Overall, it elevates T cell infiltration and enhances the antitumor activity of $CD8^+$ T cells by upregulating the ratio of $CD8^+$ T cell/$Foxp3^+$ Treg (Banerji et al., 2012; Huang et al., 2011; Postow, Callahan, & Wolchok, 2015). There are two anti-CTLA-4 monoclonal antibody drugs currently under clinical evaluation, ipilimumab and tremelimumab. Recent studies have started to assess the clinical benefits of combining various checkpoint inhibitors with chemotherapies and radiotherapies or co-administering separate immune checkpoint modulators. Since PD1/PD-L1 inhibitors block the final step of tumor immune system activation, the rationale for these attempts is to enhance the anti-tumor immune responses by promoting cancer cell death to upregulate the release and presentation of tumor antigens (A. Lee & Djamgoz, 2018). Ongoing studies on TNBC patients regarding the evaluation of the clinical significance of immunotherapeutic interventions as a monotherapy or combination therapy with conventional anticancer strategies are listed in Tables 6 and 7.

Combined use of separate immune check point inhibitors with distinct mechanisms has also been posited to sensitize patients to readily present immune responses and consequently achieve sufficient clinical benefits. The most actively evaluated strategy in TNBC is anti-PD1 plus anti-CTLA-4, and nivolumab plus ipilimumab is under phase I/II clinical evaluation (NCT02834013; multi-arm DART trial). Increased therapeutic benefits of this combination plus cisplatin regimen have been demonstrated in a *BRCA*-deficient TNBC mouse model, with enhancement in the activation of dendritic cells and tumor-infiltrating $CD8^+$/$CD4^+$ T cells (Nolan, et al., 2017). A recent study on a triple negative breast cancer mouse model has also explained the synergism of efficacy between the two drugs as a consequential event of $CD103^+$ dendritic cell activation induced by activated-$CD4^+$/$Foxp3^-$ cells, which led to elevation of IL-12 production (Beavis et al., 2018). Inhibitor of indoleamine 2,3-dioxygenase (IDO), another suppressive molecule of the immune responses, has also emerged as an agent to be clinically evaluated in combination with PD1 inhibitor. A recent study has demonstrated that, among 200 TNBC patients, more than 50% of those with a basal-like TNBC subtype showed gene expression of *IDO1*, which was closely associated with poor survival rate (S. Kim, et al., 2017). IDO is generated by tumor cells or myeloid-derived suppressor cells (MDSC) in response to IFN-γ signaling (Yoshida, Imanishi, Oku, Kishida, & Hayaishi, 1981) and critically enhances the function of FoxP3+ Treg and MDSC, attenuating the immune response (Frumento et al., 2002; Terness et al., 2002). Clinical assessment on the selective oral inhibitor of IDO, epacadostat, in combination with pembrolizumab (NCT02178722; ECHO-202 trial) showed ORR of 10% and DCR of 36% (Spira et al., 2017). Adenosine A2A receptor antagonists are also under evaluation as combination partners of PD1 inhibitor, since adenosine binds to the adenosine A2A receptor on the T cell surface, inhibits the proliferation of T cells, and promotes cancer cell death (H. Zhang et al., 2004). Preclinically, the regimens of adenosine A2A receptor antagonist plus anti-CTLA4 or anti-PD1 show favorable activities against tumor growth in a TNBC mouse model (Beavis et al., 2015; Mittal et al., 2014), supporting its potential therapeutic benefits. In fact, a clinical trial on combination therapy of CPI-444 (adenosine A2A receptor antagonist) and atezolizumab is currently underway to evaluate its actual therapeutic efficacy in TNBC patients (NCT02655822). Moreover, a study on the relationship between CDK4/6 and PD-L1 has recently revealed that CDK4/6 inhibition *in vitro* and *in vivo* upregulates the PD-L1 level by increasing its protein stability through suppression of PD-L1 ubiquitination, which is mediated by phosphorylated speckle-type POZ protein (p-SPOP). Combining CDK4/6 and PD-L1 inhibitors significantly improves the survival probability of mouse xenograft models (J. Zhang et al., 2018), implicating the potential of this regimen to further increase the therapeutic benefits of TNBC patients. A CDK4/6 inhibitor, abemaciclib, plus pembrolizumab is yet to be tested on TNBC patients; it is in clinical evaluation only for HR^+/$HER2^-$ breast cancer patients with an initial ORR of 14.3% under a good safety profile (NCT02779751). In addition, there is a trial recruiting TNBC patients regarding the use of enoblituzumab, a B7-H3 (CD276) monoclonal antibody drug, with pembrolizumab. Also, to obtain better understandings of mechanisms unclarified for the efficacy of pembrolizumab, a phase II study profiling the subsequent gene alterations in pembrolizumab-administered mTNBC patients is now underway (NCT02644369; INSPIRE trial).

Table 6
Clinical trials of PD-L1 monotherapy therapy targeting TNBC patients

Trial	Phase	Drugs	Tested patients	% with ORR by RECIST v1
NCT01848834; KEYNOTE-012 trial	I	Pembrolizumab	Advanced solid tumors including TNBC	18.5%
NCT01375842; GO27831 trial	I	Atezolizumab	Advanced or metastatic solid tumors including TNBC	24%
NCT02447003; KEYNOTE-086 trial	II	Pembrolizumab	Metastatic TNBC (mTNBC)	5%
NCT02555657; KEYNOTE-119 trial	III	Pembrolizumab	Metastatic TNBC (mTNBC)	
NCT02499367; TONIC trial	II	Nivolumab	TNBC	22%
NCT01772004; JAVELIN trial	Ib	Avelumab	Advanced solid tumors including TNBC	4.8%
NCT02926196; A-BRAVE trial	III	Avelumab	Adjuvant Treatment for High-risk TNBC	

Table 7
Clinical trials of PD-L1 combination therapy with conventional cytotoxic chemotherapeutics targeting TNBC patients

Trial	Phase	Drugs	Tested patients	Combination with	% with ORR by RECIST v1
NCT02730130	II	Pembrolizumab	Metastatic TNBC (mTNBC)	Radiotherapy	
NCT02768701	II	Pembrolizumab	Metastatic TNBC (mTNBC)	Cyclophosphamide	
NCT02819518; KEYNOTE-355 trial	II	Pembrolizumab	1) Previously untreated, locally recurrent, inoperable 2) Metastatic TNBC (mTNBC)	1) Nab-paclitaxel 2) Paclitaxel 3) Gemcitabine 4) Carboplatin	
NCT02622074; KEYNOTE-173 trial	I	Pembrolizumab	Neoadjuvant treatment for TNBC	1) Nab-paclitaxel 2) Doxorubicin 3) Cyclophosphamide 4) Carboplatin 5) Paclitaxel	
NCT02755272	II	Pembrolizumab	Metastatic TNBC (mTNBC)	1) Carboplatin 2) Gemcitabine	
NCT03036488; KEYNOTE-522	III	Pembrolizumab	1) Neoadjuvant treatment for TNBC 2) Adjuvant treatment for TNBC	1) Carboplatin 2) Paclitaxel 3) Doxorubicin 4) Epirubicin 5) Cyclophosphamide 6) Placebo	
NCT02734290	I/II	Pembrolizumab	Metastatic TNBC (mTNBC)	1) Paclitaxel 2) Capecitabine	
NCT02513472; ENHANCE-1 trial	Ib/II	Pembrolizumab	Metastatic TNBC (mTNBC)	Eribulin	33.3%
NCT01633970	Ib	Atezolizumab	Advanced or metastatic solid tumors including TNBC	Nab-Paclitaxel	41.7% 2-year follow up : 39.4%
NCT02425891; IMpassion130 trial	III	Atezolizumab	Previously untreated metastatic TNBC (mTNBC)	1) Nab-Paclitaxel 2) Placebo	56%
NCT02620280; NeoTRIPaPDL1 trial	III	Atezolizumab	Neoadjuvant treatment for TNBC	1) Carboplatin 2) Abraxane 3) MPDL3280A 4) Anthracyclin	
NCT03606967	II	Durvalumab	Metastatic TNBC (mTNBC)	1) Carboplatin 2) Gemcitabine Hydrochloride 3) Nab-paclitaxel 4) Neoantigen vaccine	
NCT03616886	I/II	Durvalumab	Previously Untreated Locally Recurrent Inoperable or Metastatic TNBC	1) Carboplatin 2) Paclitaxel 3) Oleclumab 4) (MEDI9447; anti-CD73)	
NCT03356860	II	Durvalumab	Locally Advanced TNBC	1) Paclitaxel 2) Epirubicin 3) Cyclophosphamide	
NCT02685059 GeparNuevo trial	II	Durvalumab	Early TNBC	1) Nab-paclitaxel 2) Epirubicin 3) Cyclophosphamide	61.0%
NCT02489448	I/II	Durvalumab	Clinical Stage I-III Triple Negative Breast Cancer	1) Nab-paclitaxel 2) Dose-dense doxorubicin/-cyclophosphamide (ddAC)	
NCT02628132	I/II	Durvalumab	Metastatic TNBC (mTNBC)	1) Paclitaxel	
NCT02658214	Ib	Durvalumab	Advanced TNBC patients with first-line chemotherapy	1) Gemcitabine + carboplatin + tremelimumab 2) Nab-paclitaxel + carboplatin + tremelimmab	
NCT02393794	I/II	Nivolumab	Metastatic TNBC (mTNBC)	1) Romidepsin 2) Cisplatin	

