Recently approved treatment options for patients with metastatic triple-negative and HER2-neu-positive breast cancer

Sayed Reshad Ghafouri [1], Suvarna Guvvala,[1] Catherine Jones,[2] Alexander Philipovskiy [3]

[1]Internal Medicine, Texas Tech University Health Sciences Center El Paso, El Paso, Texas, USA
[2]Texas Tech University Health Sciences Center School of Medicine, Lubbock, Texas, USA
[3]Texas Tech University Health Sciences Medical Center, Lubbock, Texas, USA

Correspondence to
Dr Alexander Philipovskiy, Internal Medicine, Texas Tech University Health Sciences Center, Lubbock, TX 79424, USA;
Alexander.Philipovskiy@ttuhsc.edu

Accepted 24 February 2022
Published Online First 15 June 2022

To cite: Ghafouri SR, Guvvala S, Jones C, *et al*. *J Investig Med* 2022;**70**:1329–1341.

ABSTRACT

Breast cancer (BC) is the most common cancer affecting women worldwide. In 2021, the estimated number of new breast cancer cases was 281 550 and about 43 500 women died from metastatic breast cancer (mBC). For women aged 20–59 years, mBC remains the leading cause of cancer death and is, therefore, an important public health concern. Only 5% of women initially present with metastatic disease. Approximately 20% of patients presenting with local or locoregional disease progress to mBC despite adjuvant therapy. Inspite of all the medicosurgical advancements, the overall prognosis for patients diagnosed with mBC remains poor, with median overall survival of approximately 31 months, although this varies based on tumor biology. In recent years, there has been significant progress in developing immunotargeted therapies such as antihuman epidermal growth factor receptor 2 (anti-HER2) or check point inhibitors that confirmed to have dramatically improve the prognosis of mBC, a historically unfavorable disease subset. Even with the major progress that has been made in understanding the biology of BC, challenges such as resistance frequency to therapies, unknown efficacy, concerns for safety of drug combination and toxicities still remain high. Therefore, a new targeted and more selective treatment approaches are the need of the hour. In this review, we aim to outline the most recently approved medications in treatment of Her2-positive and triple-negative breast cancers.

Key messages

What is already known on this topic

⇒ Systemic chemotherapy remains the backbone strategy for metastatic triple-negative breast cancer and, to some degree, in Her2-positive breast cancer (BC), which is accompanied by a myriad of adverse events.

⇒ Targeted chemotherapy has been developed with higher response and decreased adverse events.

What this study adds

⇒ This study focuses on compiling all the recently approved Food and Drug Administration targeted chemotherapy for BC.

How this study might affect research, practice and/or policy

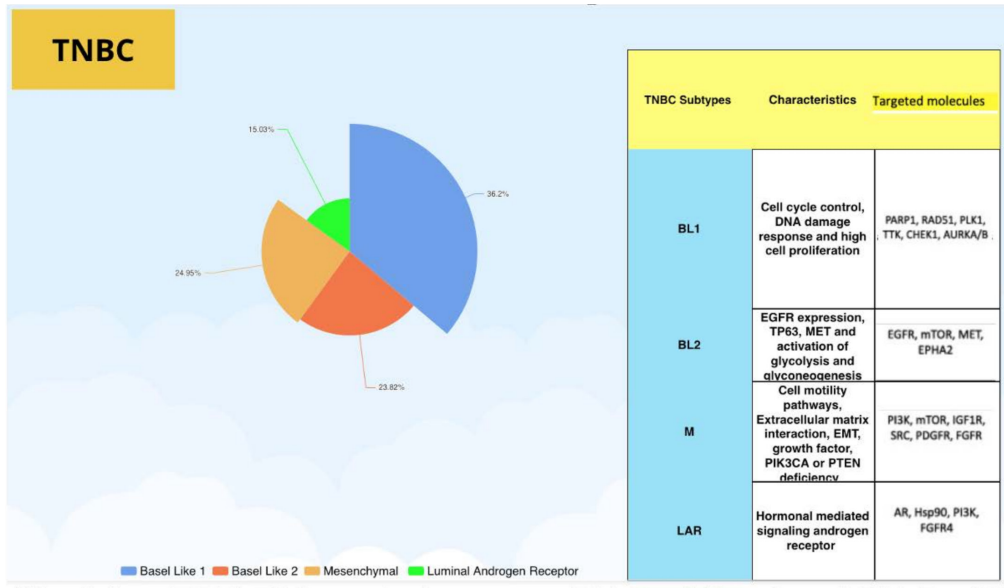
⇒ The utilization of this review can aid in comparing and contrasting the different targeted chemotherapy options and possibly aid in the choice of chemotherapy used.

INTRODUCTION

In 2021, the American Cancer Society estimated 281 550 new cases of breast cancer (BC) in the USA and 43 500 deaths from the disease.[1] From 2003 to 2018, the incidence rate of BC was stable in non-Hispanic white women, African-Americans, and Hispanics.[2] This rate can be partially explained by the progress made in screening and the early detection of BC. Since 1990, the institution of screening mammography and the use of adjuvant antihormonal therapy have contributed to a reduction of approximately 24% in the death rate from BC in the USA.[3] Multiple studies have shown substantial benefits of above interventions in disease-free survival and in overall survival (OS).[3 4]

Pathologically, BC can be divided into at least four subgroups, based on the expression of certain steroid receptors such as estrogen (ER), and progesterone (PR), or Her2 neu or a combination of those receptors.[5] Triple-negative breast cancers (TNBC) is characterized by a lack of expression of any steroid receptors or Her2 neu. TNBC represents approximately 15% of all newly diagnosed BC cases in the USA.[6] Typically, TNBC has an aggressive natural course characterized by the rapid development of chemotherapy resistance, higher recurrence rates, and poor outcomes.[7] Because of the lack of targetable receptors for TNBC, chemotherapy still remains the mainstream of treatment for those patients.[8]

In recent decades, significant progress has been made in understanding the biology of TNBC. TNBC is a heterogenic disease that



TNBC Subtypes	Characteristics	Targeted molecules
BL1	Cell cycle control, DNA damage response and high cell proliferation	PARP1, RAD51, PLK1, TTK, CHEK1, AURKA/B
BL2	EGFR expression, TP63, MET and activation of glycolysis and glyconeogenesis	EGFR, mTOR, MET, EPHA2
M	Cell motility pathways, Extracellular matrix interaction, EMT, growth factor, PIK3CA or PTEN deficiency	PI3K, mTOR, IGF1R, SRC, PDGFR, FGFR
LAR	Hormonal mediated signaling androgen receptor	AR, Hsp90, PI3K, FGFR4

Figure 1 TNBC molecular classification with their molecular targets. TNBC, triple negative breast cancer; BL1, basel-like subtype I; BL2, basel-like subtype II; M, mesenchymal; LAR, luminal androgen receptor.

can be additionally subdivided into at least four distinct subtypes based on the tumor-gene expression profiles (figure 1). These subtypes are characterized by different clinical courses and resistance to chemotherapy.[9] The basal-like subtype 1 (BL1) is usually characterized by a better progression-free survival (PFS) rate compared with the rates of other subtypes. The pathological features of BL1 tumors include a high grade tumor and a high Ki-67 proliferation index (>85%). Importantly, the BL1 subtype is highly sensitive to chemotherapy, with a response rate approaching 60%. In contrast, the BL2 subtype is clinically characterized by the worst PFS and early metastasis. BL2 has the same pathological features as BL1 but is resistant to conventional chemotherapy.[10] Two other subtypes, mesenchymal subtype (M) and luminal androgen receptor subtype, are characterized by a relatively low Ki-67 index (<50%) and an indolent clinical course with a very modest sensitivity to chemotherapy and a response rate of 10%–20%.[11] Several studies have evaluated the role of numerous genetic alterations as prognostic markers for outcomes (BRCA1/BRCA2 and PIK3CA/AKT/mTOR) and/or predictive markers for chemotherapy resistance (TP53/PIK3CA/AKT/mTOR and AR). The key component of such genetic alterations is illustrated in a schematic view and so far several agents targeting these components have been developed (figure 2).[12 13]

Another important subtype of BC is Her2-neu-positive BC, which represents another 15%–20% of all BCs and is characterized by amplification or overexpression of the so-called Her2-neu receptor.[14] The Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA) clinical trial published in 2006 was one of the first successful clinical trials that demonstrated statistically significant survival improvements among patients with metastatic HER2-neu-positive BC. The trial demonstrated a remarkable PFS duration and OS of 56.5 months among the experimental group of patients in contrast to only 18.7 months in the chemotherapy-only group.[15] The CLEOPATRA trial revolutionized and changed the paradigm of treating Her2/neu-positive BC and initiated a new era of biological therapy in oncology. Starting in 2006, a combination of chemotherapy with the anti-Her2-neu antibody become the first-line therapy for all patients with mBC whose tumors express the Her2 neu receptor. The major conclusions from the CLEOPATRA trial led to multiple additional studies and further developed the idea of biological therapy. The major problem with the CLEOPATRA-style approach was significant toxicity in chemotherapy, which limited the use of this regimen among geriatric patients. Monotherapy with herceptin alone was found to be significantly less toxic and disproportionally less effective.[16] Therefore, the next goal was to create a new approach that minimizes toxicity and improves efficacy.

The new concept involved binding a chemotherapeutic drug to the anti-Her2-neu antibody and using the antibody as a shuttle to deliver the toxic chemotherapeutic drug into the tumor cell. A new antibody drug conjugate (ADC) named trastuzumab emtansine, also known as ado-trastuzumab emtansine (Kadcyla), was successfully developed and tested in 2010.[17] The second-line therapy for patients with Her2-neu-positive BC then became the ADC trastuzumab emtansine; this conjugate demonstrated a significant objective response rate (ORR) of 43.6% among the experimental group in a clinical trial (EMILIA) (95% CI 38.6 to 48.6) and a median PFS duration of 9.6 months vs 6.4 months in the control group of patients (EMILIA trial NEJM 2012).[18] Until last year, no uniformly accepted standard of care following the administration of trastuzumab emtansine was defined. Moreover, the currently available options have limited benefits, with response rates of approximately 9%–31% and PFS durations of approximately 3–6 months as a third-line therapy.[19] To give a short overview, we summarized the newly approved targeted therapeutic agents for TNBC (table 1), describing their mechanism of actions and the outcome of main clinical trials.