As another way to enhance the therapeutic benefits of PD1/PD-L1 drugs, studies are underway regarding the co-administration of immune checkpoint modulators with other targeting agents of PI3K, VEGF, EGFR, and PARP. Targeted therapies can comprehensively sensitize the immune system by increasing T cell activation and homing; thus, the efficacy of combining PD1/PD-L1 inhibitors with targeting agents is expected to exhibit great synergism. Currently, pembrolizumab is under evaluation with the JAK1 inhibitor INCB039110 or the PI3K inhibitor INCB050465 (NCT02646748) and tyrosine kinase inhibitors of KIT, CSF1R, FLT3, and PLX3397 (NCT02452424). JAK2 inhibition was recently analyzed to significantly block PD-L1 expression in diverse TNBC cell lines, where amplification of chromosome 9p24.1 was closely associated with upregulation of JAK2 and PD-L1 (M. Chen, et al., 2018). In addition, several *in vitro* studies have reported that inhibition of the MEK or PI3K-AKT pathway could induce the elevation of PD-L1 expression in TNBC cell lines (Loi et al., 2016), supporting the therapeutic relevance of applying targeted therapies into immune checkpoint inhibitor-based regimens as to effectively promote the T cell activation. A clinical trial on durvalumab plus bevacizumab combination therapy is also under assessment (NCT2489448), based on the result from a recent report that VEGF-A creates immunosuppressive conditions by inducing suppressive immune cell accumulation and inhibiting tumor infiltration of T cells (Voron et al., 2014). Moreover, single administration of PARP inhibitors, one of the most actively evaluated and primarily considered drug types in TNBC, is demonstrated to have limitations of increasing the

expression level of PD-L1, eventually attenuating the anti-tumor immune responses. Thus, co-treating PD1/PD-L1 inhibitors with PARP inhibitors is expected to significantly increase the overall therapeutic efficacy (Jiao et al., 2017). There are also several clinical trials on-going regarding the use of PARP inhibitors with PD1 or PD-L1: pembrolizumab plus niraparib (TOPAICO trial; NCT02657889), atezolizumab plus veliparib (NCT02849496), avelumab plus talazoparib (JAVELIN PARP MEDLEY trial; NCT03330405), and durvalumab plus olaparib (DORA trial; NCT03167619). To date, the TOPAICO trial demonstrated promising results of 29% ORR and 49% DCR irrespective of *BRCA1/2* mutation or PD-L1 status, implicating the encouraging therapeutic potential of PARP and PD1/PD-L1 co-inhibition (Vinayak et al., 2018). Moreover, although clinical evaluation on combining EGFR modulators with PD1/PD-L1 inhibitors is yet underway, co-overexpression or -amplification of PD-L1 and EGFR has been preclinically demonstrated in TNBC patients (Barrett et al., 2018; Gawryletz et al., 2015), and unregulated EGFR signaling enhances the interaction between PD1 and PD-L1 by stimulating β-1,3-N-acetylglucosaminyl transferase (B3GNT3)-mediated glycosylation (C.W. Li et al., 2018). These data implicate the therapeutic potentials and obtainable clinical benefits of co-targeting EGFR and PD-L1 in TNBC patients, making it an attractive strategy to be further evaluated in the future.

3. Experimental targets for TNBC under evaluation

3.1. AMP activated protein kinase (AMPK)

The level of phosphorylated AMPK (pAMPK, Thr172) is much lower in malignant breast tissue than in normal and benign breast tissues. Reduced p-AMPK is associated with histological grade and axillary node metastasis (M.M. Fox, Phoenix, Kopsiaftis, & Claffey, 2013; H. Zhao et al., 2017). Immunohistochemical evaluation of AMPK showed that it regulates cytoskeletal forces of circulating tumor cells (CTCs) in metastatic breast cancer cells. AMPK inhibition augments microtubule stability, activates cofilin, an actin-severing protein, and ultimately promotes the formation of microtentacles, also known as microtubule-based protrusions. Microtentacle formation enhances the metastatic efficiency of circulating breast tumor cells by facilitating CTC aggregation and re-attachment (Chakrabarti et al., 2015). Furthermore, AMPK activation-mediated antiproliferation of cancer cells has been reported to be due to down-regulation of TSC2-mTOR and up-regulation of p53-p21 (Motoshima, Goldstein, Igata, & Araki, 2006; H. Zhao et al., 2017). Increase in p-AMPK (Thr172) levels by OSU-53 (Table 8), a synthetic allosteric AMPK activator (K.H. Lee et al., 2011), inhibited both p-Akt and p-MDM2, the E3 ligase responsible for Foxo3a ubiquitination and degradation, which led to an increase in Foxo3a nuclear localization and accumulation. AMPK activation-mediated accumulation of nuclear Foxo3a upregulated E-cadherin and concomitantly increased the expression of mesenchymal markers, such as YB-1, vimentin, and snail (Chou et al., 2014). Metformin (Met), a widely used anti-diabetic biguanide drug (Table 8), is also well known to activate AMPK. Patients with diabetes taking metformin had a lower incidence of cancer and mortality rate than those taking other medications (Abdelgadir, Ali, Rashid, & Bashier, 2017). Met and its derivative phenformin (Phe) (Table 8) attenuated the production of angiogenic proteins in cultured breast cancer cells along with white adipose tissue. Met and Phe inhibited tumor growth of TNBC and HER2-overexpressing cancers and their metastasis toward the lung (Orecchioni et al., 2015). The anti-cancer effects of 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) (Table 8) in TNBC have also been investigated; AICAR was the first compound to be developed as a direct AMPK activator. AICAR is converted to AICAR monophosphate (ZMP) after being absorbed into cells by the adenosine transporter. It is phosphorylated by adenosine kinase and then functions as an AMP analog through binding to the AMP binding site of AMPK (Corton, Gillespie, Hawley, & Hardie, 1995; J. Kim, Yang, Kim, Kim, & Ha, 2016). AICAR inhibits proliferation of TNBC cell lines such as MDA-MB-231 and BT-549 through inhibiting c-Myc expression, resulting in downregulation of metadherin (MTDH) expression. AICAR-induced MTDH downregulation is caused by SIRT1 activation and reduction of p-GSK3β (Ser 9) (Gollavilli et al., 2015). A recent review comprehensively summarized direct and indirect AMPK activators and their mode of action (J. Kim et al., 2016), but none have been studied in relation to TNBC except as noted above and AMPK-activating drugs have not yet entered clinical trials.

3.2. Mouse Double Minute 2 Homolog (MDM2)

MDM2, also known as E3 ubiquitin-protein ligase MDM2, binds directly to p53 and inhibits its transcriptional activity and moreover promotes its degradation, thus acting as a negative regulator of tumor suppressor p53. MDM2 has a p53 binding domain at the N-terminus

Table 8
Structures and efficacy of potent AMPK activators applied for TNBC.