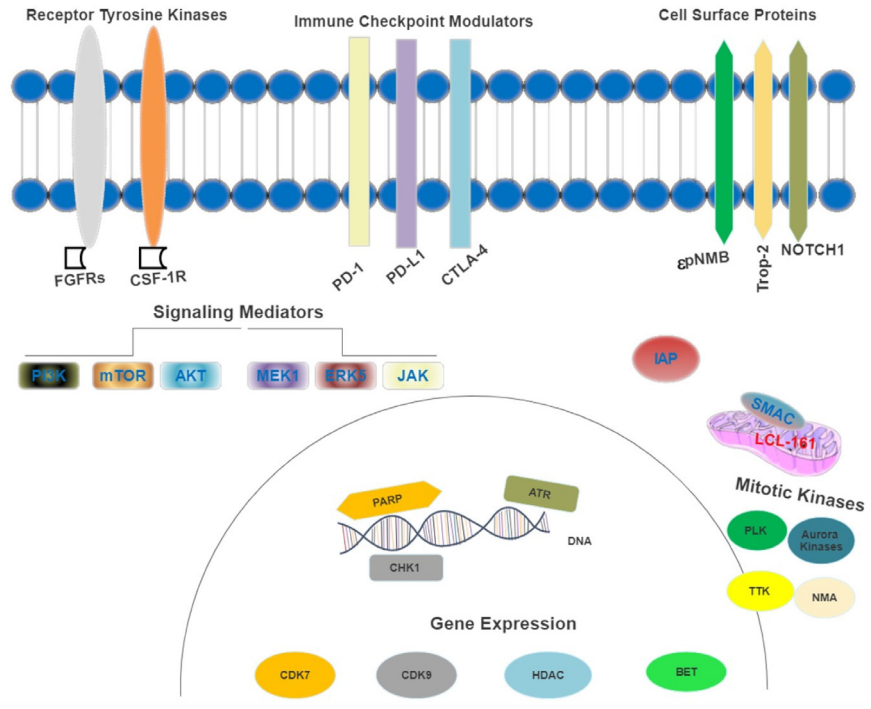


Figure 2 Schematic view of intracellular molecular pathways serves as potential targets for triple-negative breast cancer treatment. CSF-1R, colony-stimulating factor 1 receptor; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; FGFR, fibroblast growth factor receptor; PARP, poly-ADP-ribose polymerase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

TRIPLE NEGATIVE BREAST CANCER—NEWLY APPROVED TREATMENT MODALITIES

Poly-ADP-ribose polymerase inhibitors

Poly-ADP-ribose polymerase (PARP)-1 and PARP-2 are DNA sensors that are most active during the S-phase of the cell cycle and play key roles in DNA damage repair. Tumor cells with germline mutations in BRCA1/BRCA2 rely on the PARP pathway for DNA damage repair.[20 21] PARP inhibition in mutated cells traps PARP-1 on the DNA, leading to interference with the catalytic function of PARP in DNA repair. However, due to selective lethality, PARP inhibition has no effect on normal cells without a BRCA mutation.[22] PARP inhibitors are well known as semi-targeted treatments for BRCA1 and BRCA2 associated ovarian cancer and BC, but their clinical use has expanded with a better understanding of PRAP biology. In early stage clinical trials of the PARP inhibitors, the efficacy among patients with advanced BC was promising, and two phase III studies further evaluated single-agent PARP inhibition (olaparib and talazoparib), which resulted in the first regulatory approval of a PARP inhibitor for BC.[23 24] Meanwhile, several phase II and III trials are underway and have been investigating different agents of PARP inhibitors in TNBC currently pending final reports. They are summarized in table 2.

Olaparib (Lynparza)

During the last decade, several clinical trials have evaluated olaparib's effects in patients with solid malignancies harboring BRCA mutations. These trials have successfully demonstrated that olaparib is superior to conventional chemotherapy and represents a potential novel treatment standard for this high-risk population. The ICEBERG trial was one of the first trials designed to analyze the pharmacokinetic and pharmacodynamic properties of olaparib in patients with germline BRCA1/BRCA2 mutations (gBRCAm) and locally advanced BC ormBC. This trial demonstrated a statistically significant response rate of 33% among the patients in experimental group.[25 26] On January 8, 2018, the Food and Drug Administration (FDA) approved the single-agent use of olaparib for patients with gBRCAm and HER2-negative mBC based on its survival benefit noted in the OlympiAD trial. The OlympiAD trial was a multicenter, randomized phase III trial that evaluated the efficacy and safety of olaparib in patients with gBRCA1/BRCA2 metastatic HER2-negative and either ER-negative or PR-negative BC. The study demonstrated significant improvements in PFS among the olaparib group compared with the chemotherapy group (7.0 vs 4.2 months, $p<0.001$). Even though the OS was not statistically significant between the two groups (19.3 vs 19.6 months, $p=0.57$), the ORR was doubled in the olaparib group (59.9% vs 28.8%).[23] Additionally, olaparib outperformed the chemotherapy group in terms of tolerable and adverse events.[27]

Talazoparib (Talzenna)

Talazoparib is a second-generation PARP inhibitor approved by the FDA in 2018 based on the positive results of the EMBRACA trial.[28] This inhibitor was indicated for patients with locally advanced or metastatic TNBC with deleterious *gBRCAm*. de Bono *et al* were the first to evaluate talazoparib in a small phase I clinical trial designed for patients with advanced solid malignancies harboring *gBRCA1/2m*. Talazoparib monotherapy demonstrated impressive efficacy, resulting in a 50% response rate and an 86% clinical

Table 1 A brief summary of newly approved targeted therapies for TN and Her2-neu-postive BC

Classes	Mechanism of actions	Agents	Main clinical trials	FDA approval date
PARPI	PARPI act by inhibiting DNA repair and replication in cancer cells deficient in BRCA1/BRCA2-dependent homologous recombination pathways through a process known as synthetic lethality.[106]	Olaparib (Lynparza)	The ICEBERG trial: phase II, the RR was significantly high in olaparib group (33%).[25 26] The OlympiAD trial: phase III, the 7 months PFS and ORR was doubled in olaparib group (59.9% vs 28.8%).[23]	January 2018
		Talazoparib (Talzenna)	The EMBRACA trial: phase III, talazoparib demonstrated a significantly better PFS to CT (8.6 vs 5.6 months), and the OS rate was 62.6% vs 27.2%. The ABRAZO trial: phase II, the RR was 37% vs 21% in talazoparib group.[30]	July 2018
Checkpoint inhibitors (anti-PD-1/PD-L1, and CTLA-4)	CTLA-4 enhancing the activation of T lymphocytes. Targeting PD-1/PD-L1 normalize the antitumor immune response. Immune checkpoint inhibitors block these checkpoint proteins from binding with their partner proteins that allows the T cells to kill cancer cells.[107]	Pembrolizumab (anti-PD-1 antibody- Keytruda)	The KEYNOTE-522 trial: phase III, the trial demonstrated superior RR in Keytruda group after 15.5 months of follow-up (64.8% vs 51.2%).[52] The KEYNOTE-355 trial: phase III, the trial demonstrated significantly higher PFS at 9.7 months compared with CT alone 5.6 months.[55 56]	November 2020
		Nivolumab (anti-PD-1 antibody) and ipilimumab (anti-CTLA-4 antibody)	The TONIC trial: phase II, This study demonstrated modest ORR with nivolumab as only one (2%) patient had the stable disease lasting >24 weeks.[54] The Dart, SWOG S1609 trial: phase II, the preliminary result demonstrated an ORR of 12%, but 24% of patients had stable disease over 12 months.[58]	This combination has not been approved by FDA yet
NTRKI	NTRK1, NTRK2, NTRK3, and their genes encode TRK proteins. TKIs inhibit corresponding kinases from phosphorylating tyrosine residues of their substrates and then block the activation of downstream signaling pathways.[108]	Larotrectinib	The LOXO-TRK-14001, SCOUT and the NAVIGATE trials: phase I/II/III, the ORR was 75% with CRR approximately 16%. The median time to response was 1.8 months. The PFS duration in this study was not yet reached at the time of the last data cut-off. In total, 55% of the patients remained stable over 12 months.[60]	November 2018
		Entrectinib	The ALKA, STARTRK-1, and STARTRK-2 trials: phase I/II, the trials demonstrated highest RR approaching 100% among treatment-naïve children whose cancers harboring an NTRK. It was slightly less among young adults 86%, and 57% among adults.[66]	August 2019
ADCs	ADCs functions through target-dependent and target-independent mechanism. The target-dependent mechanism relies on the target-binding capacity, followed by cellular internalization and degradation with payload release. The target-independent effect is based on extracellular cleavage or leakage of the payload from the target cells acting on neighboring antigen-negative cells and stromal tissue. ADCs can also act via antibody-mediated receptor signalling pathway causing immune response activation via the Fc domain of the mAbs which also known as antibody-dependent cell-mediated cytotoxicity.[68 72 73]	Ado-trastuzumab emtansive or T-DM1 (Kadcyla)	The EMILIA trial: phase III, the outcomes of this study showed that trastuzumab emtansine significantly improved both the PFS and OS (median 9.6 vs 6.4 months). At the second interim analysis, the median OS was 30.9 vs 25.1 months. The ORR was higher with T-DM1 (43.6% vs 30.8%).[18] The TH3RESA trial: phase III, trastuzumab emtansine treatment resulted in a significant improvement in OS (median 22.7 vs 15.8 months) versus treatment of physician's choice.[109]	February 2013
		Ado-trastuzumab-deruxtecan (DS-8201)	The DESTINY-Breast01 trial: reported RR in the trial was approximately 61% with a median PFS of 16.4 months.[19] The DESTINY-Breast03 trial: phase III, this study showed that treatment with DS-8201 led to a highly significant 72% reduction in the risk of disease progression versus trastuzumab emtansine.[110]	December 2019
		Margetuximab	The SOPHIA trial: phase III, the confirmed ORR in this study was 22%, with a median DOR of 6.1 months in the margetuximab arm compared with an ORR of 16% and a median DOR of 6.0 months in the control arm.[93]	December 2020