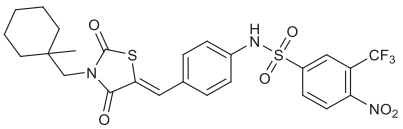
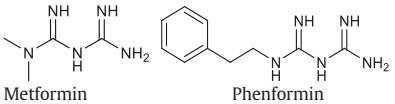
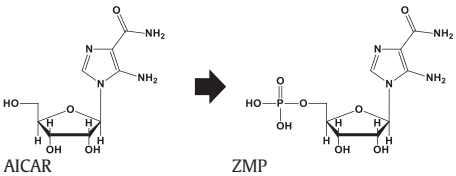
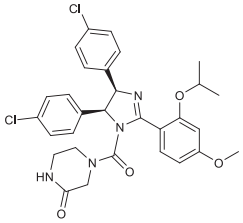
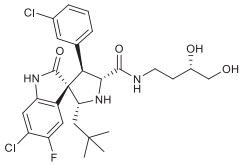
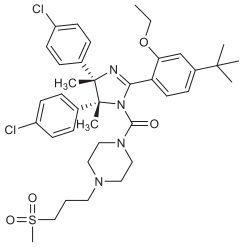
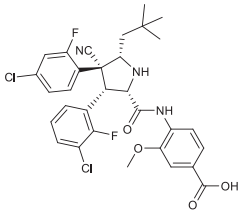
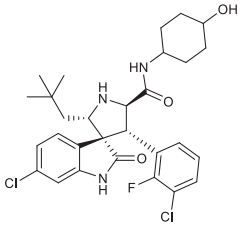
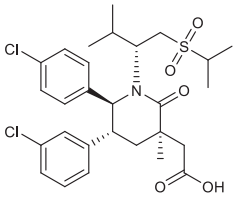
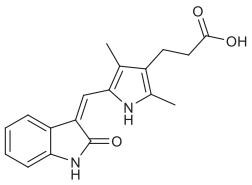
Name	Structure	Potency and clinical implication
OSU-53		- Orally bioavailable AMPK activator - EC_{50} = 0.3 μM using recombinant AMPK - IC_{50} = 5 and 2 μM, respectively, for the viability and clonogenic growth of MDA-MB-231 and MDA-MB-468 cells - Reversed mesenchymal phenotype of TNBC cells by regulating the Akt-MDM2-Foxo3a signaling axis
Biguanides	 Metformin Phenformin	- Metformin: An oral remedy for type II diabetes - Phenformin: Approved as an antidiabetic drug but withdrawn due to a high risk of lactic acidosis - Noticeably inhibited complex I of the mitochondrial respiratory chain, leading to increase in the AMP:ATP ratio with 5 mM treatment of metformin and 0.5 mM phenformin - Inhibited tumor growth of TNBC and HER2-overexpressing cancer and their metastasis towards the lung
AICAR (5-aminoimidazole-4-carboxamide riboside) and ZMP	 AICAR ZMP	- AMP mimetic AMPK activator - AICAR is converted to AICAR monophosphate (ZMP) by adenosine kinase - Downregulated MTDH via regulating SIRT1-GSK3β-c-Myc signaling axis to inhibit tumor cell proliferation and metastasis in TNBC

Table 9
Structures, efficacy and clinical implication of potent MDM2 inhibitors in TNBC.

Name	Structure	Potency and clinical implication	NCT number	Clinical trial identifier
Nutlin-3		- MDM2 inhibitor with binding affinity to MDM2 ($K_i = 36$ nM) without induction of DNA damage and p53 phosphorylation - Restored p53 activity leading to antitumor activity in a xenograft mouse model - Induces cell cycle arrest as well as cell death in tumor cells - Impedes the interaction of MDM2 with p73, E2F1, and HIF-1α - Combination of nutlin-3 with paclitaxel showed synergistic antiproliferative and apoptotic activity in TNBC		
MI-219		Its mode of action is the same as that of nutlin-3 but its binding affinity to MDM2 is higher ($K_i = 5$ nM)		
RG-7112 (RO5045337)		- The first clinical MDM2 inhibitor that binds to the p53 binding pocket of MDM2 - Its binding affinity for MDM2 is 4.9-fold higher than that of nutlin-3 - Its average IC_{50} value against wild-type p53 cancer cells is 3.8-fold higher than nutlin-3	No clinical trials for TNBC yet NCT00623870 NCT00559533	 - Phase I completed for patients with hematologic neoplasms - Phase I completed for patients with advanced solid tumors
RG-7388		- Also known as RO5503781 and idasanutlin - Mode of action identical to that of RG-7112 with higher potency and selectivity than RG-7112	Currently 9 clinical trials targeting diverse cancers, but no TNBC trials yet NCT03362723 NCT02828930 NCT02545283 NCT02670044 NCT03287245 NCT02407080 NCT02624986 NCT03135262 NCT03158389	 - Solid tumors - Acute myeloid leukemia - Polycythemia vera - Essential thrombocythemia - Non-Hodgkin's lymphoma - Diffuse large B-cell Lymphoma - Glioblastoma - No TNBC trials yet
MI-77301		- Also known as SAR405838 - Unlike nutlin imidazole-based compounds, it is a spiroindolinone small-molecule MDM2 inhibitor with almost 50 times and 15 times higher binding affinity to humans MDM2 than nutlin-3 and MI-219, respectively	NCT01985191 NCT01636479	- Phase I completed in combination with pimasertib (Mek inhibitor) for patients with solid tumors - Phase I study completed to assess the safety, tolerability, pharmacokinetics, and biological activity in patients with advanced cancer
AMG232		- Piperidinone-derived potent and selective MDM2 inhibitor - About 5 time more potent than RG-7388 based on cellular IC_{50} values - Associated with p53 stabilization and induction of MDM2, P21, and PUMA expression	- Currently seven clinical trials for the treatment of solid tumors, melanoma, myeloma, and AML leukemia as a single treatment or in combination with other therapies, but no TNBC trial yet - Two trials have been completed NCT01723020 NCT02016729	 - Phase I study in advanced solid tumor or multiple myeloma as single treatment - Phase Ib study in combination with trametinib (MEK inhibitor) in acute myeloid leukemia

and RING domain at the C-terminus (Yuan, Liao, Hsueh, & Mirshahidi, 2011). MDM2 amplification is most frequently observed in soft tissue tumors (amplification frequency of 20% in 28 human tumors) and is second most abundant in osteosarcomas (16%) (Momand, Jung, Wilczynski, & Niland, 1998). According to the Cancer Genome Atlas (TCGA), seven percent of 102 TNBC patients were reported to have MDM2/4 amplification (B.D. Lehmann & Pietenpol, 2014). As a therapeutic strategy to restore p53 activity, attempts have been made to inhibit MDM2-p53 interaction by small molecular inhibitors on the structural basis of well-defined four hydrophobic residues in p53 - Phe19, Leu22, Trp23, and Leu26 - that are essential for the MDM2-p53 interaction (Shangary et al., 2008; Shangary & Wang, 2008). Nutlin-3 and MI-219 (Table 9) are MDM2 inhibitors that block the MDM2-p53 interaction by binding directly to MDM2. This consequently leads to cancer cell arrest and death by activating the p53 pathway without inducing p53 phosphorylation or DNA damage, which makes these compounds much less genotoxic than other conventional anticancer agents (Shangary & Wang, 2008). Recent preclinical studies of the combination of nutlin-3 with paclitaxel showed synergistic antiproliferative and apoptotic activity in TNBC (Wali et al., 2017). These compounds also inhibited tumor growth and prevented cancer stem-cell-driven tumor recurrence after removal of chemotherapy in

Table 10
Multi tyrosine kinase inhibitor under clinical trial evaluation for TNBC.

Name	Structure	Potency and clinical implication	NCT number	Clinical trial identifier
SU6668		- Also known as TSU-68, NSC702827, and orantinib - Inhibitor of receptor tyrosine kinases, PDGFRβ, VEGFR2, and FGFR1 with IC_{50} values of 0.06, 2.4, and 3.0 μM, respectively. Does not inhibit EGFR - Reduced MTDH expression in TNBC and inhibited tumor cell proliferation and invasion	NCT01465464	- Phase III discontinued for hepatocellular carcinoma solid tumor (NCT01465464) - No clinical trials for TNBC yet

patient-derived xenograft models (Tosoni et al., 2017). The first clinical MDM2 inhibitor that binds to the p53 binding pocket of MDM2 is RG-7112 (Table 9), which has better potency than nutlin-3 (Vu et al., 2013). Additional clinical MDM2 inhibitors such as RG-7388, MI-77301, and AMG232 have been developed and their clinical efficacy has been studied, but no clinical trial results for MDM2 inhibitors in TNBC are available yet (Andreeff et al., 2016; de Jonge et al., 2017; Ding et al., 2013; Jung et al., 2016; Rew & Sun, 2014; Tisato, Voltan, Gonelli, Secchiero, & Zauli, 2017; S. Wang, et al., 2014).