Continued

Table 1 Continued

Classes	Mechanism of actions	Agents	Main clinical trials	FDA approval date
TROPI	Trop-family proteins, including Trop-1, Trop-2, Trop-3, and Trop-4. Only Trop-2 plays a key role in promoting tumor growth. The TROP2 inhibitor recognizes Trop-2. The small molecule, SN-38, is a topoisomerase I inhibitor, which is covalently attached to the antibody by a linker binds to Trop-2-expressing cancer cells and is internalized with the subsequent release of SN-38 via hydrolysis of the linker. SN-38 interacts with topoisomerase I and prevents re-ligation of topoisomerase I-induced single strand breaks. The resulting DNA damage leads to apoptosis and cell death.[80]	Sacituzumab govitecan-hziy (Trodelvy)	The IMMU-132-01 trial: phase I/II, this study demonstrated an impressive RR approximately 33% and the median duration of the response 7.7 months. The median PFS was 5.5 months and the median OS was 13.0 months.[81]	April 2020
Her2-TKI	TKIs are small molecular drugs that activates apoptosis and inhibiting proliferation of malignant cells. It competitively binds intracellular ATP binding domains of EGFR family due to the homological structure of the ATP, resulting in inhibiting tyrosine kinase phosphorylation, subsequently blocking downstream signals[94]	Lapatinib (Tykerb)	The NCT00078572 trial (Lapatinib plus Capecitabine for HER2-Positive Advanced Breast Cancer): phase III, the initial results of the trial demonstrated that lapatinib plus capecitabine is superior to capecitabine alone. The addition of lapatinib prolonged the TTP (8.4 months compared with 4.4 months) and indicated a trend toward improving the OS and producing fewer cases with CNS involvement at first progression.[97 98]	March 2007
		Neratinib (Nerlynx)	The ExteNET trial: phase III, at the 5-year follow-up analysis, the disease-free survival rate was 90.2% in the neratinib group and 87.7 in the placebo group.[96 97] The NEfERT-T clinical trial: phase II, the conclusion of this study showed that neratinib-paclitaxel was not superior to trastuzumab-paclitaxel in terms of the PFS.[98] The NALA trial: phase III, this study demonstrated only modest improving in PFS among patients treated with combination of neratinib with capecitabine versus lapatinib with capecitabine. More importantly was the observation that neratinib with capecitabine significantly improved median PFS in patients with CNS metastases (7.8 months vs 5.5 months).[102 103]	February 2020
		Tucatinib (TUKYSA)	The HER2CLIMB trial: phase, the overall PFS at 1 year in the experimental arm was 33.1% vs 12.3%. The median duration of PFS was 7.8 and 5.6 months, respectively. Even more impressive was the OS rate 44.9% at 2 years in the tucatinib group and 26.6% in placebo group. The median OS was 21.9 months in tucatinib group and 17.4 months in placebo group. Among the patients with brain metastases, the PFS at 1 year was 24.9% in the tucatinib group and 0% in the placebo group.[104 105]	April 2020

ADCs, antibody drug conjugates; CNS, central nervous system; CT, chemotherapy; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DOR, duration of response; FDA, Food and Drug Administration; NTRKI, neurotrophic receptor tyrosine kinase inhibitors; ORR, objective response rate; OS, overall survival; PARPI, poly-ADP-ribose polymerase inhibitor; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TKI, tyrosine kinase inhibitors; TRK, tropomyosin receptor kinase; TROPI, trophoblast cell surface antigen inhibitors; TTP, time to progression.

benefit rate.[29] ABRAZO was a two-arm phase II trial that evaluated the efficacy of talazoparib in patients with *gBRCA1/2m* mBC. The trial reported a response rate of 37% among patients who previously received three or more lines of chemotherapy (non-platinum-based regiments) and 21% in patients treated with agents.[30] In 2018, the reported results of the EMBRACA trial led to the FDA approval of talazoparib.[31] The EMBRACA trial compared talazoparib with the physician's choice of chemotherapy (gemcitabine, eribulin, capecitabine, or vinorelbine). EMBRACA was an open-label, phase III trial in which patients with advanced BC and a *gBRCA1/2* mutation were randomly assigned in a 2:1 ratio to talazoparib or chemotherapy treatment. At the primary end point of the study, talazoparib demonstrated

Table 2 The summary of ongoing clinical trials with PARP inhibitors

Agent	Trial	Phase	Design	Primary and secondary end point	Results
Niraparib (Zejula)	TOPACIO/KEYNOTE-162[36]	I/II	Phase I: dose-escalation: ascending doses of niraparib up to 300 mg/day orally on days 1–21 and pembrolizumab 200 mg intravenously on day 1 of each 21-day cycle Phase II: niraparib in combination with pembrolizumab 200 mg intravenously on day 1 of each 21-day cycle.	Phase I: number of subjects reporting dose-limiting toxicities Phase II: ORR.	To date, ORR is 29% and DCR is 49%. Median PFS in BRCAmut group is 8.1 months. Treatment-related grade≥3 AEs occurred in 27 patients (50%); most common were thrombocytopenia (13%) and anemia (11%). Follow-up is ongoing.
	BRAVO[37]	III	Controlled trial of niraparib versus physician's choice monotherapy with eribulin, capecitabine, vinorelbine or gemcitabine.	The primary end point was to assess PFS. Secondary end points included OS, PFS by local assessment (local-PFS), ORR and safety.	After the preplanned interim analysis, recruitment was halted on the basis of futility, noting a high degree of discordance between local and central PFS assessment in the PC arm that resulted in informative censoring. At the final analysis (median follow-up, 19.9 months), median centrally assessed PFS was 4.1 vs 3.1 months.
Rucaparib	RUBY[40 41]	II	Rucaparib 600 mg two times per day orally, 28-day cycle, number of cycles: until progression or unacceptable toxicity develops.	Primary end point: clinical benefit rate in 3 years with either CR, PR or SD lasting for at least 16 weeks. *Secondary end point: to assess the CR, PR, SD, PFS, OS and AEs in a 3-year time frame.	As of January 14, 2019, the median number of cycles was 2 (1–20), and 37/40 patients were evaluable for CBR. Five patients (13.5%) demonstrated clinical benefit, three PR and one SD>31 weeks. Nineteen patients had grade 3–4 toxicities. Three patients discontinued due to toxicity. Preliminary analyses showed that four patients presented high large-scale state transitions, and three presented a somatic biallelic loss of function in HR-related genes.
Veliparib	BrighTNess[47 48]	III	Arm I: veliparib+carboplatin+paclitaxel followed by doxorubicin/cyclophosphamide (AC) *Arm II: placebo+placebo+paclitaxel followed by AC. *Arm B: placebo+carboplatin+paclitaxel followed by AC.	Primary end point: to assess the PCR in the breast tissue and the lymph node tissue on completion of pre-operative systemic therapy and definitive surgery. Secondary end point: to assess PFS, OS, and the rate of eligibility for breast conservation after therapy.	As of September, 2021, those with a pathological CR had a 74% reduction in risk of an event compared with those with no pathological CR. After a median follow-up of 4.5 years, no significant differences have emerged in OS. Deaths have occurred in 12.0% of the paclitaxel/carboplatin/veliparib arm, 10.0% of the paclitaxel/carboplatin arm and 13.9% of the paclitaxel arm.
	BROCADE-3[111]	III	Veliparib placebo with carboplatin and paclitaxel	Primary end point: to assess PFS from the date the subject is randomized to the date the subject experiences a confirmed event of disease progression or to the date of death if disease progression is not reached to the date of death if disease progression is not reached. Secondary end point: to assess OS, CBR, ORR, and PFS2 measured up to 5 years after the last subject enrolled.	The median PFS was 14.5 months in the veliparib group vs 12.6 months in the control group. Serious AEs occurred in 115 (34%) patients in the veliparib group vs 49 (29%) patients in the control group. There were no study drug-related deaths.
	BROCADE[46]	II	Veliparib in combination with TMZ or in combination with carboplatin/paclitaxel compared with placebo plus carboplatin/paclitaxel (PCP).	Primary end point: to determine whether veliparib in combination with TMZ or in combination with carboplatin/paclitaxel improves PFS compared with placebo plus carboplatin/paclitaxel. Secondary end point: to assess OS, CBR, ORR, and CIPN in patients treated with veliparib plus carboplatin/paclitaxel, versus placebo plus carboplatin/paclitaxel. The tertiary end point: to assess ECOG performance status, quality of life and exploratory correlative end points.	For eliparib with carboplatin/paclitaxel versus placebo plus carboplatin/paclitaxel, median PFS was 14.1 and 12.3 months, respectively, interim median OS 28.3 and 25.9 months and ORR 77.8% and 61.3%. For TMZ versus placebo group, median PFS was 7.4 months, interim median OS 19.1 months, and ORR 28.6%. AEs (all grades) of neutropenia, anemia, alopecia, and neuropathy were less frequent with TMZ versus PCP.

AEs, adverse events; CBR, clinical benefit rate; CIPN, chemotherapy-induced peripheral neuropathy; CR, complete response; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; ORR, objective response rate; OS, overall survival; PC, Physician's choice chemotherapy; PCR, pathological complete response; PFS, progression-free survival; PR, partial response; SD, stable disease; TMZ, temozolomide.

a significantly better PFS compared with chemotherapy (8.6 vs 5.6 months). The clinical benefit rate at 24 weeks was 68.6% in the talazoparib group, compared with 36.1% in the chemotherapy group. Secondary end points from talazoparib demonstrated a better ORR of 62.6% vs 27.2 (95% CI 55.8 to 69.0).[24 32] Based on the pooled data analysis, the most common adverse reactions in the talazoparib group were anemia, neutropenia, and thrombocytopenia.

Patients who received talazoparib were also reported to have superior quality-of-life outcomes with a significant delay in the onset of a clinically meaningful deterioration in global health status.[33]

Ongoing trials with PARP inhibitors

Niraparib (Zejula)

Niraparib is a small molecule that preferentially blocks both PARP1 and PARP2 enzymes. Initially, niraparib was approved by the FDA in 2017 for the maintenance treatment of recurrent epithelial-ovarian/fallopian-tube/primary peritoneal cancer based on the results of the NOVA trial.[34] Findings from the ENGOT-OV16/NOVA trial in Europe expanded the use of niraparib to BRCA wild-type and homologous recombination deficient (HRD) negative tumors.[35] In TOPACIO/KEYNOTE-162, a phase II trial, niraparib combined with pembrolizumab was assessed in patients with platinum-resistant advanced metastatic TNBC. The ORR in the trial was 28% vs 60% for patients with BRCA-mutated TNBC. The combination therapy was safe, with a tolerable safety profile warranting further investigation.[36] Furthermore, a phase III multicenter clinical trial called the BRAVO trial was undertaken to assess the efficacy (PFS) and health-related quality of life along with the safety and tolerability of niraparib in comparison with the physician's choice of single-agent chemotherapy (eribulin, capecitabine, gemcitabine, or vinorelbine) in gBRCAm patients; however, enrollment in this trial was stopped prematurely due to the high rate of discontinuation in the control arm.[37]

Rucaparib

Rucaparib is a potent oral PARP-1, PARP-2, and PARP-3 inhibitor that showed activities in a phase I study among patients with BRCA-mutated BC.[38 39] The single-arm multicenter phase II RUBY trial enrolled patients to evaluate the efficacy and safety of rucaparib in HER2-mBC associated with a high tumor genomic loss of heterozygosity (LOH) score and/or a somatic BRCA mutation (excluding BRCA1 and/or BRCA2 germline mutations). This trial was designed to establish a proof of concept that rucaparib can improve the ORR in Her2-neu-negative mBC with HRD. Eligible patients with a high LOH score or somatic(s) BRCA mutation and ≥1 prior chemo regimen were eligible to enter RUBY and receive oral rucaparib (600 mg two times per day) continuously in a 28-day cycle until disease progression. The primary end point was the clinical benefit rate at 16 weeks. Whole-genome sequencing was performed retrospectively to further assess the potential biomarkers of the PARP inhibitor response. As of January 2019, preliminary data from the first cohort of this study demonstrated that rucaparib offered antitumor activities among a subset of patients with germline BRCA wild-type mBC whose tumor had high LOH scores.[40 41]

Veliparib

Veliparib (ABT-888) is a potent, oral, small-molecule inhibitor of PARP-1 and PARP-2 that inhibits PARP activity in xenograft models. In human cancers, veliparib was shown to cross the blood-brain barrier.[42 43] Early phase clinical trials have demonstrated promising results for veliparib in combination with cytotoxic chemotherapy. In a phase I dose-escalation study, the ORR of veliparib plus carboplatin/paclitaxel was 57% among patients with mBC receiving the maximum dose of veliparib.[44] Furthermore, pharmacokinetic of veliparib with combination of pegylated liposomal doxorubicin in recurrent gynecological cancer and TNB with long-term follow-up was studied in a phase I trial by Pothuri *et al*. The antitumor activity of this combination was observed in both sporadic and BRCA-deficient tumors.[45] BROCADE, a randomized phase II study, evaluated veliparib with temozolomide or carboplatin/paclitaxel versus placebo with carboplatin/paclitaxel in patients with mutated BRCA genes locally recurrent mBC. Numerical, but not statistically significant, increases in PFS and OS were observed in veliparib and carboplatin/paclitaxel arm compared with placebo carboplatin/paclitaxel. The addition of veliparib to carboplatin/paclitaxel significantly improved the ORR from 61.3% to 77.8% (p=0.027).[46] Considering the promising results from various clinical trials, particularly BROCADE, a multicenter phase III study named the BrighTNess trial was designed to assess the efficacy of veliparib plus carboplatin or carboplatin alone in neoadjuvant settings for patients with TNBC. The proportion of patients who achieved a pathologically complete response was higher in the paclitaxel, carboplatin, and veliparib groups compared with control group (chemotherapy alone) (53% vs 31%, p<0.0001).[47 48]

Checkpoint inhibitors (programmed cell death protein 1/programmed death-ligand 1/cytotoxic T-lymphocyte-associated protein 4 inhibitors)

The introduction of immune checkpoint inhibitors (anti-programmed cell death protein 1 (anti-PD-1) and anti-programmed death-ligand 1 (anti-PDL-1) antibodies has changed the paradigm of treatment for various solid tumors. PD-1, also known as CD279, is a 288-amino-acid type I transmembrane protein receptor. It is an apoptosis-associated molecule discovered in 1992 by Tasuku Honjo.[49] PD-L1 (also known as B7-H1 and CD274) and PD-L2 (also known as B7-DC and CD273) were first time discovered in 1999 by Lieping Chen *et al*. There are two distinct ligands for PD-1 which have inhibitory effects on T cells by inducing interleukin-10.[50] Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), also known as CD152 is a protein receptor that functions as an immune checkpoint and downregulates immune responses. Therefore, blocking the CTLA-4 with an immune checkpoint inhibitor (anti-CTLA-4 antibody) allows the T cells to be active and to kill tumor cells.[51]

Anti-PD-1 antibody pembrolizumab (Keytruda)

Pembrolizumab has shown a significant antitumor activity in patient with metastatic and locally advanced TNBC. Knowing the fact that those patients with pathological complete response after neoadjuvant chemotherapy have an excellent event-free survival, the KEYNOTE-522 trial was designed to evaluate the clinical efficacy of combining pembrolizumab with chemotherapy in neoadjuvant settings. The primary end points of this study were a pathological complete response at the time of definitive surgery and event-free survival in the intention-to-treat population. The

published results after median of 15.5 months follow-up had demonstrated that percentage of patients with a pathological complete response was 64.8% (95% CI 59.9 to 69.5) in the pembrolizumab-chemotherapy group and 51.2% (95% CI 44.1 to 58.3) in the placebo-chemotherapy group (estimated treatment difference, 13.6 percentage points; 95% CI 5.4 to 21.8; p<0.001). Additionally, 7.4% (58/784) of patients in the pembrolizumab-chemotherapy and 11.8% (43/390) of patients in the placebo-chemotherapy group had disease progression as they either had local or distant recurrence or developed a second primary tumor, or died from any cause that precluded them from definitive surgery (HR 0.63; 95% CI 0.43 to 0.93).[52] The overall results of KEYNOTE-522 was consistent with the findings from previous studies such as the KEYNOTE-173 and SPY2 trials, which demonstrated superior efficacy of combination of chemotherapy with immunotherapy when compared with immunotherapy alone.[52–54] Pembrolizumab was approved by FDA in November 13, 2020, based on results of KEYNOTE-355 trial, which demonstrated the efficacy of pembrolizumab combined with chemotherapy in patients with locally recurrent unresectable or metastatic TNBC. In this trial, the combination of pembrolizumab with chemotherapy demonstrated significantly higher PFS at 9.7 months (95% CI 7.6 to 11.3) compared with that in control arm with chemotherapy alone at 5.6 months (95% CI 5.3 to 7.5).[55 56]

Nivolumab and ipilimumab

Several phase I and II trials assessed the effects of nivolumab alone or combined with ipilimumab on patients with TNBC. The TONIC trial (phase II randomized trial) aimed to compare the immunomodulatory effects of induction chemotherapy followed by nivolumab in metastatic TNBC. This study demonstrated only modest objective RR with nivolumab as only one (2%) patient had the stable disease lasting >24 weeks.[57] More interestingly, another study lead by South Western Oncology Group (Dart, SWOG S1609), demonstrated promising efficacy of the combination of ipilimumab (anti-CTLA-4 antibody) and nivolumab in patients with mTNBC. Although the preliminary results demonstrated an overall response rate of 12%, 24% of patients had stable disease over 12-month period.[58]

Neurotrophic receptor tyrosine kinase inhibitors

Neurotrophic receptor tyrosine kinase (NTRK)1, NTRK2, NTRK3, and the neurotrophic receptor tyrosine kinase genes encode tropomyosin receptor kinase (TRK) proteins. These genes are primarily involved in neuronal development, maintenance, and protection after embryogenesis. Gene fusions involving NTRK1, NTRK2, and NTRK3 and their partner genes result in the constitutive activation or overexpression of TRK receptors, potentially leading to oncogenesis.[59 60] These fusions are consistently detected in rare cancer types such as secretory breast carcinoma, but the occurrence of NTRK fusions in common cancer types and their relationships to other therapy biomarkers remain largely unexplored.[59] NRTKs have recently garnered substantial attention as therapeutic targets in different malignancies, particularly in BC.[61] Several NTRK inhibitors such as entrectinib and larotrectinib have been approved and they are currently available in clinical use.[59 60 62]

Larotrectinib

Larotrectinib is a potent inhibitor of all three TRK proteins.[63] On November 26, 2018, the FDA announced the accelerated approval of larotrectinib in pediatric and adult human cancers that harbor NRTK gene fusions, including BC.[64] The approval of arotrectinib was based on an integrated analysis of three multicenter, open-label, single-arm clinical studies, including a phase I trial in adults, a phase I/II trial in pediatrics patients, and a phase II trial involving both adults and adolescents. According to independent reviewers, the ORR was 75% (95% CI 61% to 85%) with complete response rates approximately 16%. The median time to response was 1.8 months. The PFS duration in this study was not yet reached at the time of the last data cutoff. In total, 55% of the patients remained stable over 12 months.[60]

Entrectinib

In addition to inhibiting TRK 1/2/3, entrectinib has been shown to be active against ROS1, ALK, JAK2 and TNK2. Importantly, entrectinib can penetrate blood-brain barrier, and therefore it is a good choice in patients with central nervous system (CNS) involvement.[65] Entrectinib has been tested in multiple phases both in children and adults. Interestingly, the response rates is highest among treatment-naïve children whose cancers harboring an NTRK fusion protein and its approaching 100%. It is slightly less among young adults 86%, and 57% among adults.[66] Based on clinical data, entrectinib was approved by FDA in 2019 to use in patients whose tumors have a NTRAK gene fusion without known resistance mutation.[67]