MTBP, the MDM2-binding protein is well-known to be a transcriptional target of Myc. This protein binds to Myc and together interact at Myc-targeted promoters, augmenting the oncogenic activity of Myc and consequently promoting tumorigenesis (Grieb, Gramling, et al., 2014). *MTBP* is amplified in many types of cancers based on TCGA data analysis. *MTBP* mRNA and protein expression are highest in TNBC among breast cancer types. Breast cancer patients with high expression of both *Myc* and *MTBP* mRNA had a significantly reduced 10-year survival rate compared to the patients with high *Myc* and low MTBP mRNA levels (Grieb, Chen, & Eischen, et al., 2014; Grieb, Gramling, et al., 2014). *MTBP* knockdown using doxycycline-inducible MTBP shRNA reduced TNBC tumor growth and downregulated MTBP protein levels in tumors (Grieb, Chen, & Eischen, et al., 2014).

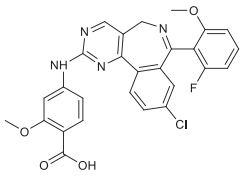
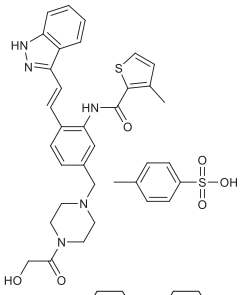
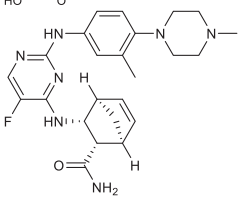
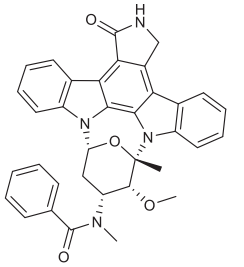
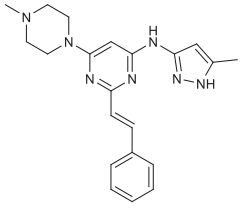
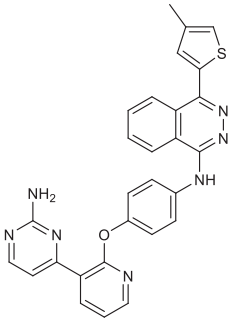
3.3. Metadherin (MTDH)

MTDH, also known as the astrocyte elevated gene 1 (AEG-1) gene, is highly overexpressed in breast tumor tissues and is involved in proliferation, angiogenesis, invasion, metastasis, and treatment resistance of breast cancer (J. Li et al., 2008). Meta-analysis of literature published from 2008 to 2016 revealed that high levels of MTDH are predictive of distant metastasis and lymph node metastasis in breast, ovarian, and cervical cancers (Hou et al., 2016). Reduction of MTDH expression by AICAR and SU6668 (multiple tyrosine kinase inhibitor, Table 10 was shown to inhibit tumor cell proliferation and invasion in TNBC patients (Gollavilli et al., 2015; Kammasud et al., 2009; L. Wang et al., 2013). MTDH may serve as potential therapeutic target for TNBC.

3.4. Cell cycle regulating targets: Aurora kinase, ATR, CHK1, WEE1 and CDC25

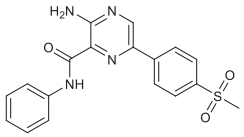
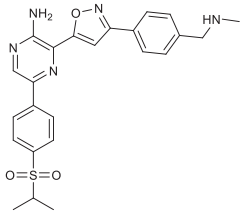
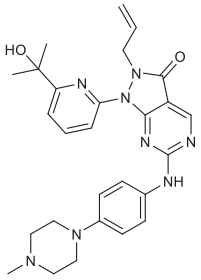
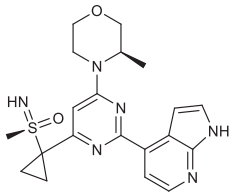
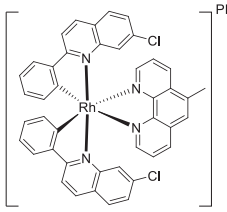
DNA damage response (DDR) and the cell cycle pathway are closely associated at multiple levels and play a critical role in the maintenance of TNBC characteristics. In case where HR is normally active, G2/M DNA damage checkpoints become activated to promote the repair system and cell cycle progression. This process is mainly regulated by CDC25, WEE1, and their upstream checkpoint kinases CHK1/2 or by ataxia telangiectasia-mutated- and Rad3-related kinase (ATR)-mediated phosphorylation of Polo-Like Kinase 1 (PLK1). Aurora-A kinase (AurA) serves as a direct upstream activator of this PLK1 and inhibits the recruitment of RAD51 to the damaged site (Cazales et al., 2005; Krystyniak, Garcia-Echeverria, Prigent, & Ferrari, 2006). DNA repair pathways are analyzed to be one of the most dysregulated pathways in TNBC (Albiges et al., 2014); thus, all of the proteins mentioned are continuously under active preclinical evaluation as a potential therapeutic targets for TNBC. AurA, a serine/threonine kinase essentially involved in mitosis, serves as an unfavorable prognostic factor to be overexpressed in TNBC patients. As AurA inhibitors, six small molecular compounds are under assessment as a monotherapy or combination therapy with other anti-cancer agents, which in all cases showed promising *in vitro* and *in vivo* anti-cancer effects of apoptosis and tumor regression (Table 11). Among them, two of the compounds are also in clinical trial; 1) Alisertib (MLN8237; selective AurA inhibitor) showed p53/p73 activity-dependent anti-tumor effects (Tentler et al., 2015) and additionally eradicated metastatic colonization by inducing autophagy via LC3B/p62 axis activation (Kozyreva et al., 2016); 2) KW-2450 (multi-kinase inhibitor of AurA and B) exhibited a significant anti-tumor activity as a monotherapy, but the effects were improved when co-administered with a selective MEK inhibitor, selumetinib (Kai et al., 2015); 3) AS703569 (pan-aurora kinase inhibitor) also induced remarkable anti-cancer effects in single administration, while combined settings with doxorubicin and cyclophosphamide regimen also have significantly inhibited the tumor recurrence *in vivo* (Romanelli et al., 2012); 4) Midostaurin (multi-target protein kinase inhibitor) also more favorably suppressed the proliferation of TNBC cell lines than non-TNBC *in vitro* (Kawai, Nakashima, Kamada, & Kikkawa, 2015); 5) ENMD-2076 (Aurora and angiogenic kinase inhibitor) showed inhibitory activity on p53-mutated or -overexpressed *in vitro* and *in vivo* preclinical models of TNBC (Diamond et al., 2013; Ionkina et al., 2017), and it is now in phase II clinical trial for advanced or metastatic TNBC patients who underwent previous treatment (NCT01639248; 4-month CBR 27.8%; 6-month CBR 16.7%); 6) AMG900 alone also showed significant inhibitory activities against both taxane-sensitive and -resistant TNBC models (Bush et al., 2013). Based on this result, a phase I trial of AMG 900 on taxane-resistant TNBC patients was conducted (NCT00858377), but failed to prove the efficacy (Carducci et al., 2018). Since aurora kinase inhibitors have showed disappointing clinical outcomes to date, investigation on combination regimens is likely to be recommended in the future. Several inhibitors of ATR and WEE1 are also under evaluation for TNBC (Table 12). The specific ATR inhibitor VE-821 (ATR IC_{50} = 26 nM) has shown preclinical selective cytotoxicity against PTEN-deficient TNBC cells (Al-Subhi et al., 2018), and VX-970 (VE-822), another analog of VE-821 with an improved potency (ATR IC_{50} = 0.2 nM), was elucidated to particularly inhibit ATR-CHK1-CDC25 signaling, significantly sensitizing the neoadjuvant chemotherapy (NAC)-resistant TNBCs to radiotherapy. However, as a single agent, VX-970 did not exhibit any noticeable anti-tumor effects (Mutter et al., 2017; Rundle, Bradbury, Drew, & Curtin, 2017; Tu et al., 2018). For this compound, phase I clinical trial is underway for TNBC patients in combination with cytotoxic chemotherapies (NCT02157792). A new approach combining WEE1 inhibitor (AZD1775) with ATR inhibitor (AZD6738) has emerged to enhance the therapeutic benefits by increasing the overall cytotoxicity. This regimen also has demonstrated additional benefits of RAD51-mediated HR suppression, sensitizing the TNBC cells to PARP inhibitors and cisplatin (Jin et al., 2018). AZD1775 alone without AZD6738 can sensitize TNBCs to cisplatin, increasing their cytotoxic response, which implicates the therapeutic potential of WEE1 inhibitors for further evaluation in clinical practice (X. Chen, et al., 2018). Expression level of cyclin E may serve as a determining factor

Table 11
Structures, efficacy and clinical implication of AurA inhibitors in TNBC.