Antibody drug conjugates (ADCs)

ADCs are gaining increasing attention as anticancer therapeutics and have been one of the fastest growing classes of drugs in recent decades.[68 69] As a biological tool for cancer therapy, a monoclonal antibody (mAb)-based strategy was developed specifically to target malignant cells while minimally affecting normal tissues.[70] ADCs are a group of drugs consisting of three well-defined compositions of mAbs conjugated to cytotoxic drugs (payloads or warheads) via a biochemical linker and mainly developed for patients with BC.[71] The most appealing functions of ADCs are their target-dependent and target-independent mechanisms. The target-dependent mechanism relies on the target-binding capacity, followed by cellular internalization and degradation with payload release. The target-independent effect, called the bystander effect, is based on extracellular cleavage or leakage of the payload from the target cells acting on neighboring antigen-negative cells and stromal tissue, thereby overcoming the heterogeneous expression of cancer antigens.[68 72] ADCs can also act via antibody-mediated receptor signaling pathway causing immune response activation via the Fc domain of the mAbs, which is also known as antibody-dependent cell-mediated cytotoxicity.[73]

Trophoblast cell surface antigen inhibitors

The trophoblast cell surface antigen (Trop), also known as epithelial glycoprotein, is a protein product of the TACSTD2

gene and found on the surfaces of multiple normal epithelial tissues, such as skin and the oral mucosa.[74] Trop-family proteins, including Trop-1, Trop-2, Trop-3, and Trop-4, were first discovered by Lipinski *et al*.[75] Among those, Trop-2 was found to play a key role in promoting tumor growth, and Trop-2 overexpression was observed in many types of malignant epithelial tumors, particularly BC.[76] Studies have demonstrated that all subtypes of BC cells express Trop-2; however, the overexpression of Trop-2 was found to be more common in aggressive TNBC and hormone receptor-positive/Her2-neu-negative subtypes.[77] Results from different studies have shown that increased Trop-2 mRNA is a strong predictor of poor clinical outcomes and decreased OS in patients with BC.[78 79] Therefore, targeting the Trop-2 receptor is very attractive strategy, particularly in advanced cancers that have very limited or no treatment options available. As a result, several Trop-2-targeted therapies, such as anti-Trop-2 antibodies and Trop-2-targeted ADC, have been developed for clinical use.[80]

Sacituzumab govitecan-hziy (Trodelvy)

Sacituzumab govitecan-hziy (SG) is the only FDA-approved Trop-2-targeted ADC, although several other agents remain under preclinical and clinical development.[76 81] On April 22, 2020, the FDA granted accelerated approval to SG for adult patients with mTNBC who have received at least two prior treatments for metastatic disease.[82] SG approval was based on the IMMU-132-01 study, which demonstrated a response rate of approximately 33% (95% (CI) 24.6 to 43.1); and the median duration of the response was noted to be 7.7 months. The median PFS was 5.5 months (95% CI 4.1 to 6.3), and the median OS was 13.0 months (95% CI 11.2 to 13.7).[81] In addition, SG was relatively well tolerated by the patients in the study.[83]

New approaches for treating HER2-neu-positive breast cancer

HER2-neu-positive BC represents about 15%–20% of all BCs and is characterized by amplification or overexpression of the so-called Her2-neu receptor conferring an aggressive tumor behavior and provide the opportunity for targeted therapies. The prognosis of patients suffering from this disease has been greatly improved with the advancement of new anti-HER2 drugs discussed below.[14] Also, a brief summary of the abovementioned agents is provided in table 3.

Ado-trastuzumab emtansive or T-DM1 (Kadcyla)

Trastuzumab emtansine (T-DM1; Kadcyla) was the first-in-class ADC approved for the treatment of HER2-positive unresectable locally advanced BC and mBC.[84] Based on the results of two multicenter phase III trials, EMILIA and TH3RESA, T-DM1 was approved by the FDA and EMA in 2013 as a second-line and beyond-line therapy, respectively, for HER2-positive BC.[85] The EMILIA study was a phase III trial that assessed the efficacy and safety of T-DM1 compared with lapatinib plus capecitabine in patients with HER2-positive advanced BC previously treated with trastuzumab and a taxane. The median PFS was 9.6 months with T-DM1 vs 6.4 months with lapatinib plus capecitabine. At the second interim analysis, the median OS was 30.9 vs 25.1 months. The ORR was higher with T-DM1 (43.6%) vs 30.8% with lapatinib plus capecitabine ($p<0.001$).[18] The outcomes of the above trials showed that trastuzumab emtansine significantly improved both the PFS and OS. Moreover, the safety profile reaffirmed trastuzumab emtansine as an efficacious and tolerable treatment for this patient population.[86]

Ado-trastuzumab-deruxtecan (DS-8201)

DS-8201 is the second FDA-approved anti-Her2 neu ADC in 2020. DS-8201 is capable of overcoming resistance to T-DM1 because of its higher payload delivery. It also offers higher membrane permeability with a resulting bystander effect and lower affinity for multidrug-resistance type 1 (MDR1) efflux transporters.[87] An open-label, multicenter phase III study (DESTINY-Breast01) evaluated ado-trastuzumab deruxtecan in adult patients with Her2-neu positive, unresectable, or mBC who had received previous treatment with trastuzumab emtansine. Patients were randomized to DS-8201 vs the physician's choice of chemotherapy to assess the PFS, OS, ORR, duration of response (DOR), and safety. DS-8201 was found to provide durable antitumor activity in heavily pretreated patients (with a median of six prior treatments). Reported RR in the trial was approximately 61% and a median PFS of 16.4 months.[19] Based on the results of the DESTINY-Breast01 trial, the FDA granted the approval for use in patients with advanced Her2-neu-positive mBC pretreated with T-DM.[88] A confirmatory phase III, multicenter, randomized, open-label active-controlled study is currently ongoing and enrolling patients with Her2-neu-positive, unresectable, and/or mBC to compare the efficacy of DS-820 vs ado-trastuzumab emtansine (T-DM1).[84 89] The preliminary results of this trial was presented at the European Society for Medical Oncology (ESMO) meeting in September 2021, showing significantly higher efficacy of DS-8201 vs T-DM1 in all prespecified measures. However, the final report is yet to be published.[90]

Margetuximab

Margetuximab is a chimeric, Fc-engineered, immune-activating anti-Her2-neu mAb that shares epitope specificity and Fc-independent antiproliferative effects with trastuzumab.[91] Margetuximab was also approved by the FDA on December 16, 2020, based on the results of the phase III SOPHIA trial.[92] In the SOPHIA trial, patients were randomized to margetuximab plus chemotherapy or trastuzumab plus chemotherapy. The main efficacy outcome measures were the PFS and OS. The median PFS in the margetuximab arm was 5.8 months compared with 4.9 months in the control arm. The median OS was 21.6 months with margetuximab and 19.8 months with trastuzumab. The confirmed ORR was 22%, with a median DOR of 6.1 months in the margetuximab arm compared with an ORR of 16% and a median DOR of 6.0 months in the control arm.[93]

Her2 tyrosine kinase inhibitors

Tyrosine kinases are important regulatory enzymes that play a key role in controlling cell proliferation, differentiation, metabolism, migration, and survival. Inhibition of

Table 3 Newly approved agents for Her2-neu-positive breast cancer

Agents	Drug classes	Main clinical trials	Mechanism of actions	FDA approval date
Ado-trastuzumab emtansive or T-DM1 (Kadcyla)	ADC	The EMILIA trial: phase III, the outcomes of this study showed that trastuzumab emtansine significantly improved both the PFS and OS (median 9.6 vs 6.4 months). At the second interim analysis, the median OS was 30.9 vs 25.1 months. The objective response rate was higher with T-DM1 (43.6% vs 30.8%).[18] *The TH3RESA trial: phase III, trastuzumab emtansine treatment resulted in a significant improvement in OS (median 22.7 vs 15.8 months) versus treatment of physician's choice.[109]	ADCs functions through target-dependent and target-independent mechanism. The targed-dependent mechanism relies on the target-binding capacity, followed by cellular internalization and degradation with payload release. The target-independent effect is based on extracellular cleavage or leakage of the payload from the target cells acting on neighboring antigen-negative cells and stromal tissue. ADCs can also act via antibody-mediated receptor signalling pathway causing immune response activation via the Fc domain of the mAbs, which is also known as antibody-dependent cell-mediated cytotoxicity.[68 72 73]	February 2013
Ado-Trastuzumab-deruxtecan (DS-8201)	ADC	The DESTINY-Breast01 trial: reported RR in the trial was approximately 61% with a median PFS of 16.4 months. *The DESTINY-Breast03 trial: phase III, this study showed that treatment with DS-8201 led to a highly significant 72% reduction in the risk of disease progression versus trastuzumab emtansine.		December 2019
Margetuximab	ADC	The SOPHIA trial: phase III, the confirmed ORR in this study was 22%, with a median DOR of 6.1 months in the margetuximab arm compared with an ORR of 16% and a median DOR of 6.0 months in the control arm.[93]		December 2020
Lapatinib (Tykerb)	Her2-TKI	The NCT00078572 trial (Lapatinib plus Capecitabine for HER2-Positive Advanced Breast Cancer): phase III, the initial results of the trial demonstrated that lapatinib plus capecitabine is superior to capecitabine alone. The addition of lapatinib prolonged the time to progression (8.4 months compared with 4.4 months) and indicated a trend toward improving the OS and producing fewer cases with CNS involvement at first progression.[97 98]	TKIs are small molecular drugs that activate apoptosis and inhibiting proliferation of malignant cells. It competitively binds intracellular ATP binding domains of EGFR family due to the homological structure of the ATP, resulting in inhibiting tyrosine kinase phosphorylation, subsequently blocking downstream signals.[110]	March 2007
Neratinib (Nerlynx)	Her2-TKI	The ExteNET trial: phase III, at the 5-year follow-up analysis, the disease-free survival rate was 90.2% in the neratinib group and 87.7 in the placebo group.[99 100] The NEfERT-T clinical trial: phase II, the conclusion of this study showed that neratinib-paclitaxel was not superior to trastuzumab-paclitaxel in terms of the PFS.[98] The NALA trial: phase III, this study demonstrated only modest improving in PFS among patients treated with combination of neratinib with capecitabine versus lapatinib with capecitabine. More importantly was the observation that neratinib with capecitabine significantly improved median PFS in patients with CNS metastases (7.8 vs 5.5 months).[102 103]		February 2020
Tucatinib (TUKYSA)	Her2-TKI	The HER2CLIMB trial: phase II, the overall PFS at 1 year in the experimental arm was 33.1% vs 12.3%. The median duration of PFS was 7.8 and 5.6 months, respectively. Even more impressive was the OS rate 44.9% at 2 years in the tucatinib group and 26.6% in placebo group. The median OS was 21.9 months in tucatinib group and 17.4 months in placebo group. Among the patients with brain metastases, the PFS at 1 year was 24.9% in the tucatinib group and 0% in the placebo group.[104 105]		April 2020

ADCs, antibody drug conjugates; CNS, central nervous system; DOR, duration of response; mAb, monoclonal antibody; NTRKI, neurotrophic receptor tyrosine kinase inhibitors; ORR, objective response rate; OS, overall survival; PARPI, poly-ADP-ribose polymerase inhibitor; PFS, progression-free survival; TKI, tyrosine kinase inhibitors; TROPI, trophoblast cell surface antigen inhibitors.

the intracellular Her2-neu signaling pathways with tyrosine kinase inhibitors presents an attractive approach to control BC progression.[94 95] In the present article, we focus on three approved drugs in the therapy of Her2-neu-positive BC.

Lapatinib (Tykerb)

Lapatinib is an oral reversible and selective inhibitor of the intracellular domains of the tyrosine kinases, Her1 and Her2.[96] Lapatinib was approved by the FDA in 2007 in combination with capecitabine to treat patients with Her2-neu-positive mBC who have received prior therapy with anthracycline, trastuzumab, and a taxane.[97] The initial results of the trial demonstrated that lapatinib plus capecitabine is superior to capecitabine alone. The addition of lapatinib prolonged the time to progression (8.4 months compared with 4.4 months) and indicated a trend toward improving the OS and fewer cases of CNS involvement at first progression.[97 98]

Neratinib (Nerlynx)

FDA approval for neratinib was based on the results of the ExteNET trial, a large phase III trial that assessed the efficacy of oral neratinib as an extended adjuvant therapy versus placebo in patients with early stage Her2-positive BC who have completed adjuvant therapy with trastuzumab.[99] At the 5-year follow-up analysis, the disease-free survival rate was 90.2% in the neratinib group and 87.7 in the placebo group.[100] The NEfERT-T clinical trial sought to determine whether neratinib plus paclitaxel would improve PFS compared with trastuzumab plus paclitaxel as a first-line therapy in recurrent and/or metastatic Her2-neu-positive BC. Patients were randomized

to receive neratinib or trastuzumab, each combined with paclitaxel. As a conclusion, neratinib-paclitaxel was found not to be superior to trastuzumab-paclitaxel in terms of the PFS.[101] Neratinib received FDA approval in 2020 based on the results of the NALA trial for use in patients with metastatic Her2-positive BC who have received at least two lines of Her2-directed therapy.[102] The NALA trial demonstrated only modest improvement in PFS among patients treated with combination of neratinib with capecitabine versus lapatinib with capecitabine. More important observation was neratinib with capecitabine significantly improved median PFS in patients with CNS metastases when compared with lapatinib with capecitabine arm (7.8 vs 5.5 months).[103]

Tucatinib (TUKYSA)

TUKYSA (tucatinib) was approved by the FDA based on the results of HER2CLIMB trial.[104] The study assessed tucatinib in combination with trastuzumab and capecitabine versus placebo with trastuzumab and capecitabine in heavily pretreated patients with progressive Her2-neu-positive mBC. The largest impact of this study was on patients with brain metastases. This is the first trial to show an OS benefit in patients with brain metastases. The overall PFS at 1 year in the experimental arm (tucatinib) was 33.1% vs 12.3% in the placebo combination group. The median duration of PFS was 7.8 and 5.6 months, respectively. The OS rate of 44.9% at 2 years in the tucatinib group vs 26.6% in placebo group was impressive. The median OS was 21.9 months in tucatinib group and 17.4 months in placebo group. Among the patients with brain metastases, the PFS at 1 year was 24.9% in the tucatinib group and 0% in the placebo group.[104 105]

CONCLUSION/DISCUSSION

TNBC has an aggressive natural course characterized by the rapid development of chemotherapy resistance, high recurrence rates, and poor outcomes. In recent decades, significant progress has been made in understanding the molecular and biological characteristics of tumors, which are essential factors for the rational development of targeted therapies. So far, several classes of targeted therapies have been developed and shown to be effective in treating patients with TNBC based on OS and PFS rates. PARP inhibitor's efficacy among patients with advanced BC were promising which resulted in the first regulatory approval of a PARP inhibitor for the BC. The introduction of immune checkpoint inhibitors (anti- PD-1 and anti-PDL-1 antibodies) has changed the paradigm of treatment of various solid tumors including TNBC. The results of several clinical and preclinical studies for PD-1/PD-L1-positive TNBC have proven that checkpoint blockage has a good outcome for these patient population. Meanwhile, NRTKs have garnered substantial attention as therapeutic targets for advanced mBC. ADCs also gained increasing attention as an anticancer therapeutics for TNBC treatment. Targeting the Trop-2 receptor is very attractive strategy, particularly in advanced cancers that have very limited or no treatment option available. As a result, several Trop-2-targeted therapies, such as anti-Trop-2 antibodies and Trop-2-targeted ADC, have been developed for clinical use. Improving treatment options for metastatic Her2-neu-positive BC will lead to improved outcomes and quality of life among patients. However, there remain many unanswered questions specially regarding efficacy and safety of drug combination along with toxicities that must be answered in order to further optimize BC treatments and outcome and improve the quality of life in this patient population.

SUMMARY

BC is the most common cancer affecting women worldwide. Despite the progress in modern BC therapy, two particular subtypes of mBC (triple-negative and Her2-positive) remain the area of significant concern. In this review, we summarized the data from multiple clinical trials that demonstrated the efficacy of new medications which is unique by itself. All discussed medicines have been recently approved by FDA and are currently available for clinicians in general oncology medical practice.

Contributors AP and SRG conceptualized, prepared the original draft, and finalized the article. AP and CJ supervised, reviewed, and edited the article. SG reviewed and edited the final version of the article.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Sayed Reshad Ghafouri http://orcid.org/0000-0003-1029-2468
Alexander Philipovskiy http://orcid.org/0000-0002-7065-9578

REFERENCES

1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA A Cancer J Clin* 2020;70:7–30.
2 Davis Lynn BC, Rosenberg PS, Anderson WF, *et al*. Black-White breast cancer incidence trends: effects of ethnicity. *J Natl Cancer Inst* 2018;110:1270–2.
3 Kaplan HG, Malmgren JA, Atwood MK, *et al*. Effect of treatment and mammography detection on breast cancer survival over time: 1990-2007. *Cancer* 2015;121:2553–61.
4 Mandelblatt J, van Ravesteyn N, Schechter C, *et al*. Which strategies reduce breast cancer mortality most? collaborative modeling of optimal screening, treatment, and obesity prevention. *Cancer* 2013;119:2541–8.
5 Eroles P, Bosch A, Pérez-Fidalgo JA, *et al*. Molecular biology in breast cancer: intrinsic subtypes and signaling pathways. *Cancer Treat Rev* 2012;38:698–707.
6 Gierach GL, Burke A, Anderson WF. Epidemiology of triple negative breast cancers. *Breast Dis* 2010;32:5–24.
7 Aysola K, Desai A, Welch C, *et al*. Triple Negative Breast Cancer - An Overview. *Hereditary Genet* 2013;2013:001.
8 Diana A, Carlino F, Franzese E, *et al*. Early triple negative breast cancer: conventional treatment and emerging therapeutic landscapes. *Cancers* 2020;12:E819.
9 Turashvili G, Brogi E. Tumor heterogeneity in breast cancer. *Front Med* 2017;4:227.
10 Lehmann BD, Jovanović B, Chen X, *et al*. Refinement of triple-negative breast cancer molecular subtypes: implications for neoadjuvant chemotherapy selection. *PLoS One* 2016;11:e0157368.
11 Lehmann BD, Bauer JA, Chen X, *et al*. Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies. *J Clin Invest* 2011;121:2750–67.
12 Wolman SR, Pauley RJ, Mohamed AN, *et al*. Genetic markers as prognostic indicators in breast cancer. *Cancer* 1992;70:1765–74.
13 Popescu NC, Zimonjic DB. Chromosome and gene alterations in breast cancer as markers for diagnosis and prognosis as well as pathogenetic targets for therapy. *Am J Med Genet* 2002;115:142–9.