Name	Structure	Potency and clinical implication	NCT number	Clinical trial identifier
Alisertib (MLN8237)		- Selective AurA inhibitor - Showed p53/p73 activity-dependent anti-tumor effects of anti-proliferation and apoptosis - Exhibits synergistic anti-cancer response in combination with p53-degradation inhibitor, nutlin-3 - Eradicates metastatic colonization by inducing autophagy via LC3B/p62 axis activation and pAKT inhibition		
KW-2450		- Multi-kinase inhibitor of AurA and B - Exhibited significant anti-cancer activity as a monotherapy; induced delay in mitotic entry, leading to accumulation of tetraploid (4N), surviving octaploid (8N), and subG1 phase - Induces significant reduction in octaploid (8N) phase, leading to increase in apoptosis when co-administered with a selective MEK inhibitor, selumetinib. - Improves anti-tumor effect in TNBC xenograft model under selumetinib co-administration		
AS703569		- Orally potent pan-aurora kinase inhibitor competitive with ATP - IC_{50} value of 4.0, 4.8, and 6.8 nM to Aurora kinases A, B, and C, respectively - Shows remarkable anti-cancer effects in single administration, while combined setting with doxorubicin and cyclophosphamide regimen demonstrated a significant inhibition of tumor recurrence *in vivo*		
Midostaurin		- Multi-target protein kinase inhibitor - Clustered with VX-680, another aurora kinase inhibitor - Inhibits both aurora kinase A and B below 50% activity at 1 μM in vitro - More favorably suppresses the proliferation of TNBC cell lines than the non-TNBC in vitro		
ENMD-2076		- Orally bioavailable aurora and angiogenic kinase (VEGFR, FGFR, PDGFR) inhibitor - Greater specificity for Aur A (IC_{50} = 14 nM) than Aur B (IC_{50} = 350 nM) - Showed inhibitory activity on p53-mutated or -overexpressed *in vitro* and *in vivo* preclinical models of TNBC	NCT01639248	- Now in phase II clinical trial for the advanced or metastatic TNBC who underwent previous treatment (4-month CBR 27.8%; 6-month CBR 16.7%);
AMG900		- Orally bioavailable, potent, and highly selective pan--Aurora kinase inhibitor - Active in multidrug-resistant cell lines - Compound alone also held significant inhibitory activities of polyploidy and apoptosis against both taxane--sensitive and -resistant TNBC models - Combination regimens of AMG900 and microtubule--targeting agents (taxanes or epothilones) showed significant tumor regression without recurrence	NCT00858377	- Phase I trial of AMG 900 on taxane-resistant TNBC patients was conducted, but failed to prove the efficacy

for the responsiveness of TNBC to AZD1775. The anti-tumor activity of the drug is stronger in cyclin E-high TNBCs; thus, for the cyclin E-low counterparts, prior use of CDK2 inhibitors is recommended for transient induction of cyclin E to sensitize the patients to AZD1775 (X. Chen, et al., 2018). Recently, rhodium (III) complex has been newly identified as a novel WEE1 inhibitor that induces cell death in *p53*-mutated TNBC cells (Yang et al., 2018). CHK1 is another target molecule importantly involved in the DNA repair process and is analyzed to be relatively overexpressed in TNBC populations (Table 13). Inhibition of CHK1 through diverse small molecules, SB218078, V158411 (CHK1 IC_{50} = 3.5 nM), PF-477736 (CHK1 IC_{50} = 4.9 nM), and AZD7762 (CHK1 IC_{50} = 5 nM), have significantly induced cell death of TNBC lines through DNA damage and apoptosis promotion (Albiges et al., 2014; C. Bryant, Rawlinson, & Massey, 2014; Rundle et al., 2017). CHK1 inhibitors indeed have shown great anti-cancer activities as a monotherapy, but the combination regimens have been demonstrated to exhibit better outcomes. Co-administration of UCN-01 (non-selective CHK1 inhibitor) or AZD7762 with gemcitabine has exhibited remarkably improved efficacy

Table 12
Structures, efficacy and clinical implication of ATR and WEE1 inhibitors in TNBC.

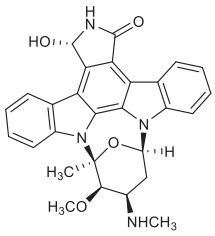
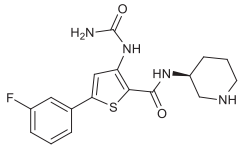
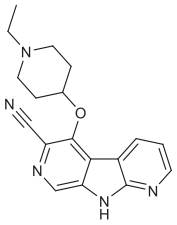
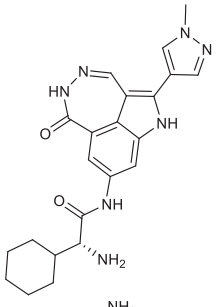
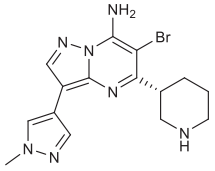
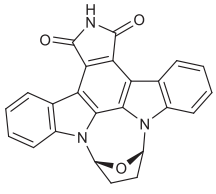
Name	Structure	Potency and clinical implication	NCT number	Clinical trial identifier
VE-821		- Specific ATR inhibitor - (ATR IC_{50} = 26 nM) - Preclinically shown to have selective cytotoxicity against PTEN--deficient TNBC cells		
VX-970 (VE-822)		- Another analog of VE-821 with improved potency (ATR IC_{50} = 0.2 nM) was elucidated to particularly inhibit ATR-CHK1-CDC25 signaling, significantly sensitizing the neoadjuvant chemotherapy (NAC)-resistant TNBCs to radiotherapy - As a single agent, VX-970 did not exhibit any noticeable anti--tumor effects	NCT02157792	- Phase I clinical trial is underway for TNBC patients in combination with cytotoxic chemotherapies
AZD1775		- WEE1 inhibitor (AZD1775) with AZD6738 (ATR inhibitor) has emerged to enhance the therapeutic benefits by increasing the overall cytotoxicity - AZD1775 alone without AZD6738 can sensitize TNBCs to cisplatin, increasing their cytotoxic response - Expression level of cyclin E may serve as a determining factor for the responsiveness of TNBC to AZD1775		
AZD6738				
rhodium (III) complex		- WEE1 inhibitor - Induces death in p53-mutated TNBC cells		