14 Slamon DJ, Godolphin W, Jones LA, *et al*. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science* 1989;244:707–12.
15 Baselga J, Swain SM. CLEOPATRA: a phase III evaluation of pertuzumab and trastuzumab for HER2-positive metastatic breast cancer. *Clin Breast Cancer* 2010;10:489–91.
16 Smith IE. Efficacy and safety of Herceptin in women with metastatic breast cancer: results from pivotal clinical studies. *Anticancer Drugs* 2001;12 Suppl 4:S3–10.
17 Krop IE, Beeram M, Modi S, *et al*. Phase I study of trastuzumab-DM1, an HER2 antibody-drug conjugate, given every 3 weeks to patients with HER2-positive metastatic breast cancer. *J Clin Oncol* 2010;28:2698–704.
18 Verma S, Miles D, Gianni L, *et al*. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med* 2012;367:1783–91.
19 Modi S, Saura C, Yamashita T, *et al*. Trastuzumab Deruxtecan in previously treated HER2-positive breast cancer. *N Engl J Med* 2020;382:610–21.
20 Skidmore CJ, Davies MI, Goodwin PM, *et al*. The involvement of poly(ADP-ribose) polymerase in the degradation of NAD caused by gamma-radiation and N-methyl-N-nitrosourea. *Eur J Biochem* 1979;101:135–42.
21 Dziadkowiec KN, Gąsiorowska E, Nowak-Markwitz E, *et al*. Parp inhibitors: review of mechanisms of action and BRCA1/2 mutation targeting. *Prz Menopauzalny* 2016;15:215–9.
22 Chen A. Parp inhibitors: its role in treatment of cancer. *Chin J Cancer* 2011;30:463–71.
23 Robson M, Im S-A, Senkus E, *et al*. Olaparib for Metastatic Breast Cancer in Patients with a Germline *BRCA* Mutation. *N Engl J Med* 2017;377:523–33.
24 Litton JK, Rugo HS, Ettl J, *et al*. Talazoparib in Patients with Advanced Breast Cancer and a Germline *BRCA* Mutation. *N Engl J Med* 2018;379:753–63.
25 Tutt A, Robson M, Garber JE, *et al*. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial. *Lancet* 2010;376:235–44.
26 Oza AM, Cibula D, Benzaquen AO, *et al*. Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial. *Lancet Oncol* 2015;16:87–97.
27 Griguolo G, Dieci MV, Guarneri V, *et al*. Olaparib for the treatment of breast cancer. *Expert Rev Anticancer Ther* 2018;18:519–30.
28 Exman P, Barroso-Sousa R, Tolaney SM. Evidence to date: talazoparib in the treatment of breast cancer. *Onco Targets Ther* 2019;12:5177–87.
29 de Bono J, Ramanathan RK, Mina L, *et al*. Phase I, Dose-Escalation, Two-Part Trial of the PARP Inhibitor Talazoparib in Patients with Advanced Germline *BRCA1/2* Mutations and Selected Sporadic Cancers. *Cancer Discov* 2017;7:620–9.
30 Turner NC, Telli ML, Rugo HS, *et al*. A Phase II Study of Talazoparib after Platinum or Cytotoxic Nonplatinum Regimens in Patients with Advanced Breast Cancer and Germline *BRCA1/2* Mutations (ABRAZO). *Clin Cancer Res* 2019;25:2717–24.
31 Hoy SM. Talazoparib: first global approval. *Drugs* 2018;78:1939–46.
32 Litton JK, Rugo HS, Ettl J, *et al*. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. *N Engl J Med* 2018;379:753–63.
33 Hurvitz SA, Gonçalves A, Rugo HS, *et al*. Talazoparib in patients with a germline BRCA-Mutated advanced breast cancer: detailed safety analyses from the phase III EMBRACA trial. *Oncologist* 2020;25:e439–50.
34 Ison G, Howie LJ, Amiri-Kordestani L, *et al*. FDA approval summary: Niraparib for the maintenance treatment of patients with recurrent ovarian cancer in response to platinum-based chemotherapy. *Clin Cancer Res* 2018;24:4066–71.
35 Del Campo JM, Matulonis UA, Malander S, *et al*. Niraparib maintenance therapy in patients with recurrent ovarian cancer after a partial response to the last platinum-based chemotherapy in the ENGOT-OV16/NOVA trial. *J Clin Oncol* 2019;37:2968–73.
36 Vinayak S, Tolaney SM, Schwartzberg LS, *et al*. TOPACIO/Keynote-162: Niraparib + pembrolizumab in patients (PTS) with metastatic triple-negative breast cancer (TNBC), a phase 2 trial. *JCO* 2018;36:1011
37 Shao N, Shi Y, Yu L, *et al*. Prospect for application of PARP inhibitor in patients with HER2 negative breast cancer. *Int J Biol Sci* 2019;15:962–72.
38 Wilson RH, Evans TJ, Middleton MR, *et al*. A phase I study of intravenous and oral rucaparib in combination with chemotherapy in patients with advanced solid tumours. *Br J Cancer* 2017;116:884–92.
39 Murai J, Huang S-yinN, Das BB, *et al*. Trapping of PARP1 and PARP2 by clinical PARP inhibitors. *Cancer Res* 2012;72:5588–99.
40 Patsouris A, Tredan O, Nenciu D, *et al*. Ruby: a phase II study testing rucaparib in germline (G) BRCA wild-type patients presenting metastatic breast cancer (mBC) with homologous recombination deficiency (HRD). *JCO* 2019;37:1092
41 Patsouris A, Tredan O, Campion L, *et al*. An open-label, phase II study of rucaparib, a PARP inhibitor, in HER2- metastatic breast cancer patients with high genomic loss of heterozygosity. *JCO* 2018;36:TPS1112
42 Chabot P, Hsia T-C, Ryu J-S, *et al*. Veliparib in combination with whole-brain radiation therapy for patients with brain metastases from non-small cell lung cancer: results of a randomized, global, placebo-controlled study. *J Neurooncol* 2017;131:105–15.
43 Donawho CK, Luo Y, Luo Y, *et al*. ABT-888, an orally active poly(ADP-ribose) polymerase inhibitor that potentiates DNA-damaging agents in preclinical tumor models. *Clin Cancer Res* 2007;13:2728–37.
44 Wesolowski R, Stover DG, Lustberg MB, *et al*. Phase I Study of Veliparib on an Intermittent and Continuous Schedule in Combination with Carboplatin in Metastatic Breast Cancer: A Safety and [18F]-Fluorothymidine Positron Emission Tomography Biomarker Study. *Oncologist* 2020;25:e1158–69.
45 Pothuri B, Brodsky AL, Sparano JA, *et al*. Phase I and pharmacokinetic study of veliparib, a PARP inhibitor, and pegylated liposomal doxorubicin (PLD) in recurrent gynecologic cancer and triple negative breast cancer with long-term follow-up. *Cancer Chemother Pharmacol* 2020;85:741–51.
46 Isakoff SJ, Puhalla S, Domchek SM, *et al*. A randomized phase II study of veliparib with temozolomide or carboplatin/paclitaxel versus placebo with carboplatin/paclitaxel in BRCA1/2 metastatic breast cancer: design and rationale. *Future Oncol* 2017;13:307–20.
47 Golshan M, Loibl S, Wong SM, *et al*. Breast conservation after neoadjuvant chemotherapy for triple-negative breast cancer: surgical results from the brightness randomized clinical trial. *JAMA Surg* 2020;155:e195410.
48 Miglietta F, Dieci MV, Griguolo G, *et al*. Neoadjuvant approach as a platform for treatment personalization: focus on HER2-positive and triple-negative breast cancer. *Cancer Treat Rev* 2021;98:102222.
49 Ishida Y, Agata Y, Shibahara K, *et al*. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. *Embo J* 1992;11:3887–95.
50 Bardhan K, Anagnostou T, Boussiotis VA. The PD1:PD-L1/2 Pathway from Discovery to Clinical Implementation. *Front Immunol* 2016;7:550.
51 Thomas R, Al-Khadairi G, Decock J. Immune checkpoint inhibitors in triple negative breast cancer treatment: promising future prospects. *Front Oncol* 2020;10:600573.
52 Schmid P, Cortes J, Pusztai L, *et al*. Pembrolizumab for early triple-negative breast cancer. *N Engl J Med* 2020;382:810–21.
53 Schmid P, Salgado R, Park YH, *et al*. Pembrolizumab plus chemotherapy as neoadjuvant treatment of high-risk, early-stage triple-negative breast cancer: results from the phase 1B open-label, multicohort KEYNOTE-173 study. *Ann Oncol* 2020;31:569–81.
54 Wang H, Yee D. I-SPY 2: a neoadjuvant adaptive clinical trial designed to improve outcomes in high-risk breast cancer. *Curr Breast Cancer Rep* 2019;11:303–10.
55 Cortes J, Cescon DW, Rugo HS, *et al*. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. *Lancet* 2020;396:1817–28.
56 Rugo HS, Schmid P, Cescon DW. Abstract GS3-01: Additional efficacy endpoints from the phase 3 KEYNOTE-355 study of pembrolizumab plus chemotherapy vs placebo plus chemotherapy as first-line therapy for locally recurrent inoperable or metastatic triple-negative breast cancer. In: *General Session Abstracts*. *American Association for Cancer Research* 2021:GS3-01-GS3-01.
57 Voorwerk L, Slagter M, Horlings HM, *et al*. Immune induction strategies in metastatic triple-negative breast cancer to enhance the sensitivity to PD-1 blockade: the tonic trial. *Nat Med* 2019;25:920–8.
58 Adams S, Othus M, Patel SP, *et al*. Dual anti-CTLA-4 and anti-PD-1 blockade in metaplastic carcinoma of the breast: dart (SWOG S1609, cohort 36). *JCO* 2020;38:1073
59 Cocco E, Scaltriti M, Drilon A. NTRK fusion-positive cancers and TRK inhibitor therapy. *Nat Rev Clin Oncol* 2018;15:731–47.
60 Drilon A, Laetsch TW, Kummar S, *et al*. Efficacy of Larotrectinib in TRK Fusion-Positive cancers in adults and children. *N Engl J Med* 2018;378:731–9.
61 Butti R, Das S, Gunasekaran VP, *et al*. Receptor tyrosine kinases (RTKs) in breast cancer: signaling, therapeutic implications and challenges. *Mol Cancer* 2018;17:34.
62 Menichincheri M, Ardini E, Magnaghi P, *et al*. Discovery of Entrectinib: a new 3-Aminoindazole as a potent anaplastic lymphoma kinase (ALK), c-ros oncogene 1 kinase (ROS1), and Pan-Tropomyosin receptor kinases (Pan-TRKs) inhibitor. *J Med Chem* 2016;59:3392–408.
63 Doebele RC, Davis LE, Vaishnavi A, *et al*. An oncogenic NTRK fusion in a patient with soft-tissue sarcoma with response to the tropomyosin-related kinase inhibitor LOXO-101. *Cancer Discov* 2015;5:1049–57.