in vitro and *in vivo* by inducing significant DNA damage to be accumulated in the tumor, leading to growth inhibition (Bennett et al., 2012). A phase I study of GDC-0425 in combination with gemcitabine (NCT01359696) has been conducted, and the results have demonstrated a preferential anti-cancer effect against *TP53*-mutated TNBCs with a good safety profile (Infante et al., 2017). CHK1 is closely related to the *TP53* mutation, of which frequently takes place in TNBCs; thus, CHK1 inhibition is particularly effective in *TP53*-mutation bearing TNBCs. In fact, the combination therapy of irinotecan and UCN-01 or AZD7762 specifically suppressed the tumor growth of *TP53*-mutation harboring TNBCs but not that of *TP53*-wild type TNBCs (C.X. Ma et al., 2012). Although a phase II clinical trial of UCN-01 on mTNBC patients in combination with irinotecan (NCT00031681) has reported unimpressive results due to the pharmacokinetic properties of UCN-01, the overall result implicated the potential of CHK1 inhibitor as a sensitizer to improve the anti-cancer activities of conventional chemotherapeutics in *TP53*-mutant TNBCs (C.X. Ma et al., 2013). As another strategy to increase DNA damage to the tumor, efficacy of combining a dihydroorotate dehydrogenase (DHODH) inhibitor, such as teriflunomide (TFN), with a CHK1 inhibitor, PF-477736, was tested. TFN reduced the dNTP level to induce DNA damage from genotoxic stress, the co-administration of a CHK1 inhibitor additionally triggered accumulation of γH2AX, overall promoting cell death (Arnould et al., 2017). Moreover, MK-8776 (CHK1 IC_{50} = 3 nM) has been reported to increase the sensitivity of TNBC to radiotherapy by suppressing irradiation-induced autophagy (Zhou et al., 2017). Other than ATR and CHK1, CDC25 has emerged recently as a potential therapeutic target for TNBC (Table 13). Inhibition of CDC25 significantly disturbed the growth of RB1-deficient TNBCs. The CDC25 phosphatase inhibitor NSC663284 showed an apparent synergism in the anti-cancer effect with the WEE1 inhibitor, MK-1775. Generally, the PI3K pathway is upregulated along with long-term inhibition of CDC25; thus, co-treating PI3K inhibitors with CDC25 modulators may also serve as an attractive strategy for TNBCs (J.C. Liu, et al., 2018; Zacksenhaus et al., 2018).

3.5. Heat Shock Protein 90 (HSP90)

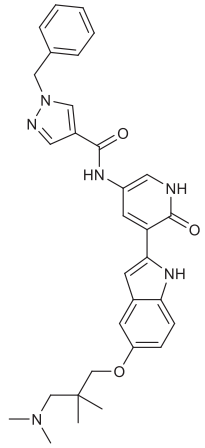
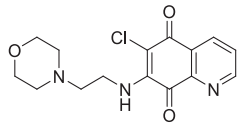
Aggressiveness of TNBC is due to its heterogeneous and complicated molecular processes; therefore, it is of interest to define a target that can cover multiple pathways simultaneously. HSP90 is a well-defined molecular chaperone that mediates the post-translational modification and stabilization of various client oncoproteins such as EGFR, HIF-1α, IGF-1R, AKT, and RAF-1 and some key components of DNA repair pathways (e.g., *BRCA*1, RAD51) (Stecklein et al., 2012; Whitesell, Mimnaugh, De Costa, Myers, & Neckers, 1994). Thus, inhibiting HSP90 is expected to comprehensively modulate diverse important signaling pathways involved in tumor progression. Up-regulated level of HSP90 is independently associated with increased recurrence rate of TNBC, and there

Table 13
Structures, efficacy, and clinical implications of CHK1 and CDC25 inhibitors in TNBC.

Name	Structure	Potency and clinical implication	NCT number	Clinical trial identifier
UCN-01		- Non-selective CHK1 inhibitor - Co-administration of UCN-01 with gemcitabine has exhibited remarkably improved efficacy *in vitro* and *in vivo* by simultaneously inducing significant DNA damage to accumulate in the tumor, leading to growth inhibition - Combination therapy of irinotecan and UCN-01 specifically suppressed the tumor growth of *TP53*--mutation harboring TNBCs but not that of *TP53*--wild type TNBCs - IC_{50} for MDA-MB-231 = 173 nM, BT-549 = 160.8 nM, SUM159 = 116.4 nM, HCC1187 = 230.5 nM (human TNBC cell lines)	NCT00031681	- Phase II clinical trial of UCN-01 in mTNBC patients in combination with irinotecan has reported unimpressive results due to the pharmacokinetic properties of UCN-01 - The overall result implicated the potential of CHK1 inhibitor as a sensitizer to improve the anti-cancer activities of conventional chemotherapeutics in TP53-mutant TNBCs
AZD7762		- Potent ATP-competitive CHK1 inhibitor - CHK1 IC_{50} = 5 nM - IC_{50} for MDA-MB-231 = 120 nM, BT-549 = 275.2 nM, SUM159 = 509.1 nM, HCC1187 = 307.7 nM (human TNBC cell lines) - Combination treatment with gemcitabine improves anti-cancer efficacy in vitro and in vivo - Co-administering with irinotecan preferentially suppressed the tumor growth of TP53-mutation harboring TNBCs		
GDC-0425		- Orally bioavailable, highly selective inhibitor of CHK1 - Preclinically caused S and G2 abrogation in combination with gemcitabine - Particularly effective in *TP53*-mutation bearing TNBCs.	NCT01359696	- Phase I study of GDC-0425 in combination with gemcitabine has been conducted, and the results have demonstrated a preferential anti-cancer effect against TP53-mutated TNBCs with a good safety profile
PF-477736		- Selective CHK1 inhibitor - CHK1 IC_{50} = 4.9 nM - Significantly induced the cell death of TNBC cell lines through DNA damage and apoptosis promotion - Co-administration with the dihydroorotate dehydrogenase (DHODH) inhibitor teriflunomide (TFN) triggers the accumulation of DNA damage, promoting cell death		
MK-8776		- Highly selective CHK1 inhibitor - CHK1 IC_{50} = 3 nM - Has been reported to increase the sensitivity of TNBC to radiotherapy by suppressing the irradiation-induced autophagy elevating Atg5 level and promoting LC3-I to LC3-II transformation		
SB218078		- Potent inhibitor of CHK1 - Induced the cell death and mitotic catastrophe of TNBC cell lines - CHK1 IC_{50} = 15 nM		

(continued on next page)

Table 13 (*continued*)

Name	Structure	Potency and clinical implication	NCT number	Clinical trial identifier
V158411		- Highly selective CHK1 and CHK2 inhibitor - CHK1 IC_{50} = 3.5 nM, CHK2 IC_{50} = 2.5 nM - Significantly induced the death of TNBC cell lines through DNA damage and apoptosis promotion (IC_{50} for TNBC cell lines; HCC1937 = 110 nM, MDA-MB-157 = 250 nM, MDA-MB-231 = 180 nM, MDA-MB-468 = 310 nM).		
NSC663284		- CDC25 inhibitor - Showed an apparent synergism in the anti-cancer effect with the WEE1 inhibitor - Co-treating PI3K inhibitors with CDC25 modulators may serve as an attractive strategy for TNBCs		