64 Wilson FH, Herbst RS. Larotrectinib in NTRK-Rearranged Solid TumorsPublished as part of the Biochemistry series "Biochemistry to Bedside.. *Biochemistry* 2019;58:1555–7.
65 Liu D, Offin M, Harnicar S, *et al*. Entrectinib: an orally available, selective tyrosine kinase inhibitor for the treatment of *NTRK*, *ROS1*, and *ALK* fusion-positive solid tumors. *Ther Clin Risk Manag* 2018;14:1247–52.
66 Drilon A, Siena S, Ou S-HI, *et al*. Safety and antitumor activity of the multitargeted pan-Trk, ROS1, and ALK inhibitor Entrectinib: combined results from two phase I trials (ALKA-372-001 and STARTRK-1). *Cancer Discov* 2017;7:400–9.
67 Marcus L, Donoghue M, Aungst S, *et al*. FDA Approval Summary: Entrectinib for the Treatment of *NTRK* gene Fusion Solid Tumors. *Clin Cancer Res* 2021;27:928–32.
68 Peters C, Brown S. Antibody-Drug conjugates as novel anti-cancer chemotherapeutics. *Biosci Rep* 2015;35:e00225.
69 Strebhardt K, Ullrich A. Paul Ehrlich's magic bullet concept: 100 years of progress. *Nat Rev Cancer* 2008;8:473–80.
70 Ryman JT, Meibohm B. Pharmacokinetics of monoclonal antibodies. *CPT Pharmacometrics Syst Pharmacol* 2017;6:576–88.
71 Lambert JM. Drug-conjugated monoclonal antibodies for the treatment of cancer. *Curr Opin Pharmacol* 2005;5:543–9.
72 Green MC, Murray JL, Hortobagyi GN. Monoclonal antibody therapy for solid tumors. *Cancer Treat Rev* 2000;26:269–86.
73 Hoffmann RM, Coumbe BGT, Josephs DH, *et al*. Antibody structure and engineering considerations for the design and function of antibody drug conjugates (ADCs). *Oncoimmunology* 2018;7:e1395127.
74 Cubas R, Li M, Chen C, *et al*. Trop2: a possible therapeutic target for late stage epithelial carcinomas. *Biochim Biophys Acta* 2009;1796:309–14.
75 Lipinski M, Parks DR, Rouse RV, *et al*. Human trophoblast cell-surface antigens defined by monoclonal antibodies. *Proc Natl Acad Sci U S A* 1981;78:5147–50.
76 Stepan LP, Trueblood ES, Hale K, *et al*. Expression of Trop2 cell surface glycoprotein in normal and tumor tissues: potential implications as a cancer therapeutic target. *J Histochem Cytochem* 2011;59:701–10.
77 Goldenberg DM, Stein R, Sharkey RM. The emergence of trophoblast cell-surface antigen 2 (TROP-2) as a novel cancer target. *Oncotarget* 2018;9:28989–9006.
78 Fong D, Moser P, Krammel C, *et al*. High expression of TROP2 correlates with poor prognosis in pancreatic cancer. *Br J Cancer* 2008;99:1290–5.
79 Zhao W, Zhu H, Zhang S, *et al*. Trop2 is overexpressed in gastric cancer and predicts poor prognosis. *Oncotarget* 2016;7:6136–45.
80 Zaman S, Jadid H, Denson AC, *et al*. Targeting TROP-2 in solid tumors: future prospects. *Onco Targets Ther* 2019;12:1781–90.
81 Fenn KM, Kalinsky K. Sacituzumab govitecan: antibody-drug conjugate in triple-negative breast cancer and other solid tumors. *Drugs Today* 2019;55:575–85.
82 Bardia A, Messersmith WA, Kio EA, *et al*. Sacituzumab govitecan, a Trop-2-directed antibody-drug conjugate, for patients with epithelial cancer: final safety and efficacy results from the phase I/II IMMU-132-01 basket trial. *Ann Oncol* 2021;32:746–56.
83 Bardia A, Mayer IA, Vahdat LT, *et al*. Sacituzumab Govitecan-hziy in refractory metastatic triple-negative breast cancer. *N Engl J Med* 2019;380:741–51.
84 Ballantyne A, Dhillon S. Trastuzumab emtansine: first global approval. *Drugs* 2013;73:755–65.
85 Dhillon S. Trastuzumab emtansine: a review of its use in patients with HER2-positive advanced breast cancer previously treated with trastuzumab-based therapy. *Drugs* 2014;74:675–86.
86 Paracha N, Reyes A, Diéras V, *et al*. Evaluating the clinical effectiveness and safety of various HER2-targeted regimens after prior taxane/trastuzumab in patients with previously treated, unresectable, or metastatic HER2-positive breast cancer: a systematic review and network meta-analysis. *Breast Cancer Res Treat* 2020;180:597–609.
87 Marcoux J, Champion T, Colas O. Native mass spectrometry and ion mobility characterization of trastuzumab emtansine, a lysine-linked antibody drug conjugate: native MS and IM-MS for trastuzumab emtansine analysis. *Protein Science* 2015;24:1210–23.
88 FDA approves fam-trastuzumab deruxtecan-nxki for HER2-positive gastric adenocarcinomas. Available: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-fam-trastuzumab-deruxtecan-nxki-her2-positive-gastric-adenocarcinomas
89 DS-8201a Versus T-DM1 for Human Epidermal Growth Factor Receptor 2 (HER2)-Positive, Unresectable and/or Metastatic Breast Cancer Previously Treated With Trastuzumab and Taxane [DESTINY-Breast03]. Available: https://clinicaltrials.gov/ct2/show/NCT03529110
90 Manich SM, Modi S, Krop I. Trastuzumab deruxtecan (T-DXd) in patients with HER2-positive metastatic breast cancer (MBC): updated survival results from a phase II trial (DESTINY-Breast01). *Ann Onc* 2021;32:S457–515.
91 Nordstrom JL, Gorlatov S, Zhang W, *et al*. Anti-Tumor activity and toxicokinetics analysis of MGAH22, an anti-HER2 monoclonal antibody with enhanced Fcγ receptor binding properties. *Breast Cancer Res* 2011;13:R123.
92 Markham A. Margetuximab: first approval. *Drugs* 2021;81:599–604.
93 Rugo HS, Im S-A, Cardoso F, *et al*. Efficacy of Margetuximab vs trastuzumab in patients with pretreated ErbB2-positive advanced breast cancer: a phase 3 randomized clinical trial. *JAMA Oncol* 2021;7:573.
94 Traxler P. Tyrosine kinases as targets in cancer therapy - successes and failures. *Expert Opin Ther Targets* 2003;7:215–34.
95 Paul MK, Mukhopadhyay AK. Tyrosine kinase - Role and significance in Cancer. *Int J Med Sci* 2004;1:101–15.
96 Gril B, Palmieri D, Bronder JL, *et al*. Effect of lapatinib on the outgrowth of metastatic breast cancer cells to the brain. *J Natl Cancer Inst* 2008;100:1092–103.
97 Ryan Q, Ibrahim A, Cohen MH, *et al*. FDA drug approval summary: lapatinib in combination with capecitabine for previously treated metastatic breast cancer that overexpresses HER-2. *Oncologist* 2008;13:1114–9.
98 Geyer CE, Forster J, Lindquist D, *et al*. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med* 2006;355:2733–43.
99 Singh H, Walker AJ, Amiri-Kordestani L, *et al*. U.S. food and drug administration approval: neratinib for the extended adjuvant treatment of early-stage HER2-positive breast cancer. *Clin Cancer Res* 2018;24:3486–91.
100 Chan A, Moy B, Mansi J, *et al*. Final efficacy results of neratinib in HER2-positive hormone receptor-positive early-stage breast cancer from the phase III ExteNET trial. *Clin Breast Cancer* 2021;21:80–91.
101 Awada A, Colomer R, Inoue K, *et al*. Neratinib plus paclitaxel vs trastuzumab plus paclitaxel in previously untreated metastatic ErbB2-positive breast cancer: the NEfERT-T randomized clinical trial. *JAMA Oncol* 2016;2:1557–64.
102 Chilà G, Guarini V, Galizia D, *et al*. The clinical efficacy and safety of neratinib in combination with capecitabine for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer. *Drug Des Devel Ther* 2021;15:2711–20.
103 Saura C, Oliveira M, Feng Y-H, *et al*. Neratinib plus capecitabine versus lapatinib plus capecitabine in HER2-positive metastatic breast cancer previously treated with ≥ 2 HER2-Directed regimens: phase III NALA trial. *J Clin Oncol* 2020;38:3138–49.
104 Shah M, Wedam S, Cheng J, *et al*. Fda approval summary: Tucatinib for the treatment of patients with advanced or metastatic HER2-positive breast cancer. *Clin Cancer Res* 2021;27:1220–6.
105 Murthy RK, Loi S, Okines A, *et al*. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. *N Engl J Med* 2020;382:597–609.
106 Helleday T. The underlying mechanism for the PARP and BRCA synthetic lethality: clearing up the misunderstandings. *Mol Oncol* 2011;5:387–93.
107 Wei SC, Duffy CR, Allison JP. Fundamental mechanisms of immune checkpoint blockade therapy. *Cancer Discov* 2018;8:1069–86.
108 Zámečníkova A. Novel approaches to the development of tyrosine kinase inhibitors and their role in the fight against cancer. *Expert Opin Drug Discov* 2014;9:77–92.
109 Krop IE, Kim S-B, Martin AG, *et al*. Trastuzumab emtansine versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer (TH3RESA): final overall survival results from a randomised open-label phase 3 trial. *Lancet Oncol* 2017;18:743–54.
110 Cortés J, Kim S-B, Chung W-P, *et al*. Trastuzumab Deruxtecan versus trastuzumab emtansine for breast cancer. *N Engl J Med* 2022;386:1143–54.
111 Diéras V, Han HS, Kaufman B, *et al*. Veliparib with carboplatin and paclitaxel in BRCA-mutated advanced breast cancer (BROCADE3): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2020;21:1269–82.