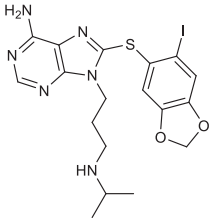
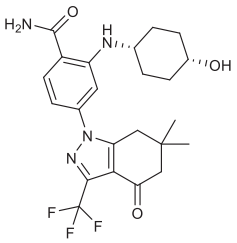
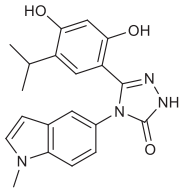
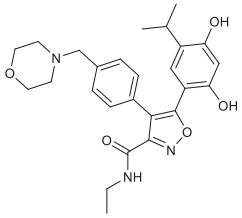
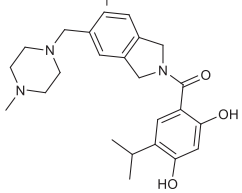
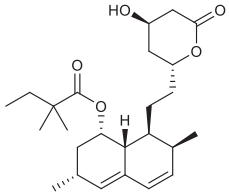
are numerous studies demonstrating the responsiveness of TNBC to various HSP90 inhibitors (Q. Cheng et al., 2012). PU-H71, a potent HSP90 selective inhibitor, has exhibited promising anti-cancer effects without toxicity by inducing complete response in TNBC xenograft models with significant tumor regression (Caldas-Lopes et al., 2009). Another orally available HSP90 inhibitor, PF-4942847, showed significant *in vitro* and *in vivo* anti-tumor activity against TNBC models by promoting apoptosis and inhibiting cell proliferation through AKT degradation (Mehta et al., 2011). Based upon these two reports, some HSP90 inhibitors are currently under evaluation for clinical application: PU-H71 is currently in phase Ib clinical trial for HER2-negative breast cancers (NCT03166085), and ganetespib (STA-9090), a second-generation HSP90 inhibitor with triazolone moiety that is structurally different from the first generation ansamycin family (e.g., geldanamycin, tanespimycin (17-AAG), and alvespimycin (17-DMAG)), is under phase II trial (ENCHANT-1 trial; NCT01677455) as monotherapy. With superior safety and activity profiles, it has been demonstrated to significantly impair the tumor growth of TNBC xenograft models either as a monotherapy or combination therapy with some conventional chemotherapeutics (Proia et al., 2014). Its beneficial anti-cancer effects are partially attributed to the blockade of HIF-1α activity and consequential downregulation of key proteins involved in angiogenesis, invasion, and metastasis (Xiang, et al., 2014). It also sensitizes the TNBC cells to paclitaxel *in vitro* and *in vivo* by inducing the degradation of glucocorticoid receptor, another well-defined client protein of HSP90 (Agyeman et al., 2016). The interim result of ENCHANT-1 has demonstrated that 5 out of 10 evaluable TNBC patients (50%) showed disease control status (Coburn, 2014). Luminespib (NVP-AUY922) is another potent second-generation HSP90 inhibitor. Although this drug is not under clinical evaluation for TNBC patients, it has been assessed *in vitro* and *in vivo* to suppress IGF-1R expression and VEGF-A excretion, overall reducing mean vascular density (Terwisscha van Scheltinga et al., 2014). It also possesses synergistic anti-cancer activity with an mTOR inhibitor, AZD8055, by attenuating the upregulation of RTKs (e.g., EGFR, HER2, HER3, and IRS-1) mediated by mTOR inhibition (Chen et al., 2014). There are also two other on-going phase I trials evaluating the combination therapy of orally bioavailable HSP90 inhibitor, onalespib (AT13387), with olaparib (NCT02898207) or paclitaxel (NCT02474173). Its combination with PARP inhibitor is based on the induction of proteasomal degradation of HSP90 client proteins, *BRCA*1 and RAD51, eventually conveying "*BRCA*-ness" to TNBC (Stecklein et al., 2012). Moreover, there are also ideas of co-administering HDAC inhibitors with HSP90 inhibitors based on the general idea that HDAC inhibitors can induce the hyper-acetylation of HSP90, leading to complete loss of its chaperone activity. However, a recent study has revealed that, among the diverse acetylation sites on HSP90, K292-acetylation solely promotes its activity, and simvastatin (HMG-CoA reductase inhibitor) directly targets this K292-acetylated HSP90 to interrupt the interaction of HSP90 with its co-chaperones and clients. Indeed, it showed significant synergistic activity with HDAC inhibitors *in vitro* and *in vivo* (Kou et al., 2018). In fact, among the diverse HDAC inhibitors, romidepsin is currently under phase I/II clinical trial in combination with cisplatin and nivolumab for mTNBC patients. In addition to the mentioned drugs, there are diverse on-going experimental attempts to identify novel small molecules targeting HSP90 to find an effective therapeutic option for TNBC (Oh, Park, & Seo, 2018; Oh & Seo, 2017; Q. Zhao et al., 2014; Qing Zhao et al., 2018). The mentioned HSP90 inhibitors and related trials are well organized in Table 14.

4. Conclusions and future directions

The National Comprehensive Cancer Network (NCCN) version 2017 recommends systemic adjuvant treatment for TNBC patients because targeted therapy is currently not available. The NCCN-preferred regimen for TNBC is doxorubicin/cyclophosphamide followed by paclitaxel, docetaxel, and cyclophosphamide. According to the European Society for Medical Oncology (ESMO) 2017 clinical practice guidelines as well as the NCCN, no data support different or specific chemotherapies for non-*BRCA*-associated triple negative advanced breast cancer (TNABC), so all chemotherapies used for HER2-negative breast cancer are recommended for TNABCs to date. ESMO guidelines actively encourage use of carboplatin in TNABC, because regardless of *BRCA* status, TNABC patients who previously underwent a neoadjuvant regimen consisting of anthracycline/taxane chemotherapeutics showed a comparable therapeutic response to carboplatin with an alleviated toxicity profile compared to docetaxel. However, with a higher priority, if TNABC patient harbors a *BRCA* mutation, regimens involving co-administration of a PARP inhibitor are recommended. Olaparib is the first PARP inhibitor to be approved by the US FDA (approved in 2018) as a therapeutic agent for metastatic breast cancer patients who carry *BRCA* gene

mutations as determined by FDA-approved genetic test (Le & Gelmon, 2018). Before FDA approval of olaparib in 2018, the first regimen for the treatment of TNBC consisted of conventional cytotoxic agents: carboplatin combination chemotherapy with an anthracycline drug such as doxorubicin, daunorubicin, or epirubicin, or the combination therapy of carboplatin plus an anthracycline drug with a microtubule dysfunction drug such as paclitaxcel, docetaxel, eribulin, or vinorelbine. Along with the approval of olaparib for use in *BRCA* mutant breast cancer, diverse clinical trials are currently underway to evaluate the therapeutic efficacy of many targeted therapies against TNBC. The PARP

Table 14
Structures and efficacy of small molecular HSP90 inhibitors currently under clinical evaluation for TNBC

Name	Structure	Potency and clinical implication	NCT number	Clinical trial identifier
PU-H71		- Novel purine-based analog - Shows potent anti-cancer effects in *in vivo* TNBC xenograft mouse model without drug resistance or toxicity - Exhibits *in vitro* anti-proliferative effects via G2/M arrest and attenuation of the Ras/Raf/MAPK pathway - Induces apoptosis through degradation of activated Akt and Bcl-xL - Suppresses the invasiveness of TNBC by inhibiting activated NF-κB, Akt, ERK2, Tyk2, and PKC	NCT03166085	- Currently in phase Ib clinical trial on HER2--negative breast cancers in combination with Nab-paclitaxel: recruiting
PF-4942847		- Orally bioavailable pyrrolodinopyrimidine--containing inhibitors of heat shock protein 90 - Low Ki value (6 nmol/L) with selectivity against AKT, among 35 other evaluated kinases - Induces AKT degradation, anti-proliferative effects, cell cycle arrest, and apoptosis in TNBC cell lines *in vitro* - Significant tumor regression in *in vivo* mouse xenograft model		
Ganetespib (STA-9090)		- Second-generation HSP90 inhibitor with a triazolone moiety - Relatively hydrophobic and smaller in size compared to the ansamycins - Blocks HIF-1α activity and alters MAPK, AKT, and mTOR signaling, exhibiting significant anti--cancer activities *in vitro* and *in vivo* - Significantly inhibits lung metastasis in *in vivo* TNBC xenograft mouse model with improved penetration, distribution, and retention rate - Increases the cytotoxic potential of the doxorubicin or doxorubicin plus cyclophosphamide regimen by increasing DNA damage and mitotic arrest - Promotes apoptosis in combination with taxanes *in vitro* and *in vivo*; induces degradation of glucocorticoid receptor, sensitizing TNBC to paclitaxel	NCT01677455	- Phase II study of ganetespib as a monotherapy in TNBC patients who have not undergone prior systemic treatment (ENCHANT-1 trial; 50% DCR)
Luminespib (NVP-AUY922)		- Orally bioavailable second-generation radical--derived HSP90 inhibitor - Suppresses *in vitro* and *in vivo* IGF-1R expression and VEGF-A excretion, reducing the mean vascular density - Reduces the RTKs (e.g., EGFR, HER2, HER3, and IRS-1) upregulated along with AZD8055 (mTOR inhibitor) treatment, increasing the anti-cancer activity		
Onalespib (AT13387)		- Orally bioavailable second-generation radicicol--derived HSP90 inhibitor - Binds to the ATP site in the N-terminal domain of HSP90 with high affinity (Kd = 0.71 nM) - Degrades BRCA1 and RAD51 creating a BRCA--deficient state	NCT02474173	- Phase I study of onalespib in combination with paclitaxel in TNBC patients: recruiting
Simvastatin		- HMG-CoA reductase inhibitor - Directly targets K292-acetylated HSP90 to interrupt the interaction of HSP90 with its co--chaperones and clients.		

inhibitor combination strategy to treat TNBC is the strategy that has been most aggressively investigated in clinical trials (Geuna et al., 2015; Le & Gelmon, 2018; X. Liu, et al., 2012; Llombart-Cussac et al., 2015; X.-D. Ma et al., 2016; J. O'Shaughnessy et al., 2011; O'Shaughnessy et al., 2014; J. Ocana & Pandiella, 2017; Roviello et al., 2016; Solinas et al., 2017; Sonnenblick et al., 2015; Teo et al., 2017; Wedge et al., 2005). A recent phase III trial showed that carboplatin was more efficacious than docetaxel in germline *BRCA1/2* mutated TNBC but not in TNBC characterized by low levels of *BRCA1* mRNA, *BRCA1* methylation, or a high score in the Myriad HRD assay (Tutt et al., 2018). However, there are concerns insisting that carboplatin alone or in combination with PARP inhibitors may have therapeutic limitations in *BRCA* mutation-bearing TNBCs. This is because platinum agents can also cause secondary *BRCA1/2* mutations, which restore the function of *BRCA* in the HR DNA repair pathway, eventually overriding the anticancer mechanism of PARP inhibitors (Mylavarapu, Das, & Roy, 2018; Norquist et al., 2011; Swisher et al., 2008). When establishing a regimen involving a PARP inhibitor, it is important to choose the appropriate PARP inhibitor among diverse analogs based on the expression status of P-glycoprotein (P-gp, also known as multidrug resistant protein and ATP-binding cassette sub-family B member 1); PARP1 inhibitors such as olaparib are a substrate for P-gp, while veliparib and CEP8938 are non-P-gp substrate PARP inhibitors (Dufour et al., 2015; Lawlor et al., 2014). P-gp overexpression can be induced by olaparib treatment and PARP1-deficiency in cancer cells and PARP null mice models (Dufour et al., 2015; Rottenberg et al., 2008; Wurzer, Herceg, & Wesierska-Gadek, 2000). Resistance of cells to paclitaxel through P-gp overexpression results in cross-resistance to olaparib but not veliparib (Vaidyanathan et al., 2016). Optimal choice of a PARP inhibitor may therefore depend on the possibility of drug-resistance, which is related to P-pg expression level that may be high in TNBC (Battistella & Klok, 2017; Boichuk et al., 2017; Hanke et al., 2018; Wishart et al., 1990). In addition to trials of PARP1 inhibitor in combination with carboplatin, a total of 43 phase III clinical trials on combining different targeted therapies to TNBC are currently listed on the clinicaltrials.gov website. The most tested drug is PD1/PD-L1 antibody drugs such as pembrolizumab (also known as MK-3475 and lambrolizumab), atezolizumab and avelumab (Roviello et al., 2016; Solinas et al., 2017). The other targeted therapies for TNBC currently under current phase III study are adagloxad simolenin (known as OBI-822, an investigational immunotherapy drug (NCT03562637)), bicalutamide (an androgen antagonist (NCT03055312)) (Arce-Salinas et al., 2016; Gucalp et al., 2013; B. D. Lehmann et al., 2011), zoledronic acid (also known as zoledronate, FDA-approved in 2001 for treatment of bone diseases like osteoporosis (NCT02595138)) (Niu, Valdes, Naguib, Hursting, & Cui, 2016), and bevacizumab (FDA-approved in 2004 as a VEGF-A inhibitor human monoclonal antibody (NCT00528567) (Fasching et al., 2018). The remaining trials are all for conventional cytotoxic anti-cancer agents as a neoadjuvant chemotherapy, but the optimal regimen in TNBC has not yet been clearly defined. Recently, immunotherapy has been actively investigated as a treatment option for TNBC in a neoadjuvant setting. Numerous studies on the addition of bevacizumab to anthracycline-taxane-based chemotherapy for TNBC failed to show apparent clinical benefits (McAndrew & DeMichele, 2018). Anti-PD-L1 antibody drugs are of great interest as cancer immunotherapy for the treatment of several cancer types including melanoma, NSCLC, urothelial cancer, renal cell carcinoma, Hodgkin lymphoma, microsatellite instability-high or mismatch repair deficient cancer, gastric cancer, colorectal cancer, hepatocellular cancer, Merkel cell carcinoma, and TNBC (Asano et al., 2018). Although anti-PD-L1 antibody drugs are highly effective, due to the general disadvantages such as high manufacturing cost, poor stability, and immunogenicity which most of the antibody drugs carry, have led many researchers to develop small molecule inhibitors of PD1 and PD-L1 to achieve better therapeutic effects (K. Li & Tian, 2018). Based on the analysis of TNBC-specific gene mutations such as *BRCA* mutations, TNBC-specific gene amplification, or overexpression of proteins such as MTBP (Grieb, Chen et al., 2014; Grieb, Gramling, et al., 2014), EGFR (Changavi et al., 2015; D. Liu, et al., 2012; Nakai et al., 2016; Park et al., 2014), AR (Rampurwala et al., 2016; Zuo et al., 2018) or PD-L1 (Asano et al., 2018; Mittendorf et al., 2014), successful targeted therapies for TNBCs are likely to be developed in future.

As is generally implied, TNBC exhibits significantly heterogeneous characteristics, so a variety of studies to identify appropriate therapeutic strategies and to predict treatment responses have been conducted based on molecular subtype. Among the seven TNBC subtypes classified by gene expression profiling, BL1 is highly sensitive to anthracycline and taxane-based neoadjuvant therapy, while BL2 exhibits a very poor response rate. However, both BL1 and BL2 are especially sensitive to cisplatin, since they harbour elevated levels of cell cycle and DNA damage response genes (B.D. Lehmann et al., 2011). In the LAR subtype, AR antagonists (e.g., bicalutamide) exhibit good therapeutic efficacy while being relatively resistant to anthracyclines / taxanes due to highly up-regulated AR signaling (Rampurwala et al., 2016). This LAR subtype is also characterized by PIK3CA mutations and is sensitive to PI3K inhibitors (B.D. Lehmann & Pietenpol, 2014). Both M and MSL subtypes, primarily characterized by highly enriched EMT and growth factor signaling pathways, respond positively to PI3K/mTOR inhibitor (e.g., rapamycin) and src inhibitor (e.g., dasatinib), while exhibiting a partial response to conventional neoadjuvant therapy (Sporikova, Koudelakova, Trojanec, & Hajduch, 2018). Finally, the IM subtype holds a unique characteristic of substantial presence of tumor infiltrating lymphocytes (TILs). Immune checkpoints (e.g., PD1/PD-L1, CTLA4) are highly enriched in this subtype and, thus, show a great therapeutic response to immunomodulatory inhibitors. Also, patients with high level of TIL better respond to adjuvant and neoadjuvant therapy, especially to platinum-agents, rather than anthracyclines (Adams et al., 2014; Denkert et al., 2015; Lehmann et al., 2016).

In addition to the TNBC subtypes, frequent mutations of *TP53*, *BRCA1/2*, *PIK3CA*, and *PTEN* may also serve as a predictive marker for therapeutic responses to anti-cancer drugs. *TP53* mutation, the most frequently-occurred somatic alteration in TNBC patients, is widely used to predict the poor response to conventional chemotherapeutics in general (Kato et al., 2009; Sakuma et al., 2011). *BRCA1* mutation is critically examined when considering the use of taxane, platinum-based chemotherapies and especially, PARP inhibitors, since these drugs are highly effective in the mutated cases (Isakoff et al., 2015; Masuda et al., 2013; Silver et al., 2010). Activating mutations of *PIK3CA* and inactivating mutations of *PTEN* are both considered favorable predictive markers for PI3K/AKT/mTOR and AR inhibitors (Beg et al., 2015; De et al., 2014; B. D. Lehmann et al., 2014). Furthermore, amplification or overexpression of growth factor receptors, such as EGFR, FGFR, and VEGFR, are mainly mentioned as therapeutic markers (B.D. Lehmann, Pietenpol, & Tan, 2015; Park et al., 2014; Sikov et al., 2015; Tolaney et al., 2015; N. Turner et al., 2010); however, they are also predictive markers for therapeutic responses to the inhibitors themselves.

Despite analysis of diverse markers for predicting the effectiveness of therapeutic strategies, it is difficult to simply conclude the exact response of each patient based on these parameters, since TNBC is a highly heterogeneous type of cancer, in which diverse oncogenic pathways are variously connected. Therefore, comprehensive consideration of TNBC biology is required to establish reasonable, appropriate, and effective therapeutic strategies for patients.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgements

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